# The
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of
# Tropical Medicine

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Ⅲ

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# TRANSACTIONS OF THE AMERICAN SOCIETY OF TROPICAL MEDICINE, SIXTEENTH ANNUAL MEETING HELD AT NEW ORLEANS, LOUISIANA, APRIL 26 AND 27, 1920

# PRESIDENTIAL ADDRESS[1]

HENRY J. NICHOLS

To begin with, I wish to thank the members for my election to the office of President of the Society. Insofar as this position is a personal reward for work, it is appreciated, and will be looked back upon with satisfaction. Insofar as it carries responsibility, I am glad to do my share in attempting to direct the affairs of the Society along useful lines. The responsibility apparently is considerable. In fact, a year ago I was told that the prognosis was bad. I began to feel that my only function might be to conduct the postmortem, but it is evident that the patient is making a good recovery from the depressing influence of war and pestilence, and, like other convalescents, is undergoing a rebound to a better state of health than ever. Under these conditions it seems indicated that the presidential address at this sixteenth meeting should be devoted to the affairs of the Society rather than to any special professional subject.

It may well be asked why a Society which has had among its recent presidents such leaders as Gorgas, Thayer, White, Stitt, Strong, Craig, Rosenau, Ashford and Bass should ever be thought to be in a precarious condition. The answer is two-fold: First, the nature of our work; second, the prevailing state of national morale. American specialists in tropical medicine are comparatively few in number and are widely scattered and it is difficult for any considerable number of them to meet at the same place at the same time. This fact makes some of our meetings very small as compared with those of the more cosmopolitan and fundamental specialties. We have about 108 active members, and our attendance is usually about ten to twenty. In comparison with the crowds so familiar in some medical meetings and so dear to Americans, this handful might seem a poor showing, but it is really only normal. Small meetings are a handicap which

[1] President's address, delivered at the Sixteenth Meeting of the American Society of Tropical Medicine, at New Orleans, April 26, 1920.

we should accept, and it is peculiarly true of the worker in tropical medicine that he must be prepared to stand on his own feet scientifically and morally. Soon after our last annual meeting I sent a circular letter to all members asking for support in making a fresh start for the Society. A number of gratifying replies were received and some of these were illuminating as showing the peculiar character of our work. It appears that many members are unable to attend meetings or contribute to the program, but are sufficiently interested to keep up their dues. Many physicians are directly concerned with tropical medicine only a few years and some have chiefly an academic interest, but still for various reasons desire to be members. These members I believe should be held, and if anything in the circular letter gave any other impression I now wish to correct it. Anyone who has other qualifications and is willing to keep up his support should be welcome.

Our relatively small meetings make it especially necessary to have some binding tie in the form of publications. The single annual volumes of transactions which for several years were edited with such devotion by the Secretary, Dr. Swan, served a very useful end in keeping members in touch with each other. Then a monthly was started, but unfortunately for personal reasons could not be continued. Recently the *New Orleans Medical and Surgical Journal*, through the public spirit of its editors, Dr. Dyer and Dr. Chassaignac, has carried us, and we are grateful for this assistance.

In looking to the future the Council has made efforts to find a more distinctive form of publication. The most feasible plan at present seems to be to publish our transactions as before in a single annual volume. Our income from dues warrants such an undertaking, and it will begin with this year. Eventually we may look forward to a special journal, possibly under the wing of the *Journal of the American Medical Association.*

The second circumstance which caused our slump was referred to as the low state of national morale. After superhuman efforts of the War, there has undoubtedly been a general let down of interest and effort which is felt in our Society. Concentration and sustained effort have naturally been succeeded by a certain amount of indifference, but they are not lost qualities and will function again by degrees. The tremendous resources of our country in natural forces and human energy will find expression and it is our duty as well as desire to play our small part as a Society in the Nation's life as best we may. The best way to be good social creatures is to organize and work in common on a common task. The tasks in tropical medicine for Americans are many, and our traditions already established in a short time are great. In the face of our national future, the Society, as the only national organization of its kind, is called on to put its affairs in order and go forward.

We now have 108 active members, 19 corresponding members, and 39 honorary members. We may look forward as a result of past experience, (1) to a small number of active younger members to carry on the meetings and publications. These members should be recruited from Government services such as the Army and Navy, the Public Health Service, and the Government services of our foreign tropical possessions; from physicians to tropical industrial companies; from practitioners in the South and in the Tropics; from medical schools and institutes in the Tropics and from schools of tropical medicine in this country. (2) To a larger number of older active members who will support the Society by membership, counsel and occasional attendance. These members will come from the same sources as the first group, or be graduates therefrom. (3) To corresponding members who will occasionally contribute to the meetings and give us points of contact with other countries; and (4) honorary members who will be a source of pride and stimulus. We also have our valued membership in the Congress of American Physicians and Surgeons, largely through the interest of ex-President Thayer. This membership should also stimulate us to live up to its standard.

In order to increase its membership and attendance, it has been proposed at different times to make the Society over into one of preventive medicine. But this field is already occupied by one or more societies, while in tropical medicine we stand alone and have our own sphere.

It has also been proposed to enlarge our membership by taking in active members from Central and South American countries.

To take such members as are qualified as Corresponding Members would certainly be desirable, but our Constitution clearly limits our active membership to American physicians. This is the American Society of Tropical Medicine in the sense of the word as used by Secretary of State Hay.

Our future policy in regard to relations with workers in tropical medicine of other countries will naturally reflect national policies. It is not for us to decide these policies in advance. Individually we may and should have our own views, but our position as a Society should be in harmony with the national spirit and with the attitude of the majority of societies in the Association of American Physicians. At present, since our position as a nation is not yet clearly differentiated, we should do what is nearest to hand, namely, to begin with our efforts, like our charity, at home.

The past two years have seen what is apparently an epoch in American Tropical Medicine—the discovery of the long sought cause of yellow fever by Noguchi. This discovery was made possible by the organization of the American Rockefeller Health Board and Institute. The findings at Guayaquil, which were reported at the last meeting, were confirmed at Yucatan this spring, and Dr. Noguchi is at present in Peru investigating another outbreak. While adding more laurels to his eager and resistless spirit, this investigator has enlarged knowledge and given us more control over nature. In connection with the same plan of work, General Gorgas is heading a party which is already en route to Africa to attempt to settle the question of the existence of yellow fever in Africa.

It remains to thank our hosts for the arrangements for this meeting. The last meeting in New Orleans, under Dr. Thayer in 1911, was one of the most successful of our history. The present one, now seventeen years since the Society started, is held here again and naturally so as this is the natural headquarters of the Society. The Society looks to New Orleans and Tulane University to lead in tropical medicine. The Secretary-Treasurer, Dr. Simon, is responsible for the program arrangements and all the details of reorganization of the Society and deserves our especial thanks.

## REPORT OF THE SECRETARY FOR 1919–1920

Your Secretary wishes to submit the following report of the activities of his office during the past year. The Society upon the whole, has enjoyed a prosperous year. Shortly after entering upon his incumbency, the President sent a circular letter to the membership, asking for their full coöperation in the up building of the Society, and at the same time suggesting that those members not in full sympathy with the purposes of the Society should resign. Your Secretary is pleased to announce that this appeal met with a generally favorable response upon the part of a large majority of the members. Partly as a result of the President's statement, but in some instances for other reasons, the following members have handed in their resignations, which are submited for your approval: Drs. E. L. L'Engle, Thos. R. Boggs, W. C. Billings, Walter Brem, Judson Daland, W. E. Musgrave, W. L. Moss. In handing in their resignation, each of these members took occasion to say a good word for the Society, giving as their excuse, other duties which took them out of touch with the affairs of the Society for the present time. In addition, it grieves me to report the death of three of our active members during the past year, namely: Drs. O. T. Logan, H. L. McNeil, and Abraham Jacobi. Likewise, one of our honorary members, Dr. Wm. Osler, passed into the Beyond several months back. With these names removed from our roll, our roster, at the present time stands as follows:

| | |
|---|---|
| Active members | 108 |
| Corresponding members | 19 |
| Honorary members | 29 |

The President has appointed no active committees during the past year. At the last annual meeting it was decided to take final action on the matter of enlarging our membership in the Latin Americas, at the present meeting. The Secretary has held these applications on file pending final action by the Council.

Another important matter to be placed before you for consideration, involves the publication of the transactions of the Society for the coming year. Acting upon instructions, your Secretary made arrangements with the *New Orleans Medical and Surgical Journal* for the publication of our transactions during the present year, upon the same bsais as the year previous, namely, a total of $250. This included the publication of the various papers in the *Journal* and the carrying of our members as regular subscribers.

At the last meeting the membership dues were raised from $4.00 to $5.00, in order to cover our constantly increasing expenditure. I am happy to report that in no single instance was complaint made upon the part of our members at this increase.

A motion introduced by Dr. Nichols at the last meeting, proposed the following change in our by-laws: That article two be amended to read as follows: The regular dues shall be paid by Active members and by Corresponding members. Honorary members shall be exempt from dues. It will be necessary to bring this up for final action at the present meeting.

Respectfully submitted,

SIDNEY K. SIMON,
*Secretary.*

## REPORT OF THE TREASURER FOR 1919–1920

*Receipts*

| | |
|---|---|
| Balance as per bank book, June 1, 1919 | $147.08 |
| Membership dues from July 1, 1919, to April 15, 1920 | 493.00 |
| Total | $640.08 |

*Disbursements*

| | |
|---|---|
| Rockefeller Foundation (refund of dues) | $8.00 |
| Miss Louise Collins, stenographer fees | 15.00 |
| Total exchange | 1.30 |
| Dr. C. Y. White, expense 1919 meeting | 42.50 |
| Office of Dr. S. K. Simon, stamps | 5.00 |
| *New Orleans Medical and Surgical Journal*, 1918 publications | 250.00 |
| Dr. D. Rivas, stationery | 5.25 |
| Tulane Printing Press, printing | 18.90 |
| Total exchange | 1.45 |
| Total | $347.40 |

| | |
|---|---|
| Balance on hand April 15, 1920 | $292.40 |
| Library Fund | 30.83 |
| Total resources at present date | $323.23 |

SIDNEY K. SIMON,
*Treasurer.*

## MINUTES OF ANNUAL MEETING

The sixteenth annual meeting of the American Society of Tropical Medicine was called to order on Monday, April 26, 1920, in the Gold Room of the Grunewald Hotel, New Orleans, with the President, Major H. J. Nichols, in the Chair.

In addition to the Secretary-Treasurer, Dr. S. K. Simon, the following members were present: Drs. John M. Swan, Isadore Dyer, C. C. Bass, V. G. Heiser, I. I. Lemann, J. B. Guthrie, G. W. McCoy, Howard. A number of guests were also present. The President read his address, entitled "The American Society of Tropical Medicine."

Dr. John M. Swan presented a paper with lantern slide demonstration, entitled "Medical Notes on San Domingo and Haiti." No discussion.

In the absence of Dr. J. F. Schamberg, his paper entitled, "Report of a Case of Yaws in an American Soldier of the American Expeditionary Forces," was read by Dr. Nichols, and afterwards discussed by Drs. Swan and Nichols.

Dr. J. B. Guthrie then read a paper on "Blood Findings in Yellow Fever." Discussed by Drs. Bass, Swan, McCoy and Guthrie.

The final paper of the first days session, "On the Prevalence of Carriers of *Endamoeba dysenteriae* Among Soldiers Returned from Overseas Service," contributed by Major C. A. Kofoid, was read by the Secretary in the absence of the essayist. Discussed by Drs. Simon, Bass, Swan, Howard.

The second session of the scientific program was called to order on Tuesday, April 27, 1920, 9.30 a.m. with the President and Secretary in their respective Chairs, and the following members present: Drs. McCoy, Dock, Kraus, Graves, Bass, Amesse, Levy, Swan, Heiser, Lemann, Guthrie.

The opening paper "Contributions to Medical Science Developed Under the Auspices of the United States Interdepartmental

Social Hygiene Board," contributed by Dr. W. T. Snow, was read by his associate, Dr. Thompson. This paper was discussed by Dr. McCoy.

The next paper "An Attempt to Explain the Greater Pathogenity of *Plasmodium falciparum* as Compared with Other Species," was read by Dr. C. C. Bass, and discussed by Drs. Dock, Kraus, Graves, Bass.

M. V. King read a paper entitled "Natural Malarial Infection in Anopheles Mosquitoes," which was discussed by Drs. Kraus, Bass, Dock, King.

A paper on "Hymenolepis in St. Louis," was read by Dr. Dock, and discussed by Drs. Simon, Levy, Bass, Amesse, Graves.

Dr. I. I. Lemann read a paper "Report of a Case of Bacillary Dysentery with Edema of the Abdominal Walls and Pseudo Membranes in Vagina." Discussed by Drs. Simon, Bradburn, Lemann.

The final paper was presented by Dr. Kraus, "Studies of Monilia in Connection with Sprue." Discussed by Drs. Bass, Levy, Graves, Kraus.

The Secretary read extracts of a letter received by him from Dr. E. J. Wood, Wilmington, N. C., in regard to the probable presence of Sprue in the United States, and the opinions held by the British Tropical Authorities concerning this disease.

The Society, by a rising vote, extended thanks to the New Orleans members for their part in arranging for the success of the meeting.

## MINUTES OF THE COUNCIL MEETING OF THE AMERICAN SOCIETY OF TROPICAL MEDICINE, ANNUAL MEETING, 1920

The Council was called to order on Monday, April 26, 1920, at 5.00 p.m. in the private office of the Secretary, 3439 St. Charles Avenue, New Orleans.

The following members of the Council were present: Drs. Swan, Nichols, Bass, Heiser, and Simon.

The President gave an extemporaneous résumé of the activities of the Society during the preceding year.

The report of the Secretary and Treasurer was read and approved. Final action was taken in regard to the matter of admission of new members from the Latin Americas. A motion was carried to the effect that prospective members in the Latin Americas, who had previously indicated their desire to become active members, through the solicitations of the Membership Committee, be required to submit their application in regular form and in strict accordance with the provisions of the by-laws. A motion was also passed empowering the Treasurer to drop those members whose dues were found to be in arrears for a period of over three years. It was ordered however, that no member be dropped until a registered letter, enclosing statement for the full amount of dues, be sent to the delinquent member, with request that the postal authorities confirm receipt of the letter.

In view of the financial difficulties in which the Society was placed an amendment to the by-laws was adopted, fixing the dues of Corresponding members at $3.00.

The following resignations were presented to the Council by the Secretary and accepted: Drs. Fraser B. Gurd, John T. Halsey, Edmond L'Engle, W. C. Billings, Thos. R. Boggs, Judson Deland, W. L. Moss.

The following resignations were also submitted, but upon vote of the Council were ordered not accepted: Drs. A. H. Sellards, Chas. P. Emerson, Walter Brem, W. E. Musgrave.

The following were elected to active membership: Drs. Francis B. Johnson, Kenneth M. Lynch, Moise D. Levy, Frederick Wade.

The question of the publication of the transactions of the Society was debated at some length. It was finally decided that for the ensuing year (1920–1921), the proceedings of the Society be published in a separate volume, to be sent to each individual member. The manuscripts presented at the meeting might be submitted for publication to any journal the member might see fit. Copies of the transactions were to be submitted for sale to libraries and others wishing to purchase them at a charge not to exceed $3.00.

The following officers were elected for the coming year:

*President*, Dr. John M. Swan, 457 Park Avenue, Rochester, N. Y.
*First Vice-president*, Dr. Karl F. Meyer, 191 Frederick Street, San Francisco, Cal.
*Second Vice-president*, Dr. Victor G. Heiser, Rockefeller Foundation, 61 Broadway, New York City
*Secretary*, Dr. S. K. Simon, 3439 St. Charles Avenue, New Orleans, La.
*Assistant Secretary*, Dr. Allen J. Smith, University of Pennsylvania, West Philadelphia, Pa.
*Treasurer*, Dr. S. K. Simon, 3439 St. Charles Avenue, New Orleans, La.
*Councillors*
Dr. Geo. Dock (1 year), Washington University, St. Louis, Mo.
Dr. C. L. Furbush (2 years), 1501 Spruce Street, Philadelphia, Pa.
Dr. Jos. F. Siler (3 years), Med. Corps, U. S. A., S. G. O., Washington, D. C.
Dr. J. H. White (4 years), 1720 17th Street, N. W., Washington, D. C.
Dr. Chas. S. Butler (5 years), U. S. N. Hospital, Great Lakes, Ill.

Dr. W. S. Thayer, 406 Cathedral Street, Baltimore, Md., was elected delegate to the American Congress of Physicians and Surgeons, with Dr. H. J. Nichols, Army Medical School, as alternate.

# LIST OF MEMBERS

*December, 1920*

## ACTIVE MEMBERS

Arnou, Dr. Ramon Ruiz................................San Juan, Porto Rico
Ashford, Dr. Bailey K..............2 San Cristobal, San Juan, Porto Rico
Ammesse, Dr. J. W..................520 Metropolitan Building, Denver, Col.
Ammerman, Dr. Chas C......................331 4th Avenue, Pittsburgh, Pa.
Anders, Dr. James M..................1605 Walnut Street, Philadelphia, Pa.
Baetjer, Dr. Walter A..............Johns Hopkins Hospital, Baltimore, Md.
Boyd, Dr. Mark F..........................................Galveston, Texas
Barlow, Dr. Nathan..........................................St. Louis, Mo.
Bass, Dr. C. C..................................1551 Canal, New Orleans, La.
Barker, Dr. Lewellys F................1035 Calvert Street, Baltimore, Md.
Bell, Dr. Geo. S........................Medical Building, New Orleans, La.
Bates, Dr. L. B.........................................Ancon, Canal Zone
Blue, Dr. Rupert..................U. S. P. H. S. & M. S., Washington, D. C.
Beall, Dr. Khleber H....................................Fort Worth, Texas
Bonny, Dr. Sherman C................203 Metropolitan Building, Denver, Col.
Boyd, Dr. John C................1621 22nd Street, N. W., Washington, D. C.
Butler, Dr. Chas S........................U. S. N. Hospital, Great Lakes, Ill.
Barrett, Dr. Harvey P.......................1915 Park Drive, Charlotte, N. C.
Creel, Dr. Richard H...................U. S. P. H. S., Washington, D. C.
Craig, Dr. Chas. F................Army Medical School, Washington, D. C.
Cole, Dr. Rufus, Rockefeller Hospital, 66th Street and Avenue A, New York City
Coplin, Dr. W. M. L.......................606 S. 48th Street, Philadelphia, Pa.
Clark, Dr. Herbert C....................................Ancon, Canal Zone
Converse, Dr. Geo. M..................U. S. P. H. S., San Francisco, Cal.
Carter, Dr. H. R............................U. S. P. H. S., Baltimore, Md.
Chamberlain, Dr. W. P..........Surgeon General's Office, Washington, D. C.
Deaderick, Dr. Wm................Dugan-Stuart Building, Hot Springs, Ark.
Darling, Dr. S. T.
Professor of Hygiene Faculty, Sao Paulo, Brazil; 61 Broadway, New York City, Please forward
Darlington, Dr. Thos............27 Washington Square N., New York City
Dunham, Dr. E. K......Bellevue Hospital Medical College, New York City
Dock, Dr. Geo........................Washington University, St. Louis, Mo.
Duval, Dr. Chas. W....................8 Richmond Place, New Orleans, La.
Elliott, Dr. John B., Jr............Maison Blanche Annex, New Orleans, La.
Fenton, Dr. Thos. H..................1319 Spruce Street, Philadelphia, Pa.
Futcher, Dr. T. B....................3 West Franklin Street, Baltimore, Md.

Furbush, Dr. C. L....................1501 Spruce Street, Philadelphia, Pa.
Garrison, Dr. P. E..Surgeon General's Office, U. S. Navy, Washington, D. C.
Graves, Dr. M. L....American National Insurance Building, Galveston, Texas
Guthrie, Dr. Clyde G....................................Indiana, Pa.
Guthrie, Dr. J. B...............Maison Blanche Building, New Orleans, La.
Igaravidez, Dr. Gutierrez..........................San Juan, Porto Rico
Hume, Dr. E. H.....................Hunan Yale Hospital, Changsha, China
Hiatt, Dr. Houston B................................High Point, N. C.
Hall, Dr. Maurice C.................................Detroit, Mich.
Henson, Dr. Graham E...............St. James Building, Jacksonville, Fla.
Houghton, Dr. Henry S.
Harvard Medical School of China, 7 Siccawei Road, Shanghai, China
Heiser, Dr. V. C....Rockefeller Foundation, 61 Broadway, New York City
Hatch, Dr. J. L......................50 East 50th Street, New York City
Harris, Dr. H. E...............Jefferson Medical College, Philadelphia, Pa.
Harris, Dr. Seale......................Empire Building, Birmingham, Ala.
Hitchens, Dr. A. Parker..........Army Medical School, Washington, D. C.
Johns, Dr. Foster M.......................1551 Canal, New Orleans, La.
Johnson, Dr. Francis B........Charleston Medical College, Charleston, S. C.
Kraus, Dr. Wm.....................Physicians Laboratory, Memphis, Tenn.
Lemann, Dr. I. I...........................3523 Prytania, New Orleans, La.
Leys, Dr. James F.......................U. S. N. Hospital, Newport, R. I.
Leidy, Dr. Jos.........................1319 Spruce Street, Philadelphia, Pa.
Long, Dr. John D.....................432 Call Building, San Francisco, Cal.
Levy, Dr. Moise D....................................Galveston, Texas
Ludlow, Dr. Clara S........U. S. A. Medical Museum, Washington, D. C.
Lynch, Dr. Kenneth M..........Charleston Medical College, Charleston, S. C.
Kofoid, Major C. A.................University of California, Berkeley, Cal.
McCaw, General W. D.............Army Medical School, Washington, D. C.
McElroy, Dr. John B.......................................Memphis, Tenn.
McLester, Dr. J. S......................3917 Cliff Road, Birmingham, Ala.
McConnell, Dr. Guthrie...........2601 Hamsphire Road, Cleveland, Ohio
McCoy, Dr. Geo. W................Hygienic Laboratory, Washington, D. C.
Martinez, Dr. I. Gonzales..................Box 753, San Juan, Porto Rico
Matas, Dr. Rudolph................2255 St. Charles Avenue, New Orleans, La.
Miller, Dr. H. W..Washington Sanitarium, Takoma Park, Washington, D. C.
Meyer, Dr. K. F....191 Frederick Street, Crossways Apt., San Francisco, Cal.
Mink, Dr. A. J..........................U. S. N. Hospital, Bremerton, Wash.
Moore, Dr. John T...................Kress Medical Building, Houston, Texas
Nichols, Dr. H. J...................Army Medical School, Washington, D. C.
Ousterhout, Dr. Paul.....................................Belton, Texas
Pierce, Dr. C. C...........1119 Lamont Street, N. W., Washington, D. C.
Querens, Dr. P. L......................Cusach Building, New Orleans, La.
Rosenau, Dr. W. J.................Harvard Medical School, Boston, Mass.
Rivas, Dr. D.................University of Pennsylvania, Philadelphia, Pa.
Ransom, Dr. B. H..........Bureau of Animal Industry, Washington, D. C.
Rucker, Dr. W. C.
2131 Bancroft Street, Treasury Department, Washington, D. C.

Seeman, Dr. Wm. H....................1551 Canal Street, New Orleans, La.
Simon, Dr. Sidney K..............3439 St. Charles Avenue, New Orleans, La.
Sailor, Dr. Jos........................1830 Spruce Street, Philadelphia, Pa.
Siler, Dr. J. F., Medical Corps, U. S. A.,..........S. G. O., Washington, D. C.
Shattock, Dr. Geo. C......................205 Beacon Street, Boston, Mass.
Skinner, Dr. Henry..........................................Narberth, Pa.
Strong, Dr. R. P........Harvard University Medical School. Boston, Mass.
Swan, Dr. John M......................457 Park Avenue, Rochester, N. Y.
Snow, Dr. Wm. F......................105 West 40th Street, New York City
Smith, Dr. Allen J,
University of Pennsylvania Medical Laboratory, West Philadelphia, Pa.
Stitt, Admiral E. R..................Navy Department, Washington, D. C.
Todd, Dr. John L......................McGill University, Montreal, Canada
Talbot, Dr. Paul T............Maison Blanche Building, New Orleans, La.
Tasker, Dr. Arthur N......c/o Surgeon General's Office, Washington, D. C.
Thayer, Dr. W. S......................406 Cathedral Street, Baltimore, Md.
Tyzzer, Dr. E. E............Harvard University Medical School, Boston, Mass.
Van Wart, Dr. R. M.......................3431 Prytania, New Orleans, La.
Walker, Dr. E. L., Hooper Foundation for Medical Research, San Francisco, Cal.
Weis, Dr. Jos. D............................3431 Prytania, New Orleans, La.
White, Dr. C. Y......................1808 Diamond Street, Philadelphia, Pa.
White, Dr. J. H..................1720 17th Street, N. W., Washington, D. C.
Whitmore, Dr. E. R............1108 16th Street, N. W. Washington, D. C.
Wood, Dr. E. J......................201 Chestnut Street, Wilmington, N. C.
Wade, Dr. H. W......................University of Philippines, Manila, P. I.
Wright, Dr. Barton L...................U. S. N. Hospital, Pensacola, Fla.
Zeiler, Dr. A. H......................Brockman Building, Los Angeles, Cal.

## CORRESPONDING MEMBERS

Castellani, Prof. A.........................................Colombo, Ceylon
Charles, Col. R. Havelock..Indian Office, Whitehall, London, S. W., England
Daniels, Dr. C. W...................29 Harley Street, London, W., England
Goodhue, Dr. E. S..................The Doctorage, Holualoa, Kona, Hawaii
Goodhue, Dr. W. J...............................Kalaupapa, Molokai, H. I.
Labrado, Dr. Mario G.........................................Havana, Cuba
Liston. Capt. W. Glen..........Plague Research Laboratory, Bombay, India
Lukis, Sir Pardey....................Director General I. M. S., Simla, India
Mackie, Dr. J. Percival........................................Bombay, India
Pareja, Dr. Weneslao................................Guayaquil, Eduador
Padreso, Dr. Alexandrino...............................Sao Paulo, Brazil
Park, Dr. Wm. H.........................................Soo Chow, China
Perry, Sir Allen................Colombo Medical College, Colombo, Ceylon
Rogers, Major Leonard...................11 Elysium Row, Calcutta, India
Stanton, Dr. A. T.,
Institute for Medical Research, Kuala Lumpur, Federated Malay States

## HONORARY MEMBERS

Agramonte, Prof. Aristides..........University of Havana, Havana, Cuba
Blanchard, Prof. Raphael........226 Boulevard St. Germain, Paris, France
Calmette, Dr. A..............................Institute Pasteur, Lille, France
Choksy, Dr. M. H..........Arthur Road, and Martha Hospital, Bombay, India
Chagas, Dr. Carlos..............................................Brazil
Cofer, Dr. L. E......................U. S. P. H. & M. H. S., Seattle, Wash.
Flexner, Dr. Simon...................Rockefeller Institute, New York City
Guiteras, Dr. John...........................University of Havana, Cuba
Grassi, Prof..................................................Rome, Italy
Howard, L. O., Ph.D....U. S. Department of Agriculture, Washington, D. C.
King, Dr. W. W.
Medical Officer, U. S. P. H. & M. S. Service, San Juan, Porto Rico
Kolle, Dr. W......Koch's Institute for Infectious Diseases, Berlin, Germany
Kitasato, Prof.,
Kitasato Institute for Infectious Diseases, Tokyo at Sankocho, Shibakii
Tokyo, Japan
Laveran, Prof. A..........................Pasteur Institute, Paris, France
Liceaga, Dr. Edouardo..................................Mexico City, Mexico
Manson, Sir Patrick,
21 Queen Ann Street, Cavendish Square, W., London, England
Montizambert, Dr. F.,
Office of the Director General of Public Health, Ottawa, Canada
Martin, Dr. Chas. J.,
Lister Institute of Preventive Medicine, Chelsea Gardens, London, England
Nuttall, Prof. Geo. H................................Cambridge, England
Ogata, Dr................................University of Tokio, Tokio, Japan
Paltauf, Prof...........................University of Vienna, Vienna, Austria
Roux, Prof..................................Pasteur Institute, Paris, France
Ross, Sir Ronald G..36 Harley House, Regents Park, London, N. W., England
Stockman, Prof. Ralph...................................Glasgow, Scotland
Salmon, Dr. D. E.......................University of Montevideo, Uruguay
Stiles, Dr. Chas. Wardell......U. S. P. H. & M. H. S., Washington, D. C.
Trotter, Dr. E. E.............................................Honolulu, H. I.
Welch, Prof. Wm. H..............Johns Hopkins University, Baltimore, Md.
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# MEDICAL NOTES ON THE DOMINICAN REPUBLIC AND HAITI[1]

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The island of Santo Domingo or Haiti, after Cuba, is the largest of the West India Islands. It was discovered by Columbus on his first voyage in 1492. It is situated between latitude 17°35′ North and 20° North so that it is well within the tropics, and lies between Cuba on the west and Puerto Rico on the east. Although it is within the tropical zone, it has an equable climate, on account of the prevalence of the northeast trade winds. The records of the Department of Agriculture of the Dominican Republic show that from 1910 to 1917 the average mean annual temperature was 77.9°. The average mean monthly temperature during this period exceeded 80° F. in June, July, August and September, only. The highest recorded temperature during the seven years referred to was 93.2°; the lowest, 56.8°. The average monthly rainfall was 4.3 inches. In 1917 the total rainfall was 51.8 inches and there were 112 days with rain.

The island is crossed from east to west by two mountain ranges, which divide the country into a narrow, north coastal plain; a central valley, about 25 miles in width; and a south coastal plain about 25 to 30 miles in width.

Politically, the island is divided into the Dominican Republic, which occupies the eastern two-thirds; and the Republic of Haiti, which occupies the western third.

## THE DOMINICAN REPUBLIC

Between December 8, 1919, and February 12, 1920, I visited every province of the Dominican Republic; Santo Domingo,

[1] Read before the sixteenth annual meeting of the American Society of Tropical Medicine.

Azua, Barahona, Samana, La Vega, Pacificador, Santiago, Espillat, Monte Christi, Puerto Plata, San Pedro de Macoris, and Seybo.

The government of the Dominican Republic is a military government set up under the authority and by the direction of the government of the United States, on November 29, 1916, by Captain H. S. Knapp, U. S. N., Commander of the Cruiser Force of the United States Atlantic Fleet, because of a violation of Article III of the treaty between the United States and the Republic of Santo Domingo, concluded February 8, 1907, ratified July 8, 1907, and proclaimed July 25, 1907.

The governor is a rear admiral of the United States Navy. His cabinet is composed of naval and marine corps officers. Each province has a native, civil governor appointed by the military governor and a health officer appointed by the Secretary of State for Sanitation and Beneficence. Each city or town has an ayuntamiento, appointed by the military governor. The judiciary is in the hands of the duly authorized Dominican officials, under the oversight and control of the military governor. The police of the country is in the hands of the Guardia Nacional Dominicana, which is composed of native Dominicans officered by men selected from the United States Marine Corps. The United States Marines are being recalled from all districts which are not the seat of bandit disturbance uncontrollable by the Guardia.

The country is a rich agricultural and cattle raising country. The principal export crops are sugar, cacao, tobacco, honey, and coffee. Beeswax, cotton, goatskins and hides of cattle, molasses, cocoanuts and woods are also exported in considerable quantities.

The people live on plantains, yams, bananas, oranges and other tropical fruits and vegetables which they raise. All of the flour and most of the rice is imported. The meat used is killed in the late afternoon and sold before noon the next day, as there are no cold storage plants available. The fisheries are undeveloped. All materials for clothing, agricultural machinery, tools and implements, cement, drugs and chemicals, mineral oils, and manufactures of iron and steel are imported.

At the present time a census is being taken. The available figures show that there are between 700,000 and 800,000 people in a country about one third the size of the state of Pennsylvania. The natives are a mixture of the Spanish and Negro races. The native Indian blood has, in my judgment, entirely disappeared. The natives are said by various observers to be from 85 to 95 per cent illiterate.

The people are not philanthropically or charitably inclined. The majority of the existing hospitals are supported by lotteries. The purchase of a ticket in a lottery cannot be called an act of charity. The hospitals supported by these lotteries were all running at much less than their capacity (30 to 50 per cent).

In the entire country I saw but one genuine charity. In La Vega there is an orphan asylum for girls which was built and equipped, and is supported, by a blind man of means. Beggars are allowed to go from house to house or from store to store unhindered.

The untidy habits of the people and the lack of public water supplies and sewerage systems make sanitation difficult. The tropical sun, the frequent heavy showers, and the northeast trade winds are a great advantage in sanitation. There are none of the scavenger birds found in the country. In all towns and cities the human excreta are deposited in pit privies; there are a few septic tanks. In the country, soil pollution is common and if the population were more dense would be a menace. Flies and mosquitoes abound. The Secretary of State for Sanitation and Beneficence is attempting to apply all the factors of modern sanitation and vital statistics to the country as fast as the money at his disposal and the personnel with which he has to work will allow. In 1918, 1.77 per cent of the total administrative budget was appropriated for sanitation. In 1919, 1.87 per cent was so appropriated. This year the appropriation is 4.18 per cent and amounts to $182,991. In addition, each municipality is required to appropriate 10 per cent of its funds for sanitation if its total receipts are below $10,000 and 15 per cent if its income equals that figure or is above it.

The number of physicians in the country is very small, about one physician to every 8700 people. Nearly all of these physicians are located in the cities and towns. Many villages have no physician and many children are born and many individuals

TABLE 1

*Prevailing diseases*

| CITY AND PROVINCE | MALARIA | SYPHILIS | TUBERCULOSIS | INTESTINAL PARASITES | SPECIAL |
|---|---|---|---|---|---|
| Santo Domingo | x | x | x | x | Few lepers—elephantiasis |
| Los Llanos (S. P. de Macoris) | | | | | Infantile tetanus |
| Bani, Santo Domingo | Moderate | x | x | ? | Yaws and typhoid fever |
| Azua, Azua | x | Not much | x | ? | Fevers not classified: filaria; infantile tetanus |
| San Juan, Azua | x | x | x | Suspected | Typhoid fever; filaria |
| Las Matas, Azua | x | | | ? | Respiratory infections; diseases of the stomach |
| Barahona, Barahona | x | x | 0 | Suspected | 1000 cases of yaws; dysentery, typhoid fever, pneumonia |
| Sanchez, Samana | x | x | x | x | |
| Samana, Sanama | | | x | x | |
| La Vega, La Vega | x | x | x | x | Typhoid fever; yaws |
| San Francisco de Macoris, Pacificador | x | x | x | x | Yaws |
| Moca, Espillat | x | x | x | x | Intestinal infections |
| Santiago, Santiago | x | x | Not much | x | Typhoid fever; yaws |
| Monte Christi | x | x | Not much | x | Typhoid fever; yaws |
| Puerto Plata, Puerto Plata | x | x | x | x | Typhoid; elephantiasis; diphtheria; leprosy |
| Seybo, Seybo | x | x | x | x | Yaws; typhoid fever; leprosy |

get sick and die without medical attention. The majority of the native physicians have received their education at the University of Santo Domingo. This University has no dissecting room, no pathological, bacteriological or chemical laboratory. No hospital ward work or dispensary work. There are several of the native physicians who have studied in Paris, Barcelona, Edinburgh, and the United States. These physicians say that the prevalent diseases of the people are syphilis, malaria, tuberculosis, and intestinal parasites. In certain districts they are said to have typhoid fever, filariaris, yaws, leprosy and intestinal and respiratory infections (see table 1).

From 85 per cent to 90 per cent of the population is said to have syphilis. I am of the opinion that a great deal of confusion exists in the diagnosis between cases of syphilis, yaws, staphylococcus and streptococcus skin infections and also feel that it is possible that some form of leishmaniasis may be present.

I am of the opinion that the amount of malaria present in the country is much overestimated. There are very few physicians who make an attempt to diagnosticate malaria by staining the blood for the parasite. Out of a collection of 150 mosquitos sent to Dr. C. S. Ludlow of the Army Medical Museum in Washington, only two belonged to the genus anopheles. Further collections of mosquitos are to be made and sent to Dr. Ludlow for determination (see table 3).

A tabulated statement of the different hospitals erected and operating partially, and erected but not operating is appended (table 2).

In Santo Domingo City and in Santiago there are Sales de Succoro, which are dispensaries under the charge of the municipal physicians, where first aid can be given.

The Secretary of State for Sanitation and Beneficence has placed orders for the equipment of twelve venereal disease dispensaries which are to be established in twelve cities. A Leprosarium is being constructed about 15 miles from Santo Domingo City. In addition to the orphan asylum in La Vega there is one in Santiago and one in Santo Domingo City. Neither is filled to its capacity. An insane hospital is being built in Santo Domingo City.

TABLE 2

*Hospitals*

| NAME | LOCATION | METHOD OF SUPPORT | BEDS | NURSES | DOCTORS | REMARKS |
|---|---|---|---|---|---|---|
| Seibo Hospital | Seibo | Dominican Chapter, American Red Cross, and $40 per month ayuntamiento | 20 | C. P. M. one trained, one practical | 1 U. S. Navy | Has enlisted men from Marine Corp receiving instruction |
| La Romana | Romana Sugar Estate | Romana Sugar Estate | 20 for laborers; 10 for whites | One trained, one practical | 1 chief physician; 1 assistant at Guaiamati; 3 practicantes | |
| Hospice San Antonio | San Pedro de Macoris | Lottery | 30, men only | Roman Catholic Sisters | 1 medical director; 8 civil physicians —all have private practices | People in San Pedro de Macoris say difficult to have patients admitted |
| Puerto Plata | Puerto Plata | Lottery; ayuntamiento and subscription | 27 men and women | One trained, one practical | 2 civil and 1 Navy | Wellsituated, clean |
| Hopital Militare | Santo Domingo City | Appropriations from government | 100–125—men and women | One trained | 1 director; several practicantes | Needs thorough renovating |
| Societe la Humanitaria | La Vega | Lottery | 50—men and women | Roman Catholic Sisters | 1 in charge; also private practice; 4 civilians | Incomplete |

| | | | | | | |
|---|---|---|---|---|---|---|
| San Rafael | Santiago | Lottery | 60 | 0 | 0 | Not in operation although completed and equipped |
| Bienfaisance de Padre Bellini | Santo Domingo City | Lottery | 100—34 actually filled | Roman Catholic Sisters | Doctors from city | Old Men's Home |
| Amigos del Povres | Santo Domingo City | Lottery | 56 | Roman Catholic Sisters | Doctors from city | Old Women's Home |

TABLE 3

*Mosquitoes sent to Dr. C. S. Ludlow from the Dominican Republic, December, 1919 and January, 1920*

| | |
|---|---|
| *Anopheles vestipennis* | 2 |
| *Culex fatigans* | 63 |
| *Culex similis* | 4 |
| *Stegomyia fasciata* | 18 |
| *Wyomyia phroso* | 4 |
| *Wyomyia agnostips* | 2 |
| *Mansonia titillans* | 8 |
| *Aedes portoricensis* (taeniorrhynchus) | 3 |
| *Aedes sollicitans* | 9 |
| Spoiled | 37 |
| | 150 |

## HAITI

The Republic of Haiti has about the same physical characteristics as the Dominican Republic. It occupies the western third of the island of Santo Domingo; but, while it is about one-half the size of the Dominican Republic, it has about three times the population; two and one-half millions. The people are more nearly pure black than the Dominicans. During the French Revolution the blacks and the mulattoes united in driving out or massacring the whites and later the negroes succeeded in driving out or massacring the mulattoes.

The prevailing diseases are the same as in the Dominican Republic: Venereal diseases, malaria, intestinal parasites, tuberculosis, filariasis, yaws. The local physicians and the navy doctors say that these diseases are all more numerous and more severe than in the Dominican Republic. This is probably due to the larger population and its greater density. The hospitals that do exist are superior to those in the Dominican Republic and are better supported. Sanitation is being pushed by the sanitary engineer of Haiti, a navy doctor, loaned to the Haitian government by the United States navy at the request of the State Department. The appropriation for sanitation in 1920 was 5.75 per cent of the total budget of the government of Haiti, and amounted to $268,200.00.

The great need of this country, as of the Dominican Republic, is education. In the line of public hygiene and sanitation the same conditions pertain as are found in the Dominican Republic. The people need nurses. To this end the sanitary engineer has established a training school for native nurses in the hospital at Port au Prince. The school is directed by a navy nurse and is doing good work. The pupil nurses are crowded in a building that is unsuitable for them.

# AN ATTEMPT TO EXPLAIN THE GREATER PATHOGENICITY OF PLASMODIUM FALCIPARUM AS COMPARED WITH OTHER SPECIES

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Of the three common species of malaria plasmodia, *P. vivax, P. malariae* and *P. falciparum,* the latter is far the most pathogenic. This greater pathogenicity is observed and reported wherever malaria prevails throughout the world. The number of deaths caused by infection with *P. vivax* and *P. malariae* is insignificant as compared with the number produced by *P. falciparum.* In fact, practically all deaths caused by malaria are caused by *P. falciparum* and almost none by the other species. Not only are nearly all deaths caused by it, but it causes almost all of the pernicious clinical types of malaria.

One of the explanations offered for this greater pathogenicity is that the organism produces a more harmful or more powerful toxin. This explanation is theoretical entirely. Another explanation offered is the larger number of parasites that are present in the blood of many of the more pernicious and destructive cases. It is undoubtedly true that the number of parasites is very much larger in the blood of the severer cases due to *P. falciparum* than in those due to other species, but I am not familiar with any definite explanation for this fact. The object of the present paper is to bring up for discussion an explanation which has not previously been advanced so far as I know and which, though theoretical, is based upon definite facts. It offers to explain the greater pathogenicity, without the necessity of the supposed greater toxicity. In fact, if one should judge by the number of parasites present in the blood, one would be inclined to think that *P. falciparum* is less toxic than the other parasites, if indeed there is any toxin produced by either.

The general impression is that malaria parasites grow and reproduce in the circulating blood. As a matter of fact, however, the asexual parasites found in the circulating blood are most, if not all of them, more or less accidentally or incidentally swept into the blood stream from the capillaries in those organs and tissues where much larger numbers are lodged and growing. Growth and reproduction of malaria parasites takes place chiefly, if not entirely, in the smallest blood vessels of certain organs and tissues of the body. To a certain extent, it takes place in capillaries of all organs and tissues, but the parasites are usually more numerous in the bone marrow, spleen, brain and liver in the order named.

*P. vivax* and *P. malariae* have more or less ameboid activity and are therefore more likely to move about and to pass through or be dislodged from the capillaries than *P. falciparum*, which has extremely little ameboid movement. This may be observed by watching large asexual parasites of the different species under the microscope. The ameboid parasites give one the impression that in the event of lodging in front of narrow places in the capillaries, they would change their shape and at least tend to pass through such places very much like the blood cells do. As a parasite gets larger and larger, most of them finally lodge and remain until segmentation takes place.

After segmentation, the much smaller parasites can of course be swept out of a capillary in which the larger parasite has been retained. This lodging of the parasites of these two species is no doubt the explanation for the fact that the number of small parasites present, which is largest soon after the paroxysm, becomes smaller and smaller as the parasites get older and larger. It is true that occasionally a few of the ameboid parasites, including rosettes, appear from time to time and sometimes some of the rosettes actually burst while in the circulating blood. It is not at all probable, however, that any of the merozoites produced in the circulating blood succeed in attaching themselves to other erythrocytes and survive.

In falciparum infection, only ring forms of the schizonts are found in the general circulation. As soon as these parasites reach the proper age and size they disappear from the circulation and do not reappear until merozoites are produced, some or many of which may appear.

The size and age at which young *P. falciparum* disappear from the circulation is different in different individuals. It is quite conceivable that the explanation of this may be the probability that there is slight variation in the size of the capillaries of different individuals. We see a greater number of large parasites in the blood of very young children than we do in that of older persons. In fact, almost all of the large falciparum schizonts that we ever see in ordinary blood preparations are from babies under one year of age, in whom it is supposed the capillaries are larger and more patulent than they are in older persons.

Most or all of these parasites disappear from the circulating blood by the time they are ten or twelve hours old. It appears that by the time this age is reached the parasite has attained a size which does not permit it to pass through the places in which they lodge. Only comparatively small falciparum parasites, therefore, can pass through the places in which parasites lodge and through which much larger vivax and malariae parasites can pass.

If we take cultures of *P. falciparum* in which the parasites are much older and larger than those found in the circulating blood of infected persons, say thirty-six or forty hours old, and study them under the microscope, I believe that we can recognize and demonstrate a very striking quality which very probably affects their transportation by the circulating blood. If we place a droplet of culture containing such parasites on a microscope slide, cover it with a cover glass and observe the parasites under the microscope while making pressure on the cover glass with a very delicate instrument, we observe a very remarkable and impressive condition. It is noticed that when pressure is made on the cover glass the erythrocytes present which do not contain any parasites flow back and forth with the current as the pressure is increased or decreased. On the other hand, the erythrocytes containing the large parasites remain fixed between the cover glass and slide and do not move with the current. At once, one gets the impression that the substance of the parasites is much more resistant to pressure than that of the blood cells. Not only is the consistency much firmer, but the parasite is so large and thick that it holds the cover glass off of the thinner blood cells.

In fact, if one makes and stains preparations of large falciparum schizonts, many of the parasites appear to be much thicker than the erythrocytes which contain them. The impression is very similar to that produced by the nuclei of nucleated erythrocytes, in which case sometimes the nucleus is not in sharp focus when the sharpest focus is on the erythrocyte.

The other species of parasites, on the other hand, do not show this apparent firmer consistency. It is very reasonable, therefore, to assume that the greater pathogenicity of *P. falciparum* results largely from the condition just explained which favors the production of very much larger numbers of parasites, as is known to occur in the pernicious cases. It is not probable that the few merozoites produced in the circulating blood by either species succeed in getting into other cells. They are probably all destroyed in the circulation. It is only those parasites that are produced in the capillaries and succeed in attaching themselves to other cells before they are swept out that survive and reproduce. They probably are the chief source of the clinical symptoms in malaria.

In the few instances in which autopsies have been made in cases where *P. vivax* or *P. malariae* were either the cause of death or at least were found present, the number of parasites found in the tissues is extremely small compared with the number of parasites found in autopsies where death was caused by *P. falciparum*. In such instances, frequently the tissues are so packed with malaria parasites as to add some color, produced by the pigment present in the parasites, as well as that retained in the tissues after the parasites have been destroyed.

One of the most striking pictures of the manner in which disease is produced by specific parasites is that seen in sections or smears from the brain and other organs of patients dying of estivoautumnal malaria. In the capillaries of the brain most of them may be so obstructed with parasites that no blood could possibly pass through them. Anemia of the brain results from so many capillaries being obstructed, producing coma as anemia of the brain produced in any other way does. It may be of interest to note in this connection that coma is one of the most prominent symptoms in a very large per cent of all cases of malaria resulting in death. Pernicious symptoms referable to other organs are quite likely produced in a similar manner.

If the lodgment of parasites in the capillaries is largely responsible for the pernicious symptoms, the question may arise as to why the gametes do not also lodge in the capillaries in the same way. Perhaps there is a tendency for them to lodge and in fact it is quite possible that only certain individuals possess such blood vessels as are necessary to be most favorable for the exit of gametes. The gametes are ameboid parasites and in the instance of *P. falciparum* their shape is such as to favor their passage through narrow spaces. In fact, there is some doubt as to whether the crescent has any ameboid ability whatever. Shape and size may be the favorable influences upon which its ability to pass through the capillaries depends.

In conclusion, the theoretical explanation offered for the greater pathogenicity of *Plasmodium falciparum* is that the shape of the parasite and unyielding consistency of the substance of which it is composed results in parasites lodging in capillaries to greater extent and there multiplying in larger numbers, more of which survive, than occurs in the other species. The ameboid activity is greater and the cytoplasm is less resistant to pressure in the other species, which is unfavorable to their lodging in the capillaries, causing more of the segmentation to take place in the circulation where the merozoites produced are promptly destroyed. This theoretical explanation is based largely upon the observation that artificially cultivated falciparum parasites are more resistant to pressure, that they have little or no ameboid motion in contrast with the other species and upon the finding at autopsy of much larger numbers of capillaries obstructed by falciparum parasites.

# NATURAL MALARIA INFECTION IN ANOPHELES MOSQUITOES[1]

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In 1917 a series of examinations was made of *Anopheles* mosquitoes collected under natural conditions to determine the rate of infection in malarial regions. The collections for the study were made at Mound, La., and at Parchman, Miss., under the direction of Capt. D. L. Van Dine of the Bureau of Entomology, and the specimens were shipped to New Orleans for dissection.

At Mound the mosquitoes were taken from negro tenant houses on a plantation typical of the Mississippi river delta country and specimens from this source were received from December, 1916, to June, 1917, with an additional number the following October.

The Parchman collections were made in buildings occupied by the negro convicts on the state penitentiary farm during the months from May to November, 1917. This farm is located in Sunflower county, Mississippi, and consists of about 15,500 acres of delta land, most of which is cleared and in cultivation. Nearly 1400 convicts are kept on the farm and are divided among fourteen buildings scattered about over the property. The buildings are large wooden or brick structures with two or three barred rooms or "cages" in which the convict laborers sleep. The doors and windows are screened but not effectively, as shown by the numbers of mosquitoes collected on the inside of the rooms.

Owing to the war the studies were interrupted at the end of the first season and, although a large number of mosquitoes had been dissected, the results are not considered entirely complete as showing the rate of infection under normal conditions. This

[1] In coöperation with Dr. C. C. Bass of Tulane University and with the International Health Board of the Rockefeller Foundation.

is due to the facts that at Mound the collections were made mostly during the winter and spring months, a time at which it was to be expected that infections would be few or absent, and at Parchman it was found, from data collected during the summer, that the human infection rate was much lower than in the surrounding territory. It is evident that the mosquito rate would be affected by these conditions.

During the twelve months of the study the total dissections and examinations numbered 5878 mosquitoes divided among three species of *Anopheles* as follows:

| | |
|---|---|
| *A. quadrimaculatus* | 5673 |
| *A. crucians* | 169 |
| *A. punctipennis* | 36 |

As *quadrimaculatus* is by far the predominating species and as none of the 200 specimens of *punctipennis* and *crucians* was infected the remainder of the discussion of the data will be limited to the one species.

Of the 5673 *A. quadrimaculatus* examined from all sources, 31 or 0.54 per cent were infected. All of these showed stomach infections but only two contained sporozoites in the salivary glands. That is, only two of the entire series were in the infective stage at the time of capture.

The exact ratios of infection for the full series are as follows:

| | NUMBER EXAMINED | INFECTED | PER CENT |
|---|---|---|---|
| Stomachs | 5411 | 31 | 0.57 |
| Glands | 5561 | 2 | 0.03 |

The gland examination was not recorded unless three or more lobes were secured or the stomach unless it was free of blood and in good condition.

The first infected specimen was collected at Mound on May 7 and the first specimen with gland infection (also from Mound) was collected on May 15. The last infected specimen was taken at Parchman on October 4. However, the abundance of mosquitoes was decreasing rapidly at this time and only a comparatively few were examined after this date.

From the vicinity of Mound, 1986 mosquitoes were examined and of these, 12 or 0.60 per cent were infected. By dividing the year into two parts, however, November to April as winter and May to October as summer the following ratios are seen:

| | NUMBER EXAMINED | INFECTED | PER CENT |
|---|---|---|---|
| Winter | 1375 | 0 | 0 |
| Summer | 611 | 12 | 1.96 |

A few collections were made during July, August, September and October in two negro cabins just outside the boundaries of the Parchman farm and of 102 examinations, five or 4.9 per cent were infected. Combining these with the summer infections at Mound gives an index for unscreened negro cabins of 2.38 per cent, which is probably more nearly the normal rate of infection than that found on the penitentiary farm. The sporozoite rate for the same 713 specimens was 0.14 per cent. This is perhaps lower than would be found in a larger number of examinations, or with more collections in the fall of the year.

The collections on the penitentiary farm were made from May to November in 13 of the buildings occupied by the convicts and of 3488 specimens examined (exclusive of a few in November) only 14 or 0.40 per cent were infected, one of these being a gland infection. One building gave a rate of 1.43 per cent and the others varied from 0 to 0.83 per cent.

Of the 611 specimens from Mound in the summer months, 11 infections, 3.46 per cent, were found in 318 mosquitoes collected inside the houses, one infection was from mixed lots recorded as having been collected both inside and under houses but no infections in 124 specimens taken under the houses or in 77 from other buildings.

Of the total dissections from Parchman, 11 of the infected mosquitoes were among 1644 mosquitoes collected inside the buildings, 3 infections were from 1536 mosquitoes in mixed lots, about half of which were collected inside and half outside the buildings, but no infections from 312 mosquitoes taken underneath the buildings or from stables and other places.

As an indication of previous blood meals records were kept of ova development in the dissected specimens. Of 5224 specimens so recorded, 87 per cent were found to contain developing ova and the percentage for both Mound and Parchman was nearly the same, varying less than 4 per cent.

Over half of the infected mosquitoes had not more than 6 oocysts each but a number were found with over 50 per stomach and at least 4 contained over 100 oocysts. The general average for the entire series was approximately 30.

Blood examinations of the convicts on the Parchman farm were made at three-week intervals during the season, under the direction of Dr. Bass. The parasite rate for all examinations from May 6 to October 21, exclusive of those who received special quinine treatment, was 11.4 per cent. Malaria surveys at Mound in August gave a parasite rate of 17.5 per cent in 1916 and 15.5 per cent in 1917. The August rate at Parchman was 9.6 per cent. The Parchman surveys were made with the thick smear method and those at Mound with the thin smear.

The gamete rates, as indicated by estivo-autumnal gametes only, showed more of a difference for the two places than the parasite rates. The May to October gamete rate for Parchman (estivo-autumnal) was 0.77 per cent with only 0.11 in August. In the August surveys at Mound the gamete rate was 3.96 per cent in 1916 and 3.09 in 1917.

The proportion of mosquitoes infected in different localities is of course subject to a great deal of variation and depends upon the susceptibility of the species of *Anopheles* present, the number of human gamete carriers on which to feed and many other factors. As examples of rather extreme conditions of natural infection some of the studies reported from India and Africa are of interest.

Bentley (1) reports mosquito examinations from a section of Bombay in which the "endemic index" or parasite rate among the children was over 40 per cent and in which he found 10 per cent of 827 mosquitoes with infected stomachs and 3.5 per cent of 826 specimens with sporozoites in the glands. The latter is spoken of as the "sporozoite rate" and the record is of interest also as giving a comparison of this rate with the percentage of stomach infections.

Liston in 1908 (cited by Bentley (1) ) found an infection rate of 25 per cent in one species of *Anopheles* in Bombay and an endemic index among the natives of 50 per cent.

Stephens and Christophers (2) report a sporozoite rate in Mian Mir, India, of 4.3 per cent in 252 specimens of one of the susceptible species of *Anopheles*. The endemic index in this place was 52 per cent. At Ennur with an endemic index of 54 per cent the sporozoite rate in 96 mosquitoes examined was 8.6 per cent. In another report these authors (3) also refer to examinations made in Africa in which a sporozoite rate as high as 50 per cent was found.

These rates are much higher than those obtained in my work in this country but it is hardly possible to make satisfactory comparisons as there is so much variation in the different regions in the habits of the species of *Anopheles* concerned and in the living conditions of the residents. Further dissections are also required in our malarial districts before definite statements as to the normal rate of mosquito infection may be attempted.

I wish to make acknowledgment of assistance received during the course of the work as follows: to the late Dr. A. H. McCray for many of the dissections, to Mr. C. P. Trotter for the collection of material at Parchman, to Messrs. D. L. Van Dine and J. K. Thibault, Jr., for the malaria records from Mound and to Dr. C. C. Bass for the Parchman malaria records.

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# ON THE PREVALENCE OF CARRIERS OF ENDAMOEBA DYSENTERIAE AMONG SOLDIERS RETURNED FROM OVERSEAS SERVICE[1]

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Dysentery has long been known as one of the major horrors attendant upon war. Its effects are recorded not only in the roll of honor and the pension lists, but in reduced levels of health and resistance to disease of survivors and in widely spread foci of infection which follow in the wake of dispersing armies. This is especially true of the dysenteries and diarrheas of protozoan origin due to intestinal infections by *Endamoeba dysenteriae*, by the flagellates *Giardia*, *Chilomastix* and *Trichomonas*, and, to a less extent, by the ciliate *Balantidium*.

In contrast with the bacillary infections producing dysentery, the protozoan infections appear, in the light of our present knowledge, to be more persistent and to pass more readily into the carrier phase in which the host may apparently have normal health, though liable to relapses. In this carrier phase the infected person is discharging intermittently great numbers of encysted stages of the parasite and becomes a permanent menace to the health of his family and associates as a source of new initial infections in the family and community. Medical literature of the last century bears witness to the ravages of dysentery in our Civil War and thereafter and of the efflorescence of dysentery and liver abscess in the United States after the Spanish-American and Philippine Wars, and in Germany after the return of the troops from the Boxer expedition.

The recent World War with its Egyptian, Mesopotamian, Balkan, and Turkish campaigns, and its Western Front with

[1] Read at the New Orleans meeting, American Society of Tropical Medicine, April 26, 1920.

troops of intermingled nationalities, has afforded unprecedented facilities for the appearance of epidemics of dysentery and for the establishment of carriers of the infective agent. The extensive laboratory surveys and determinations of protozoan and bacillary infections, which have been published as a result of the war indicate that many of the cases in the epidemics were of bacillary origin, while the fecal examinations of dysenteric convalescents, as well as those of non-dysenterics has brought to light high percentages of carriers of the dysenteric ameba.

On the other hand, the number of carriers of the bacilli of dysentery appear to be relatively few among such patients. It seems probable from the statistical results that much dysentery of amebic origin passed undetected or was masked or preceded by that of bacillary origin.

For purpose of illustration it will suffice to note the summary of the results of the fecal examinations, mainly of convalescent dysenteric patients from the Western Front, made at the Liverpool School of Tropical Medicine by Matthews and Smith (1919). They report 23,024 examinations of 4068 cases with the following results:

*Percentages of infection by protozoa in 4068 dysenteric patients among British soldiers at Liverpool*

| PROTOZOAN | NUMBER OF CASES INFECTED | PERCENTAGE INFECTED OF TOTAL EXAMINED | PROBABLE PERCENTAGE OF INFECTION BASED ON EXPECTATION AFTER SIX EXAMINATIONS |
|---|---|---|---|
| *E. histolytica* | 494 | 12.1 | 23 |
| *E. coli* | 1,208 | 29.7 | 50 |
| *E. nana** | 279 | 16.6 | |
| *G. intestinalis* | 669 | 16.4 | 26.3 |
| *C. mesnili* | 148 | 3.6 | 12 to 15 |
| *T. intestinalis* | 29 | 0.7 | |

* Based on last 1674 cases examined.

Ravaut (1916) and other French observers noted the increased incidence of amoebic infections among the French soldiers and citizens as the war progressed and traced some of the initial outbreaks to contacts with colonial troops of African origin or previous service.

The degree of infection among our own soldiers both overseas and home service is indicated by the results of examinations of returning soldiers in Debarkation Hospital No. 3, at New York City, and of home service men of the Port of Embarkation who had not been overseas, reported by Kofoid, Kornhauser and Plate (1919). This investigation included 2144 overseas and 559 home service men and revealed 276 and 22 infections respectively of *Endamoeba dysenteriae* or 19.9 and 3.9 per cent in the two groups. A later report on this work by Kofoid (1920) shows infections in 2300 overseas men and 576 home service, as indicated in the accompanying table.

This tabulation indicates 297 cases or 12.8 per cent infection with *Endamoeba dysenteriae* among the overseas men to 25 or 4.3 per cent among the home service men, a three-fold increase. The home service group contained many men of foreign origin and a number of Florida negroes, a less typical assemblage of American citizens than the overseas troops. Furthermore, these results all rest, in the main, on single examinations. Had six consecutive examinations been made in each case it is highly probable that the percentages of infection detected would have been doubled, and perhaps trebled. The overseas men represented over six hundred different military units and included men who had not been out of Brest and Bordeaux, as well as seasoned veterans. Infections were by no means confined to men from the front. Many, but not all of the infected men who were interviewed reported a history of diarrhea or of a typical dystenteric attack, often recurrent. Very few of the men had dysenteric symptoms at the time of examination. They were in the carrier stage.

It is evident from investigations in European laboratories and from the data given above, that the War is returning into civil life great numbers of men who are carriers of the *Endamoeba* of human amebiasis. If 12.8 per cent of our approximately 3,000,000 overseas men became infected, there would be 384,000 such carriers or 768,000 if twice this percentage are infected.

An additional check on the degree of infection among soldiers of the home service group and in an overseas group with maxi-

*Tabular summary of infections by intestinal parasites in 2300 overseas troops and 576 home service troops of the U. S. Army at Debarkation Hospital No. 3, New York City, N. Y.*

Cases of infection

| | | | | CESTODA | | | NEMATODA | | | RHIZOPODA | | | | | | FLAGELLATA | | | | | MISCELLANEOUS | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | TOTAL | NEGATIVE | POSITIVE | Dibothriocephalus latus | Hymenolepis nana | Taenia saginata | Hookworm | Trichuris trichiura | Ascaris lumbricoides | Endamoeba coli | Endamoeba nana | Endamoeba dysenteriae | Endamoeba gingivalis | Dientamoeba fragilis | Amoeba limax | Trichomonas intestinalis | Tricercomonas intestinalis | Embadomonas intestinalis | Chilomastix mesnili | Giardia intestinalis | Sporozoa | Blastocystis hominis | Phycomycete spore |
| Overseas. . . . . . . | 2300 | 763 | 1537 | 0 | 10 | 0 | 160 | 136 | 26 | 473 | 675 | 297 | 1 | 1 | 3 | 3 | 3 | 4 | 97 | 131 | 7 | 781 | 194 |
| Home service. . . | 576 | 243 | 333 | 1 | 3 | 2 | 22 | 14 | 1 | 92 | 161 | 25 | 1 | 1 | 1 | 3 | 1 | 4 | 20 | 37 | 4 | 181 | 57 |
| **Percentages of infection** | | | | | | | | | | | | | | | | | | | | | | | |
| Overseas. . . . . . . | 2300 | 33.1 | 66.9 | 0.0 | 0.4 | 0.0 | 6.9 | 5.9 | 1.1 | 20.5 | 29.3 | 12.8 | 0.1 | 0.1 | 0.1 | 0.1 | 0.2 | 0.2 | 4.2 | 5.7 | 0.3 | 34.1 | 8.4 |
| Home service. . . | 576 | 42.2 | 57.8 | 0.2 | 0.5 | 0.3 | 3.8 | 2.4 | 0.2 | 15.9 | 27.8 | 4.3 | 0.2 | 0.2 | 0.2 | 0.5 | 0.2 | 0.7 | 3.5 | 6.4 | 0.7 | 31.4 | 9.8 |

*Tabular summary of infections in 91 overseas troops, 34 home service troops, and 29 troops of unknown status examined at University of California, Berkeley, Calif.*

| | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overseas . . . . . . . | 91 | 6 | 85 | 0 | 0 | 0 | 1 | 4 | 0 | 44 | 64 | 61 | 0 | 0 | 0 | 1 | 0 | 0 | 4 | 6 | 0 | 65 | 16 |
| Home service. . . | 34 | 5 | 29 | 0 | 0 | 0 | 1 | 1 | 0 | 10 | 22 | 9 | 0 | 0 | 0 | 2 | 0 | 0 | 2 | 1 | 0 | 19 | 6 |
| Unknown status | 29 | 6 | 23 | 0 | 0 | 1 | 1 | 0 | 0 | 8 | 14 | 12 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 14 | 1 |
| **Percentages of infection** | | | | | | | | | | | | | | | | | | | | | | | |
| Overseas . . . . . . . | | 6.6 | 93.4 | 0.0 | 0.0 | 0.0 | 1.1 | 4.4 | 0.0 | 48.4 | 70.3 | 67.0 | 0.0 | 0.0 | 0.0 | 1.1 | 0.0 | 0.0 | 4.4 | 6.6 | 0.0 | 71.4 | 17.5 |
| Home service. . . | | 14.7 | 85.3 | 0.0 | 0.0 | 0.0 | 2.9 | 2.9 | 0.0 | 29.1 | 64.8 | 26.5 | 0.0 | 0.0 | 0.0 | 5.8 | 0.0 | 0.0 | 5.8 | 2.9 | 0.0 | 55.9 | 17.6 |
| Unknown status | | 20.7 | 79.3 | 0.0 | 0.0 | 3.4 | 3.4 | 0.0 | 0.0 | 27.6 | 48.3 | 41.4 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 3.4 | 0.0 | 0.0 | 48.3 | 3.4 |

mum exposure to infection has been afforded by a series of examinations made in conjunction with the Infirmary of the University of California and the California State Board of Health during the past year on returned soldiers who are now students of the University.

The results of these examinations are appended to the preceding table. There have been to date 154 soldiers examined for intestinal protozoa by us at Berkeley. Of these 91 are overseas men, 34 home service, and 29 as yet undetermined. The number of carriers of *Endamoeba dysenteriae* in the three groups are 61, 9, and 12, or 67, 26.5 and 41.4 per cent respectively. The infection in the overseas men is more than twice as heavy as in home service men. It is noteworthy that the infections by some of the other intestinal protists and by whipworm are also increastd in overseas men as compared with those in the home service ones. For example *Endamoeba coli* is increased from 29.1 per cent to 48.4 per cent, *Giardia intestinalis* from 2.9 to 6.6 per cent, *Blastocystis hominis* from 55.9 to 71.4 per cent and *Trichuris trichiura* from 2.9 to 4.4 per cent.

The degrees of infection detected in these examinations are as a whole, distinctly higher than those found by us at New York. The difference results from the following causes. (1) A larger number of examinations in most cases, (2) increased accuracy in examination as the result of experience, and (3) the probability that this group of overseas men had a maximum degree of exposure in the period of greatest spread of the contagion on the Western Front and (4) possibly the longer time for the development of infections before examination.

Whereas the men examined at New York received, in the main, only a single examination, we have been able to make a total of 589 examinations of the 154 men at Berkeley, an average of 3.8 examinations per man. Only 33 of them had but a single examination while 66 had 6. This increase in the number of examinations per man from about 1 at New York to 38 at Berkeley, might be expected to at least double the percentage of infection by *Endamoeba dysenteriae* detected in the examinations. We find, however, that the percentage rises from 12.8 to 67 per cent instead of 26.6 per cent so that other factors than the number of examinations must be operative to account for the increase in percentage. It seems probable that increased accuracy resulting from experience contributes only a small part of this.

These records of infection by *Endamoeba dysenteriae* rest upon careful identification of the organism in the encysted stage in preparations stained in iron haematoxylin, as well as in the temporary iodine-eosin stain of Donaldson. The possibility of confusion with other organisms is largely eliminated by the concurrent determinations made of all other known protists in the stools.

The overseas men of this group belonged mainly to the 91st Division which saw hard service in the Argonne drive and later on the Belgian front in the closing days of the campaign. Many of them testify to the widespread prevalence of intestinal troubles and dysentery during both field campaigns. No critical evidence is available to determine the relative amount of bacillary and amoebic infections during the campaigns or at present.

This percentage detected in our overseas men (67 per cent) is over 50 per cent higher than the expected percentage in the men examined at Liverpool or New York. The Liverpool statistics were gathered several years prior to ours from men retired from the front at that time. Our men had the exposure to the cumulative effects of spreading contagion in the last year of the war.

Not a few of the home service men examined at Berkeley were in the Southern training camps in a territory where infection by *Endamoeba dysenteriae* is to some extent endemic, though the probability of much increase in these infections as a consequence of exposure within army camps is relatively slight owing to examinations of foodhandlers, and effective measures of fly control, which prevailed in the army camps, but less effectively in their environs.

The men examined in New York were convalescent patients in transit from Europe to various camps in the United States for discharge, and were recently from the zones of exposure to infection. The men examined in Berkeley have had an additional six months to almost a year for the parasites to multiply or die out. Evidence for so-called spontaneous cure of such infections rests in the main on an inadequate number of stool examinations.

The sequelae of such infections are varied. The dysenteric syndrome is only one of several manifestations. The clinical histories of cases of amebiasis may exhibit abscess of liver, lungs, or brain, inflammation of the appendix, enlarged spleen resistant to quinine, long bone and joint rheumatism, and obscure and rebellious types of skin infections. The carriers we have detected exhibit none of these consequences, though some of them are clinically in subnormal health at present. Some are apparently normally robust, but all are potential sources of infection since their faeces intermittently contain cysts, the cause of contagion.

The data here presented are indicative of several conclusions in regard to so-called tropical amebic dysentery.

1. The number of carriers of amebiasis in the United States has been greatly increased by the infections in soldiers returning from overseas.

2. A larger number of carriers than has hitherto been suspected exists in the normal population in this country.

3. The dysenteric syndrome is not an essential feature of the disease and the infection is by no means limited to the tropics.

4. The carrier phases are persistent and afford possible foci of contagion.

5. The percentage of carriers relapsing or developing serious sequelae is as yet unknown.

It is obvious that the prevalence of carriers of amebiasis in this country demands increased vigilance on the part of the federal, state, and municipal health authorities. The fact that the organism can not multiply outside of the body and that the progress of the contagion under normal conditions of sanitation is slow, makes an epidemic of amebiasis quite improbable. Its spread by food handlers, by household contacts, and, in favoring circumstances of poor sanitation, by flies and water, will make its progress all the more insidious because it is not catastrophic and because an unknown but probably large number of infected persons exhibit no symptoms of disease, or no symptoms associated with dysentery.

Increased attention is called for on the part of the practitioner in all obscure intestinal cases to the possibility that *Endamoeba dysenteriae* is the etiological factor or accessory to the disease.

It is also eminently desirable that the United States Public Health service, the Red Cross, and other social service agencies coöperate to detect and free, as far as feasible, our returned soldiers from the incubus of this infection in a thorough and effective manner. We owe it to them and their families and to the community, and it is not impossible of accomplishment.

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# STUDY OF A CASE OF YAWS, CONTRACTED BY AN AMERICAN SOLDIER IN FRANCE

JAY FRANK SCHAMBERG AND JOSEPH VICTOR KLAUDER

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The following is a brief history of a patient who was admitted to the Dermatological Service of Dr. Jay Frank Schamberg at the Philadelphia General Hospital. The history, skin lesions, and laboratory findings pointed to yaws. A diagnosis of this disease was made.

T. M., White. Age twenty.

Born and lived in this country until 1917, at which time he joined the Royal Canadian Army and was sent to France, remaining there until August, 1919. During almost all of this time he was stationed at Etappes as a member of the Royal Canadian Dragoons (a cavalry outfit). The members of this organization were composed only of Americans and Canadians. Etappes was a large base for cavalry and infantry troops. There were thousands of soldiers at this base—Canadians, Australians, New Zealanders, South Africans (white men) New Foundlanders, Chinese (labor battalion). There were no soldiers from Algeria or India, indeed no men other than white men, except negroes from Canada and Australia. The longest time he was away from this base was for about three months, which was spent in Cambrai and its environment. The only time he saw dark skinned soldiers was when he would meet them in the streets or in such places as saloons and Y. M. C. A. huts. At no time was he in very close contact with them, such as sleeping in the same barracks, etc.

In May, 1919 he was taken sick and sent to a hospital in England. The first symptoms he noticed were rheumatic-like pains in knees and shoulders which were at times severe enough to incapacitate him. He had no other complaint. While in the hospital he had a fever for a short time, pain in joints gradually disappearing. Was discharged in September. Arrived in Canada in October and came to his home in Philadelphia. About this time he first noticed lesions on palms followed in a week later by similar lesions on scalp and soles of feet. Denies ever having had syphilis, last exposure was eight months ago.

On admission to the Philadelphia General Hospital December 30, 1919, he presented lesions on the palms, soles, scalp, nose, forearm and penis. The lesions in general are distinctly fungated and granulomatous in appearance. Sharply circumscribed, varying in size from a large pea to a nut. The surface is covered with a brownish-yellow crust, which on being detached discloses a raw surface consisting of red or yellowish fungoid granulations secreting a thin slightly purulent secretion. The lesions exhale an offensive odor. On the scalp there are present five distinct areas of circumscribed infiltrated raised patches, exhibiting a distinct elevated border and central depression with a firm brownish-yellow crust. In the throat there is a large, whitish, streaky patch, less inflammatory than mucous patches. Scattered upon the palmer aspects of the fingers are pinhead and larger-sized conical, papular reddish elevations, with central horny plugs. As central plugs fall out they leave a depressed central pit. These lesions bear some resemblance to follicles. Castellani refers to similar lesions as a peculiar pitted framboeside of the palms. On the prepuce are numerous wartlike excrescences which bear some resemblance to condyloma acuminata.

A dark field examination of the serum obtained from the surface of some of the lesions disclosed many treponemata having the morphological characteristics of treponema pallidum. A Wassermann performed with cholesterolized, alcoholic syphilitic liver and acetone insoluble lipoid antigens was 4+.

Neoarsphenamine 0.9 gram was administered which caused a disappearance of many of the lesions and a marked improvement in others. Sixteen days later a second dose was given which caused a complete disappearance of the remaining lesions. Up to the present time (an elapse of nine weeks) the patient has remained entirely well. No further treatment has been given.

Since the administration of neoarsphenamine weekly Wassermann reactions, up to the present writing, have been positive. The last degree of positive reaction obtained has been 3+ with a cholesterolized antigen; 2+ with an alcoholic syphilitic liver antigen and a 2+ with an acetone insoluble lipoid antigen.

One of the skin lesions was excised and was used to inoculate four rabbits intratesticularly. In two, positive results were obtained after an incubation period of thirty-four days. A second strain has been grown in rabbits, six out of eight being successful. Average period of incubation, twenty-four days. Ten cubic centimeters of the patient's citrated blood was injected intravenously into rabbits with negative results. Attempts to inoculate the anterior chamber of the eye in rabbits were negative. Attempts to inoculate a monkey's eyebrow have been so far unsuccessful.

Complement fixation tests were performed with an antigen made from a yaws nodule from an infected rabbits's testicle. Salt solution was used in making the antigen rather than alcohol. The reaction with the serum of the yaws patient yielded slight but definite degree of complement fixation. A duplicate test performed with the pooled sera of three syphilitics whose Wassermann reaction was 4+, yielded negative reactions. Further immunological study of the yaws lesion showed the following:

Hyperkeratosis of the acanthosia of the epidermal tissues; extensive lymphoid and polymorphonuclear infiltration of corium. Absence of blood vessel changes. Treponemata in the leucocytic areas of the apices of the papillae, subjacent to the rete.

From a personal communication Castellani writes:

From the description you give and the photos, I would diagnose the case as one of yaws. I am not aware of the disease having been previously recorded in France, but of course during the war a large number of native troops and native workmen were imported into France from tropical countries, and they may have imported the disease with them. As regards mode of infection I am inclined to give more importance to direct contact than to insect carriers. Of course, in the tropics there is no doubt that in many cases the disease is carried by flies.

The diagnosis of yaws is supported by the following: The history and clinical features of the skin lesions, and the histological appearances. The finding of treponema in the lesions definitely places the disease as either yaws or syphilis. The difficulty in staining the treponema is suggestive of its being pertenuis rather than pallida.

The resistance experiments of Neisser, Baermann and Hulberstader have not as yet been carried out because of our unsuccessful attempt so far to infect a monkey. Cross infections with syphilis and yaws in the rabbit, after treatment with arsphenamine have not as yet been conducted.

# REPORT OF A CASE OF BACILLARY DYSENTERY WITH DIPHTHERITIC MEMBRANE IN THE VAGINA AND EDEMA OF THE ABDOMINAL WALL[1]

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The points of interest in this case are indicated in the title of the paper. These points have seemed of sufficient importance to warrant this report because none of the standard texts mention them and apparently they have not previously been described in the literature.

Mrs. A. O. was seen November 15, 1919, at Touro Infirmary in consultation with Dr. W. P. Bradburn through whose courtesy I am permitted to make this report. The patient was a white married woman of forty-eight years. On November 3 she had eaten a cream puff which did not seem fresh. The next day she had severe pains in the epigastrium and loose bowels with straining. On November 5 nausea began. All symptoms increased until November 10 at which time she was first seen by Dr. Bradburn. At that time Dr. Bradburn described her as being in a state of collapse; the surface covered with a cold perspiration, the pulse weak and rapid. There was slight rigidity of the upper abdomen and apparently a mass about the size of an orange in the epigastrium. This apparent "mass" disappeared within a few days. After her admission to Touro Infirmary November 10, she was given glucose and sodium bicarbonate each 5 per cent solution by proctolysis, calomel grain $\frac{1}{4}$ every two hours and later paregoric ʒ1 every three hours. No food was given, only water being allowed. When first seen by me, November 15, she had improved but her face was still somewhat pinched, the temporal fossae were sunken and the general appearance was that of great prostration. The bowel movements had continued to be numerous, bloody and mucous, and extremely offensive. Patient had vomited once though she suffered greatly from nausea. There was marked edema of the

[1] Published in the J. A. M. A., December 18, 1920.

abdominal wall, slightly greater in the upper right quadrant. The patient flinched slightly when pressure was made in the liver region but the abdomen in general was not tender. The liver edge was felt three fingers breadth below the costal margin on deep inspiration. The heart and lungs were negative. At the introitus of the vagina a roughened, corrugated elevation was felt. The vaginal walls, vault and cervix felt edematous. On inspection with the speculum the rough, corrugated elevated area proved to be due to a thick, tenacious, dirty-grey membrane which was pulled off with difficulty and left a superficial bleeding ulceration. On the cervix there was also an erosion and membrane. Rectal examination (digital) revealed nothing abnormal. The patient's blood gave a strong agglutination with the Shiga bacillus. Dr. John A. Lanford, pathologist of Touro Infirmary was also able to recover Shiga bacilli from cultures made from the vaginal pseudo membrane and from the cervix. Other laboratory examinations were without special interest. The blood showed a moderate leucocytosis (17,000) with 85 per cent neutrophiles. The urine had a trace of albumen and a heavy indican. The feces revealed no parasites and no ova. There were pus, blood and epithelial cells present. The stools were copious, liquid and offensive.

In addition to supportive measures, the principal features of the treatment were:

1. Liquid diet without milk.
2. Sodium sulphate solution daily into the duodenum by means of the Jutte tube.
3. Irrigations of the vagina three times daily with 1:1000 permanganate solution.

Improvement began almost at once. Practically all symptoms had disappeared in three weeks and by the end of the month (December 15), the patient had entered fully into convalescence. In February, 1920, Dr. Bradburn reported her in perfect health in every way.

It will be noted that the croupous pseudo membrane in the vagina in this case corresponds exactly with those universally described as occurring in the bowel of dysentery patients; in other words the bacilli seem to act upon the vaginal mucous membrane as they do upon the intestinal. The question arises as to the manner in which they were introduced into the vagina. The most plausible explanation would seem to be that the contamination was directly from the rectal discharges by proximity, especially as the inflammatory process was most extensive and intense at the introitus and seemed to be ascending. Or the infection may have been by contiguity within the pelvis. In this connection it seems pertinent to cite the opinion of Flexner and Sweet (quoted by Castellani and Chalmers) as to the mode of production of the pseudo membranes in the bowel. They claim that the bacilli may abound in the small intestine where no pathological lesion may be found but they give rise to toxins one of which acts on the lower bowel, the other on the nervous system. The excretion of the first toxin causes an exudation of lymph into the submucosa and later into the mucosa. This lymph coagulates and is invaded by a cellular exudate and in due course the glands and the tissue of the mucosa and muscularis mucosae are destroyed by coagulation necrosis with thrombosis of vessels. If the ulcers of the lower bowel and the false membrane there are produced by the excretion of this toxin, it might be asked whether this vaginal condition could be produced in the same way. Another theory may be suggested, namely, that the infection was carried to the vagina by the blood stream. Cases of bacillary dysentery septicemia have been reported (Markman, Rosenthal—quoted by Castellani; de Sautelle, J. A. M. A., 1914, **63**, p. 1853). However there was nothing else in our patient's condition to warrant such a supposition. Unfortunately no blood culture was made.

I have no explanation to offer as to the production of the edema of the abdominal wall. Its appearance was analogous to the edema frequently noted on the thoracic wall over empyemata and over abscesses of the liver.

# THE CLASSIFICATION AND DIFFERENTIAL DIAGNOSIS OF THE AESTIVO-AUTUMNAL MALARIA PLASMODIA

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The experiences of the various armies with malarial infections during the world war has reawakened interest in the parasites concerned in their etiology, especially with regard to the question of the plurality of species. Several recent observers have recorded what they believed to be transmutations of the species that have been generally accepted by protozoologists and have subscribed to the belief of Laveran, that there is but one species of plasmodium concerned in the etiology of the various clinical types of malaria observed in man.

In this contribution it is not my purpose to discuss the merits of this contention, beyond stating that sufficient evidence has not yet been presented proving that transmutation of species occurs in the malaria plasmodia and none of the evidence so far presented is of such a character as to invalidate, in the least, the facts that prove, in the opinion of most qualified observers, the existence of distinct species of malaria plasmodia. The experimental evidence proving that the direct inoculation, into susceptible individuals, of blood containing any of the well-recognized species of malaria plasmodia is invariably followed by the appearance of the inoculated species in the blood of the inoculated and the occurrence of the characteristic febrile paroxysm of the species inoculated, is amply sufficient to establish the existence of these species, and when there is added to this evidence the results of more than 100 mosquito experiments,

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which are recorded in the literature, in which the species of plasmodia obtained by the mosquito from the infected individual invariably appeared in the blood of individuals bitten by the insects, accompanied by the characteristic clinical symptoms usually produced by that species, one must admit that the proof of the plurality of species is practically incontrovertible.

## CLASSIFICATION

At the present time there are three species of malaria plasmodia causing infection in man recognized by the vast majority of authorities, i.e., *Plasmodium malariae* Marchiafava et Celli (1), the cause of quartan malarial fever; *Plasmodium vivax* Grassi et Feletti (2), the cause of tertian malarial fever; and *Plasmodium falciparum* Welch (3), the cause of aestivo-autumnal or subtertian malarial fever.

While practically all authorities accept these three species of malaria plasmodia as distinct, numerous investigators believe that more than one species of plasmodium is concerned in the etiology of the aestivo-autumnal fevers or that sub-species of *Plasmodium falciparum* exist which are morphologically and clinically distinct. Thus Grassi and Feletti (4) recognize two species of aestivo-autumnal or pernicious plasmodia; Mannaberg (5) and Manson (6), three species, a pigmented quotidian, an unpigmented quotidian and the malignant tertian; and Marchiafava and Bignami (7) two species, a quotidian and tertian.

In 1901, as a result of the study of hundreds of malarial infections contracted in Cuba and the Philippine Islands, I accepted Marchiafava and Bignami's classification and described (8) two species of plasmodia associated with the aestivo-autumnal infections that I studied, one sporulating in the infected individual in twenty-four hours and causing a quotidian fever, the other sporulating every forty-eight hours and causing a peculiar type of tertian fever. Further study of these two species convinced me that the evidence was not sufficient to entitle the quotidian plasmodium to *specific* rank, and in 1909 I proposed a classification (9) in which the quotidian parasite is considered as a subspecies of *Plasmodium falciparum* and gave to it the name: *Plasmodium falciparum quotidianum.* This classification of the malaria plasmodia is as follows:

Order. *Haemosporidia.*

Genus. *Plasmodium.*

Species. I. *Plasmodium malariae,* Marchiafava et Celli, 1885.

II. *Plasmodium vivax* Grassi et Feletti, 1890.

III. *Plasmodium falciparum* Welch, 1897.

Sub-species. I. *Plasmodium falciparum quotidianum* Craig, 1909.

In descriptions of the aestivo-autumnal plasmodia, published at various intervals (9), (10), (11), (12), I have shown that *Plasmodium falciparum* and *Plasmodium falciparum quotidianum* are distinguishable morphologically, differ in the time consumed in their life-cycle in man, and produce characteristic febrile paroxysms. *Plasmodium falciparum* completes its life-cycle in the blood of man and sporulates every forty to forty-eight hours, the paroxysms of fever occurring every other day, while *Plasmodium falciparum quotidianum* completes its life-cycle in the blood of man in twenty-four hours, producing a paroxysm of fever every day, the temperature curve being a quotidian one. I have not been able to confirm the existence of an unpigmented quotidian plasmodium, as described by Mannaberg and by Manson, although I have examined many thousand blood preparations from aestivo-autumnal infections and have searched carefully for such a parasite.

The majority of textbook writers do not accept more than one variety of aestivo-autumnal plasmodium, although they admit that clinically both the tertian and quotidian types of fever occur. They explain the occurrence of these clinical types by asserting that *Plasmodium falciparum* sometimes sporulates in twenty-four hours and sometimes in forty-eight hours, an assumption that is at variance with the biological laws regarding sporulation as illustrated in the other species of malaria plasmodia. *Plasmodium malariae,* the quartan plasmodium, does not sporulate sometimes in thirty hours and sometimes in seventy-two hours, but always in seventy-two hours; nor does *Plasmodium vivax*, the tertian plasmodium, sporulate sometimes in twenty-four hours and sometimes in forty-eight hours, but always in approximately forty-eight hours, and to claim that *Plasmodium falciparum* is so marked an exception to the rule as illustrated by sporulation in the other malaria plasmodia is illogical and simply begs the question. Those who believe in only one species of malaria plasmodium use the same argument, claiming that under certain conditions the plasmodium sporulates in twenty-four hours, in forty-eight hours, or in seventy-two hours, but it is almost impossible to believe that such a variation exists in any one species of plasmodium, and, to my mind, the assertion that *Plasmodium falciparum* sporulates sometimes in twenty-four hours and sometimes in forty-eight hours, producing each time a different number of merozoites and a different type of febrile paroxysm, is no more worthy of belief than that there is but one species of plasmodium with three different life-cycles in man, as shown by the variations in the time of sporulation.

Many careful students of the malaria plasmodia believe that at least two varieties or species of *Plasmodium falciparum* exist and the trend of recent scientific opinion is in favor of the recognition of more than one species of this plasmodium. Bass (13), who first cultivated the malaria plasmodia and has had the advantage of studying the morphology and development of the aestivo-autumnal plasmodia in pure cultures, states "that there are at least two and probably more sub-divisions of the aestivo-autumnal parasite" and that a majority of the students of the subject believe that there are at least two different species. Bass accepts the quotidian and tertian species and in the contribution mentioned describes their morphology and development in cultures. In a personal communication he writes that he feels certain that there are two distinct species, differing in their morphology, as observed in blood preparations, and retaining these differences during their development in cultures.

Since the publication of the contributions referred to earlier in this paper I have continued my observations upon the aestivo-autumnal plasmodia, as opportunity offered, and new data regarding the differentiation of *Plasmodium falciparum* and *Plasmodium falciparum quotidianum* have been secured, the results being confirmatory of the existence of the two species mentioned, and it is believed that their publication will be of interest and value to students of malaria. The photomicrographs illustrating this paper are typical pictures of both species as the plasmodia are observed in stained preparations of the blood of infected individuals, and, I think, prove beyond question the difference in the size and other morphological features of the parasites.

## DIFFERENTIAL DIAGNOSIS

### *Morphological*

In the differential diagnosis of the aestivo-autumnal plasmodia both morphological and clinical differences are of importance, and while a differential diagnosis of *Plasmodium falciparum* and *Plasmodium falciparum quotidianum* should be based upon a careful study of the morphology and cycle of development of the plasmodia, it is true that in uncomplicated cases a differential diagnosis may be made from a study of the temperature charts of the two infections. For this reason, it is necessary to consider in any adequate presentation of the subject, both the morphology of the plasmodia and some of the clinical phenomena produced by infection with them.

*Plasmodium falciparum* and *Plasmodium falciparum quotidianum* differ markedly from one another in their morphology, these differences being quite as marked as the morphological differences between *Plasmodium malariae* and *Plasmodium vivax*, and one who is able to differentiate the latter species should have little difficulty in distinguishing the former in suitable preparations. The differentiation into separate species of *Plasmodium malariae* and *Plasmodium vivax* depends chiefly upon differences in the size of the two plasmodia, the number of merozoites produced at the time of sporulation, and the periodicity of the sporulation, and the same is true of the differentiation of the aestivo-autumnal species, as they differ essentially from one another in all of the characters mentioned.

In differentiating between the aestivo-autumnal plasmodia one should study both living, unstained plasmodia in the blood of infected individuals as well as blood smears stained with some modification of the Romanowsky stain. The numerous excellent modifications of the latter stain have unfortunately resulted in the almost total neglect of the examination of fresh unstained preparations of blood in the study and diagnosis of the malaria plasmodia, but it should not be forgotten that, after a little practice, all species of malaria plasmodia may be as easily recognized in unstained preparations as in stained, and in the study of the morphology and life-cycle of the plasmodia in man the living parasites should always be observed if material is available.

### *Morphology in unstained preparations*

In unstained preparations of blood, the tertian aestivo-autumnal plasmodium, or *Plasmodium falciparum*, in its earliest intracorpuscular stage of development, is noted within or upon the infected erythrocyte as a hyaline "ring" or disc, from 2 to 3 microns in diameter, well defined and sluggishly motile, the periphery of the plasmodium undulating and sending forth minute pseudopodia at irregular intervals. By reason of the amoeboid motion the "ring-forms" frequently become disc-like in shape. The rings are somewhat irregular in shape, one portion of the ring being considerably broader than the remainder, thus giving rise to the so-called "signet-ring" form, an appearance practically never observed in the quotidian aestivo-autumnal "rings." Infection of the erythrocyte with more than one parasite occurs but not as frequently as with the quotidian plasmodium, and it is rather rare to find more than two plasmodia in a corpuscle, while in the quotidian sub-species three, and even four, plasmodia are quite frequently observed within an infected erythrocyte. The ring-forms of this species are frequently as large as the ring-forms of *Plasmodium vivax* but are distinguished from those of the latter species by the thickening at one portion of the periphery giving rise to the "signet-ring" appearance and by the thicker appearance of the ring-form, the ring-form of the benign tertian plasmodium being very thin and delicate in appearance.

The ring-forms gradually increase in size until, at the end of from sixteen to eighteen hours, they may measure as much as 3.5 microns in diameter, and at this time a few fine grains of reddish-brown or almost black pigment may be observed, generally lying in the enlarged area of the ring-form. The pigment is apparently sluggishly motile, the motility, as in all malaria plasmodia, being due to cytoplasmic currents within the body of the parasite. After the development of pigment the ring-form is soon lost, the parasite increases in size, becomes more clearly defined, the cytoplasm appearing very refractive and slightly granular under very high magnifications. As the parasite develops the pigment tends to collect in a more or less solid mass, at or near the center of the organism. After the development of pigment the amoeboid motility of the parasite is retained for several hours but is sluggish in character and gradually disappears.

In the usual infection only the ring-forms and pigmented ring-forms are observed in the peripheral blood, the larger pigmented forms occurring only in severe infections, unless a very careful and prolonged examination of the blood be made, when, even in average infections, a very few pigmented forms can generally be demonstrated.

When fully developed, just prior to sporulation, the pigmented forms of *Plasmodium falciparum* occupy from two-thirds to three-quarters of the infected erythrocyte and sometimes organisms are noted that practically fill the infected cell. Sporulation occurs every forty-eight hours in uncomplicated infections, but may be delayed for as long as fifty hours or occur as early as forty-four to forty-six hours, but it never occurs in twenty-four hours as claimed by those who believe in only one species of aestivo-autumnal plasmodium. At the time of sporulation the parasite generally fills from two-thirds to almost the entire erythrocyte, the pigment being collected in a solid, oval or spherical mass at or near the center. The merozoites or spores appear as hyaline, refractive, oval bodies, collected about the mass of pigment in a more or less regular manner. It is difficult to determine their number in the fresh unstained blood preparations but careful examinations made by myself, have shown that they may vary in number from 10 to 30, the average number varying between 18 and 24. Sporulation occurs within the infected erythrocyte but not infrequently the infected cell is so entirely filled with the sporulating organism that very little of it can be observed. The sporulating forms occur very rarely in the peripheral blood, and only in very severe or pernicious infections, but in blood obtained by splenic puncture these forms may be found in large numbers.

The infected erythrocyte, in infections with *Plasmodium falciparum*, is never enlarged, as it invariably is in infections with the benign tertian plasmodium, but is usually slightly smaller than the normal blood corpuscles and of a slightly darker green color. Crenation of the infected cells is frequently observed, especially in those corpuscles containing nearly fully developed or sporulating parasites, but the wrinkled, shrunken appearance so frequently observed in erythrocytes infected with *Plasmodium falciparum quotidianum* is never observed, in my experience.

Bass (14) states that in cultures *Plasmodium falciparum* develops to almost the diameter of the red blood corpuscle and often produces 24 or more merozoites. He also calls attention to the fact that the ring-form is frequently as large as that of the benign tertian plasmodium and may be considerably thicker and heavier in appearance. In fact, most of the ring-forms of this species possess a larger amount of cytoplasm than do those of *Plasmodium vivax*, so that in examining blood containing only these forms, one is very apt to believe them to be tertian plasmodia rather than aestivo-autumnal, owing to the almost universal, although erroneous teaching, that the ring-forms of *Plasmodium vivax* are larger than those of *Plasmodium falciparum.*

*Plasmodium falciparum quotidianum*, in unstained preparations of blood, examined immediately upon removal of the blood from the infected individual, is first noted in the infected erythrocyte as a very minute hyaline ring, generally a little over 0.5 micron in diameter, though frequently parasites are observed that measure scarcely 0.5 micron in diameter. The very minute size of the ring-forms of this species in their earliest stage of development in man is an important differential point and it is undoubtedly true that the parasite is generally overlooked at this time unless one is an expert in the examination of blood from malarial infections, owing to the minuteness of the rings.

At first the outline of the ring is indistinct but it soon becomes well defined and amoeboid motility develops, the periphery of the ring sending out minute pseudopodia at irregular intervals, the motion being so rapid that only a careful examination will detect it. The typical ring-form is often lost during the periods of amoeboid motility, the parasite appearing triangular or disc-like in shape, but amoeboid activity is not constant and for long periods of time may be absent, the typical ring-form being retained.

In from two to four hours the ring-forms increase in size to about one micron in diameter and become more distinct and refractive. The outline of the ring is more delicate than in the ring-forms of *Plasmodium falciparum*, owing to the smaller amount of cytoplasm, and the "signet-ring" appearance, so common in the ring-forms of the latter species is not observed in the ring-forms of *Plasmodium falciparum quotidianum*, the ring appearing of the same thickness throughout, and consisting of a delicate hyaline ring of cytoplasm enclosing a minute spherical area of the same color as the infected corpuscle. At this time amoeboid activity is not as marked as in the earlier stage of development and is often entirely absent. I have never observed pigment in a ring-form of this species but in infections with *Plasmodium falciparum* the ring-forms are frequently pigmented, as already noted. Double and triple infections of the red blood corpuscle frequently occur and in fatal pernicious cases some of the red blood corpuscles may contain as many as five or six of the ring-forms.

When pigmentation occurs the ring-form is lost, the parasite appearing as a hyaline, oval or spherical disc containing one or two rather coarse granules of dark brown or almost black pigment, situated at the periphery or near the center and perfectly motionless. At this stage of development the organism seldom fills more than one-fifth of the infected erythrocyte, which is shrunken and crenated in appearance and of a dark olive-green color.

After the appearance of pigment the parasite gradually increases in size until at the end of twenty-two to twenty-four hours it fills from one-third to one-half of the infected erythrocyte. The pigment is collected in a very small solid block, spherical or irregular in shape, at or near the center of the organism, which is well defined and refractive. Amoeboid activity has entirely ceased and evidences of sporulation are noted, consisting in delicate striations dividing the parasite into several minute spores or merozoites. Owing to their very minute size, generally less than 0.5 micron in diameter, it is very difficult, and often impossible, to distinguish the number of the merozoites in living, unstained specimens, but in stained preparations they are found to number from 6 to 18, the average being from 12 to 14, as shown by my counts of many hundred sporulating plasmodia of this sub-species.

In *Plasmodium falciparum quotidianum* sporulation occurs at the end of twenty-four hours and I have never observed a case of infection with this plasmodium in which it was delayed for more than an hour or two or occurred earlier than twenty-two hours. In uncomplicated infections sporulation always occurs every twenty-four hours, thus differentiating it from *Plasmodium falciparum,* in which sporulation occurs every forty-eight hours.

At the time of sporulation the plasmodium fills about one-half of the infected erythrocyte, in the vast majority of infections, but sometimes not more than one-third of the infected cell is occupied by the parasite. I have never observed quotidian plasmodia practically filling the erythrocyte as is common in infections with *Plasmodium falciparum.* At this stage the infected erythrocyte is generally considerably distorted in shape, shrunken in appearance, of a dark olive-green color, and often the hemoglobin appears retracted about the plasmodium.

In infections with the quotidian aestivo-autumnal plasmodium the invaded erythrocyte always presents marked morphological changes due to the growth and development of the organism. These changes are more marked than in infections with *Plasmodium falciparum* and consist in reduction in size, a crenated and shrunken appearance of the cell, and a change in color to a very dark olive-green or "brassy" appearance. The so-called "brassy bodies," i.e., infected erythrocytes presenting a shrunken appearance and of a brass-like color, are more frequently observed in infections with the quotidian aestivo-autumnal plasmodium than with the tertian species, but they are not characteristic of quotidian infections.

Bass (15) states that in cultures the quotidian aestivo-autumnal plasmodium produces about 16 merozoites at the time of sporulation and that the sporulating plasmodia occupy about one-half or slightly more of the infected erythrocyte, while the sporulating forms of the tertian aestivo-autumnal plasmodium fill almost the entire cell. He also calls attention to the very small ring-forms, the ring-forms of the tertian species being much larger.

*Stained preparations*

The staining reactions of the quotidian and tertian aestivo-autumnal plasmodia are similar, and when Wright's stain or other modification of the Romanowsky stain is employed, the cytoplasm stains a robin's egg blue while the chromatin of the nucleus stains a ruby-red or violet, depending upon the time that the stain is allowed to act.

The young ring-forms of the tertian aestivo-autumnal plasmodium, or *Plasmodium falciparum* present a ring of blue-stained cytoplasm containing one or more dots of chromatin. The comparative thickness of the ring-form of this species is well shown in stained preparations and many of the rings present a marked enlargement, generally situated at a point directly opposite the dot of chromatin. The chromatin, stained a ruby-red or violet, occurs in the form of one or more spherical dots, situated at the thinnest portion of the ring. While one dot of chromatin is most common, in some infections there occur two dots of this substance, situated close together or at widely separated portions of the periphery of the ring, and rarely more than two dots are observed. Sometimes the two dots of chromatin are in apposition or definitely merged into one another.

In some of the ring-forms of this species pigment may be observed lying in the expanded portion of the ring and appearing as greenish brown, minute granules in stained preparations. Pigmented rings can generally be distinguished in stained preparations if carefully searched for, but such ring-forms are never observed in the quotidian sub-species.

In stained preparations the ring-forms of *Plasmodium falciparium* vary from two to three microns in diameter, but may, in isolated instances, measure as little as one and one-half and as much as three and one-half microns in diameter. They are characterized by their large size, as compared with the quotidian sub-species, the larger amount of cytoplasm, which is expanded at some portion of the periphery of the ring-form, in the vast majority of plasmodia, and by the presence, frequently, of pigment in the expanded portion of the ring.

The larger, pigmented plasmodia of this species present a blue-stained cytoplasm in which may be observed a small amount of chromatin in the form of fine grains collected within an unstained vesicular area representing the nucleus. The pre-sporulating plasmodia consist of a mass of blue-stained cytoplasm in which lie small, irregular clumps of ruby-red chromatin and a small amount of greenish black pigment collected in an irregular mass near the center of the parasite.

The sporulating forms, in stained preparations, almost fill the infected erythrocyte and measure from 5 to 6 microns in diameter. The spores, or merozoites, are arranged more or less regularly around a mass of greenish pigment, each merozoite consisting of a small blue-stained, oval or spherical mass of cytoplasm containing a spherical ruby-red dot of chromatin. The merozoites can be easily counted and vary in number from 10 to 30, the average running between 18 and 24.

The infected erythrocyte, in stained preparations, may or may not appear crenated and stains a pink color. A few basophilic granules may be noted frequently, the so-called Maurer's dots. As a rule, the infected erythrocyte is not reduced in size or distorted in shape as observed in most stained preparations.

*Plasmodium falciparum quotidianum*, in stained preparations, may be readily distinguished from *Plasmodium falciparum*. The ring-forms are characterized by the small amount of cytoplasm and the relatively large amount of chromatin, while the larger forms are distinguished by their small size and the smaller number of merozoites in the sporulating plasmodia.

The smallest intracorpuscular forms of this sub-species are so very minute that they may be overlooked, in stained preparations, even by those who are more or less expert in examining malarial blood. They measure as little as 0.5 micron, or even less, in diameter, the smallest consisting of a minute granular mass of chromatin, stained pink or red in color, enclosed in a very minute amount of cytoplasm, stained blue, but so small in quantity that it requires the most careful examination to detect it. In this stage of development these plasmodia may be mistaken for a very small blood-plate or mere cellular detritus, as the true ring-form is not present, and it is undoubtedly the fact that at this time the plasmodium is very frequently overlooked or mistaken for something else.

At a slightly later stage of development the true ring-form is present but is often so very minute that very careful examination is necessary in order to demonstrate it. In these minute rings the cytoplasm is represented by a delicate blue-stained ring which contains somewhere along its circumference an irregular, semi-lunar mass of red or violet stained chromatin. The amount of chromatin is very large as compared with the amount of cytoplasm and ring-forms are frequently observed in which the chromatin comprises one-half or even more of the ring, and sometimes almost the entire plasmodium appears to be composed of chromatin.

In this sub-species the chromatin is not arranged in the form of a spherical dot or dots at some portion of the circumference of the ring, but usually occurs as a semi-lunar shaped mass forming a portion of the ring, in some instances almost the entire ring being formed of one or more of these semi-lunar masses of chromatin, practically no cytoplasm being visible. The center of the ring, i.e., the portion of cytoplasm enclosed by the ring-form, is absolutely colorless and the plasmodia look as though they were stamped into the substance of the infected erythrocyte with a punch. This appearance is very characteristic of the ring-forms of *Plasmodium falciparum quotidianum* in stained preparations, the ring-forms of *Plasmodium falciparum* presenting an entirely different appearance, the center of the ring staining pink, as does the remainder of the erythrocyte. In pernicious infections with the quotidian aestivo-autumnal plasmodium almost every infected corpuscle will present this colorless spot surrounded by the cytoplasm and chromatin of the parasite and when multiple infection of the erythrocytes occurs, as is frequently observed in such infections, the invaded erythrocytes present a very characteristic appearance, looking as though they were filled with small holes, each surrounded by the cytoplasm and chromatin of the tiny plasmodium. The fully developed ring-forms do not show the unstained central portion mentioned, the enclosed portion of the erythrocyte staining pink. The fully developed ring-forms present a larger amount of cytoplasm forming a portion of the ring but even in these forms the relative amount of chromatin to cytoplasm is greater, and it appears as irregular ragged masses at some portion of the periphery of the ring or as a semilunar shaped mass or masses forming a considerable portion of the ring. As in the smaller ring-forms, some of the fully developed rings appear to be composed almost entirely of chromatin, due to the large size of the semi-lunar mass or the merging of two such masses. Such forms are illustrated in figures 1, 3, 5 and 9.

This peculiar richness of the ring-forms of the quotidian subspecies in chromatin, and its arrangement within the ring, is a most important differential feature, for in the ring-forms of the tertian species the chromatin is very small in amount in comparison with the amount of cytoplasm and is arranged in the form of one or two perfectly spherical dots at some portion of the periphery of the ring and never in irregular clumps or semilunar masses which comprise a large portion of the ring, as in the quotidian sub-species. The photomicrographs accompanying this contribution well illustrate the differences in the amount and arrangement of the chromatin in the two aestivo-autumnal plasmodia.

The pigmented and pre-sporulating forms of the quotidian plasmodium contain a comparatively small amount of blue-stained cytoplasm and a relatively large amount of chromatin, arranged in the form of irregular granular clumps or threads scattered throughout the cytoplasm. Pigmented ring-forms are never observed, as in the tertian species, the ring-form being lost before pigmentation begins. In the pre-sporulating plasmodia the chromatin is situated irregularly throughout the cytoplasm while the pigment is collected in a small spherical or irregular mass at or near the center of the plasmodium. The pigmented and pre-sporulating forms are small, seldom exceeding three microns in diameter, generally measuring about two microns in diameter and filling less than one-half of the infected erythrocyte.

The sporulating quotidian plasmodia measure from two and a half to three microns in diameter, in the vast majority of instances, but smaller and slightly larger forms may be observed in some infections. They fill about one-half or a little more of the infected erythrocyte and appear to be composed mostly of chromatin owing to the fact that the merozoites are composed very largely of this material. The plasmodia at this stage of development are seen to consist of numerous oval or spherical collections of very finely granular chromatin, stained a pink or reddish-violet, each imbedded in a very minute mass of blue-stained cytoplasm. The pigment appears almost black in stained preparations and is collected in a solid block or irregular clump at or near the center of the sporulating plasmodium.

When sporulation is complete the merozoites, or spores, are visible as distinct oval or round, very minute bodies, stained a dark red or violet and surrounded by a minute amount of blue-stained cytoplasm. They are very small, not measuring more than one-half micron in diameter in stained preparations, and it is often very difficult to determine their exact morphology owing to their minute size. They are characterized by the relatively large amount of chromatin, the merozoites generally appearing to be composed almost entirely of this substance, and the amount of cytoplasm is so small that it is often almost invisible. The fact that the merozoites of *Plasmodium falciparum quotidianum* are so largely composed of chromatin distinguishes them from the merozoites of the tertian aestivo-autumnal plasmodium, in which the chromatin is limited to a small dot situated in a relatively large amount of cytoplasm.

The number of merozoites varies considerably in different plasmodia but in the counts that I have made of many hundred sporulating plasmodia of this sub-species, I have never observed more than eighteen merozoites nor less than 6, the average running between 12 and 14, the latter number being most frequently encountered in individual plasmodia. As already stated the sporulating plasmodia seldom fill more than one-half of the infected erythrocyte while the sporulating forms of *Plasmodium falciparum* fill practically the entire blood corpuscle in the majority of instances and as many as 24 merozoites may be commonly observed.

In stained preparations the erythrocytes infected with the quotidian sub-species are almost always distorted in shape and the cytoplasm stains poorly, basophilic granulation often being present. The characteristic unstained portion of the cell surrounded by the ring-form has already been noted, and is probably due to a vacuole. It constitutes one of the most important differential points in the diagnosis of the quotidian aestivo-autumnal plasmodium at this early stage of development, as it is never observed in the cells infected with the ring-forms of the tertian aestivo-autumnal plasmodium. In the latter the substance of the erythrocyte enclosed by the ring-form may stain poorly but there is never the absolute lack of color and the "hole-like" appearance that is noted in infections with the quotidian sub-species.

Double, triple, and quadruple infections of the erythrocyte with quotidian ring-forms are observed and double and triple infections are very common, much more so than in infection with the tertian species. Owing to their distorted shape it is often impossible to determine whether the erythrocytes infected with the quotidian species are reduced in size but in cells that have preserved their shape it is noted that there is a considerable reduction in size, as compared with uninfected cells surrounding them.

The *gametes* of *Plasmodium falciparum* and *Plasmodium falciparum quotidianum* are practically indistinguishable except in size. They are crescentic in shape, the so-called "crescents" and in both fresh and stained preparations of blood their morphology and staining reactions are the same. However, the gametes of the quotidian sub-species are smaller than those of the tertian species, by at least one-third, and are more plump, both the microgametocyte and the macrogametocyte being kidney-bean in shape rather than crescentic.

## SUMMARY

The differential diagnostic points in the morphology and development of *Plasmodium falciparum* and *Plasmodium falciparum quotidianum*, as observed in the blood of man and mentioned in this contribution are best summarized in tabular form and the following table has been prepared and will be found useful in differentiating the aestivo-autumnal plasmodia. It should be remembered that the differentiation of these plasmodia does not rest upon any single morphological peculiarity but rather upon the summation of all the differential points considered.

*Differential diagnosis of the aestivo-autumnal malarial plasmodia (stained preparations)*

| PERIOD OF DEVELOPMENT | PLASMODIUM FALCIPARUM | PLASMODIUM FALCIPARUM QUOTIDIANUM |
|---|---|---|
| 1. Length of cycle in man | Forty-eight hours | Twenty-four hours |
| 2. Earliest intracorpuscular stage | Ring-form. Average diameter, 1.5 microns | Minute oval body. Average diameter 0.5 micron |
| 3. Morphology of ring-form | | |
| a. Size | 1.5 to 3.5 microns in diameter | 0.5 to 1 micron in diameter |
| b. Cytoplasm | Well defined. Relatively large in amount | Poorly defined. Relatively very small in amount |
| c. Chromatin | Relatively small in amount, composed of one or two spherical dots | Relatively large in amount, composed of irregular or semi-lunar masses, forming a large part of the ring-form |
| d. Pigment | Present. Fine grains in expanded portion of ring | Never present in the ring-form |
| e. Effect on erythrocyte | Slightly reduced in size | Reduced in size. Distorted in shape frequently. Peculiar hole-like appearance in portion enclosed by ring-form |
| 4. Morphology of pigmented and presporulating forms | | |
| a. Size | 1.5 to 6 microns in diameter | 1 to 3 microns in diameter |
| b. Cytoplasm | Large in amount. Well defined | Small in amount and poorly defined |
| c. Chromatin | Relatively small in amount | Relatively large in amount |
| d. Pigment | Small granules and irregular clumps | Smaller in amount. One or two solid blocks |
| e. Effect on erythrocyte | Reduced in size | Reduced in size and distorted in shape |

| PERIOD OF DEVELOPMENT | PLASMODIUM FALCIPARUM | PLASMODIUM FALCIPARUM QUOTIDIANUM |
|---|---|---|
| 5. Morphology of sporulating forms | | |
| a. Size | 5 to 6.5 microns in diameter | 3 to 3.5 microns in diameter |
| b. Cytoplasm | Well defined. Large in amount | Poorly defined owing to small amount |
| c. Chromatin | Each merozoite has a small spherical dot | Each merozoite is composed almost entirely of chromatin |
| d. Pigment | Irregular mass | Solid minute block |
| e. Effect on erythrocyte | Reduced in size. Sporulating plasmodium almost fills erythrocyte | Distorted in shape. Slightly reduced in size. Sporulating plasmodium fills only about one-half or slightly more of the erythrocyte |
| f. Number of merozoites | 10 to 30 | 6 to 18 |

## DIFFERENTIAL DIAGNOSIS

### *Clinical*

As I have stated, not only do *Plasmodium falciparum* and *Plasmodium falciparum quotidianum* differ markedly morphologically but they also differ in the clinical symptoms produced in the human host by their presence. In fact, there is just as much difference in the clinical type of infection produced by these two parasites as there is in the clinical infections due to *Plasmodium vivax,* the benign tertian plasmodium, and *Plasmodium malariae,* the quartan plasmodium. The clinical symptoms produced by the latter plasmodia do not differ essentially except in the time at which the febrile paroxysms occur and the character of the temperature curve, and the same statement is true of infections with the two aestivo-autumnal plasmodia, except that the character of the temperature curve differs even more strikingly in infections with these plasmodia than in those with the benign tertian and quartan plasmodia.

*Relative frequency of occurrence*

Just as infections with the quartan malaria plasmodium are rare as compared with infections with the benign tertian parasite, so are infections with the quotidian aestivo-autumnal plasmodium as compared with infections with the tertian species. In 1662 aestivo-autumnal infections that I personally studied, 1473 were caused by *Plasmodium falciparum* and only 189 by *Plasmodium falciparum quotidianum*. These infections were all observed in patients coming from localities where both species were present but there are many localities where the tertian aestivo-autumnal plasmodium occurs and where the quotidian sub-species has not been observed. Thus, at Camp Stotsenburg, Philippine Islands, both aestivo-autumnal plasmodia were present, although the quotidian sub-species was comparatively rare, but at Camp McKinley, some sixty miles from Stotsenburg, the quotidian sub-species was never found although the tertian aestivo-autumnal species caused a considerable proportion of the malarial infections at that post.

The comparative rarity of the quotidian sub-species is one of the chief reasons for its not having been generally recognized as a distinct plasmodium, just as the rarity of the quartan plasmodium caused it to be overlooked for long periods of time in various localities. For instance, during the early years of work upon the Panama Canal it was officially reported repeatedly that the quartan plasmodium did not occur in the Canal Zone but later it was found that, while rare, as it is in almost every locality, it was present but had remained unrecognized. The same condition prevails today in many localities as regards the recognition of the quotidian aestivo-autumnal plasmodium and if one remembers the exceedingly minute size of the "ring-forms" of this sub-species, which are the forms usually noted in the peripheral blood, and the infrequency of infections with this parasite, I think that it is evident why so many observers in malarial regions have failed to note its presence or have not recognized it, when present.

*Time of febrile paroxysm*

In uncomplicated acute infections with *Plasmodium falciparum* the plasmodia sporulate every forty-eight hours and thus cause a febrile paroxysm every other day, while in uncomplicated acute infections with *Plasmodium falciparum quotidianum* sporulation occurs at the end of every twenty-four hours and the febrile paroxysm is quotidian in character. Unfortunately, it is rather exceptional to observe absolutely regular paroxysms in aestivo-autumnal infections, as previous treatment with quinine or the natural tendency of these infections to irregularity, due to anticipation or retardation of sporulation, often obscures the real periodicity of the paroxysms. However, in typical uncomplicated cases, *Plasmodium falciparum* causes a febrile paroxysm every forty-eight hours and *Plasmodium falciparum quotidianum* one every twenty-four hours.

In infections with the tertian aestivo-autumnal plasmodium sporulation may be observed as early as forty-two or forty-six hours and it may be retarded as long as fifty hours but I have never observed a case of infection with this species in which sporulation occurred in twenty-four hours, as it does in the quotidian sub-species. In infections with the latter plasmodium sporulation sometimes occurs as early as twenty-two hours or as late as twenty-six hours but I have never observed an infection with this plasmodium in which sporulation occurred later than twenty-six hours. In cultures Chamberland (16) states that *Plasmodium falciparum* sporulates at forty to forty-eight hours and Bass states that sporulation occurs at the end of forty-eight hours.

*Character of temperature curve*

Aside from the marked difference in the time of occurrence of the febrile paroxysm, the most typical clinical difference between acute infections with the two aestivo-autumnal plasmodia consists in the character of the temperature curve produced by infection with them. In uncomplicated cases the type of temperature curve produced by *Plasmodium falciparum* is absolutely characteristic and unlike that met with in any other febrile condition, while that produced by the quotidian sub-species is a typical quotidian curve which differs in no particular from quotidian curves observed in many infections.

The peculiar and characteristic temperature curve noted in acute uncomplicated infections with *Plasmodium falciparum* was first carefully described by Marchiafava and Bignami and is well illustrated in the temperature charts that accompany this contribution, which were obtained from soldiers suffering from tertian aestivo-autumnal fever and who volunteered to go without quinine treatment in order that typical temperature charts might be secured.

Upon reference to these charts it will be noted that, at the onset of the fever, corresponding to the sporulation of the plasmodia, the temperature rises rapidly to 102°, 103° F. or higher. Following this rapid rise there occur slight oscillations in the temperature covering several hours, during which time it may fall from 0.5° to 1°. This period of oscillation is followed by a distinct fall, or pseudo-crisis, the temperature generally dropping from 1.5° to 2°, or even 3°, and this fall in the temperature is often mistaken for the true crisis. However, the temperature again rapidly rises, often to a height greater than that attained during the initial rise and then falls rapidly to normal or even below normal. When the pseudo-crisis is very marked the temperature may fall to almost normal and in these cases the temperature curve may resemble that due to the quotidian sub-species, there being apparently a quotidian rise in temperature.

From this brief description of the temperature curve in typical tertian aestivo-autumnal infections, it may be noted that it can be divided into five quite distinct stages, as follows: 1, the initial rise; 2, the period of oscillation; 3, the pseudo-crisis; 4, the precritical rise, and 5, the true crisis. It will also be observed, from a study of the temperature charts, that the actual febrile period in this type of infection is much longer than it is in infections with any other species of malaria plasmodium, covering practically the greater portion of forty-eight hours. In most acute uncomplicated infections with this plasmodium the temperature actually remains elevated for from thirty-eight to forty hours, and sometimes even longer, whereas in other malarial infections the temperature is seldom above normal for as long as twenty-four hours unless there be double or triple infections. This point is of great value in differentiating infection with *Plasmodium falciparum* from infections with other malaria plasmodia.

The temperature curve in acute uncomplicated infections with *Plasmodium falciparum quotidianum* is of an entirely different character, consisting of a daily abrupt rise in temperature to 103° F. or more, succeeded by as abrupt a fall to normal, or below, the entire febrile paroxysm only lasting from eight to ten hours, in the vast majority of infections. However, the temperature curve in this type of infection often becomes irregular, the paroxysms tending to run into one another, thus giving rise to an irregular or almost continuous fever. The typical quotidian curve produced by this plasmodium is similar to the curves observed in a double infection with the benign tertian plasmodium and only a microscopical examination of the blood will show its true etiological nature. Thus, while it would be possible to diagnose a typical infection with *Plasmodium falciparum* by the character of the temperature curve alone, it would be impossible to do so in infection with the quotidian sub-species, as exactly similar curves may occur in multiple infection with either the benign tertian or the quartan plasmodium.

It should be remembered that while the temperature curves here described as characteristic of the two aestivo-autumnal plasmodia are those typical of each infection, marked variations in the curves are commonly observed which destroy their value for differential purposes. These deviations from the typical are due to many factors, the most important of which are insufficient medication with quinine; mixed infections with both aestivo-autumnal plasmodia or with the benign tertian or quartan plasmodium; double infections; anticipation or retardation of the paroxysms; slight elevations of temperature between the paroxysms, or complication with other acute or chronic infections.

In the study of malarial infections due to the aestivo-autumnal plasmodia, especially those due to *Plasmodium falciparum*, no dependence, so far as differential diagnosis is concerned, can be placed upon a temperature chart that records only the morning and evening temperature, for such charts are worse than useless because they are always misleading. In the study of these fevers the temperature should be taken and recorded every three or four hours and only by so doing can one secure a picture of the actual temperature curve in these cases. It is also necessary to omit the use of quinine if it is desired to obtain a typical chart and all of the temperature curves reproduced in this contribution were obtained from volunteers who received no quinine until the exact nature of the temperature was ascertained. As this procedure cannot be followed in actual practice, and as quinine, if given improperly, as it so often is, will render the most typical malarial temperature atypical, it is easily understood why so few really typical temperature curves of the two types of aestivo-autumnal infection are observed in general practice.

## CONCLUSION

The evidence that the aestivo-autumnal malaria plasmodia comprise at least two distinct forms rests upon differences in morphology, in the length of the life-cycle, and in the clinical picture of the infections which are produced by them. The morphological differences between *Plasmodium falciparum* and *Plasmodium falciparum quotidianum* are as constant and distinctive as those between *Plasmodium vivax* and *Plasmodium malariae*, while the striking difference in the temperature curve caused by these two plasmodia still further serves to differentiate them. The quotidian plasmodium causes a simple intermittent quotidian curve, indistinguishable from that observed in a double infection with the benign tertian plasmodium, while the tertian aestivo-autumnal plasmodium causes a temperature curve which is most typical and which differs markedly from that observed in any other type of malarial infection and which is diagnostic in itself. When, in addition, we find always associated with infections characterized by these varying temperature curves, distinctive plasmodia that differ morphologically and in their time of sporulation, these differences being constant and easily recognized by the trained observer, it must be admitted that the evidence is most convincing as to their specific character.

Unfortunately, there is no direct experimental evidence that these two plasmodia are distinct species, as we have no records of the experimental production of quotidian aestivo-autumnal malaria by direct inoculation of blood containing *Plasmodium falciparum quotidianum* into susceptible individuals or through the bites of experimentally infected mosquitoes, for while there are numerous successful experiments recorded of the production of aestivo-autumnal malaria both by direct inoculation of infected blood and by the bites of infected mosquitoes, no effort was apparently made to ascertain the exact species of aestivo-autumnal plasmodium used in the experiments, it apparently being taken for granted that there is but one species of this plasmodium.

In a recent publication Darling (17) describes two cases of experimental infection with the tertian aestivo-autumnal plasmodium in which the initial paroxysms were tertian or subtertian in character while subsequent ones became quotidian and uses these cases as an argument in support of the non-existence of the quotidian sub-species. An inspection of the charts published in his paper shows, that beyond some irregularity, as would be expected in experimental infections, the temperature curves are essentially those of tertian aestivo-autumnal malaria, and that the administration of quinine in all probability produced the atypical features of the temperature noted after its administration. There is absolutely nothing in the charts of these experimental cases which would negative the existence of the tertian and quotidian aestivo-autumnal plasmodia, as he has evidently mistaken the typical temperature curve of tertian aestivo-autumnal infection, which practically covers forty-eight hours, with, in these cases, a very marked remission at the end of twenty-four hours (probably due to quinine) for quotidian periodicity. His statement that the diagnosis of *Plasmodium falciparum quotidianum* was chiefly made before the Romanowsky stains were in general use is also hardly correct, as Marchiafava and Bignami used these stains in differentiating the two species and I have never employed any other stain than some modification of the Romanowsky, chiefly Wright's stain, in studying the malaria plasmodia.

I believe that the evidence summarized in this contribution is almost sufficient to entitle *Plasmodium falciparum quotidianum* to *full* specific rank, in which case, of course, the name would have to be changed, but until this can be absolutely proven by rigid experimental evidence I believe that this plasmodium should be regarded as a sub-species of *Plasmodium falciparum.*

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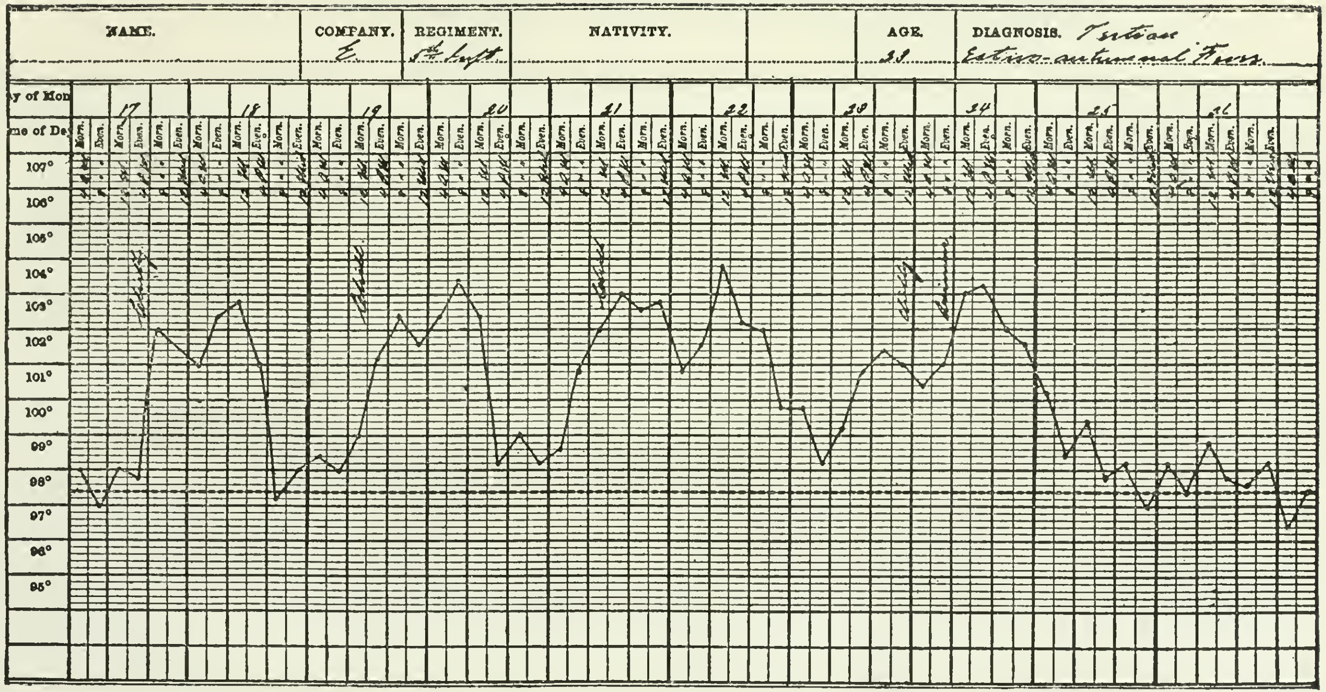



CHART I. TEMPERATURE CURVE OF TERTIAN AESTIVO-AUTUMNAL MALARIAL FEVER

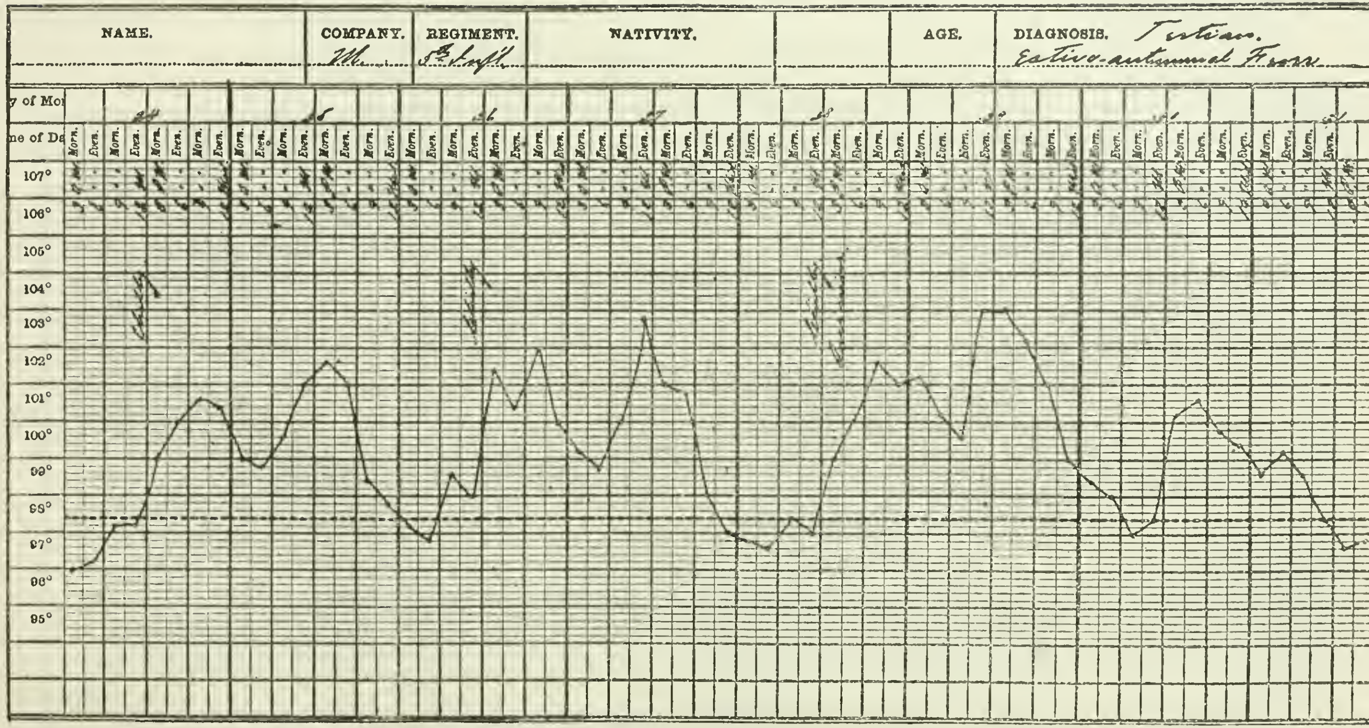



Chart II. Temperature Curve of Tertian Aestivo-autumnal Malarial Fever

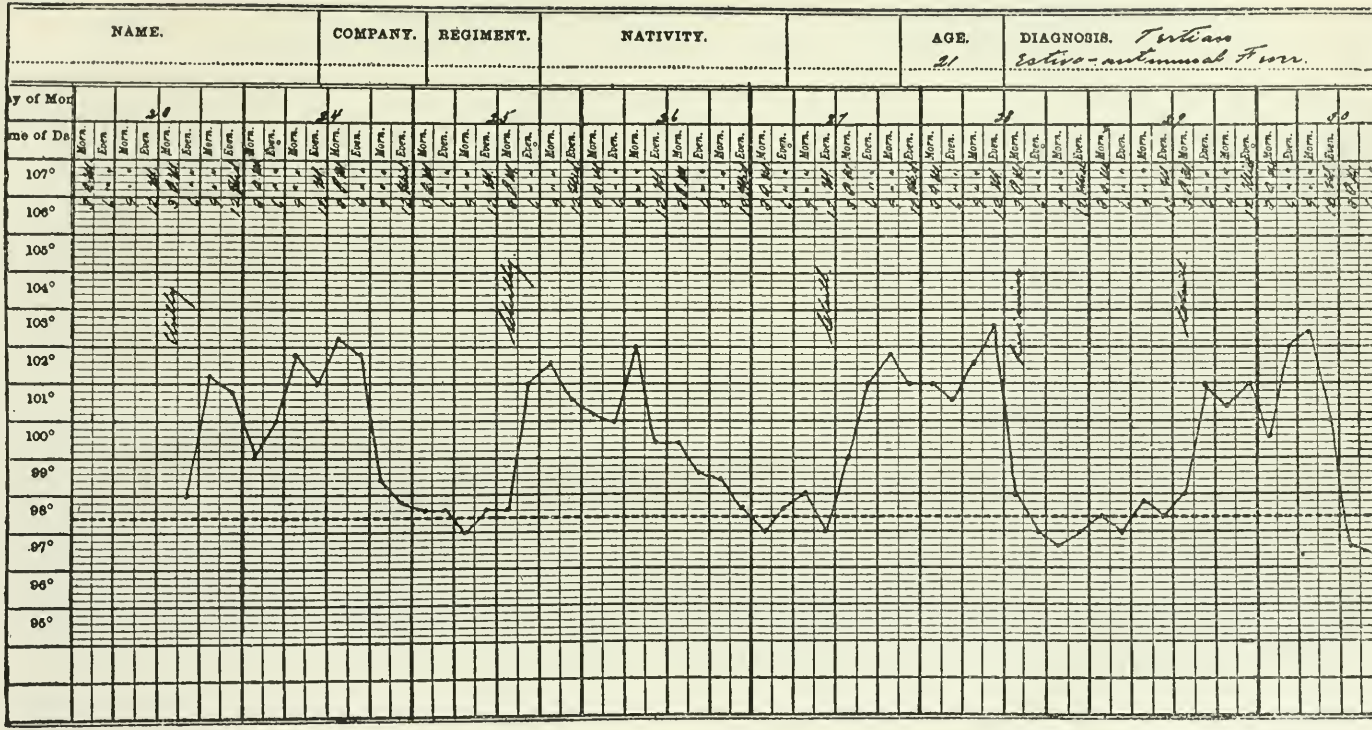



Chart III. Temperature Curve of Tertian Aestivo-autumnal Malarial Fever

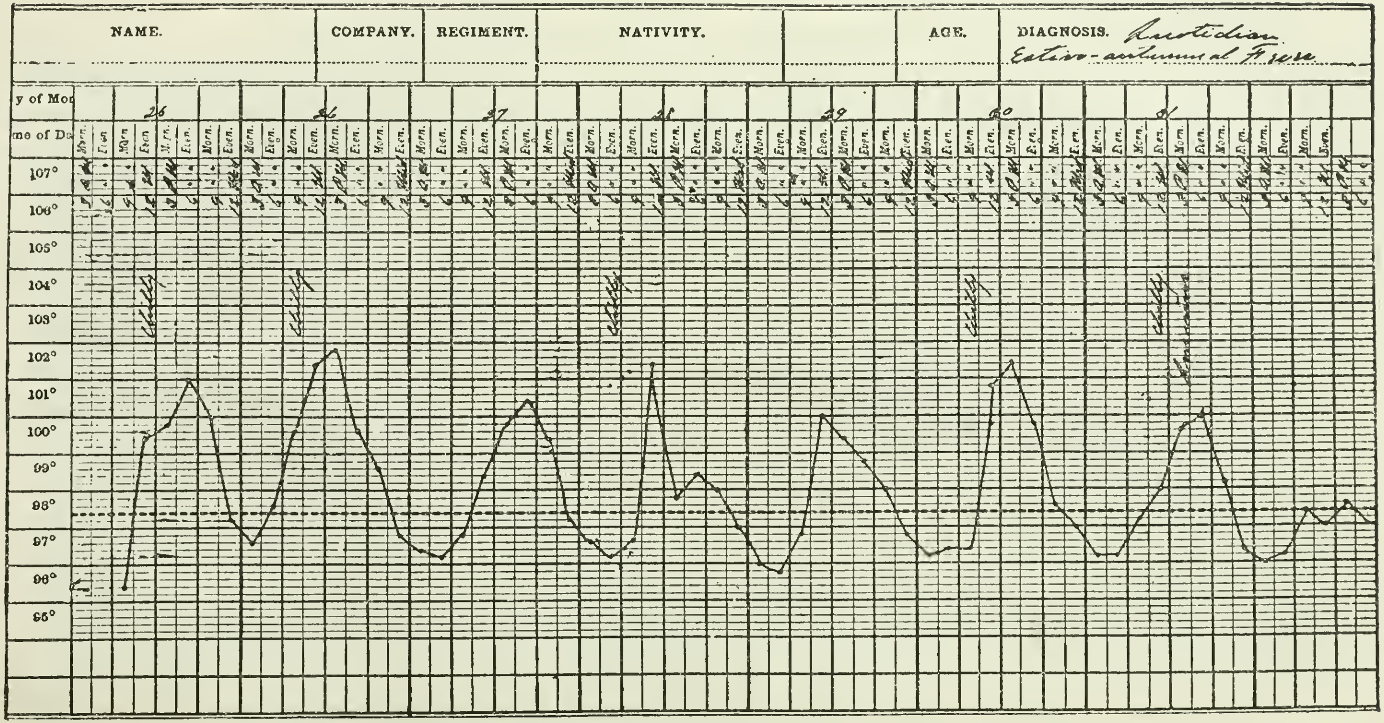



Chart IV. Temperature Curve of Quotidian Aestivo-autumnal Malarial Fever

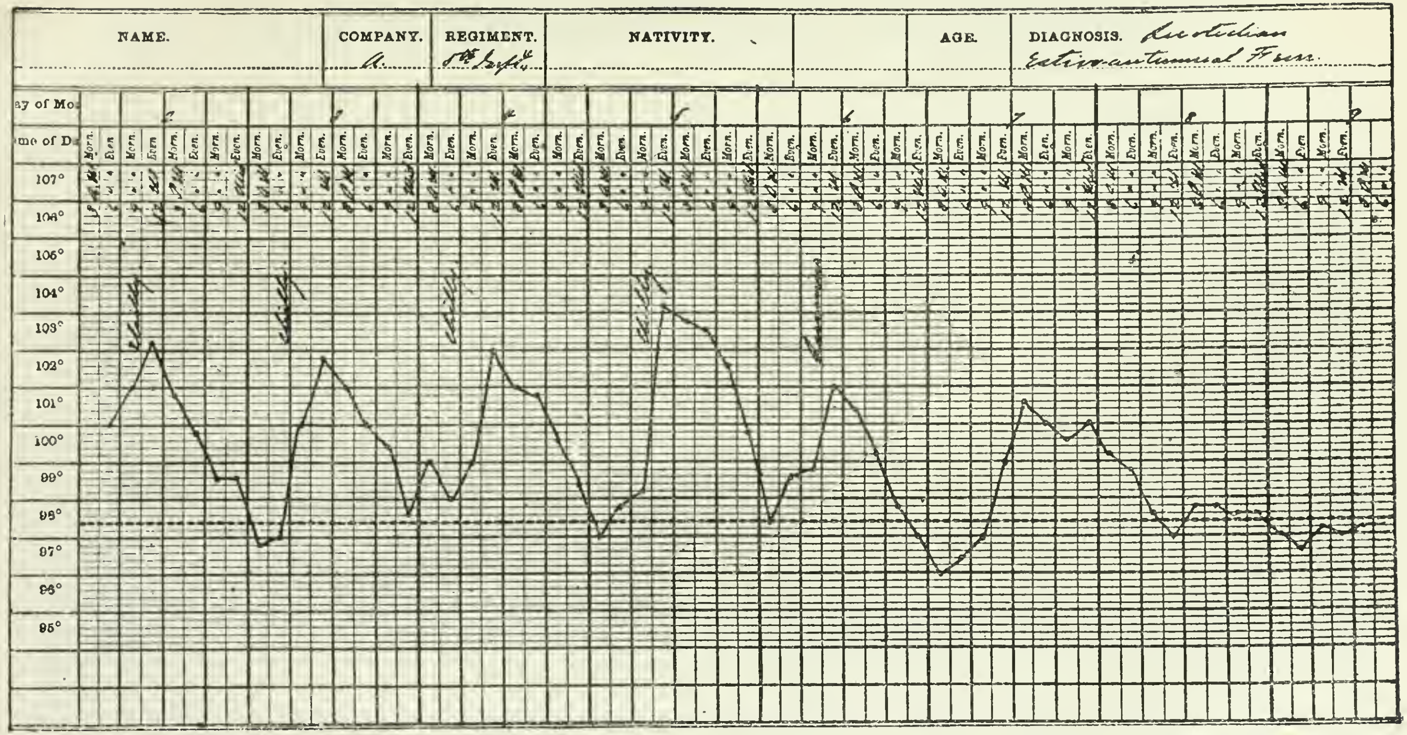



CHART V. TEMPERATURE CURVE OF QUOTIDIAN AESTIVO-AUTUMNAL MALARIAL FEVER

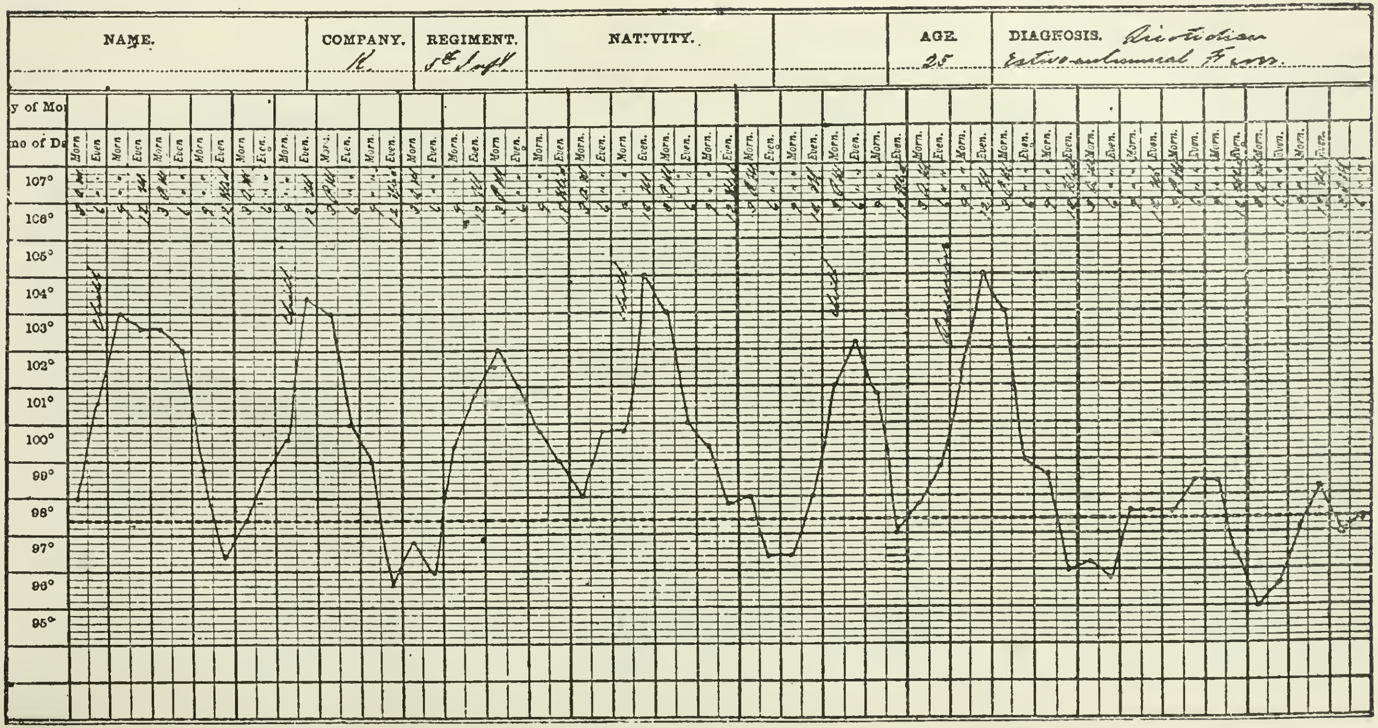



CHART VI. TEMPERATURE CURVE OF QUOTIDIAN AESTIVO-AUTUMNAL MALARIAL FEVER

## EXPLANATION OF PLATES

The photomicrographs are of plasmodia observed in the peripheral blood of infections with the tertian and quotidian aestivo-autumnal parasites and are chosen to illustrate the chief morphological differences between them.

Fig. 1. *Plasmodium falciparum quotidianum.* Ring-forms. Note relatively large amount of chromatin, one of the "rings" appearing to be composed almost entirely of this material. (In all the photomicrographs the very dark staining portion of the plasmodia represents the chromatin.) Note minute size of parasite. × 1600.

Fig. 2. *Plasmodium falciparum.* Ring-form. Note dot of chromatin, and expanded portion of the "ring." Note large size of the ring compared with the ring-forms in figure 1. × 1600.

Fig. 3. *Plasmodium falciparum quotidianum.* Ring-forms. Note minute size and large amount of chromatin, comprising a large portion of the ring. Also "hole-like" appearance of portion of erythrocyte enclosed by the ring-forms. Triple infection of one erythrocyte. × 1600.

Fig. 4. *Plasmodium falciparum.* Ring-form. Note two small dots of chromatin, expanded portion of cytoplasm of the "ring," and the large size as compared with the ring-forms of the quotidian sub-species. The ring-form in this species fills almost as much of the erythrocyte as the three ring-forms of the quotidian parasite shown in figure 3. × 1600.

Fig. 5. *Plasmodium falciparum quotidianum.* Ring-forms. Note minute size, and large amount of chromatin. × 1600.

Fig. 6. *Plasmodium falciparum.* Typical ring-forms. Compare with ring-forms of quotidian plasmodium. × 1600.

Fig. 8. *Plasmodium falciparum.* Double infection of erythrocyte with ring-forms. Compare with Figure 7, noting relative size of plasmodia and morphology of the "ring." × 1600.

Fig. 9. *Plasmodium falciparum quotidianum.* Typical ring-forms. Note triple infection of erythrocyte and large amount of chromatin, arranged as a semi-lunar mass forming a considerable portion of the "ring." × 1800. Although magnified 200 diameters more than the ring-forms of *Plasmodium falciparum,* shown in Figure 8, the "rings" are still much smaller than those of the latter species and entirely different in morphology.

Fig. 10. *Plasmodium falciparum quotidianum.* Sporulating form and ring-forms. Note that sporulating form fills only about half of the erythrocyte. × 1600.

Fig. 11. *Plasmodium falciparum.* Half-grown pigmented form. Note that though only half grown it fills as much of the erythrocyte as the sporulating form of Plasmodium falciparum quotidianum. × 1600.

Fig. 12. *Plasmodium falciparum quotidianum.* Sporulating and ring-forms. Note that only half of the erythrocyte is filled by the sporulating form and the extremely minute size of the ring-form in the erythrocyte below and to the left of the sporulating form. × 1500.

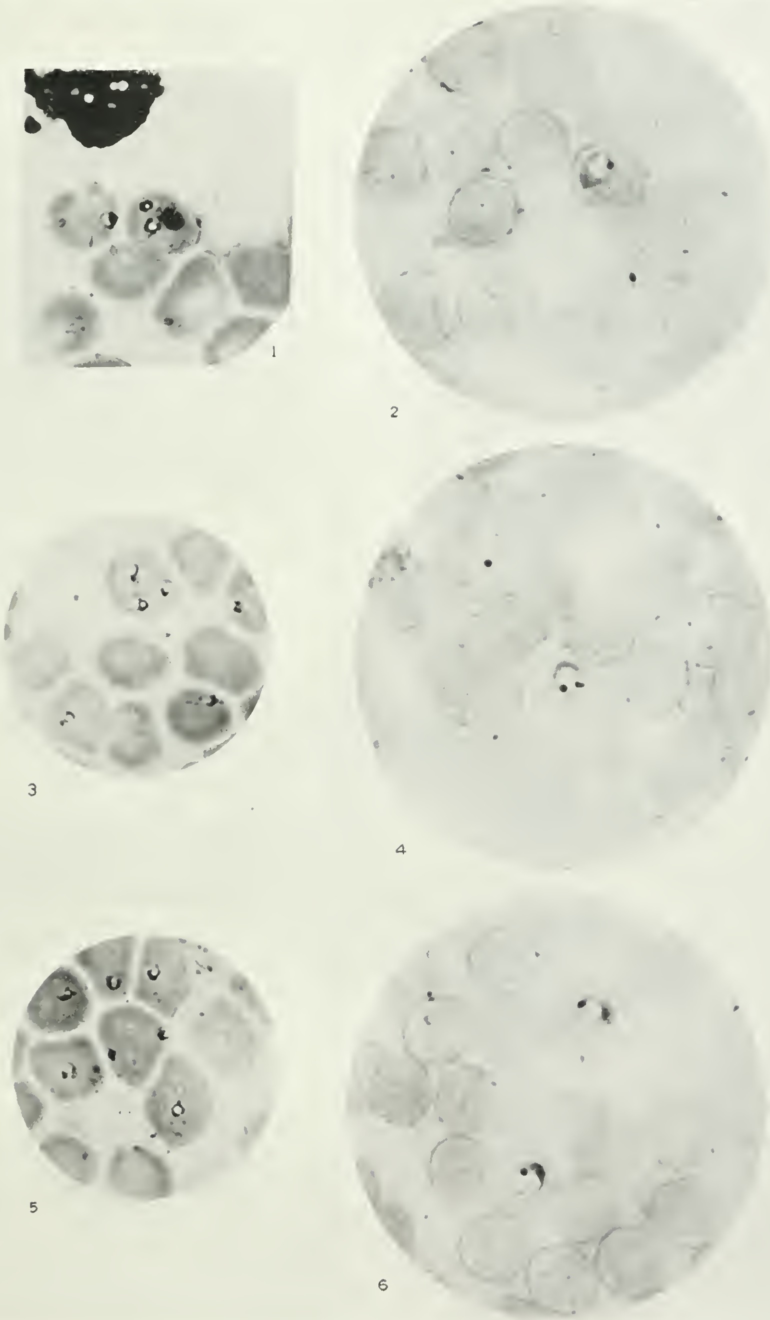
Fig. 13. *Plasmodium falciparum.* Sporulating form. Note that the infected erythrocyte is almost entirely filled by the plasmodium. × 1500.

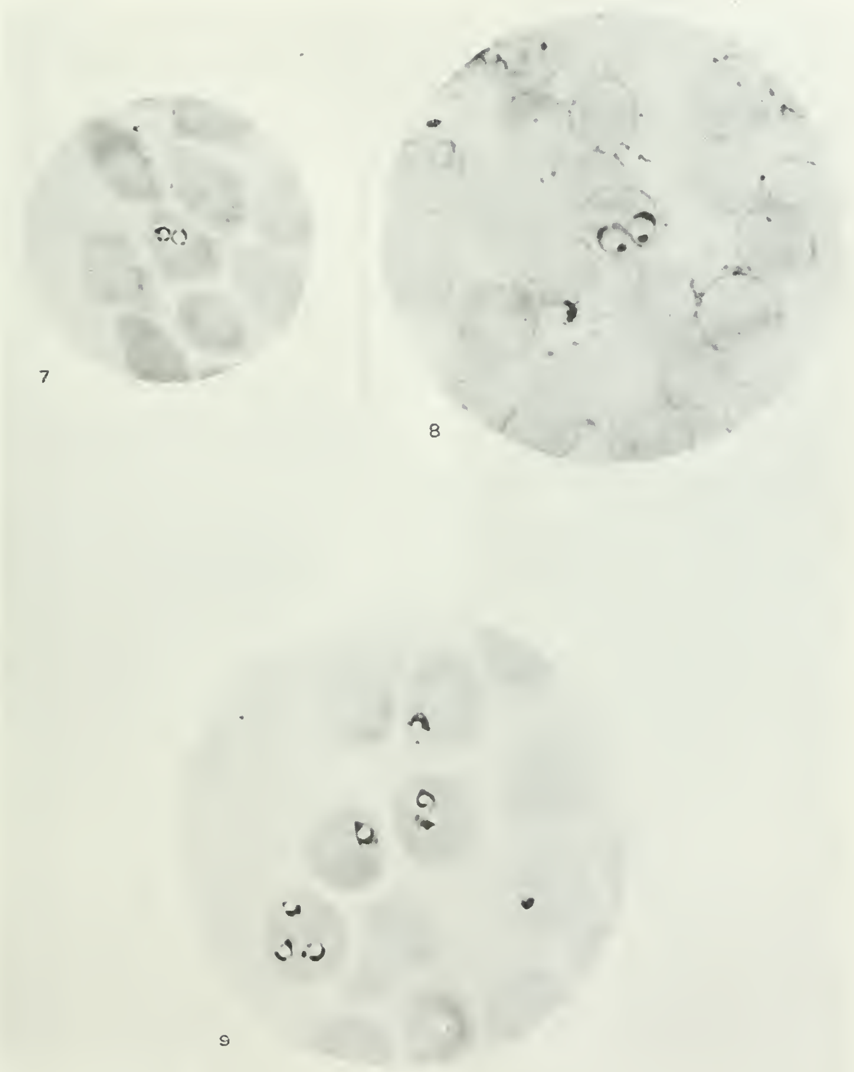
FIG. 14. *Plasmodium falciparum quotidianum.* An unusually large sporulating plasmodium filling slightly more than one-half of the erythrocyte. × 1800.

FIG. 15. *Plasmodium falciparum.* This plasmodium is near the pre-sporulating stage but almost fills the infected erythrocyte. It is shown for comparison with the quotidian plasmodium in figure 14 to illustrate the difference in the size and the amount of erythrocyte occupied by the parasites. Although the tertian parasite is only about two-thirds grown it occupies more of the infected erythrocyte than the sporulating quotidian parasite and is about the same size. × 1800.

NOTE: In the photomicrographs of the ring-forms of *Plasmodium falciparum* the deep staining of the expanded portion of the "ring" is not due to the presence of chromatin but to the comparatively large amount of cytoplasm which takes a deep blue stain. The chromatin in these ring-forms is shown as a spherical dot or dots generally opposite the expanded portion of the "ring."

PLATE I

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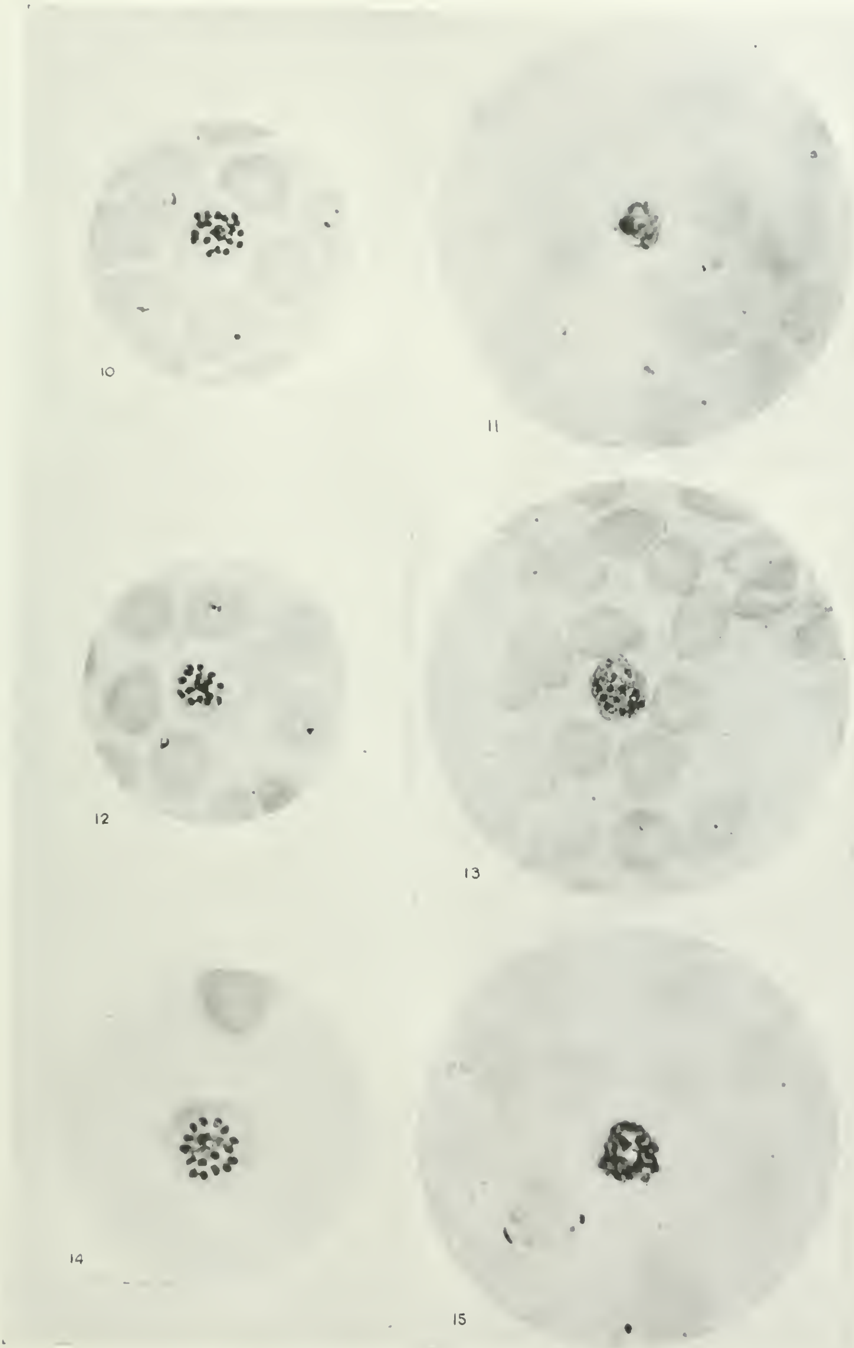
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# TRANSACTIONS OF THE AMERICAN SOCIETY OF TROPICAL MEDICINE, SIXTEENTH ANNUAL MEETING HELD AT NEW ORLEANS, LOUISIANA, APRIL 26 AND 27, 1920

*Continued*

## CONTRIBUTIONS TO MEDICAL SCIENCE DEVELOPED UNDER THE AUSPICES OF THE UNITED STATES INTERDEPARTMENTAL SOCIAL HYGIENE BOARD

WILLIAM F. SNOW

If tropical medicine were based on the study of diseases of great prevalence in the tropics irrespective of limitation to the tropics, syphilis and gonococcus infections would occupy a place of great importance in the deliberations of this Society. Of course this is not the case, but the seriousness of the venereal disease problem in tropical countries and the earnest effort which the United States government is now making to develop more effective ways and means for combating these diseases seem to warrant such a paper as this at the present session. For many years isolated efforts in the fields of research and medical treatment have been directed toward the control of syphilis and gonorrhea, and particularly in recent years under the leadership of the American Social Hygiene Association, a definite propaganda for enlisting popular support of an adequate public health campaign has been carried on. These efforts eventuated in the development during the war of comprehensive army and navy plans for control of these diseases among the armed forces. The American Social Hygiene Association, with coöperating bodies, placed before Congress the need for a national civilian attack being made simultaneously with that of the military authorities, and in 1918 the law was passed creating the United States Interdepartmental Social Hygiene Board and the new

Division of Venereal Diseases of the United States Public Health Service. The function of the former is to pioneer the way in the matter of working out scientific and administrative details and to direct special work for the protection of the armed forces, which cannot advantageously be undertaken by the United States Public Health Service or the army and navy authorities; the function of the new Division of Venereal Diseases is to promote the national and state public health activities in combating the venereal diseases.

Four million one hundred thousand dollars was appropriated by this act for the fiscal years 1918–1920. The expenditure of this sum has been largely instrumental in securing the expenditure of at least two million dollars by the several states and an additional million and a half by local volunteer agencies. In addition, the American Social Hygiene Association has expended upwards of seven hundred thousand dollars on important supplementary activities which could not be financed from the public funds available. All of these funds have been expended with the primary object of preventing new infections. No accurate estimate exists for the amounts expended by the people and institutions for the private diagnosis and treatment of infected persons for their own sake as distinct from protection of the public, but it would seem to be safe to say that several millions of dollars have been added annually to the budgets of dispensaries and hospitals and to the incomes of private physicians as a result of the organized campaign against the venereal diseases. The purpose of mentioning these sums aggregating upwards of ten million dollars is to indicate that a really serious effort is now being made, on a nation-wide scale, to bring this dangerous group of human-contact diseases under social control. It is believed that many workers in the field of tropical medicine are in a position to discover new and better methods, or at least to promote the campaign in tropical countries.

As reprints describing the work of the United States Interdepartmental Social Hygiene Board and of the United States Public Health Service Division of Venereal Diseases will be distributed, no detailed statement is required here. It is desirable, however, to review our knowledge of the venereal diseases from a point of view of preventive medicine. We know that syphilis and gonorrhea in their various medical and surgical manifestations are actually or potentially communicable diseases due to identified organisms. Their methods of transmission are known, and a practical laboratory and clinical technique has been worked out for diagnosing each of them; they are widely prevalent throughout the world among individuals of every race, sex, age, and condition of people; they find their chief opportunity for dissemination in the intimate, personal contact of infected individuals with other individuals who are susceptible; they are largely, but not exclusively, transmitted through promiscuous sex relations—particularly those relations defined as prostitution; recent methods of therapy make practicable the shortening of the period of infectivity and improve the chances of ultimate recovery of the patient submitting to early and thorough treatment; once contracted, they may run their course to practical recovery, or to a resting stage with or without medical assistance, but under present conditions an unknown and large percentage of those infected never completely regain their health or cease to be carriers. Syphilis in its early stages is especially a public danger, while in its late manifestations the damage is largely confined to the individual himself. Gonorrhea, on the contrary, while a public danger at all times, is particularly damaging to the individual in its early, acute development, and later becomes an insidious danger to those intimately associated with him, especially within his home and family.

In a word, we know the cause of these diseases; we know that human "carriers" afford their chief mode of dissemination; we know that in prevalence and injury to the people they are not outranked by any others of the communicable disease groups; and we know that theoretically we should proceed to apply these facts exactly as we apply the similar facts concerning other preventable diseases. Reduced to simplest terms this means the adoption and enforcement of (1) measures for the discovery, treatment and control of individuals already infected, (2) measures for the elimination of conditions of environment favoring the dissemination of the infections, (3) measures for the protection of individuals not infected.

For some years the public health aspects of this problem have been theoretically more hopeful and practically more hopeless than for any other against which sanitarians have directed their efforts. For anything more than an academic discussion it is necessary to recognize that the application of our knowledge depends upon bridging that no man's land between the views of the old-time physician who says there is nothing to do about venereal diseases except to treat patients who have intelligence enough to apply, and the old-time moralist who says that these diseases are essentially a check upon sexual immorality and that any measure should be opposed which in the least degree may be interpreted as lessening the maintenance of moral standards. The medical profession, as well as health officers, have been quick to endorse the theory of preventive measures against these diseases but slow and inconsistent in applying them. One only has to run over parallel columns contrasting our venereal disease control procedure with the measures we employ to combat smallpox, cholera, diphtheria, typhoid fever, hookworm, malaria, and the other diseases now understood by the people, to prove to himself that we have not fearlessly attacked the venereal diseases or even made an effort worthy the name until recently, to study all the means by which we might adapt the principles of preventive medicine to curbing the ravages of these great criminals of biology—the treponema and the gonococcus.

In combating syphilis, not only must the medical and social aspects of the problem be dealt with but the moral and religious as well. It is generally understood that yellow fever would still be a matter of the greatest dread, instead of almost a matter of history, if the epidemiologist had not supplemented by field observations the evidence of pure science and developed practical methods of dealing with the reduction of exposures to the bite of the insect-carrier of infection. Likewise, it must become recognized that the epidemiologist may not hope to succeed against syphilis and gonococcus infections unless he deals equally practically with the human carriers of these infections—the women who practice prostitution, and the men who seek sexual relations with them. It may not be considered strictly scientific to compare these so-called human carriers with the mosquito hosts of such diseases as yellow fever and malaria but the general analogy holds. It may fairly be maintained that were prostitution to cease for a generation, syphilis and probably gonorrhea would be brought under complete control.

It is the duty of the scientist to examine carefully the possibilities of eliminating these human carriers of the venereal diseases. Sir William Osler once said to some of us by way of illustrating the necessity for an ever-present freshness of viewpoint in studying a medical problem: "You must bear in mind that there are three ways of eradicating malaria, all of which are theoretically equally effective: (1) You might kill all the malaria parasites, (2) you might kill all the mosquito carriers, (3) you might kill all the people." This observation applies to the eradication of syphilis and gonorrhea, but it happens, as in the case of malaria eradication, that we do not wish to kill all the people, and we have not yet devised ways of killing all the parasites or of eliminating all the carriers. Much may be expected, however, from attempting to kill the treponema and the gonococcus by effective medical treatment of patients and to reduce the numbers of carriers and exposures by adequate social measures.

In an effort to direct the attention of scientists and the medical profession to this phase of the problem, and to stimulate efforts to improve our knowledge and our technique, the United States Interdepartmental Social Hygiene Board undertook to finance investigations of various sorts calculated to improve our fighting equipment.

Some twenty-five American universities or medical schools have received grants totaling over two hundred thousand dollars for promoting researches to perfect better methods of diagnosis and treatment or prevention of infection. The 138 men and women engaged upon this work are studying problems as diverse as attempts to prepare synthetic products for treatment of gonorrhea, for shortening the period of infectivity, and social studies of the syphilitic's family and community relations to determine how best to deal with follow-up service and early detection of other cases. There is, for example, need for better therapeutic agents for treatment of gonorrhea. A product named mercurochrome "220" has been developed at Johns Hopkins under the direction of Dr. Hugh Young in the Brady Urological Institute which is now being tested out clinically. Its deep non-irritating tissue penetration and nontoxic qualities suggest great possibilities for its use in rendering exposed and infected persons non-infectious. Other work of this character is being carried on at the Universities of Wisconsin and Nebraska. In the latter, Dr. Edwin G. Davis and his associates are endeavoring to develop a new internal urinary antiseptic, particularly in the use of certain of the aniline dyes. These researches at Nebraska are along lines similar to certain others being carried out in the Brady Urological Laboratory. It has been possible to predict with reasonable accuracy the drug most likely to be excreted, and so to modify the compounds administered as to produce an antiseptic compound when excreted by the kidney. The power of penetration of these compounds through the urethral mucosa and their other antiseptic properties both in vitro and in the urinary tract are now being studied.

Dr. A. S. Lovenhart, of the University of Wisconsin, is extending this character of research to various compounds of arsenic and mercury which might be synthesized and made soluble in lipoids thereby showing a possible predilection for the central nervous system. Aside from its interest in the venereal disease campaign, this work, correlated as it is with work which is being done by Dr. W. Lee Lewis, of Northwestern University, and Dr. Roger Adams, at the University of Illinois, both of whom are engaged in developing new synthetic compounds of arsenic which Dr. Lovenhart will test out in his laboratory, presents an example of scientific teamwork which is significant of what may be done by men located in quite widely separated laboratories. In the University of Minnesota, Dr. A. D. Hirschfelder and Dr. H. G. Irvine are studying, both in the laboratory and the clinic, the possibilities of phenol alcohol derivatives in their relation to antisepsis and the chemotherapy of the gonococcus and the treponema. Dr. Thomas Addis, of Stanford University, is attempting to devise ways of increasing the permeability of the meninges of the brain to anti-syphilitic drugs, and Dr. L. G. Roundtree and Dr. C. B. Nixon, of the University of Minnesota, are studying the chemical and physical properties of the cerebrospinal fluid in leutic and non-leutic cases.

A series of studies of the treponema and the gonococcus group are being made to determine possible new lines of attack. Dr. R. A. Kinsella, of St. Louis University, is studying the growth peculiarities, immunizing properties and modes of infection in experimental animals. Dr. W. P. Larsen and Dr. J. F. McClendon, of the University of Minnesota, are working on the permeability of bacterial membranes. Dr. G. H. Smith and Dr. M. C. Winternitz, of Yale University, are carrying out another series of studies of identification, culture, and serological reactions of the gonococcus. Dr. John C. Torrey, of Cornell University, is working on a serological study of the gonococcus in the hope that new information regarding the homogeneity or heterogeneity of various strains may lead to the general use of a complement fixation test. Dr. George S. Graham, of the X-ray Laboratory of the General Electric Company, Schenectady, is studying the possibilities of generalized infection of lower animals with treponema and the gonococcus in order to broaden our basis for experimental, clinical, and pathological observation of syphilis and gonorrhea. Dr. P. C. Jeans, of Washington University, St. Louis, is studying a series of placentas for evidence of syphilis and for comparison with the mother's blood and later examinations of the children. The great value in early treatment of congenital syphilis of any accurate basis of detection by this means is evident. In addition, Dr. Jeans and his associates are studying the identification of treponema in necropsy tissues from married men under fifty years of age whose family histories are well known. Dr. Bertha M. Maine and Dr. Rose Hirschler, of the Women's Medical College, Philadelphia, are simultaneously studying syphilis in pregnant women and new-born children in relation to the efficacy of treatment. Dr. Engman and his associates at Washington University, are endeavoring to determine the status of the latent syphilitic patient as a source of conjugal infection.

Investigations of a somewhat different character but presenting interesting possibilities are being carried out elsewhere. Dr. M. C. Winternitz and Dr. G. H. Smith, of Yale University, are examining a series of postmortem specimens to determine the facts about presumptive lesions of syphilis of unusual occurrence; the facts concerning infections unaccompanied by manifest anatomical changes are being studied, and many other points related to what might be termed atypical cases are being reviewed. An extensive study of central nervous system changes in neurosyphilis cases is being made at the Massachusetts State Psychiatric Institute along lines planned by the late Dr. E. E. Southard, the work involving the minute examination of a large series of brains and spinal cords. If there should be developed any way to predetermine the value of treatment of such cases, an immense social and economic gain would result from advising families and patients regarding the long and expensive treatment. In this same direction of cutting down the expense and uncertainty of treatment, Dr. William Jack, in association with Dr. Hugh Young, of Johns Hopkins University, is trying to develop a simpler technique and less expensive therapy for gonorrhea. In the same laboratory, Dr. E. O. Swartz is studying the value of certain penetrating dyes for the treatment of chancroids. Dr. R. D. Herrold, of the John McCormack Institute for Infectious Diseases, of Chicago, in association with Dr. Ludwig Hecktoen, is endeavoring to develop a standard for declaring a patient cured of gonorrhea. This work involves other studies of the life history and serum reactions of the gonococcus. The great value of any practical results is evident. Similarly, Dr. R. L. Rigdon, at Stanford University, California, and Dr. A. S. Spalding are jointly searching for better methods of treatment of acute and chronic gonorrhea in both men and women through devising close supervision of patients and systematically checking their progress.

The Wassermann test is under review and experimentation in Dr. T. Ordway's laboratory at the Albany Medical College, and Dr. R. C. Rosenberger, at Jefferson Medical College, is working on the simplification of the clinical diagnosis of syphilis. Dr. Reed Hunt is extending his studies of the toxicity of arsphenamine, neo-arsphenamine, and other products for the treatment of syphilis, and the practical technique of safeguarding the patient from poisoning. Dr. A. S. Warthin, of the University of Michigan, assisted by eight associates, is carrying on a three-year study of the diagnosis technique for determining latent syphilis, particularly in relation to simplifying and shortening the time required for staining treponema in the tissues.

The social and economic effects of syphilis and gonorrhea to the family and indirectly to the nation are of the greatest importance, but the case records and other data essential for profitable studies are very limited. The clinical material for this purpose is exceptional in the field of syphilis at the Massachusetts State Psychiatric Institute, and a study has been undertaken there. The established ward and out-patient services available to the Psychiatric Institute yield a large number of neuro-syphilitics (paretics, tabetics and atypical forms), yearly. In this research, Dr. Southard planned to deal mainly with the handling of the syphilitic family for the prevention of further infection and for the treatment of those already infected to prevent further syphilis. The social service problems involved are extremely difficult, and the technique is somewhat intricate, requiring rather expert scientific social workers. The information resulting from this investigation will indicate the size of the problem, its cost to the community, and the best methods of handling the situation. The information so secured should be put into a form available to all social agencies and particularly to those working in child welfare agencies and hospitals. It is to be hoped that the Interdepartmental Board will extend its grants for researches of this character to other institutions which can show an accumulation of accurate data and adequate facilities for such social-medical studies.

This brief and necessarily superficial and non-technical sketch of the principal researches being promoted by the United States Interdepartmental Social Hygiene Board has been given to show how extensively—from north to south and east to west—our scientific laboratory directors and clinicians are coöperating in this work. A total of probably two hundred and fifty thousand to three hundred thousand dollars is being expended in addition to the usual expenditures of institutions and such work of the United States Public Health Service Hygiene Laboratory as supervising and studying the preparation and distribution of arsphenamine and similar drugs. It would seem inevitable that much new and practical knowledge would result. Those who are interested in tropical medicine and familiar with laboratory and epidemiological methods in its field are peculiarly qualified to still further promote this great fight against the venereal diseases. In practice, the application of the program which has been developed cannot proceed until the details of effective measures are understood and demonstrated to be practical and the support of public opinion for an active campaign has been secured. The public is interested in the conservation of health as a whole and looks upon the eradication of any one disease or group from that point of view. An individual having a program for the prevention or control of a disease is helpless unless he can popularize his knowledge and secure community action. Just here is where the members of this Society can be of still further influence. When the public does wake up to the possibilities of prevention, it desires to do everything at once and get the job over with; from battling to get his program recognized, the advocate of a special campaign finds himself battling to have unsettled questions laid on the table until a careful decision as to policy and method can be made. All public health progress has followed this course. Only by preceding popular knowledge and interest by a vanguard of steady scientific opinion and approval of the steps of a program have our preventive medicine triumphs been accomplished and medical knowledge made to function safely through our channels of democratic government and community action. Only recently has society become willing to consider the application of law, social protective measures, recreational, educational, character building, and moral and religious training facilities to the prevention of exposure of its members to the venereal diseases. The analogy between screening the uninfected portions of a population against the mosquito carrier of malaria and screening them against the human carrier of venereal diseases through employing measures for combating prostitution is just becoming apparent to large numbers of citizens. There was a time in the history of preventive medicine when the public were taught by the medical profession to hang pieces of asafedita about their necks or to put saucers of carbolic acid under the sick bed. No doubt these measures did some good in the same way that our quarantine signs placed before the quarters of scarlet fever cases do some good now in inducing the well to keep at a distance from the known sick, but such measures are being largely replaced by more effective and more intelligent methods. Similarly the scarlet-letter and the painted-lady labels have in their time served as indications of the desire of the public to have the well kept away from the morally and physically sick of vice districts. But likewise these crude and cruel methods are giving way to more intelligent and far more effective measures which take cognizance of a well-rounded program for moral, medical, and social rehabilitation of those who are spreaders of venereal disease and immoral practices. Just as joint investigations on new medical measures are being promoted by the Interdepartmental Board, so joint social and moral welfare investigations are being encouraged, and an even more extensive program of research into educational methods is being financed in coöperation with some thirty normal schools and universities.

Although the congressional act under which the United States Interdepartmental Social Hygiene Board operates is unusually broad and generous in its provisions, there are necessarily many phases of the social hygiene program into which the federal government cannot enter. These are being turned over to the American Social Hygiene Association to foster in order that no stone may be left unturned at this time in an effort to accomplish what we know to be scientifically true—that syphilis and gonorrhea may in time be brought completely under control and added to the lengthening list of great world-wide scourges against which man has successfully struggled through the past ages. The limits of this paper do not permit of a summary of the researches and activities of the federal and state agencies and the volunteer associations in social, educational, moral and administrative fields mentioned, or for that matter even in the medical and scientific fields. Your suggestions and observations are desired, however, and any letters addressed to the United States Interdepartmental Social Hygiene Board, Washington, the United States Public Health Service, Washington or the American Social Hygiene Association, 105 West 40th Street, New York City, will be forwarded to the proper officer or person and further information sent you on any part of the complex campaign against the venereal diseases.

# HYMENOLEPIS NANA; POSSIBLE CERCOCYSTIS STAGE[1]

ALFRED GOLDMAN[2]

*From the Medical Clinic of Barnes Hospital, Washington University School of Medicine, St. Louis*

Since the prediction of Stiles (1) that *Hymenolepis nana* would prove to be a common intestinal parasite in the United States, cases have been reported with increasing frequency, and the indications are that it is the most common tapeworm in many parts of the United States.

Ransom (2) compiled the United States cases up to 1904, reporting twenty-five cases, all but one of the twenty-five having been reported after 1902.

Deaderick (3), in reporting two new cases in 1910, found that the number had reached thirty-three.

Schloss (4) in the same year reported twenty cases of *Hymenolepis nana* in 280 children examined for intestinal parasites and only five cases of *Tenia saginata.*

Amesse (5) reported one case from Professor Howland's service at Bellevue Hospital.

M. A. Wood (6) reported three cases of *Hymenolepis nana* from Houston, Texas.

Bass and Gage (7) reported fifteen cases out of 577 persons examined in New Orleans, and only three cases of *Tenia saginata.*

H. B. Wood (8), from records of examinations made during 1911 and the first quarter of 1912 in the state laboratories of the South, found *Hymenolepis nana* in 1004 of 62,785 persons examined, and only ten cases of *Tenia saginata.*

[1] Reprinted from the Archives of Internal Medicine, September, 1920, **26**, 373–380.

[2] This paper was read in abstract by Dr. George Dock at the meeting of the American Society of Tropical Medicine, held at New Orleans, April 27, 1920. In the discussion that followed it was shown that *Tenia saginata* is much less common in some places than it was about thirty years ago.

Deaderick and Thompson (9) stated that during 1911–1913, of 56,543 infections found by the Rockefeller Sanitary Commission, 1879, or 3.3 per cent, were dwarf tapeworm.

Gerber (10) reported the first case from Boston.

Judkins (11) found seventy-one cases among 15,000 people examined throughout Texas.

McNeil (12) reported six cases of *Hymenolepis nana* in the Southern Pacific Hospital in Houston, Texas.

Greil (13) found seventy-five children under twelve years of age in Montgomery, Ala., with dwarf tapeworm infection.

Frey (14) reported that out of 118 cases of parasite infections in the Texas State Orphan Home, 32.6 per cent were *Hymenolepis nana.*

Van Liere (15) reported one case in twenty foreign students examined at the University of Wisconsin.

Willets (16) reported six cases in the Georgia State Sanitarium.

Lyon (17), in a study of 477 patients at the Walter Reed General Hospital, found two cases of dwarf tapeworm and five cases of *Tenia saginata.* The latter, however, were diagnosed before being referred to the hospital.

Kofoid and Kornhauser (18) examined the stools of 1200 American soldiers who had been overseas and of 300 home service men. In the former series there were seven cases of *Hymenolepis nana;* in the latter none.

DeBuys (19) studied 595 children from seven different institutions in New Orleans, and found *Hymenolepis nana* in fifty-five cases, or 9.25 per cent. No other tapeworms were found.

Lucke (20) reported 230 cases of dwarf tapeworm in 35,000 white and black troops at Camp Zachary Taylor, Kentucky. *Tenia saginata* was found twelve times.

Notwithstanding the fact that the parasite has been one of the most frequently encountered, according to the reports of several authors, yet in many localities *Hymenolepis nana* has either not been looked for or has not been found. So far as is known there are no case reports from the region of St. Louis.

The following cases occurred in that city in the B. family, colored. The family came to St. Louis from Mississippi early in 1917. There were eight children, seven of whom were infected with the dwarf tapeworm and the eighth with *Ascaris lumbricoides*. The mother had pin worms, the father was free from parasites. The first patient was sent into Barnes Hospital from the out-patient pediatric service; the others were seen at their home.

### REPORT OF CASES

*Case 1.* F. B., male, aged five years, born in Mississippi. Entered Barnes Hospital, January 19, 1920, on account of severe diarrhea. In October, 1919, he began having numerous loose mucoid stools with blood, sometimes bright red, sometimes tarry. Considerable straining at stool, no vomiting or pain; appetite greatly increased. Physical examination showed moderate distention of abdomen. Red blood cells, 4,160,000; hemoglobin, 80 per cent; eosinophilia, 7 per cent. Stool was liquid, light yellow, with mucus, benzidin positive; very many ova of *Hymenolepis nana.*

Treated with male fern January 21; no worms recovered. Stools egg free up to January 28, an interval of seven days. Treatment repeated February 10 and at least one thousand *Hymenolepis nana* worms were obtained. Stools were egg free up to February 23, when many small circular bodies from 5 to 15 microns in diameter were observed. February 24, thymol, 15 grains, was given, and one worm was found. Stools egg free to March 15, an interval of eleven days. March 19 male fern was given but vomited, and March 20 another dose was given through a tube. Many tags of tissue containing heads of dwarf tapeworm embedded within the tissue were found. No whole worms or segments were observed. Stools egg free to March 29, an interval of ten days. Discharged from hospital April 4, Stool on discharge, soft, brown, little mucus, no blood; dwarf tapeworm eggs, from 1 to 3 per low power field. April 18, condition good, stool as on April 4. May 28, patient had had measles in interim and was very anemic; passing considerable blood in stools. Stool was soft, yellow and blood streaked and contained large numbers of *Hymenolepis nana* eggs.

*Case 2.* J. B., male, aged one year seven months, born in St. Louis. February 22, no symptoms; physical examination negative; stools hard, brown, few *Hymenolepis nana* eggs found; eosinophils, 3 per cent.

*Case 3.* E. B., female, aged three years, born in Mississippi as were all the others. All through January had four or five loose stools a day.

For the past four months has frequently had similar symptoms. Complains of abdominal pain during these periods. February 22, stool gray-brown, much mucus, many *Hymenolepis nana* eggs; eosinophils, 6 per cent.

*Case 4.* A. B., female, aged eight years. At three years passed twenty-three ascarides (?). Occasional short attacks of diarrhea for past four months, with abdominal pain. Nausea and vomiting, frequently with dizziness. Patient is anemic and drowsy. Hemoglobin, 70 per cent; red blood cells, 3,500,000; white blood cells, 9000; eosinophils, 9 per cent. February 22, stool soft, gray, with considerable mucus. Very many *Hymenolepis nana* eggs. March 29, course of male fern. Several thousand *Hymenolepis nana* worms obtained. April 17, general condition good; no symptoms since treatment. No *Hymenolepis nana* eggs found in stools.

*Case 5.* A. B., male, aged eight years. Complains of frequent frontal headaches. Examination negative; eosinophils, 3 per cent. February 22, stool normal; no eggs found in preparations. March 27, very many *Hymenolepis nana* eggs.

*Case 6.* R. B., male, aged nine years. No symptoms; physical examination negative; eosinophils, 2 per cent; stool normal; few *Hymenolepis nana* eggs.

*Case 7.* M. B., female, aged eleven years. For the past year has had attacks of diarrhea, the last one early in February. Frequently has tenderness in abdomen and gets dizzy at times. Recalls no symptoms previous to past year. Patient anemic; has slight abdominal tenderness. February 22, stool normal; very many *Hymenolepis nana* eggs. Eosinophils, 7 per cent; red blood cells, 3,800,000; white blood cells, 8000. March 29, course of male fern; at least one thousand worms obtained. April 17, few *Hymenolepis nana* eggs found. No symptoms since treatment.

The morphology of the worms does not differ essentially in any respect from the usual descriptions. Specimens were sent to Dr. C. W. Stiles, who kindly reported that he identified the worms as *Hymenolepis nana,* the eggs belonging to the same.

In Case 1, the larger number of very young specimens found, the smallest being 3 by 0.15 mm., is noteworthy. The largest specimens were 15 mm. in length, the maximum width 0.6 mm. Senna, cited by Ransom (2), noticed in feces containing *Hymenolepis nana* eggs many small rounded bodies measuring from 5 to

30 microns in diameter. The smaller of these were homogenous with a thin membrane, while the larger were more granular and tended to become oval, with thicker membrane. Senna thought these might be eggs in the course of development which had prematurely escaped from the uterus, but finding similar bodies in two cases in which he could not demonstrate the presence of *Hymenolepis nana,* he was left in doubt as to their true nature. In case 1, of this series, thirteen days after the second course of male fern and before the eggs had reappeared in the stools, there were found a large number of homogenous structures from 5 to 15 microns in diameter, bounded by a thin membrane. The next day, for the first time, *Hymenolepis nana* eggs were observed, with fewer of the smaller structures. These were not observed again.

## SYMPTOMS

Of the seven cases four had definite symptoms, which, in the absence of other factors, may be attributed to the dwarf tapeworm. Two of the children had no symptoms and in both cases very few eggs were found. One patient with a heavy infection had long-standing headache, which may possibly have been due to the parasites. The most frequent symptoms were abdominal pain, or tenderness, and diarrhea, found in four cases. There were anemia, dizziness and headache in two cases, increased appetite in one case. The presence of blood in case 1 is interesting. Innes, cited by Ransom, in reporting a necropsy on a case, states that he found bloody extravasations on the mucous membrane of the ileum, which may have been the points of attachment of the tapeworms lying free in the intestine.

Eosinophilia, according to Schloss (21) and others a constant finding in cases showing symptoms, ranged from 2 to 9 per cent. In the children with definite symptoms it was from 6 to 9 per cent, while in the others it was from 2 to 3 per cent.

Treatment was instituted in three cases and an apparent amelioration of symptoms occurred in all. Case 1, after four courses of treatment, still showed a few eggs in the stool on the day of the patient's discharge. Subsequently, after an attack of measles, his intestinal symptoms reappeared. In case 4 apparently complete cure was obtained after one course of male fern. In case 7 few eggs showed after one course of treatment.

## MODE OF INFECTION

The development as well as the manner of infection of the dwarf tapeworm is unknown. There is a form of tapeworm common in rats, the *Hymenolepis murina* of Dujardin, which morphologically is very similar to *Hymenolepis nana*. Grassi (2), quoted by Ransom, found this parasite common in rats in Catania, where also the dwarf tapeworm was common. In a series of carefully conducted experiments, he showed that the feeding of mature segments of *Hymenolepis murina* to rats was followed by infection with this tapeworm. The eggs liberate six-hooked embryos in the small intestine, which enter the villi of the last part of the ileum and there become transformed into cercocysts. The position of each cercocyst is in the dilated central lymphatic cavity of the villus. Subsequently, the cercocyst leaves its position in the villus and becomes changed to the adult worm, and is attached to the epithelium of the intestines. Just how the latter stage ensues is not noted. Joyeux (22) repeated these experiments successfully.

Grassi, Lutz and Ransom consider *Hymenolepis nana* of man identical with the rat hymenolepis, but Braun, Loos and others doubt this. Grassi, Loos, Stiles (23), Schnell (24), and Joyeux (25) were unable to transmit the infection to rats and mice. Stiles states that the "form from rodents is entitled to at least subspecific rank." Castellani (26) states that the dwarf tapeworm of man is probably distinct from the rat type.

Minchin and Nicholl, and later Johnston (27), state that they found cysticercoids of *Hymenolepis murina* in the body cavity of *Xenopysylla cheopis* and *Ceratophyllus fasciatus*, but Joyeux states that he was unable to transmit the infection experimentally in these and other fleas.

Grassi fed worms and eggs of both types to eight individuals and in only once case were adult tapeworms found. In this case, a boy of five began to pass eggs fifteen days after ingesting several segments of the rat hymenolepis and later expelled fifty worms on treatment. In another instance a boy who was previously free from *Hymenolepis nana* was infected after a month during which time he was collecting the feces of an infected patient. Grassi himself raises objections to these cases because of the high incidence of *Hymenolepis nana* in the locality and because worms may be present, although the stools are egg free.

The experiments of Grassi, together with the failure to find an intermediate host, have led to the assumption that the mode of infection is direct, and that man himself, like the rat, may be the intermediate host. Stiles accepts this possibility. As possible evidence of direct infection, Grassi cites cases of dwarf tapeworm infection in several individuals, previously egg free, in whose families there were known to be cases of *Hymenolepis nana*. Schloss (21) cites two similar cases in his series. The frequent findings of infection in several members of the same household would also point to the possibility of a direct infection. Thus the Hygienic Laboratory staff (28) found five cases in the same ward of an insane asylum. Magnenat, quoted by Stiles (1), reported four cases in the same family. In all but one of Schloss' cases several members of the same family were infected. Carpenter (29), in discussing DeBuys' paper before the American Pediatric Society, described an epidemic of *Hymenolepis nana* in a foundling asylum in Philadelphia and thinks the infection was direct. Rats examined by him were negative.

I attempted to determine the mode of infection of the dwarf tapeworm. The feeding of eggs and mature segments to six rats and six mice was negative. Attempts to incubate the eggs following their mixture with artificial gastric juice were also negative.

The house of family B was carefully inspected and found to be in a very unsanitary condition. The children played around the floor a great deal so that chances for coprophagia were very favorable. There were no rats. Several bedbugs were examined and were negative for cysticerci. Several lice from the head of case 4 were also negative.

There was an old pet dog with which the children were very intimate. A stool from the dog, obtained while the dog was at the B. home, showed several eggs, which were exactly similar to eggs of *Hymenolepis nana*, the characteristic filaments of the latter being present. There were also present trichomonads and eggs of *Dipylidium caninum* and *Tenia serrata*. The dog was removed from the home and daily examinations of stools were made, but hymenlepis eggs could no longer be found. Two weeks later a necropsy was made and *Dipylidium caninum* and *Tenia serrata*, but no *Hymenolepis nana* were recovered.

The presence of the parasite in all but the oldest boy, age twelve, is of interest. In case 5, no eggs were observed in the specimen of February 22 after twelve examinations, while on March 27 the stool was loaded with them. The difficulty of ridding the host of all the worms is a striking feature. It has been stated by Ransom and other authors that one course of treatment is frequently not sufficient. In two of my three cases which were treated eggs showed subsequently. In case 1 four courses of treatment were given and at the end of these there were still many eggs present. The large number of very young forms following the second treatment was striking.

Following the last administration of the vermifuge, the fu'l dose being repeated next day because of the vomiting of the male fern, there were passed a number of mucoid looking tags of tissue, but no worms. The largest of these pieces were 20 by 10 mm. Each had from two to eight heads of *Hymenolepis nana* studded throughout it, but no segments could be found. Microscopically, there were observed the rostellum, a row of hooklets, four suckers and a small caudal appendage. Surrounding each head there could be seen in the unstained specimen a definitely clear area. In the stained specimen, there was seen microscopically a sac-like structure, completely surrounding each head. The shape of the structures varied, some being elliptical, others ovoid, still others approaching a spherical shape. Grossly, both the head and the sac could be seen in the stained tissue. It does not seem likely that the adult worm could develop within the sac-like structure.

Figures 1 and 2 show the relative size and shape of the head and sac. The tissues were stained several times with hematoxylin-eosin and also with methylene blue, but no nuclei could be seen. I felt that the structures might possibly represent the

Fig. 1

Fig. 2

Figs. 1 and 2. Head of Dwarf Tapeworm Surrounded by Sac-Like Structure. Head Shows Some Details

cercocyst stage of the dwarf tapeworm, thus indicating that man himself may be the intermediate host. The occurrence of autoinfection is proved by the large number of worms present and the difficulty in getting completely rid of them.

## SUMMARY

1. A review of the literature shows that the dwarf tapeworm is the most common tapeworm in many parts of the United States.

2. The first cases of *Hymenolepis nana* from St. Louis are reported.

3. A possible cercocyst stage of *Hymenolepis nana* is demonstrated in man.

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# STUDIES OF MONILIA IN CONNECTION WITH SPRUE

WILLIAM KRAUSS

*Memphis*

Cases of stomatitis with intestinal disturbances have been encountered in the Memphis territory for an indeterminate time. Such as I recall were characterized by chronicity and persistence in spite of all treatment. One of these had been to various health resorts and diet institutions all over the country. He had been to every prominent doctor in Memphis, had had several negative Wassermann tests and bismuth meals, but every diagnostic test tried left the problem unsolved. Two others also had buccal ulcers, gastric pain, intermittent diarrhea, weakness and emaciation. All of them improved on skim milk diet. Their present history is not known to me. No suspicion of pellagra attached to any of these cases.

From time to time physicians have asked me about the possible prevalence of sprue in the South as an endemic disease. Until recently I have always denied this, explaining that sprue-like symptoms were not uncommon. This was precisely the case with respect to our earliest cases of pellagra. Wood (1) has contributed two articles, rather vaguely suggesting an extensive prevalence of sprue, principally on the ground of diarrhea with anemia. Boyd (2) reported his cultural experiments upon the stools of patients with sprue-like symptoms in a paper entitled: "Is Sprue Endemic in the South?"

The etiology of sprue is still under discussion. It is not necessary, before this audience, to call attention to the studies of Ashford and Michel, in Porto Rico. Many writers, notably Castellani and Chalmers (3), and Rogers and Nicholls (4) do not support the claims of Ashford with reference to his *Monilia psilosis* Ashford, 1914. On the other hand, Boyd (1), Oliver (5) and Sturtevant (6) have corroborated his findings.

That tropical sprue is a distinct clinical entity seems established. Hill diarrhea is quite distinct, and self-limited, or at least relieved by return to lower altitudes. Pseudo-sprue will doubtless come into use as a term resorted to by those defending a special etiology. Castellani describes a pseudo-sprue due to a bacillus closely related to the Flexner type. Wood says many cases of sprue in the South are being treated as cases of pellagra. The past history of the disease is rather nebulous. A white diarrhea was noted in a colony of North Carolina in 1737 by an Irish Colonial surgeon. The Dutch name "sprew" was anglicized by Manson, in 1880. It was through the weight of his influence and after the Lettsomian lecture of Sir Jo Fayrer that sprue became recognized as a clinical entity.

We will leave the definition of sprue to the textbooks.

As to etiology, we have had the helminthic theory, which brought out the santonin treatment, tried out by Ashford with indifferent success; the protozoan theory (of course) incriminating endamebae and flagellates; the climatic theory, the theories involving the influence of diet, diathesis, food deficiency, pancreatic disease, abuse of calomel, etc.

Naturally, the chemistry and biology of the stools have been the subjects of much study. Rogers and Nicholls reported complement fixation with streptococcus viridans and treated patients with apparent benefit by the use of the corresponding antigen. Before them, Kohlbrügge (1801) reported finding *Oidium albicans* in Javanese sprue, and his findings were corroborated by others. Subsequently, Castellani made a study of monilia associated with sprue and enumerated: *M. enterica*, *M. faecalis*, *M. insolita*, *M. intestinalis*, and later, *M. decolorans* Castellani and Low.

According to Castellani these differ slightly in their behavior to litmus milk but, for the most part, readily ferment glucose, levulose, maltose and galactose, again differ in saccharose: All are indifferent to the other sugars, including lactose, are Gram-positive, do not liquefy gelatin, produce no cloudiness on broth, peptone water or serum, and form white, or nearly white colonies on glucose agar.

At the American Congress of Physicians and Surgeons (1912) Ashford reported the uniform finding of a *Monilia* morphologically very characteristic and different from any heretofore described. Later (7, 8) he published two monographs, describing the morphological and cultural characteristics of his organism. He has found it as a contaminator of Porto Rican bread. At his instance Michel (9, 10) made complement fixation, and toxicity tests and described a technic for making autogenous vaccine. He reports striking success from its use. Castellani is disposed to regard Ashford's *Monilia* as identical with his *M. enterica* and disputes its pathogenicity. Beneke opposes the monilia theory on the ground of uniformly finding a bacillus in the mouth ulcers.

On the chemical side of the problem we find unanimity as to the presence of a high percentage of fat in the stool, which has led many into the belief in a primary disease of the pancreas, developed by unaccustomed climatic conditions. There is said to be a notable absence of biliary coloring matter in the lower bowel, which led to the name "diarrhea alba." The urobilin reaction, however, is positive. Ordinarily the stools are described as putty-colored, frothy and pultaceous, alternating with watery consistence. There is nothing in the published post-mortem findings to throw light on the etiology.

The occasion for this study was a patient who had been under treatment for pellagra seven years previously. At that time some of our doctors were giving arsphenamin rather freely in the treatment of pellagra. She objected to this and to "get away from local ethics" went to New Orleans to consult Dr. Bass. She reports that he had her case under advisement for several days and then established the diagnosis of sprue, and that he had told her she did not have nor had ever had pellagra. Upon her return home she was put upon the classical treatment and improved well enough to do her professional work in cool weather, spending her summers in Denver.

During 1919 she learned about Dr. Michel and his vaccine. At first he sent stock vaccine to her physician but advised him to have autogenous vaccine made locally. The bacteriologist of a local hospital could not isolate any organism corresponding to the monilia described in Michel's reprint and in the meantime Dr. Michel had prepared a vaccine from material sent all the way from Memphis. This treatment was used with varying success and owing to interruptions in shipments her physician requested me to take charge of the entire case.

This patient is a professional woman of high standing, fifty-five years old. Her only absence from the United States was a three years' sojourn in Germany doing graduate work. This was prior to her illness. To the best of her recollection, her first symptoms were "acute indigestion or ptomain poisoning." There had been diarrhea, sore mouth, sore tongue, painful deglutition, epigastric and hypogastric pain, various nervous symptoms, mostly of the neuritis type, emaciation, anemia, prostration. There had never been any dermatitis. There are now at times mental exaltations, paresthesias and neuritic pains.

Her height is 5 feet 10 inches, her weight 92 pounds. Says it has been as low as 85 pounds. Spare but firm musculature, carriage erect and a general bearing of vigor entirely out of proportion to build. Takes physical culture exercises daily and does a hard day's professional work. Blood pressure 105–65, pulse 96 to 110.

Chest negative, no hemic murmur. Area of hepatic dulness diminished, spleen not enlarged. Exaggerated reflexes. Red cells, 2,420,000, white 5400, hemoglobin 70–80 (Sahli), erythrocyte picture about normal.

During periods of exacerbation abdomen is rather large but soft; pressure elicits only diffuse soreness and fine gurgling. Says she has attacks of prostration at night and at such times her surface is very cold and her husband is unable to find her pulse. Her mouth is dry, slightly reddened, no ulcers. She is very positive, however, that ulcers appear when her condition is very bad. Her diet has consisted of peptonized milk, buttermilk, with an occasional egg. Sometimes she can take a gallon of milk a day.

The stools are grayish, never quite white, occasionally mustard-colored like those of pellagra. They vary from very thin to hard. The semisolid stools are pultaceous; the thin ones are moderately frothy, effervescence easily seen. The odor reminds of yeast at times but often it is fetid. Fat is demonstrable in the stool but there are no visible globules. Urine negative.

With respect to the effect of the bacterin she reports about as follows: A week or ten days after her last injection she has her "knockdown feeling." She then has neuritic pains, great prostration, sore spots in the mouth, painful deglutition, great abdominal distension and foamy stools. After a dose of bacterin she has a "stimulating reaction," with much local and focal pain, increased bowel activity, followed by an indescribable "knockdown feeling." On the third and fourth day she feels "like a fighting chicken."

Leaving out her bacteriology I would be unable to corroborate the diagnosis of sprue. There is very little suggestion of pellagra in the case.

On January 24, she was given the contents of a 1 cc. ampule of Michel's bacterin. Stools were obtained on the morning of the 26th and 27th.

On the fourth day after plating, the fourth dilution showed a white pinhead colony. The lower dilutions were rejected. In all subsequent culture work we found it expedient to keep the primary emulsion in the inactivating bath at 56° for two hours before plating. This did not prevent cultures of monilia from developing.

*Description of the organism*

Upon 4 per cent glucose agar: after three days a white round colony. On the fifth day colony has a creamy color with a central elevated and more opaque nucleus surrounded by a smooth halo of a more transparent portion. The fifth day colony is about 3 mm. in diameter. Hanging drop preparations show mostly round cells averaging 4 to 5 micra in diameter. Larger ones are oval or quite elongated; some of these buds are two to three times the length of the round ones. Very long hyphae can be seen, some of them extending over the entire field. These become very long in older cultures. Smears show the younger forms to be Gram-positive but the larger ones and the hyphae are uniformly Gram-negative, using acetone as a decolorizer. Cultures upon 2 per cent glucose broth in Durham tubes produce gas in three or five days. The growth is thready and granular and does not cloud the medium. Upon litmus milk coagulation and decoloration always occurred. Gas was not formed. The decoloration is slow, requiring forty-eight hours or more. Older litmus cultures show peptonization and an alkaline reaction. In stabs mycelia regularly form in the deeper portion. After a week, the agar colonies exhibit a fine diffusion downward. Asci and cryptococcus forms were never observed. In the hanging drop motile nuclei could be observed. For lack of time, a strictly systematic cultural study was not made. We expect to do so on fresh specimens later, if we succeed in securing them. Our stock culture has undergone contamination. My reason for reporting this incomplete study at this time is that I wanted to bring the matter before this society and get some helpful discussion.

The following chronological table completes the patient's history to date:

*Table*

*January 24, 1920.* Michel vaccine, 1 cc. in arm. Usual reaction. Pain and prostration, no fever, diarrhea, subsidence of symptoms on third day.

*January 26.* Stool obtained, two specimens.

*January 27.* Morning stool.

*January 29.* Feel well; sense of being stimulated.

*January 31.* Single colony in fourth dilution, subcultured. Patient feeling badly, "all knocked down" again.

*February 2.* Michel vaccine—usual reaction.

*February 5.* Washed off subculture—phenolated; shaker, incubator.

*February 7.* Patient's "best day."

*February 9.* Feeling pretty well—decides to postpone vaccine, only one dose being left.

*February 13.* Feeling badly; depressed and apprehensive; wants me to wire Surgeon General to hurry Dr. Michel.

*February 14.* Pains returning, very wretched, 15th also. Patient receives last dose Michel vaccine (14th at home).

*February 13.* Inject pig with 10 cc. suspension.

*February 14.* Pig very ill, diarrhea, anorhexia, abdominal pain on pressure.

*February 15.* Pig very much prostrated, falls down, refuses food.

*February 16.* Pig nibbles at food.

*February 17.* Pig more lively; next day apparently voracious; complete recovery.

*March 3.* 0.5 cc. new vaccine, reaction "quite as usual" but milder.

*March 6.* Patient very much better than for long time.

*March 13.* 1 cc. vaccine—reaction severe, local swelling, arm very red. Patient says she is used to such reactions. Much prostration, diarrhea.

*March 16.* "Feeling fine."

*March 20.* 1 cc. vaccine. *Very marked local and general reaction.* much prostration. Ordered week's rest in bed. Regains spirits gradually.

*April 3.* 0.5 cc. vaccine. "Very pleasant reaction." This vaccine was made from a new culture. General condition so improved as to arouse comment of friends.

*April 10.* 1 cc. stock pyocyaneus vaccine—to test patient's psychic reaction. Reports reaction slight and very different; no marked negative phase, no diarrhea.

*April 17.* 1.5 cc. new monilia vaccine. Reports reaction pleasantest yet experienced—like a tonic.

*April 24.* Patient calls to say she thinks she is well now. Has gained 10 pounds in weight.

In the meantime—since February 26—we have been making cultures upon random samples of feces from the pellagra hospital and diarrhea cases at the Memphis General Hospital. Out of 112 cultures from 42 patients we obtained monilia-like cultures twice, both from pellagrins. One of these died four days after the specimen was obtained. This culture came up strong on the third day. Plate culture upon 4 per cent glucose agar 2 produced white round colonies. Culture in Durham tubes gave gas with glucose. Litmus milk showed acid, clot, decoloration, no gas. Hanging drop showed colonies like yeast. All cells were oval; budding was observed. The glucose broth tubes had a pellicle on the 7th day; the medium was not clouded. (Species so far not determined, but decidedly different from the organism isolated from our patient.)

An attempt will be made to get and study further cultures from our patient. She expresses herself as immensely grateful to Dr. Michel and his wonderful work.

## SUMMARY

1. An yeast-like organism has been isolated from the feces of a patient upon whom the diagnosis of sprue was made seven years previously.

2. The killed cultures, prepared by the method of Michel, injected into a 300-gram guinea pig, produces symptoms very similar to those described by Michel for *Monilia psilosis* Ashford (1914).

3. Vaccine prepared from this culture caused symptomatic reactions in the patient which to her were indistinguishable from those resulting from vaccine made in Porto Rico.

4. Control injections of alien vaccine did not evoke such symptoms.

5. Careful adjustment of dosage and spacing of intervals, with some readjustment of habits and diet, resulted in striking improvement in the general condition of the patient.

6. Owing, perhaps, to delay in the study of the cultural characteristics, we have been unable to verify all the postulates of Ashford as to species.

7. Cultures from random patients from the General Hospital and from the pellagra hospital failed to show up any organisms that could be confused with the monilia herein described.

*Note—July 10, 1920:* With the advent of hot weather there was a sharp relapse following overexertion. I found two distinct ulcers in her mouth but was unable to get any monilia in the culture. She had very characteristic morning diarrhea, pale grey and foamy. The first dose of bacterin stopped the diarrhea. Enforced rest restored her usual condition.

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## TO THE MEMBERS OF THE AMERICAN SOCIETY OF TROPICAL MEDICINE

The seventeenth annual meeting of the American Society of Tropical Medicine will be held in Hot Springs, Arkansas, in the fall of 1921, in conjunction with the meeting of the Southern Medical Association. Members who desire to read papers at the meeting are requested to send the titles of their communications to the President or to the Secretary as early as possible.

Physicians who are not members of the Society may be invited to read papers setting forth the results of original observations on subjects connected with Tropical Medicine at the suggestion of a member of the Society and upon approval by the officers. The member suggesting that such an invitation should be extended is requested to have the author submit a summary of the contents of his communication with the request for the issue of the invitation.

Papers read at the meeting will be published in the American Journal of Tropical Medicine.

S. K. Simon,
*Secretary.*

J. M. Swan,
*President.*

# THE COURSE OF MIGRATION OF ASCARIS LARVAE

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Recent investigations by Stewart and others have demonstrated that when eggs of *Ascaris lumbricoides* containing fully formed vermiform embryos are swallowed, they hatch in the intestine and release the embryos which do not immediately settle down, but leave the intestine and pass to the liver, then to the lungs and finally back to the intestine by way of the trachea, esophagus, and stomach. During this journey, which commonly requires about ten days, the larvae not only attain a size much larger than that of the newly hatched worms, but undergo developmental changes. This migration and development can be followed in laboratory animals (guinea-pigs, rabbits, rats and mice), there being no apparent essential difference from that occurring in the pig (experimentally verified in various respects) and presumably (by indirect evidence) in man, except that in the first instance the larvae are unable to continue their development to maturity after returning to the intestine and soon pass out of the body in the feces to perish. In young sheep and goats the larvae after returning to the intestine from the lungs may reach a development well on the way to maturity, so that these animals may be considered to hold an intermediate position, with reference to their suitability as hosts of the adult stage of the parasite, between the less suitable laboratory animals that have been mentioned and the normal host animals (man and pig) in which the worms can develop to fertile maturity. The regular occurrence of this curious migration of Ascaris larvae from the intestine to the lungs and back again to the intestine must be accepted as a well-established fact.

From the facts that have been collected by various investigators with reference to the migrations of Ascaris larvae (Stewart; Ransom and Foster), particularly when these facts are considered in the light of observations that have been made relative to the paths of migration followed by Ancylostoma and Strongyloides larvae in the body (Looss; Fülleborn; and others), it would seem that the most likely path of migration from the intestine to the lungs is the obvious one suggested by Stewart (1917), namely, the portal and pulmonary blood streams. This, however, has not been well verified step by step experimentally so far as shown in available publications. Inasmuch as Yoshida (1919) has expressed certain conclusions from results obtained by him in experimental work that are quite at variance with what on the basis of former knowledge would have been expected, we began last year a new series of experiments bearing on the question of the course of migration of Ascaris larvae. Some of our results have been given in a preliminary communication read at a meeting of the American Society of Zoologists in December, 1920 (Ransom and Cram, 1921). The experiments and observations we have made have clearly demonstrated the passage of the larvae in the portal vein to the liver, thence by the hepatic veins and vena cava to the right side of the heart, from which of course they reach the lungs by the pulmonary arteries. Furthermore we have found that many newly hatched larvae also pass from the intestine to the mesenteric lymph nodes, especially the ileocolic nodes, so that it appears probable that migration to the heart may occur also by way of the lymphatic vessels, without involving the portal circulation, though larvae have not actually been recovered in course of passage along this pathway beyond the mesenteric nodes. Finally we have shown that the larvae are commonly present in recently infected animals in the peripheral lymph nodes where their presence can be reasonably explained only on the assumption that they have been carried there in the systemic circulation. In short, we have been unable to confirm Yoshida's conclusion that the migration of the larvae is effected chiefly by their active burrowing through the tissues of the body, and on the contrary hold to the conclusion that, apart from burrowing for microscopic distances in the intestinal wall, liver, and mesenteric nodes, the principal, if not practically the only, means by which Ascaris larvae reach the lungs from the intestine is by transport in the circulating blood and lymph.

## METHODS

In our experiments we used about 100 animals, mostly guinea-pigs, but also a few rabbits and mice. To infect the animals we used exclusively eggs removed from the uteri of gravid female ascarids obtained from the intestines of swine. The eggs were incubated at room temperature for several weeks in a shallow depth of 2 per cent formalin solution contained in petri dishes. The guinea-pigs and rabbits were infected by placing large quantities of the incubated eggs in the back of the mouth by means of a medicine dropper and causing the animals to swallow. The mice were allowed to eat bread crumbs with which large quantities of Ascaris eggs had been mixed.

At various intervals after infection the guinea-pigs and rabbits were killed by chloroforming unless they had already died from the infection or from other causes, and larvae were looked for in various locations. The mice were killed at certain periods after infection, preserved in toto after skinning, decalcified, and celloidin sections for microscopic examination made across the entire thorax or abdomen. Sections of the heart, liver, and lungs of infected guinea-pigs were also made in various cases after various intervals following infection. These sections were useful in comparison with the examinations that were made of the freshly killed or recently dead animals.

In cases in which examinations were made of the abdominal and pleural cavities, these cavit es were opened carefully to avoid so far as possible the danger of contamination with larvae from the contained viscera and neighboring structures, large blood-vessels, etc. The cavities were washed out with a small quantity of physiological salt solution, about 20 cc. in the case of guinea-pigs, and a correspondingly larger quantity in the case of rabbits; the washings were then centrifuged and the sediment examined under the microscope. Blood was drawn from the portal vein, vena cava and right side of the heart with hypodermic syringes, using small needles, and discharged into centrifuge tubes containing a few drops of 2 per cent sodium citrate solution to prevent coagulation, and then centrifuged. The sediment was examined microscopically for larvae. Blood examinations were not made in the case of animals that died from their infection.

The liver, lungs, lymph nodes, thyroid, etc., were examined by making press preparations of the fresh tissues between thick glass slides, using a Greenough binocular and a low power monocular microscope (16 mm. objective) for the examination. The supplementary examination of fixed and sectioned specimens has already been mentioned.

## RESULTS OF EXPERIMENTS

We shall omit from this paper the detailed records of the history of the numerous animals used in the experiments. Tabular statements, however, are given which show most of the findings that enter into the questions discussed. The findings in cases in which only microscopic sections were examined are not included in the tabular statements. It has seemed desirable to consider our findings under various headings as will appear hereafter in order to simplify their discussion as well as to facilitate their presentation in tabular form. These headings relate to the various organs and locations examined in the experimental animals. Certain organs, such as the spleen, kidneys, pancreas and alimentary tract, were not examined in the present series of experiments, nor were all organs and locations included under the different headings examined in every case. Owing to the difficulty of discovering the larvae, especially when they are still very small, it is far from certain in many instances that they were actually absent when they were not found; consequently, negative results given in the tables mean that the larvae were not found rather than that they were definitely determined to be absent. It should also be noted that the examinations were not always equally thorough. Much more time was spent in some instances than in others in searching for larvae. This search is often very tedious in the case of certain organs and tissues and the discovery of the parasites when they are present in small numbers is frequently the result of luck rather than of industrious endeavor. Wholly negative cases, that is, cases in which no larvae were discovered in any part of the body, are not included in the tabulations. Such cases occasionally occur even among animals examined soon enough after feeding with eggs for larvae still to be present in the body in considerable numbers as judged by other cases.

PORTAL VEIN

Blood was drawn from the portal vein and examined in 18 cases with results shown in table 1.

TABLE 1

| DURATION OF INFECTION | NUMBER OF CASES EXAMINED | NUMBER OF CASES POSITIVE | NUMBER OF LARVAE COUNTED | SIZE OF LARVAE |
|---|---|---|---|---|
| 17–24 hours | 10 | 5 | 6, 9, 10, 18, 437 | 200–275$\mu$ |
| 2 days | 4 | 3 | 1, 3, 19 | 280–310$\mu$ |
| 3 days | 2 | 0 | | |
| 4 days | 1 | 0 | | |
| 5 days | 1 | 0 | | |

From the data given it is evident that larvae are common in the portal vein one and two days after infection (pl. I, fig. 1). Inasmuch as 437 were recovered in one case (seventeen hours after infection) it is clear that the portal vein is an important path of migration from the intestine to the liver. It is also clear that the larvae reach the portal vein soon after hatching. There are two apparent routes by which the larvae may get into the portal vein, after hatching and burrowing into the intestinal wall (text-fig. 2). They may enter venous capillaries and thus directly reach the portal circulation, or they may enter lymphatics, pass to the mesenteric lymph nodes (in which they are commonly present soon after infection), then in the nodes enter venous capillaries and thus less directly reach the portal circulation (text-fig. 5). Which of these routes is the more important has not been determined.

The presence of the larvae in the portal vein was first reported by Ransom and Foster (1920, p. 36), but the findings of the single case in which 2 larvae were recovered two days after infection were not accepted as conclusive owing to the fact that the possibility of contamination was not sufficiently excluded.

## LIVER

The liver was examined in 68 cases with results shown in table 2.

TABLE 2

| DURATION OF INFECTION | NUMBER OF CASES EXAMINED | NUMBER OF CASES POSITIVE | LARVAE RECORDED PRESENT IN | LARVAE NUMEROUS IN | LARVAE VERY NUMEROUS IN | SIZE OF LARVAE |
|---|---|---|---|---|---|---|
| 17–24 hours | 15 | 13 | 3 | 6 | 4 | 210–320$\mu$ |
| 2 days | 7 | 7 | 2 | 4 | 1 | 315$\mu$ |
| 3 days | 5 | 5 | 3 | 1 | 1 | 215$\mu$ |
| 4 days | 6 | 6 | 5 | 1 | | 315$\mu$ |
| 5 days | 5 | 4 | 4 | | | 200–340$\mu$ |
| 6 days | 6 | 2 | 1 | 1 | | 320–560$\mu$ |
| 6–7 days | 5 | 1 | 1 | | | 600$\mu$ |
| 7 days | 5 | 1 | 1 | | | ? |
| 8 days | 7 | 0 | | | | |
| 9 days | 4 | 0 | | | | |
| 10 days | 2 | 0 | | | | |
| 12 days | 1 | 0 | | | | |

The larvae become numerous in the liver within twenty-four hours after infection. They are brought to this organ in the portal circulation. We have found them in interlobular veins in sections of the liver of a guinea-pig and of a mouse seventeen and eighteen hours after infection (pl. I, figs. 2, 3). In numerous sections of the livers of mice and guinea pigs killed seventeen hours to two days after infection, we have failed to find larvae in the biliary ducts. The newly hatched larvae apparently not only find it necessary to escape promptly from the lumen of the digestive tract to avoid the action of the digestive fluids or in search of more oxygen, but also probably are not inclined, or are unable, to move against a current, which if true could be taken as an explanation of their failure to use the gall duct as a pathway from the intestine to the liver.

Many of the larvae are evidently stopped in the liver by the capillaries which act as a sieve but others pass through promptly (text-fig. 3). The larvae that accumulate in the liver commonly do not show much increase in size during the first four days after infection, though many of them are considerably larger by the fourth day, reaching a maximum of about 600$\mu$ in length, four to six days after infection. After the fifth day they are usually so scarce as to be found with difficulty, and often none are found even after many repeated examinations. In the present series of experiments no larvae were found in the liver later than seven days after infection.

Sections of the liver show that the larvae pass across the lobules from the interlobular to the central or intralobular veins; we have found them in sections not only in the interlobular veins (seventeen and eighteen hours after infection), but also in the intralobular veins (seventeen and eighteen hours, two days, three days and twenty-four to seventy-two hours after infection) and large branches of the hepatic veins (seventeen hours and three days after infection), as well as in the zone between the interlobular and intralobular vessels (seventeen and eighteen hours, two days, three days, twenty-four to seventy-two hours, four days, five days, and seven days after infection); (compare text-fig. 3, pl. I, figs. 4-6).

## VENA CAVA

Blood was drawn from the vena cava and examined in 33 cases with results shown in table 3. (See next page.)

That the larvae pass from the liver to the heart in the vena cava and that this is an important route of migration are amply demonstrated by the data shown in the table, in accord with what would be expected from anatomical and physiological considerations as to the circulation of the blood. Large numbers of larvae are passing along the vena cava within twenty-four hours after infection, and larvae may still be recovered from this vein as late as six or seven days after infection. During the latter part of the first week after infection larger larvae are found than during the first few days, corresponding with the growth of the larvae in the liver.

TABLE 3

| DURATION OF INFECTION | NUMBER OF CASES EXAMINED | NUMBER OF CASES POSITIVE | NUMBER OF LARVAE COUNTED | SIZE OF LARVAE |
|---|---|---|---|---|
| 17–24 hours | 7 | 7 | 1, 1, 7, 53, 54, 101, 103 | 275–290$\mu$ |
| 2 days | 5 | 5 | 3, 13, 16, 23, 45 | 310–315$\mu$ |
| 3 days | 3 | 2 | 2, 6 | 330$\mu$ |
| 4 days | 4 | 3 | 2, 4, 9 | 470–595$\mu$ |
| 5 days | 2 | 1 | 21 | 480$\mu$ |
| 6 days | 1 | 0 | | |
| 6–7 days | 1 | 1 | 2 | 535$\mu$ |

TABLE 4

| DURATION OF INFECTION | NUMBER OF CASES EXAMINED | NUMBER OF CASES POSITIVE | NUMBER OF LARVAE COUNTED | SIZE OF LARVAE |
|---|---|---|---|---|
| 17–24 hours | 6 | 3 | 1, 38, 322 | 290–300$\mu$ |
| 2 days | 4 | 2 | 24, 39 | 310$\mu$ |
| 3 days | 2 | 0 | | |
| 4 days | 2 | 0 | | |
| 5 days | 2 | 1 | 18 | 340–420$\mu$ |
| 6 days | 2 | 0 | | |

TABLE 5

| DURATION OF INFECTION | NUMBER OF CASES EXAMINED | NUMBER OF CASES POSITIVE | NUMBER OF CASES LARVAE RECORDED PRESENT | NUMBER OF CASES LARVAE NUMEROUS | NUMBER OF CASES LARVAE VERY NUMEROUS | SIZE OF LARVAE |
|---|---|---|---|---|---|---|
| 17–24 hours | 11 | 2 | 2 | | | |
| 2 days | 7 | 2 | 2 | | | |
| 3 days | 5 | 3 | 3 | | | 250$\mu$ |
| 4 days | 6 | 5 | 4 | | 1 | |
| 5 days | 5 | 5 | 2 | 1 | 2 | 250 –640$\mu$ |
| 6 days | 6 | 6 | 1 | 3 | 2 | 280$\mu$–1 mm. |
| 6–7 days | 5 | 5 | 2 | 3 | | 600 –860$\mu$ |
| 7 days | 5 | 5 | 1 | 3 | 1 | 516 –825$\mu$ |
| 8 days | 7 | .7 | 1 | 3 | 3 | 600$\mu$–1.7 mm. |
| 9 days | 4 | 4 | | 4 | | 560$\mu$–1.7 mm. |
| 10 days | 4 | 4 | | 3 | 1 | 860$\mu$–1.7 mm. |
| 11 days | 2 | 2 | 2 | | | |
| 12 days | 1 | 1 | 1 | | | 1.7 mm. |
| 19 days | 1 | 1 | 1 | | | 1.1 mm. |
| 30 days | 1 | 0 | | | | |

## HEART (RIGHT SIDE)

Blood was drawn from the right side of the heart and examined in 18 cases with results shown in table 4. (See opposite page.)

The recovery of larvae from the right side of the heart provides further evidence of the carriage of the larvae in the circulation. They have been found not only in blood drawn from the heart seventeen to twenty-four hours, two days and five days after infection, but also in sections, in one case in the right ventricle seventeen hours after infection (pl. II, fig. 7). We have not looked for them in the left side of the heart except in sections, which have been negative. From the heart the larvae naturally pass to the lungs in the pulmonary arteries. Ransom and Foster (1920, p. 36) found a single larva in blood drawn from the pulmonary artery of a guinea-pig three days after infection, but, owing to the fact that the possibility of contamination was not altogether excluded, this finding was not accepted as conclusive. It is conceivable that in cases in which the foramen ovale is imperfectly closed some of the larvae might pass from the right to the left auricle and thus be distributed in the systemic circulation without passing through the lungs (text-fig. 1, *F.o.*).

## LUNGS

The lungs were examined in 70 cases with the results shown in table 5. (See opposite page.)

From the data given it is seen that the larvae are likely not to be found in the lungs in examinations made during the first few days after infection, though they have been discovered as early as seventeen hours after infection (pl. II, fig. 8). During the first few days however, the larvae are difficult to find, not only because they are still small, but because they are actually scarcer than they are later. This is evident from sections as well as from press preparations of fresh lungs. From four days until ten or twelve days after infection they can be found in the lungs almost invariably in animals that have swallowed large numbers of eggs, and are particularly numerous six to ten days after infection. As early as six days after infection some of the larvae in

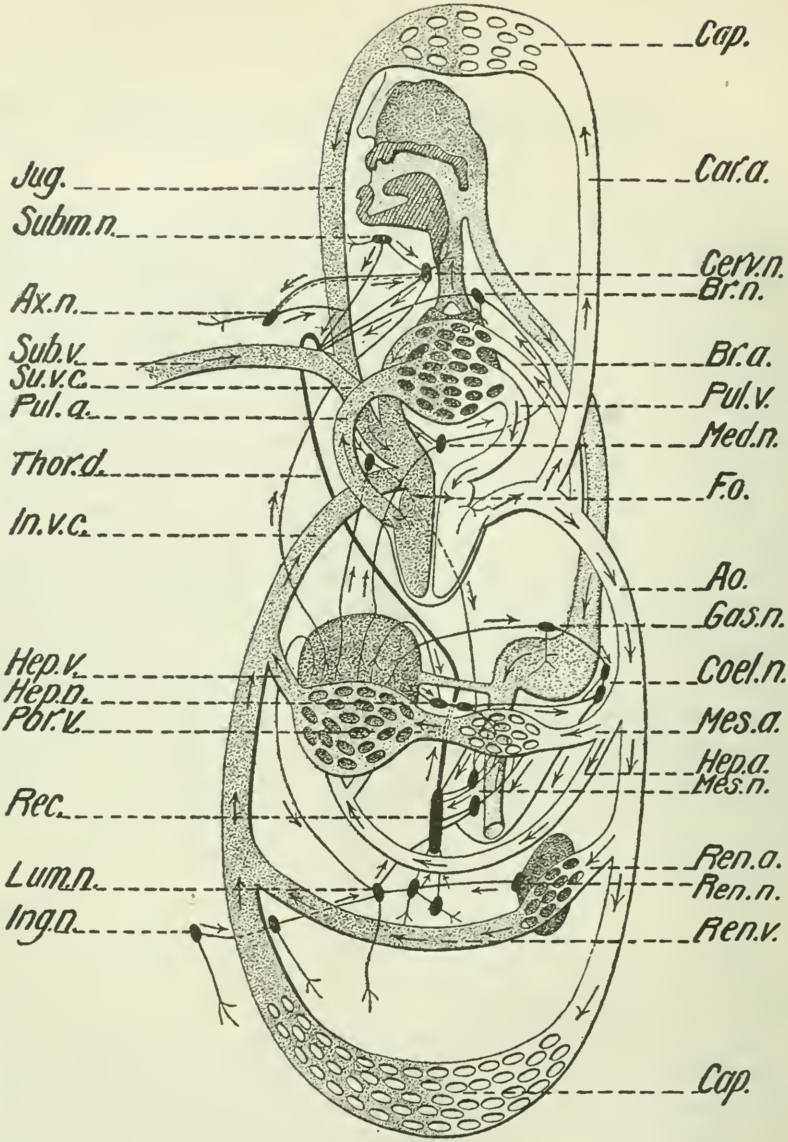


Fig. 1. Scheme of Circulation

Arrows showing direction of blood and lymph flow and paths of migration of Ascaris larvae, including both theoretically possible and proved paths. For explanation of abbreviations see footnote on opposite page.[1]

[1] *Ao.*, aorta; *Ax.n.*, axillary nodes; *Br.a.*, bronchial artery; *Br.n.*, bronchial nodes; *Cap.*, peripheral capillaries; *Car.a.*, carotid artery; *Cerv.n.*, cervical nodes; *Coel.n.*, coeliac nodes; *F.o.*, unclosed foramen ovale; *Gas.n.*, gastric nodes; *Hep.a.*, hepatic artery; *Hep.n.*, hepatic nodes; *Hep.v.*, hepatic vein; *In.v.c.*, inferior vena cava; *Ing.n.*, inguinal and iliac nodes; *Jug.*, jugular vein; *Lum.n.*, lumbar nodes; *Med.n.*, mediastinal nodes; *Mes.a.*, mesenteric artery; *Mes.n.*, mesenteric nodes; *Por.v.*, portal vein; *Pul.a.*, pulmonary artery; *Pul.v.*, pulmonary vein; *Rec.*, receptaculum chyli; *Ren.a.*, renal artery; *Ren.n.*, renal nodes; *Ren.v.*, renal vein; *Su.v.c.*, superior vena cava; *Sub.v.*, subclavian vein; *Subm.n.*, submental or supra-hyoid nodes; *Thor.d.*, thoracic duct.

the lungs may reach a size (about 1 mm.) commonly observed among those migrating to the intestine by way of the trachea and esophagus. Larvae of the usual maximum length attained in the lungs (1.7 mm.) may be observed seven days after infection. Some of the larvae that reach the lungs, and of course all of those arriving the first few days after infection, are no larger or but little larger than when first hatched, but others have already undergone considerable growth (up to 595$\mu$ in length, judging from the maximum observed length of larvae recovered from the vena cava).

As already noted, the larvae in the lungs are obviously brought there from the right side of the heart in the pulmonary arteries. As in the liver the capillaries act as a sieve and prevent many of the larvae from continuing their journey with the circulating blood. Those that are stopped soon pass into the alveoli where they have been found in sections as early as seventeen hours after infection. We have also found them in small blood vessels (?arteries or veins) in sections of the lungs of a mouse provided with food heavily laden with Ascaris eggs from seventy-two until twenty-four hours before it was killed (pl. II, fig. 9). In view of the scarcity of larvae in the lungs during the first few days after infection, it seems probable that many of them being still of small size are not stopped in the lungs but force their way or are forced through the capillaries and return with the circulation to the heart (text-figs. 1, 4). Whether larvae much larger than when newly hatched can thus return to the lungs from the heart is less certain. Fülleborn (1914) has presented evidence tending to show that larvae of considerable size, such as those of Ancylostoma, may return from the lungs to the heart, although it is possible that the facts observed by Fülleborn, as noted elsewhere, trace back to the passage of larvae from the right to the left side of the heart through an unclosed foramen ovale.

The migration of the larvae from the lungs to the intestine through the trachea and esophagus has been discussed elsewhere (Stewart; Ransom and Foster; Yoshida) and need not be specially considered here. Sufficient to say that by eleven or twelve days after infection most of the larvae have moved on into the intestine, and are noticeably scarcer in the lungs than on preceding days. This statement as to relative scarcity however, should be qualified by the statement that the most heavily infested animals usually die earlier than eleven days after infection.

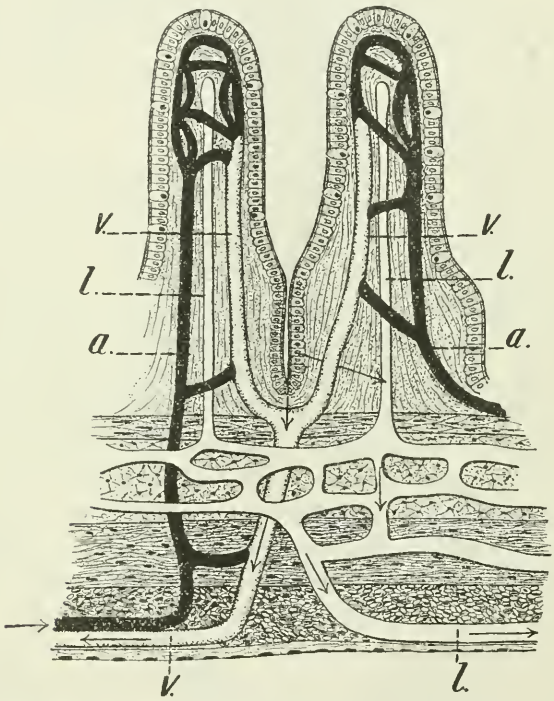


FIG. 2. CROSS SECTION THROUGH WALL OF SMALL INTESTINE (DIAGRAMMATIC)

Arrows indicate direction of blood and lymph flow, and paths presumably followed by Ascaris larvae. *a.*, *a.*, arterial capillaries; *l.*, *l.*, lymph vessels carrying lymph and larvae to mesenteric nodes; *v.*, *v.*, venous capillaries carrying blood and larvae to portal vein.

Ascaris larvae perhaps require a copious supply of oxygen to insure their growth during early stages of development and this condition is fulfilled in the lungs. This would explain the rapid growth of the larvae in the lungs as compared with the slower growth apparent in the case of larvae in other locations, and it may have a bearing on the failure of many larvae in other locations to grow beyond their original size, or to reach commonly the size attained by those that get to the lungs. Fülleborn (1914) has stated that Strongyloides larvae fed to dogs appear regularly to die in the stomach or intestine, unless they save themselves by burrowing into the visceral wall and reaching the circulation. He would explain their death in such cases as probably resulting from a lack of oxygen. According to this view the larvae in passing through the lungs in cases of percutaneous infection become biologically altered so that they are able to continue their existence on reaching the intestine, not succumbing in the stomach or intestine, as do those that enter the body through the mouth. According to Fülleborn, Ancylostoma larvae are more resistant to a lack of oxygen than Strongyloides larvae. In an earlier paper, Fülleborn and Schilling-Torgau (1911) state that Strongyloides larvae after passing through the lungs are apparently better able to withstand the digestive juices than before passing through the lungs. With reference to Ancylostoma larvae, Miyagawa (1916) has observed that after passing through the lungs the larvae appear to be more resistant to the action of human gastric juice than before their passage through the lungs, as shown by experiments in vitro.

In the case of Ascaris larvae, not merely their passage through the lungs but also a certain amount of growth and development appears necessary to enable them to withstand prolonged action of artificial gastric juice. We have placed larvae of various sizes taken from the lungs of guinea pigs into an artificial gastric juice (scale pepsin (U. S. P.) 2.5 grams, sodium chlorid 2 grams, hydrochloric acid (1.19 specific gravity) 10 cc., water 1000 cc.) and kept them in this fluid at a temperature of 35°C. After three hours all larvae 800$\mu$ long or less were dead, while those 1 mm. or more in length were mostly all alive and active. After twenty hours in the warm fluid some of the latter were still alive. The results of these experiments show that Ascaris larvae from the lung 1 mm. or more long are highly resistant to the action of a digestive fluid, whereas smaller larvae from the lungs up to at least 800$\mu$ in length die in less than three hours. In physiological salt solution under the same conditions small (550$\mu$ long) as well as large larvae survive, even after twenty hours' exposure.

MESENTERIC LYMPH NODES

Ileocolic lymph nodes were examined in 18 cases, in some of which other mesenteric nodes also were examined. The results are shown in table 6.

The findings as to the presence of larvae in the mesenteric lymph nodes show that large numbers are collected by these nodes beginning within twenty-four hours after infection (pl. II, fig. 12). In guinea-pigs (observations not made on other animals) more larvae go to the ileocolic than to other mesenteric nodes. Presumably the larvae reach the lymph nodes in question as a result

TABLE 6

| DURATION OF INFECTION | NUMBER OF CASES EXAMINED | NUMBER OF CASES POSITIVE | SIZE OF LARVAE | REMARKS |
|---|---|---|---|---|
| 20–24 hours | 4 | 4 | 210–320$\mu$ | Numerous especially in ileocolic |
| 3 days | 2 | 2 | 225–300$\mu$ | Numerous especially in ileocolic |
| 5 days | 3 | 3 | 240–500$\mu$ | Numerous in 2 cases; some dead, some alive |
| 8 days | 2 | 2 | 400–500$\mu$ | Two larvae in 1 case, 1 in the other (?dead or alive) |
| 9 days..... | 1 | 1 | 560$\mu$ | One larva (? dead or alive) in ileocolic |
| 10 days | 2 | 1 | 800$\mu$ | One larva (? dead or alive) in ileocolic |
| 11 days | 1 | 0 | | |
| 12 days | 1 | 1 | 720$\mu$ | One larva (dead) in ileocolic |
| 19 days | 2 | 0 | | |

of entering the lymphatics in the wall of the intestine that drain into these nodes (text-figs. 2, 5). In fact Fülleborn (1920), in a recent paper, states that he has found the larvae in lymphatics in the intestinal wall as well as in the mesenteric lymph nodes. Many of the larvae die in the nodes without progressing further, as in cases examined five days after infection many dead as well as living larvae have been seen. They are still commonly numerous five days after infection, but in each of 2 cases examined eight days after infection were very scarce, and were also rare in cases examined nine to twelve days after infection, and absent in 2 cases examined nineteen days after infection. They evidently increase in size in the nodes, as large numbers approaching $500\mu$ in length have been observed five days after infection. Still larger larvae have been observed later than five days after infection (largest $800\mu$), but in these cases only a single larva was found and the possibility is not excluded that the larvae in these cases were brought in the systemic circulation and had already made their growth before their arrival.

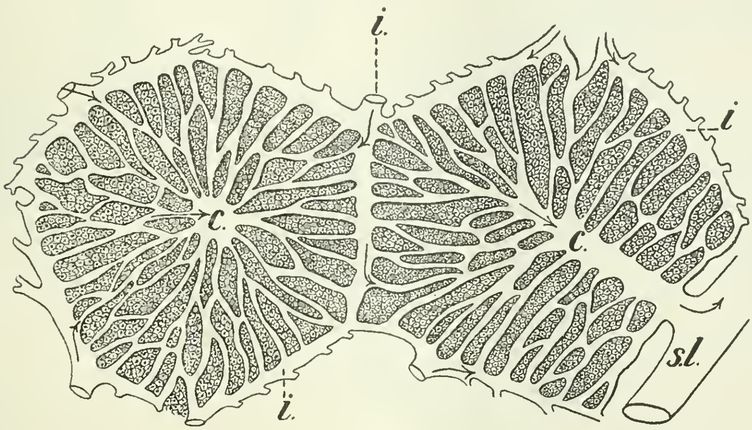


FIG. 3. TWO LOBULES OF LIVER, CENTRAL VEIN IN ONE CUT ACROSS, IN OTHER CUT LONGITUDINALLY (DIAGRAMMATIC)

Arrows indicate direction of blood flow and demonstrated paths of migration of Ascaris larvae. *c.*, *c.*, central or intralobular veins; *i.*, *i.*, interlobular veins bringing blood and larvae to the lobules from the portal vein and communicating by a capillary plexus with the central veins; *s.l.*, sublobular vein carrying blood and larvae from the central veins to a hepatic vein. (After Schäfer, slightly modified.)

From a comparison of the findings in various cases it seems evident that many of the larvae that enter the mesenteric nodes continue their migrations. Some perhaps enter the abdominal cavity, others perhaps pass into blood capillaries in the nodes and then go to the liver in the portal circulation (text fig. 5, *v.*), and others, as a third alternative (text fig. 5, *e. l.*), perhaps follow the lymphatics to the receptaculum chyli and thence by way of the thoracic duct pass to the right side of the heart.

PERIPHERAL LYMPH NODES, THYROID AND THYMUS

Lymph nodes outside the abdominal and thoracic cavities were examined in 25 cases in some of which, rarely with positive results, the thyroid or thymus or both were also examined. The results are shown in table 7.

TABLE 7

| DURATION OF INFECTION | NUMBER OF CASES EXAMINED | NUMBER OF CASES POSITIVE | NUMBER OF LIVING LARVAE | SIZE | NUMBER OF DEAD LARVAE | SIZE | NUMBER OF LARVAE ? ALIVE OR ? DEAD | SIZE |
|---|---|---|---|---|---|---|---|---|
| 20–24 hours | 4 | 1* | | | | | 1 | 250μ |
| 3 days | 2 | 2 | 0,1 | 280μ | | | 2, 7† | 240–260μ |
| 5 days | 3 | 2 | 7‡, 2 | 240–480μ | 6§, 3‡ | 200–560μ | 1, 1 | 220–320μ |
| 6–7 days | 4 | 4 | | | | | 6, 1, 1, 6‡ | 240–640μ |
| 8 days | 2 | 1 | | | | | 6 | 480–640μ |
| 9 days | 1 | 0 | | | | | | |
| 10 days | 3 | 2 | | | 4**, 0 | 600–700μ | 0, 1 | 640μ |
| 11 days | 2 | 1 | | | 1 | 1.4 mm. | | |
| 12 days | 1 | 1 | | | | | 1 | 840μ |
| 19 days | 2 | 1†† | | | 3 | 760μ | | |
| 30 days | 1 | 1 | 1 | 1.2 mm. | | | | |

* Another guinea pig in this group had 2 larvae (? alive or dead) 240μ long in a bronchial node.

† One of these larvae was found in the thymus.

‡ One of these larvae was found in the thyroid.

§ Two of these larvae were found in the thyroid.

** The guinea pig in which these larvae were found in the prescapular nodes had also 2 larvae (? dead or alive) 640μ long in a bronchial node.

†† This guinea pig also had a dead encapsuled larva 1.2 mm. long in a bronchial node, and the other guinea pig with negative peripheral nodes, thyroid and thymus had a dead encapsuled larva 1.2 mm. long in a bronchial node.

The data given in the above table show clearly that Ascaris larvae commonly reach the systemic blood vessels and are distributed to various parts of the body, apparently after passing the pulmonary capillaries, though it may be possible that in some cases they pass over from the right to the left side of the heart through an unclosed foramen ovale (text-fig. 1). According to Morris's text book of anatomy (second edition revised, 1900) the upper part of the foramen ovale is unclosed in the adult human being in 1 out of 5 cases. Unfortunately, in our experiments on guinea pigs we did not take note of the condition of the foramen ovale and we have not seen any statements as to the persistence of an open foramen in guinea-pigs after birth. Recently, however, in a guinea-pig killed eight days after infection we have found 2 Ascaris larvae in a deep cervical lymph node, one of which was alive (600 by 25$\mu$), the other dead (800 by 35$\mu$). The foramen ovale in this animal was closed. Obviously the presence of the larvae in superficial lymph nodes can not reasonably

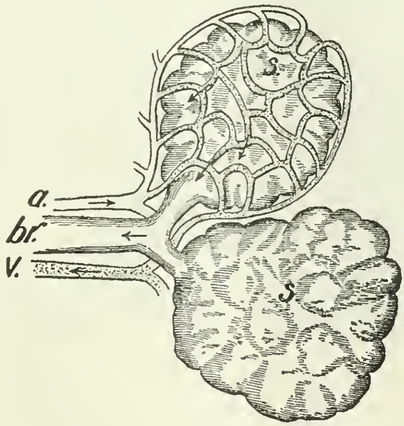


Fig 4. Air Sacs and Terminal Bronchus with Blood Vessels (Diagrammatic)

Arrows indicate direction of blood flow and course of migration of Ascaris larvae. *a.*, branch of pulmonary artery breaking up into a capillary plexus surrounding an air sac; *br.*, terminal bronchus; *s.*, *s.*, air sacs; *v.*, branch of pulmonary vein. Larvae carried from the heart in the pulmonary artery may pass across the capillary plexus and be returned to the heart by the pulmonary vein, or leave the blood vessels and pass into the air sacs, finally migrating out of the lungs by way of the air passages. (After Davison).

be accounted for by assuming that they migrated there against the flow of the lymph current and past the numerous valves of the lymphatics (text-fig. 1), or that they reached the nodes (or thyroid or thymus), in which they have been found, by actively burrowing their way through the tissues, especially in cases such as that in which a larva was found twenty-four hours after infection in a lymph node beneath the chin (submental or suprahyoid). The presence of larvae in the spleen, kidney and other viscera not in the usual course of migration, in which they have been encountered by different observers, in our opinion is logically explained by their carriage to these organs in the systemic circulation (text-fig. 1), just as in the case of those found in peripheral lymph nodes, and it is not necessary nor justifiable

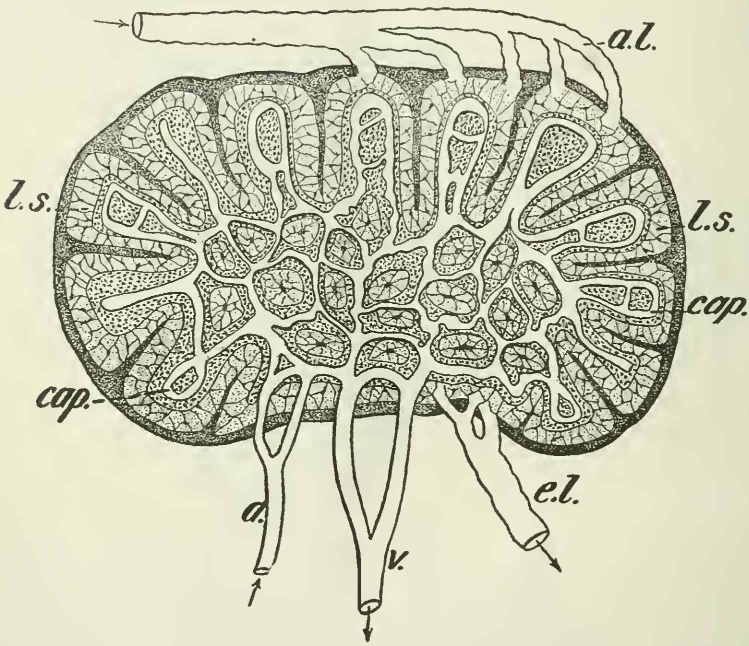


Fig. 5. Section of Mesenteric Lymph Node (Diagrammatic)

Arrows indicate the direction of the blood and lymph flow and possible paths of migration of Ascaris larvae. *a.*, arteriole entering lymph node and breaking up into a capillary plexus among the lymph sinuses; *a.l.*, afferent lymphatics bringing lymph and larvae from the intestine; *cap.*, capillaries; *e.l.*, efferent lymphatics carrying lymph and larvae to the receptaculum chyli; *l.s.*, lymph sinus; *v.*, venule carrying blood and larvae from the node to the portal vein. (After Sharpey, greatly modified.)

to assume that they penetrate into them from the abdominal cavity. They commonly die rather soon in the lymph nodes; dead ones have been observed as early as five days after infection and they have been found already encapsuled in lymph nodes nineteen days after infection. They may, however, survive for considerable periods as shown by the fact that in one case thirty days after infection a living larva (1.2 mm.) was recovered from a lymph node beneath the chin (submental or suprahyoid).

Apparently the larvae that are located in the peripheral lymph nodes, thyroid and thymus may grow and even reach a size in these locations similar to that attained by larvae in the lungs, as for example, in the case of the one just mentioned (in a submental node.) Our observations however, do not exclude the possibility that the large larvae observed in the locations in question had already made their growth before reaching these locations. There is, however, no doubt that the larvae may undergo some growth in the mesenteric nodes and it is likely that they may do likewise in the peripheral nodes. The largest larva observed in a lymph node was a dead larva 1.4 mm. long found in an inguinal node eleven days after infection.

Fülleborn (1914) has conducted experiments on dogs with the larvae of Ancylostoma and Strongyloides, the results of which indicate that the larvae can reach the intestine in the systemic circulation, and, also, in the case of Strongyloides, the kidneys. Presumably in such cases they are pumped out in the blood from the left side of the heart, to which, according to Fülleborn, they are carried in the pulmonary veins after passing through the pulmonary capillaries (or after penetrating into veins in the lungs of larger size than capillaries), and are transported in the systemic arteries to the intestine, where they are stopped in the capillaries and finally force their way or are forced into the intestinal lumen. Strongyloides larvae presumably reach the kidneys by way of the renal arteries. We may suggest that an imperfectly closed foramen ovale would afford a possible route from the right to the left side of the heart, so that in some cases it would not be necessary from a theoretical standpoint for the larvae to pass the pulmonary capillaries in order to get into the systemic circulation from the right side of the heart (text-fig. 1). Recently Fülleborn (1920; 1921) has recorded the presence of young Ascaris larvae in the kidney and brain of experimental animals and has noted also that larvae taken from the lungs of one animal and injected into the carotid artery of another have been recovered from the lungs of the latter an hour later.

In the case of Ascaris, inasmuch as it has been demonstrated that the larvae are often carried in the systemic circulation to various parts of the body, it is evidently not impossible that some of them may be carried to the intestine and enter its lumen (text-fig. 1). Whether, however, larvae sufficiently developed to withstand the action of the digestive fluids or other conditions in the lumen of the intestine that are evidently unfavorable to young larvae, are actually thus carried to the intestine is questionable.

### ABDOMINAL CAVITY

The abdominal cavity was examined in 66 cases with results shown in table 8.

TABLE 8

| DURATION OF INFECTION | NUMBER OF CASES EXAMINED | NUMBER OF CASES POSITIVE | NUMBER OF LARVAE RECOVERED | SIZE OF LARVAE |
|---|---|---|---|---|
| 17–24 hours | 16 | 0 | | |
| 2 days | 7 | 0 | | |
| 3 days | 4 | 1 | 1 | |
| 4 days | 6 | 1 | few | |
| 5 days | 3 | 1 | 3 | 480$\mu$ |
| 6 days | 6 | 0 | | |
| 6–7 days | 6* | 3* | 1, 4, 5 | 310–600$\mu$ |
| 7 days | 2* | 2* | 1, 1 | 413$\mu$, 585$\mu$ |
| 8 days | 7* | 1* | 2 | 560$\mu$ |
| 9 days | 5* | 2* | 3, 8 | 516–850$\mu$ |
| 10 days | 3* | 1* | 7 | 525$\mu$–1.2 mm. |
| 11 days | 1* | 0 | | |

* Cases thus designated were of animals that died from the infection. Three of the six-day cases died and 3 were killed by chloroforming, but all 6 were negative.

From the data given it seems evident that Ascaris larvae do not commonly occur in the abdominal cavity. Not only were none recovered in any case among 23 guinea-pigs examined one or two days after infection, although they were commonly found in other locations, but there were few found in the abdominal cavity among guinea-pigs examined on later days and then only in a few cases.

Stewart (1921) also failed to find larvae in the abdominal cavity during the first forty-eight hours after infection (3 cases examined), and Fülleborn (1920) notes that in the case of experiments on dogs with dog ascarids he failed to find larvae in the abdominal cavity although the mesenteric nodes were filled with them. Furthermore it should be noted that in our experiments in most of the cases in which the larvae were found the animals had died from the infection and probably in most instances were not examined until at least several hours after death. The observations we have made do not support the conclusion reached by Yoshida (1919) that the newly hatched larvae regularly penetrate the wall of the intestine, enter the abdominal cavity, and then burrow into various abdominal -viscera (liver, spleen, kidneys, pancreas, etc.) or through the diaphragm into the pleural cavity. Not only have we usually failed to find larvae in washings from the abdominal cavity, but in numerous sections of the liver of animals killed at various intervals after infection and in sections of the abdomen of mice (seventeen, and twenty-four to seventy-two hours after infection) we have seen no evidence of the penetration of larvae into the surface of the liver nor have we found them in the abdominal cavity in the mouse sections, although the larvae were common in the liver in the sections in question.

We were careful in our examinations of the abdominal cavity to avoid injury to bloodvessels, intestine, liver, etc., as it was evident that contamination might easily occur from such sources. We presume that Yoshida was equally careful and hence are unable to explain the discrepancy between our findings and those of Yoshida who discovered many larvae in the abdominal cavity of two guinea-pigs killed twenty and twenty-four hours after infection, and varying numbers, in some cases many, in several other guinea pigs killed forty-one to seventy-five hours after infection, the animals having been infected by feeding them Ascaris eggs. Even though our technique was not sufficiently thorough in execution to find larvae in every case in which they may have been present, it seems hardly possible that we should have missed them uniformly in the considerable number of cases killed during the first two days after infection, in which moreover we commonly found larvae in the bloodvessels, liver, heart, etc.

As to those found on later days in our experiments, it is quite possible that they had escaped into the abdominal cavity, not from the intestine but from other sources such as the liver, some of them, perhaps most of them, after the death of the host animal.

### PLEURAL CAVITY

The pleural cavity was examined in 60 cases with results shown in table 9.

TABLE 9

| DURATION OF INFECTION | NUMBER OF CASES EXAMINED | NUMBER OF CASES POSITIVE | NUMBER OF LARVAE RECOVERED | SIZE OF LARVAE |
|---|---|---|---|---|
| 17–24 hours | 13 | 0 | | |
| 2 days | 7 | 0 | | |
| 3 days | 3 | 1 | 1 | |
| 4 days | 6 | 1 | 1 | |
| 5 days | 2 | 1 | 4 | 480μ |
| 6 days | 6 | 3* | 9, 13, 27 | 225–360μ |
| 6–7 days | 6* | 5* | 2, 2, 13, 19, 35 | 516–775μ |
| 7 days | 2* | 2* | 5, 7 | 300–635μ |
| 8 days | 7* | 7* | 2, 2, 3, 4, 5, 12, 14 | 400μ–1 mm. |
| 9 days | 4* | 4* | 1, 1, 3, 7 | 600–850μ |
| 10 days | 3* | 2* | 6, 15 | 410μ–1.4 mm. |
| 11 days | 1* | 0 | | |

* Cases thus designated are of animals that died from the infection. Three of the six-day cases that were killed by chloroforming were negative.

As in the case of examinations of the abdominal cavity it will be observed from the data given in the above table that during the first two days after infection we failed to recover any larvae from the pleural cavity in a considerable number (20) of cases examined, and that among a smaller number of cases examined three, four and five days after infection, we encountered larvae in the pleural cavity only rarely and in very small numbers. In animals examined six to ten days after infection, however, we nearly always discovered larvae in the pleural cavity, sometimes in rather large numbers (up to 35). All of the animals examined six to ten days after infection, except 3 out of 6 that were examined six days after infection, died from the infection, and were not always promptly examined, whereas those examined earlier than six days after infection were chloroformed and examined promptly after death. The pleural cavity in the three that were chloroformed six days after infection was negative. This difference may be of importance in relation to the occurrence of larvae in the pleural cavity of the animals examined in our experiments, earlier and later, respectively, than six days after infection. Furthermore it is of interest to note that in the pleural cavity of animals dying six to ten days after infection, in addition to larvae, there were numerous shreds of the pleural membrane. In these cases therefore it seems not unlikely that the larvae present in the pleural cavity had escaped into the cavity from the lungs, many of them perhaps after the death of the host animal. So far as our observations go, there is no evidence that the larvae in the pleural cavity had reached this location as a result of burrowing through the diaphragm from the abdominal cavity. Also, in numerous sections examined we have found no indication of the penetration of larvae into the lungs from its surface, nor in sections of the entire thorax of several mice killed seventeen hours, and twenty-four to seventy-two hours after infection, have we discovered larvae in the pleural cavity.

Stewart (1921) failed to find larvae in the pleural cavity during the first forty-eight hours after infection (3 cases examined).

Yoshida (1919) found larvae in the pleural cavity in small numbers in 8 out of 10 guinea-pigs killed and examined twenty to seventy-five hours after feeding with Ascaris eggs, the largest number counted being 11. Also in 4 out of 9 cases in which he injected into the abdominal cavity larvae isolated from the livers of other guinea-pigs killed forty-eight to seventy-five hours after feeding with Ascaris eggs, he found in the pleural cavity, when the animals died or were killed after a lapse of less than twenty hours up to sixty-six hours after injection, a few larvae. He also found larvae, sometimes many, in such cases in the lungs. Likewise he found a few in the lungs in two cases in which guinea-pigs had received injections of larvae into the pleural cavity and were examined after death which occurred in less than twenty hours. He states that the appearance of larvae in the pleural cavity after injection into the abdominal cavity clearly proves their direct migration from the abdominal cavity and though admitting that "some larvae in the abdominal cavity might have reached the lungs, passing through the liver and heart by the way of a bloodvessel" he believes that the majority "have proceeded directly to the lungs, piercing through the diaphragm." Apparently Yoshida did not examine the blood of his experimental animals. He also expresses the following conclusions:

> Larvae hatched out in the intestine immediately proceed to the abdominal cavity piercing through the intestinal wall. Larvae in the cavity may wander everywhere freely, that is, some to the liver, spleen, pancreas, or kidneys in the cavity and others piercing the diaphragm to enter the pleural cavity, finally penetrating into the lung from its surface. Thus it is believed that the larvae migrate in every direction, boring through various organs or tissues by means of their own power of piercing, but not by the way of bloodvessels. . . . . Some larvae in these organs [liver, spleen, etc.] may go back in the abdominal cavity and proceed to the pleural cavity to invade the lungs, the important place for their further development, and those remaining probably perish in these organs.

We do not consider that the results of Yoshida's experiments necessarily lead to the principal conclusions that he has reached, especially when they are considered in the light of the observations we have made. It may be admitted as a possibility that larvae occasionally follow the paths of migration that he has indicated, but it seems certain that the important path of migration is that by way of the circulation, perhaps in the lymphatics as well as in the bloodvessels. At least in our experiments the larvae have been traced in large numbers, step by step, in the portal vein, liver, vena cava and right side of the heart on their way from the intestine to the lungs, in addition to which the findings with reference to the occurrence of larvae in the mesenteric lymph nodes indicate that some may pass from the intestine to the receptaculum chyli and thence to the heart in the lymphatic system.

## CONCLUSIONS

Assuming that in guinea-pigs and other small mammals the behavior of Ascaris larvae up to the time of their return to the small intestine is essentially the same as in their normal hosts, the following conclusions may be drawn as to their migrations.

After hatching, the larvae burrow into the wall of the small intestine and enter either lymphatic vessels or venules.

In the lymphatics they are carried to the mesenteric lymph nodes, especially the ileocolic nodes in the case of the guinea-pig. In heavily infected animals they are numerous in these nodes, one to five days after infection, and within five days may attain about double their original length. Some die but others continue their migrations. Those that escape from the mesenteric nodes have three apparent routes of migration open. (1) They may burrow out into the abdominal cavity. (2) They may enter blood capillaries in the nodes and pass to the liver in the portal circulation. (3) They may pass in the lymphatic vessels to the receptaculum chyli and thence to the right side of the heart. The two last alternatives appear the most probable but none of the three has been actually demonstrated.

Larvae appear in the portal vein at least as early as seventeen hours after infection and may still be passing to the liver two days after infection, reaching the portal vein either as a result of entering venules in the intestinal wall or as a result of entering lymphatic vessels in the intestinal wall, in the latter case having to pass through the mesenteric lymph nodes.

Larvae carried to the liver in the portal circulation are distributed by the interlobular veins. They pass through the capillary plexus between the interlobular vessels and the central or intralobular vessels, enter the latter and are carried into the hepatic veins. They may pass rapidly through the liver or be delayed in their passage. They may be found in the interlobular and intralobular vessels, in the zone between these vessels, and in the hepatic veins as early as seventeen hours after infection. Those that are delayed in the liver undergo growth and development, and may attain a length of $600\mu$ four to six days after infection.

Leaving the liver by the hepatic veins the larvae are carried to the right side of the heart in the vena cava. They may be recovered from the vena cava as early as seventeen hours and as late as six or seven days after infection, their size corresponding with the growth undergone during their stay in the liver. They may be recovered from the right side of the heart as early as seventeen hours and as late as five days after infection, and no doubt may still be passing from the liver to the heart on later days.

From the right side of the heart the larvae obviously are carried in the pulmonary arteries to the lungs where they are stopped by the capillaries. They may be found in the lungs as early as seventeen hours after infection. In the lungs they enter the alveoli, and after further development and growth to a length ranging from about 1 mm. to about 2 mm. or a little more, commonly to a length of about 1.5 mm., they pass on into the intestine by way of the trachea, esophagus and stomach. Some larvae apparently are not delayed in the lungs more than a short time but return to the heart in the pulmonary veins, and are then distributed to various parts of the body in the systemic circulation.

Larvae may be found in the peripheral lymph nodes as early as twenty-four hours after infection, which location obviously they could not have reached in so short a time unless brought there in the systemic circulation, and may be found still alive in these nodes as late as thirty days after infection. Dead larvae may be found in the lymph nodes as early as five days after infection and may be found already encapsuled as early as nineteen days after infection. In the peripheral lymph nodes (and in the thyroid and thymus) the larvae may either undergo growth or be brought to such locations after attaining a considerable size, larvae up to a length of 1.4 mm. having been recovered in the peripheral lymph nodes. It is possible that larvae may sometimes reach the lymph nodes without passing through the pulmonary circulation; in cases in which there is an unclosed foramen ovale it is conceivable that they may pass directly from the right to the left side of the heart and thus enter the systemic circulation without passing through the lungs.

During the early days of infection larvae occur rarely and in relatively small numbers in the abdominal and pleural cavities of animals killed by chloroform, and more commonly and in larger numbers five to ten days after infection in the abdominal and pleural cavities of animals that have died from the infection.

Our observations do not support the conclusions of Yoshida that migration of the larvae from the intestine to the lungs is an active one on the part of the larvae, effected by their burrowing through the wall of the intestine into the abdominal cavity. then into the pleural cavity through the diaphragm and finally into the lungs from their surface. Such a migration, if it occurs at all, must be very rare compared with the regular course of migration.

On the other hand it has been clearly shown that the larvae are carried to the lungs in the blood stream by way of the portal and pulmonary circulations, and there are indications that they may also reach the right side of the heart from the intestine by way of the mesenteric lymph nodes and lymph vessels without passing through the liver.

In vitro Ascaris larvae 1 mm. or more in length isolated from the lungs of infested animals commonly survive the action of artificial gastric juice at 35°C. during three hours or more. Larvae less than 800$\mu$ in length die under these conditions within three hours. Small as well as large larvae survive in physiological salt solution kept at 35°C. for a period of three hours, and even for as long as twenty hours.

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## PLATE I

PHOTOMICROGRAPHS × 150

Fig. 1. Ascaris larva in blood smear from portal vein of guinea pig killed seventeen hours after feeding Ascaris eggs.

Fig. 2. Section of liver of guinea pig killed seventeen hours after feeding Ascaris eggs. Larva in interlobular vein.

Fig. 3. Section of liver of mouse killed eighteen hours after feeding Ascaris eggs. Larva in interlobular vein.

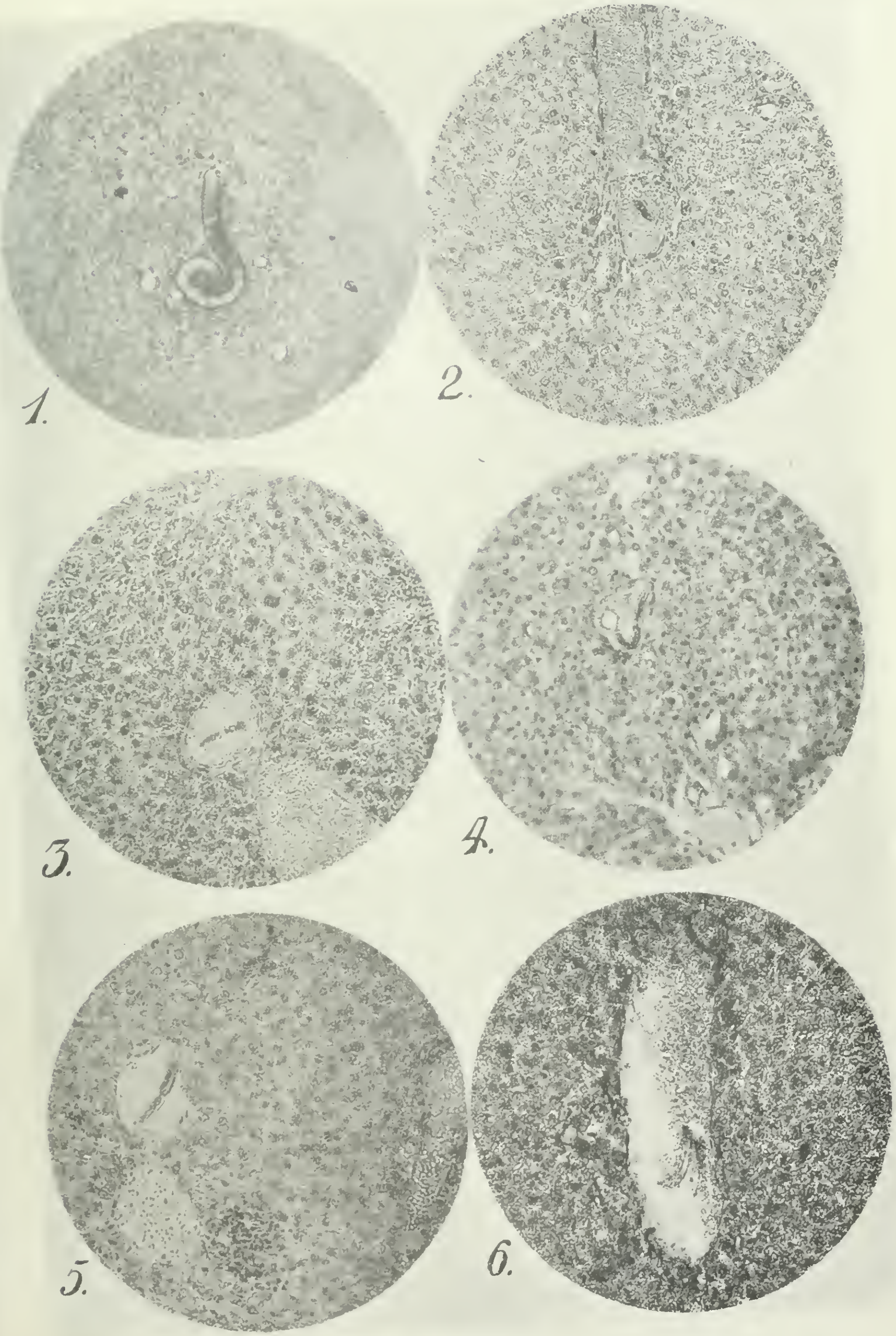
Fig 4. Section of liver of guinea pig killed forty-one hours after feeding Ascaris eggs. Larva in lobule about midway between an interlobular vein (below) and a central or intralobular vein (above).

Fig. 5. Section of liver of mouse killed twenty-four to seventy-two hours after infection (repeated feedings with Ascaris eggs). Larva in central or intralobular vein. Another larva at top of figure. Interlobular vein at right. Mass of leucocytes beside the central vein near bottom of figure.

Fig. 6. Section of liver of guinea pig killed seventeen hours after feeding Ascaris eggs. Larva in small branch of hepatic vein.

COURSE OF MIGRATION OF ASCARIS LARVAE

B. H. RANSOM AND E. B. CRAM



## PLATE II

PHOTOMICROGRAPHS × 150

Fig. 7. Larva amid blood in section of heart (right ventricle) of guinea-pig killed seventeen hours after feeding Ascaris eggs.

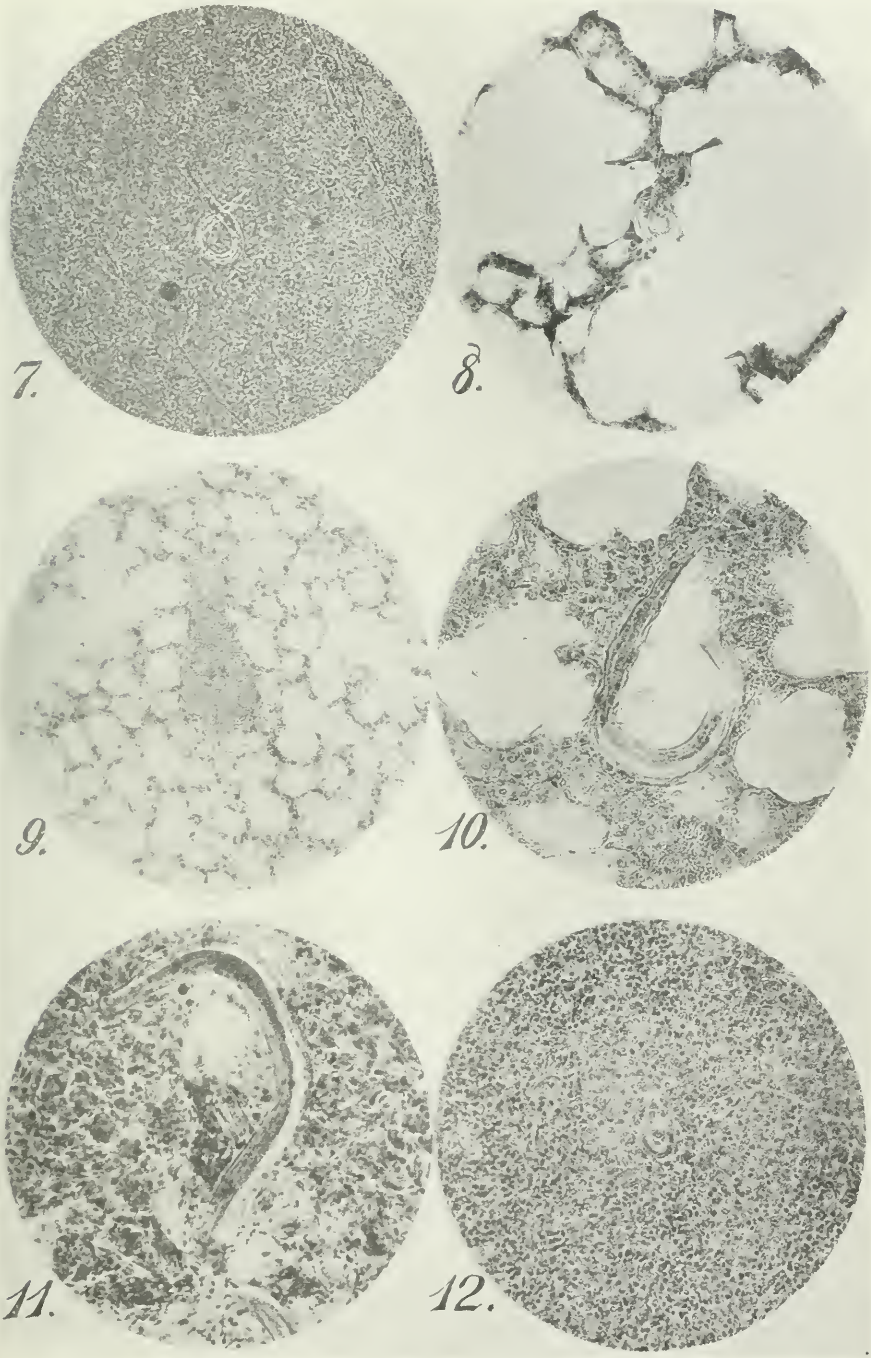
Fig. 8. Section of lung of guinea-pig killed seventeen hours after feeding Ascaris eggs. Larva at center of figure.

Fig. 9. Section of lung of mouse killed twenty-four to seventy-two hours after infection (repeated feedings with Ascaris eggs). Larva in small blood vessel (? vein).

Fig. 10. Section of lung of guinea-pig killed five days after infection. Larva in an alveolus. Note the larger size as compared with those shown in preceding figures.

Fig. 11. Section of lung of guinea-pig killed eight days after feeding Ascaris eggs. Note the still larger size of the larva as compared with that shown in figure 10. The surrounding tissue is becoming solidified.

Fig. 12. Section of mesenteric node of guinea-pig killed twenty-four hours after feeding Ascaris eggs. Larva at center.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# A METHOD FOR THE CULTIVATION OF BALANTIDIUM COLI

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The cultivation of the parasitic intestinal protozoa has been attempted time and again with but partial success. At present, only Hinkelman (1, 2) has reported successful cultivation of *Balantidium coli*. Hinkelman's finding balantidia in the blood and urine as well as feces is so unusual as to throw considerable doubt on the organism with which he is dealing. The work reported in this paper was concluded without knowledge of Hinkelman's papers.

The following notes on the cultivation of *Balantidium coli* are offered as a preliminary communication on the subject, and represent the results obtained using the medium to be described, in carrying the organism through eleven successive transfers covering a period of thirty-two days. In future articles, data will be submitted on the cultivation of *Blastocystis hominis* and *Trichomonas intestinalis*.

The case of balantidial disease from which the culture material has been obtained, is one developing in a native Carolinian who has been under constant observation for the past few years. A detailed report of the case has been given elsewhere (Nisbet, (2)). The patient has been examined from time to time during the past four years and only twice were the stools free from the ciliates.

A number of factors must be taken into consideration in the cultivation of *Balantidium coli* in vitro. Walker (3) found that 0.85 per cent sodium chloride solution is hypertonic while water is hypotonic for *Balantidium coli*. He found 0.5 per cent salt solution to represent the proper tonicity for this organism. This work corroborates Walker's findings.

Partial anaerobic conditions favor the growth of the balantidia. Balantidia in a fluid medium exposed to air on a slide will disintegrate in a short time, even when kept in a moist chamber to prevent drying. If kept in a test tube, or other vessel, under a layer of fluid several centimeters in depth the life of the organism may be prolonged a day or two. This observation led to the practice of inoculating the material containing the ciliates into the lower portions of the culture tubes. It was also noted that in examining the tubes to determine growth active balantidia were to be found only in the lower half of the medium, that is under a layer of medium approximately 50 mm. in depth.

While no systematic work has been done as yet to determine the optimum temperature, in general the balantidia were more active and multiplication apparently took place more rapidly when a temperature of 37° to 38°C. was maintained. On one occasion, through accident, the temperature was allowed to fall below 35°C. and although the organisms lived, their motility was not as great as at the higher temperature. Lower temperatures may be unfavorable because of the increased bacterial growth.

## METHOD

Samples of about 0.1 cc. of undiluted feces containing mucus were inoculated into tubes containing inactivated human blood serum and 0.5 per cent salt solution in the proportion of one part of serum to sixteen parts of salt solution. This medium is faintly alkaline to litmus. Tubes having a diameter of 10 mm. and a length of 150 mm. were used, each tube containing about 8 cc. of the medium, giving a depth of about 100 mm. The material containing the balantidia was inoculated with a capillary pipette into the bottom of the tubes. These were then incubated at 37°C. and examined after twenty-four hours.

An apparent increase in numbers with the presence of many dividing forms was considered satisfactory evidence of growth in a given subculture. Usually only moderate growth took place during the first twenty-four hours, while forty-eight to seventy-two hours seemed to be the optimum time for maximum growth. In general, subcultures were inoculated every second day; however this plan could not be strictly adhered to as in some transfers all the organisms would die and the transfer would have to be repeated. In this way eleven successive transplants were made covering a period of thirty-two days. Because of the press of other work, a period of five days was allowed to elapse after the eleventh transplant, at the end of which time the organisms had disappeared from the cultures.

In this work no effort has been made to isolate the individual strains of bacteria growing with the balantidia though this, doubtless, is an important factor in their cultivation. The most difficult task has been to prevent overgrowth of the bacteria present, and considerable effort has been expended along this line. It was found that by using only a very small quantity of feces the numbers of bacteria in the initial inoculation were markedly decreased. By placing the material containing the balantidia at the bottom of the culture tube and by having 100 mm. of medium in the tube there was not an excessive growth of bacteria, provided the temperature of the incubator was maintained at 37° to 38°C.

In those cultures in which there was only a moderate clouding of the medium, due to bacterial growth, it was found that optimum balantidial growth took place. In no instance was there a decided multiplication of balantidia where the medium was almost clear, denoting a lack of bacterial growth, or where the medium was very cloudy and contained sediment from excessive bacterial growth. In making successive transfers a small quantity of the sediment containing bacteria and balantidia was inoculated at the bottom of the fresh culture tube and as a rule some of the older medium was added to the upper portion of the tube to insure the proper amount of bacterial growth.

Encysted forms were seen in some but not all of the cultures. Apparent conjugation was encountered on only one occasion. Organisms undergoing simple division were commonly seen and, as stated above, their presence together with apparent increase in numbers was considered conclusive evidence of the success of a given subculture.

Further work on the simplification and improvement of this method is being carried out at the present time.

## SUMMARY

*Balantidium coli* has been successfully cultivated in vitro through eleven transplants over a period of thirty-two days.

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# THE MONILIAS OF THE GASTRO-INTESTINAL TRACT IN RELATIONSHIP TO SPRUE

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CONTENTS



I

In a previous communication (1), one of us (Boyd, 1920) called attention to the existence in Texas of indigenous cases of a disease considered to be sprue, and reported the isolation of Ashford's monilia from them. The potential importance of this disease demanded that the scope of these observations be extended. During the past two years there has been conducted in this laboratory a study of the monilias of the gastro-intestinal tract in relationship to sprue, the results of which are presented in this paper.

II

Since the previous communication there have come to our attention three additional cases presenting the symptomatology of sprue. Their clinical histories are as follows:

*Case 3.* Patient M. C., female, negro, aged twenty-seven. Occupation laundress. Resident of Houston, Texas. Admittted to the Medical Service of the John Sealy Hospital, August 29, 1920.

Family and past history negative.

Present illness: For some time prior to her admission the patient had been experiencing a diarrhoea in which three or four stools were passed daily, but without blood or mucous. Severe cramps were experienced following a hearty meal. She had been running a temperature which was higher in the afternoon and night. She had a cough, but no expectoration and recently had experienced some night sweats. About two months prior to admission her condition improved sufficiently to permit her to return to work, but her symptoms soon returned in a greater severity and a gradual loss of weight began.

Physical examination: The patient is very emaciated and weak. The tongue is more red than normal and she has several small white patches on the mucosa of the palate. She complains of general sensitiveness of the buccal mucosa. Examination of the chest is negative, and repeated examinations of the sputum fail to reveal tubercle bacilli, although the radiographer reports the existence of a tuberculous broncho-pneumonia of each upper lobe. Otherwise all physical findings are negative. The stools are semi-solid, yellow and contain considerable mucus.

She continued to become physically weaker and more emaciated until early in October, when the administration of an autogenous vaccine made from the monilia isolated from her stools was begun. From October 8 to November 17 eleven doses were given, which was the only treatment. Following this her condition improved considerably so that she could walk. Her bowels were moving only twice daily and the movements were of normal character. In December she returned to Houston and discontinued the vaccine. Later indirect reports of her condition were not favorable.

Diagnosis: 1, Tuberculous broncho-pneumonia; 2, sprue.

*Case 4.* Patient M. G. White female, aged forty-two. Resident of Galveston, Texas. Patient of Dr. G. H. Lee at St. Mary's Infirmary, to whose courtesy we are indebted for the privelege of reporting.

Family and past history negative.

Present illness: In December, 1920, she developed a diarrhoea associated with an extremely sore mouth and ulcers underneath the tongue, about the lips and the inner surface of the cheeks, and white patches on the mucosa. The stools were large, thin, putty colored, frothy and of excessive amount. Emaciation followed the advent of these stools. About the same time she developed symmetrical dark spots (but not a dermatitis) on the backs of her hands, the index and middle fingers and about the elbows. She became very emaciated.

Physical examination is negative.

An autogenous vaccine was prepared from the monilia isolated from the stools and its administration began in February. At the same time she was given cacodylate of soda intravenously in three grain doses, every other day. At the end of March her condition improved in some respects. The bowel movements were not over two or three per day, though soft, the buccal distress had ceased, though she was still undernourished. During April the above improvement was lost, and she experienced a return of the diarrhoea.

Diagnosis: Sprue.

*Case 5.* White female, aged forty-three, always a resident of south Texas in the vicinity of Austin. Patient of Dr. Allen G. Heard, to whose courtesy we are indebted for this account.

Present illness: For thirteen years the patient experienced an intermittent diarrhoea, in which the stools would be thin and watery, and light in color. In the intervals between the diarrhoeal attacks the stools would be bulky, light gray and frothy. The patient's normal weight was 160 pounds, but during a diarrhoeal attack she would become very emaciated, though some gain was noted in the interdiarrhoeal periods. Her principal complaint was an intense pain in the mediastinum extending to the epigastrium. There was considerable discomfort from vomiting at times. She also complained of sore mouth.

Physical examination: There were no patches or ulcers noted on the buccal mucosa at the time of examination. The tongue was clean, and irregularly and deeply fissured. Her skin was noticeably dark, but devoid of any eruption or dermatitis. The liver was markedly diminished in size. The abdomen has a bloated appearance, conspicuous by reason of the emaciation of the patient, and she complains of a sense of abdominal fullness. Mentally the patient is normal. She has 4,000,000 red blood cells and 75 per cent hemoglobin. She recently died during a diarrhoeal attack.

Diagnosis: Sprue.

The symptomatology of these five cases (including the two previously reported) from the standpoint of sprue, is summarized in table 1.

## III

In addition to a study of the monilias from the five cases considered to be sprue patients, we have made an extensive study of the gastro-intestinal flora of other patients in an endeavor to ascertain the frequency with which monilias are encountered, and the types that occur. Repeated specimens from 34 control patients were examined. Monilias were isolated from 17 of these controls. These were all patients in the medical service of the John Sealy Hospital, and we are indebted to Dr. M. D. Levy for the specimens examined. The character of these controls is shown in table 2.

TABLE 1

*Summary of symptomatology of patients considered to have sprue*

| CHARACTERISTIC | PATIENTS | | | | |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 |
| Sex | M | F | F | F | F |
| Age | 3½ | 56 | 27 | 42 | 43 |
| Race | W | W | N | W | W |
| Duration illness | 3 mo. | 6 yr. | 1 yr. | 4 mo. | 13 yr. |
| Mouth: | | | | | |
| Sensitive mucosa | No | Yes | Yes | Yes | Yes |
| Color tongue | | Red | Red | Red | |
| Tongue fissured | No | No | No | No | Yes |
| Crombie's ulcers | Yes | | | Yes | |
| Tender gums | | Yes | | | |
| Thrush patches | | Yes | Yes | Yes | |
| Epigastric fullness | | | Yes | | Yes |
| Diarrhoea: | | | | | |
| Present | Yes | Yes | Yes | Yes | Yes |
| Intermittent | | Yes | Yes | Yes | Yes |
| Stools: | | | | | |
| Bulky | Yes | Yes | | Yes | Yes |
| Frothy | Yes | | Yes | Yes | Yes |
| Anemia | No | No | Yes | No | Yes |
| Dermatitis | No | No | ? | ? | No |
| Mental condition | o.k. | Melancholia | o.k. | o.k. | o.k. |
| Concurrent trouble | Epileptoid attacks | None | Pulmonary tuberculosis | None | None |

IV

Since this study was primarily undertaken to ascertain the frequency with which *Monilia psilosis* is encountered, we present an abstract of the characteristics of this organism as given by Ashford in 1917 (2).

1. *Morphology.* It is a large round, bright, clear cut "yeast-like" organism, from 4 to 7 micra in diameter, globular rather than oval in shape, with at most a few granules, usually a vacuole and a nucleus in its interior. The contour is always sharp and well defined. Reproduction is by gemmation, by which large numbers of smaller "yeasts" are thrown off. Intermingled with these are blunt ovals which under the hanging drop often become hyphae. It always produces mycelial elements.

TABLE 2

*Control patients examined for Monilia psilosis (positive)*

| NUMBER | AGE | SEX | RACE | DIAGNOSIS |
|---|---|---|---|---|
| I | 40 | M | W | Pellagra |
| II | 77 | M | W | Senile dementia |
| III | 4 | F | W | Convalescent from measles |
| IV | 70 | M | W | Chronic myocarditis, chronic nephritis |
| V | 35 | M | W | Chronic aortic and mitral insufficiency |
| VI | 50 | M | W | Pernicious anemia |
| VII | 25 | F | W | Syphilitic hepatitis |
| VIII | 68 | M | W | Chronic ulcerative pulmonary tuberculosis |
| IX | 38 | M | W | Chronic ulcerative pulmonary tuberculosis |
| X | 40 | M | W | Papilloma of rectum |
| XI | 4 mo. | F | Mex. | Thrush, generalized tuberculosis |
| XII | 30 | F | N | Pellagra |
| XIII | 34 | F | W | Thrush |
| XIV | 4 | M | W | Tuberculosis of the hip |
| XV | 10 | M | W | Tuberculosis of the spine |
| XVI | 8 | M | W | Tuberculosis of the spine |
| XVII | 36 | M | W | Chronic pancreatitis |

There are many strains that do not produce mycelium in glucose. The articles of hyphae are clear cut and not usually very granular. They are of all sizes, from two to five micra wide and of all lengths, sometimes to more than a thousand micra. Budding takes place near the extremity of the article and offers no peculiarity except there never are sterigmata. The articles are usually straight. The extremities are rounded and may bulge slightly. Branching is not frequent.

2. *Litmus milk.* Does not render it acid.

3. *Gelatine.* *M. psilosis* and perhaps other species produce a fine, long, hair-like extension into the non-liquefied medium (inverted pine

tree). A monilia which produces a short fringe-like, even, close, brush-like extension from the line of the stab, is apparently not *M. psilosis*. Gelatine is never liquefied.

*4. Sabouraud's 4 per cent agar, plus 2.* Typically the growth is a very faint greenish, creamy, soft, elevated growth, with clearly defined borders, and generally a mycelial extension into the medium. It may at times present a true cream color. The growth is shining, glistening and brilliant at times. These characteristics are best observed at the end of seven days, after which times the culture may present the following changes:

*a.* A dirty cream, with a hard parchment-like covering.
*b.* A soft dirty cream.
*c.* A honey comb, muddy growth.
*d.* A heaped-up mass of twisted root like convolutions.
*e.* A pitted, even, crater-like, dirty growth.
*f.* A green, honeycomb growth.

*5. Fermentation tests.* The only sugars normally fermented are glucose, levulose and maltose (typically, always), saccharose (often) and galactose (occasionally). He never accepts as *M. psilosis* a "yeast" which fails to ferment maltose, though animal passage may restore its vigor.[1] There is no clouding of the medium, a more or less abundant sediment of growth collects, a pellicle is rarely formed. The most rapid gas production is from glucose, then levulose, then maltose, except when saccharose is fermented, in which case gas is liberated more rapidly than in glucose. Gas production after seven days usually means contamination.

## V

The method used for the isolation of monilias from feces was similar to that described by Ashford. Specimens of feces were plated out upon Sabouraud's medium. One or two large loopfuls of the feces were transferred to a cooled and hardened plate of Sabouraud's medium and spread over the surface of three plates consecutively by means of a glass spreading rod. It was necessary to use American made peptone and glucose in the manufacture of this medium, in place of the French brands given by Sabouraud in his formula.

[1] Ashford does not state the medium in which tests are made.

Plates were incubated forty-eight hours and transplants made on slants of Sabouraud's from all suspicious colonies. The young colonies of monilias are capitate in form and of a glistening creamy white color.

Routine tests were run on every monilia isolated, on the following carbohydrates in peptone water, viz., levulose, galactose, saccharose, mannite, maltose, lactose and dextrose, and the fermentation results recorded after five days, at which time they become constant.

Giant colonies were secured by inoculating the center of the medium in a petri dish, sealing the plates with paraffine and incubating the plates for fifteen days.

Hanging blocks were employed for the study of the morphology and development of the organisms.

All attempts to induce ascospore formation by cultivation on gypsum blocks failed.

It was found that when peptone water was used as the basic medium for testing the ability to ferment carbohydrates, that uniform results were secured, regardless of the length of time a strain had been under artificial cultivation. Five days incubation is necessary in order that constant results be secured. On the other hand, when meat extract broth was used as the basic medium, the fermentation results secured were extremely variable and inconstant. The growth in broth carbohydrate medium is more abundant, but the rate at which a carbohydrate was attacked was much slower, ten days incubation being necessary as a minimum before constant results were secured. From our experience with this group of organisms it would seem highly desirable to conduct all fermentation tests in peptone water, as thereby constant results are secured, regardless of the length of time a strain has been under artificial cultivation. Bahr (1915) (3) also noted this.

## VI

From 22 cases (5 sprue patients and 17 controls) monilias have been isolated, all of which conform to Ashford's description of *Monilia psilosis* as previously given in abstract. While these

22 cultures appear to conform to Ashford's description, a detailed study of their characteristics shows that three well defined types or groups may be recognized among them, any one of which fulfills this description. These types we have designated A, B and C. Other cultures of yeast-like organisms were secured, from both the sprue cases and controls. Study of these however showed them to be closely allied if not identical with the true yeasts and hence they are not included in this report. However no other species of *Monilia* were found.

The characteristics of types A, B and C are presented for purposes of comparison in table 3.

Fig. 1. Type A in Which the Mycelium is a Third of the Diameter of the Colony

Fig. 2. Giant Colony of Type B Showing Short Radiating Mycelium

These strains are distinguishable from one another by the following characteristics:

1. The presence or absence of mycelial prolongations from the periphery of giant colonies on Sabouraud's medium. Type C does not produce such a fringe. (Figs. 1, 2, 3.)

2. The fermentation of saccharose: Type A produces acid and gas from saccharose, type B produces acid only, while type C does not ferment this carbohydrate.

3. The development of aerial hyphae from the surface of the growth at the bottom of the slants of Sabouraud's medium after one week's growth or more. Such hyphal threads are produced by types A and B, but not by type C. (Fig. 4.)

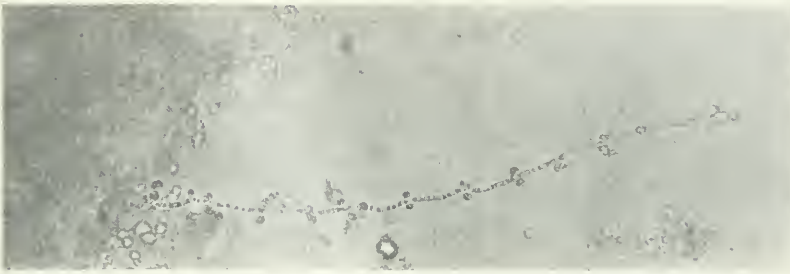

FIG. 3. PERIPHERAL HYPHA DEVELOPING FROM A COLONY OF YEAST-LIKE CELLS IN A HANGING-BLOCK, CULTURE OF TYPE A

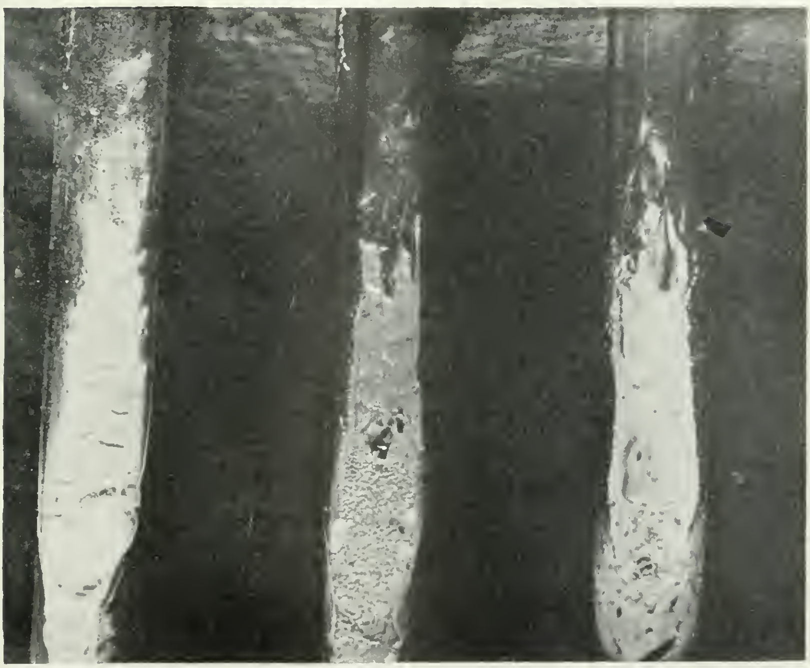

FIG. 4. SIX WEEKS' OLD CULTURES ON SLANTS OF SABOURAUD'S AGAR. FROM LEFT TO RIGHT TYPES, A, B AND C

TABLE 3

*Characteristics of the types of Monilia psilosis*

| MEDIUM | CHARACTERISTIC | A | B | C |
|---|---|---|---|---|
| Sabouraud's agar slants (young culture) | Surface | Smooth, moist, glistening | Smooth, moist, glistening | Smooth, moist, glistening |
| | Color | Creamy | Creamy | Creamy |
| | Mycelium | Radiating into medium, 0.3 to 0.4 cm. | Similar to A | Few or none |
| Sabouraud's agar slants (old cultures) 2 months or more (fig. 4) | Surface | Pitted and moist or dry and wrinkled | Pitted, moist | Pitted, moist |
| | Color | Creamy | Creamy | Creamy |
| | Mycelium | Clusters of aerial hyphae at the bottom of slant | A few clusters of aerial hyphae | No aerial hyphae |
| Giant colonies on Sabouraud's (fig. 1 and 2) | Surface Young | Raised, moist, glistening | Raised, moist, glistening | Raised, moist, glistening |
| | Old | Smooth or wrinkled | Smooth or wrinkled, with ridges radiating from center | Smooth or wrinkled, with ridges radiating from center |
| | Color | Creamy | Creamy | Creamy |
| | Mycelium | Fringe like about periphery, 3–10 mm. long | Fringe like about periphery, 1–3 mm. long. | None present |
| | Size | 2–3 cm. diam. | 2–3 cm. | 2–3 cm. |
| Fermentation tests in peptone water after 5 days | Glucose | Acid and gas | Acid and gas | Acid and gas |
| | Mannite | No change | No change | No change |
| | Lactose | No change | No change | No change |
| | Galactose | Acid and gas | Acid and gas | Acid and gas |
| | Levulose | Acid and gas | Acid and gas | Acid and gas |
| | Maltose | Acid and gas | Acid and gas | Acid and gas |
| | Saccharose | Acid and gas | Acid | |
| | Litmus milk | Unchanged | Unchanged | Unchanged |
| Gelatine stabs. | Fir tree? | Yes | Yes | Yes |

TABLE 3—*Continued*

| MEDIUM | CHARACTERISTIC | A | B | C |
|---|---|---|---|---|
| Hanging blocks (fig. 3)....... | The observations of all three types were identical. The colonies are of yeast like cells reproducing by budding. A large spherical cell may be partially or wholly surrounded by daughter cells. The younger oval cells near the edges of the colony frequently (rare in C) produce long septate simple hyphae, bearing at the distal extremities of the hyphal cells spherical or slightly oval cells, either singly or in chains of three or four. The hyphal cells are constricted at the point of contact with their fellows in the chain | | | |
| Morphology.... | The observations on all three types are identical. The yeast like cells vary in size, in the case of young daughter cells, of from 1.3 to 1.5 micra, to 4.5 to 6.0 micra in the case of the large spherical cells. The hyphal cells are 1.5 micra in diameter and from 28 to 35 micra in length | | | |

The similarity of all three types is very close, but the resemblance between types A and B, distinguished only by the degree of their fermentation of saccharose, is closer than between these two and type C, which is without action on saccharose, does only rarely and sparsely produce mycelial prolongations from giant colonies and does not produce aerial hyphae.

It has to be admitted that the separation into these three types is upon characteristics that are not especially marked, and that the points of similarity are more evident than those of dissimilarity. A suggestion that these divisions are artificial rather than representing natural groups is afforded by the fact that cultures of type C after prolonged artificial cultivation tend to show definite increase in the number of mycelial prolongations into the substrate and in the production of aerial hyphae. The types may therefore represent variations of a single species of monilia, rather than separate species of that genus.

Through the courtesy of Dr. B. K. Ashford of San Juan, Porto Rico, we recently received an authentic culture of the organism described as *Monilia psilosis*. It was submitted to the same routine that we employed in the study of the strains isolated locally. The following results were secured:

*a.* On Sabouraud's agar slants, in young culture, the growth is moist, glistening, creamy white in color. A sparse growth of mycelium extends into the substrate at the base of the slant.

*b.* Giant colonies are raised, moist, glistening, and smooth. At the end of two weeks the colony is 20 mm. in diameter. A very few radiating mycelial threads extend from the edge of the colony into the substrate.

*c.* In hanging block no radiating hyphae were developed.

*d* Fermentation tests: Dextrose, levulose, galactose, and maltose are fermented with the production of acid and gas. No action on mannite, lactose or saccharose.

*e.* Litmus milk is unchanged.

*f.* Gelatine stab: a slight inverted fir tree is produced.

*g.* The morphology is the same as that previously noted in our own strains.

As a result of our comparison, it is our opinion that the culture received from Ashford is identical with our type C, as saccharose is not fermented, while very little tendency to form mycelial extensions into the substrate is noticeable.

## VII

A limited number of feeding experiments were conducted with type A strains, isolated from cases of sprue. Guinea pigs were employed. They were normally fed on oats, alfalfa hay, and green clover. No organisms resembling any of the types of monilia were found in their feces prior to experimentation.

*Pig 1.* On May 24 was fed on oats over which a saline suspension of a twenty-four hour culture of type A, isolated from case 1, had been poured. Forty-eight hours later the pig had a slight diarrhoea which increased markedly. Plates prepared from the stools showed large numbers of type A to be present, which was recovered in pure culture. Death occurred on May 30.

At autopsy the buccal mucosa was found congested and covered with white patches. The intestines were markedly congested. The stomach and intestine were filled with gas to fully three times their natural size. The viscera appeared normal. Type A was recovered from scrapings of the buccal mucosa, the duodenal contents, and the contents of the small intestine and colon.

*Pig 2.* Fed on June 2nd in the same manner as pig 1 with a culture of type A that had been recovered from the preceding pig. The pig showed no ill effects from the feeding but died after three weeks.

On autopsy the animal showed no abnormal conditions except for a few white patches on the buccal mucosa from which type A was recovered.

*Pig 3.* Received two feedings June 2nd and 9th of type A from case 1. At the end of seven days from the last feeding the pig developed a diarrhoea which continued until its death on June 28. After the diarrhoea began type A was recovered from the stools on several occasions.

On autopsy the buccal mucosa was found to be red, but with no white patches. The stomach and intestines were very much distended with gas. The small intestine was markedly congested and bound together by numerous adhesions. Type A was recovered from the mouth, stomach, duodenum and colon.

*Pig 6.* This pig, was fed on January 14 with type A isolated from case 3, mixed with fresh cows' milk. This strain had been under artificial cultivation for about three months and had received four transplantations. The milk was abnormal food and for several days the pig refused to eat. A second feeding of type A was given January 23. The pig became emaciated. During the week before death, apples were added to the diet. Death occurred February 4. Type A was recovered from the stools several times.

At autopsy the buccal mucosa was found to be reddened, but aside from the emaciation and a very small liver, the findings were negative. Cultures from the mouth were negative, but type C was recovered from the stomach and colon.

*Pig 7.* Received two feedings of type A isolated from case 3 on the same dates as the preceding pig. The pig was given a fruit diet of apples and an occasional banana for four weeks. Beginning with the second day, type A was continuously isolated from the stools for four weeks, until the pig was put back upon a normal diet. Aside from a slight loss of weight, the pig showed no ill effects from the experiment.

*Pig 8.* Was fed cultures of type A on the same dates as pig 6, but received a vegetable diet of carrots, sweet potato, turnips and cabbage for four weeks. For two weeks type A was recovered from the stools, but then disappeared. The animal showed no ill effects.

*Pig 9.* This pig was fed in a similar manner as the foregoing three, but kept on a normal diet of alfalfa hay, oats and clover, with two feedings of type A. This was recovered from the feces for three weeks, and then disappeared. The animal showed no ill effects.

The foregoing results of experimental feedings are by no means conclusive, but suggest that in some instances this monilia may produce an acute gastro-enteritis, and reproduce some of the clinical manifestations of sprue. Since cultures were not made from the heart's blood, the existence of a mycotic septicemia is undetermined. The results correspond with the feeding experiments reported by Ashford (1916) (4).

VIII

Three types were isolated from our series of cases and are shown in table 4.

TABLE 4

| | TYPE A | | TYPE B | | TYPE C | |
|---|---|---|---|---|---|---|
| | Mouth | Feces | Mouth | Feces | Mouth | Feces |
| Sprue patients.... | 3 | 1, 2, 3 | 2 | 4, 5 | | 4 |
| Control patients.. | | I, II, III, V, VI, X, VII, IX, XIV, XV, XVI, XVII | XI, XVII | IV, VIII | XIII | XII |

The data presented in the foregoing table may be summarized as follows:

Type A has been isolated from 15 patients, of whom three were cases of sprue and twelve were controls. It was recovered from the mouth of one and from the feces of all fifteen.

Type B has been isolated from 7 patients, of whom three were cases of sprue and four were controls. It was found in the mouths of three and in the feces of four.

Type C has been isolated from three patients, of whom one was a case of sprue and two were controls. It was recovered from the mouth of one control, and in the feces of two patients.

In one of the sprue cases (3), the same type (A) was isolated from the mouth, duodenal contents and feces. This is the only instance where the same type appeared to prevail throughout the entire gastro-intestinal tract. Case 2 had type B in the mouth and type A in the feces, while case 4 had both types B and C in the feces. These results, taken in connection with the feeding experiment in pig 6, where type A was fed and type C recovered, seem to confirm the opinion earlier expressed that these types merely represent variations in a single species of *Monilia*.

Two of the series of control cases (XI, XIII) were cases of thrush, and from the mouth's of these types B and C alone were isolated, and were absent from the stools. The feeding experiments with type A indicate that it may produce thrush like lesions in guinea-pigs. Thrush is generally considered to be produced by two species of fungi (1) *Monilia albicans* and (2) *Endomyces albicans*, the two species being differentiated from each other by the production of ascospores within the hyphae of the latter. Castellani (1914) (5) states that *Monilia albicans* liquefies gelatine, while none of the other species he describes possess this property. The ability to produce acid and clot in milk is common to *M. albicans* and a number of the other species he describes. If these differential criteria are correct, it is apparent that we are here dealing with clinical cases of thrush produced by *M. psilosis*, for *M. psilosis* does not liquefy gelatine or produce acid and clot in milk. We did not encounter any monilia answering to the above description of *M. albicans*. Bahr's (1915) studies do not indicate that he encountered *M. albicans*, even though his conclusions are to the effect this organism is the cause of sprue, if Castellani's criteria are correct. From his data it would appear that some his types, insofar as his data upon fermentation reactions and litmus milk reactions are concerned, correspond to ours. Thus our type A corresponds to Bahr's type F, our type B to his type L and out type C to his type E. He isolated types E and F from 14 and 17 of 106 cases of sprue, and which were exceeded in frequency only by one other type (G), which he encountered in twenty cases.

IX

On the other hand, the data we have collected do not forcibly impress us with the opinion that *Monilia psilosis* is the cause of sprue, by reason of the fact that 50 per cent of our controls, including the thrush cases, were harboring what appears to be the same organism that we have recovered from cases presenting the symptomatology of sprue. The animal feedings are suggestive of the possession of pathogenic properties by this organism, but we do not feel that the evidence we have supports the view that this organism bears specific relationship to sprue. Since it is present in a larger proportion of controls, than we probably are justified in regarding as healthy carriers of a pathogenic organism, it appears that some other factors are of causative importance in the production of sprue, besides its mere presence in the gastro-intestinal tract.

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# CORRECTION

In the January, 1921, number of the American Journal of Tropical Medicine there appeared an article by C. A. Kofoid and O. Swezy, on "Prevalence of Carriers of Endamoeba dysenteriae Among Soldiers Returned From Overseas Service." At the time of publication the Editor was unaware that this article had been previously published. In fact, however, this article had already been published in the July, 1920, number of the *New Orleans Medical and Surgical Journal.* Credit for previous publication should have been given to this *Journal*, with its permission for re-publication. The Editor regrets this mistake, especially as the *New Orleans Medical and Surgical Journal* has for years given practical support of the American Society of Tropical Medicine by publishing its Transactions.

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# RELAPSING FEVER IN PANAMA[1]

## THE HUMAN TICK, *ORNITHODOROS TALAJE*, DEMONSTRATED TO BE THE TRANSMITTING AGENT OF RELAPSING FEVER IN PANAMA BY HUMAN EXPERIMENTATION.

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There were six cases of relapsing fever in Ancon Hospital during the last week of March and the first week of April of this year (1921). All six patients were white American boys between eleven and twenty years of age. All had spent several nights in the native town of Arraiján within the two weeks previous to their admission to the hospital. Four of these boys were from a party of five who went to Arraiján hunting on March 15, 1921, and two were from a party of four who went there on March 21, 1921.

*First party.* The boys of this party all lived in Balboa, Canal Zone. They left Balboa for Arraiján on March 15, 1921, and arrived there a few hours later the same day. Arraiján is a native village of about 600 population outside the Canal Zone, approximately 8 miles from Balboa. As the trade winds of the dry season sometimes become sufficiently cool at night to cause sleeping outside to be rather unpleasant, the first night was spent in a hut belonging to a Chinaman, who keeps a store in this village. This Chinaman with his wife, who is a native Panamanian, and three children, had been living in the hut but upon the arrival of the American boys, moved into the store to live while the boys occupied the hut. All five boys slept in the hut the first night, three of them sleeping on a wide bamboo bed, the other two occupying hammocks. They were so badly bitten by insects during the night that three of them spent the second and third nights sleeping out in the "bush." On the fourth night they again occupied the hut in company with the other two boys and all returned to Balboa the next day (March 19, 1921). Between March 25–27 four of the five were admitted to the hospital with relapsing fever. All of the boys showed marks of many insect bites. The youngest boy, H. C., who first became ill, showed the greatest number of these bites, he being literally covered with them. It is likely that mosquitoes, biting flies and ticks found in the jungle were responsible for some of these bites, but it was quite evident from the history given that many were received while they were sleeping in the hut. They

TABLE 1

| NUMBER | INITIALS | HOSPITAL NUMBER | AGE | DATES AT ARRAIJAN | DATE ADMITTED TO HOSPITAL | TEMPERATURE ON DAY OF ADMISSION | TIME SICK ON ADMISSION | MINIMUM AND MAXIMUM INCUBATION PERIOD |
|---|---|---|---|---|---|---|---|---|
| *First party* | | | | | | | | |
| | | | | | | °F. | *days* | *days* |
| 1 | B. B. | 236909 | 19 | March 15–19 | March 25 | 103 | 1 | 5– 9 |
| 2 | H. C. | 236908 | 19 | March 15–19 | March 25 | 102 | 2 | 4– 8 |
| 3 | F. S. | 236938 | 19 | March 15–19 | March 27 | 103 | 1 | 7–11 |
| 4 | H. S. | 236929 | 16 | March 15–19 | March 27 | 102 | 1 | 7–11 |
| *Second party* | | | | | | | | |
| 1 | J. T. B. | 237060 | 12 | March 22–23 | April 1 | 103.5 | 2½ | 7– 8 |
| 2 | G. E. | 237083 | 20 | March 22–24 | April 2 | 103.5 | 2 | 7– 8 |

all agreed that the insects which attacked them during the night in the hut were small, reddish bugs which were full of blood when found. This description, so far as it goes, conforms to that of the larvae of the human tick, *Ornithodoros talaje* (Guerin-Meneville). Two of the boys came to the Laboratory later and when shown the larvae of *O. talaje* appeared to recognize them and thought they were the same as the insects that had attacked them while in the hut.

*Second party.* A second party consisting of four white American boys living in Pedro Miguel, Canal Zone, also went to Arraiján for a few days outing, arriving there on March 21.

The first night was spent in the "bush" but during the three following nights, March 22, 23 and 24, three of the boys slept in the Chinaman's hut that had been occupied by the other party but three days previous. One member of the party did not sleep in the hut at all, remaining outside every night. One of the boys, J. B., remained in the hut but two nights, returning to Pedro Miguel on March 24. The other three boys remained one more night and returned March 25. On April 1, J. B., the first boy to return and the youngest in the party, was admitted to Ancon Hospital with relapsing fever. The following day a second boy was admitted also with relapsing fever. (A third boy reported at Pedro Miguel Dispensary a few days later with a temperature of over 103° F. No malarial organisms were found on the examination of his blood and as he was not a Canal employee he was not sent to the hospital. He did not return to the Dispensary at a later date.) The fourth boy who slept outside did not become ill.

Each of the boys who was a patient in the hospital received a single dose of Neo-salvarsan, the dose varying between 0.2 and 0.9 gram. All made quick and complete recoveries.

## INSPECTION AT ARRAIJÁN

One of us (L. H. D.) accompanied by Sanitary Inspector I. W. Pickett, of Pedro Miguel District, made a visit to Arraiján for the purpose of making an examination of the hut and bed which had been occupied by both parties of boys and where, from all indications, they had received their infection. The hut was of the native style, so often found in the villages in the interior of Panama. It was built of poles and thinly plastered on the outside with mud and ashes, had an overhanging thatched roof and no floor other than the ground. The bed was a very crude affair consisting of four sticks driven in the ground and supporting a frame of black palm poles extending from one stick to the other, with two additional poles extending across the center to add further support. The body of the bed was then filled in with bamboo poles about ½ inch in diameter and cut to proper length. No nails were used in this construction, light strips of bark being used to bind the bamboo poles to the cross pieces of the frame and the latter to the crotched sticks. This bed was nearly square and occupied one side of the small room where it was located. The room being without windows was very dark even at midday, therefore the bed was taken apart and moved out of doors into the sunlight for examination. There it was found that human ticks, *Ornithodoros talaje*, were present in large numbers. They were found in the small crevices of the black palm frame and in the ends of the bamboo poles near the first exposed joint. They evidently go into hollow joints of the ends of the bamboo poles to deposit their eggs and molt. About 250 adults and nymphs and 75 unfed larvae were collected from the bed, nearly every joint being infested. Many of the villagers watched the work with much interest and some of them volunteered the information that nearly all of the houses in Arraiján were infested with "Chinche mamones," as they are called by the natives. A few of them modified this statement by saying that all of the older houses in the village were badly infested but that the newer ones were free from them. Our stay in the village was too short to permit investigation of other huts, however most of the huts in the village were of the same type as the one we visited.

The human ticks are somewhat similar in habits to the bedbug, remaining secreted in the cracks and crevices of the beds and walls by day and coming out at night to feed on the occupants. After becoming engorged with blood they again return to a place of secretion. Therefore one of these huts provides an ideal place of abode for them as hiding places are innumerable.

## ANIMAL INOCULATIONS WITH TICKS

### *Naturally infected ticks injected into rats*

On April 7, 1921, 22 ticks, 16 adults and 6 nymphs, that had been collected from the bed in the Chinaman's hut at Arraiján on April 1 and kept in an incubator at 37° C. for five days, were macerated in 2.5 cc. of normal saline solution and this divided into equal parts and injected into two white rats, no. 2 and no. 3.

TABLE 2

*Result of blood film examination rat 2*

| DATE | RESULT | NUMBER OF FIELDS EXAMINED |
|---|---|---|
| April 8, 1921 | Negative for spirochaetes | 600 |
| April 9, 1921 | Negative for spirochaetes | 600 |
| April 10, 1921 | Negative for spirochaetes | 600 |
| April 11, 1921 | Negative for spirochaetes | 600 |
| April 12, 1921 | Negative for spirochaetes | 600 |
| April 13, 1921 | *Positive for spirochaetes* | |

The first spirochaete was found in 120 fields; the second in 3 fields; the third in 40 fields; the fourth in 10 fields and the fifth in 3 fields. This rat was killed while blood was being taken from it to inject into another rat. The rat was autopsied (Animal Autopsy No. 1959) by Dr. H. C. Clark, who found many spirochaetes in smears of crushed heart muscle.

TABLE 3

*Result of blood film examination rat 3*

| DATE | RESULT | NUMBER OF FIELDS EXAMINED |
|---|---|---|
| April 8, 1921 | Negative for spirochaetes | 600 |
| April 9, 1921 | Negative for spirochaetes | 600 |
| April 10, 1921 | Negative for spirochaetes | 600 |
| April 11, 1921 | Negative for spirochaetes | 600 |
| April 12, 1921 | Negative for spirochaetes | 600 |
| April 13, 1921 | *Positive for spirochaetes* | 1 in 140 |
| April 14, 1921 | Negative for spirochaetes | 600 |
| April 15, 1921 | Negative for spirochaetes | 600 |
| April 16, 1921 | *Positive for spirochaetes* | 1 in 315 |
| April 17, 1921 | Negative for spirochaetes | 600 |
| April 18, 1921 | Negative for spirochaetes | 600 |
| April 19, 1921 | *Positive for spirochaetes* | *2 in 251 |
| April 20, 1921 | Negative for spirochaetes | 600 |
| April 21, 1921 | Negative for spirochaetes | 600 |
| April 22, 1921 | Negative for spirochaetes | 600 |
| April 23, 1921 | Negative for spirochaetes | 600 |
| April 24, 1921 | Negative for spirochaetes | 600 |
| April 25, 1921 | Negative for spirochaetes | 600 |

* These had their ends close together as though they might have divided by transverse fissure a short time previous. Two more were found in 6 fields later.

Each rat received part of the fluid intraperitoneally and part subcutaneously. Dark field examinations and stained smears of this fluid failed to show the presence of spirochaetes.

### TRANSMISSION EXPERIMENT

*Spirochaete infection carried from rat to monkey by tick bites*

April 15, 1921, a number of larvae were fed on infected rat no. 309. After molting and developing into first stage nymphs, 24 of these were placed on monkey no. 68 to feed on May 7. All

TABLE 4

*Result of blood film examination monkey 68*

| DATE | TIME | TEMPERATURE | RESULT | NUMBER OF FIELDS EXAMINED |
|---|---|---|---|---|
| | | °F. | | |
| May 8, 1921 | 10 a.m. | 102.6 | Negative for spirochaetes | 1000 |
| May 9, 1921 | 10 a.m. | 100.8 | Negative for spirochaetes | 1000 |
| May 10, 1921 | 10 a.m. | 101.8 | Negative for spirochaetes | 1000 |
| May 11, 1921 | 10 a.m. | 102.0 | Negative for spirochaetes | 1000 |
| May 12, 1921 | 10 a.m. | 101.4 | Negative for spirochaetes | 1000 |
| May 13, 1921 | 10 a.m. | 102.4 | Negative for spirochaetes | 1000 |
| May 14, 1921 | 10 a.m. | 102.8 | Negative for spirochaetes | 1000 |
| May 15, 1921 | 10 a.m. | 102.6 | Negative for spirochaetes | 1000 |
| May 16, 1921 | 10 a.m. | 103.2 | *Positive for spirochaetes** | |
| May 17, 1921 | 10 a.m. | 106.2 | *Positive for spirochaetes* | Average 2 per field |

No further examinations made.

* The first spirochaete was found in 40 fields; the second in 49 fields; the third in 101 fields; the fourth in 4 fields and the fifth in 18 fields.

of them attacked, 21 becoming engorged, the other 3 although attacking and taking some blood did not become engorged. With but one exception they all remained attached for about three and a half hours and it was then necessary to remove them as none detached themselves although fully engorged. The one exception after becoming engorged detached in two hours and fifteen minutes. This was the only one observed to secrete any (coxal?) fluid while attached. One of the three that attached but did not engorge was dissected and examined and spirochaetes were demonstrated in the coelomic fluid.

### SMEARS FROM TICKS

The most of the ticks brought from Arraiján were saved for animal and human inoculation. However a few were set aside for direct examination. These were kept in an incubator with a temperature of 35° C. for six days, then kept at room temperature (21° to 28° C.) for two days and then smears were made from fluid which exuded after pulling off a leg and from gut contents. These smears were stained with a polychrome stain (Hasting's) and examined. Smears were made from males, females and nymphs. Spirochaetes with both the morphology and staining characteristics of the relapsing fever spirochaete were found in coelomic fluid smears and also in gut content smears (possibly contaminated with coelomic fluid) of the seventeenth tick examined, which was a deplete female.

### INOCULATION OF THE HUMAN SUBJECT

The evidence to incriminate the tick as the transmitting agent of relapsing fever in Panama now seemed as complete as could be obtained without experimental human inoculation and permission to do this was requested and granted.

Three soldiers, Otto F. Lueckhert, Kenneth K. Glover and Lewellyn N. Jourden of Company A., Military Police, Quarry Heights, Canal Zone, who volunteered to be inoculated, were admitted to Ancon Hospital on April 19, 1921, and the work undertaken. This research work or investigation would have been impossible had it not been for the active coöperation of Col. H. C. Fisher, Chief Health Officer of the Panama Canal, General C. W. Kennedy, Commanding General of the Panama Canal Department of the United States Army, Col. H. A. Webber, Department Surgeon and Col. L. T. Hess, Superintendent of Ancon Hospital.

As it was possible that only a small number of the ticks brought from Arraján might be infected it was decided to inoculate one man with blood from the infected white rat to prove that the spirochaete recovered in its blood was the spirochaete of relapsing fever, to inoculate a second man with a suspension of ticks brought from the bamboo bed in Arraiján, above referred to, and to allow ticks from this bed to bite a third man.

We felt confident that the first man would have relapsing fever, concerning the other two we felt doubtful, but considered that in the event that they did contract the disease this additional proof would incriminate the tick as the transmitting agent of relapsing fever in Panama beyond all question of a doubt.

*Case I. Human subject inoculated with rat blood containing relapsing fever (?) spirochaetes. (Rat infected by ticks, O. talaje, from bed where the original relapsing fever cases presumably had been infected.)*

O. F. L., Ancon Hospital No. 237516 (Army Serial No. R105716). White American, age thirty years, was admitted to Ancon Hospital on April 19, 1921, for this investigation. His family history was negative. He had had the common diseases of childhood but otherwise had always been healthy. On the day of admission he stated that he had never felt better in his life. A complete and careful physical examination showed him to be in excellent physical condition. For two months previous to his admission he had not been away from the sanitated areas of the Canal Zone nor in any place where he might have been exposed to either malaria or relapsing fever infection.

April 19, 1921. O. F. L. was injected with 1.5 cc. of blood taken directly from white rat No 311, which rat's blood film at the time showed one spirochaete in 600 fields. Equal parts of this blood were injected subcutaneously on each side of the median line of the abdomen. One-half cubic centimeter of blood from this same rat was also diluted with an equal quantity of citrate solution and injected into his right arm.

*April 4, 1921. Rat 2 was inoculated with one-half of 2.5 cc. of normal saline solution in which twenty-two (22) ticks from Arraiján had been macerated. For details see paragraph "Animal inoculations with ticks."*

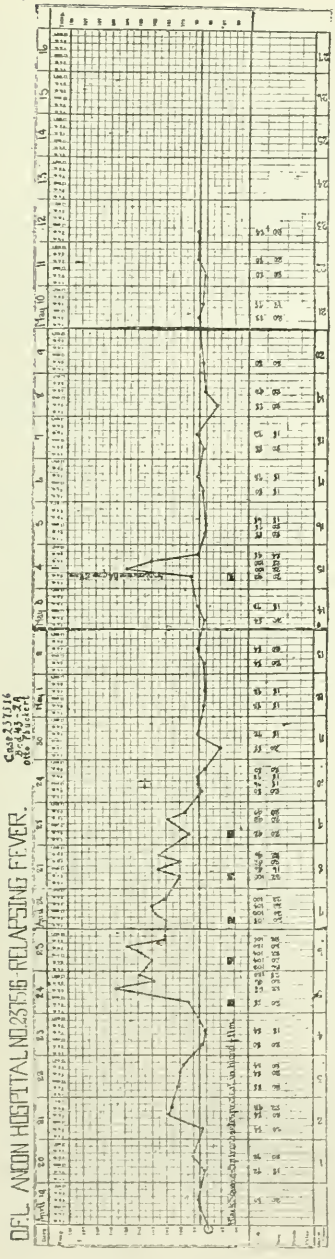
*April 13, 1921. Rat 310 was inoculated from rat 2.*

*April 16, 1921. Rat 311 was inoculated from rat 310.*

*April 19, 1921. Patient O. F. L. was inoculated from rat 311.*

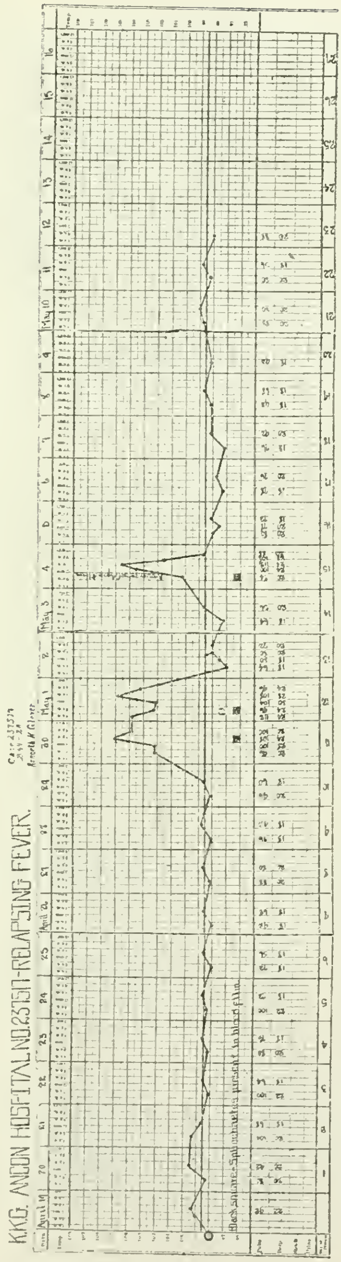
April 21 and 22, 1921. Although during these two days he had fever varying from 100° to 100.8° F. he did not feel sick and no spirochaetes could be found in his blood.

April 24, 1921. During the night of April 23–24, 1921, he had a severe frontal headache and slept scarcely any. At 8 a.m. his temperature was 99.4° F. and a blood film made at 9 a.m. contained spirochaetes, averaging one in 200 fields.




CASE I. RELAPSING FEVER CAUSED BY INJECTING THE VOLUNTEER PATIENT WITH WHITE-RAT BLOOD

The rat had been infected with a strain of spirochaetes obtained by injecting rats with naturally infected ticks.




CASE II. RELAPSING FEVER CAUSED BY INJECTING THE VOLUNTEER PATIENT WITH NATURALLY INFECTED TICKS

April 25, 26, 27, 29, 1921. During these four days he had headache except when it was relieved with phenacetin and codiene, slept very poorly at night, had no appetite and vomited several times. His fever, which was 104.5° F. on April 24, gradually fell by lysis during these four days, reaching normal on April 29, 1921. Spirochaetes were found in blood films made on each of these days.

May 4, 1921. On this date he had a relapse with symptoms similar to those of the first attack. Spirochaetes were again present in a blood film. A 0.4 gram dose of arsphenamine given at 11 a.m. cut the attack short and he made an uneventful recovery. He was kept under observation in the hospital for seven days after his temperature reached normal and for seven days more as an outpatient.

*Case II. Human subject inoculated with suspension of macerated ticks. (O. talaje from bed where the original relapsing fever cases presumably had been infected.)*

K. K. G. Ancon Hospital No 237517 (Army Serial No. 6414102). White American, age nineteen years, was admitted to Ancon Hospital on April 19, 1921, for this investigation. His family history was negative. He had had the common diseases of childhood. A complete and careful physical examination showed him to be in excellent physical condition. For two months previous to his admission he had not been away from the sanitated areas of the Canal Zone nor in any place where he might have been exposed to either malaria or relapsing fever infection.

April 19, 1921, 11 a.m. He was given a subcutaneous inoculation in the left arm of 1.5 cc. of sterile water containing a suspension of 31 adult ticks and 7 larvae ticks, all *Ornithodoros talaje* which had been collected from the bed in Arraiján on April 1, 1921. These ticks were ground in a mortar under aseptic precautions. At 5.30 p.m. the arm around the site of inoculation was red and warm, the reaction appearing very much like that seen after an injection of typhoid prophylactic. However the arm was not tender and there was no general reaction. At this time 5000 units of tetanus antitoxin were given (this as a precautionary measure).

April 20, 1921. The redness had extended the entire length of the upper arm but the arm was not tender and there was no general reaction. After this date the local reaction rapidly disappeared, except for a hard lump at the site of inoculation about the size of a filbert, which lasted for about two weeks.

TABLE 5

*Result of blood film examination O. F. L.*

| DATE | TIME | RESULTS | NUMBER OF FIELDS EXAMINED |
|---|---|---|---|
| April 19, 1921 | (Before inoculation) | Negative for spirochaetes | 600 |
| April 20, 1921 | 9 a.m. | Negative for spirochaetes | 600 |
| April 21, 1921 | 9 a.m. | Negative for spirochaetes | 600 |
| | 5 p.m. | Negative for spirochaetes | 600 |
| | 8 p.m. | Negative for spirochaetes | 800 |
| April 22, 1921 | 9 a.m. | Negative for spirochaetes | 800 |
| April 23, 1921 | 9 a.m. | Negative for spirochaetes | 700 |
| April 24, 1921 | 9 a.m. | *Positive for spirochaetes* | 2 in 400 |
| April 25, 1921 | 9 a.m. | *Positive for spirochaetes* | 1 in 54 |
| April 26, 1921 | 9 a.m. | *Positive for spirochaetes* | 3 in 70 |
| April 27, 1921 | 9 a.m. | *Positive for spirochaetes* | 1 in 400 |
| April 28, 1921 | 9 a.m. | *Positive for spirochaetes* | 2 in 200 |
| April 29, 1921 | 9 a.m. | Negative for spirochaetes | 600 |
| April 30, 1921 | 9 a.m. | Negative for spirochaetes | 600 |
| May 1, 1921 | 9 a.m. | Negative for spirochaetes | 600 |
| May 2, 1921 | 9 a.m. | Negative for spirochaetes | 600 |
| May 3, 1921 | 9 a.m. | Negative for spirochaetes | 600 |
| May 4, 1921 | 9 a.m. | *Positive for spirochaetes* | 1 in 51 |
| May 5, 1921 | 9 a.m. | Negative for spirochaetes | 600 |

TABLE 6

*Result of blood film examination K. K. G.*

| DATE | TIME | RESULT | NUMBER OF FIELDS EXAMINED |
|---|---|---|---|
| April 19, 1921 | (Before inoculation) | Negative for spirochaetes | 600 |
| April 20, 1921 | 9 a.m. | Negative for spirochaetes | 600 |
| April 21, 1921 | 9 a.m. | Negative for spirochaetes | 600 |
| April 22, 1921 | 9 a.m. | Negative for spirochaetes | 600 |
| April 23, 1921 | 9 a.m. | Negative for spirochaetes | 600 |
| April 24, 1921 | 9 a.m. | Negative for spirochaetes | 600 |
| April 25, 1921 | 9 a.m. | Negative for spirochaetes | 600 |
| April 26, 1921 | 9 a.m. | Negative for spirochaetes | 600 |
| April 27, 1921 | 9 a.m. | Negative for spirochaetes | 600 |
| April 28, 1921 | 9 a.m. | Negative for spirochaetes | 600 |
| April 29, 1921 | 9 a.m. | Negative for spirochaetes | 600 |
| April 30, 1921 | 9 a.m. | Negative for spirochaetes | 3000 |
| | 12 noon | *Positive for spirochaetes* | Average 1 in 600 |
| May 1, 1921 | 9 a.m. | *Positive for spirochaetes* | Average 1 in 100 |
| May 2, 1921 | 9 a.m. | Negative for spirochaetes | 600 |
| May 3, 1921 | 9 a.m. | Negative for spirochaetes | 600 |
| May 4, 1921 | 9 a.m. | *Positive for spirochaetes* | Average 1 in 270 |
| May 5, 1921 | 9 a.m. | Negative for spirochaetes | 600 |

His temperature was taken twice daily, morning and afternoon, a white blood count was made every morning, a urinalysis was made every morning, and blood films were stained and examined every morning. The routine procedure was to examine 600 fields of each film.

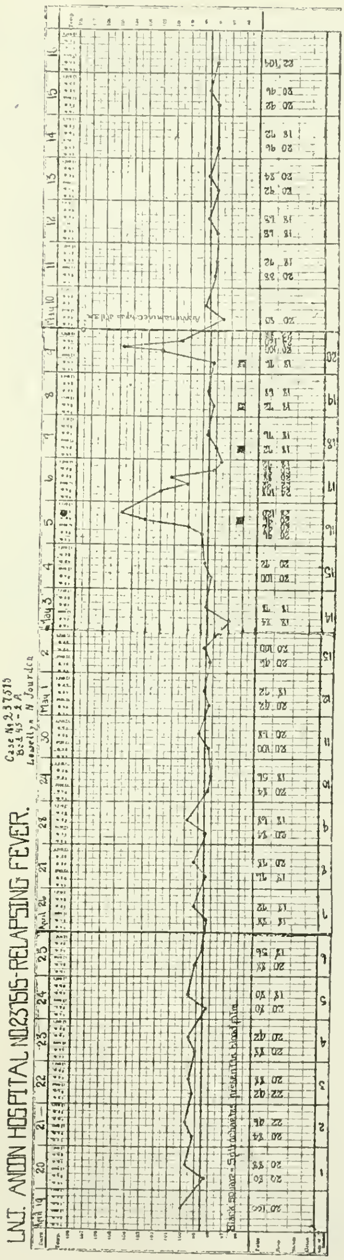
April 30, 1921, eleven days after inoculation, his temperature rose to 102.2° F. at 8 a.m. and to 105° F. at 4 p.m. Blood films made at 9 a.m. were negative for spirochaetes (3000 fields examined); films made at 12 noon, at which time his temperature was still 102.2° F., contained 1 spirochaete in 600 fields.

April 30, 1921, and May 1, 1921. During these two days he had fever, a severe headache and complained of aching all over his body. He slept but one or two hours during either night. Five grains of phenacetin and one-quarter grain of codiene were given in capsule every four hours as needed for the headache and made him fairly comfortable. He had no appetite and showed considerable prostration. He had no true chill but did have chilly sensations from time to time and desired to be constantly covered with a blanket. His spleen was not enlarged to palpation or percusion and there was no jaundice.

May 4, 1921. He suffered an attack similar to that on April 30 and May 1. His temperature was 100.2° F. at 8 a.m. and spirochaetes were present in a blood film made at 9 a.m., averaging one in 280 fields. A 0.4 gram dose of arsphenamine was given at 11 a.m. and following this he made an uneventful recovery. He was kept under observation in the hospital for seven days after his temperature reached normal and for seven days more as an outpatient.

*Case III. Human subjects bitten by ticks.* (*O. talaje from bed where the relapsing original fever cases presumably had been infected.*)

L. N. J. Ancon Hospital No. 237515 (Army Serial No. R280766). White American, age twenty years, was admitted to Ancon Hospital on April 19, 1921, for this investigation. His family history was negative. He did not remember having had the common diseases of childhood. About eight years ago he had a severe attack of scarlet fever. In 1913 he had three attacks of appendicitis. On admission he was found by complete and careful examination, to be in excellent physical condition. He left the United States on October 20, 1921, and arrived here in November. He was stationed in Colon from the time of his arrival until about one and one-half months ago, since then he has been stationed at Pier 18, Balboa, Canal Zone. For two months previous to his admission he had not been away from the sanitated areas of the Canal Zone nor in any place where he might have been exposed to either malaria or relapsing fever infection.




Case III. Relapsing Fever Caused by Allowing Naturally Infected Ticks to Bite Volunteer Patient

April 19, 1921. Thirty-seven ticks, 29 adults, 1 nymph and 7 larvae, were placed on his left upper arm and forearm. Only 6 of these could be induced to attack and feed. Of these 6, 4 adults and 1 nymph became fully engorged and secreted a clear colorless fluid termed "coxal fluid" by various observers on ticks of the family Argasidae; the sixth took blood but detached before engorgement and apparently secreted no fluid. Blood oozed from each bite site and mixed with the clear fluid and this mixture upon drying formed a small scab. No excreta was noticed. The patient was instructed not to scratch the bitten areas. He stated that but one bite stung sharply, the others giving the sensation of a faint prick, like a mild mosquito bite. Four of these bites were on the upper arm 2 inches above the elbow on the anterior surface and 2 were about the same distance below the elbow.

April 22, 1921, p.m. Ticks were again placed on this man's left arm, 4 attacked. Three of these were adults, 1 a large female and the fourth a nymph. One of the adults became partially engorged and did not secrete any fluid. The other 3 each secreted fluid after drawing blood. This fluid usually covered the site of the bite. One, the large female, engorged in about fifteen minutes, detached itself and then quickly secreted a quantity of fluid on the bite. None of the 4 took more than thirty minutes to engorge.

April 23, 1921. p.m. Ticks were again fed on this man's left arm on the anterior surface. Eleven adults and 3 young larvae became engorged. Nine of the adults secreted (coxal ?) fluid. The other 2 adults and the 3 larvae did not secrete any fluid.

April 25, 1921, p.m. One more tick was fed on this man's left forearm. This tick became nearly engorged but detached in about thirty minutes without secreting any fluid.

To summarize: Twenty-five ticks brought from the hut in Arraiján on April 1, 1921, fed on this man's arm sometime during the seven days between April 19 and April 25, both inclusive. This was their first feeding after collection. The bites remained in evidence and became more prominent on May 3, 4, and 5.

May 5, 1921. This patient remained well until noon of this date, when a severe headache developed. He did not mention this until his four o'clock temperature was taken, which was 103°F. Blood films made at this time contained spirochaetes. The first spirochaete was found after searching 60 fields, the second one after 437 fields, the third after 287 fields, the fourth after 212 fields and the fifth after 97 fields. He said that he ached all over, was chilly and could not eat.

He kept covered with a blanket. He stated that he slept very little during the night of May 5–6. His face was flushed and he was somewhat prostrated. No other sign or symptoms were noted.

May 6, 1921. He felt much better and at 8 p.m. and his temperature was again normal.

TABLE 7

*Result of blood film examination L. N. J.*

| DATE | TIME | RESULT | NUMBER OF FIELDS EXAMINED |
|---|---|---|---|
| April 19, 1921 | (Before inoculation) | Negative for spirochaetes | 1000 |
| April 20, 1921 | 9 a.m. | Negative for spirochaetes | 1000 |
| April 21, 1921 | 9 a.m. | Negative for spirochaetes | 1000 |
| April 22, 1921 | 9 a.m. | Negative for spirochaetes | 1000 |
| April 23, 1921 | 9 a.m. | Negative for spirochaetes | 1000 |
| April 24, 1921 | 9 a.m. | Negative for spirochaetes | 1000 |
| April 25, 1921 | 9 a.m. | Negative for spirochaetes | 1000 |
| April 26, 1921 | 9 a.m. | Negative for spirochaetes | 1000 |
| April 27, 1921 | 9 a.m. | Negative for spirochaetes | 1000 |
| April 28, 1921 | 9 a.m. | Negative for spirochaetes | 1000 |
| April 29, 1921 | 9 a.m. | Negative for spirochaetes | 1000 |
| April 30, 1021 | 9 a.m. | Negative for spirochaetes | 1000 |
| May 1, 1921 | 9 a.m. | Negative for spirochaetes | 1000 |
| May 2, 1921 | 9 a.m. | Negative for spirochaetes | 1000 |
| May 3, 1921 | 9 a.m. | Negative for spirochaetes | 1000 |
| May 4, 1921 | 9 a.m. | Negative for spirochaetes | 1000 |
| May 5, 1921 | 9 a.m. | Negative for spirochaetes | 1000 |
| May 5, 1921 | 4 p.m. | *Positive for spirochaetes* | Maximum 1 in 97<br>Minimum 1 in 604 |
| May 6, 1921 | 9 a.m. | Negative for spirochaetes | 1600 |
| May 7, 1921 | 9 a.m. | *Positive for spirochaetes* | 1 in 405 |
| May 8, 1921 | 9 a.m. | *Positive for spirochaetes* | 1 in 309 |
| May 9, 1921 | 9 a.m. | *Positive for spirochaetes* | 1 in 823 |
| | 4 p.m. | Negative for spirochaetes | 1000 |
| May 10, 1921 | 9 a.m. | Negative for spirochaetes | 1000 |
| May 11, 1921 | 9 a.m. | Negative for spirochaetes | 1000 |
| May 12, 1921 | 9 a.m. | Negative for spirochaetes | 1000 |

May 8, 1921. He felt well on this date but search of blood films made at 9 a.m. revealed one spirochaete in 309 fields.

May 9, 1921. At 4 p.m. he suffered a relapse, his temperature rising to 102° F. A blood film made at this time showed one spirochaete in 823 fields. At 6 p.m. his temperature was 104.8° F.

May 10, 1921. At 8 a.m. his temperature was 97.6° F. and he felt much better. At 9 a.m. he was given a 0.4 gram dose of arsphenamine and following this he made an uneventful recovery. He was kept under observation in the hospital seven days after his temperature reached normal and for seven days more as an outpatient.

(See temperature charts at the end of this article.)

## LITERATURE

A large amount of work by many investigators has been done upon the relapsing fevers of Asia, Europe, Africa and the Americas. It may be possible that the human transmission work detailed in this paper has been previously done, if so it is our desire to give credit where it belongs and to contribute this report as additional proof that relapsing fever is transmitted by the tick. However, in the literature at hand we were not able to find where this had been done and as our opportunity to carry out this investigation with naturally infected ticks was so exceptional we did not feel justified in waiting until we could make a still more exhaustive search of the literature. The Manual of Tropical Medicine by Castellani and Chalmers, third edition, 1919, gives a fairly comprehensive review of the literature and as a supplement to that we reviewed all the Tropical Diseases Bulletins which we have received during the past four years.

According to Castellani and Chalmers the relapsing fever of Europe, caused by the *Spiroschaudinnia recurrentis* or *S. obermeyeri*, is transmitted by the louse ("Most authorities consider lice to be the carriers," p. 443) and the relapsing fever of India, caused by *S. carteri*, "is spread by the louse in all probability." Concerning the relapsing fever of West Africa they state it is "an acute specific relapsing fever caused by *Spiroschaudinnia duttoni* Novy and Knapp, 1906, and spread by *Ornithodoros moubata* Murray." In the paragraph entitled History they further state:

Nabarro, in August, 1903, was the first to observe a spirochaete in human beings in Uganda, but as his publication, through no fault of his own, did not appear until much later, his discovery was forestalled by those of Ross and Milne in 1904, and Dutton and Todd, also in

1904, who found the cause of the tick fever to be a spirochaete, the latter observers also proving that it was introduced into the blood by the bite of a tick, *Ornithodoros moubata.*

Dutton and Todd (1) above referred to made a very careful study of relapsing fever in West Africa in 1904–1905. They were able to infect monkeys and a white rat with relapsing fever by allowing naturally infected ticks to feed on them; to transmit the spirochaete from animal to animal; and to transmit the spirillum by the bites of young ticks newly hatched in the laboratory from eggs laid by infected parents. In addition they collected a large amount of evidence pointing to the tick as the common transmitter of this disease. This work has been generally accepted as proof that relapsing fever may be transmitted by the tick *O. moubata.* However, they do not state that they transmitted the disease by allowing either naturally or artificially infected ticks to feed on the human subject.

Castellani and Chalmers make no reference to the possible transmitting agent of relapsing fever in North and Central America. Referring to the Relapsing Fever of South America they state "According to Robledo, this parasite is carried by *Ornithodoros turicatus.*" Robledo (2) apparently bases his statement upon the frequency with which he has found his cases to have been bitten by ticks. The part of his article referring to the tick reads as follows:

Autant que j'ai pu l'observer, notre parasite a été toujours transmis aux malades par la piqûre *d'Argas americanus* (*Ornithodoros chinche* P. Gervais, 1859). Cet acarien, très abondant dans les régions chaudes de Colombie, sourtout dans les maisons abandonées, où reste de l'herbe, de la paille, etc., s'attaque aux voyageurs avec une grande avidité. Sa piqure est suivie presque toujours d'une démangeaison très intense, et parfois de vésicules, surtout chez les individus à peau fine.

En dépit de mes efforts pour tranmettre la fièvre récurrente a l'aide de *Pediculus capitis*, jamais je n'ai réussi. Mais, peut-être n'ai-je pas été placé dans de bonnes conditions et est-il possible que la maladie soit quelquefois transmise par cet insecte?

## IDENTIFICATION OF THE SPIROCHAETE

The amount of work which we have done thus far does not permit us to apply a specific name to the spirochaete with which we have been working; however, we feel that that part of the work of identification which has been completed should be included in this paper and is therefore given. Relapsing fever spirochaetes are differentiated by agglutination reactions, immunity experiments and animal reactions. We have not yet secured cultures of the various types of spirochaetes or their respective agglutinating sera so therefore have not performed any agglutination tests. The following is a summary of the animal reactions to the different types of the spirochaete as given by Darling.[3]

*Group A.* The group causing a relapsing or recurring infection in man, monkeys, white mice and white rats, including *Sp. Duttoni* and the tick–fever of Africa.

*Group B.* The group causing the infection in man, monkeys and white mice, but with a single paroxysm in white rats. This group comprises the relapsing fever of Panama and the two cases studied by Carlisle.

*Group C.* The group causing a recurring infection in man and monkeys but failing to cause an infection in small rodents with blood direct from human sources, yet causing an infection in small rodents after a preliminary passage through the monkey. This group includes the relapsing fever of Europe, caused by *Sp. Obermeieri*.

*Group D.* The group causing a recurring infection in man and monkeys but only transient infections in white rats and white mice. This group includes the relapsing fever of Bombay caused by *Sp. Carteri*.

The results obtained by inoculation of our spirochaete into white rats, white mice, monkeys, guinea-pigs, rabbits and wild rats are given below.

### *White rats*

Injection of infected material into the white rat, either by the subcutaneous or intraperitoneal method, is usually followed by a prompt appearance of spirochaetes in the blood stream in from twenty-four to forty-eight hours. The initial appearance, however, may be delayed for one or two days longer.

The subsequent course of infection varies in different rats but it is usual to find spirochaetes in large numbers on the second and third days following their initial appearance and in small numbers at irregular intervals thereafter up to the thirteenth day. This statement is based on a series of eleven rats examined daily for eleven days or longer. There was a return of the spirochaetes in the blood stream after an apparent freedom, in seven but not in four. The return of the spirochaetes was characterized by the small number present, their irregular time of appearance and the short period of time in which they could be found in the blood stream.

Seven of those white rats may have had a continued spirochaetosis as described by Darling (4). He states

> The infection in white rats is characterized by the rapid disappearance of spirochaetes from the blood stream. The disappearance is not complete but it is rarely possible to demonstrate the spirochaetes in the peripheral blood twenty-four hours after the height of the infection.

However if we accept the return of spirochaetes in the peripheral blood after an apparent absence of several days duration, although few in number, as evidence of a relapse in rodents we may conclude that some white rats but not all are subject to relapse.

In all tables given a Bausch and Lomb $\frac{1}{12}$ oil immersion objective and $5\times$ eyepiece were used.

### *White mice*

The reactions in white mice agree in the main with those obtained by Darling in 1907, as will be seen by reference to table given below showing results obtained in our series. Darling states

> In the initial paroxysm there is a greater number of spirochaetes per field per day and the duration of the paroxysm is somewhat longer

than subsequent ones. The first paroxysm lasts about three days. The period between the first and second paroxysm is from four to five

TABLE 8

*White rats inoculated with relapsing fever spirochaetes April and May, 1921*

| RAT NUMBER | DAYS EXAMINED | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 |
| Rat 293 | 0 | 2 | 600 | 0 | 1 | 0 | 1 | 1 | 3 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Rat 306 | 0 | 30 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Rat 308 | 1 | 50 | 200 | 0 | 0 | 0 | 1 | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Rat 309 | x | 900 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Rat 311 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Rat 312 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Rat 333 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 1 | 0 | x | x | x | x | x | x | x | x |
| Rat 444 | 3 | 25 | 600 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | x | x |
| Rat 327 | 0 | 2 | 800 | x | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | x | x | x | x | x | x | x | x |
| Rat 329 | 0 | 3 | 300 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | x | x | x | x | x | x | x | x | x | x |
| Rat 372 | x | 0 | 10 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | x | x | x | x | x | x | x | x | x | x |
| Summary............ | + | + | + | + | + | 0 | + | + | + | + | + | + | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Numerals = Number of spirochaetes found in 300 fields.
0 = No spirochaetes found in 300 fields.
x = No examination made.

TABLE 9

*White mice inoculated with relapsing fever spirochaetes April and May, 1921*

| MOUSE NUMBER | DAYS EXAMINED | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 |
| Mouse 326 | 0 | 15 | 90 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | x | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Mouse 325 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | Died | | | | | | | | | | | |
| Mouse 323 | 6 | 18 | 0 | 0 | 0 | 0 | 0 | 2 | | Killed | | | | | | | | | | | |
| Mouse 363 | 36 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 6 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Mouse 365 | 30 | 24 | 0 | 0 | 0 | 0 | 1 | 9 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | x | x |
| Mouse 366 | 24 | 9 | 0 | 0 | 0 | 0 | 0 | 24 | 0 | 0 | 6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Numerals = Number of spirochaetes found in 300 fields.
0 = No spirochaetes found in 300 fields.
x = No examination made.

days. The second paroxysm lasts from two to three days. This may be followed by an intermission of four or five days, and followed by a third relapse lasting two or three days.

### *Monkeys*

The reaction in the *Macaccus rhesus* is comparable to that of man. One or more relapses occur and the animal during the attack is irritable and refuses to take his food. The temperature curve, while not reliable, usually shows a rise of one or two

TABLE 10

*Monkeys inoculated with relapsing fever spirochaetes April and May, 1921*

| MACACCUS NUMBER 317 | | | MACACCUS NUMBER 318 | | |
|---|---|---|---|---|---|
| DAYS | SPIROCHAETES SEEN IN 600 FIELDS | TEMPERATURE | DAYS | SPIROCHAETES SEEN IN 600 FIELDS | TEMPERATURE |
| | | °F. | | | °F. |
| 1 | 0 | 100.4 | 1 | 1 | 100.2 |
| 2 | 2 | 102.5 | 2 | 48 | 102.4 |
| 3 | 300 | 103.6 | 3 | 1200 | 102.8 |
| 4 | 900 | 105.4 | 4 | 1200 | 102.2 |
| 5 | 0 | 102.6 | 5 | 0 | 101.0 |
| 6 | 0 | 101.4 | 6 | 0 | 101.2 |
| 7 | 0 | 101.0 | 7 | 0 | 101.6 |
| 8 | 9 | 102.2 | 8 | 8 | 102.2 |
| 9 | 20 | 101.8 | 9 | 3600 | 104.2 |
| 10 | 600 | 103.6 | 10 | 0 | 101.8 |
| 11 | 24 | 102.4 | 11 | 0 | 102.0 |
| 12 | 0 | 100.4 | 12 | 0 | 101.0 |
| 13 | 0 | 101.4 | 13 | 0 | 102.0 |
| 14 | 0 | 101.6 | 14 | 0 | 100.4 |
| 15 | 0 | 101.4 | 15 | 10 | 101.4 |
| 16 | 0 | 101.4 | 16 | 150 | 101.8 |
| 17 | 0 | 101.8 | 17 | 0 | 101.4 |
| 18 | 0 | 103.8 | 18 | 0 | 101.8 |
| 19 | 0 | 103.0 | 19 | 0 | 102.6 |
| 20 | 0 | 102.4 | 20 | 0 | 103.2 |
| 21 | 0 | 103.4 | 21 | 0 | 102.4 |
| | | | 22 | 0 | 102.8 |
| | | | 23 | 0 | 103.0 |

degrees at the height of the infection. There is also an apparent loss of weight. It will be noted that two relapses occurred in monkey No. 318 while monkey No. 317 had but one. The spirochaetes, after their first appearance, showed a daily increase in number until the height of the infection was reached, after which they abruptly disappeared from the peripheral blood to reappear as a relapse in from three to five days.

Monkey 317 received, on April 27, 1921, 1.5 cc. of heart's blood (citrated) from rat 362. Rat 362 had 10 spirochaetes to 100 fields at the time the blood was withdrawn. This strain of spirochaetes was obtained from experimental human case O. F. L.

Monkey 318 received, on April 23, 1921, 2 cc. of heart's blood from rat 304. Rat 304 had 1 spirochaete in 100 fields at the time the blood was withdrawn. This strain of spirochaetes was obtained from (J. T. B.), a relapsing fever patient in Ancon Hospital and had been passed through three white rats and one wild (cotton) rat.

### *Guinea-pig and rabbit*

An adult guinea-pig and adult rabbit resisted infection. Guinea-pig 331 and rabbit 330 each received on May 7, 1921, 0.75 cc. of heart's blood from rat 328. Rat 328 had 4 spirochaetes in 100 fields on the date of inoculation. Daily films were made for ten days succeeding inoculation and 300 fields examined daily but no spirochaetes were found.

### *Wild rats*

The black rat (*Mus rattus*) and the cotton rat (*Sigmodon hispidus chiriquensis*) were found to be susceptible to infection with this spirochaete, reacting in a general way the same as the white rat.

TABLE 11

| MICRONS | 4–6 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of parasites | 1 | 0 | 1 | 10 | 10 | 13 | 11 | 17 | 8 | 21 | 6 | 10 | 8 | 4 | 0 | 5 | 2 | 2 | 1 |

Films were made from man, rat and monkey and the spirochaetes were drawn as encountered. No appreciable difference existed in the length of the spirochaetes whether they were from man, monkey or rat. The day of the paroxysm (whether second, third or fourth) did not materially affect the average length of the spirochaete, although a slight increase in length occurred as the paroxysm advanced.

### *Morphology and division*

*Dark field preparations.* The movements of the spirochaete whether in the fresh blood or in Noguchi's medium are characterized by a rapid spring-like spiral movement which propels the organism for a distance of about twice its length. The systole is preceded by a short diastolic period during which the organism partially doubles on itself as though gathering itself together for its spring forward or backward as the case may be. Occasionally one extremity of a spirochaete becomes anchored to the cover slip and it lashes its body around this pivot. The attached extremity is circular in outline. At times when con-

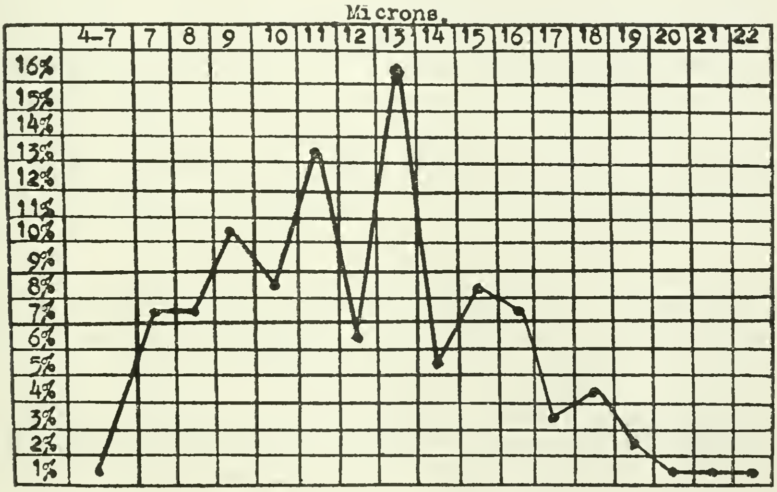



Fig. 1. Measurement of Spirochaetes. Length of Spirochaetes. (130 Measured)

Blood films dried and stained with Hasting's stain. Measured by the camera lucida method. Shortest form measured 4.6 microns in length. Longest form measured 22. microns in length.

ditions are unfavorable and just before motion ceases there is a distinct vibratory non-progressive movement. After all movement has stopped the spirochaetes are seen as refractile chains held together by a poorly refractile envelope.

In rats blood taken when the infection is at its height, both long and short forms are seen but the long forms predominate. If Noguchi's medium is then richly inoculated, with 1 cc. or more of blood, and examined six and twenty-four hours later the majority of the spirochaetes will be found to have increased enormously in length. Agglutinated masses are present and end to end chains of spirochaetes common. Although many dark field preparations were examined a terminal tuft was never observed. The ends of the spirochaete tapered into a delicate point and in some instances the short forms with the terminal whip as described by Novy and Knapp were noted. It is probable however that the terminal whip on the short form is a product of division and does not represent an organ of locomotion.

*Division.* The act of dividing by transverse division was unmistakably observed in four instances in dark field preparations made from Noguchi's medium. The process was a violent one and consumed the greater part of one hour for its completion. The spirochaetes seen to divide were about 20 microns in length and had about six "turns." Each of these four was observed before division began and there was no evidence, even suggestive, that any one of them was other than a single organism. Division began by an alternate pulling of the future halves of the organism. This movement was similar to the normal movement of the spirochaete but more violent. It continued for some time until finally the spirochaete pulled apart in the middle. After the division V or Y shapes were assumed or a further separation occurred until there was an interval between the daughter cells about four times their length. The latter forms were, however, connected by a thin invisible filament as was evidenced by the fact that a movement of one carried the other in the same direction. They finally separated completely and passed out of the field as daughter cells, each about half the length and with half the number of turns characterizing the mother cell. The daughter cells do not always begin movement after their formation possibly because of the energy expended in the process of division.

*Granular bodies.* In some spirochaetes one or two highly refractile granules were noted. These granules were not dislodged or thrown off by violent movement of the spirochaete. Spirochaetes have also been observed to take up granules from the preparation under study and to run them up and down their length; however this is a transient condition of but a few seconds duration as they are quickly thrown off. While watching a spirochaete in the act of division in one instance, two granular bodies, one in each half, were seen to move rapidly up and down the spirochaete, each however remaining in its respective half. These granules were not thrown off during an observation period of one hour and when the act of division was completed one granule remained in each daughter cell as a motionless object.

*Stained films.* The spirochaetes in blood films stained with Hasting's stain were seen in a variety of forms. A few straight forms without curves were seen, some with only one or two curves were seen and others showed both fine and coarse curves in the same organism. The average adult spirochaete however had about six curves which were more or less uniform in size. Evidence of transverse fission was quite marked. Many long forms presented a thin drawn-out central portion; also two small spirochaetes joined together by a long extremely narrow filament were seen from time to time. As a whole the pirochaetes stained in a uniform manner. No vacuoles were seen in our specimens. One or two areas which did not take the stain were seen in some of the longer forms. These achromatic spaces have been quite generally accepted as having something to do with the act of division. A single, round body, well stained and somewhat larger in diameter than the spirochaete itself was seen in several spirochaetes. Sometimes this occurred at the extreme end of the spirochaete and sometimes near the center. This was probably the same body which was seen as a refractile granule in the dark field preparations.

## SUMMARY

Two white rats have been infected with relapsing fever by inoculating them with a suspension of macerated naturally infected ticks, *Ornithodoros talaje*.

Typical spirochaetes have been found in naturally infected ticks in Panama.

One monkey, *Macaccus rhesus,* has been infected with the relapsing fever of Panama by feeding a number of larvae (*O. talaje*) upon an infected white rat and twenty-two days later allowing the same ticks as first stage nymphs to feed on the monkey.

Three human beings, volunteer patients, have been infected with relapsing fever as follows:

1. The first by a subcutaneous injection of blood from a white rat which had been infected with relapsing fever by a combined subcutaneous and intraperitoneal injection of naturally infected ticks.

2. The second by a hypodermatic injection of a suspension of naturally infected ticks.

3. The third by being bitten by naturally infected ticks.

Tabulations of the results obtained by inoculating white rats, white mice and monkeys, *Macaccus rhesus*, with the spirochaetes of the relapsing fever in Panama are presented. Also a brief allusion is made to their measurements and appearance in cultures.

## CONCLUSION

The human tick, *Ornithodoros talaje*, has been proven to be the transmitting agent of the replasing fever in Panama by human experimentation.

## SUMMARIO

Dos ratas blancas infectadas con la fiebre recurrente por medio de la inoculacion de una suspensión macerada de garrapatas (*Ornithodoros talaje*) naturalmente infectadas.

En Panamá se han encontrado espiroquetes típicos en garrapatas naturalmente infectadas.

Después de haber conseguido que un número de larvas (*O. talaje*) se alimentaran sobre una rata blanca ya infectada, se consiguió la infección de un mono, *Macaccus rhesus*, veintidós días más tarde, permitiendo que las mismas garrapatas, en estado de ninfas de primer grado, se alimentaran sobre el cuerpo del mismo.

Tres seres humanos, pacientes voluntarios, fueron infectados con la fiebre recurrente, de la manera siguiente:

1. El primero, mediante una inyección sub-cutanea de sangre obtenida de una rata blanca que había sido ya infectada con la

fiebre recurrente por medio de una inyección combinada, cutánea é intra-peritoneal, de garrapatas naturalmente infectadas.

2. El segundo, mediante una inyección hipodérmica de una suspensión de garrapatas naturalmente infectadas.

3. El tercero, permitiéndosele que fuera picado por garrapatas naturalmente infectadas.

Se presentan cuadros demonstrativos de los resultados obtenídos inoculando ratas y ratoncillos blancos y monos (*Macaccus rhesus*) con los espiroquetes de la fiebra recurrente de Panamá. Así mismo se hace una alusión de su tamaño y apariencia en cultivos.

### CONCLUSION

Se demuestra, por experimentos humanos, que la garrapata humana (*Ornithodoros talaje*) es el agente transmisor de la fiebre recurrente de Panamá.

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Headquarters Panama Canal Department,
Quarry Heights, Balboa Heights, C. Z.,
May 17, 1921.

General Orders, }
No. 26. }

*Recognition of Unusual Service*

The following named enlisted men of Company A, Military Police, Panama Canal Department:

Private Kenneth K. Glover, 6414102,
Private Otto F. Lueckert, R-105716, and
Private Lewellyn N. Jourden, R-280766,

entered Ancon Hospital on April 19, 1921, and each voluntarily allowed himself to be inoculated "with suspected relapsing fever material in order to determine the intermediate host" in the transmission of relapsing fever in Panama. Each suffered an acute attack of relapsing fever, but from which all happily have recovered.

By means of the coöperation and voluntary assistance of these men, it has been proven that the human tick *Ornithodorus talaje* (Guerin-Meneville) is the transmitting agent of relapsing fever in Panama.

These three men were selected from approximately thirty men of Company A, Military Police, who volunteered for this experiment. By their self-sacrifice they have aided in establishing a scientific fact which will aid in the control of disease and result in less sickness and loss of life among our troops operating in the field and on the Isthmus. The Department Commander desires to commend these soldiers for their devotion and self-sacrifice, and the other soldiers who, though not called upon to undergo this ordeal, showed their willingness to imperil their lives in the cause of humanity. A copy of this order will be filed with their service records.

(201.4)

By command of Brigadier General KENNEDY:

H. O. WILLIAMS,
*Chief of Staff.*

*Official.*
J. W. CRAIG,
Adjutant.
True Copy:

# THE CULTIVATION OF TRICHOMONAS HOMINIS

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There are many different species of Trichomonas, three of which have been described as parasitic in man. These are *Trichomonas buccalis*, Goodey and Wellings; *Trichomonas hominis,* Davaine; and *Trichomonas vaginalis,* Donné. It is even possible that these three species are the same but this has not yet been proved.

In 1915 Lynch cultured *Trichomonas hominis* from the intestine in neutral and acid bouillon and kept it alive for three days at 30°C. By transferring to new media he was able to carry the culture through five or six generations.

Ohira and Noguchi (1917) report the cultivation of the Trichomonas from the human mouth calling it *Tetratrichomonas hominis.* According to Kofoid's (1920) recent review of the nomenclature of the flagellates, Ohira and Noguchi were working with *Trichomonas buccalis.* They cultured it on a mixture of ascitic fluid and Ringer's solution, using equal portions and found that it gave much better results than Lynch's bouillon medium. They carried their strains for over twenty generations.

Boyd (1918) reports the cultivation of *Trichomonas hominis* on a non sterile medium which was a mixture of faecal material and physiological saline.

Pringault (1920) used Ohira and Noguchi's medium for the cultivation of *Trichomonas intestinalis,* i. e., hominis, very successfully.

Recently (1921) Reuling has cultured *Trichomonas vaginalis.* He tried many media but says the flagellates never lived longer than twenty-four hours on any of the media except that described by Ohira and Noguchi. (One-half Ringer's solution and one-half ascitic fluid). On this medium *Trichomonas vaginalis* divided, reaching its greatest period of reproduction on the fourth or fifth day. On the following day all the organsims had completely disappeared. He kept them at 37°C.

On April 7 a stool containing *Trichomonas hominis* was sent to this laboratory. Several test tubes of different kinds of media were inoculated with the material by means of a sterile platinum loop and incubated at 35°C. On May 4 a single individual was isolated from the general culture and used to start a "pure line" of Trichomonas. A very simple method was used to isolate the pure line. Small drops of the medium in which the Trichmonas were not very plentiful, i.e., young or, old cultures, were placed on cover slips which were then inverted over depression slides and examined. Trichomonas is plainly visible under the high dry objective. When the drop was found to contain only one Trichomonas the corners of the cover slip were cut off with scissors and the remaining small piece of glass with its single Trichomonas was dropped into a test tube containing Locke-egg medium. This was then incubated at 35°C. and in a few days the medium was swarming with Trichomonas. The pure line as well as the general stock culture are now (June 7) both in a normal condition after more than eight weeks of cultivation on sterile media. Transfers to new media have been made every second, sometimes every fourth day, depending on the general condition of the cultures. All cultures are kept in a constant temperature chamber at 35°C.

Many individuals in the pure line of Trichomonas have been carefully studied. They have four anterior flagella and an undulating membrane with a lateral marginal flagellum which leaves the membrane toward the posterior part of the animal. These cultured flagellates measure from 7 to 10$\mu$ in length and from 5 to 8$\mu$ in width. They are very active in the liquid media, moving by means of their flagella. The formation of pseudopodia was not observed.

## MEDIA

A medium which is the combination of a hen's egg and Locke solution proved most successful for the cultivation of Trichomonas hominis. A hen's egg is thoroughly shaken up in a flask with glass beads. To this is added 200 cc. of Locke solution which is made in the following way.

| | *grams.* |
|---|---|
| Sodium chloride | 0.9 |
| Calcium chloride | 0.024 |
| Potassium chloride | 0.042 |
| Sodium carbonate | 0.02 |
| Dextrose | 0.25 |
| Distilled water | 100 cc. |

This was heated over a hot water bath and kept in constant motion for fifteen minutes. It was then filtered through cotton with a suction pump and about 6 cc. of the filtrate put into test tubes These were autoclaved for twenty minutes under fifteen pounds of pressure.

An ovomucoid medium was made from the whites of two eggs, which were thoroughly shaken up with glass beads. To this was added 200 cc. of 0.7 per cent sodium chloride solution. This was cooked for half an hour over a hot water bath and kept all the time in constant motion. It was then filtered, tubed and autoclaved just as the Locke-egg medium.

On the Locke-egg medium Trichomonas appeared in greatest numbers on the second day after inoculation. Then as many as 23 organisms could be counted in the field of a number 16 objective, 10 ocular. These were of all sizes, large ones preparing to divide and smaller ones which had already divided. This difference in size even in the pure line cultures was very noticeable when the Trichomonas appeared in great numbers at the height of their reproductive period. On this medium they rarely lived longer than six days.

On the ovomucoid medium they usually reached their greatest period of productivity on the third day. The cultures lived from six to ten days, a few lived 11 days. When a few drops of sheep serum or, better still, human serum were added the organism appeared in even greater numbers. At times from 40 to 45 Trichomonas could be counted in one field. These rich cultures also died more quickly, no doubt due to the accumulation of waste products.

Trichomonas did not encyst in any of the cultures. Nothing resembling a real cyst was ever found. They would become less active in the older cultures. Then they would round up and usually form a large vacuole. Soon they would go to pieces. Pringault describes the same process as taking place in his cultures. Perhaps these rounded organisms are the same as Lynch describes as cysts but I cannot consider them as such. They are of very short duration. One rarely finds them the day after the active Trichomonas have disappeared.

These media have proved so successful for the cultivation of intestinal protozoa that it seemed wise to share them with other investigators. The fact that neither ascitic fluid nor serum is necessary makes the media available for all investigators and teachers even though they are not connected with hospitals or public health laboratories.

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# A CONTRIBUTION TO THE STUDY OF MYCETOMA IN NORTH AMERICA

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CONTENTS



## I. INTRODUCTION

The disease whose North American occurrence we are considering is variously designated in the literature as "Madura foot," "Madura disease" or "Mycetoma." The disease referred to under these terms is usually understood as commonly and primarily affecting the foot and secondarily other parts of the body. Following the classification of Pinoy, noted later, the scope of the meaning of the term mycetoma has been extended by some authors, notably by Chalmers and his collaborators, to a marked extent. Thus Chalmers and Archibald (1917) define mycetoma as "including all growths and granulations which produce enlargement, deformity or destruction in any portion of the tissues of men or animals, and which are caused by the invasion of the infected area by fungi, belonging to different genera and species, which produce bodies of varying dimensions,

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color and shape composed of hyphae, and sometimes chlamydospores, embedded in a matrix. These bodies, which are capable of giving rise to mycelial filaments on germination, are termed *grains*, and are found either embedded in the pathological tissue forming these growths and granulations, or escaping freely in the discharge therefrom." Thus the extension of the name as defined above enlarges its scope to an extent almost embarrassing particularly through the inclusion of the actinomycoses, as noted later. Though recognizing the soundness of the definition as above given, yet for the purpose of our paper we shall use mycetoma in the narrower and older sense, restricting ourselves to diseases of the above character occurring in the extremities, particularly the lower.

### *Historical review*

According to Hirsch (1886) mycetoma evidently came under the observation of the earlier European physicians in India. Kämpfer mentions the disease as early as 1712. Subsequent writers appear to have seen the disease, but it is apparent that in many instances it was confused with elephantiasis. The designation Madura foot, by which it is quite commonly known, was first introduced by Colebrook in 1846, while the term mycetoma was introduced by Vandyke Carter in 1860. Ballingal in 1855 appears to have been the first to have carefully described the disease, while the appearance of Vandyke Carter's (1874) monograph "On mycetoma or the fungus disease of India" gave us a classical account of the disease which has never been excelled. Both of these writers regarded the disease as a parasitic process caused by fungi, while Carter in addition endeavored to study the causative organism. His work in this direction, which was done prior to the day of the development of bacteriological technique, was later proven erroneous, which circumstance however does not detract from the value of his monograph. Later observations extended the geographical range over which the disease is encountered to include the tropical and subtropical areas of both continents, even extending into the temperate zones. Carter recognized two clinical varieties, the ochroid and the melanoid, based upon the color of the granules observed in the discharge from the sinuses. He considered, as was but natural, that both types were due to the same fungus. As a result of histological studies of the granules, Kanthack (1893) gave support to Carter's views. In the next year Boyce and Surveyor (1894) showed by similar methods that separate and distinct types of fungi were concerned in the production of the ochroid and melanoid varieties. Kanthack had already observed that the ochroid type was due to a streptothrix, but made the error of concluding the melanoid type was due to the same organism. Boyce and Surveyor showed that a true mould was responsible for the melanoid variety. The first successful cultivation of a fungus from the ochroid variety was reported by Vincent (1894) from North Africa, while Wright (1898) first isolated a mould from the granules of a case of the melanoid variety in the United States. Successful animal inoculations (monkeys) have been secured with a streptothrix from ochroid granules, and was first accomplished by Musgrave and Clegg (1907) in the Philippines. Pinoy (1913) reports successful inoculations with true moulds cultivated from both types of granules. Pigeons were employed, but the results were inconstant.

## II. KNOWN ETIOLOGY OF MYCETOMA

The earlier classification of mycetomata on the basis of the color of the grains has been superseded by one based upon the nature of the causative fungus, since recent investigations by Brumpt, Pinoy and others have revealed the multiplicity of organisms which can produce these fungus tumors. Pinoy (1913) proposed the following classification, which has since been largely followed:

1. The actinomycoses, including those whose grains are composed of thin, non-septate filaments, and
2. The true mycetomata (the maduramycoses of Chalmers and Archibald) whose grains are formed by thicker septate filaments with a distinct membrane surrounding the cells.

The old classification of Vandyke Carter based on the color of the granules alone, is inadequate, since it is now known that the grains of any one type may be produced by a variety of widely different fungus parasites. Chalmers and Archibald (1917) propose the following classification, which is a combination of the foregoing two:

1. Maduramycoses:
   - *a.* Black grained maduramycosis
   - *b.* White or yellow grained maduramycosis
   - *c.* Red grained maduramycosis
2. Actinomycoses:
   - *a.* Black grained actinomycosis
   - *b.* Yellow grained actinomycosis
   - *c.* Red (sometimes yellowish) grained actinomycosis

Brumpt (1913) gives the following organisms as capable of producing mycetomata:

1. Fungi producing true mycetomata:
   - *a.* *Sterigmatocystis nidulans*, var. *nicollei*, Pinoy, from North Africa
   - *b.* *Aspergillus bouffardi*, Brumpt, from east Africa
   - *c.* *Madurella mycetomi*, Laveran, from east Africa
     *Madurella tozeuri*, Nicolle and Pinoy, from North Africa
   - *d.* *Indiella mansonii*, Brumpt, from India
     *Indiella reynieri*, Brumpt, from France
2. Fungi producing actinomycotic mycetomata
   - *a.* *Actinomyces* (Discomyces) *madurae*, Vincent, (syn. *A. indica*) from Africa and India
     *Actinomyces somaliensis*, Brumpt, from east Africa
     *Actinomyces pelletieri*, Laveran
     *Actinomyces asteroides*, Eppinger, from Europe, Asia and Africa
     *Actinomyces freeri*, Musgrave and Clegg, from the Philippines
     *Actinomyces braziliensis*, Lindenberg, from South America

Chalmers and Archibald (1917) in a careful review of the reported species, regard *A. madurae* (syn. *A. indica*) and *A. pelletieri* as identical, and also regard *A. freeri* and *A. braziliensis* as being identical with *A. asteroides*. To this list of fungi capable of causing mycetoma, these authors have added the following:

1. a. *Glenospora khartoumensis*, Chalmers and Archibald, from the Sudan
   *Glenospora semoin*, Chalmers and Archibald, from India
   b. *Scedosporium sclerotiale*, Pepere, from Sardinia
   *Scedosporium apiospermum*, Saccardo, from Sardinia
2. a. *Actinomyces* (*Nocardia*) *convoluta*, Chalmers and Christopherson, from the Sudan

We have omitted including North America in the range of the species of *Actinomyces*, where such was given by Chalmers and Archibald, as from a careful perusal of their papers and our own survey of the field we feel their data are altogether inadequate to identify the forms concerned.

Thus in all, at least thirteen species of fungi have been ascertained to be capable of producing mycetoma, all of which with one exception have been reported from the eastern hemisphere. Our study will show that Pinoy's classification will apply to the disease as encountered in North America, though the actinomycoses are of most common occurrence, and also add another species to the list of fungi capable of producing the maduramycoses.

### III. OCCURRENCE OF MYCETOMA IN NORTH AMERICA

The earliest report of mycetoma in North America is by M'Questin (1874) who reported three cases observed in Sonora, Mexico. Two years later, Kemper and Jameson (1876) reported a case of mycetoma in a resident of Indiana. The accuracy of the diagnosis in this case has been questioned by some of those who subsequently reported cases, yet nevertheless we are inclined to the view that Kemper and Jameson were correct in their diagnosis. Other cases were subsequently reported by Adami and Kirkpatrick (1895), Hyde, Senn and Bishop (1896), Pope and Lamb (1896) Wright (1898), Arwine and Lamb (1899), Albertini and Desvernine (1901) who reports two cases, Cicero (1912) who reports 6 cases, Allison (1912), Sutton (1913) who reports 3 cases, Ocaranza (1914) who reports 4 cases, Burres (1916) and Winslow (1917). To this series of 26 cases it is our privilege to add 4. For this opportunity we are indebted to

TABLE 1

*Epidemiology of North American cases of mycetoma*

| NUMBER OF CASE | REPORTER | YEAR REPORTED | PLACE DISEASE RECOGNIZED | SEX | RACE | AGE AT ONSET | RESIDENCE AT ONSET | OCCUPATION | NUMBER |
|---|---|---|---|---|---|---|---|---|---|
| 1 | M'Questin | 1874 | Hermosillo, Mexico | M | Mexican | Adult | Mexico | | 1 |
| 2 | M'Questin | 1874 | Hermosillo, Mexico | M | Mexican | Adult | Mexico | | 2 |
| 3 | M'Questin | 1874 | Hermosillo, Mexico | M | Mexican | Adult | Mexico | | 3 |
| 4 | Kemper and Jameson | 1876 | Muncie, Ind. | M | White | 24 | Indiana | Drygoods clerk | 4 |
| 5 | Adami and Kirkpatrick | 1895 | Montreal, Canada | M | White | 11 | Canada | | 5 |
| 6 | Hyde and Senn | 1896 | Chicago, Ill. | M | White | 7 | East Iowa | Dental student | 6 |
| 7 | Pope and Lamb | 1896 | Ft. Stockton, Texas | M | Mexican | 19 | Texas | | 7 |
| 8 | J. H. Wright | 1898 | Boston, Mass. | F | White | 25 | Massachusetts | Housewife | 8 |
| 9 | Arwine and Lamb | 1899 | Ft. Ringgold, Texas | M | Mexican | 43 | Texas | Rancher | 9 |
| 10 | Albertini and Desvernine | 1900 | Havana, Cuba | F | Negro | 44 | Cuba | Laundress | 10 |
| 11 | Albertini and Desvernine | 1900 | Havana, Cuba | M | Negro | 31 | Cuba | Farmlaborer | 11 |
| 12 | Cicero | 1912 | Mexico City | M | Mexican | Adult | Mexico | Farm laborer | 12 |
| 13 | Cicero | 1912 | Mexico City | M | Mexican | Adult | Mexico | | 13 |
| 14 | Cicero | 1912 | Mexico City | M | Mexican | Adult | Mexico | | 14 |
| 15 | Cicero | 1912 | Mexico City | M | Mexican | Adult | Mexico | | 15 |
| 16 | Cicero | 1912 | Mexico City | M | Mexican | Adult | Mexico | | 16 |
| 17 | Cicero | 1912 | Mexico City | M | Mexican | Adult | Mexico | | 17 |
| 18 | Allison | 1913 | Kingsville, Texas | M | Mexican | 77 | Mexico or Texas | Gardener | 18 |
| 19 | Sutton | 1913 | Kansas City, Mo. | M | Mexican | 21 | Mexico or Texas | Laborer | 19 |
| 20 | Sutton | 1913 | Kansas City, Mo. | F | White | 12 | Texas | Housewife | 20 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 21 | Burres | 1915 | Panama | M | Indian | 36 | Panama | | 21 |
| 22 | Winslow | 1917 | Baltimore, Md. | M | Negro | 26 | Maryland | Farm laborer | 22 |
| 23 | Ocaranza | 1914 | Guaymas, Mexico | M | Mexican | Adult | Mexico | Ranch laborer | 23 |
| 24 | Ocaranza | 1914 | Guaymas, Mexico | M | Mexican | Adult | Mexico | Ranch laborer | 24 |
| 25 | Ocaranza | 1914 | Guaymas, Mexico | M | Mexican | Adult | Mexico | Cowboy | 25 |
| 26 | Ocaranza | 1914 | Guaymas, Mexico | M | Mexican | Adult | Mexico | Ranch laborer | 26 |
| 27 | Boyd and Crutchfield | 1921 | Galveston, Texas | M | Negro | 18 | Texas | Longshoreman | 27 |
| 28 | Boyd and Crutchfield | 1921 | Houston, Texas | M | Mexican | 11 | Mexico | Laborer | 28 |
| 29 | Boyd and Crutchfield | 1921 | Douglas, Ariz. | M | Mexican | 40 | Arizona | Laborer | 29 |
| 30 | Boyd and Crutchfield | 1921 | Galveston, Texas | M | Negro | 22 | Texas | Farm laborer | 30 |
| 31 | Hammack | | Los Angeles, Cal. | | | | | | 31 |
| 32 | Hammack | | Los Angeles, Cal. | | | | | | 32 |

Dr. A. O. Singleton of this institution for one, to Dr. H. L. D. Kirkham of Houston for a second, to Dr. H. S. McGee of Douglas, Arizona, for the third, while the fourth occurred in the dermatological service of one of us in this institution.

In connection with this study we made every effort to learn of unreported cases of mycetoma. Only one case was brought to our attention as a result of a request for information that was inserted in the Journal of the American Medical Association, and that was a case that had been previously reported. Dr. Roy W. Hammack of Los Angeles, California, informs us that two cases have been seen in the Los Angeles County Hospital. Dr. E. S. Lain of Oklahoma City informs us that a migratory case was seen at his clinic at that city in 1920. Inquiries were addressed to the medical superintendents of the United Fruit Company at various stations throughout Central America. Dr. F. C. Watson at Almirante, Panama, and Dr. N. P. McPhail at Puerto Barrios, Guatemala, have never observed the disease. Dr. A. A. Facio at Port Limon, Costa Rica, informs us that a few cases have come under his observation. Burres (1916) states that a few cases have been observed in the Santo Tomaso Hospital, Panama. No Panamian cases are recorded in the Proceedings of the very active medical society of the canal zone. It therefore appears likely that mycetoma is not frequently encountered in North America.

In the above table (table 1) 30 cases are considered from an epidemiological standpoint, and are arranged in chronological order according to the year of their report. The numerals here employed to designate individual cases will be hereafter employed to designate the same cases.

*Epidemiological incidence of mycetoma*

Only 1 case has been recorded from Canada in a person who had never been out of the Dominion. A total of 13 (plus 2 from Los Angeles) are known from the United States. Of these 9 could not have contracted infection outside the country. Of the remaining 4, 1 can certainly be credited to Mexico. One case (8) that of Wright's black grained mycetoma, may possibly be credited to Italy. The patient, an Italian woman, had been in America an uncertain number of years before her onset. No other case of black grained mycetoma is known from North America, while other cases have been observed in Italy. Thirteen

cases are reported from Mexico, one from Panama, and 2 from Cuba. The approximate location of their residences at onset is shown on the map of North America. It is interesting to note that of the 15 cases from the United States, 7 have been recognized in residents of Texas.

Only 3 of these 30 cases are women.

Five cases are Caucasians, 5 negroes, 1 an Indian, and 19 for want of a better designation may be described as native Mexicans, though probably actually Indians.

In 17 instances the age at the onset of the disease is known. In only one case did it occur during the first decade of life. In four instances the onsets were in the second decade, and in six instances in the third decade. The fourth and fifth decades witnessed the onset of 2 and 3 cases, while 1 occurred in the eighth decade. The onset, therefore, is most common between the ages of ten and thirty.

Nineteen of the patients were laborers by occupation, and of these, 14 were agricultural laborers. The occupations of the remainder when stated, are quite diverse, though one would infer that most if not all the remainder lead quite active lives out of doors.

These observations are in accord with the experience summarized in Vandyke Carter's classical study of the disease in India.

## IV. ONSET OF MYCETOMA

Two types of predisposing factors may be recognized which are closely related to the incidence of the disease among rural laborers. Fourteen cases went barefooted to such degree that the practice may be said to have been habitual. Several other cases may be presumed on good grounds to have avoided footwear to a similar extent, while a few on occasion appear to have gone barefooted out of doors. Secondly, it is important to note that 12 cases give a history of some form of traumatism to the affected member a variable period before the onset. These injuries were either contusions (6 cases) or punctured or incised wounds (6 cases), in most cases apparently received out of doors while barefooted. In one case (11) the onset very closely followed the traumatism, while in 3 cases the onset occurred within three months of the injury, while in 4 cases the relationship is not stated. In case 18, the time elapsing between the injury and onset is about twenty-five years, an interval of such duration as to throw serious doubt on the relationship, though it would appear that an indolent nodule persisted on the foot during that interval. The punctured wounds were most commonly produced by thorns (4 cases). The contusions were variously produced by a falling flat iron, a falling bag of oil cake, horse stepping on foot, a fall from a horse, the foot being caught between two ore cars, and the bite of an alligator gar. It appears possible that the trauma may have directly inoculated the parasite into the tissues of the foot, or that the practice of going barefooted brings the foot into direct contact with the infective agent which may then possibly enter through the ducts of the sweat glands. Climatic conditions that permit barefootedness probably account for the greater frequency of the disease in the tropics and sub-tropics.

In 6 cases (19, 21, 22, 28, 29, 30) the local injury previously noted completely healed before the onset of the disease. In only 4 cases (19, 22, 28, 29) were the initial lesions of mycetoma observed at the site previously traumatized.

In 8 cases (4, 5, 6, 8, 11, 19, 28, 29) the initial lesions appeared on the plantar surface of the foot, in 2 (30, 22) on the sides and in 2 (20, 10) the anterior portion of the foot, but not the toes, was first involved. The character of the initial lesion is subject to considerable variation. In 5 cases (4, 10, 11, 27, 29) early swelling of the foot was noted, either local or general in character, which only in 1 case (4) was painful, although in 2 others (9, 30) pain was an early and prominent symptom. The most constant initial lesion was the development of one or more nodules in the skin (5, 6, 11, 19, 20, 21, 28) which are variously described as "nodules," "button-like" tumors, "warts," etc. In case 20 the summits of the nodules were crowned with discharging sinuses. In only 1 case (11) did swelling of the foot precede the development of nodules. In 1 case (4) vesicles were the first sign noted, a red spot in another (9), an abscess (22) and in 2 (11, 28) an increased pigmentation of the skin of the affected area was noted. In 29 cases the disease occurred in the feet, and where stated the right foot was attacked in 6 cases and the left foot in 10 cases, while in 1 case (21) both feet were involved, though not simultaneously. In 1 case (25) of

TABLE 2

*Onset of North American mycetoma*

| NUMBER OF CASE | PREVIOUS TRAUMA | CHARACTER OF TRAUMA | | SITE OF TRAUMA | HEALING OF LOCAL INJURY | TIME BETWEEN INJURY AND ONSET | PLACE WHERE FIRST LESIONS NOTED | CHARACTER OF ONSET | EXTREMITY AFFECTED | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Puncture | Contusion | | | | | | Right foot | Left foot | Hand |
| 1 | | | | | | | | | | | |
| 2 | | | | | | | | | | | |
| 3 | | | | | | | | | | | |
| 4 | | | | | | | Blebs on sole | Swollen, red, painful | x | | |
| 5 | | | | | | | Sole, near toes | "Button" of flesh | x | | |
| 6 | | | | | | | Sole | Hard nodule on skin | | x | |
| 7 | | | | | | | | | x | | |
| 8 | | | | | | | Sole, near toes | | | x | |
| 9 | | | | | | | | Pain, later red spot | | x | |
| 10 | Yes | | Yes | Right foot | Yes | | Near toes | Swelling | x | | |
| 11 | Yes | | Yes | Left foot | | Continuous | Sole | Swelling, nodules | | x | |
| 12 | | | | | | | | | | | |
| 13 | | | | | | | | | | | |
| 14 | | | | | | | | | | | |
| 15 | | | | | | | | | | | |
| 16 | | | | | | | | | | | |
| 17 | | | | | | | | | | | |
| 18 | Yes | | Yes | Right foot | Small nodule | About 25 years | | | x | | |
| 19 | Yes | Yes | | Left sole | Yes | 1 month | Site injury | Subcutaneous lump | | x | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 20 | Yes | | Yes | Foot | | 1 year | Base great toe | Small discharge nodules | | x | |
| 21 | Yes | Yes | | Foot | Yes | | | Small wart | x | x | |
| 22 | Yes | Cut | | Left instep | Yes | 2 months | Site injury | Abscess | | x | |
| 23 | | | | | | | | | | | |
| 24 | | | | | | | | | | | |
| 25 | Yes | Yes | | Hand | | | | | | | x |
| 26 | | | | | | | | | | | |
| 27 | Yes | | Yes | Left instep | No | | | General swelling | | x | |
| 28 | Yes | Yes | | Left 3d toe | Yes | 3 weeks | Site injury | Blackening skin | | x | |
| 29 | Yes | | Yes | Left foot | Yes | $1\frac{1}{2}$ years | Dorsum foot | Swelling and pain | | x | |
| 30 | Yes | Yes | | Right sole | Yes | 2–3 months | Side ankle | Pain | x | | |
| 31 | | | | | | | | | | | |
| 32 | | | | | | | | | | | |

Ocaranza's series, the hand was the seat of the disease. In no instance, except in case 29, were the early manifestations observed by the attending physician. These accounts are therefore from histories given by the patients.

The recorded data from which the foregoing summarizations are made are given in table 2. It is to be noted that in only 14 cases is information regarding the onset given.

In no essential feature does the onset of North American mycetoma as just described, differ from that described by Vandyke Carter in what he designates as the early stage. He mentions the following four different types of onset:

1. The appearance of an area of localized induration of the skin, slightly elevated with ill defined edges, the color darker than usual, livid, no tenderness or heat and without any external apertures, or

2. The spontaneous appearance of a vesicle, with the underlying tissue swollen and hard, or

3. The appearance of a small lump or nodule projecting above the surface of the skin, deep seated, firm and fixed, and usually greater than ½ inch in diameter, or lastly

4. The appearance of small abscesses or boils.

All these may be recognized in the foregoing account.

### *Clinical course of mycetoma*

The recorded clinical course of the disease in this series of cases is presented in table 3.

In general the disease appears to run a slowly progressive course, extending over a considerable period of time. Usually the disease has been of several years duration when first seen by its describers. Only 2 cases (4, 8) were seen when the disease was less than a years duration, in 5 cases of from one to five years duration, in 4 cases from five to ten years and in 4 cases from ten to fifteen years and in 1 case it was of sixteen years duration when first seen. Usually the development is slow and gradual, but in cases 4, 8 and 9 the course was more rapid than usual.

The local symptoms do not vary materially. The most constant symptom, which appears invariably, is that of a local or general swelling of the foot, that may proceed to such an extent that all of the concavities of the external surface are obliterated. In 10 instances (4, 5, 6, 7, 9, 19, 20, 22, 28, 29) it was noted that the swelling was accompanied by tenderness on pressure, although the degree of painfulness would appear to vary materially with different cases. This is described as very severe, (4, 7, 9, 20, 22), variable (19, 28, 29) or little (5, 6). One patient (19) describes a sensation of fullness in the affected foot, another (9) states the foot is too heavy to carry, while a third (27) complains of numbness. Two (22, 30) complain of stiffness of the joints, in both of whom the swelling was most marked about the ankle. As the disease progresses locomotion appears to be increasingly difficult. In only 2 (5, 22) was it impossible, while 2 others (7, 20) could only get about with a crutch.

In fifteen cases the surface of the invaded areas of the foot was irregularly studded with nodules, whose character will be described later. The summits of these nodules mark the orifices of sinuses communicating with the interior of the foot. Some of these are scabbed over and evidently healing, others are open and discharge a scanty quantity of a thin sero-sanguinolent fluid. In 4 cases (4, 8, 22, 30) sinuses existed without the usual nodules having been present at any stage of the disease.

Trophic disturbances were only noted in 1 case (19) where there was a hypersecretion of sweat over the affected area.

In 2 cases it is noted (5, 22) that the leg muscles of the affected extremities appear atrophied.

In 7 cases (22, 23, 24, 27, 28, 29, 30) an absence of any systemic reaction attributable to the disease was noted. One patient (7) complained of an aching in the groin, while in another (22) the inguinal glands were enlarged.

Marked weakness, associated with emaciation was noted in 5 instances (1, 2, 3, 4, 7), though in some cases the nutritional deficiences appear to be due to the handicap of earning a livelihood which the disease first produced, rather than to any direct systemic influence.

TABLE 3

*Clinical course of North American mycetoma*

| NUMBER OF CASE | PROGRESS OF DISEASE | | | DURATION | SYSTEMIC EFFECTS | | | LOCAL SYMPTOMS | | | USE OF FOOT IN WALKING | EARLY STAGES | | COMMENT |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Rapid | Moderate | Slow | | Nutrition | Fever | Weakness | Pain | Swelling | Other | | Sinus on nodule | Sinus but no nodule | |
| 1 | | | Yes | | Poor | | Yes | | Yes | | | Yes | | |
| 2 | | | Yes | | Poor | | Yes | | Yes | | | Yes | | |
| 3 | | | Yes | | Poor | | Yes | | Yes | | | Yes | | |
| 4 | Yes | | | 6 months | | | Yes | Severe | Yes | | | | Yes | |
| 5 | | | Yes | 10 years | | | | Slight | Yes | | Until late | Yes | | |
| 6 | | | Yes | 13 years | | | | Slight | Yes | | Yes | Yes | | |
| 7 | | | Yes | 8 years | Poor | | Yes | Const. | Yes | | Yes | Yes | | Ache in groin |
| 8 | | Yes | | 6 months | | | | | Yes | | | | Yes | |
| 9 | | Yes | | 2 years | | | | Severe | Yes | | | Yes | | Foot too heavy |
| 10 | | | Yes | 6 months | | | | | | | | Yes | | |
| 11 | | | Yes | 3 years | | | | | | | | Yes | | |
| 12 | | | | | | | | | | | | | | |
| 13 | | | | | | | | | | | | | | |
| 14 | | | | | | | | | | | | | | |
| 15 | | | | | | | | | | | | | | |
| 16 | | | | | | | | | | | | | | |
| 17 | | | | | | | | | | | | | | |
| 18 | | | Yes | 7 years | | | | | Yes | | Difficult | Yes | | |
| 19 | | | Yes | 3 years | | | | Slight | Yes | Fullness | | | | local sweating |
| 20 | | | Yes | 11 years | | | | Severe | Yes | | Yes | Yes | | |
| 21 | | | Yes | 16 years | | | | | Yes | | Both feet | | | Not simultaneous |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 22 | | | Yes | 3 years | | None | | Severe | Yes | | Impossible | | Yes | Large glands groin |
| 23 | | | | | Good | None | None | | Yes | | | | | |
| 24 | | | | | Good | None | None | | Yes | | | | | |
| 25 | | | | | | | | | Yes | | Hand affected | | | |
| 26 | | | | | | | | | Yes | | | Yes | | |
| 27 | | | Yes | 5 years | Good | None | None | | Yes | Numbness | No | Yes | | |
| 28 | | | Yes | 11 years | Good | None | None | Slight | Yes | | | Yes | | |
| 29 | | | Yes | $1\frac{1}{2}$ years | Good | None | None | Some | Yes | Itching | Yes | Yes | | |
| 30 | | | Yes | 12 years | Good | None | None | | Yes | Induration | Difficult | | Yes | |

In Ocaranza's case of mycetoma of the hand, the hand and fingers were greatly swollen, with consequent loss of mobility in the fingers.

It would appear that the infection does not usually tend to extend beyond the foot, no matter how long the disease existed. In only 4 cases (9, 18, 22, 27) is any extension of the disease beyond the ankle noted, and that but for a short distance. It is to be recalled that case 22 had enlarged inguinal glands, which might possibly be due to an extension of the invasion. In these cases the disease was of two, seven, three and five years duration respectively.

In 1 case a slight local elevation of temperature in the affected foot was noted, but it does not appear that a systemic febrile reaction has ever been observed.

In no instance has any tendency toward a spontaneous limitation of the infection been observed. Progress of extension may be slow, but extension is always taking place. The potentialities in this direction have never been described or observed.

Thus in its clinical manifestations, North American mycetoma runs a course identical with that described by Vandyke Carter from India.

*Histories of new cases*

The histories of the new cases of mycetoma which we are reporting, and which have been discussed in the previous summarization, are presented herewith:

*Case 27* (Singleton). (Fig. 3, 4.) This patient was admitted to Sealy Hospital on three separate occasions before his foot was amputated. The histories secured each time are widely divergent upon even the simplest points of fact. The following summary represents a cautious and conservative analysis of these.

Male negro, aged twenty-three, longshoreman. Born and raised in Galveston. Five years previously, while scuffling, he injured his left ankle, but the skin was unbroken. Following this the foot would undergo transitory periods of swelling, but return to normal size. About two years later, while working at his occupation, a 200-pound sack of cotton seed cake fell on his left instep and broke the skin. The foot commenced to progressively enlarge, nodules and sinuses appeared, which discharged a thin, bloody pus. Since then the foot has been continuously getting larger and feels very hard and stiff. At irregular intervals sinuses appear. They last three or four days and heal. The places they occupied remain very sore. The sinuses do not open or discharge very much except when the patient is standing on the foot or working. The nodules are apparent for two or three weeks before the sinuses appear.

At the time of his last admission to the hospital in August, 1917, the swelling extended nearly half way up the leg. The general physical examination was negative. The leg was amputated 4 inches below the knee. Recovery from the operation was uneventful. The pathological description of the foot is given later.

*Case 28* (Kirkham). (Fig. 5.) Male Mexican, aged twenty-two, laborer. Resident of Houston for the past two years. Previous residence and birthplace, Neuvo Leon, Mexico. Eleven years previously he ran a thorn into the third toe of the left foot while barefooted. This was followed by slight local swelling and pain which soon subsided. In about three weeks it was noted that the skin on the dorsum of the injured toe was blackened. This black area extended, until in one year's time it had spread to the adjoining toes and for a short distance over the dorsum of the foot. At the end of another year there appeared a small nodule, which on injury would exude a thin yellowish watery fluid which was slightly blood tinged. The condition gradually extended until the swelling extended to the ankle. Ordinarily the foot is not painful, but any severe jar would cause intense pain which incapacitated him for several days. Granules were first noted in the discharge from the sinuses about one year ago.

In July, 1920, he was admitted to St. Joseph's Infirmary, Houston, where the foot was amputated in the lower third of the leg. Recovery from the amputation was uneventful. His general physical condition prior to the amputation was negative. The description of the foot is given in the section on pathology.

*Case 29* (McGee). Male Mexican, aged forty. Resident of Douglas, Arizona and vicinity for twenty years. Laborer.

In October, 1917, he caught the left foot between the bumpers of two small cars. The foot was swollen and tender, but the skin was not abraded. No bones were broken. Patient complained of pain in the second toe and on the dorsum of the foot at the base of the toes. He returned to work in November. In the following October he noted a small swelling on the ball of the left foot, which was painless and did not interfere with walking. In April, 1919, he noted some swelling on the dorsum of the foot, with itching and no pain. This swelling was in the region of the former injury. When seen in December, 1919, the patient complained of swelling and tenderness on both the dorsum and sole, and an incision was made into the bottom of the foot. Some granular pus was expressed, while a similar incision was later made in the dorsum. These incisions were very slow to heal and drained pus for several weeks. In July, 1920, the dorsal tumor was excised. It appeared to rest upon the tendon sheaths and was easily excised, except over the bases of the second and third toes. The skin flaps covering the wound sloughed away and it was necessary to graft. He was discharged in August, 1920, with the wound practically healed. Most of the time since the operation there have been one or more discharging sinuses on the dorsum and nodules have developed at the base of the second and third toes. In the discharge from the sinuses are at times found very small white granules. The patient walks around with no discomfort and refuses amputation.

Study of the tissue removed is reported in the section on pathology.

*Case 30* (Crutchfield). (Fig. 30.) Male negro, aged thirty-four. Farm laborer. Resident of Grapeland, Texas.

A little over twelve years ago he ran a thorn into the sole of the right foot near the metatarsal-phalangeal articulation while barefooted. He removed the thorn and the wound healed. About three months later, while plowing, he felt a stinging pain on the inner side of the right ankle. Shortly after the ankle started swelling. At intervals small softenings would appear under the skin on the sides of the ankle, which would rupture and discharge a bloody pus, in which granules were not noted. These would heal in the course of a few weeks. When active on the foot the ankle would swell, but upon resting for some days the swelling would subside. The ankle is painful. His general physical condition is good. The process is not extending and has remained stationary for many years. He was admitted to Sealy hospital in November, 1920, when some granules were removed from the existing sinuses by irrigation. It was decided to try the effect of exposure to x-ray before advising amputation. In February, 1921, when it was seen that the x-ray-exposures were without effect, amputation was advised, in which the patient concurred, but up to the time of this writing he has not returned to the hospital for that purpose. A small piece of tissue was removed from the vicinity of one of the sinuses, which is considered in the section on pathology.

## V. PATHOLOGY

### *Observations previously recorded*

*1. External changes in the foot.* The following statements summarize the observations of those who have previously studied cases of North American mycetoma:

The most common and characteristic change is the *swelling* of the foot previously noted. When the foot is examined rather early in the course of the disease this may be definitely localized (6, 8, 22). The early swelling probably represents the original nidus of invasion and may apparently develope in any region of the foot. As the invasion spreads to all the tissues of the foot, the swelling likewise progresses until the entire foot may appear twice or three times the normal size. Most of the cases observed have been of this degree. From the ankle or slightly above, to the tarsal-metatarsal articulations, the entire foot is swollen, the normal concavities are replaced by convexities, which are more noticeable on the plantar aspect, and may progress to such an extent that the toes are considerably elevated and are not in contact with the ground.

The swelling only rarely involves the toes, and was only observed in one instance (7). The swelling of the foot does not appear to cause their separation or spreading one from another, on the other hand they are commonly closely in contact.

The second most characteristic change is the development of numerous *sinuses* or *fistulae* within the foot that extend to the surface, produce a necrosis of the overlying skin, and from the opening thus formed discharge a scanty quantity of a very thin, sero-sanguinolent fluid, which contains a variable number of the characteristic granules, later to be described. These sinuses may make their appearance on any portion of the external surface of the foot, or proximal surfaces of the toes. Their individual activity is apparently of rather brief duration, as they tend to soon close, the skin heals over the opening and a scar is left. New sinuses are constantly forming and old ones healing. The zone of invasion appears to extend considerably beyond the zone in which sinus formation is taking place, but the sinuses are observed upon the area of swelling, when the latter is limited. Their number is variable.

With reference to the third characteristic, the cases may be divided into two series, those in which semi-pedunculated masses of tissue develope on the skin, and those in which these masses do not appear (4, 8, 22, 30). When they do appear, their development always precedes the opening of a new sinus, which appears upon their summit. With the closing of the sinus the mass appears to decrease somewhat in size and to become more dense. These masses vary considerably in size of the same and different feet, most commonly appearing from 4 to 6 mm. in diameter, with a few 10 mm. or thereabouts. Most frequently the summits appear to have a slightly greater diameter than the base of the mass, hence the suggestion of pedunculation, but sometimes the base may be wider than the summit. These masses, which we will call nodules, may be either discrete or confluent, and as a rule their distribution over the area of involvement is uneven. The region in which they appear to develope in greatest luxuriance is on the dorsal surface above the metatarsals. They may attain an elevation of from 1 to 2 mm., or perhaps rarely higher. Their outline, when discrete, is round or ovoid. The color of the nodules is in marked contrast to the normal color of the skin, probably due to an increased vascularity. The color varies from a white, in the case of a beginning nodule, to a deep red or pink or violet in the case of a mature, sinus crowned individual. In a negro, the nodule tends to appear paler than the healthy skin. The sinuses which crown the nodules give the suggestion of a depression to their summits. In connection with the division adopted in the beginning of this paragraph, it is interesting to note that Vandyke Carter states that such nodules have never been noted in the black variety, and do not appear to be invariably seen in the pale variety in North American experience.

*2. Internal changes in the foot.* But a disappointingly few observers of mycetoma have described the internal gross or microscopical tissue changes. Scarcely half a dozen observations are on record.

Upon opening the amputated foot, most writers comment upon the great degree of discolorization of the tissues in the invaded area which in advanced cases may be so great that identification of anatomical structures is impossible. The sinuses are seen to be the external apertures of fistulae which penetrate to the depth of the foot in various directions and are extremely tortuous. The deepest extend to the bony tissues, where their termination is a cavernous expansion in the bone. Such expansions are also seen in the course of the sinus. These usually contain compact aggregations of the granules.

All those who note the connective tissue describe a hyperplasia, which is further described as being either spongy (6), or as having undergone a fatty degeneration (7). In the localized case described by Wright (8), the hyperplastic areas of connective tissue are said to have formed myxoma like nodules.

Pope and Lamb describe an arterial congestion in their case (7) and note the existence of hemorrhagic infarcts.

Muscular tissue appears to be peculiarly vulnerable to the disease. It underwent changes described as complete disintegration (4), especially involving the deeper muscles, or a fatty degeneration (7). Sutton states the tendons in one of his cases (20) had mostly disappeared, and also that the sinuses showed a tendency to follow the tendons.

In the advanced cases of the disease, involvement of the osseous tissues appeared to be universally present, the particular bones affected depending upon the localization of the disease or the degree of the extension. A rarifying and hyperplastic osteitis is always produced, which may completely involve any bone or group of bones. Sectioning of the diseased area with a knife may be done without any bony resistance being felt. Several observers deny the existence of caries, which is only noted by Adami and Kirkpatrick (5).

Joint involvement appears to be rather unusual. It is only noted by Adami and Kirkpatrick (5) who call attention to the destruction of ligaments and an erosion of the joint surfaces.

*3. Histological changes.* Cutis: Both Hyde and Senn (6) and Sutton (19) call attention to an increase in the dimensions of the epidermal cell spaces and the latter notes an increase in the prickle cell layer. Both observe a leucocytic infiltration into the corium.

Reaction about the granules: This includes a consideration of the histological structure of the sinuses. Immediately about the granules in a sinus is a dense aggregation of polymorphonuclear leucocytes, many of which are necrotic. In a few instances giant cells have been noted in their vicinity. The fistulae show a tendency to obliteration through the formation of granulation tissue, fibroblasts and the development of connective tissue. Proliferation of endothelial cells has been quite frequently noted. In one instance (6) has a round cell infiltration of the walls of blood vessels been observed. Plasma cells and mast cells may be seen in the cellular exudate in a fistula. In no instance has any attempt at encapsulation of the granules been noted.

Giant cells. Wright (8) noted prominent giant cells with peripheral nuclei and irregular outline in close contact with the granules in his case. Sutton mentions occasional giant cells in one of his cases (19) while Hyde and Senn (6) note such giant cells with both central and peripheral nuclei.

Pigment: Arwine and Lamb (9) and Allison (18) call attention to the deposit of pigment throughout the tissues of the diseased area.

Granules: These will be considered in connection with etiology.

*4. Pathology of new cases.* We have had opportunity to study pathological changes in three specimens of mycetoma. This includes the foot of Allison's case (18) which was deposited in the Pathological Museum of the Medical Department of the University of Texas; Singleton's case (27); and Kirkham's case (28). Histological studies were made of the changes in these specimens, and in addition, through the courtesy of various physicians, we have had opportunity to study the tissue of the following of the earlier reported cases (6, 7, 8, 9, 18, and 19). For this opportunity we are indebted to Dr. J. W. Walker of Chicago; Dr. Maude Abbott of Montreal; Dr. J. H. Wright of Boston; Col. Geo. R. Callender, Curator of the Army Medical Museum; Dr. R. L. Sutton of Kansas City and Dr. H. S. McGee of Douglas, Ariz.

*Gross pathology*

*Case 18* (Allison). (Fig. 1, 2.) Specimen of right foot in good state of preservation. The transverse diameter of the foot is not appreciably increased, but the vertical diameter is very nearly twice that of normal, while the increase would appear to be greatest below the bony arch. The toes are not separated and, owing to the swelling of the sole, do not touch the plantar support. The normal concavity of the sole is lost (flat foot), but the sole is not appreciably convex. The toes have a light purplish tint.

Dorsum: On the dorsal aspect are numerous tuberculations, some discrete, some confluent, from 3 to 12 mm. in diameter, most numerous across the dorsum for about 7 cm. posterior to the toes and extending on the external side to below the malleolus. There is one group posterior to the external malleolus and the suggestion of a group developing on the inner aspect of the ankle above the internal malleolus. These tuberculations or nodules are flattened on the top, shaped like a truncated cone, with poorly defined borders that do not overhang. On the summits of some are the external openings of sinuses, which are slightly depressed and may be scabbed over.

These nodules are pinkish in color and the epidermal wrinkles appear smoothed out over their surface. One nodule is present on the dorsum of the fourth toe, otherwise the toes are not involved.

Plantar: In the center of the sole is a pinched out sinus opening about 8 mm. in diameter. There are four more, widely separated, anterior to this, over the "ball," and on the external side, near the "ball" is a group of three small yellow nodules, that have been flattened, which are from 3 to 5 mm. in diameter. These are sharply circumscribed and separated from the normal epidermis. These are the only lesions on the sole.

Internal changes: The specimen was opened by a single longitudinal incision, beginning between the second and third toes, through the heel and extending up the leg between the long bones. The incision passed through the shaft of the third metatarsal which was softened and transversed in every direction by sinuses.

The central and anterior dorsal regions of the foot appear to be involved, though a region of involvement extends through to the ball. The plantar fat appears normal, and the plantar tendons are unaltered.

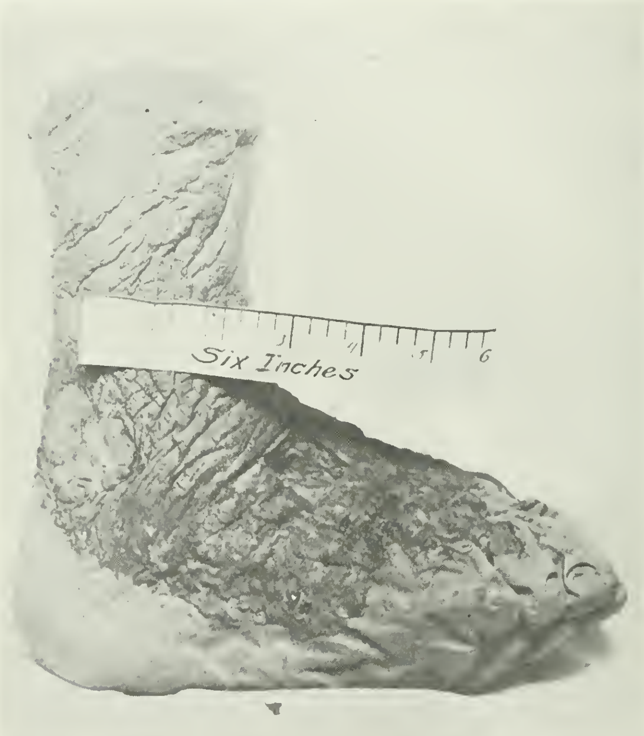


FIG. 1. FOOT OF CASE 18 (ALLISON)

The anterior portion of the os calcis is softened, its cancellous structure is largely lost and it contains numerous tortuous tunnels from 1 to 2 mm. in diameter. There is a great increase in the amount of subcutaneous connective tissue on the dorsum, which appears of a violet color. There are numerous tortuous sinuses, extending through the involved region, from 2 to 5 mm. in diameter, and with numerous cavernous expansions. They are deeply embedded in dense connective tissue. They have a wall of varying thickness, not over 1 mm. and yellowish in color. There is an extension of the area of invasion on the anterior aspect of the ankle, the extension apparently taking place along the fascial planes and is not marked externally in any way. The sinuses are most numerous at either end of the metatarsal bones. Below the metatarsal phalangeal articulations a group of sinuses extend

FIG. 2. SAGITTAL SECTION OF FOOT OF CASE 18

toward the plantar surface. In the sinuses and their expansions are small granules, from 0.5 to 1 mm. in diameter, lying either singly or in mulberry like masses, which may entirely fill the lumen of the canal. They are a dirty white or pale ochre in color. The sinuses between the granules appear to be filled with necrotic material. A few are filled with a slightly opaque gelatinous material. A probe passed into the foot through one of the openings into sole penetrates the diseased area in the center of the foot. The joint surface between the third metatarsal and the inner cuneiform appears obliterated.

*Case 27* (Singleton). (Fig. 3, 4.) Left foot in good state of preservation. It has a swollen puffy appearance, especially marked on the plantar aspect. The normal areas of concavity are all obliterated and replaced by convexities. The toes are not swollen or spread apart. By reason of the plantar swelling the toes are elevated over two inches from the plantar support. The entire foot has a distinct purplish appearance most noticeable on the plantar surface, where the cornified epithelium has been denuded.

Dorsum: At the base of the great toe, at the base of the third and at the base of the fourth toe are respectively, two two, and one small nodules, over some of which the epithelium has been denuded and which were evidently sinus crowned, though the orifices are closed by a scab. There are no nodules elsewhere on the dorsum.

Plantar: On the sole and extending well up on the sides to where the epithelium blends with that of the dorsum, are numerous nodules in various stages of development, none extending anterior to the "ball," but extending posteriorly to the back of the heel. These present the following characteristics:

1. Small areas of slight though visible elevation of the skin, not over 2 mm. in diameter, where the corrugations are noticeably thinned. Their outline is indistinct and the color is somewhat lighter.

2. Elevations of a definite rounded convexity from 2 to 5 mm. in diameter, and up to 2 mm. in height, round or oval, with fairly definite edges and an ochre yellow color. Some may show a definitely pointed apex of a darker color.

3. Elevations of a character similar to that just described, but whose apices are marked by fistulous openings from 1 to 3 mm. in diameter, connecting with the interior of the foot.

Internal changes: The foot was divided into eight sections by seven transverse incisions. The first incision, across the ball of the foot, was made completely with the knife, in all the others, the bony structures required sawing.

The subcutaneous fat has altogether disappeared from the plantar surface, except at the extreme anterior end, and only minute lobules remain on the dorsum. In its place there is a great increase in dense connective tissue, most marked on the dorsum where it is 2 cm. thick, but extending entirely throughout the foot. Muscles have nearly alto-

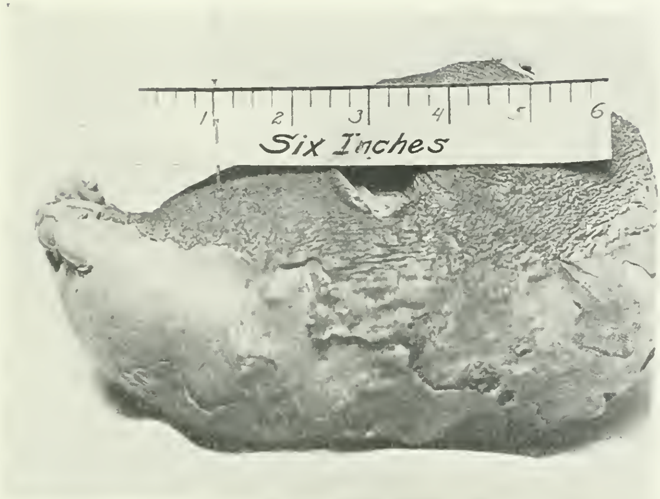


Fig. 3. Foot of Case 27 (Singleton)

Fig. 4. Transverse Section of Foot of Case 27

gether disappeared. The bones for the most part have not been destroyed, and of all tissue have been the least altered. The fifth metatarsal has undergone a marked rarefying and proliferating osteitis. The striking feature of the interior are the numerous, exceedingly irregular sinuses which perforate the tissues in every direction, but are most abundant below the bony arch. They vary in diameter from 1 to 6 mm. and may lie singly or in groups of two or three, in which case the entire group is surrounded by a dense fold of connective tissue. The lumena are either filled with a clear gelatinous material or amorphous debris, in which lie mulberry like granules up to 4 mm. in diameter and of a white or pale yellow color. Some of these sinuses have a very thin wall, while others have a lining from 1 to 2 mm. thick. The large granules lie in spherical caverns in the course of a sinus, the size of a cavern being proportionate to that of the grain which occupied it. They are excavated in soft or bony tissue alike. The course of the sinuses is very tortuous and they may be branched. They communicate with the exterior through the openings previously noted. Along the dorsum of the foot is an aggregation of sinuses, which, surrounded by dense fibrous tissue, extend for fully three inches.

None of the joint cavities appear to be involved, although excavations may be in contact with the joints, and only separated from them by the capsule.

*Case 28* (Kirkham). (Fig. 5.) Left foot in good condition. The anterior half of the foot is markedly swollen, which extends to and includes the toes. The heel and ankle appear normal. The toes are not separated. While some of the swelling is present on the plantar aspect, the greater portion is dorsal. The foot is not colored or tinted.

Dorsum: Extending posteriorly for about 5 cm. from the insertion of the toes are numerous nodules of a rounded or oval outline, about 4 mm. in height and varying from 2 to 25 mm. in diameter. Their borders are perpendicularly elevated, with a domed summit, or else the whole nodule is convex. They extend on the second toe nearly to the nail. On the outer side a few extend posteriorly nearly to the vertical plane of the external malleolus. Where most abundant they are in close contact and may coalesce. The apex of many is ulcerated, and the ulcerations mark the openings of definite sinuses, extending into the foot. The color of the nodules is paler than the normal skin. Some of the nodules are slightly polypoid.

Plantar: A nodule similar to the foregoing may be seen on either side of the third toe. None are seen on the sole, except a small cluster about 2.5 cm. posterior to the tarsophalangeal articulation of the great toe. These nodules protrude through the epidermis of the sole, which seems to be punched out at their base. They are yellowish in color and several are marked by sinus openings.

Internal changes: The foot was divided into eight sections by seven transverse incisions. It was necessary to use the saw to cut bone in each section.


Fig. 5. Foot of Case 28 (Kirkham)

The subcutaneous fat on the plantar aspect appears normal in amount, but it has disappeared from the dorsum. The dorsal tendons have partly disappeared. Most muscles, except those attached to the os calcis have disappeared. The place of the fat is taken by a dense mass of connective tissue, which extends to the bones.

Above the bony arch are numerous sinuses, some lying singly, others closely grouped, surrounded by dense strands of connective tissue. Most are from 1 to 2 mm. in diameter, though they may have expansions 4 mm. wide. A few are filled with translucent material, others appear empty. In some are seen yellowish, mulberry shaped granules, not over 1 mm. in diameter, apparently filling the entire lumen of the tunnel. The sinuses are lined by a yellowish necrotic membrane of varying thickness. The sinuses extend up to the summits of the cutaneous nodules. These nodules have a base in the form of an inverted cone, extending from 5 to 10 mm. into the connective tissue. Below the bony arch a few sinuses are seen. All are localized to the anterior half of the foot.

FIG. 6. FOOT OF CASE 30 (CRUTCHFIELD)

*Case 30* (Crutchfield). (Fig. 6.) Description of the living foot is given. The swelling of the right foot is limited to the region of the ankle, the protuberences of the malleoli being obscured. On the outer side the swelling extends about an inch posteriorly and inferiorly to

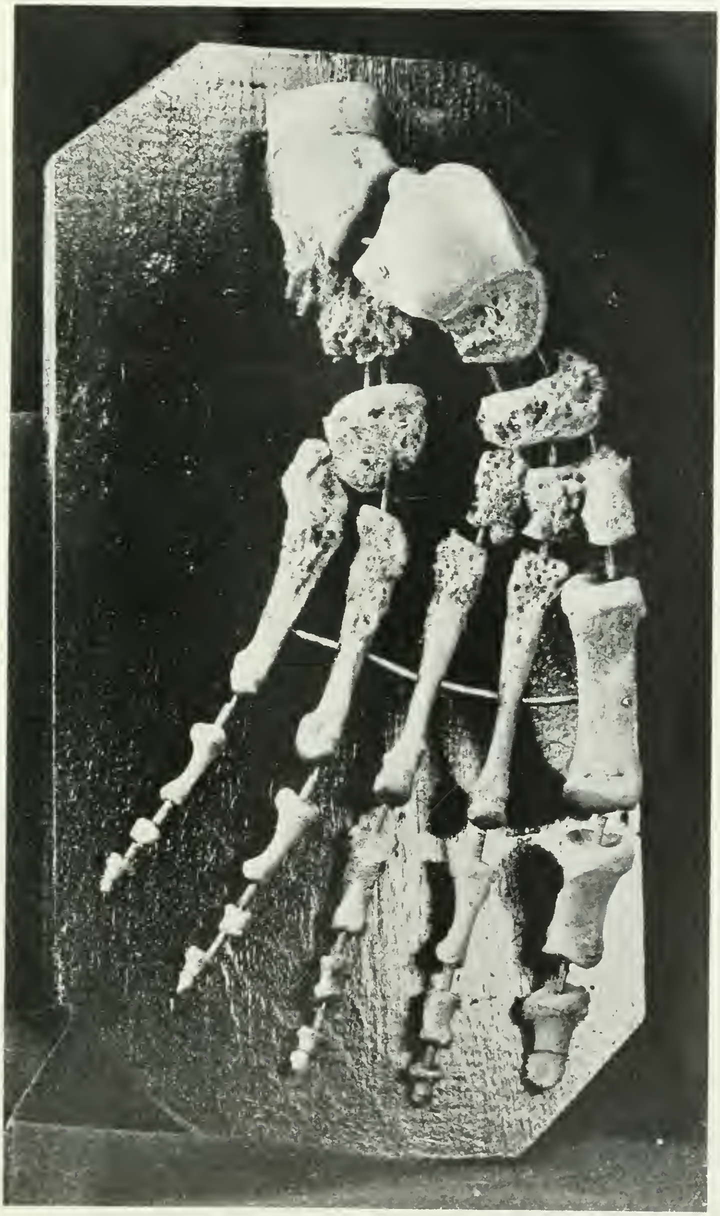

FIG. 7. BONES OF THE FOOT OF CASE 5 (ADAMI AND KIRKPATRICK)

Specimen in the Medical Museum of McGill University. Photo by the courtesy of Dr. Maude Abbott.

the malleolus and two to three inches anteriorly. Most of the swelling appears to be on the outer aspect. On the outer aspect of the ankle are two sinuses which have been recently opened. Four other healed sinus openings, filled with scar tissue are also present. Two such scars are visible on the inner aspect of the ankle. There are no nodules anywhere on the foot. The openings of the sinuses are not elevated. X-ray examination shows a periostitis of the tarsal bones. The granules secured from the sinuses by irrigation were pearly white and about 2 mm. in diameter and very irregular in shape.

*Pathological histology*

Our own observations of the histological changes in mycetoma may be summarized as follows:

Skin: In no instance was the rete Malpighii increased in thickness, but more commonly it showed a definite thinning. In one instance the spaces between the cells seemed to be increased, while in another the nuclei failed to stain. The germinal cells of this layer show some tendency to project downward into the corium in long finger like processes. Atrophy of the papillae was quite commonly observed. A hyperplasia of connective tissue in the zone between the sweat glands and the germinal layer was quite common. A few specimens showed evidence of polymorphonuclear infiltration into this zone, but accumulations of lymphocytes were more common. Atrophy of some of the sweat glands was noted. Many that were not atrophied were surrounded by definite zones of fibroblastic proliferation. Hemorrhage into the corium was noted in one instance, and traces of old hemorrhagic infiltration as indicated by blood pigment, were seen twice.

Over a nodule the rete Malpighii is very much thinned out, and the papillae are markedly atrophied. In the event that a sinus crowns its summit the rete is entirely eroded away. At the periphery of a nodule there may be considerable hyperplasia of the rete and of the papillary layer. Nodules which are not sinus crowned consist of a hyperplasia of young connective tissue with areas in which there is considerable dense infiltration with small round cells. Nodules which are sinus crowned are filled with an accumulation of polymorphs, in which may be seen the granules interspersed with a few lymphocytes. Capillary loops project themselves into the interior from the margin. The nodule evidently develops as a result of the internal pressure of a cell infiltration on the overlying corium.

Deeper tissues: The most characteristic feature of the interior tissues is the very extensive hyperplasia of connective tissue throughout the diseased area. The formation of new connective tissues goes hand in hand with the extension of the disease, while where the process is becoming quiescent or is inactive, it rapidly undergoes hyaline degeneration. For the most part this replacement tissue is very dense. though sometimes looser deposits are seen. In very few instances are any traces of adipose tissue seen where the disease has prevailed. The remaining islands are small and frequently infiltrated with lymphocytes.

An increased vascularity is noted when the connective tissue is not dense, but the dense degenerated areas seem devoid of blood vessels. Extravasation of blood into the tissue is not infrequent, and its presence may be noted either by the presence of red blood cells or by yellow brown pigment. Round cell infiltration of vessel walls was not noted although accumulations of such cells in the vicinity of arterioles and venuoles was seen in two instances.

Sinuses: The sinuses have a definite wall of either dense or fairly loose strands of connective tissue. Usually the inner part of the wall is heavily infiltrated by round cells. In the event that a granule is not present in the interior, the entire lumen is occupied by an infiltration of small round cells. In the vicinity of a granule the prevailing cell about it is the polymorphonuclear, though in some instances extensive proliferation of epithelioid cells or endothelial cells is seen in close proximity to the granule. Where these are much in evidence, giant cells are usually observed. The giant cells are round or oval, with peripherally grouped nuclei ranging in number from 20 to 50 or more. In Wright's case (8) the giant cells were irregular in outline, with long thread like extensions and frequently occupied a position in close contact with the granule, while a number of

TABLE 4

*Summary of the histological pathology*

| Morbid change | Cases studied by number | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 6 | 7 | 8 | 9 | 18 | 19 | 27 | 28 | 29 | 30 |
| I. Cutis: | | | | | | | | | | |
| Necrosis of prickle cell layer? | | | | | | Yes | | | | |
| Separation of cells of prickle cell layer? | | | | | | | | | | |
| Downgrowth of prickle cells? | Yes | | | | | | Yes | | | |
| Leucocytes in corium? | | | | | | | | Yes | | |
| Hemorrhage in corium? | | | | | | Yes | | | | |
| Papillae atrophied? | Yes | | | | Yes | Yes | | | | Yes |
| Hyperplasia of connective tissue? | Yes | | | | Yes | Yes | Yes | Yes | | |
| Atrophy of sweat gl.? | | | | | Yes | | Yes | | | Yes |
| Round cells about sweat gl.? | Yes | | | | Yes | | | | | Yes |
| Blood pigment? | | | | | Yes | | | | | Yes |
| II. Connective tissue: | | | | | | | | | | |
| Hyperplasia? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Loose? | | | | | | | | | Yes | |
| Dense? | | | Yes | | Yes | Yes | Yes | Yes | Yes | Yes |
| Hyaline degeneration? | | | | | Yes | | Yes | Yes | Yes | Yes |
| Fat obliterated? | Yes | | | Yes | Yes | | Yes | | Yes | Yes |
| Increased vascularity? | | | | | | | | | Yes | Yes |
| Hemorrhagic infilt.? | | | | | | | | | Yes | |
| Blood pigment? | | | | Yes | Yes | | | | Yes | Yes |
| III. Sinuses: | | | | | | | | | | |
| Wall—dense? | Yes | | Yes | | | | | Yes | Yes | |
| Wall—loose? | | | | Yes | Yes | | Yes | | | Yes |
| Wall—infiltrated with round cells? | | | Yes | | Yes | | Yes | Yes | | Yes |
| Lumen—round cells? | Yes | | | | Yes | | Yes | | | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Lumen—epithelioids? | | | Yes | | | | Yes | | Yes | |
| Lumen—giant cells? | | | Yes | | | | Yes | Yes | Yes | |
| Lumen—polymorphs? | Yes | | Yes | | Yes | | Yes | | Yes | |
| Lumen—granulation tissue? | Yes | | | | | | | Yes | Yes | Yes |
| Lumen—hemorrhages? | | | | | | | | | Yes | |
| About—granules | | | | | | | | | | |
| polymorphs? | Yes | | Yes | | Yes | | Yes | Yes | | |
| round cells? | | | | | | | | | | |
| IV. General | | | | | | | | | | |
| Fibrosis of sinuses? | | | | | | Yes | Yes | | | |
| Russell's bodies? | | | | Yes | Yes | Yes | | Yes | Yes | |
| Round cell infilt. about blood vessels? | | | | | Yes | | | | Yes | |

*Note:* Only positive information is recorded in above table.

such cells might nearly surround a granule. In this case the arrangement of epithelioid cells and lymphocytes in some places exactly simulated a tubercle. The type of necrosis is apparently liquefactive and involves the polymorphonuclears more particularly. Hemorrhages into the sinus lumen, may be seen manifest either as a small infiltration with red cells or as a thrombus occupying the entire lumen. Old hemorrhages are suggested by pigment deposits. Efforts at repair are constant, capillary loops being projected into the sinus even when a granule is present. The interior of vacated sinuses may be altogether filled with such capillary loops and finally its location is only revealed by an interlacing mass of loose connective tissue.

Russell's bodies: In 5 cases these were noted in sections stained by the Gram-Weigert method. They are spherical, gram positive, homogeneous bodies, which are scattered irregularly throughout the tissue, either in sinuses or at a distance, and vary considerably in size. This ranges from 1 to 8 micra. The largest are seen singly or in groups of not over four, the medium sized spherules are in compact grape-like bunches. These aggregations are as a rule composed of bodies of the same size, with the exception that groups of spherules of about 4 to 6 micra in diameter may have the smaller size interspersed among them. There apparently is no cellular reaction about them. It is probable that these are degeneration products derived from the tissues.

The foregoing description applies to all the material studied, except that from case 30. Case 8, being due to a different fungus than the bulk of the cases, presented a different type of tissue reaction, characterized by a hyperplasia of dense connective tissue, fibroblastic proliferation, an abundance of a peculiar type of giant cells and with very little evidence of suppuration. Case 30 also has as its causative organism a fungus different from those previously considered. Unfortunately, we only had for study a small piece of biopsy tissue removed from the margin of an open sinus, in which no granules were present. Consequently our histological observations on this case are very incomplete. The cutaneous papillae were very markedly atrophied.

The sweat glands were likewise atrophied and surrounded by a definite infiltration of round cells. There was considerable blood pigment in the subcutaneous tissue. The subcutaneous fat was markedly diminished, and was replaced by a hyperplasia of dense connective tissue, much of which was undergoing hyaline degeneration. The sinus possessed a loose wall of connective tissue, which was infiltrated with round cells. Its lumen was completely filled by granulation tissue.

## VI. ETIOLOGY OF MYCETOMA IN NORTH AMERICA

### *a. Previous observations on the parasite in tissue and culture*

M'Questin evidently did not observe the granules and one gains the impression he confused the fungating nodules with the parasite. His report was published the same year as Vandyke Carter's monograph, before the idea that the granules represented the form assumed by the parasite in the tissues had become current. Kemper and Jameson in the case (4) whose authenticity has been challenged by Wright (1898) and whose doubt has been echoed by some later reporters, observed brilliant, yellowish white granules, lying singly or in mulberry like aggregations, lying within the sinuses. Most of the later reporters have called attention to the granules either in the discharge or lying within the fistulae. However, Cicero only reports granules in 1 (16) of his 6 cases, Sutton does not mention them in one of his cases (20), Burres does not mention them in the account of his case of mycetoma involving both feet and Ocaranza only mentions them in one (26) of his four cases. We feel certain that while any case of chronic swelling of the foot associated with discharging sinuses, in which granules are not found should be provisionally regarded as mycetoma, yet we believe that if these above mentioned cases had been more carefully studied, the characteristic granules would have been easily recognized. In case 30 of our series, of twelve years standing, the patient had never noticed granules in the discharge, yet they were easily secured by the irrigation of the sinuses.

In 9 of the 26 previously recorded cases is specific mention made of the granules. In 1 instance (8), black granules were observed. In all the others the color is variously described as whitish, pale yellow, or yellowish. In Wright's case (8), the granules were less than one millimeter in diameter, irregular in shape and single. Their microscopical appearance was not described. The pale granules are most commonly the size of a pin head or slightly larger, when single they are rounded in shape, though commonly present in mulberry like or "fish roe" like aggregations of irregular, though rounded shape. Their consistency is soft. In 10 instances they were examined microscopically and in 6 instances cultures were made from them.

As a result of microscopical study, many reporters have been struck by the resemblance offered to the granules of actinomycosis. Thus Adami and Kirkpatrick describe them as identical, Hyde, Senn and Bishop and also Allison remark on the general resemblance, Arwine and Lamb consider them a variety, and Winslow characterizes them as actinomycosis.

Microscopically, the granules reveal a zonal structure to all who have observed them. General agreement in distinguishing a central and peripheral zone exists. The central zone may variously consist of a dense central tangle of mycelium; or be granular and faintly staining with but few filaments, or a mycelium may be altogether indistinguishable. The peripheral zone is generally noted to be composed of radial filaments, which are described by Hyde and Senn as deeply staining, wedge shaped bodies. The free terminii of these filaments have usually (5, 6, 9, 10, 11) been observed to be clubbed, though Allison (18) records their absence, while Sutton in 1 instance describes a hyaline peripheral zone (19). Adami and Kirkpatrick state that the clubs bifurcate. In 3 cases (10, 11, 18) branching of the mycelium was noted and in 1 case (6) it was stated not to occur. Segmentation of the mycelium is denied in 1 case (10), though Hyde and Senn report the existence of branching forms (6), and coccus forms are noted in 2 other instances (11, 18). Hyde and Senn, Arwine and Lamb, and Allison report the filaments of the granules to be Gram negative, while Albertini and Desvernine (10) observe them to be positive. Thus in the bulk of North American cases the granules appear to be composed of a streptothrix.

In 6 cases the granules were inoculated onto culture media. In Wright's case of black grained mycetoma, cultures yielded a true mould or hyphomycete, whose characters will be considered later. In the other 5 instances the reports of the cultural studies are so inadequate as to be practical useless in giving us an idea of the organism. Albertini and Desvernine made cultures from both their cases, but do not report the results secured from (10). From (11) they grew a streptothrix which grew as small white colonies on glycerine agar at 37°C.; in a similar manner on potato, and in potato infusion produced small white flakes which fell to the bottom of the tube, leaving the medium clear. They do not describe chromogenesis. Smears and cultures of their organism were submitted to Dr. Vincent who is quoted as giving a diagnosis of *Streptothrix madurae*. When one recalls the pronounced red chromogenesis of Vincent's streptothrix (syn. *Actinomyces indica*) these facts are difficult to reconcile. Allison reports successfu cultures from case 18, yielding a gram positive streptothrix. Growth occurred on plain agar in ten days at 37°C. In plain broth growth was visible in six days and occurred as small round furry balls which adhered to the sides and bottom of the tube, leaving the medium clear. Growth was most rapid on glucose agar, being visible in three days. Rounded, elevated, discrete white colonies were formed, which later developed a slightly pink margin. A similar growth occurred on potato. On blood serum it grew with difficulty and did not produce liquefaction. The organism was not studied in pure culture. Sutton stares that cultures from case 19 were repeated failures. He also reports the isolation of an organism from case 20 that was reported as *Streptothrix madurae* by Dr. Tobey of Harvard, but no account of its characteristics is given.

No successful animal inoculations have been reported.

It can therefore be said that while the morphology of the organism in the tissues, as revealed in the white or pale yellow grains, indicates that the parasite is a streptothrix, yet no sufficiently extended cultural observations have been made that would permit of the identification of the particular species concerned, nor can the reported identification of *Streptothrix madurae* (*Actinomyces indica*) be accepted unreservedly.

As a result of our study we believe the recorded North American cases of mycetoma can be classified into three groups, depending upon the kind of parasite causing the disease, namely, (1) Mycetoma with black grains produced by a hyphomycete; (2) Mycetoma with white grains produced by an ascomycete, and (3) Mycetoma with white grains produced by a streptothrix.

*b. Mycetoma with black grains produced by a hyphomycete*

Only one case of this type of mycetoma has been observed in North America, namely case 8, observed by Wright in Boston, in the person of an Italian woman. The fact that mycetoma of this type has also been observed in Italy, makes it appear possible for this to be a case of imported infection, although the history of the patient is not sufficiently clear to settle the question. The granules, according to Wright, are of an irregular or mulberry shape, of a black or dark brown color and usually less than 1 mm. in diameter. They are hard, rather brittle and not readily broken up. After treatment of the granules with strong alkalies and bleaching agents, the greater part of their mass is seen to consist of ovoid or rounded, translucent bodies of varying sizes, closely packed together, having homogenous interiors or containing a few refractive granules. Among these granules typical septate, branching hyphae may be seen, sometimes showing dilations or varicosities of their segments. The ovoid or rounded bodies seem to be dilated or degenerated hyphal segments, for not only may they be seen in continuity with the hyphae, but transitions between them and the hyphae with swollen segments may be made out. No undoubted spore bearing organs were observed, but occasionally a large, spherical, thick walled body containing smaller, rounded or ovoid or elongated refringent bodies was seen.

The following description of the appearance of the granules in tissue sections is made from hematoxylin and eosin stained sections which we had the opportunity to study through the courtesy of Dr. Wright. The granules are fairly regular and compact in outline, and may be somewhat rounded, lobate or reniform and do not appear to be aggregations of similar units. They are not separated from the cellular exudate of the sinus by any homogenous zone staining diffusely with eosin. They are not stained by hematoxylin and have a light yellow brown color. A distinct mycelium is not discernable. The central portion of the granule appears to be of a less dense character than the periphery. The central portion appears to be a rather loose reticulum of broad branching bands, which coalesce at the periphery to form a denser radial zone. The margin is not irregular. The broad branching bands noted are very suggestive of mycelium. These bands themselves seem to be surrounded by or embedded in a yellowish brown pigmented material, which is very uniformly distributed.

Cultures were obtained by Wright by inoculating granules onto potato, broth, potato infusion and on plain and glucose agar. Growth was apparent in four or five days. The mould possessed a mycelium whose threads were from three to eight micra in diameter, with a definite wall, septate and formed lateral branches. In the older filaments the diameter at the septate may be increased. No organs of fructification were seen.

The growth appeared as a typical mycelium with aerial hyphae, pale brown in color on potato and grayish on agar, while the young extensions at the periphery of the growth were white. On potato small drops of a dark coffee colored liquid appeared on the surface. In broth and potato infusion the growth produces large spherical puff ball masses, composed of radiating mycelium, with a definite surface layer of mycelium in broth. In potato infusion and on agar cultures of considerable age, there appeared numerous black spherical bodies. 1 mm. or less in diameter, that were considered sclerotia.

No successful animal inoculations were secured with either granules or cultures.

Wright did not suggest the classification of this fungus. Brumpt (1913) proposes its assignment to the genus *Madurella*. This genus, as emended by Pinoy, has the following characteristics:

Genus *Madurella* Brumpt, emend. Pinoy

Sterile fungi with septate filaments, reproducing by fragmentation of the thallus. The oidia are produced secondarily by the division in two of the fragmented filaments. Develop best at 37°C. Produce black grained mycetoma in man.

It further apparently coincides very closely with the description given for *M. mycetomi*, Laveran, which is as follows:

*Madurella mycetomi*, Laveran

Mycelium greyish white, yellowish when old, blackening the substrate in carbohydrate culture media. The oidia vary from two to five micra in diameter. Black sterile sclerotia are produced, from 0.5 to 1 mm. in diameter, and form in the depths of the medium. Cultures difficult to obtain. Inoculation into pigeons possible, but inconstant.

This fungus has been found to be the cause of a black grained mycetoma occurring in India, Northern Africa and Italy.

c. *Mycetoma with white grains produced by an ascomycete*

The only case referable to this group is case 30, one of our series of four new cases. Three opaque, yellow white granules were secured by the irrigation of an open sinus with a syringe, before x-ray treatment was inaugurated. These were rounded, not over 2 mm. in diameter and moruliform in shape. When pressed underneath a cover slip and examined microscopically, they appeared to be composed of aggregations of smaller bodies, at the periphery of which there were observed a large number of short clavate projections or knobs (fig. 12). The granules were soft in consistency and smeared out readily. When stained by Gram's method, the smear is seen to be composed of a Gram negative material, mostly in rectangular masses of a uniform size, together with a limited number of spatulate bodies, with a dense oval Gram positive center and a Gram negative outer wall which presents the spatulate shape (Fig. 13). These bodies are also acid fast. They correspond to the solitary conidiaspores seen in cultures, and to the spatulate projections from the periphery of the granule.

Sections of a grain show it to be a dense homogeneous network of mycelial threads which cannot be differentiated into zones (Fig. 14).

Fig. 8. Giant Colonies of Allescheria Boydii on Sabouraud's Agar. Incubated at 37°C. for Three Weeks

Some of the above granules were washed by passing through several changes of sterile saline, teased out into fragments and the fragments planted onto the surface of slants and into the depths of plain agar, Sabouraud's agar, Huntoon's agar and dextrose agar. Two sets of each were prepared, one inoculated at 37°C. and the other at room temperature. By forty-eight hours, each granule on the surface of a tube of slanted media, regardless of the temperature of incubation, was surrounded by a delicate fringe of mycelium, which rapidly extended. The deep implantation did not show growth until the fifth day, which was only evident from those granules not submerged over 5 mm. from the surface. Those planted at greater depths did not grow. In every instance growth radiated from the implanted granule and occurred at no other point, No bacterial growth took place.

FIG. 9. GIANT COLONY OF ALLESCHERIA BOYDII ON PLAIN AGAR AFTER THREE WEEKS INCUBATION AT 37°C.

The growth on plain agar and Huntoon's agar is identical, though somewhat more vigorous on the latter. A discrete giant colony two weeks old has the following appearance; colony 50 mm. in diameter and marked by four concentric zones of aerial hyphae, between which the mycelium has produced few aerial threads (fig. 9). The inner zone is about 3 mm. in diameter and marks the center of the colony, the site of the original granule fragment. The hyphae of these zones are of a light gray color, while in the intervening spaces it is a darker, brownish gray in color and relatively sparse. Scattering irregularly over the intervening

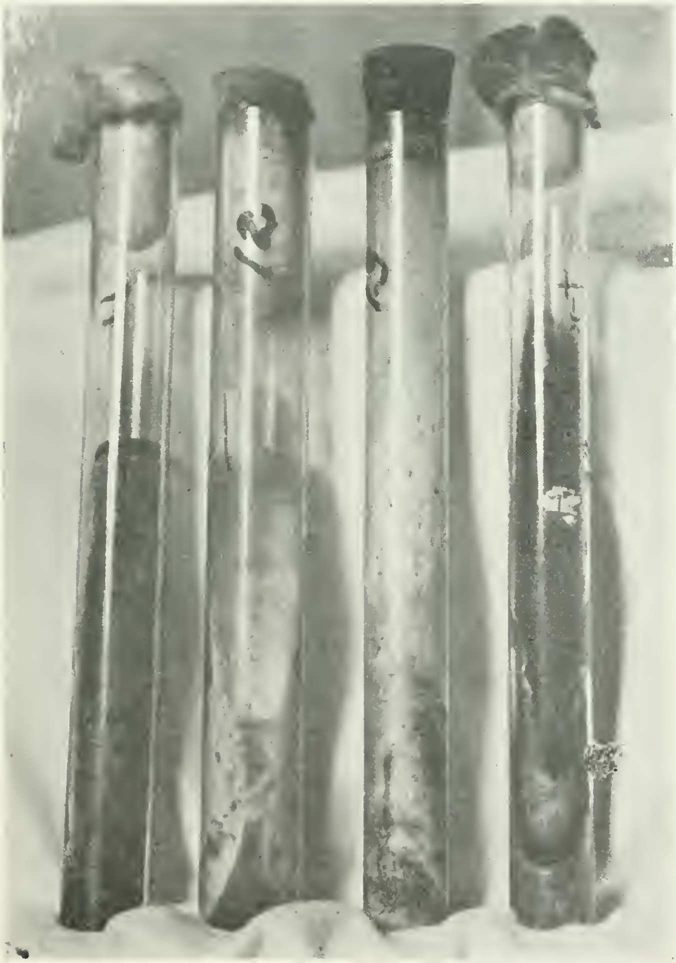

Fig. 10. Cultures of Allescheria Boydii

From left to right (1) plain agar, (2) Sabouraud's agar, (3) potato (4) beer wort. The dark specks on the mycelium in cultures 2 and 3, and the wholly dark character of the growth in (4) are the perithecia.

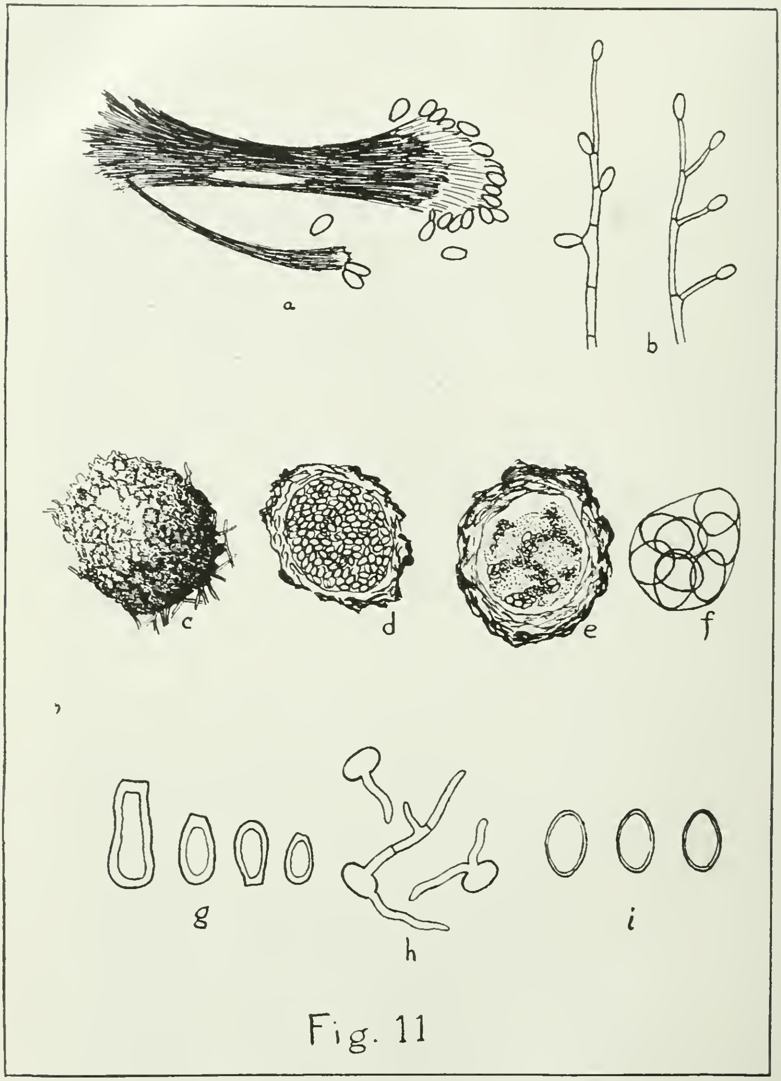


Fig. 11. Morphology of Allescheria in Culture

a, Coremium; b, Conidia with conidiaspores; c, Exterior of perithecium; d, Section of a mature perithecium filled with spores; e, Section of an immature perithecium, showing a few asci; f, A mature ascus with eight spores; g, Conidiaspores from a coremium; h, Germinating conidiaspores; i, Ascospores.

spaces are numerous small black bodies, about 0.25 mm. in diameter, in close contact with the substrate and in no case

FIG. 12. MORPHOLOGY OF ALLESCHERIA IN TISSUE

Margin of a granule from case 30, flattened under a cover slip. Drawn with camera lucida, using one-sixth objective. The spatulate bodies appear to be conidiaspores.

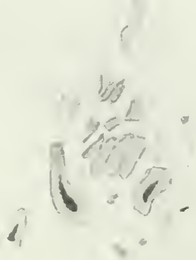

FIG. 13. MORPHOLOGY OF ALLESCHERIA IN TISSUE

A granules smeared and stained by Gram. Drawn with camera lucida, using one-twelfth objective. A conidiaspore and mycelial fragments are seen.

observed on aerial hyphae. Microscopical examination of these shows them to be coremia (Fig. 10).

On Sabouraud's agar the growth is decidedly different. The colonies are smaller and the type of zoning previously described is less noticeable. The colony is characterized by the marked extent to which delicate hyphae are formed, which have a pale greenish gray color, except at the periphery of the colony, where

Fig. 14. Section of a Granule from Case 30, to Show the Morphology of Allescheria in Tissue

Drawn with camera lucida using two-thirds objective. Excepting the knob like projections from the periphery, very little structure is noted.

*Note*: In figures 15, 16, 17, and 18, from left to right, the cultures are of *A. mexicana*, *A. asterioides* and *A. bovis*, incubated at 37°C. for two weeks.

it is white (fig. 8). No organs of fructification are visible to the naked eye. No coremia are noted until the cultures are several weeks old. With age the hyphae become a grayish brown in color.

Microscopically the cultures present the following characteristics: The mycelial threads are slender, from 3 to 4 micra in diameter and possess a definite cell wall. The threads are septate. Branching is lateral and usually opposite. On salt agar the terminal cells of filaments become very much swollen. No intercalary spores or swellings are noted on the filaments. On aerial hyphae, conidiaspores are borne, each conidiaspore being solitary on the top of an erect conidiaphore. These conidiaspores are elongated, elliptical or ovoid, unicellular and may have a slight constriction about their center. They average 7.5 micra in length to 3 micra in breadth. The distal extremity may be more rounded than the proximal. They are darker in color than the hyphae, but not markedly so. Conidia of this type are noted on the surface pellicle of liquid media, and on the following solid media, viz., dextrose, ascitic and blood agars, potato and Loeffler's medium. In the growth on Sabouraud's, starch and wort agar, as well as in plain agar and on the surface pellicle of liquid media, the small black bodies previously noted as coremia are found, in addition to the type of solitary conidiaphores already described. These consist of numerous erect conidiaphores which have become fused together into a cylindrical bundle, whose base rests upon the substrate. They are slightly constricted at the middle, resembling sheaves of bound grain. Each conidiaphore of this group bears a single conidiaspore similar to those already described. The hyphal threads of the coremia are very dark. Some of these bundles may split in the process of handling and assume a stellate appearance, remaining joined together at the base. These coremia are about 0.3 mm. in height. On beer wort, Sabouraud's, and potato, perithecia are developed. These are spherical or ovoid and may attain a diameter of 200 micra or more. Their walls are rough and formed of a dense interlacing of hyphae, and unless mature, are very difficult to crush. When mature they are coal black in color. The walls are up to thirty micra in thickness. The mature perithecia are apparently devoid of any aperture for the discharge of spores. When rendered transparent by bleaching with antiformin, their interior is found to be filled with a tightly packed mass of spores. In sections of immature perithecia, definite asci could be made out, containing eight spores. The ascospores are very uniform in size, contrasting in this with the conidiaspores, which showed some variation, particularly in length. The ascospores are elliptical, with slightly pointed ends, symmetrical and measure 7.5 micra by 4.5 micra (Fig. 11).

Additional cultural characters of this fungus are as follows: The fungus is strongly aerobic, only a scant growth of white balls of radiating filaments taking place in the depths of liquid media, some of which adhere to the glass. On the surface of liquor media a dense seal of mycelium is formed, from which ascend aerial hyphae. None of the following carbohydrates in peptone water are fermented, viz., mannite, galactose, xylose, rhamnose, mannose, lactose, saccharose, maltose and dextrose. Plain milk and Loeffler's blood serum are gradually peptonized and gelatine is liquefied. Blood is not hemolyzed, but in agar gradually becomes green. In old cultures on glycerine potato, the growth extends over the entire surface of the potato, the hyphae atrophy and the surface of the potato appears coal black due to the closely set perithecia which give its surface a slightly knobbed appearance.

### *Animal inoculations*

*Guinea-pig 1.* A granule was inoculated under the sole pad of the right hind foot. No local changes occurred, and the animal was in perfect local and general health four months later.

*Guinea-pig 2.* On January 22, was given an introperitoneal injection of perithecia from a culture on wort agar. It remained in good health and was killed on March 2. The abdominal and thoracic viscera were all normal. The omentum was coiled up and adherent to the abdominal wall at the site of inoculation. Between its point of attachment and the stomach, it contained three abscesses, about half a centimeter in diameter, with dense walls. The black perithecia of the injection were visible in the pus. Smears of the pus failed to show bacteria. Some of the perithecia had liberated their ascospores, but none showed signs of germination, nor were any mycelial filaments found. No granules, other than the black perithecia, were found. Cultures of the pus on Sabouraud's agar resulted in the recovery of the fungus.

Histologically, no evidence of proliferation of the fungus was noted in sections of the abscess wall. The type of cellular reaction is suggestive of foreign body irritation. Perithecia in various stages of disintegration are lying in nests of epithelioid cells. A few are lying in small collections of polys, while in most instances the polys have succeeded in penetrating to the interior of the perithecium. A few ovoid giant cells with peripheral nuclei are present. These epithelioid nests are surrounded by dense connective tissue.

*Guinea-pig 3* was intraperitoneally injected with conidiaspores from a culture on plain agar on January 22. The animal remained in good health and was killed on March 2. The viscera were all normal. The omentum was coiled up and adherent to the belly wall at the site of inoculation. It contained an abscess about 0.5 cm. in diameter, with a dense fibrous wall. Smears of the pus failed to reveal any bacteria, or conidiaspores or mycelium. Cultures were made on Sabouraud's agar and the fungus was recovered.

In sections of the abscess wall no proliferation of the fungus was noted. The tissue shows the characteristic proliferative changes of an acute inflammatory process, a dense accumulation of polys, most of which have undergone liquefaction. The wall of the abscess contains an abundance of granulation tissue.

We therefore hold the view that these inoculations did not succeed in infecting the animals, the reaction observed being of the foreign body type.

After having determined the foregoing characteristics of this ascomycete, it was submitted to Dr. C. L. Shear, mycologist of the Bureau of Plant Industry, United States Department of Agriculture, for identification. This Dr. Shear very kindly performed. We take this opportunity of acknowledging our indebtedness to him for his valuable assistance. Under date of April 29, 1921, Dr. Shear gave us the following report:

> We have now verified to our satisfaction the life history of the fungus you sent and also believe after a study of the literature that it is an undescribed species. It seems to belong to the genus *Eurotiopsis* described by Costantin and renamed *Allescheria* by Saccardo on account of the other name having been previously used for another organism. I would propose the name *Allescheria Boydii* for this fungus. . . . I will prepare a description of the species for publication in some mycological journal.

The genus *Allescheria* belongs to the sub-family *Hyalosporae* of the family *Perisporiaceae* of the ascomycetes. Clements (1909) gives the following description of this family:

*Family 16. Perisporaceae.*

Mycelium superficial, dark, filamentous, sometimes lacking, rarely forming a firm stroma; conidia or pycnidia rarely present; perithecium without a mouth or opening irregularly, usually globose, membranous or coriaceous, rarely carboneous, appendages usually lacking; asci mostly numerous, clustered, more or less cylindric, mostly 8-spored, paraphyses regularly lacking, spores various.

Saccardo (1899) (vol. 14) gives the following brief diagnosis of this genus and of the known species:

*Allescheria* Sacc. et Syn. *Eurotiopsis* Cost. Ann. Inst. Past. XI (1897) p. 1—43, nec Karst. (1889) (Etym. a cl. mycologo bavarico A. Allescher). —Perithecia globulosa, minuta, tenui-membranacea. Asci globosi. Sporidia ovata, utrimque acuta. Conidia catenulata, in sporophoris acrogena, dein ob ramulum laterem (dein apice conidiophorum) compressa.

1. *Allescheria Gayoni* (Cost.) Sacc. et Syn. *Eurotiopsis Gayoni* Cost. l. c.

*Hab.* in farina amylacea aliisque substantiis organicis, Paris Galliae. —Perithecia 50–80 micra diam. Sporidia 6 by 4 micra. Conidia alba v. rosea, ovoides, 12 by 10 micra.

Under date of May 19, 1921, Dr. Shear further reported regarding this organism:

The principal differences between the Costantin fungus and yours appear to be in the size of the perithecia, the asci, ascospores and conidia and the presence of a coremium form in your fungus. Coremia, however, are known to be uncertain in their appearance in culture and apparently require special conditions for their development.

*d. Mycetoma with white grains produced by a streptothrix*

As far as we can judge, all of the North American cases reported, with the exception of cases 8 (Wright), 4 (Kemper and Jameson) and 30, the last of our series, belong to this group, although in a number of instances assignment to this group is by inference rather than from any description by the reporter which permits of this classification. The following description of the fungus as it appears in the granules is based on a personal study of material from cases 6, 7, 9, 18, 19, 27, 28 and 29.

The granules vary greatly in size, the larger being composed of aggregations of the smaller. The smaller granules may be round or ovoid and less commonly lobulated in shape. The large granules, while more or less rounded or ovoid, are yet distinctly lobulated or moruliform. Except in case 19, the granules are surrounded by a zone, from 10 to 40 micra in diameter which is narrowest in the smaller granules and broadest in the larger, which stains diffusely and homogeneously with eosin. This zone is radially striated. In the broader zones, a radial splitting with the exhibition of distinct clubs is seen. The outer diameter of the clubs is greater than the inner and the free ends are rounded. In some instances migratory cells, polymorphs and lymphocytes, have penetrated between the clubs for fully half the thickness of the zone. In the narrower zones, clubbing cannot be made out. In a few instances, the zone did not completely surround the granule.

While we regard the foregoing eosin staining zone as one of clubs, yet it is certain that the structures we here regard as clubs are not as distinct as those seen in granules from infections that have been regarded as characteristically actinomycotic. Unna (1896) calls attention to this distinction and gives the following staining method for the differentiation of the granules from actinomycosis and mycetoma:

*a*. Stain sections containing granules with acid fuchsin.
*b*. Wash.
*c*. Stain with hematoxylin.
*d*. Wash.
*e*. Fix with aniline xylol.
*f*. Decolorize in anilin.
*g*. Dehydrate and mount.

He states that by this method the rays of the actinomycosis granules are stained brilliantly with acid fuchsin, while in mycetoma only the younger clubs are stained by this method and much more faintly, while the colioid fan shaped clubs are not stained at all. Sections containing mycetoma granules were stained by this method, and as a control, tissue from a case of bovine actinomycosis was employed. We found the granules of the latter to be surrounded by a distinctly red zone of clubs, while the clubs of the mycetoma granules did not stain.

Within this zone the streptothrix is found in varying degrees of juvenility or senescence. It stains well by hematoxylin, but better by Gram's stain. The area occupied by the fungus can be divided into two well defined zones. The outer zone in the case of a presumably actively growing granule, completely surrounds the granules. This zone is composed of a dense interlacing mass of a Gram positive mycelium, which may be so dense that the individual threads cannot be distinguished. In the case of an older granule this zone may not completely surround the granule but forms an arc of greater or less length about the periphery. In the compound granules, when this incompleteness is noted, the persistance most commonly is along the exterior aspects of the lesser granules. From this zone scattering threads may project a variable distance into the zone of clubs, some penetrating across its entire width. The central zone contains Gram positive mycelial threads very widely separated from one another, so that its lesser density is very apparent.

The mycelial threads themselves are about 0.5 micra in diameter, though variations in the thickness of the same filament are observable. The filaments are not usually straight for a distance greater than 5 micra. They branch laterally and repeatedly; and the branches in turn branch. Some threads appear perfectly homogeneous, others appear beaded, while others appear as chains of spherical cocci. The coccoid forms are only found in the central zone of a granule. Some filaments have rounded expansions in their course, about twice the diameter of the threads, that are suggestive of chlamydospores. The terminal ends of the mycelial threads are knobbed or spatulate. In the central zone the chains of coccoid forms may have broken up, so that only widely scattered cocci are seen. None of the large spherical Gram positive (Russell) bodies previously noted, were seen in, or in contact with any granules.

Granules crushed and smeared, and then stained by Gram's method, react amphoterically. Gram positive filaments and coccoid forms are seen, as well as Gram negative filaments. A filament may be alternately Gram positive and negative for some distance, or a Gram positive span may shade off into a span that reacts negatively It appears that these Gram negative filaments formerly occupied the central zone.

The smaller or younger granules show all these zones in the most typical manner, the outer zone of dense mycelium entirely encircling the granule. The central zone contains a considerable amount of Gram positive filaments with a minimum of the coccoid chains. As the granule ages or enlarges, the number of coccoid forms in the center increases and the entire filaments diminish. At the same time the continuity of the outer zone may be interrupted. In the senescent granules, one observes that the dense network of mycelial threads at the periphery is much thinner, cocciod forms appear, while these are the only form observed in the central zone. In the oldest granules the central zone may appear entirely devoid of any Gram positive elements, and a peripheral mycelial zone is not observable, though the position it originally occupied is manifest from a collection of the cocciod forms.

*Cultural study of Streptothrix*

We did not possess a culture of the streptothrix isolated from any of our series of new cases. An old culture from case 28 was received, but was not viable. Through the kindness of Dr. Hamock of Los Angeles, we were furnished with a culture of the streptothrix from one of his two cases of mycetoma. Our collection of stock cultures contained a strain carried under the name of *Streptothrix madurae*, which had originally been secured from the University of Iowa, but whose previous origin is unknown. From our study of this organism we believe it to be *Actinomyces* (*Streptothrix*) *asteriodes*, by which designation it will be known in the subsequent pages. We secured a strain of the aerobic streptothrix of actinomycosis (*Actinomyces bovis*) from Dr. John S. Buckley of the United States Bureau of Animal

Fig. 15. Actinomyces mexicana (Left) in Infusion Broth

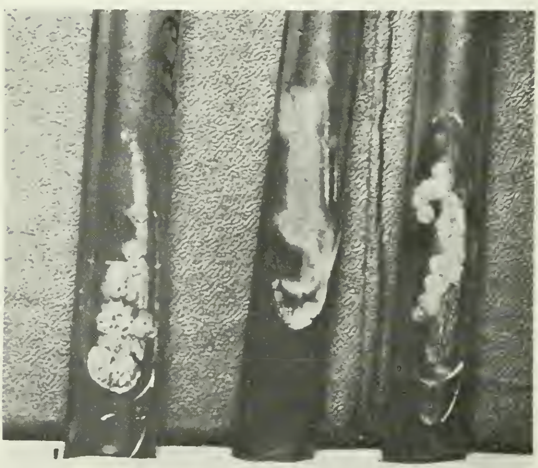

Fig. 16. Actinomyces mexicana (Left) on Dextrose Agar

Industry, but did not succeed in locating a strain of the anaerobic type in any laboratory in the United States to which we wrote. A comparative cultural study of these three forms on a variety of media was made. Our observations are presented herewith:

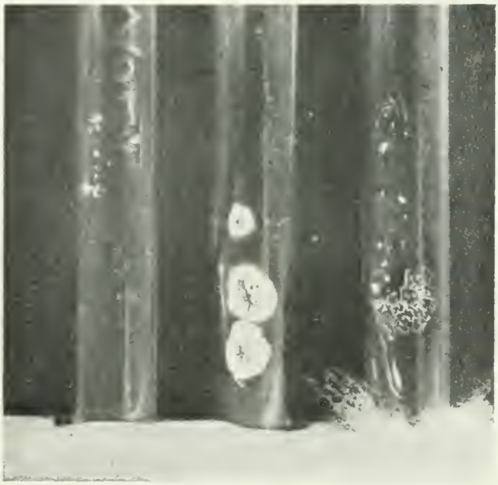

FIG. 17. ACTINOMYCES MEXICANA (LEFT) (NO GROWTH) ON BEER WORT AGAR

FIG. 18. ACTINOMYCES MEXICANA (LEFT) (SLIGHT GROWTH) ON PLAIN POTATO

*1. Fermentation of carbohydrates*

Peptone water containing 1 per cent of the following carbohydrates was employed: dextrose, maltose, mannite, saccharose, galactose, lactose, rhamnose, mannose, xylose and levulose, and was tinted with litmus and tubed in Durham's tubes.

*a*. Los Angeles streptrothrix. None of the above carbohydrates are fermented, after two weeks incubation at 37°C. Growth occurs as small white balls, not over 1 mm. in diameter, which accumulate in the bottom of the tube. Medium clear.

*b. Actinomyces asteroides.* None of the above carbohydrates are fermented after two weeks incubation at 37°C. Growth occurs as a very much wrinkled white pellicle over the surface, formed by the confluence of small colonies. Medium clear.

*c. Actinomyces bovis.* None of the above carbohydrates are fermented after two weeks incubation at 37°C. In all tubes large flocculent white balls of growth occur, up to 3 mm. in diameter, which accumulate as a sediment or adhere to the walls of the tube. Medium clear. After three weeks there is a tendency to form a surface pellicle.

### *2. Protein cleavage*

*1. Blood agar slants.* Meat infusion agar of plus one reaction to which approximately 20 per cent of defibrinated sheep's blood was added. Incubated at 37°C.

*a*. Los Angeles streptothrix. Colonies discrete, of irregular rectangular outline, from 3 to 4 mm. in diameter, margin abruptly elevated for 1 to 2 mm. with an umbilicate center. Surface powdery. Colonies surrounded by a narrow zone of hemolysis.

*b. Actinomyces asteroides.* Colonies 1 mm. or less in diameter, confluent, flat and dry. At first transparent, surface later becoming white and powdery. No hemolysis.

*c. Actinomyces bovis.* Colonies 2 to 3 mm. in diameter, round, convex and umbonate, smooth and glistening and white. Surrounded by a narrow zone of hemolysis.

*2. Gelatine.* A 15 per cent solution of gelatine in distilled water, neutral to phenolphthalin, poured into petri dishes, was employed. Incubated at room temperature.

*a*. Los Angeles streptothrix. Liquefication evident after twenty-four hours. Growth slow. In three days surrounded by a zone of liquefication 10 mm. in diameter.

*b. Actinomyces asteroides.* Slight growth, no liquefication.

*c. Actinomyces bovis.* Liquification evident after twenty-four hours. In three days surrounded by a zone of liquefication 5 mm. in diameter.

*3. Milk.* Skimmed milk, tinted with litmus, was employed. It was incubated at 37°C.

*a.* Los Angeles streptothrix. Very slow growth, producing peptonization without previous clotting in three weeks incubation.

*b. Actinomyces asteroides.* In two weeks a rather thick pellicle formed yellow in color. No acid, gas or clot. No peptonization.

*c. Actinomyces bovis.* In two weeks a thick folded surface pellicle formed. No acid or gas. A light curd is formed which rapidly undergoes peptonization.

*4. Loeffler's blood serum.* Incubated at 37°C.

*a.* Los Angeles streptothrix. Growth very slow. Discrete colonies of rectangular outline, conical, 2 to 3 mm. in diameter, elevated from 1 to 2 mm. from the surface at their center, colorless, smooth and moist. No liquefaction in three weeks.

*b. Actinomyces asteroides.* A heaped up, very much folded, confluent growth of ocher yellow color, turning powdery after two weeks. No liquefaction.

*c. Actinomyces bovis.* Circular, discrete colonies, 3 to 4 mm. in diameter, flat, dry. Liquefaction in three days.

### *3. Synthetic media*

*1. Krainsky's synthetic medium for actinomyces,* made up according to the following formula:

| | |
|---|---|
| Dextrose | 10.0 grams |
| $NH_4Cl$ | 0.5 gram |
| Asparagin | 1.5 grams |
| Agar | 15.0 grams |
| Distilled water | 1000.0 cc. |

Incubated at 37°C.

*a.* Los Angeles streptothrix. Successful growth only secured after repeated inoculations. Colonies discrete, not over 2 mm. in diameter, circular, slightly convex, rounded, moist and white. Sends mycelial projections for 2 to 3 mm. into the substrate.

*b. Actinomyces asteroides.* Growth compact, very slow spreading, convex, opaque, light tan in color, surface smooth, with suggestion of powdery efflorescence.

*c. Actinomyces bovis.* Growth mycelial, very flat and in intimate contact with medium or slightly below surface. Pale lemon yellow in color, translucent. Center is marked by a powdery white efflorescence.

*2. Conn's synthetic citrate agar for actinomyces,* made up according to the following formula:

| | |
|---|---|
| Citric acid | 5.0 grams |
| $NH_4Cl$ | 0.5 grams |
| $K_2HPO_4$ | 0.5 grams |
| Glycerine | 6.0 cc. |
| Agar | 15.0 grams |
| Distilled water | 1000.0 cc. |

Dissolved and made neutral to phenolphthalein. Incubated at 37°C.

*a.* Los Angeles streptothrix. Grows with difficulty. Colonies small, white, opaque, convex and moist.

*b. Actinomyces asteroides.* Grows readily. Colonies 3 mm. in diameter, becoming confluent. Circular, markedly convex, smooth, dry, opaque and white. Where confluent the growth tends to become heaped up and has a slight white tint.

*c. Actinomyces bovis.* Growth luxuriant, spreading over nearly the entire surface of the agar slant. Growth flat at margin, in center heaped up in rounded tuberculations. Dry, opaque with whitish efflorescence.

*3. Waksman's modification of Czapek's medium for actinomyces,* made up according to the following formula:

| | |
|---|---|
| $MgSO_4$ | 0.5 grams |
| $K_2HPO_4$ | 1.0 grams |
| KCl | 0.5 grams |
| $FeSO_4$ | 0.01 grams |
| $NaNO_3$ | 2.0 grams |
| Saccharose | 30.0 grams |
| Agar | 15.0 grams |
| Distilled water | 1000.0 cc. |

Incubated at 37°C.

*a.* Los Angeles streptothrix. No growth in three weeks.

*b. Actinomyces asteroides.* Growth slow and scanty. Colony myceloid, penetrating deeply into the substrate. Margin flat, in contact with medium, center heaped up, opaque, white and powdery. General appearance dry, translucent except in center.

*c. Actinomyces bovis.* Growth slow and scanty. Myceloid. Growth in intimate contact with substrate, into which it penetrates. Surface flat, marked by concentric rings of powdery efflorescence.

*4. Common nutrient media*

1. *Meat infusion broth* of plus one reaction (Fig. 15).

*a.* Los Angeles streptothrix. Medium remains clear. Growth occurs as a sediment of flakes.

*b. Actinomyces asteroides.* Medium clear, a folded white pellicle on the surface.

*c. Actinomyces bovis.* Medium clear. A heavy sediment of large fluffy balls.

2. *Ascitic fluid infusion broth* of a neutral reaction.

*a.* Los Angeles streptothrix. Medium clear, sediment of small fluffy balls.

*b. Actinomyces asteroides.* Medium clear, a folded pellicle of pale yellow color on the surface.

*c. Actinomyces bovis.* A folded white surface pellicle, no sediment.

3. *Meat infusion agar* of a plus one reaction.

*a.* Los Angeles streptothrix. Discrete colonies, 2 cm. in diameter. Rectangular edges, abruptly elevated, 1 to 2 mm. high. Center pointed or umbilicated. Smooth, moist, slightly yellow in color.

*b. Actinomyces asteroides.* Flat confluent growth, central part folded in fine wrinkles, folds yellowish, white and powdery between folds.

*c. Actinomyces bovis.* Large round discrete colonies, with a white powdery surface. Radial wrinkles.

4. *Ascitic agar* of a neutral reaction.

*a.* Los Angeles streptothrix. Convex, round, discrete colonies. Moist, slightly translucent.

*b. Actinomyces asteroides.* Confluent growth, opaque, white, powdery and wrinkled.

*c. Actinomyces bovis.* Large, discrete colonies, 1 cm. in diameter. A central area 3 mm. in diameter, crateriform and elevated. This central area outside the crater is in white powdery wrinkled folds. The outer zone is flat, moist and yellowish.

5. *Litmus lactose agar*, neutral reaction.

*a.* Los Angeles streptothrix. Colonies similar to those on plain agar, except they are colored blue from the litmus.

*b. Actinomyces asteroides.* Colonies are similar to those on plain agar, but are not colored.

*c. Actinomyces bovis.* Large, discrete round white colonies, very much wrinkled. Outer wrinkles concentric. Center heaped up in irregular folds. Surrounded by an outer zone of mycelial prolongation.

6. *Dextrose agar* of a neutral reaction (Fig. 16).

*a.* Los Angeles streptothrix. Colonies similar to those on plain agar.

*b. Acinomyces asteroides.* Colonies similar to those on plain agar.

*c. Actinomyces bovis.* Colonies similar to those on plain agar.

*7. Glycerine agar* of a neutral reaction.

*a.* Los Angeles streptothrix. Growth very slow. Colonies small, 1 mm. or less in diameter, translucent, markedly convex, tending to become wrinkled.

*b. Actinomyces asteroides.* A compact wrinkled growth, higher at the margins and center than in the intervening space, edge abruptly elevated, margin white, center folds ocher yellow.

*c. Actinomyces bovis.* Compact, elevated, irregularly and heavily wrinkled, white, surface powdery.

### *5. Media especially adapted to fungi*

*1. Beerwort agar,* prepared according to the formula given by Eyre (fig. 17).

*a.* Los Angeles streptothrix. Grows poorly and only secured after repeated inoculations. Flat, in intimate contact with substrate, finely translucent, pale yellow. Somewhat resembles that of *A. bovis.*

*b. Actinomyces asteriodes.* White colonies with an elevated central portion, from which radiate short folds of a golden yellow color.

*c. Actinomyces bovis.* Colony very much elevated, irregularly folded into fine wrinkles of a translucent lemon yellow color, covered with a whitish efflorescence when two weeks old.

*2. Sabouraud's dextrose agar.*

*a.* Los Angeles streptothrix. No growth.

*b. Actinomyces asteroides.* No growth.

*c. Actinomyces bovis.* No growth.

*3. Potato,* either plain or glycerinated (fig. 18).

*a.* Los Angeles streptothrix. Growth very slow, only visible after three weeks. Not over 1 mm. in diameter, flat, slightly elevated, white. Potato unchanged.

*b. Actinomyces asteroides.* Flat, elevated, with projecting tuberculations. The general tint is yellow, while the tuberculations are orange. The growth is more elevated on the glycerine potato. Potato unchanged.

*c. Actinomyces bovis.* Very much folded and heaped up, white, powdery. Potato unchanged.

The foregoing observations upon the streptothrix isolated from the granules of a case of North American actinomycotic mycetoma may be summarized as follows:

*a. Culturally* it is an aerobic fungus, growing best at 37°C., not fermenting any carbohydrates, slightly hemolyzing blood serum; growing very sparsely on synthetic media adapted to saprophytic actinomyces; producing a sediment of small spherical balls or flakes in liquid media while the fluid remains clear; on solid media with either a meat extract or meat infusion base it produces large elevated colonies, somewhat conical in shape, sometimes with a crateriform or umbilicate summit, moist, translucent and of a creamy yellow tint. Cultures have a faint fecal odor.

*b. Microscopically.* The hyphae are about 0.7 micra in diameter and except on Loeffler's blood serum are of very uniform diameter. The filaments are tortuous, especially on those mediums where the colonies are large and umbilicated. Branching occurs at frequent intervals. The branches are lateral, and may divide a short distance from the parent hypha. The ends of hyphae may be slightly swollen. On blood agar and Loeffler's blood serum, arthrospores or chlamydospores are noted. The hyphae on the latter are of very uneven diameter. The hyphae may fragment into bacilliform fragments. They are Gram positive, but may show Gram negative intervals, and are not acid fast. No conidiaspores were noted on any culture medium. On plain potato a few hyphae were noted whose threads stained Gram negative, but in whose interior were small Gram positive coccus like bodies, of a diameter less than the filament.

Cultures were inoculated subcutaneously into one guinea pig and intraperitoneally into two guinea-pigs, without results. Cultures four days old were used, and massive doses were given.

The organisms of this group, whether pathogenic or saprophytic, are very imperfectly known. Confusion in the nomenclature has still further clouded the situation. Thus the pathogenic species have been variously referred to the following genera by different authors: *Streptothrix* Cohn, 1875; *Actinomyces,* Harz, 1877; *Discomyces,* Rivolta, 1878; *Nocardia,* Trevisan, 1889, *and Cohnistreptothrix*, Pinoy, 1913, to mention those names more commonly employed. Several illuminating reviews of the validity of these names under the rules of botanical nomenclature have recently appeared, and as a consequence the question of generic nomenclature must be regarded as materially clarified, although the question of the valid species of the genus yet requires considerable study. We shall regard the report of the Committee of the Society of American Bacteriologists on Characterization and Classification of Bacterial Types (1920) as the ultimate authority on bacterial nomenclature, and accept *Actinomyces*, Harz, 1877 as the correct generic name for these organisms under the laws of botanical nomenclature.

The characteristics of this genus, as given in the foregoing report are as follows:

Class Schizomycetes
Order Actinomycetales
Family Actinomycetaceae

Genus *Actinomyces*. Organisms growing in the form of a much branched mycelium, which may break up into segments that function as conidia. Sometimes parasitic, with clubbed ends of radiating threads conspicuous in lesions in the animal body. Some species micro-aerophilic or anaerobic. Non-motile.

The type genus is *Actinomyces bovis*, Harz.

The characteristics of the known pathogenic species of this genus have been reviewed by Chalmers and Christopherson (1916). The following differential table has been mainly prepared from their summarization (table 5).

There is some reason to believe that the actinomyces described by Allison from case 18 may be identical with that which we have studied from the Los Angeles case, as they are both aerobes, both grow best 37°C., both produce spherical balls of mycelium in broth and neither liquefy blood serum. They differ in their chromogenesis however. In this group of fungi, however, chromogenesis is a variable quality in one and the same species, and consequently its differential value is slight.

From a consideration of the more essential characteristics presented in the foregoing table, it does not appear that this

TABLE 5

*Differential table of pathogenic members of the genus Actinomyces*

| SPECIES | BACILLARY FORMS | ARRANGEMENT OF FILAMENTS | CLUBBING OF ENDS | GRAM REACTION | ACID FAST | OXYGEN REQUIREMENTS | OPTIMUM TEMPERATURE | BROTH | AGAR | POTATO | GELATINE | MILK | BLOOD SERUM | NOTES |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | °C. | | | | | | | |
| *A. bovis*.......... | None | Radial | Yes | Positive | No | Aerobe | 37 | Dry pellicle or spherical balls at bottom. Clear | Circular colonies onies crateriform or wrinkled. Efflorescence | Raised, wrinkled, white efflorescence | Liquefied | Peptonized | Liquefied | |
| *A. asteroides*...... | Yes | | None | Positive | Yes | Fac. anaer. | 37 | Pellicle, clear | Smooth, raised, white, later pink | Yellowish in center, pink or white edge | No liquefaction | No peptonization | No liquefaction | From mycetoma |
| *A. liquefaciens*.... | | | None | Positive | | Aerobe | | Floating flakes | Discrete, creamy superficial | Small, yellow, white efflorescence | Liquefied | | Liquefied | |
| *A. indica*......... | | Radial | None | Positive | No | Fac. anaer. | 37 | Spherical colonies at bottom | Pinkish to red Umbilicate | Pinkish to red | Slow liquefaction | Peptonized | Liquefied | From mycetoma |
| *A. krausei*........ | Yes | Tangled | Yes | | | Fac. anaer. | 37 | Pellicle | Slight yellow on glycerine agar | No growth | No growth | | | |
| *A. somaliensis*.... | | | | | | | | | | White, folded becoming yellow | | | | From mycetoma |
| *A. israeli*......... | Yes | Radial | Yes | | | Obl. anaer. | 37 | Flaky masses on bottom | Sparse | Sparse | No growth | No change | Not liquefied | |
| *A. thibiergi*....... | Yes | Radial | Yes | | | Fac. anaer. | 37 | | | | | | | |
| *A. convoluta*...... | Yes | | | | | Fac. anaer. | 30 | Flocculi, clear No pellicle | Folder, buff color | Buff colored, folded, white efflorescence | No liquefaction | No peptonization | Liquefied | From mycetoma |
| *A. garteni*........ | | Tangled | None | | | Aerobe | | | Gray-white, wrinkled | White colonies, medium greenish | Liquefied | | Liquefied | |
| From case 18..... | | | | | | Aerobe | 37 | Spherical balls Clear | Elevated, discrete, white, later pink margin | Similar to agar | | | | From mycetoma |
| *A. mexicana* (Los Angeles) | Yes | | Yes | Positive | No | Aerobe | 37 | Sediment spherical balls. Clear | Heaped up, yellowish crateriform. No efflorescence | Scant, white | Liquefied | Peptonized very slowly | No liquefaction | From mycetoma |

Data from Chalmers and Christopherson, J. H. Wright, Musgrave and Clegg, Vincent, and Waksman.

actinomyces can be identified with any of the pathogenic forms previously described. Neither does it appear to coincide with any of the species of saprophytic North American actinomyces described by Waksman and Curtis (1916) or Conn (1917). We therefore are of the opinion that this species is one hitherto undescribed.

It does however, present some points of similarity to *Actinomyces asteroides* and *Actinomyces indica*, to such an extent that it may be regarded as an intermediate form. These points of similarity and dissimilarity may be summarized as follows:

| CHARACTER | A. ASTEROIDES | ACTINOMYCES FROM LOS ANGELES | A. INDICA |
|---|---|---|---|
| Broth | Floating, flat particles or pellicle | Sediment of spherical colonies | Sediment of spherical colonies |
| Agar | Smooth, white or yellowish. May become umbilicate | Heaped up, yellowish, crateriform or umbilicate | Pinkish to red, umbilicate |
| Gelatine | No liquefication | Slow liquefication | Slow liquefication |
| Milk | No peptonization | Very slow peptonization | Peptonized |
| Blood serum | Not liquefied | Not liquefied | Liquefied |
| Potato | Grows well, yellow | Scant growth, white | Grows well, pink to red |

Consequently we regard the organism as one hitherto undescribed. On the basis of the foregoing characteristics we propose the name *Actinomyces mexicana* for the species.

## VII. TREATMENT

In reviewing the treatment of the North American cases of Madura foot, one must conclude that treatment is far from satisfactory or successful.

The local treatment in these cases has been varied. Applications of antiseptic lotions have in many instances been used—at other times irrigations with germicidal or counter irritant solutions, cauterization (actual or by chemicals), have in no instance proved successful. The end results have all been the same and amputation has been the final resort.

Internal medication has met the same end as that of local treatment. Reasoning from analogy, potassium iodide has been given in some of these cases with no beneficial results.

In our case (30) realizing that many diseases produced by fungi are benefited by x-ray, we began treatment by the use of the x-ray. After the first treatment the patient sensed a marked relief from the pain and discomfort of which he complained, and the sinuses showed a marked decrease in the discharge and in fact had apparently healed over. Two months later after the second treatment, we were disappointed to see some new sinuses forming and one old sinus had re-opened. The patient had a marked sense of relief and was able to use a heretofore useless extremity with considerable facility. After the third treatment the patient had apparently a decrease in the activity of the process. The fusiform swelling was considerably reduced and the patient had much better control over the foot. After the fourth treatment the patient failed to report at the appointed time for treatment but reported that his foot was much better; that it was less swollen and that the sinuses were no longer discharging.

Blastomycosis and actimycosis and similar diseases respond so well to x-ray therapy that we had hoped a good result might be obtained in Madura foot, but considering the pathology of the disease after observation of the last case we conclude that this is a hopeless measure so far as a return to normal is concerned. If we consider that the lesion in Madura foot is associated with an over production and replacement of the normal structures by fibrous tissues, we realize that even a sterilization of the area by the use of x-ray could not hope to do more than stop the progress of the disease and leave the foot in the condition it might be in, for the fibrous replacement has already occurred and we are not able to rejuvenate normal tissue and replace this fibrosis.

We have felt that if the disease could be seen early enough before extensive destruction has taken place, that x-ray might be of value, but after there has been a widespread involvement there is little hope to cure an already destroyed tissue.

Since the Madura foot is in truth an involvement of the subcutaneous tissue before a skin involvement, we realize that it is very difficult to see the patient early.

The conclusions we would draw from a review of old cases and observations upon our series are that:

1. Local treatment is of no value as a curative measure or in checking the progress of the disease.
2. Internal medication is of no value.
3. X-ray may possibly delay or check the disease at the stage in which it is seen.
4. There is such widespread infiltration and destruction with fibrous tissue replacement that even if the disease is checked the member would remain practically functionless.
5. Early amputation with an artificial limb offers the best solution to the treatment of the disease.

## VIII. SUMMARY

The type of fungus infection of the extremities known as mycetoma is comparatively rare in North America. It is relatively more common in the tropics and sub-tropics then in the temperate zone, and apparently more common in semi arid regions than elsewhere. The majority of the reported cases have occurred among Mexicans (probably Indians). Its onset may occur at any age period, though it is most common between the ages of twenty and thirty. The occurrence of a case in a woman is very unusual. Most of the cases are laborers by occupation, and of these the majority are engaged in agricultural pursuits. The other cases regardless of occupation, appear to have lead quite active lives out of doors.

The extent to which the patients habitually went barefooted is very striking. Associated with habitual barefootedness, a large proportion of patients received injuries to the affected foot, either of the nature of contusions or incisions, before the onset of the disease. Presumptively the trauma either inoculated the fungus into the subcutaneous tissues or otherwise favored invasion.

Usually the earliest sign of invasion consists in the appearance of one or more fungating nodules on the skin, sometimes at the site of the previous trauma, which sooner or later are crowned with a discharging sinus. Early swelling of the foot is another common symptom, at first local and later general, which may or may not be painful. Less frequently the first symptoms may be variously (1) the formation of vesicles, or (2) an abscess, or (3) a pigmentation of the skin. In all except one case the feet were the site of invasion, the left foot being more commonly attacked than the right. In one instance both feet were involved. The hand was only involved once.

The disease tends to run a slowly progressive course extending over a considerable period of years (as long as sixteen years) with apparently no tendency to self limitation, though but slight spread beyond the affected extremity is noted. The affected member may be swollen to several times the normal size, which may seriously interfere with locomotion. There is an absence of any definite systemic reaction. Marked weakness associated with emaciation is common.

Over the skin of the invaded area are invariably present a variable number of discharging sinuses. If nodules are present the sinuses open on the nodule summits. Nodules are not invariably present, and there is some suggestion that their presence or absence varies with the causative organism. From the sinuses is discharged a scanty volume of a thin sero-sanguinolent fluid, in which may be occasionally noted the characteristic granules. The nodules are most in evidence on the dorsum of the foot and may either be discrete or confluent. The activity of any given sinus is apparently of rather short duration, and where nodules exist, their formation precedes the appearance of a sinus.

Internally, there is very extensive disorganization of all the tissues of the invaded area. Fatty tissue disappears and the muscles disintegrate. There is a marked hyperplasia of dense connective tissue which tends to undergo an early hyaline degeneration which may account for the purplish color quite characteristic of the invaded areas. The invaded area is penetrated in every direction by fistulous channels or sinuses, which open externally through the nodules noted. These sinuses are lined by granulation tissue infiltrated with round cells and in their lumen may be found either necrotic debris, serous fluid, extravasated blood and a varying number of the characteristic granules which usually lie in cavernous expansions in the sinus. These sinuses may extend to the bones and granules may lie in excavations in the bony tissue. The bones of the invaded area undergo a rarifying and hyperplastic osteitis and may become very spongy. Joint involvement is apparently rare. The process appears to show a tendency to spread along fascial planes.

Histologically, the most characteristic feature appears to be the proliferation of fibroblasts, either with the granulation tissue which lines the sinuses and which tends constantly to effect their closure, or independantly of the granulation tissue. There is but a limited accumulation of polymorphonuclear leucocytes, which are chiefly found in the immediate vicinity of a granule. No evidence of phagocytosis of the fungus by any type of cell was noted. Round or oval multinucleated giant cells are common. Russell's bodies are frequently seen. The changes in the skin are solely secondary to those taking place within the foot. The development of a nodule appears to be due to the internal pressure in the subcutaneous tissues produced by an extending sinus. The skin does not present any change of note. The extensive production of granulation tissue is responsible for the frequency with which blood appears in the discharge from a sinus, as well as the evidences of a past and recent hemorrhage into the tissues.

The granules are dense circumscribed colonies of the causative organism, which was not found apart from these aggregations. They are visible to the naked eye, and may vary from black, to white or pale ocher in color. The light colored grains are soft in consistency. According to the type of fungus producing the grains, the North American cases may be divided into three groups.

The first group includes but a single case. This is the sole case in which the granules were black in color and from which were cultivated a hyphomycete probably identical with *Madurella mycetoma*, Laveran, a recognized cause of black grained mycetoma in India, Africa and Italy. The tissue reaction in this case differed from that presented by the other cases. In addition to the hyperplasia of dense connective tissue, there was an abundance of a peculiar type of giant cell, frequently in contact with the granule, a proliferation of endothelial cells so that tubercle like structures were formed and very little evidence of suppuration. There were no fungating nodules on the skin.

The second group is likewise represented by but a single case in which the granules were white in color and from which were cultivated a hitherto undescribed ascomyte reported as *Allescheria Boydii*, Shear. The small piece of biopsy tissue removed from this case did not permit a histological study of value. There were no fungating nodules on the skin.

Most of the remaining reported cases may be assigned to the third group, in which the granules vary from white to ocher in color and are composed of a streptothrix belonging to the genus *Actinomyces*. Study of a culture from one case showed it to to differ from the previously described species of *Actinomyces*, and the name of *Actinomyces mexicana*, Boyd and Crutchfield, is proposed. Clinically and pathologically the characteristics of the disease in this group of cases does not differ from that usually accepted for that group of fungus infections known as actinomycosis, and variously produced by several other species of this genus. The granules are however, of a larger size and not surrounded by the same type of clubs as those noted in the characteristic clinical types of actinomycosis produced either by *A. bovis* or *A. israeli*. The organism is powerfully proteolytic, as is also the *Allescheria*, a property that may account for the ability to produce the sinuses. The fungating nodules of the skin are characteristically found in the cases of this group.

From a therapeutic standpoint the treatment is wholly surgical. A variety of drugs have been employed, both locally and systemically but without effect. Surgical treatment involves an excision of the area of invasion, which if seen early may only require the removal of a small area of tissue, but if the process is extensive amputation of the member may be the best course to pursue. In any event, the line of the excision should pass into the healthy tissue well beyond any apparent evidence of invasion, as other wise not all the fungus may be exterpated, and the process continue to extend.

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# ACRODYNIA: ITS PLACE IN MEDICINE AND ITS RELATION TO PELLAGRA

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The term acrodynia (ακρος an extremity, ὀδύνη pain) was coined about 1830 in France to meet the need of a word to designate a condition regarded as altogether new and hitherto undescribed under any other single designation. The first recognized account of the disease was in 1828 and until the term acrodynia was introduced it was known as the malady of Paris or the *epidemie de Paris.*

From the earliest account in the literature until this day no publication has failed to refer to its striking similarity to pellagra and in every instance there has been expressed the possibility of its cause being explained by some dietetic error either of a toxic or a deficient sort.

My own interest in the subject was aroused by experience with pellagra during the period 1907-1918 when the disease was so prevalent in the southern states where it assumed the gravest proportions. The history of the appearance of pellagra in this section is unlike any other chapter in medical history and offers many attractive problems yet to be solved. Why it should have appeared out of a clear sky as it were to rage with remarkable virulence and in an acute form hitherto unknown in medical literature and to spend itself like a tropical storm after a decade of terrific toll in life and efficiency remains a medical mystery.

With the problem of pellagra is intimately linked the problem of acrodynia and with the final solution of the one will likely come a solution of the other.

Recently my interest was revived by a brief article by Dr. F. G. Crookshank (1). The present communication is largely inspired by this article and is an effort to show the error of conclusions therein reached. This writer briefly stresses the fact that acrodynia in Paris preceded by only a few months the pandemic influenza of 1830 and that later outbreaks were related in a general way and in a similar manner to influenza. He believes that acrodynia in 1828 and 1829 bore the same relation to influenza as did the poliomyelitis in Sweden in 1917-1919 as, according to his view, has been the case with other epidemics of encephalitis, of myelitis, of meningitis and of neuritis. To quote his words:

> Acrodynia, it may be said, represents a *neuritic* type of the nervous cases and epidemics that invariably precede, accompany, or follow, in some place or places, epidemic and pandemic influenza.

Crookshank tells of a case which came under his care in the London Hospital in 1918 during the height of the epidemic of lethargic encephalitis. This case and another he connected with the epidemic. In one of the cases he makes the following interesting note:

> The illness commenced with formications, and with blebs on the hands, proceeded to gangrene, and the patient died of an ascending central myelitis, recalling forcibly the sixteenth century epidemics which by a delusion originating in the eighteenth, has come to be regarded as due to ergotism. The young woman of whom I write was actually suspected of having been poisoned by ergot.

This case so closely corresponded with scores of cases seen in the South during 1907-1910 that I wrote Dr. Crookshank for more detailed description. I learned, what was already a reasonable suspicion, that the skin lesions occured on the backs of the hands. Quoting his letter:

> It was one of the "types" of encephalomyelitis (as I call it) and I know there have been *epidemics* of the type of this case in the past, during the influenza periods, recorded as "ergotism," etc.

As a matter of fact the description of the case was as classical a picture of pellagra as is to be found in any literature of any period since the recognition of this disease. In this connection it might not be amiss to mention that pellagra is by no means unknown in Great Britain. During 1919 and 1920 I saw two cases in Guy's Hospital and a most typical case (2) in the Royal Infirmary, Edinburgh in the service of Dr. Edwin Bramwell. Dr. Cranston Low in Edinburgh had given the disease careful study and the accuracy of his work is attested by the splendid wax models of the skin lesion which he has made. He thinks pellagra much more prevalent in Scotland than usually recognized. Dr. L. W. Sambon has collected 180 cases in Great Britain.

Even the most critical would accept Dr. Crookshank's case as one of pellagra. Certainly the diagosis is being generally accepted in many cases far less typical than is this.

As stated above the first recorded account (3) of the disease, acrodynia, was published in 1828 and was an observation of that year in Paris. M. Genest records his embarrassment at having no name to designate the condition. It was generally recognized as new and hitherto undescribed in the literature. He stated that at the end of the previous winter, which was not notable for rigor nor length nor unusual humidity, the disease appeared in many widely separated quarters of Paris. In the accounts are mentioned as initial symptoms vague indefinite digestive errors which are common to many disorders and which, consequently, attracted little attention. The interval between this manifestation and the definite signs of the disease varied to such a marked degree that it was of no help in the recognition.

The disease first appeared in the Faubourg St. Germain, the barracks of L'Oursine, the vicinity of the Faubourg du Temple (la Courtille), of the Hotel-de-Ville and finally in the Lombard section. Numerous observations were made simultaneously in different sections of Paris by a number of observers. Each was seeing a new and strange malady and as a result of there being no exchange of experience the accounts are so varied that it is difficult in some instances to accept the fact that all are describing the same condition.

The general trend of the reported observations is that of a functional neurosis. It was obvious that there were more than one type of the condition just as in lethargic encephalitis, for example. After five months of sporadic occurrence there was no longer any doubt but that the disease was epidemic. This observation was made in the month of August. This is a matter of importance for many writers have seen fit to offer as a means of differentiation from pellagra the occurrence in winter. Many of the victims seem to have been the inmates of the various hospitals in Paris and not a few were of the bed-ridden chronic type. In the Faubourg du Temple there occurred 300 cases among the men of two batallions. As an example of the great prevalence of acrodynia it is recorded that in the Hospice of Marie-Therese with a roll of 40 inmates 36 were victims. The number of cases increased so rapidly that by September 6 the Faubourg du Temple was completely evacuated. Vigorous efforts were then put forth to improve the sanitary condition of this place but there was no evidence that such steps improved the situation.

On August 26, 1828, M. Chomel (4) called the attention of the Academy of Medicine to the disease and a commission was named to study it. By the autumn of that year it was very generally distributed and it would appear from the accounts that former victims were the subjects of recurrences. It was rare to find a household without a case. Ordinarily the husband, the wife, the children and servants were simultaneously attacked.

It did not appear that the poor were any more frequently affected than the well-to-do.

There was great diversity in the manifestations as before stated.

The following types were described:

1. Cases presenting numbness of the feet and hands with shooting pains, without digestive disturbances and without ophthalmic symptoms or edema. The patient in question was taken sick on August 1. Her hands were cold but not so painful as her feet. On the soles of the feet and the external and internal edges and also *on the nodosities*

*of the articulations of the phalanges* was found an erythema. The hands likewise showed the lesion in the middle of each articulation. The erythema would disappear on pressure but was not slow to return. Pressure was quite painful.

2. Edema of different parts of the body, loss of appetite, vomiting, tingling and shooting pains in hands and feet and erythema in the same locations. The attack in this case appeared in the middle of June. The eyes were quite painful and the lids swollen. There was epigastric colic but no diarrhoea. On August 8 there was a recurrence with edema of the face, legs and feet. Slight diarrhoea appeared later. The soles of the feet were painful. The lateral aspects of the feet and toes had a red hue not unlike chilblains. The epidermis of the toes and the soles exfoliated in great flakes. There was marked loss of sensation. The diarrhoea was repeated many times.

3. The attack began with digestive derangement, swelling of the face, numbness of the feet with shooting pains also which likewise affected the hands. Black coloration of the skin of the feet is mentioned and also some subjective eye symptoms. The patient became unable to feel the contact of the bed clothes. This disturbance of sensation was limited to the soles and the lateral surfaces of the feet. The black coloration is described as extending over the whole body except the face where there was some superficial pigmentation. The skin lesion was compared to scrofula.

4. The representative of this class was a woman delivered in March. Formerly she had been annoyed with a mild degree of tingling and numbness and with black spots suggesting to the observer the skin lesion seen in scurvy. The delivery caused a marked lighting up of the disease process. Sensory symptoms in hands and feet became pronounced. The skin was covered by black areas of varying size occupying positions over the breasts, back, neck and limbs. There was marked anorexia. She was treated in St. Lazaire ward, Hotel Dieu in the service of M. Racamier. The spots later became coalescent and varied markedly in size. There was variation in the color of the skin lesion but brown seemed to predominate. The line of demarcation between sound and diseased skin was sharply drawn. The observer compared the skin lesions to ecchymoses.

There were other cases recorded in this communication but they added nothing to the picture. It was interesting to note some of the complications, however. One case presented hallucinations of sound. Another was the victim of intestinal perforation. The post-mortem examination in one of the few fatal cases was negative except for inflammatory changes found in the sciatic nerve. It will be recalled that the distinguished Louis was the pathologist who performed the post-mortem investigations.

The medical journals of Paris of the year 1828 and the year following contain many references to the new epidemic which was causing few deaths but much misery. In the same journal with the article of Genest appears a communication by M. Chomel (4) whose name was intimately connected with the new disease from its first appearance to its disappearance a few years later In his account of the skin lesion of the palms and soles will be noted that the erythema curved around the nails so that it is obvious that the posterior surfaces of the hands and the superior surfaces of the feet were more affected than some writers record. His account of the total helplessness of the bed-ridden victim from multiple neuritis reminds one forcibly of the picture so often noted in pellagra.

In a journal of November 29, 1828, M. Chomel (5) stated that one-fourth of the hospital beds were given over to the victims of the new disease. In its recognition emphasis was first put on the pain in the hands and feet declared to be worse at night than during the day. The pain was increased by pressure and shoes became unbearable. Many of the patients elected to wear heavy gloves and socks without shoes continuously. The sensory disturbances became so exaggerated that articles could not be recognized by the sense of touch. It was noted in some cases that the victims could lose their shoes from their feet without being aware of it. There was much restriction of movement of the small joints and it became impossible to flex and extend the fingers completely. The victim was unable to fasten the buttons of his clothes. The gait described was quite peculiar: the legs were kept wide apart as though there were some affection of the external genetalia. Many of the patients were unable to move in bed at all.

Chomel gave a more exact account of the skin lesion which is described as stopping at the external and internal borders of the soles and palms. In some instances the upper surfaces of the toes were affected. The lesion was regarded as an inflammatory process which resulted in the destruction of the superficial layers of the skin with abundant exfoliation. There was also involvement of the skin beneath the nails and the result was a thinning and elongation producing a peculiar appearance which one familiar with pellagra will readily recall. Chomel mentioned the occasional occurrence of the skin lesion on other parts than the hands and feet. He observed a roseolar eruption which healed promptly. There was a variation in the color of the process as well as the duration. In some instances edema was noted. In his clinic the mucous surfaces were not infrequently affected by the inflammatory process. Ophthalmia, diarrhoea, vomiting and even otorrhoea and also angina are recorded as occasional findings. A marked tendency to remissions was observed. These remissions seemed to have occurred within a few days after leaving the hospital in some cases. Remissions are notable occurrences in pellagra but one does not note them as occurring so closely on the wake of recovery from an attack. In one case of this series a death occurred and Louis performed the autopsy with all his exactness. The spinal cord was exposed and nerve trunks followed throughout their course but nothing accountable for death was discovered. Again this recalls experience with pellagra. Many sudden deaths occurred especially in children and frequently there was no definite cause discoverable at autopsy. The same negative autopsy findings were recorded in the cases of acrodynia in the service of M. Andral who had the pathological assistance of M. Fouquier. Ergot was suspected as a cause as one would reasonably expect and to it were added as possibilities bad wine, humidity and faulty housing conditions. The escape of infants from the disease was used as an argument against a nutritional disease. It will be recorded later that acrodynia in infants has caused much interest in the disease in very recent times.

It seems remarkable that the condition should have passed so completely from view after this period. This would appear as one of the strongest arguments against its right to existence as a separate disease entity. Had it persisted as observed in Paris it could not have escaped attention but if it was only the atypical manifestation of another condition its disappearance is easily explained. Until recently there was hardly a reference to it in the literature of the day. The Third Series of the Index Catalogue of the Library of the Surgeon General has no mention of the word acrodynia. No modern test book of medicine mentions it and the works on dermatology have only a brief reference to it with no recent cases added to the literature of the period 1828-1830.

Not many years after this period (1848) that brilliant Irishman, Robert James Graves (6) (1796-1853) in his Clinical Lectures refers to the malady thus:

> It began (frequently in persons of good health) with the sensations of severe pain in the skin of the hands and feet, accompanied by so acute a degree of sensibility that the patients could not bear the parts to be touched. After a few hours, or later, anesthesia supervened; and the patients became incapable of distinguishing the shape, texture or temperature of bodies in the parts affected, the power of movement also declined and finally complete paralysis followed, involving the four limbs. Persons laid in bed powerless and helpless, and thus continued for weeks or months.

After quoting the above abstract from Graves the Medical Press and Circular (London) for November 3, 1920, notes that no other physical findings were noted except this paralysis. Improvement was established after varying periods with the almost invariable return of sensation and motion. No pathological changes were recorded by Graves. He adds "the phenomena were scarcely explicable on any other hypothesis than that of some general cause circulating in the blood, affecting the nutrition and functional activity of the nerve trunks, rather than of the nerve centres." No reference is made to the skin lesions but there can be no mistake about it being acrodynia for it is referred to as the "*epidemie de Paris*" of 1828.

The history of acrodynia engaged the attention of those clinicians who recorded it in 1828 and some, at least, were loath to accept it as a new disease. One of the writers of that period was disposed to regard it as identical with a condition described by Thomas Jordanus (7) in 1577 occurring in Moravia. Jordanus called the disease *nova luis* but the term *luis Gallica* is also used to designate it. He regarded the disease as quite similar to *luis Indicae* but showing definite points of distinction. It is clearly set forth that sexual contact and all other sorts of close communication never led to the spread of the new disease. Reference is made also in this work to *luis venera*. The report gives an account of an epidemic occurring in the town of Brünn in Moravia. It is described as a disease killing few but being nevertheless dreadful because of the distressing symptoms caused thereby. Within the space of two or three months it had caused real consternation as 80 of the town people were affected and 100 in the immediate neighborhood while in the country districts a still large number of cases occurred. It is stated that the victims numbered those of noble rank as well as the poor and it is particularly emphasized that matrons of unblemished reputation and virgins of uncontaminated chastity well as men of recognized probity were attacked. The writer laments the fact that through an ancient custom all skin diseases were disregarded by the doctors and given over to the barbers and "other imposters" for treatment. The dignified doctor seems to have regarded such a triviality as an external skin affection to be beneath his august attention.

There were three public baths near the wall of the city where the people were in the habit of going "to cleanse the filth of the body." After cutting the skin with scalpels blood was drawn by the cupping glasses. The origin of the disease was attributed to one of these baths:

Thence was the origin of the disease, there the germ was received, the virus came from there, the poison there was caught. For on the very day of the winter solstice, which the astronomers define by the entrance of the sun into the constellation of Capricorn, the people held carnival in the feast of Lucia. I mean to say that two weeks before the sacred celebration of the nativity of the Savior, in a very severe winter, in the year of the restoration of our salvation, 1577, whoever entered (at the bath) the Laconian or sweating chamber, and perforated their skin by the use of the scalpel, and by putting to it cupping-glasses, all at once are believed to have been infected.

The account is most unsatisfactory and difficult to connect with any disease. It is recorded that symptoms did not appear for from eight days to one month and began with torpor and sluggishness attended with marked mental depression. An awful heat is said to have come on the marks of the cupping glasses followed by abscesses and ulcers. The loathsomeness described is much more in accord with a common picture seen wherever many pellagrins are cared for than would have been the case in acrodynia, assuming for the moment that this latter is a definite disease entity separate from pellagra. In some cases it is said that the whole body was sprinkled with pustules, the face disfigured, with areas of skin involvement compared to scurvy on the back, breast, abdomen, feet and other parts. There was much secretion and crusting. After the skin lesions cleared up the joints, the forearms, the upper arms, the calves, shins and feet to the bottoms are described as being attacked by certain prickings like sharp stings or as if cut with saws or tortured with hot forceps. The motor weakness of a multiple neuritis is described at considerable length. The pain was ceaseless and the victims got no rest night or day. Upper respiratory symptoms are mentioned in detail recalling the account of Byfield's recent acrodynia cases in infants. These wretched creatures, according to the account, presented a strikingly similar mental picture to that seen in pellagra. They avoided conversation and fled from the sight of men leading a sedentary life. Much of the account is given up to an investigation of Adam, the keeper of the baths, who seems to have been suspected of some sort of witchcraft and whose persecution the indignant people were determined on because of their belief in his guilt in having inflicted this poison on them. A large part is given up to the most extraordinary plan of therapeutics conceivable.

As mentioned above the opinion was held in 1828 that this condition described so imperfectly by Jordanus was acrodynia and no less an authority than Dr. Crookshank agrees in this view. For my own part it fits in much better with the picture of mental and physical misery seen in pellagra.

Since 1907 there has occurred a great many cases of pellagra in North Carolina (8). It has been my privilege to study a large series of these cases with the result that many unusual manifestations have been recorded and many variations from the established text-book picture. The disease is almost as protean as syphilis and after studying this unusually large series of cases exceptions and variations are daily occurring. It will be appreciated that the observer recording from a score to a hundred cases and drawing therefrom statistical conclusions is apt to be led astray just as would be the case in any other study. Among the variations of other times in pellagra is edema. It has never occurred in my experience and yet is frequently a notable symptom. It was recorded in a case of pellagra occurring in Bellevue Hospital in 1888, an account of which was given in a personal communication by Dr. Rowland G. Freeman who was a house officer at that time. During our early experience there was abundant evidence of pellagra failing to conform to type. It will be recalled that the first cases recorded in the South were acute and fulminating in type while the classical accounts on which we had to depend in the Italian literature recorded it as a chronic disease and the only reference to an acute condition was an acute exacerbation It was on this account that a certain degree of tardiness in the diagnosis was due. It will be appreciated that if we could have a type of pellagra unknown to the Italians it must be an exceedingly protean disease and each succeeding year has confirmed this view.

The distribution of the skin lesion in pellagra in the large proportion of cases is perfectly typical but there is a certain proportion of the cases in which the most marked variations are noted. Recently some of the atypical locations of my cases were recorded with photographs. These locations included the perineum, the backs of the knees, the palms of the hands and soles of the feet, a row of small rounded deeply pigmented areas conforming to the spinous processes of the dorsal vertebrae, the posterior superior spines of the ilea, the external malleoli of the feet, the balls of the great toes and areas on the back below the scapulae. The study of the skin lesions of the covered portions of the body opens up a new field in pellagra which brings it so close to acrodynia that the one really merges into the other. In a number of cases the skin lesions in pellagra occurred in a perfectly typical manner except that in addition to the usual locations the erythema also occurred on the soles of the feet and the palms of the hands. In this series of cases is one of a negress of twenty years seen in 1918 with the following note entered:

A vesiculated or bullous area of the palms of the hands and the pronator quadratus area. An area of erythema at each angle of the mouth. Pellagrous vaginitis. No salivation but marked stomatitis. Marked diarrhoea. Great pain in the hands and balls of the feet. The most definite erythema of the soles of the feet. Typical skin lesion of both elbows. Mental condition normal. A definite history of edema. No eye symptoms at this time.

The pain in the hands and feet, the history of edema, the lack of mental symptoms, the erythema of the palmar and plantar surfaces form a fairly complete picture of acrodynia according to the early French account. The eye symptoms, it is true, are lacking but these are not essential and are frequently recorded in pellagra. To this account of acrodynia was added all the classical symptoms necessary for a certain diagnosis of pellagra.

In this series of cases there is one of a white woman who came in from the country seeking relief for terrific pain in hands and feet. She was found in the waiting room with her shoes off because of the pain. The story she told coupled with the physical findings seemed to justify the diagnosis of acrodynia which was so recorded. Examination showed a pustular lesion of the sole of the left foot. While there was no skin lesion in the other foot yet she suffered with burning and tingling alike in both feet which was severe enough to keep her awake at night. The year before she had suffered a like attack but the skin lesion was more between the toes as well as on the upper surfaces. At the time of the examination there was just the beginning on the palms of both hands of a pustular lesion attended with burning. There was also complaint of formication. There was complaint of irritation of the eye lids but no lesion was apparent to account for the discomfort. The tongue was red-edged but no complaint was made. The bowel activity remained normal throughout. There was no complaint of any gastric discomfort. Owing to pain the patient could not wear her shoes. Walking caused increase of pain. Examination of the feet showed definite swelling. Later the tongue became sore and the skin lesion extended to the skin between the fingers. The tendon reflexes were absent.

This case seemed to satisfy all the requirements according to the classical description of acrodynia and the diagnosis was made without hesitation though the patient came from a section were pellagra was occurring in great numbers and in a year when it was peculiarly prevalent. On her return in a few weeks the diagnosis of acrodynia was withdrawn as the patient then presented a typical picture of pellagra with the usual skin distribution added to the palmar and plantar lesion which had justified the diagnosis of acrodynia.

Great pain in the hands and feet is a common complaint in pellagra. Indeed, it is questionable whether this complaint is not as much recorded in the cases of pellagra as in acrodynia. From the earliest literature of pellagra to the present day neuritic pain has occupied a prominent place and it has been thought that the pain was in some cases responsible for the suicides so common during its course.

Another point of the first importance is the fact that the skin lesion of acrodynia was not strictly confined to the plantar surfaces in all cases. Valleix (9) in his account of acrodynia has this significant paragraph:

Un phénomène qu'on peut regarder comme caractéristique étai la rougeur érythemateuse des pieds et des mains, occupant les deux faces dans cette dernière partie et bornée à la face plantaire dans les extrémités inférieures. La *rougeur erythemateuse* se montrait aussi dans d'autres parties du corps; et, en outre, dans un assez grand nombre de points, notamment sur l'abdomen et aux plis des articulations, on voyait apparâitre une teinte brune ou noirâtre de la peau, quinétait pas le phénomène le moins remarquable de cette singuliere effection.

Another point of first importance is the neurological lesion of acrodynia as a means of separation from pellagra. It is not generally recognized that in pellagra there frequently occurs a definite multiple neuritis. Recently it was my privilege to watch a case of pellagra in the Royal Infirmary, Edinburgh, in the service of Dr. Edwin Bramwell (2). The diagnosis could not be questioned. The most careful neurological study was made and the diagnosis of multiple neuritis was left in no doubt. This was the only neurological abnormality. Such cases are, by no means, rare or even unusual. No one would question that the bed-ridden helpless condition of the reported cases of acrodynia was due to any other cause than multiple neuritis.

Recently William Weston reported a series of cases studied by him which he designates acrodynia. In this diagnosis he had the concurrence of J. W. Babcock who, as well as Dr. Weston, has had extraordinary experience with pellagra in South Carolina during the past decade. The description of Dr. Weston's cases is certainly not that of typical pellagra but it is a debatable point whether or not there is justification for the use of a new term.

Following closely on the publication of Weston's paper is that of A. H. Byfield which he designated "pellagra-acrodynia (?)" there by clearly but briefly stating an attitude which has been held by many on this subject for a long time. In this carefully prepared account of a condition occurring in epidemic form there is much which suggests pellagra. The lack of diarrhoea and stomatitis in children is not a strong argument against pellagra for it is a common occurrence for both to be absent much more frequently than in adults. It is to be remembered that in pellagra there frequently occur eye symptoms which are mentioned in most of the accounts of acrodynia. In one fatal case of pellagra, a child of ten years, there was an extreme degree of palpebral conjunctivitis with ectropion following a general erythema of the face. In one of Byfield's cases there was photophobia, weakness and constipation and

"After this a rash broke out on the chest, abdomen and back, later involving the arms, legs and face. The hands and feet seemed to have been 'dipped in hot water.' They were red and swollen and subsequently desquamated. No blisters were observed. The itching was marked."

Well do we recall the hospital attendant who was discharged in disgrace because he allowed the demented patient to step into a bath of too hot water. Later it was sown that the patient's symmetrical bullous dermatitis of the feet was the result of pellagra and not of hot water at all.

It should be stated that there occurred in Byfield's series of cases catarrhal symptoms, falling of the hair and loss of teeth which I have not noted in pellagra. From the description it should be considered that there may have been superimposed on the pellagrous dermatitis a seborrhoeic dermatitis, a condition so commonly noted in children, and that this may have altered somewhat the typical pellagrous picture.

Weston (10) refers to the epidemic reported by Strachan under the name malarial multiple peripheral neuritis regarding it as acrodynia. 510 cases were reported. It manifested itself in the following symptoms: numbness and burning in the palms and soles, impaired vision and hearing, eczematous lesions on the tops of the eye-lids, angles of the mouth, muco-cutaneous margins of the nostrils, motor pains of the upper and lower extremities and death in some instances from paralysis of the respiratory muscles. There was also trophic changes, altered gait, absent knee jerks in one-half the cases and exaggerated in 23 per cent, blunting of sensation and wasting of muscles.

Lavinder and Babcock (12) state that the inflammation of the muco-cutaneous borders in this condition as mentioned by Strachan (13) included the eye-lids, lips, urethra, anus and vulva and that this group of symptoms were among the first to appear. These writers say that Dr. F. M. Sandwith was opposed to the diagnosis of pellagra in these cases and Sir Patrick Manson naturally opposed the explanation of malaria suggesting that the whole subject needed further study.

The fact is granted that these skin and muco-cutaneous lesions were not typical but it is certain that many *recurrences* of pellagra are recognized by no more symptoms than these and often by much fewer. I have made the diagnosis of pellagra in many cases with fewer or less typical skin lesions. The justification for this was a knowledge acquired by a study of the manifestations of the recurrences. Few would agree to accepting this group of symptoms as sufficient for a diagnosis; it is only by a review of the whole course of the disease that apparently trivial manifestations become fraught with tremendous importance. If year after year the patient has noted a tiny erosion at the angles of the mouth as the very first indication of the appearance of the erythema, and if we are able to confirm the value of this indicator by the later appearance of the skin manifestations in typical form, then surely the acceptance of such a trivial sign as one of great importance is well justified. It is on such a basis that the accounts of many of the so-called cases of acrodynia are to our conception cases of pellagra of an atypical sort or incompletely developed, or occurring in a season of irregular manifestation. It should be recalled that the histories of some of the cases of pellagra show that for several years the mouth symptoms or the digestive symptoms or both occurred before there was the typical skin manifestation.

This is not the only instance of a similar confusion to be found in the literature. It will be recalled that *psilosis pigmentosa* was a term coined by Cuthbert Bowen (14) in Barbadoes for a disease condition characterized by diarrhoea, salivation, loss of flesh and symmetrical erythema of the backs of the hands and the tops of the feet. The published illustrations of the distribution of the skin lesion of the hands and feet together with the account of the disease leave no possible doubt but that the disease is pellagra. It is really one of the best accounts of pellagra in English. It is interesting to note in this connection that L. W. Sambon and his associates recently studied pellagra in Barbadoes.

A similar error occured in Rhodesia. P. A. Nightingale (15) reported the outbreak of a peculiar disease characterized by symmetrical erythema, diarrhoea and stomatitis. With the description were published plates clearly supplying the last point of evidence necessary for the positive diagnosis of pellagra. The disease, like the appearance in the southern states in 1907-1910, was acute and fulminating thereby markedly differing from the Italian accounts on which it was necessary to depend at that time for any information.

## CONCLUSIONS

1. In the light of the fact that one seeing large numbers of cases of pellagra would make a diagnosis of acrodynia based on the classical symptoms: palmar and plantar erythema, neuritic pains in the feet and hands, neurological signs of multiple neuritis, presence of conjunctival irritation; and in the absence of stomatitis and diarrhoea with the later appearance of other symptoms, making the diagnosis of pellagra self-evident, the difficulty of such a differentiation is obvious. A careful review of all the available cases of so-called acrodynia shows that at least a small percentage can by all rights be classified as pellagra. Pellagra being a protean disease is subject to manifold variations in type so that it is necessary in many of the cases recorded as acrodynia to follow them through a considerable period of time before excluding pellagra. A study of the atypical distribution of the skin lesions of pellagra must be carefully made before entering into a final diagnosis of acrodynia. In this connection it is to be remembered that extreme degrees of vaginitis, of scrotal and perineal lesions, mouth lesions and of lesions of large portion of the skin surface occur in pellagra. A case in point is that of a negro man whose palms and soles are affected

and whose lower lip is everted, swollen, cracked and fiery red complaining of formication and burning of the skin and of burning and smarting of the eye-lids and dimness of vision. Closer examination revealed typical symmetrical erythema of the backs of the hand, symmetrical lesion of the skin of the scrotum, a lesion of the skin of the buttocks. The lesion of the skin of the feet conforms remarkably to the description of the early French observers of acrodynia. The erythema had extended beyond the soles to the skin between the toes.

In acrodynia there is observed the skin lesion on the tops of the toes about the nails and on the posterior surfaces of the fingers which is often as much skin lesion as is observed in pellagra and the location also is that of the latter condition. The literature records many cases of palmar and plantar erythema with exfoliation presenting striking evidence otherwise of pellagra. This palmar and planter distribution has been frequently encountered in South Carolina by Lavinder and Babcock. For my own part I believe acrodynia is pellagra assuming one of its numerous variations which is not uncommon. The proof of the correctness of this is best found in the study of the subsequent course of the process, in a careful comparison of the neurological conditions and in a survey of the food conditions.

2. If pellagra and acrodynia are one and the same disease and if the epidemic occurring in Moravia in 1577 recorded by Thomas Jordanus is to be accounted identical with acrodynia or the malady of Paris of 1828, "things equal to the same thing being equal to each other" it is a reasonable assumption that the sixteenth century epidemic was pellagra. Certainly the vague and unsatisfactory description given by Jordanus comes much nearer fulfilling the requirements of pellagra than of acrodynia assuming that the two conditions were separate and distinct. If this condition is pellagra then it becomes possible to trace that disease to a much earlier period than ever before for the first authentic record of it is the observation of Casal in 1735. By such an occurrence in the 16th century it would be possible to disassociate the disease from the introduction of Indian corn or maize into Europe.

3. The association of so called acrodynia with lethargic encephalitis by Crookshank seems, therefore, unjustified because the nutritional state of the people is the determining factor in pellagra and therefore in socalled acrodynia. It must be forcibly recalled that in 1830, almost at exactly the same time that acrodynia was first being observed in Paris, Briere de Boismont presented to the Academy of Science a communication setting forth that within a few miles of Paris pellagra was rampant and that its existence was not properly appreciated. Among the few who were alive to the importance of such a report was J. M. G. Hameau (16) of Teste de Buch. His writings were of the greatest importance and did great good in directing attention to a disease at that time occurring in great numbers but attracting almost no attention probably because of the poor class of peasantry affected.

It is perfectly true that debilitating conditions seem to predispose to the outbreak of pellagra judging from the incidence of the disease in hook-worm subjects. There is not forthcoming, however, any evidence to prove that following the pandemic of influenza in the United States there was any increase in pellagra. On the contrary during 1919–1921 there has been noted by the physicians in eastern North Carolina interested in the disease that there has been a striking decrease in the number of cases though statistical evidence will show that this section suffered severely from influenza being one of the first sections seriously affected in 1918.

The proof of the possibility that pellagra occurred as early as 1577 in central Europe opens up a new field of important historical research.

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# CHRYSOPS COSTATA, A BLOOD-SUCKING FLY FROM CUBA

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Last winter, in the cool and dry season from November till March, I was bitten in Habana repeatedly by a blood-sucking chrysops fly. Curiously enough none of the Cuban residents knew the fly and even good observers, experts of tropical medicine and entomology, did not remember to have had similar experiences.

I think, therefore, a short notice may be justified, though it is not a new species, but the well known Chrysops costata Fabr. of Central America, as I am informed by Dr. W. Horn, the Director of the German Entomological Institute in Berlin-Dahlem, to whom I sent several specimens for determination.

The chrysops flies are not without importance in the human pathology. I mention only the role played by the African species Chrysops dimidiatus in the transmission of Filaria loa. Considering the most voracious manner in which, according to my experiences, the fly sucks the blood of human beings, it does not seem impossible, that still other relations of chrysops flies to infectious diseases of man may be discovered in the future.

The experiences that I have had with this genus are the following: All my observations were made in the garden of the Las Animas Hospital in Habana. It is a large piece of land with many trees, shrubs and pasture and a small creek run through it, which perhaps may offer the fly the facilities for breeding-places, in or near the water. Usually there are feeding on the grassland some horses, which may ordinarily furnish the necessary blood for the fly. There are also some cows and several small animals. When passing through the places where the horses usually stand, I have been bitten about a dozen times by the fly, and always on the part of the head which has the hairs. I must mention that I always wear the hair cut quite short, whereas most people here have their hair grown to some length; perhaps that may explain why just I was bitten, whereas the people of the country apparently are not attacked by the fly. The fly has bitten me at any time of the day, at noon, when the sun was standing high, and at the early morning hours before sunrise.

Every time what happened was the same thing. I never remarked anything of the approach of the fly, but quite suddenly and unexpectedly I felt a very painful sting, as with a needle, always on some part of my head, so that I was always immediately induced to touch the place with my hand. The first times I crushed the fly in that way. But later I could easily catch it living, because it was so eager in sucking blood, that it was not driven away by the movement of the hand. When caught it does not try to escape, but remains in rather passive position between the fingers. Generally I found it filled with a little blood.

It seems that the fly is not very common here. Besides those specimens which I caught on my head, I scarcely remember to have seen it, either near the horses or on them.

The chrysops flies are widely distributed in the whole world in a great number of species, they are easily known from the black band on the wings. Also the species called costata is well known and a detailed description does not seem necessary here. My principal purpose was merely to call the attention to the fly as sucking human blood.

# THE WASSERMANN REACTION IN MALARIAL FEVERS

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From a clinical standpoint the Wassermann reaction is generally looked upon as a specific test for syphilis. This statement is made with a clear understanding that in some few exceptions, false or "pseudo-positive" reactions may occur, but a test which will give positive results in some 90 per cent to 98 per cent of cases, from a clinical standpoint, may be looked upon as specific.

Larkin, Levy and Fordyce (1) have found a positive reaction in practically 100 per cent of cases of florid syphilis, and in 94 per cent of active tertiary. Craig in 90 per cent primary cases, in 96 per cent secondary and 87.4 per cent tertiary cases obtained a positive Wassermann reaction. These figures merely show the comparatively slight variations that do occur with different workers and with cases in different stages of the disease. It is not within the scope of this paper however, to discuss all conditions affecting the Wassermann reaction on the blood.

In a very interesting article, Henes (2) attempts to show that the Wassermann reaction depends upon the cholesterol content of the blood. All serologists are agreed that the Wassermann reaction, while not being a specific test from an immunological standpoint, results from the production of certain lipoids in the blood stream by the spirocheta pallida. Henes quotes numerous references to sustain his contention. Some work by Bittrof is noted, in which positive reactions were obtained following injuries to such organs as the brain, liver and spinal cord, organs known to be rich in lipoids and injuries of which are known to produce a hypercholesterinemia. He makes the statement that positive Wassermann reactions in diseases other than syphilis, yaws and leprosy, are without doubt due to technical errors or to a cholesterinemia upsetting the interpretations. Kolmer (3) and his co-workers have also found that administration of lipoids increases the antilytic and complement fixing power of blood serum.

Some of the more common conditions accompanied by an increase in the cholesterol content of the serum are chronic nephritis, pregnancy, jaundice and convalescent typhoid, and in these conditions positive Wassermann reactions have been reported as occurring, the positive Wassermann becoming weaker and gradually disappearing as the cholesterol content of the serum decreased. Daland reported such an experience with a case of uremia in which the Wassermann at first a 3 plus, became in three weeks a 1 plus. It is known that during uremia and terminal stages of nephritis the cholesterol content of the blood is decidedly less than during the chronic stages of the disease.

Strickler, Munson and Sidlick (4) recently have attempted to show that the action of arsphenamine in non-syphilitic individuals having a negative Wassermann before taking the drug, will produce a positive reaction. These workers suggest that the arsenic products liberate some lipoidal substance which is responsible for the positive Wassermann reaction.

Kolmer's (5) experience with blood from rabbits tested after giving arsphenamine is directly opposed to Strickler's conclusions. He is of the opinion that arsphenamine will not produce changes in non-syphilitics that would result in a positive Wassermann reaction. However, very recently he and Lucke (6) have reported the result of their studies on the histological changes occurring in the liver, brain, and kidneys as a result of arsphenamine administration, and their studies show that even where no reaction is evident following the administration of the drug, the liver and brain will show definite evidence of injury such as a beginning focal necrosis. It is easily conceivable that following such trauma to these organs a hypercholesterinemia results which if we accept Henes conclusions, may produce a fixation of the complement.

A review of the pathological changes occurring in malaria especially those due to the plasmodium falciparum shows focal necroses in the liver and frequently punctiform hemorrhages in the brain and spinal cord. It is thus seen that an increase in the cholesterol content of the blood serum should result from these injuries to organs so rich in lipoidal substances.

Positive Wassermann reactions in malaria especially in the febrile paroxysms have been reported by Stitt (7), Day and McNitt (8), and by Craig (9) in his section on the Wassermann reaction in Hazen's book on Syphilis. Kolmer (10) and Castellani and Chalmers (11) state that in their experience the Wassermann reaction is uniformly negative in malaria.

In an exhaustive study of the Wassermann reaction in malaria made by Thomson and Mills (12) in 1919, they reviewed the literature to this date and classified the findings of other observers into four groups, as follows:

*a.* Those who have found the Wassermann reaction positive when malaria parasites were present in the blood, and found that the reaction persisted in some cases after several weeks treatment with quinine.

(*b.*) Authors who found that the Wassermann was positive only when malaria parasites were present in the peripheral blood.

(*c.*) Those who obtained positive results only during the paroxysm of the fever, and even then only in a few cases.

(*d.*) Those who found the Wassermann universally negative in all cases of acute malaria.

In the series studied by Thomson and Mills, 130 cases of definitely diagnosed malaria were examined at every possible stage of the infection, only eight of which gave positive Wassermann reactions, and in all of these eight cases they were able to definitely diagnose the presence of a syphilitic infection. They draw the following conclusions:

(1) That the Wassermann reaction conducted according to a recognized standard method does not give a positive reaction in malaria at any stage of the disease. (2) If a positive Wassermann reaction is obtained in a case of malaria it is either due to undiagnosed syphilis or to faulty technic. Iyengar (13) in

India, found in 98 cases of malaria positive Wassermann reactions in 7 cases, in all of which he was able to find positive physical findings, or a history of syphilitic infection. He also noted no change in the reaction of the serum following quinine; his conclusions being that malaria has no influence upon the Wassermann reaction.

In a review of some 200 cases of malaria treated in the wards of the John Sealy Hospital during the past few years, we were able to find 50 cases wherein a Wassermann reaction had been done and an analysis of our results is herewith presented. The technic for the test was a modification of the Noguchi reaction, liquid reagents instead of paper being used. The series included 25 cases of tertian infection and 25 of æstivo-autumnal.

There were four cases giving a positive Wassermann in whom the history and physical findings were negative; three with tertian malaria and one with æstivo-autumnal. One of these cases gave a positive Neisserian history. We were unable to obtain a history of any sort from two cases that reacted positively, in both cases the physical examination being negative. One case was a Mexican with hypospadias, an æstivo-autumnal infection; the other a Russian with tertian infection. The Wassermann reaction was positive on all of these cases during the febrile period. On one case we had a second Wassermann during the afebrile period which was also positive. The serum of another of these cases became negative after injections of mercury salicylate.

There were 13 cases with physical findings and a history of luetic infection reacting positively to the Wassermann test; seven of these cases were tertian and six were æstivo-autumnal; Ten of the tests were made during the febrile paroxysm and four during the afebrile period—one case having a second test done during the afebrile period which was positive, to determine whether the fever had any influence upon the reaction.

There were 31 cases with a negative history and physical examination with a negative Wassermann reaction. Fourteen of these cases were tertian and seventeen were æstivo-autumnal. In all except four of the cases the blood for the test was obtained during a marked febrile reaction, and at a time when many parasites were present in the peripheral circulation. One case of æstivo-autumnal malaria with a negative reaction was a case of chronic parenchymatous nephritis, with ascites and general anasarca. Another of these cases of æstivo-autumnal malaria coming to autopsy, showed no evidence of luetic infection.

With a negative reaction occurring in 27 cases of malaria during the febrile period, it does not appear to us that malaria has much influence upon the Wassermann reaction. If an increase of the cholesterol content of the blood does occur as a result of the injury to the liver and brain it apparently is not sufficient to influence the antilytic power of the blood serum. It appears to us that the four cases reacting positively with negative history and physical examination were in all probability luetic cases, inasmuch as one case became negative after mercurial treatment and another was still positive in the afebrile period. We fully realize that the above series of cases is rather a limited one upon which to base any definite conclusions, but our impression is that when a positive Wassermann reaction is obtained during a malarial infection, we have a luetic infection in addition.

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# THE WASSERMANN REACTION IN MALARIA[1]

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The available literature on this subject fairly well represents the usual difference of opinions that exist whenever the Wassermann reaction is in question.

Bates (1) of this laboratory, in reviewing the Wassermann reaction in 164 cases of malaria, in 1912, felt that malaria did not affect the Wassermann reaction.

Craig (2) in reviewing his Wassermann results, attributes the occurrence of positive reactions in three instances to have been caused by malaria. The positive reactions were obtained during the febrile stage and were followed by negative reactions during convalescence.

Sutherland and Mitra (3) conclude that non specific reactions may be obtained during an acute attack of malaria and advise waiting until the blood is free of parasites—say one week— before withdrawing blood for a Wassermann. Table 1, taken from their article, partially tabulates the reports made to February 1915.

Thompson and Mills (4) present a detailed historical review of the subject. They are of the opinion that the recorded non-specific reactions obtained in malaria will not admit of scrutiny. They cite their study of 135 cases as evidence that malaria is not a factor to be considered in their positive reactions.

De Jong (5) concludes that non specific reactions may be obtained during the active stages of malaria and parallels the anomaly with the occurrence of such reactions sometime encountered in the acute stages of other specific fevers.

[1] Published by permission of Colonel H. C. Fisher, Chief Health Officer, The Panama Canal.

These conflicting reports serve as an invitation to those laboratories concerned, to examine their individual techniques in so far as it relates to malaria.

In a survey of this nature the technique used is of importance. The degree of sensitiveness of antigens may be, in a measure, responsible for the varying results obtained by the authors cited. I wish to emphasize the point that the study here reported is based on the influence of malaria on the Wassermann reaction only in so far as cholesterinized antigens are concerned.

## TECHNIQUE

The human system of Noguchi with certain departures, was used in this series.

Antigens:[2] Two antigens were used. They were antigen "A," alcoholic extract of normal human heart fortified to the point of half saturation with cholesterin and antigen "B," same as "A" except that the extract was saturated with cholesterin.

The antigenic dose of "A" was five units, and that of "B" one unit.

The two antigens gave parallel readings. The employment of two antigens whose antigenic dose is one and five units respectively, serve as a valuable indicator of the accuracy of theother reagents used in the test.

*Red blood cells.* Dose was 0.1 cc. of a 5 per cent suspension of packed human cells (total volume in tubes 0.5 cc.)

*Complement and amboceptor.* Titrated separately on the day of the test and two units of each used.

*Patients' serum.* 0.05 cc. of inactivated serum used.

The cases studied are divided into three groups: Acute malaria, chronic malaria, and cases not classified.

[2] The antigens in use by this laboratory today and the method of titrating the complement differ from that used by Bates in 1912. In Bates' series the antigens were not cholesterinized. He used both the plain extract and antigen prepared after Noguchi's technique. (See reference No. 1.)

### ACUTE MALARIA

This group comprises 101 cases. Only those patients with well marked malarial paroxysms are included. The blood for Wassermanns was obtained before medication and as often thereafter as was deemed advisable. The reactions obtained are tabulated in table 2.

A summary of the double plus reactions in relation to evidence of syphilis and to the effect of medication is shown in table 3. It will be noted that in five instances malaria was the apparent cause of double plus reactions.

A summary of the one-plus, plus-minus, and anticomplementary reactions is given in table 4. The fact that all gave negative reactions during convalescence, is worthy of note.

### CHRONIC MALARIA

Fifteen autopsies (6) comprise this group. The Wassermann reactions were consistent with the pathological findings. (See table 5.)

### CASES NOT CLASSIFIED

There were five cases encountered in this series which for want of a classification are considered under this heading. In these cases there were histories of chills and fever within a week of admission, sexual forms of the malarial parasites were demonstrated, but no paroxysms of malaria occurred during their stay in the hospital.

The data obtained in these cases is analysed in table 6.

### DISCUSSION

The occurrence of false positive reactions in malaria might be explained on the ground of anti-complementary action. Serologists in those hospitals admitting a large number of malarial cases have no doubt noted the tendency of certain malarial serums to cause delayed negative reactions. Aside from passing observations, the occurrence of five anticomplementary reactions in the small number of tests reported becomes significant when the cases giving these reactions yield negatives during convalescence. It seems reasonable to assume that certain malarial serums possess an increased degree of anticomplementary tendency and that this at times, may not be sufficient to manifest itself in the serum control but when combined with the natural anticomplementary factor of antigens becomes capable of causing double plus readings.

## SUMMARY AND CONCLUSIONS

Non specific positive reactions were obtained in 4.9 per cent of a total of 101 cases of acute malaria.

Chronic malaria, in the small number reported (16) did not interfere with the Wassermann reaction.

The occurrence of non-specific reactions in malaria is believed to be due to the presence of an undetected increase in the anti-complementary factor.

I wish to thank the physicians and nurses of Ancon Hospital for their patient coöperation in this study.

TABLE 1

| | CASES | POS. W. R. | PERCENTAGE |
|---|---|---|---|
| Czknaworow | 13 | | |
| Manu, Muscel, Vasilin | 12 | | |
| Schoe | 38 | 22 | 57.89 |
| Weinfurter | 1 | 1 | 100.00 |
| Bates | 167 | 37 (30 lues) | 22.15 (4.19) |
| Fletcher | 50 | | |
| Sutherland and Mitra | 50 | 9 | 18.00 |
| | 331 | 69 | 21.00 |
| Deducting the known luetic cases | | 39 | 11.8 |

TABLE 2

*Acute malaria*

| WASSERMANN RESULT BEFORE MEDICATION | | | | WASSERMANN REACTION AFTER MEDICATION | | | |
|---|---|---|---|---|---|---|---|
| No. | Date | Parasite | Wassermann result | Date | Quinine days given | Antiluetic, treatment, days given | Wassermann result |
| 1 | June 21 | E. A. | + | June 24 | 3 | 0 | − |
| 2 | June 17 | Tertian | ++ | June 28 | 7 | 0 | + |
| | | | | July 2 | 11 | 4 | ++ |
| | | | | July 23 | 36 | 25 | + |
| | | | | August 2 | 45 | 38 | + |
| 3 | June 10 | E. A. | +− | June 24 | 3 | 0 | − |
| 4 | June 23 | E. A. | − | June 26 | 3 | 0 | − |
| 5 | June 24 | E. A. | − | July 1 | 7 | 0 | − |
| 6 | June 24 | E. A. | − | July 2 | 8 | 0 | − |
| 7 | June 24 | E. A. | − | July 2 | 8 | 0 | − |
| 8 | June 28 | E. A. | − | July 3 | 6 | 0 | − |
| 9 | June 28 | E. A. | − | July 3 | 6 | 0 | − |
| 10 | June 28 | Tertian | − | July 1 | 3 | 0 | − |
| 11 | June 27 | E. A. | − | July 1 | 4 | 0 | − |
| 12 | June 29 | E. A. | − | July 2 | 3 | 0 | − |
| 13 | June 29 | E. A. | − | | | | |
| 14 | July 6 | E. A. | − | July 16 | 9 | 0 | − |
| 15 | July 6 | Tertian | − | July 15 | 8 | 0 | − |
| 16 | July 15 | Tertian | − | July 19 | 3 | 0 | − |
| 17 | July 16 | E. A. | − | July 19 | 3 | 0 | − |
| 18 | July 21 | E. A. | − | July 27 | 6 | 0 | ++ |
| | | | | July 29 | 9 | 0 | ++ |
| | | | | August 2 | 9 | 0 | − |
| | | | | August 4 | 2 | 0 | ++ |
| 19 | July 19 | E. A. | − | July 22 | 2 | 0 | − |
| 20 | July 26 | Quartan | − | August 2 | 6 | 0 | − |
| 21 | July 26 | E. A. | − | July 30 | 4 | 0 | − |
| | | | | August 2 | 8 | 0 | Anticomplementary |
| 22 | July 24 | E. A. | − | August 2 | 8 | 0 | − |
| 23 | July 23 | E. A. | − | July 26 | 3 | 0 | − |
| 24 | July 28 | E. A. | − | | | | |
| 25 | July 29 | E. A. | − | August 5 | 6 | 0 | − |
| 26 | August 2 | Tertian | − | August 9 | 7 | 0 | − |
| 27 | August 3 | E. A. | − | | | | |
| 28 | August 3 | E. A. | − | | | | |
| 29 | August 4 | Tertian | − | August 9 | 4 | 0 | − |
| 30 | August 4 | Tertian | ++ | August 9 | 4 | 0 | ++ |
| 31 | August 3 | E. A. | − | August 9 | 5 | 0 | − |
| 32 | August 4 | Tertian | − | August 9 | 4 | 0 | − |

TABLE 2—*Continued*

| WASSERMANN RESULT BEFORE MEDICATION | | | | WASSERMANN REACTION AFTER MEDICATION | | | |
|---|---|---|---|---|---|---|---|
| No. | Date | Parasite | Wassermann result | Date | Quinine days given | Antiluetic, treatment, days given | Wassermann result |
| 33 | August 5 | E. A. | ++ | August 9 | 3 | 0 | − |
| | | | | August 11 | 5 | 0 | + |
| | | | | August 12 | 6 | 0 | + |
| | | | | December 4 | 120 | 0 | − |
| 34 | August 5 | E. A. | − | August 9 | 4 | 0 | − |
| 35 | August 5 | E. A. | Anticomplementary | August 9 | 4 | 0 | Anticomplementary |
| | | | | August 11 | 6 | 0 | − |
| 36 | August 5 | E. A. | − | August 12 | 6 | 0 | − |
| 37 | August 9 | E. A. | − | August 12 | 3 | 0 | − |
| 38 | August 9 | E. A. | Anticomplementary | August 12 | 3 | 0 | − |
| 39 | August 9 | E. A. | ++ | August 16 | 6 | 0 | ++ |
| | | | | August 23 | 8 | 0 | Anticomplementary |
| 40 | August 9 | Tertian | − | | | | |
| 41 | August 10 | E. A. | − | August 17 | 7 | 0 | − |
| 42 | August 12 | E. A. | − | | | | |
| 43 | August 12 | E. A. | −− | August 18 | 6 | 0 | − |
| 44 | August 14 | E. A. | − | August 19 | 5 | 0 | − |
| 45 | August 14 | E. A. | − | | | | |
| 46 | August 16 | E. A. | − | August 23 | 7 | 0 | − |
| 47 | August 16 | E. A. | − | August 23 | 7 | 0 | − |
| 48 | August 14 | Tertian | − | | | | |
| 49 | August 14 | E. A. | − | | | | |
| 50 | August 17 | E. A. | − | August 23 | 6− | 0 | − |
| 51 | August 16 | Tertian | − | August 23 | 7 | 0 | − |
| 52 | August 18 | E. A. | − | August 23 | 5 | 0 | − |
| 53 | August 16 | E. A. | − | August 21 | 5 | 0 | − |
| 54 | August 23 | E. A. | − | August 23 | 3 | 0 | − |
| 55 | August 23 | E. A. | ++ | August 26 | 3 | 0 | ++ |
| | | | | August 30 | 6 | 0 | − |
| | | | | September 1 | 7 | 0 | ++ |
| | | | | September 2 | 9 | 0 | ++ |
| | | | | September 4 | 10 | 3 | ++ |
| | | | | September 7 | 13 | 5 | + |
| | | | | September 16 | 22 | 11 | − |
| | | | | September 20 | − | 15 | + |
| | | | | September 23 | − | 18 | ++ |
| | | | | October 19 | − | − | − |
| | | | | October 25 | − | − | − |

TABLE 2—*Continued*

| WASSERMANN RESULT BEFORE MEDICATION | | | | WASSERMANN REACTION AFTER MEDICATION | | | |
|---|---|---|---|---|---|---|---|
| No. | Date | Parasite | Wassermann result | Date | Quinine days given | Antiluetic. treatment, days given | Wassermann result |
| 56 | August 26 | E. A. | – | August 30 | 4 | 0 | – |
| 57 | August 25 | E. A. | – | September 2 | 8b | 0 | – |
| 58 | August 26 | E. A. | – | September 30 | – | 0 | – |
| 59 | August 24 | E. A. | – | August 30 | 6 | 0 | – |
| 60 | September 2 | E. A. | ++ | September 7 | 5 | 0 | – |
| | | | | September 9 | 7 | 0 | – |
| | | | | September 13 | 11 | 0 | – |
| 61 | August 31 | E. A. | – | September 2 | 2 | 0 | – |
| 62 | August 31 | E. A. | Anticomplementary | September 2 | 2 | 0 | – |
| 63 | September 1 | E. A. | – | | | | |
| 64 | September 3 | E. A. | ++ | September 7 | 4 | 0 | ++ |
| | | | | September 9 | 6 | 0 | – |
| | | | | September 13 | 10 | 0 | – |
| | | | | September 16 | 13 | 0 | – |
| | | | | September 20 | 17 | 1 | + |
| | | | | September 23 | 0 | 3 | – |
| 65 | September 1 | Tertian | – | | | | |
| | September 6 | | – | | | | |
| 66 | September 8 | Tertian | – | September 13 | 5 | 0 | – |
| 67 | September 9 | E. A. | ++ | September 13 | 4 | 0 | ++ |
| | | | | September 23 | 14 | 0 | ++ |
| | | | | October 20 | – | 27 | ++ |
| | | | | December 11 | – | – | ++ |
| 68 | September 13 | E. A. | – | September 16 | 3 | 0 | – |
| 69 | September 15 | E. A. | – | September 20 | 5 | 0 | – |
| 70 | September 15 | E. A. | – | September 20 | 5 | 0 | – |
| 71 | September 15 | E. A. | – | September 20 | 5 | 0 | – |
| 72 | September 17 | E. A. | ++ | September 20 | 3 | 0 | ++ |
| | | | | October 22 | 30 | 27 | ++ |
| | | | | December 14 | – | – | ++ |
| 73 | September 21 | Tertian | – | September 23 | 3 | 0 | – |
| 74 | September 20 | E. A. | – | | | | |
| 75 | September 18 | E. A. | – | September 20 | 2 | 0 | – |
| 76 | September 23 | E. A. | – | September 30 | 7 | 0 | + |
| 77 | September 20 | E. A. | – | September 23 | 3 | 0 | – |
| 78 | September 22 | E. A. | Anticomplementary | September 23 | 8 | 0 | – |
| 79 | September 21 | E. A. | Anticomplementary | September 26 | 6 | 0 | Anticomplementary |
| | | | | September 29 | 9 | 0 | – |

TABLE 2—*Concluded*

| WASSERMANN RESULT BEFORE MEDICATION | | | | WASSERMANN REACTION AFTER MEDICATION | | | |
|---|---|---|---|---|---|---|---|
| No. | Date | Parasite | Wassermann result | Date | Quinine days given | Antiluetic, treatment, days given | Wassermann result |
| 80 | September 22 | Tertian | – | September 30 | 8 | 0 | – |
| 81 | September 22 | E. A. | – | September 23 | 1 | 0 | – |
| 82 | September 26 | E. A. | – | | | | |
| 83 | September 27 | E. A. | ++ | September 30 | 3 | 0 | ++ |
| | | | | October 14 | 17 | 14 | ++ |
| | | | | October 21 | 24 | 21 | ++ |
| 84 | September 24 | E. A. | – | September 27 | 3 | 0 | – |
| | | | | September 30 | 6 | 0 | ++ |
| | | | | October 4 | 10 | 0 | ++ |
| | | | | October 18 | 14 | 2 | – |
| | | | | October 25 | 21 | 9 | + |
| 85 | September 24 | Tertian | – | October 7 | 7 | 0 | – |
| 86 | September 29 | Tertian | – | October 4 | 4 | 0 | – |
| 87 | September 30 | E. A. | – | October 4 | 3 | 0 | – |
| 88 | October 2 | Tertian | – | October 7 | 5 | 0 | – |
| 89 | October 4 | Quartan | ++ | October 7 | 2 | 0 | ++ |
| | | | | December 4 | 60 | 0 | – |
| 90 | October 7 | Tertian | – | October 14 | 7 | 0 | – |
| 91 | October 7 | Tertian | + | October 11 | 3 | 0 | – |
| 92 | October 7 | Tertian | – | | | | |
| 93 | October 7 | Tertian | – | | | | |
| 94 | October 8 | Tertian | – | October 14 | 6 | 0 | – |
| 95 | October 14 | Tertian | ++ | October 25 | 10 | 0 | ++ |
| | | | | November 21 | 36 | 24 | ++ |
| | | | | December 13 | 48 | 46 | ++ |
| 96 | November 17 | Tertian | – | November 21 | 3 | 0 | + |
| | | | | November 25 | 7 | 0 | + |
| | | | | November 28 | 11 | 0 | + |
| 97 | October 14 | Tertian | ++ | October 21 | 6 | 3 | ++ |
| | | | | October 25 | 10 | 7 | ++ |
| | | | | October 28 | 13 | 10 | ++ |
| 98 | October 4 | E. A. | ++ | October 21 | 1 | 0 | ++ |
| | | | | October 25 | 5 | 0 | ++ |
| 99 | October 25 | Tertian | – | November 1 | 7 | 0 | – |
| 100 | October 21 | E. A. | ++ | October 25 | 2 | 0 | ++ |
| | | | | November 1 | 7 | 4 | ++ |
| 101 | July 26 | Tertian | ++ | August 2 | 3 | 0 | – |

Interpretation of symbols:
++ indicates complete inhibition of hemolysis.
+ indicates slight hemolysis.
+– indicates slight inhibition of hemolysis.
– indicates complete hemolysis.

TABLE 3

*Acute malaria, double plus reactions from table 1*

| CASE NO. | EVIDENCE OF SYPHILIS | | | | INFLUENCE OF TREATMENT | |
|---|---|---|---|---|---|---|
| | Conclusive | Suggestive | Negative | Data incomplete | Quinine | Antiluetic |
| 2 | | + | | | Both given at the same time | |
| 30 | + | | | | None in 4 days | |
| 33 | | | + | | Negative in 3 days and after four months | |
| 39 | + | | | | None in 14 days | Insufficient |
| 55 | | + | | | Both given at the same time | |
| 60 | | | + | | Negative in 6 days | |
| 64 | | | + | | Negative in 6 days | |
| 67 | + | | | | None in 60 days | |
| 83 | | | | + | Both given at the same time | |
| 89 | | | + | | Negative in 60 days | |
| 95 | | | + | | None in 60 days | None |
| 97 | + | | | | None in 10 days | None |
| 98 | | + | | | Both given at the same time | |
| 100 | | | | + | None in 10 days | Insufficient |
| 101 | | | + | | Negative in 3 days | |
| Summary...... | 4 | 3 | 6 | 2 | | |
| Total cases.... | 101 | | | | | |

TABLE 4

*Acute malaria, one plus, plus-minus, anticomplementary group*

| CASE NUMBER | REACTION | WASSERMANN REACTION BECAME NEGATIVE AFTER QUININE WAS GIVEN FOR DAYS |
|---|---|---|
| 1 | + | 3 |
| 3 | +− | 3 |
| 91 | + | 3 |
| 35 | Anticomplementary | 6 |
| 38 | Anticomplementary | 3 |
| 62 | Anticomplementary | 2 |
| 78 | Anticomplementary | 8 |
| 79 | Anticomplementary | 9 |

Summary: All cases falling into this group gave negative reactions in from two to nine days.

TABLE 5

*Chronic malaria*

| AUTOPSY NO. | FILMS FROM BRAIN, SPLEEN, BONE MARROW | | EVIDENCE OF SYPHILIS | WASSERMAN REACTION | |
|---|---|---|---|---|---|
| | Malarial pigment | Malarial parasite | | Ante-mortem | Post-mortem |
| 5724 | + | − | − | 0 | − |
| 5731 | + | − | − | − | 0 |
| 5739 | + | + | − | − | 0 |
| 5751 | + | + | − | − | 0 |
| 5788 | + | − | − | − | 0 |
| 5793 | + | + | − | − | 0 |
| 5820 | + | + | − | 0 | − |
| 5822 | + | + | − | 0 | − |
| 5846 | + | − | + | 0 | ++ |
| 5862 | + | − | − | 0 | − |
| 5879 | + | + | + | + | ++ |
| 5885 | + | − | − | − | 0 |
| 5892 | + | + | + | ++ | − after treatment |
| 5905 | + | + | − | − | 0 |
| 5928 | + | − | + | ++ | 0 |

The Wassermann reactions were consistent with the autopsy findings.

TABLE 6

*Malaria not classified*

| WASSERMANN REACTION BEFORE MEDICATION | | | | WASSERMANN REACTION AFTER MEDICATION | | | |
|---|---|---|---|---|---|---|---|
| No. | Date | Malarial parasites | Wassermann | Date | Quinine | Anti-luetic treatment | Wassermann |
| | | | | | *days* | *days* | |
| 1 | August 12 | E. A. crescents | + | August 13 | 1 | 0 | ++ |
| | | | | August 16 | 4 | 0 | + |
| | | | | August 21 | 6 | 0 | − |
| | | | | August 29 | 14 | 0 | − |
| 2 | August 12 | E. A. rings and crescents | ++ | August 15 | 3 | 0 | ++ |
| | | | | August 22 | 8 | 0 | +− |
| | | | | August 26 | 11 | 0 | ++ |
| | | | | October 7 | − | 50 | + |
| 3 | August 28 | E. A. crescents | − | November 3 | 5 | 0 | − |
| 4 | August 23 | E. A. crescents | − | August 26 | 3 | 0 | − |
| 5 | June 24 | Tertian gametes | − | July 5 | 12 | 0 | − |

Summary: No evidence of syphilis was found in either case numbers one or two.

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# PUBLIC HEALTH IN THE DOMINICAN REPUBLIC

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In considering public health in the Dominican Republic, we naturally take into account the program, the present status, and the outlook.

The practical cessation of constructive health activity early in 1921 and the uncertainty of resumption of the program, both of these matters being dependent upon political conditions in the Republic, prevent us from following this logical order of discussion. It seems inadvisable to introduce any reference to political conditions, although it is difficult to present the subject intelligently without so doing, even in a purely professional journal.

Dr. J. M. Swan, president of the American Society of Tropical Medicine, has communicated in No. 1, volume I, of this Journal (January, 1921) certain political, geographic, demographic and statistical information relating to Dominica and Haiti. This information was gathered in the field survey conducted by him for the American Red Cross, from December, 1919, to February, 1920. In 1920 the International Health Board of the Rockefeller Foundation, through its representative, Dr. John B. Grant, also made a survey and rendered a report containing further valuable data, collected in July and August of that year, particularly with reference to hookworm prevalence. It is neither necessary nor desirable to parallel or duplicate these observations in my paper.

The logic of events (politically) has deprived this accumulated data of much of its immediate value. It should be read, however, by all students of public health in the American tropics. In the main, I find the observations accurate, although I cannot subscribe, after personal observations, to all of the deductions recorded by the reporters. It is inevitable that the personal equation must influence and likewise tint the views and opinions of the observers. Nor do I imagine that my own observations are entirely free from such influence.

In 1920 the writer went to Santo Domingo at the instance of the secretary of sanitation, military government of the Dominican Republic, under leave of absence from the state health department of Pennsylvania, to lend such aid as might be possible to the health authorities there, represented by the Department of Sanitation and Beneficence of the United States military government, now in force in Dominica. As most people know, Dominica occupies the eastern two-thirds of the island of Haiti, is entirely distinct from the republic of that name and has for its capital the ancient and historically important city of Santo Domingo. The Dominican Republic is also known by the name Santo Domingo—originally applied to the entire island. I returned in March, 1921, after five months service, further serious action being impossible at that time.

Of the American undertakings in the Dominican Republic, I mention only those projected for health and sanitation and offer my single criticism first.

It is this: The program adopted is too elaborate for the country, considering its population and its resources, and there is indicated by this program a lack of the sense of perspective and proportion. The exact population is unknown, but it certainly is less than one million persons and the total area of Dominica is about equal to one-third the extent of Pennsylvania; it is moreover very sparsely populated. In 1920 Dr. Swan (American Red Cross) estimated this population at 700,000, while Dr. Grant (Rockefeller Foundation) estimates it at 800,000. In my judgment the actual population is less than either of these estimates.

According to the official report of the governor's medical aide on October 9, 1920 there had been spent in 1920 upon sanitation and public health $657,000 and the projected expenditures for

Fig. 1. National Laboratories, Santo Domingo, R. D.

Fig. 2. National Laboratories, Santo Domingo, R. D.

1921, as per budget estimation, were $1,000,000. Considering the fact that in 1916 the native government spent but $30,000 for health, it is hard to escape the conviction that such expansion of expenditure is beyond the bounds of reason and good government.

The sanitary and health undertakings included the promulgation of a sanitary law and a sanitary code. This code is a comprehensive one and covers nearly all of the numerous health necessities of a modern and civilized state. It is hard to predict what will happen to it when the Dominican Republic resumes operations; just as it is hard to predict the fate of other laws, however beneficent, promulgated by executive order during military occupation. My criticism of this code is that it is rather too elaborate for a country as primitive as the Dominican Republic.

It must be admitted that, to a large degree, the sanitary and health organization exists principally on paper and that the code is enforced in a corresponding manner. This remark does not apply, however, to such basic matters as quarantine, vaccination and attempted control of communicable diseases.

A system of reporting of vital and morbidity statistics is also nominally in force as a result of our organization and while the bureau constantly gained efficiency up to January, 1921, it is far from being a dependable source of information as yet. Death reports are fairly complete, but in the absence of census statistics and with very incomplete reporting of disease, the rates of incidence of special diseases cannot be depended upon if based solely upon bureau reports. As in most Catholic countries, the collection of vital statistics is aided considerably through the performances and records of the church.

There is great need for study of the incidence of certain diseases known to prevail extensively, particularly malaria, the intestinal infections, and parasitic infections and infestations. A demonstration hookworm survey has already been made by the International Health Board and the results indicate the usual variation of distribution according to aridity of soil and density of population (see discussion later in this paper).

Fig. 3. Group of Buildings, Leper Colony, Nigua, R. D.

Fig. 4. Concrete Double Cottages for Two Lepers, Leper Colony, Nigua, R. D.

The hygienic laboratories, which, as director of national laboratories, I undertook to develop in 1920 and bring to a fair stage of efficiency, could carry out these studies and its routine work perfectly well if the direction be wise and if adequate funds and personnel could be maintained. One of the first effects of the financial crisis of January, 1921, was to put an end, at least for the time being, to the extending of laboratory activities. As preventive medicine rests so completely upon the foundation of laboratory investigation, this setback to public health was a serious one. In a communication of May 15, word comes that both biological and chemical national laboratories and many of the schools are now closed. It is possible that one of the great American foundations might be induced to come to the rescue in operating some of these institutions temporarily.

Other undertakings of undoubted merit and desirability, already accomplished in part, are the supervision of health in the schools, the erection and establishment of hospitals in Dominican towns and a system of sanitary inspection of towns and markets. The installation of a department of sanitary engineering and the supervision and examination of milk and water supplies at the national laboratory were also well launched undertakings at the beginning of 1921, but have since been abandoned in great part, for lack of funds.

The conquest of smallpox through widespread vaccination, quarantine, and the isolation of all detected cases, is already a practically accomplished fact and one which reflects credit upon the capable and conscientious secretary of the Department of Sanitation and Beneficence, Dr. Reynolds Hayden, Commander, United States Navy (see later remarks concerning smallpox). Evidence of the effective pioneer work of his predecessor in Santo Domingo, Dr. P. E. Garrison, U. S. N., were also noted in many directions.

Another achievement carried nearly to completion by Dr. Hayden was the erection of a national leper colony. The writer also had the honor of serving as medical director of leper hospitals and it was with great disappointment that plans for transferring all known lepers to the new colony were abandoned or indefinitely postponed in February. Preparations were then well under way to begin on March 1st, the modern treatment of leprosy developed in the past few years in the Philippines, Hawaii and California and the cases suitable for such experimentation had been carefully studied and designated. At present the Santo Domingo lepers are quartered at San Lazaro Hospital, an ancient and most inadequate institution in the Dominican capital Later in this paper I shall speak of leprosy more concretely.

A protective campaign against the introduction of plague from Gulf of Mexico ports and from Porto Rico (where the disease reappeared in February) and also an anti-rat campaign in Dominican ports were outlined by the director of laboratories at the request of the Secretary of Sanitation but their carrying out was interrupted by lack of funds and the program was reduced to a substitute, skeleton scheme, limited to quarantine measures and watchful waiting. The all-important matter of wholesale rat destruction had to be abandoned for lack of funds. In its place was substituted an educational effort, through an appeal to the people to practice individual rat-proofing of their premises and the destruction of rats by individual householders. This substitute plan cannot fail to be inadequate and to yield small results. The disastrous effect of introducing rats infected with plague into the Dominican Republic, where the rat population is extremely large and where rat control measures are practically unknown, can well be imagined.

I had the privilege of bringing this matter to public attention in the January Bulletin of the department; the article appearing in Spanish (La amenza de la peste y de las ratas).

One of the most interesting duties assigned to me during my stay in Santo Domingo was the investigation of a prison outbreak of beriberi. This investigation was completed just before my return to the United States and an account of this beriberi outbreak will be published as a separate report, shortly.

There is no lack of problems, of both health and sanitation, awaiting investigation but surveys and studies which do not lead to corrective effort are more or less wasteful and futile.

In general terms it may be said that the construction efforts of the military government in Santo Domingo seem to be patterned somewhat after our insular government in the Philippine Islands of the early days.

The ability to put across, completely and adequately, an elaborate sanitary program in any country depends upon one of two conditions. Either there must be unlimited and unquestioned authority, backed by governmental aid, military and fiscal—or there must be a highly developed public health conscience, such as we have in some but by no means all of our American communities.

In the last analysis all of our successful governmental experiments—so far as they have actually succeeded—have been by reason of the first-named condition. Witness the Philippines and Panama. As this condition of authority, governmental support and adequate financial backing relaxes, the structure weakens and falls into a state of greater or less inefficiency and ineffectiveness.

## NATIONAL LABORATORY

At the close of the calendar year 1920, the writer rendered a report of the laboratory operations for the year with certain observations and opinions touching efficiency and the possibility of increased future usefulness. The national laboratory consisted of two sections—a biological section and a chemical section—under the supervision of the director; the chemical section being administered by a sub-director who was a trained and experienced American chemist. The various determinations requested of the laboratory were made in these two departments according to their character, an exception being made in the case of urinalysis—both the chemical and biologic investigations of urine being made in the biological laboratory. The year's work was of creditable character but would have been greatly increased in volume in 1921, had the national laboratory been continued. In the report mentioned the director expressed the opinion that relatively too much attention was given to urinalysis, at the expense of biologic examinations relating to the diagnosis of the bacterial infections and parasitism, which cause a large percentage of the morbidity throughout the republic. The opinion was also expressed that the physician who does not make use of the diagnostic laboratory, particularly in the tropics, is not practicing medicine intelligently—whether engaged either in civil or military practice or in the practice of preventive medicine. It was planned to increase the usefulness of the national laboratory by extending the utilization of its diagnostic facilities during 1921.

Conceiving the proper functions of such a laboratory to be activities of practical helpfulness, rather than research, the rational extending of its influence should be along such lines, with an aim to the betterment of the public health.

Another field of useful work was recognized in the examining of large groups of persons, for intestinal parasitism and malarial and filarial infections, utilizing for this work groups in institutions of correction or detention, the prisons, hospitals, leper colony, etc. Naturally the complement to such investigation would be corrective medication and preventive sanitation.

It was also recommended that a branch laboratory be established, either in the interior of the island (Santiago) or at Puerta Plata on the north coast; and that a suitable technician from the national laboratory be detached for service there as local director; the sub-laboratory to be entirely auxiliary to the national laboratory and subject to complete direction therefrom.

For the year 1920 the operations of the Laboratory, tabulated by months, were as follows:

*Biological section*

| | *Number of examinations* |
|---|---|
| January, February and March | 342 |
| April | 146 |
| May | 193 |
| June | 149 |
| July | 178 |
| August | 175 |
| September | 110 |
| October | 119 |
| November | 118 |
| December | 345 |
| Total | 1875 |

*Chemical section*

| | |
|---|---|
| January, February and March | 112 |
| April | 43 |
| May | 98 |
| June | 51 |
| July | 27 |
| August | 10 |
| September | 4 |
| October | 13 |
| November | 38 |
| December | 10 |
| Total | 406 |

The total number of laboratory examinations for the year was 2,281.

It will be noted that the number of biologic examinations made in December, alone, exceeded the total number made in January, February and March, and that the work done in December greatly exceeded that of any previous month.

In the chemical section, on the other hand, there was a decrease in the number of examinations made, operations for the final three months of the year totalling but 61, against 112 for the first three months of the year. This decrease was in line with the director's conception of the relative importance of biologic diagnostic operations, as compared with purely chemical examinations indirectly related to public health.

A further analysis of the year's laboratory reports, divided bacteriologically and chemically, shows that there were 870 complete or partial chemical and biological examinations of urine; 181 examinations of blood for malaria parasites, filaria, hemoglobin, serum reactions, morphology, white and red cell counts, culture for bacteria, etc.; 172 examinations of feces for parasites, parasite eggs, blood, bacteria, etc.; 16 examinations of pus for bacteria, spirochetae, etc.; 196 examinations of sputum for tubercle bacilli, pneumococci and bacteria in general, protozoa, etc.; 367 examinations of secretions, exudates, tissue, skin, etc., for bacilli of leprosy and diphtheria, spirochetae; bacteria in general, blood, pus, cells, tubercle bacilli, cytologic study, etc.; 73 miscellaneous examinations.

In the chemical section the 406 investigations made included the following products: Drugs; dyes and colors; fruits, canned and dried; fish, canned and dried; vegetables, canned; liquors, wines, beers, bottled water; essential oils and lard; milk, fresh and canned; butter and cheese, goats' milk and mothers' milk; beans, sugar, rice, flour, bread, pastries and biscuits; sausages; chocolate, coffee and fresh water.

The laboratory reports for January and February, 1921, are not reported here. In a general way they showed great relative increase in the biological work, particularly with regard to stools and blood; the January and February examinations approximating in number, each month, those for December, 1920.

Both of the reports to which I have referred above comment upon the inadequate character of Dominican medical instruction and the facilities for both college and hospital teaching. These criticisms are, perhaps, fair, but there is, nevertheless, a small group of medical men in the capital, continentally trained in Europe or America. These men read extensively and compare favorably in understanding of tropical diseases with groups in certain communities of the southern United States.

The number is small, to be sure, but the men included are men of attainments in a clinical way. It is true that they have never engaged in administrative preventive medicine. I did not find the microscope to be an unknown instrument among them, as might perhaps be inferentially supposed from some accounts. There are enough technicians in Santo Domingo to carry on a creditable laboratory if they were supervised by an American director trained in public health and laboratory management and interpretation.

## THE SANITARY LAW AND CODE

Dr. J. B. Grant, in his report for the International Health Board (Rockefeller Foundation), analyzes the organization of the public health department and gives a summary of the principal duties of the secretary of sanitation. He also recites some of the provisions of the sanitary law and code.

The law was promulgated by executive order of the military governor in October, 1919, and the code was promulgated in similar manner in September, 1920. The code consists of 300 articles and 24 chapters. The administrative features contain some novel methods of enforcement and punishment of violations. The modus operandi is suited to a purely military government but will surely fail under civil self government. As I have already remarked, the organization exists principally on paper and the enforcement of all health measures except those related to quarantine is practically unattempted. Even under a purely military government an executive personnel is indispensable.

Before the breakdown of December, 1920, and January, 1921, Dr. Grant rated the efficiency of the department, after less than two years existence, above that of the Sanidad of Porto Rico at the end of its twenty years of organization. Although I have no recent personal knowledge of Porto Rican conditions I am not able to so visualize them, taking into account the military character of one government and the civil character of the other.

It is true that the infant mortality of Santo Domingo is less than that of Porto Rico and it is also true that the prevalence of anemia of parasitic origin is lower than in Porto Rico. These conditions, however, may be explained in large part by the poverty of the Porto Ricans. This poverty, in turn, depends upon density of population, the population per square mile in Porto Rico exceeding that of Santo Domingo many times. The fertility and productivity of Santo Domingo are so great and its resources are so abundant that the problem of existence there should be and is simpler than in Porto Rico. Under such conditions nutrition and resistance should be high and contact between individuals must be less intimate.

## SPECIAL DISEASES

*Malaria.* From both laboratory and clinical observations I was able to determine the varieties of malaria prevailing in Santo Domingo. Owing to the scarcity of anophelines in the capital city, new infections are not propagated among the people who reside in and confine their residence to the city. There are, nevertheless, many carriers, some "silent" cases, and numerous fresh clinical cases among the residents of the city, while the guardia (native militia) and marines, in their excursions from the capital into the interior and in their camps in the provinces, furnish a fairly large and constant supply of malaria cases. There is a constant flow of natives from the city to the country and *vice versa*, farmers, workmen, gardeners, sugar cane workers, peons, etc. Moreover, many of the better class of people living in suburban homes suffer more or less constantly from malaria and most of these suburban homes are infected with anopheles mosquitoes. House screening is practiced scarcely at all as yet.

Subtertian, tertian and quartan cases abound in about the order mentioned, if my experience is trustworthy. Except in those cases studied microscopically, the differentiation is seldom made and never with absolute accuracy. The pure clinician would probably take issue with me, basing his observations on apparent periodicity of symptoms and the statements of his patients; but to one experienced in the clinical phases and laboratory study of malaria the difficulty of determining the type of infection with certainty, from briefly observed symptoms and incomplete histories, is sufficiently manifest. Combined infections (tertian and subtertian; or quartan combinations with the two tertians) are not uncommon. In passing I may state that I encountered more quartan parasites in months in Santo Domingo than in years of observation in Cuba, the Philippines and the Balkans. Whether or not this be pure coincidence I am unprepared to state. It is conceivable that the African origin of part of the population may also account originally for the larger sprinkling of quartan cases, possibly introduced from that continent.

With regard to the existence of two distinct species of "falciparum" parasites (estivo-autumnal parasites, crescent form gametes) I am still open-minded. I brought back a fair sized collection of stained specimens for study. One could profitably devote at least six months of intensive study to Dominican malaria alone. Material is abundant for all reasonable purposes and easily accessible.

*Intestinal parasites.* Routine examinations of the stools of all patients admitted to the general and military hospitals of Santo Domingo were made during November, December, January and February with results not unlike those found in the other American tropics, including the Philippines. Eggs of the common intestinal worms *Ascaris lumbricoides, Trichocephalus dispar,* and uncinaria (*Necator americanus*) were found in many stools, regardless of admission causes. The embryos of *Strongyloides stercoralis* and *endamebas coli* and *dysenteriae* were also encountered.

The reported prevalence of hookworm infestation, as determined in Dr. Grant's survey, based on about 2000 stool examinations from inhabitants of all parts of the island, was found to be 52 per cent, and he estimates the percentage for the country at 50 per cent. This figure was obtained by taking percentages of separate areas as regards population and soil, prorating the infestation by the ratio of each area's population to the whole and averaging. It is interesting to note that our routine laboratory study of unselected cases for four months gave approximately a similar rate. The figures for ascaris infestation and other intestinal parasites are not available. Specimens of all the common parasites or their ova were secured, including the tapeworms and one specimen of *Schistosomum mansoni* ova (lateral-spined eggs) was encountered. The individual from whom this specimen was secured was a young man who had visited Porto Rico and had resided in Haiti within recent years. Moderate anemia and neurasthenic symptoms were present; also a coincident whipworm infestation (trichocephalus dispar). Diarrheal cases and dysenteric stools yielded specimens of endamebas (histolytica) and flagellates (trichomonas, et al.)

In staining certain stool smears for amebae, numerous spirochetae were demonstrated but their significance, if any exists, is purely speculative.

Sputum examinations for bronchial spirochetosis or bronchomoniliasis and for the ova of the lung fluke (*Paragonimus westermani*) were negative.

Tuberculosis, as indicated by positive sputum specimens examined in the laboratory, is apparently common, but as the cases demonstrated were general hospital cases no deductions whatever, as to prevalence, are permissible.

Pneumococci associated with lobar pneumonia and diphtheria bacilli associated with the clinical disease were demonstrated in the laboratory.

With regard to syphilis prevalence, there are absolutely no criteria for basing an estimate for Santo Domingo. Limited military statistics are, of course, available, but it is by no means certain that they represent or approximate the rate in the general population. These military statistics may, in fact, be either better or worse than the population at large. Wassermann testing has not been practiced extensively and we are quite in the dark as to the prevalence of syphilis in Santo Domingo. Doubtless the rate is high. The manifestations of nerve syphilis, as indicated by various paralyses, tabes, etc., are far more common than in the Philippines, if one may judge by the number of cases in the persons of crippled beggars seen upon the streets.

In a localized district not far from the capital, yaws is known to prevail quite extensively and an expedition from the Harvard Medical School recently visited Santo Domingo and conducted research study concerning this disease.

Rumors of cases of guineaworm among the natives of a certain section also came to me while in Santo Domingo but I was unable to investigate or confirm the reports.

Yellow fever has been unknown for years. However, the distributing mosquito (*Stegomyia fasciata*) abounds in Santo Domingo and other towns and is in fact one of the most numerous varieties.

Dengue, also, is endemic in the country and filariasis, another mosquito-borne disease, is fairly common in and about Santo Domingo both with and without elephantiasis. One case of reversed (?) periodicity in a policeman performing night duties was seen at the laboratory, the embryos being detected in his blood taken at our laboratory during the daytime.

Malta fever has also been observed in Santo Domingo, one of the university faculty having made some epidemiologic observation of cases in connection with Dominican goats (personal communication).

Typhoid fever and the paratyphoid fevers occur endemically and Widal testing and blood cultures for diagnosis were carried out in the laboratory. These diseases would probably be more prevalent but for the fortunate circumstance that a large part of all the milk used is boiled before transportation or consumption and that much of the drinking water used in the towns is rainwater collected in cement cisterns above ground, cisterns unlikely from their location to be contaminated fecally. Nearly all of the well water examined during the four months of my observations was found to be contaminated, even deep wells in the limestone of the capital showing the presence of colon bacilli and gas formers. This deep contamination, of course, is quite characteristic of wells in limestone rock. Some very unusual subterranean caverns occur in the neighborhood of Santo Domingo and it is not surprising that rock faults in this vicinity permit these deep wells to be polluted.

*Leprosy.* Leprosy received especial attention in January and February, 1921, because of the approaching time for the opening of the national leper colony, located at Nigua on the coast, fifteen miles west of the capital. The forty double cottages of concrete, the administration building, the kitchen and dining hall and dormitory buildings for the Sisters were then more than 90 per cent. completed. Arrangements had been made for twelve Spanish nuns from Europe to assume institutional care of patients and supervise the conduct of the colony. With the financial impassé of January the work of completing and equipping the buildings was suspended and the whole project was discontinued. Within the past few weeks (July, 1921), I have learned that hopes are still entertained for the completion and opening of this colony and that funds for this purpose may perhaps be found. Money for operation expenses will also be needed, of course. Preparatory to the transfer of the Santo Domingo cases of leprosy to the colony, seventeen were critically examined by the writer. Detailed instructions for the preparing of the mixed esters of chaulmoogric acid and the sodium salts from chaulmoogra oil were requested and received from Dr. E. L. Walker of the Hooper Foundation for Medical Research, of San Francisco, with a view to the preparation of our own materials for treatment at the new colony and provisions for the reception of eighty patients had been made.

The department did not expect that this treatment for leprosy, which has recently been much acclaimed, would fulfil all the promises made for it. The claims made are believed to be extravagant and have led to a false conception on the part of the people as to the curability of leprosy. Early diagnosis and careful selection of cases are necessary to secure even symptomatic cures. All of the Santo Domingo cases studied were proper ones for detention but by a loosely applied standard several might have been paroled. All had taken large doses of chaulmoogra oil by mouth for years and indeed there were at large in Santo Domingo at the time quite a number of lepers who had been paroled in previous years and considered but slightly menacing to their fellows. The fallacy and folly of such a policy are manifest from both clinical and historical viewpoints. Only with the permanent segregation of lepers throughout the countries of Europe, in lazarettos, following the great diffusion of the disease immediately after the Crusades and the Middle Ages did leprosy practically disappear from the continent. The best students of the disease today are conservative in their claims for treatment by esters and chaulmoogrates.

Nearly, if not quite all, of the Santo Domingo cases are cases of mixed leprosy wherein the signs of nodular, macular and nerve leprosy are combined. Indeed it seems quite probable that most cases of leprosy everywhere are of the so-called mixed variety from their onset, although the manifestations of one or other of the clinical groups of skin leprosy may be far more evident than the clinical signs and effects of nerve leprosy, particularly in the early years of the disease. The sequence in which the human tissues are invaded, skin, mucosa, nervous tissue, etc., may frequently vary, but the early involvement of more than one of these tissues is practically inevitable in every case of leprosy, having in mind the distribution of the bacilli by both blood and lymph streams.

*Smallpox.* Santo Domingo has been visited by smallpox in years past but until its reappearance there in 1920 the country has been practically free from the disease for nearly a generation. Some of the older Dominican physicians informed me that in previous epidemics extensive vaccination was performed, at least in the vicinity of the capital. During the year 1920 cases were introduced across the border by natives from Haiti, where an epidemic of considerable proportions was raging. A controversy as to the identity of the Haitian disease, whether it was smallpox or "alastrim," so-called Kaffir milk-pox, continued there for some time. Meanwhile the Dominican government, through the efforts of its Secretary of Sanitation, Dr. Hayden, successfully prepared for the advent of the disease by wholesale and countrywide smallpox vaccination. In due time the disease appeared in the country and proved to be true smallpox. The clinical picture, its amenability to control by vaccination and every essential diagnostic feature were present. I saw the first fifteen cases at the capital and observed the disease from its earliest to its latest stage. It differed not at all from smallpox as I have seen it in Cuba, the Philippines and the United States. Moreover, it originated from so-called cases of "alastrim" in Haiti. It is but fair to state that the diagnosis of smallpox was subsequently adopted in public health reports from Haiti. Our control efforts through vaccination were extremely successful but the usual anti-vaccination propaganda was carried on by unfriendly newspapers. Charges to the effect that the vaccine furnished by three well known American firms contained the "streptococci of erysipelas" were made by a Dominican physician in the interior of the island. Accordingly, culural tests of specimens of vaccine of all makes were made in the national laboratory with constant negative findings. Upon direct examination under the microscope, of vaccine smears from all of the different American manufacturers, streptococci and staphylococci in small numbers were found, the chains appearing to be diplo-streptococci in most instances. As stated above, however, no cultures were obtainable from these specimens. The secretary of sanitation thereupon issued a circular calling attention to the requirements of the United States Pharmacopoeia and United States Dispensatory for vaccine virus. The last editions of these publications contain specifications that vaccine shall be free from pathogenic microorganisms and that a special examination of each lot of virus shall be made to determine the absence of such organisms and of tetanus spores and toxins. Attention was called to the fact that the vaccine in use conformed to these specifications and that cultural tests of all samples were negative. This bulletin was effective in quieting unfriendly clamors against vaccination.

Unless we are prepared to adopt a new name for a disease whenever it undergoes sufficient attenuation or modification to greatly reduce its mortality rate, I see no reason for changing the name of the mild form of smallpox which has prevailed, not only in the West Indies recently, but for some time past in the United States. The same observation is true concerning the exanthemata in general and the recently declining curves in mortality rates probably indicate lessened virulence of many of the infectious diseases from causes or circumstances not understood.

## CONCLUSION

The writer has not attempted, in this presentation, to discuss exhaustively any of the various phases of public health in Dominica nor any of the diseases which occur among the Dominican people. A large and fruitful field for endeavor, along the lines of preventive medicine and epidemiology, exists in this old-new country, well named the Land of Promise. It is sincerely to be hoped that ways and means may be found whereby, with the friendly acquiescence of the Dominican people, a suitable public health program may be agreed upon, activities resumed and the work carried to its logical conclusion in the interets of medical and sanitary science and the welfare of the Dominican people.

# DERMATITIS VENENATA PRODUCED BY AN IRRITANT PRESENT IN THE STEM SAP OF THE MANGO (MANGIFERA INDICA L.)[1]

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In Hawaii and other places where the mango grows, it is well known that certain skin lesions may develop in children and in susceptible adults who have handled or eaten the fruit.

The mango (*Mangifera indica L.*) is a plant belonging to the order Anacardiaceae. To this order also belong the wi fruit (*Spondias dulcis*) grown in tropical and subtropical countries, the cashew nut (*Anacardium occidentale* and *A. orientale*) found in tropical America and Asia, the pistachio nut (*Pistacia vera*) of the Mediterranean region, the pepper tree (*Schinus molle*) of California and elsewhere, the lacquer tree (*Rhus vernicifera*) of Japan, the poison oak of California (*Rhus diversiloba*), the poison oak of the eastern United States (*Rhus toxicodendron*) and the poison ivy vine (*Rhus radicans*). The mango is a native of India but is now grown in all tropical and subtropical countries. The family consists of about five hundred varieties and more are being produced by grafting, budding and inarching. The bearing season in Hawaii, where over forty varieties are grown, is from January to August; however the fruit may be

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obtained in the markets during the entire year. It is a large upstanding tree, 30 to 40 feet in height. The leaves are dark green, lustrous and elongated. The fruit, which contains a flattened pit, is large, green, reniform and fleshy. When ripe it may turn yellow or red and has a delightful flavor. In the stems of the fruit are a number of large ducts which contain a thin viscous sap. When the stems are broken, from $\frac{1}{2}$ to 1 mil of this sap flows out and often covers the leaves or fruit, on which it hardens forming a thin, lustrous, varnish-like surface.

Higgins (1) says, "Much of the evil reputation which some would fix upon this fruit arises from a lack of knowledge of the methods of handling it. In the case of some people the rind of the mango produces sores upon the mouth and face." Concepcion (2) states that "It is a common belief among the people of the Philippine Islands that the transient rashes of erythematous type occurring during the hot season are caused by the eating of mangos (*Mangifera indica L.*)."

The skin lesions which occur after contact with mangos include erythema, edema, macules, papules, vesicles and pustules, followed by scaling, pigmentation and often by scar formation. It is the opinion of many that contact with any portion of the plant is sufficient to produce the disease in susceptible individuals. Poisoning has been reported to have occurred following exposure to the smoke of burning mango branches. The information obtained from these various sources and from cases seen, indicate that there is something present in the mango plant which at times produces a severe dermatitis.

It is the object of this paper to report clinical histories of cases, to give the results of experimental work done to determine the nature and source of the etiologic agent, to discuss the clinical signs and symptoms of mango dermatitis, and to recommend treatment for the disease.

## CLINICAL HISTORIES

*Case 1.* C. P. F. Male, white, blonde, thin skinned, age forty-two, architect, born in United States. Good general health and of stable nervous type. No diseases of childhood except epidemic parotitis. Had severe rhus dermatitis every year between the ages of twelve and twenty-five years. No history of food or drug poisoning, hay fever or asthma. When twenty-nine years of age came to Hawaii. Developed dermatitis two weeks after arrival. Thought it was rhus poisoning. Was told that rhus did not grow in Hawaii. Soon found that disease followed eating mangos. Had attacks of varying severity every year following contact with mangos. Used a solution of zinc sulphate without benefit. Boric acid solution slightly beneficial. Mango trees in his yard are "chutney" variety. Never has attacks after eating fruit peeled by wife. Pulp of fruit is not irritating. Had one attack after trimming mango trees. Lesions usually occur on hands between fingers, on fore-arms and around mouth. Frequently has lesions on genitals. Latent period twenty-four to forty-eight hours. On the first day has tiny, itching blisters, which coalesce on the second day. Itching increases in severity and lasts a week or longer if not treated. No real pus formation. Blisters contain a yellow serum. Lesions desquamate for a week after vesicles disappear. No systemic disturbance noted at any time. Zinc sulphate at first relieved the itching, but does not do so now. Boric acid solution stops the itching and turns the blisters brown. Does not seem to shorten the disease. The treatment with alcohol and ether stops the itching and the lesions subside in about four days. No change in susceptibility since the first attack. Patient states that the mango dermatitis is similar to a mild rhus dermatitis.

*Case 2.* F. L. Nurse. Leahi home. White, fair, thin-skinned, female. Born in United States. Thirty-five years old. Normal physically except for the present complaint. Often had mild dermatitis, caused by rhus, when a child. In 1919, while in Washington, D. C., had primrose dermatitis on chin and face. Patient came to Hawaii, October 1920. Had eaten Florida mangos, bought in northern markets, without ill effect. Since arrival here has eaten "common (Hawaiian) mangos" frequently.

July 5, 1920, ate three "chutney" mangos. Bit out stems and peeled fruit with thumb. Felt slight burning of lips within few minutes, which subsided at the end of an hour. On the morning of July 6, noticed two collections of vesicles on lips, which she thought were "cold sores." There was also a small vesicle on the tip of the nose. All lesions itched and burned intensely. July 7, not suspecting that mangos were responsible for the dermatitis, she ate two more "chutney" mangos. Lips were swollen. The crops of vesicles had spread and new ones had appeared. July 8. In the morning had small collections of blisters on upper chest. The lesions on the nose, lips and chin had

FIG. 1. CASE 2

Mango dermatitis. Miss F. L. Photographed on ninth day of disease. Shows edema of left eyelids, left cheek and lower lip; broken vesicles on little finger left hand, at bend of right elbow and on neck. Induration and desquamation left cheek, with exudation of serum.

spread and the itching was worse. Wore gauze dressing around the neck and under the chin. Left side of neck red and swollen. Talcum powder used in treatment. July 9. First seen by doctor, who advised Arnold's treatment. July 10. Unable to obtain alcohol, so used ether alone, in morning. Condition much worse by night. July 11, Worse. Lesions apparently spread by ether application. July 12. Unable to work. Left eyelids swollen shut. Conjunctivae apparently normal. Speech interfered with by the swelling of lips. Skin of left cheek hot, red, swollen, rough and leathery. Many patches of vesicles exuding yellow serum. Appearance of neck and chest similar. Many vesicles on fingers of left hand. Few patches of vesicles on right hand and at bend of elbow. Awoke with slight headache after restless night, due to intense itching. July 13. Worse except for swelling which had decreased slightly. Left eyelids swollen shut. Right upper lid puffy and red. Vesicles on hands increased in size and number. Itching still intense. Temperature 99°F. Pulse 75. July 14. Used alcohol after ether, followed by a soothing lotion. Except that some of the vesicles had become pustular, and that the swelling was generally less severe, no change was noted. Chemical and microscopic examination of urine normal. Red blood count 4,850,000. Hemoglobin 85 per cent (Tallquist). White blood count 8200. Polymorphonuclears 52 per cent. Large mononuclears 2 per cent. Small mononuclears 40 per cent. Eosinophiles 5 per cent. Basophiles 1 per cent. Photograph of lesions taken (fig. 1). July 15. Improving. Swelling and itching lessened. Many areas beginning to desquamate. July 18. Itching about gone. Still shows desquamation and pigmentation. Patient left for another island.

*Case 3.* H. H. J. White. Age forty-three, male, Major M. C., brunette, thin skin, excellent health and stable nervous type. No previous illnesses. No skin diseases except rhus dermatitis. Very severe, type unknown. Had every summer between tenth and eighteenth years. First ate mango in the Philippines. No dermatitis. Had treated cases there but did not acquire it.

First attack occurred in Hawaii, June, 1920, after eating "peach mango," which he picked and peeled himself. First noticed a stiffness and tenseness of lips. The mucous membrane was roughened. Swelling occurred first about one eye and then the other. Spread over cheeks. Later developed on scrotum. Lasted three to four days. No vesicles or papules. Swelling, redness and itching were the prominent symptoms. Treated with witch hazel and 50 per cent alcohol. Used cold compresses for swelling. Latent period twenty-four to thirty-six hours.

Second attack very mild. Lasted twenty-four hours. Mucocutaneous junction of lips tense and rough. A few lesions on penis. Since being warned to avoid contact with the stem sap, has been able to eat mangos after being careful to peel with knife, cut out stem end and wash hands with caustic soap. Has also used alcohol after washing hands. Either this prophylaxis is efficient or susceptibility has decreased. Patient states that the dermatitis is similar to that produced on him by rhus.

*Case 4.* Mrs. Y. Housewife, white, age forty-two. Born in United States. Good general health. No history of hay fever or asthma. Had an eruption after eating strawberries several years ago. History of rhus dermatitis unknown.

Ate first mango in Panama in 1914. This was followed in two days by a "rash" on cheeks, neck, fore-arms and back of hands. Had suffered with eczema, therefore did not suspect mangos as the cause. As this was near the end of the mango season, she did not eat any more till 1915, when she developed the same symptoms as in the first attack. All of the fruit eaten had been bought at the commissary, therefore she did not come in contact with mango leaves. Erythema and swelling appeared on cheeks, neck. fore-arms and hands in twenty four hours, followed later by small vesicles in crops. Lips not affected. Itching so intense as to cause her to scratch in her sleep. Since arrival in Hawaii has had similar dermatitis after eating mangos. Treated with boric acid ointment without improvement. Lesions began to disappear in one week.

*Case 5.* S. C. Son of Colonel M. C. White, male, schoolboy, age fourteen, thin skinned. Excellent health and normal nervous type. Had measles, pertussis and varicella. Neither had rhus nor any other plant dermatitis. Had fish poisoning a few years ago. Several months ago ate first mango, variety unknown, which he peeled with hands.

Was sick that night with "indigestion" and fever of 101°F. At the end of twenty-four hours had rash over face and neck. Worse on cheeks. Skin very red and showed marked swelling in "clumps." Some swelling of eyelids. No vesicles. Sores in corners of mouth. Very many macules and papules on cheeks. Lesions were worse second day and lasted four days, after which they disappeared. Treatment with warm saline was started after the second day. There was neither exudation of serum nor scaling. Some spreading of lesions occurred after the first day. No fever except on afternoon of the day of contact. Bowels loose on same afternoon but normal thereafter. No nausea or headache.

One month later ate another mango, which he peeled with fingers. Later accidentally rubbed fingers on mouth and face. A dermatitis similar to the first attack developed in about sixteen hours. More severe on cheeks. After second day treated with hot saline. Disappeared on the fifth day. This case did not go on to the stage of vesiculation; which possibly explains the favorable results obtained with warm saline applications.

*Case 6.* Yai. Japanese, female, age nineteen, servant, dark, thin skinned, born in Japan. Good health and stable nervous type. Does not speak English so could not obtain complete history. Ate first mango eight months ago, while in Hilo, Hawaii. Was badly poisoned, and "sick several weeks." Face and arms swollen. When she arrived here was told by friends that mangos were harmless. Ate several after biting off peel. Two days later developed many vesicles around mouth, with marked swelling of lips, cheeks and eyelids; accompanied by intense itching. Was given Arnold's treatment and the lesions disappeared in about a week.

*Case 7.* T. A. Z. Private, U. S. Army. White, male, blonde, thin skinned, age twenty-one. Good general health and stable nervous type. In May, 1920, was unable to do duty for one week, because of dermatitis which followed the eating of five mangos. Face, eyelids, nose and lips intensely swollen. Many papules and vesicles over face and neck. Some lachrymation. Temperature and pulse normal. Wassermann negative. Urine normal. Later after eating one mango, had another similar attack. Lips so intensely swollen as to appear white. Patient thinks that he is poisoned more readily when perspiring.

*Case 8.* H. Child, white, female, blonde, thin skinned, age seven, born in United States. Has been poisoned many times by eating mangos or by picking the fruit. Develops "sores and rash" over area of contact about mouth and also on back of hands. Once picked mango and later touched neck with hands producing area of urticaria in twenty-four hours.

*Case 9.* Mrs. S. M. C. White, female, age thirty, blonde, thin skinned, wife of medical officer. Born in the United States. Fair general health. Nervous type. No previous illness or skin disease except rhus dermatitis which she had in Maryland and Virginia. No history of asthma, hay fever or food poisoning.

May 1, 1921, in the afternoon, handled some mangos but did not eat the fruit. At bed time noticed burning of lips and redness of nose. The following morning had many vesicles on lips and nose. These lasted one week and spread over face. Lips swollen. Treated with saturated solution of magnesium sulphate.

Two weeks later lifted small son out of a mango tree. Twenty-four hours later developed similar dermatitis over flexor surfaces of arms, between fingers, and on chest and neck. Burned some that day and itched that night. Vesicles lasted one week. Treated with ammoniated mercury ointment, magnesium sulphate solution and sulphur ointment at different times. No subjective symptoms.

On another occasion stood near a fire when mango leaves, wood and fruit were burning. Three hours later her whole face, neck and arms began to itch. Became red in six hours. Used alcohol and sulphur ointment. Later itching very intense. Both eyes swollen shut. Crops of vesicles on flexor surfaces of arms and between fingers. Treated with alcohol and ether. Began to subside in twenty-four hours after treatment started. All signs gone in about one week. Patient states that the second attack was very similar to rhus dermatitis.

*Case 10.* Mrs. E. A. F. White, female, age thirty, brunette, thin skinned. Born in United States. Good general health. Stable nervous type. No previous illnesses or skin diseases except rhus dermatitis which she has had often. When a child she had many severe attacks affecting hands and eyes; four since puberty, on face, hands and neck. No history of fish or food poisoning. Has been poisoned by the sap from the poinsettia. Small blisters containing a thin milky exudate occurred between fingers and disappeared in three days.

First attack of mango dermatitis occurred in September, 1919, after taking one bite of a chutney mango from the tree which produced the dermatitis in case 1. Eighteen hours after biting the stem end of the mango she noticed an intense itching of lips which were covered with small vesicles. Six hours later her lips were much swollen. Itching so severe as to prevent sleep. Next day lesions spread to nasal folds of cheeks and to fore-head. Used a saturated solution of boric acid.

Irritation began between fingers. On the fourth day the left eye was swollen shut. On fifth and sixth days yellow serum oozed from points on the affected areas. On the seventh day treated with ether and alcohol every half hour. This caused much oozing, and the lesions began to clear up. The skin was red, tough, leathery and scaly. "Like sunburn." Desquamation began at the end of one week. Entirely well in three weeks.

Second attack occurred after walking under same tree. Struck on neck by new leaf. Three hours later noticed a red area "like branding," which itched. Used ether and alcohol several times that night, also a lotion. No spreading. Next morning was like a second degree burn. Started with small vesicles which ran together forming a large blister two by seven inches. Opened blister, let out serum and applied alcohol. Lesions disappeared gradually after drying up and scaling, like "dandruff," Lasted two weeks. Thickening of skin noticeable for months afterwards.

Third attack followed unknown contact. Irritant was probably brought in by child. Appeared on both cheeks and itched after a few hours. Treated with ether and alcohol immediately. Followed the same course as the second attack. Latent period for itching three to four hours, for blisters fifteen hours. No fever except in affected areas. Bowels and kidneys acted normally. Had bad headache. No nausea. Duration of disease not more than three weeks. Skin was left noticeably thickened for three to four months. Treatment with boric acid solution and hot soap suds was of no value. Best results obtained with ether and alcohol. Patient imagines she is more susceptible. States that the disease is similar to rhus dermatitis.

*Case 11.* Mrs. C. E. F. F. White, female, age fifty-five, housewife, fair, thin-skinned, excellent health. Born in United States. Nervous and excitable. Previous illnesses unknown. Rhus history negative. Has had a rash after eating shell-fish. No other skin diseases.

First attack of mango dermatitis less than one week after reaching Honolulu. Had erythema over nose and cheeks. Some erythema on hands. Mild itching. Had not eaten mangos but had touched leaves of a tree which overhung the path that she frequently walked in. The tree was one of the first planted on the island and was probably of the chutney variety. Ether and alcohol were used at once, followed by calamine lotion. Was much better the following day and well on second day.

*Case 12.* Soldier's wife. Housewife, white, thirty-five, good health, phlegmatic, neither blonde nor brunette. Had severe attacks of rhus dermatitis repeatedly.

Ate first mangos after her arrival here a few weeks ago. Picked fruit from tree and ate without removing peel, smearing sap and juice all over face. First symptoms appeared three days after contact. Continued eating the fruit for two days after first signs appeared. Macules and vesicles appeared on skin near lips, followed by a generalized edema over whole face. The vesicles coalesced forming large blebs. When seen on the fifth day, had blebs on lips, edema; erythema and intense itching from the hair line to the level of the larynx. Both ears intensely swollen. Many vesicles on hands around hair follicles. On the sixth day ether, alcohol and calamine lotion were given without benefit. Both eyes swollen shut. Swelling of lips and ears increased. More vesicles on hands. On seventh day still worse. Stopped ether and alcohol. Used diachylon ointment. Eighth day markedly improved. Discharged on ninth day as cured.

Latent period three days. No lesions on mucous membranes. Type of mango unknown. Temperature 100°F. on first day seen. Had headache and loss of appetite. Patient said this was exactly like her attacks of rhus dermatitis.

*Case 13.* Mrs. W. P. White, female, thirty-five, thin-skinned, brunette. No previous illnesses excepting severe rhus dermatitis, which she had every year in California, for sixteen years.

First attack occurred after picking a number of green chutney mangos, none of which she ate. She noticed that the sap was smeared over both arms and hands. Washed hands with grain alcohol but did not wash arms. Two days later intense itching, redness and swelling of both fore-arms, especially marked on the flexor surfaces. Many blisters, "pin head" in size appeared and later coalesced forming blebs. Lesions not entirely healed for three weeks. No systemic disturbance except slight nausea on first day of disease. Tried soothing application and was given "salty tasting powders" by her doctor.

Second attack. Underclothing had been hung under mango tree after being laundered. Two days after wearing, and without any direct contact with mangos, the patient developed lesions on the left thigh similar to those described above. These areas were about the size of a silver dollar. The patient stated that the lesions were similar to those seen in rhus dermatitis.

## EXPERIMENTAL

### *I. Cutaneous tests, for foreign protein sensitization*

It was thought that the lesions, observed in certain susceptible individuals, following contact with mangos might possibly have been the result of a specific cutaneous reaction produced by a foreign protein present in some portion of the plant.

*Experiment 1.* Antigens were prepared from the ripe fruit and green leaves of a chutney mango tree. These antigens were made by extracting the leaves; and the peel and pulp of the fruit each with distilled water, normal sodium chloride solution, alcohol 95 per cent, ether, and chloroform, for twenty-four hours at room temperature. Cutaneous tests made with these fifteen antigens, by applying one drop of each to a scarified area on the skin of the flexer surface of the fore-arm, were negative in thirteen individuals, none of whom gave a history of mango dermatitis, at the end of two hours, twenty-four hours and thereafter.

*Experiment 2.* Antigens made from fresh leaf, peel and pulp, by the foregoing method from a mixture of Jamaican, Pyrie, and chutney mangos, were tested by the cutaneous method on five non-susceptible individuals. Three gave negative results throughout. In two cases, at the end of two hours the chloroform antigen of mango leaf produced a faint, irregular reddening.

*Experiment 3.* Antigens were prepared in a manner similar to that used in experiment one, of materials obtained from a chutney mango tree; the fruit of which was known to have produced dermatitis. These antigens were used for making cutaneous tests on twelve non-susceptible individuals. All results were negative.

*Experiment 4.* After several weeks the antigens used in experiment three, which were found to be sterile, were used to test four individuals, who had never been poisoned by mangos, but who gave a previous history of rhus dermatitis. In one case the ether and chloroform solutions, of both peel and leaf, produced slight reddening in twenty minutes. This temporary reaction was probably due to traces of stem sap in the leaf and peel antigens. All reactions were negative after twenty-four hours.

*Experiment 5.* A fresh supply of material was obtained from a chutney mango tree, the fruit of which was known to have caused severe cases of dermatitis. Antigens were prepared, by the method used in experiment one, from the leaf, peel and pulp; and in addition from the sap obtained from the broken stems of the fruit. These antigens were used to test two individuals, both of whom gave a history of repeated accidental mango poisoning; and one control person with a negative history. No reaction was noted at the end of one hour, either in the susceptible persons or in the control. At the end of twenty-four hours one of the susceptible persons complained of slight itching at the point of application of ether solution of peel. In forty-eight hours both susceptible persons showed reactions consisting of reddened edematous areas, which itched intensely, with the sap suspensions alone. Tests with the other antigens were negative. The susceptible persons at the end of seventy-two hours, had marked reactions with lesions similar to those which occur in accidental mango dermatitis; including erythema, edema, papules and vesicles, accompanied by intense itching. In addition to these reactions one susceptible person showed a slight reddening of the skin produced by the ether and chloroform peel antigens and the saline leaf antigen. The other showed a temporary reddening with the alcohol antigen. Treatment of one susceptible individual, which was begun at the end of eighty hours because of the intense itching, was continued for three days. All lesions were healed by the seventh day. No dermatitis was produced in the negative control.

In view of the fact that several mild reactions were obtained with the various leaf and peel antigens in the previous experiment, and that marked reactions occurred with the antigens containing stem sap, the following experiment was carried out to determine whether or not all of these reactions might not have been due to the presence of dried or fluid sap.

*Experiment 6.* Materials were obtained from the same tree as in experiment five. The leaves were carefully selected and those containing traces of sap were discarded. The fruit was washed with soap and water, rubbed dry, and the stem ends excised to avoid possible contamination of the antigens with stem sap. Saline antigens were made of leaf, peel, pulp and sap; and these were applied to the skin of the fore-arms of one very susceptible, and four non-susceptible individuals. There was no reaction in any instance at the end of seventy-two hours, in areas to which the peel, pulp and leaf antigens were applied. The sap antigens produced a marked localized dermatitis, which occurred in the susceptible individual on the second day and in two of the non-susceptible persons after seven days. This experiment seemed to prove that the irritant was present only in the sap; and that the faint reactions obtained in experiment five with leaf and peel antigens, were possibly due to contamination by stem sap.

*II. Tests made on unbroken skin, using untreated materials*

*Experiment 7.* Fresh untreated sap from the stems of chutney mangos, was applied to the unbroken skin of the face of five non-susceptible individuals. Three of these, at the end of twenty-four hours, showed lesions at the point of contact, indistinguishable from those seen in mango dermatitis. The application of sap to the inner surface of the finger of a susceptible individual produced a similar result. All leslons healed in seven days.

*Experiment 8.* Fresh specimens of untreated stem sap from chutney, Jamaican and Pyrie mangos respectively, were applied to the unbroken skin of the fore-arms of seven non-susceptible persons. Marked reactions occurred in three instances with the chutney sap; while all tests with the other saps were negative. In another instance dermatitis was produced by both chutney and Pyrie saps, applied to two non-susceptible individuals.

*Experiment 9.* Fresh stem sap from both ripe and green chutney mangos, produced similar positive reactions upon the unbroken skin of one susceptible and four non-susceptible persons.

*Experiment 10.* Undarkened, chutney stem sap, after standing exposed to the air in an open test tube for one week produced a positive reaction when applied to two non-susceptible, and one susceptible, individuals.

Dark amber colored, resinous sap, which had dried on the stems of chutney mangos for two weeks, failed to produce dermatitis.

*Experiment 11.* Dermatitis was not produced in susceptible or non-susceptible persons, by the local application of either fresh tree sap, or old dark resinous tree sap, from the trunks of Pyrie or chutney mangos.

*Experiment 12.* Untreated sap-free leaf, peel and pulp, of chutney and Pyrie mangos, failed to produce dermatitis when applied to eleven non-susceptible and two susceptible individuals.

### *III. Tests made with treated materials*

*Experiment 13.* Fresh chutney stem-sap heated in the water bath for five minutes, at 56°C., and 80°C. and 100°C., failed to produce dermatitis when applied to five non-susceptible, and one susceptible, individuals.

*Experiment 14 A.* To determine whether or not the irritant present in stem sap was volatile, specimens of both fresh and old chutney stem sap were heated for five minutes over a bunsen burner, in stoppered test tubes, from which extended glass tubes one meter in length. The tubes were then broken off, outside the stopper, and washed out several times with ether. The residues obtained by the evaporation of this ether, failed to produce irritation when applied to the skin.

*Experiment 14 B.* The above experiment was repeated following the same technique, with the exception that the end of the glass delivery tube was immersed in toluol contained in a second test tube. After heating the first tube for five minutes over a bunsen burner the toluol in the second tube was poured into a watch glass and evaporated at room temperature. The residue obtained did not produce dermatitis following applications to the skin of one susceptible and five non-susceptible individuals. The heated sap left in tube one, produced a positive reaction on one very susceptible person.

Ether and toluol were used in this experiment because both have been shown, in other experiments, to dissolve the irritant present in fresh stem sap.

The apparently contradictory results obtained following the heating in this experiment and in experiment eight; in which the saps heated to 56°C., 80°C., and 100°C. failed to produce dermatitis, may possibly be due to rapid oxidation accelerated by the moisture in the latter.

Because of the similarity which exists between mango and rhus dermatitis, and in view of the botanical relationship between the plants, it was thought possible that the irritant might be a substance similar to lobinol, the dermatitant of poison oak.

*Experiment 15 A.* A mixture of leaves, bark and dried fruit stems, from a chutney mango tree, were extracted following the technique used by McNair (3) for obtaining lobinol from *Rhus diversiloba.* A dark green liquid of the consistency of mineral oil was obtained.

A small portion of this liquid was applied to scarified areas on the fore-arms of twenty-five individuals none of whom had ever had mango dermatitis. The results were negative. Slight itching and erythema occurred in one susceptible person and another susceptible person failed to react.

*Experiment 15 B.* A small amount of fresh chutney stem sap was extracted with 95 per cent ethyl alcohol, at room temperature, for two hours. The McNair technique was followed from this point on. A small amount of a dark green, oily liquid was obtained. This preparation was applied to scarified areas on the fore-arms of six non-susceptible individuals, two of whom developed positive reactions at the end of one week; and to one susceptible individual who had a positive reaction at the end of forty-eight hours. This reaction, which was characterized by itching and erythema, progressed to the stage of vesiculation in seventy-two hours.

*Experiment 16 A.* Two-tenths of a mil amounts of twenty-four-hour-old chutney stem sap were dropped into various solvents including water, normal salt solution, 95 per cent ethyl alcohol, ether, chloroform, carbon tetrachloride, carbon bisulphide, benzin, xylol, toluol, methyl alcohol and a mixture of

TABLE 1

*Reactions resulting from application of residues from twenty-four hour old chutney stem sap to unbroken skin*

| SOLVENTS | VISIBLE LOSS IN AMOUNT BY SOLUTION | RESIDUES FROM EVAPORATED SOLUTIONS | J. S. S. | | | Z. E. B. | | | C. F. B. | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 1 hour | 24 hours | 48 hours | 1 hour | 24 hours | 48 hours | 1 hour | 24 hours | 48 hours |
| Water, cold, distilled | None | Small, flat, crystalline plates, colorless | Negative | Negative | Negative | Negative | Negative | Negative | Negative | Negative | Negative |
| Saline 0.85 per cent | None | Small, flat, crystalline plates, colorless | Negative | One vesicle | Negative | Negative | Negative | Negative | Negative | Negative | Negative |
| Ethyl alcohol 95 per cent | None; sap turned white, hard | Greasy colorless film | Negative | One vesicle | One vesicle | Negative | Vesicles many | Vesicles many | Negative | Very many vesicles | Pustules very many |
| Ether | Slight | Greasy colorless film | Negative | Vesicles many | Vesicles very many | Erythema | Negative | Negative | Erythema and itching | Vesicles very many | Great many pustules |
| Chloroform | Slight | Greenish greasy film | Negative | One vesicle | One vesicle | Negative | One vesicle | Edema, erythema; One vesicle | Negative | Negative | Negative |
| Benzin | None | Greenish greasy film | Negative | Negative | Negative | Negative | Negative | Negative | Negative | Negative | Negative |
| Carbon tetrachloride | None | Grass-green; greasy film | Negative | Many vesicles | Many vesicles | Negative | Two vesicles | Many vesicles | Negative | Many vesicles | Many vesicles |
| Carbon bisulphide | None | Colorless greasy crystals | Negative | Edema; erythema; itching | Edema; erythema; itching | Negative | Three vesicles | Three vesicles | Erythema | Very many vesicles | Very many pustules |
| Xylol | Slight | Emerald green; oily film | Negative | Edema; erythema; itching | Edema; erythema; macules | Negative | Negative | Negative | Erythema | Negative | Negative |
| Toluol | Slight | Light green; oily film | Erythema; itching | Itching; very many vesicles | Itching; very many vesicles | Erythema; itching | Itching; very many vesicles | Itching; very many vesicles | Edema; erythema; itching | Very many pustules; itching | Very many pustules |
| Methyl alcohol | None | Faint green; oily film | Negative | One vesicle | One vesicle | Negative | One macule | Negative | Negative | One vesicle | One vesicle |
| Ether and chloroform mixed | Slight | Faint green; oily film | Negative | Negative | Negative | Negative | Negative | Negative | Negative | Negative | Negative |
| Untreated sap | | | Negative | Negative | Negative | Negative | Negative | Negative | Negative | Negative | Negative |

Solvents alone gave no reaction.

chloroform and ether. After shaking at intervals for twenty minutes, the solvents were poured into watch glasses and allowed to evaporate at room temperature. The residues obtained were very small in amount, dark green and oily, excepting those from water, saline and carbon bisulphide, which were crystalline, greasy and transparent.

Each of these residues were applied to the unbroken skin of the fore-arms of three non-susceptible individuals. Positive results were obtained with the residues from all the solvents

Fig. 2. Experimental Mango Dermatitis

Photograph of fading lesions on fore-arm of test individual, J. S. S., in experiment 16, taken twenty days after application of residues.

excepting water, saline, benzine and the mixture of chloroform and ether. The fact that the untreated stem sap controls failed to produce dermatitis in these non-susceptible individuals, while concentrated extracts produced severe lesions, is a striking illustration of the quantitative nature of the reaction.

One test individual (J. S. S.), on whom the dermatitis became so severe as to require active treatment, was awakened on the fifth night by intense itching. There was marked local edema around all the points of application. Alcohol and ether were applied followed by a fatty ointment. On the following day many new papules and vesicules were seen between old test lesions. Erythema and itching were more pronounced. On the twentieth day there was still some swelling, pigmentation was marked, and scarring was seen where the reactions had been most severe. Photograph of fore-arm taken this day, (figure 2). The lesions produced by the toluol extract were most severe, indicating a greater solubility of the irritant in this solvent than in the others.

*Experiment 16 B.* On another occasion the fresh stem saps of Jamaican, chutney and Pyrie mangos were concentrated in the same manner as in experiment 16 A. These residues were tested on five non-susceptibles individuals with similar results.

*Experiment 17.* The evaporated residues from the toluol extraction of ripe and green chutney stem saps produced similar positive reactions when applied to either non-susceptible or susceptible individuals. Toluol extracts of old, brown, sap dried on stems for two weeks; and of both fresh and old chutney and Pyrie tree saps failed to produce dermatitis.

### *Oxidase*

The sap which flows from the broken stem, of mango fruits and from the injured bark of the tree, like that obtained from other plants of the order Anacardiaceae, soon hardens and becomes a shiny, varnish-like substance; which turns brown in a few days and later becomes almost black. Experiments indicate that the dark resin-like sap contains none of the irritant present in fresh stem sap. Possibly this darkening, and the accompanying loss of toxic properties may be due to oxidation. Fresh stem sap from chutney, Pyrie and Jamaican mangos each gave a positive reaction for oxidases with the gum guaiac test.

### *Attempts to extract the irritant from mango leaves, peel and pulp*

*Experiment 18 A.* Sap-free leaves from chutney, Pyrie, Jamaican and Hawaiian mango trees were bruised in a large stone mortar, and extracted twenty-four hours with ether, and toluol, respectively. The clear solvents were poured into watch glasses and evaporated at room temperature. Clean pieces of peel and pulp from the four varieties of trees were each carried through a similar process.

None of the twenty-four residues produced dermatitis when tested on five non-susceptible individuals, including two persons who were very sensitive to sap residues.

*Experiment 18 B.* Another test was made using residues from toluol extraction of sap-free leaves, peel and pulp (chutney), on five non-susceptible and one susceptible individual. The toluol extract of sap was used for a control. No reaction occurred with the leaf, peel or pulp residues in any case. The control sap residues produced marked dermatitis. This experiment indicates that the irritant is not extractable by toluol from clean leaves, peel or pulp.

*Feeding experiment*

*Experiment 19.* Chutney stem sap was given in one-half mil doses, by mouth to a healthy rabbit on three successive days. On the fourth day, after washing out fecal matter with water, five-tenths of a mil of sap was injected as high as possible into the rectum. The rabbit was killed on the fifth day by a blow on the head. No pathologic lesions were found in the gastro-intestinal tract or elsewhere. Urine collected from the bladder contained neither casts, albumin nor sugar. Histologic examination of sections from liver, kidneys and spleen showed them to be normal.

*Reaction*

The reaction of fresh chutney stem sap is acid as shown by the indicators; litmus, phenol red and methyl red. One cubic centimeter of a 1 : 50 suspension of sap in distilled water was neutralized by two tenths of a mil of $\frac{N}{100}$ sodium hydroxide, using phenolphthalein as an indicator.

*Hemolysis*

Fresh stem saps from chutney Jamaican and Pyrie mangos are actively hemolytic when brought into contact with human erythrocytes either directly or when diluted in normal salt solution. This action is possibly due to the acid present in the sap.

## CLINICAL DATA

The dermatitis venenata caused by mangos resembles that produced by members of the rhus family, the cashew nut, Fox (4), and other plants belonging to the order Anacardiaceae. The irritant principle present chiefly or entirely in the sap, which flows freely from the broken stems of the fruit, produces dermatitis only when brought into actual contact with the skin. For this reason primary lesions most frequently occur on exposed parts of the body, such as the lips, cheeks, eyelids, inner surfaces of the fingers and flexor surfaces of the fore-arms. Secondary lesions may develop on unexposed parts, particularly the male genitalia, following transfer of the irritant by the patient's hand.

Clinically the disease may be divided into periods of latency, prodromes, maximum signs and symptoms, and of decline. The period of latency, which may last from one hour to more than a week, represents the time which elapses between contact with the irritant and the development of the primary signs. The variation in this time is probably influenced by differences in the amount and condition of the irritant, the thickness and condition of the skin and by the presence of water, salts or lipoids on the skin. The period of prodromal symptoms is characterized by slight erythema and vague skin irritation, which may rapidly develop into definite itching. This stage lasts from a few hours to several days and is not sharply separated from the following one. In the period of maximum signs and symptoms the patient is usually seen first by the physician. Itching is so severe that it often causes loss of sleep. The erythematous areas have spread. Localized edema appears and there is frequently marked swelling of the cheeks, eyelids and lips which may last from three to seven days, or disappear in a few hours; and is often accompanied by thickening and induration of the skin covering these parts. The edema may be so severe as to close one or both eyelids, or to cause swelling of the lips sufficient to interfere with speech. The lesions itch intensely; and from the broken skin, which results from scratching, exudes a yellow serum which dries and forms crusts. Many papules are seen in these edematous areas. These often develop into vesicles. The skin of the cheek in one severe case, remained thickened and leathery for three months. Vesicles, varying in size from one half to three millimeters, occur in from one to seven days; either discretely or in aggregations, which often coalesce and form blebs. These vesicles contain a clear yellow serum. They may disappear by absorption thus ending the disease, but more commonly they become pustules. The serum from vesicles does not reproduce the disease when inoculated into the skin of another susceptible individual. Pustules, which may develop from preëxisting vesicles, or independently, at the end of two days or more, last from twenty-four to ninety-six hours. The tops may be scratched off forming crusts or they may be absorbed. The period of decline is short and is characterized by a decrease in swelling, redness and itching; and by desquamation, which is often accompanied by pigmentation, and in severe cases by definite scar production. Lesions generally develop in the following sequence: erythema, macules, edema, papules, vesicles and pustules; followed by desquamation and healing. However all of these may be present in one case at the same time. In experimentally produced mango dermatitis, caused by the application of concentrated extracts of stem-sap all of the lesions described above occur in severe form.

Apparently the dermatitis is not produced by absorption of the irritant from the gastro-intestinal tract as was thought by many. Concepcion (2) reports four experiments in which he fed mangos to nursing mothers; and was able in this way to produce papulo-vesicular lesions upon the breasts and other exposed parts of the skin. Similar lesions later developed upon exposed parts of the nursing infants, which he concluded, were caused by substances carried in the mothers' milk. As nothing is said concerning the care taken to prevent contact between the skin and the stem-sap of the mangos, which has been proven to contain a definite irritant, those experiments do not appear to be conclusive.

None of the cases seen here had any systemic disturbance following the ingestion of mangos. No case developed without actual contact of the sap with the skin. When given to rabbits by mouth, or injected into the rectum, chutney stem-sap, which contained enough irritant to cause severe skin lesions, failed to produce any demonstrable pathologic change, either gross or histologic, in the gastro-intestinal canal, liver, kidney or spleen.

The resistance shown by different individuals to the irritant present in mango stem-sap varies, and the apparent immunity of certain persons is probably always relative rather than absolute. The variations in the degree of susceptibility of the same individual are possibly due to differences in the condition of the skin at various times, and to variations in the amount or condition of the irritant. Persons who are not affected by contact with the amount of sap obtained by eating mangos develop severe lesions when concentrated extracts of sap are applied to the skin surfaces. This difference in susceptibility is similar to that reported by McNair (5) in rhus dermatitis.

Apparently no racial immunity exists among Caucasians, Japanese, Chinese, or Hawaiians as cases are known to have occurred in members of all these races. The dermatitis has been seen in both blondes and brunettes in equal proportions. In the cases collected here there were four males and nine females. Mango dermatitis occurs more frequently in children than in adults. This may be due to the thinness of the child's skin, as well as to the lack of care exercised by children in handling and eating the fruit.

## TREATMENT

The irritant contained in mango stem sap is soluble in ether, chloroform, 95 per cent ethyl alcohol, toluol, xylol, carbon tetrachloride, carbon bisulphide and methyl alcohol. The treatment aims at the solution of the irritant and its removal. The most practical application of this principle was first used by Major H. L. Arnold, Medical Corps, United States Army, who at the time considered the irritant to be a glucoside present in the leaf or fruit. This treatment consisted of mopping off the lesions with successive pieces of gauze saturated with ether, followed by a similar mopping with 95 per cent alcohol. A lotion containing zinc oxide 10 grams, phenol 2 grams, glycerol 2 grams and aqua mentha piperita enough to make 200 mils, was then used to allay itching. This treatment is efficient, when applied early, if the patient is careful to use clean gauze for each application, and to wipe off all the dissolved irritant. Caution is necessary because of the liability of spreading the irritant by the use of ether alone, as occurred in one case (case 2). The use of fatty ointments without previous treatments with ether and alcohol, is not advisable, possibly for the same reason. It is possibly better to wash the parts with warm water and soap after the ether-alcohol applications in order to mechanically remove all traces of the irritant from the skin. Any bland soothing lotion may be used to allay irritation; and cold compresses may be necessary to relieve the edema and swelling. Different individuals have used a number of remedies, including solutions of zinc sulphate, of magnesium sulphate, potassium permanganate, and boric acid; ointments containing ammoniated mercury or sulphur; and caustic soap. None of these have resulted in shortening the course of the disease.

## SUMMARY

1. Dermatitis venenata similar to that caused by plants of the Rhus family is often produced by the mango (*Mangifera indica L.*).

2. Mango dermatitis is characterized by itching, erythema, intense edema, macules, papules, vesicles and pustules followed by pigmentation, desquamation and often by definite scar production.

3. Experiments show that the lesions are not the result of specific foreign protein skin reactions; but are produced by a non-protein skin irritant, which is present chiefly or entirely in the stem-sap of either ripe or green fruit.

4. The irritant is not volatile. It is soluble in toluol, xylol, ether, alcohol, chloroform, carbon-bisulphide, carbon tetra-

chloride and methyl alcohol. It has not been found in either fresh or old bark tree-sap, or in old, dark, gummy stem-sap. It is probably destroyed by an oxidase present in the stem-sap.

5. No marked differences were noted in the amounts of irritant present in stem-saps from mangos of different varieties.

6. The dermatitis is most commonly seen in children and in certain susceptibile adults. Variations in susceptibility are probably influenced by differences in the thickness and condition of the skin, and in the amount and state of the irritant.

7. The most efficacious treatment used here has been early applications of ether, followed by 95 per cent alcohol, to remove the soluble irritant and the use of a lotion containing phenol, to allay itching. Neither ether alone nor fatty ointments, should be used because of the danger of spreading the irritant.

8. Seven of thirteen cases studied were extremely susceptible to rhus poisoning. In the remaining six cases there was no history of rhus dermatitis, nor of contact with the plant. Of these six cases, two had previously had fish poisoning, and one strawberry poisoning.

9. Mangos may be eaten even by susceptible persons, without danger of developing dermatitis, if care is taken to avoid contact with stem sap.

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# THE TREATMENT OF TRICHURIASIS WITH LECHE DE HIGUERON[1]

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To the laboratory man in the tropics doing routine stool examinations, the parasite, *Trichuris trichiura,* or as formerly known, *Trichocephalus dispar,* becomes almost a friend, for its eggs are surely to be found in practically every specimen of feces. It was this prevalence of the parasite which interested me in the subject, and finally led to the experiments which I report in this paper.

An examination of the literature discloses at once, two interesting facts: first, that this parasite is not a harmless inhabitant of the caecum as has been commonly supposed, but that it can give rise to severe symptoms or even death, especially in young children; and second, that there is no specific treatment.

I quote from the literature as collected by Fanthom, Theobald, and Stevens in "Animal Parasites of Man," in which they have thoroughly reviewed the literature.

Whilst many authors consider the whipworm as a harmless parasite of the large intestine (Leichtenstern, Eichhorst, Askanazy), the large number of severe and even fatal cases caused by it trichocephaliasis increase so much that the *Trichuris trichiura* must be excluded from the group of harmless intestinal parasites.

The anterior part of the body of the parasite is usually fixed in the mucous membrane and according to Askanazy feeds on the blood of its host. Moosbrugger, Schulze, Kahane, Vix, Girard, and Blanchard all found changes in the mucous membrane of the gut. Kahane had an

[1] This work done in 1917 under a Wm. O. Moseley Traveling Fellowship, Harvard Medical School.

[2] Published with permission of the Surgeon General, U. S. Army, who is not responsible for any opinion expressed or conclusions reached herein.

opportunity of seeing, at the Pasteur Institute, Trichocephali with the anterior part of the body penetrating not only the mucosa but also into the muscularis of the gut wall.

In several autopsies I performed during the course of this work I had an opportunity of observing, soon after death, this manner of attachment. In one case is particular in which 37 of these worms were found, the head of the caecum appeared covered with fine moving threads. The parasites were found with about one-half inch of the cephalic end buried under the mucosa and were removed with some difficulty. The site of attachment was congested and the mucosa showed, in some cases, small areas of hemorrhage. The whole head of the caecum was markedly congested in contradistinction to the adjacent colon and ileum which were normal.

From this mode of attachment, it is easily understood how Trichocephali, especially when they are numerous in the gut, cause local irritation and inflammatory conditions consisting of frequent attacks of diarrhea, sometimes twenty times a day, lasting for months, resisting all remedies, and accompanied by colicky pains and symptoms of peritonitis. The stools often have blood mixed with fluid, very glassy, jelly-like mucus, more or less abundantly, as in the cases of Moesasca, Moosbrugger, Kahane, Girard, Poledne and Rippe. Nausea and vomiting are rarer symptoms (l.c.).

Barth found the brain normal in a man who died with meningitic symptoms, but the intestines were full of Trichocephalus dispar; Gibson records the rapid cure of serious cerebral symptoms after the expulsion of Trichocephalus, as do also Pascal, Burchhardt, and Rippe. Moosbrugger was the first to draw attention to the grave anaemic conditions induced by Trichocephalus; Moesacsa and Becker to progressive grave anaemia. Trichocephalus anaemia is accompanied by marked reductions in the number of red blood corpuscles, of the specific gravity, and of the hemoglobin, well marked morphological changes in the red cells, macro, micro, and poikilocytosis and nucleated red cells (l.c.).

In discussing this infection with Drs. Urueta, Rodriguez, and Fernandez of the United Fruit Company's Hospital in Santa Marta, Colombia, the interesting fact was mentioned that a specific remedy, Leche de Higueron, was commonly known and used in that country, and had been reported by several Colombian physicians. The legend goes that this sap of the white fig tree was first used by the farmers of that country as a vermifuge for swine with such success that it was tried by physicians in humans infested with intestinal worms. Cuervo Marquez in his "Geografia Medica Y Patologia de Colombia" credits Doctors Robeldo, Toro Villa, Posada Berrio, Uribe and Cardenas y Puerta with its introduction into our therapeutic armamentarium and considers it specific for *Trichuris trichiura.* His account of the drug follows:

> The juice or sap of the Higueron, "Ficus glaborata," of the family of the Urticacea, possesses a specific action for Trichocephalus. . . . The milk or sap is obtained from slashes in the bark, or by cutting off a branch and collecting in a jar the juice, which flows abundantly. When fresh drawn, it has an acid reaction, is of syrupy consistency, has a styptic taste, ferments very easily, thereby increasing its acidity and acquiring a disagreeable odor. It is soluble in water and glycerine and insoluble in ether and alcohol.

Fanthom and others speak of the use of the milk of the Higueron "Ficus laurifolia" in the treatment of hookworm but do not mention its use for trichuriasis.

The cases which I wish to report may be divided into those treated in Colombia with the fresh juice, and those in Costa Rica, where the sap was preserved in chloroform. In order to determine the effect, if any, of the chenopodium treatment on trichuris infestation, a series of cases was studied in which this parasite was found together with ascaris or hookworm or both. The stools passed during the twenty-four hours following chenopodium treatment were carefully saved in a large bucket, diluted in water, and strained through three layers of gauze. The worms were then picked off the gauze and identified. The stools resulting from the treatment of 55 cases were thus examined. It was found that while chenopodium expelled large numbers of both ascaris and hookworm, in only one case was *Trichuris trichiura* passed and then only two worms were found. In this chenopodium series, as well as that with Leche de Higueron, no effort was made to choose those cases which showed numerous eggs in the stool. The cases were from those excreting the ova in the stools taken as nearly consecutively as circumstances would allow. Having established that chenopodium with the attendent catharsis could not be relied upon to remove *Trichuris trichiura*, Leche de Higueron was tried. In this series, the fresh juice was obtained on one of the outlying plantations, sent in by rail and put on ice as soon as received. It was then used until it soured, usually four or five days afterward.

The same routine treatment was followed as with chenopodium except that Leche de Higueron was substituted for chenopodium. The day preceding the treatment, the patient was given liquid diet and at 8 p.m., 30 cc. of cream of tartar in a glass of sweetened water. On the day of the treatment, he received at 6 a.m., 16 cc. of the fresh Leche de Higueron in a half cup of milk, repeated at 8 a.m. This was followed by 60 cc. of castor oil at 10 a.m. When the chloroformed juice was used, the dose raised to 20 cc. or 30 cc. and magnesium sulphate was given in place of castor oil.

Eighteen cases of trichuriasis were treated in Santa Marta. Of these cases, 8 had had chenopodium treatment to remove ankylostoma and ascaris, but had passed no trichuris as a result of that treatment. A period of from five to eighteen days (average eight days) was allowed to elapse before they were put on Leche de Higueron treatment. Three of these 8 cases still showed ankylostoma present after chenopodium while 4 others of the remaining 10 cases showed either hookworm or ascaris in conjunction with trichuris.

*Cases treated with fresh Leche de Higueron*

| CASE NUMBER | WORMS PASSED | CASE NUMBER | WORMS PASSED |
|---|---|---|---|
| S-1 | 4 trichuris | S-10 | 1 trichuris |
| S-2 | 0 trichuris | S-11 | 7 trichuris |
| S-3 | 6 trichuris | S-12 | 13 trichuris |
| S-4 | 0 trichuris | S-13 | 0 trichuris, 1 ascaris |
| S-5 | 1 trichuris | S-14 | 1 trichuris |
| S-6 | 1 trichuris | S-15 | 0 trichuris |
| S-7 | 0 trichuris | S-16 | 1 trichuris |
| S-8 | 2 trichuris | S-17 | 0 trichuris |
| S-9 | 12 trichuris | S-18 | 0 trichuris |

It will be seen that in this series of 18 cases, the parasite was passed in 11 or 61 per cent of cases following the treatment, while in but one case was ascaris or ankylostoma affected.

In Costa Rica, 12 cases were treated with juice preserved in chloroform. None of these were given chenopodium treatment before administration of Leche de Higueron. Ten of these cases showed ankylostoma or ascaris or both with trichuris on entrance.

*Cases treated with chloroformed Leche de Higueron*

| CASE NUMBER | WORMS PASSED | CASE NUMBER | WORMS PASSED |
|---|---|---|---|
| C-1 | 0 trichuris | C-7 | 10 trichuris, 1 ascaris |
| C-2 | 1 trichuris, 1 ankylostoma | C-8 | 0 trichuris, 1 ankylostoma |
| C-3 | 0 trichuris | C-9 | 4 trichuris, 1 ascaris |
| C-4 | 0 trichuris | C-10 | 0 trichuris, 6 ascaris |
| C-5 | 101 trichuris, 125 ankylostoma. | C-11 | 0 trichuris, 1 ascaris |
| C-6 | 4 trichuris, 1 ascaris | C-12 | 16 trichuris, 1 ankylostoma |

In this series of 12 cases, 6 or 50 per cent passed trichuris following treatment and in case C-5, 101 of the parasites as well as 125 hookworms were expelled.

It is to be noted in this series, that there was a more marked action on ascaris and ankylostoma than in that using the fresh juice, for in 9 cases one or the other of these parasites were expelled. Whether or not this action is due to the presence of chloroform, I do not know.

On account of the short stay of these cases in hospital, and under local hospital conditions, it was possible to examine but six cases of these series, following treatment. Of these, two showed rare trichuris eggs and four were negative.

When the pure juice was used, there were usually no subjective symptoms. Occasionally an individual complained of a burning sensation in the rectum and around the anus. This however was never more than a temporary discomfort of a few hours duration. This symptom for some reason or other was always absent in the negroes treated. The chloroformed juice had a sickening sweet taste and gave some discomfort from the frequent eructations of gas it caused.

On this account, and on account of the possibility of toxic effect from the ingestion of chloroform, it would seem advisable to expel the chloroform by gentle heat, just before administration.

Addition of an equal amount of chloroform, and storage in the ice box preserved the sample used in the treatment of the Costa Rica series for thirty-four days at which time it was still unfermented. Trikresol, 0.5 per cent and glycerine 50 per cent prevented fermentation. One sample autoclaved at 10 pounds steam pressure for ten minutes remained unfermented for six weeks when it was discarded. Only the chloroformed juice was used in treatment.

This small series of cases is here reported that the attention of the profession may be drawn to this ubiquitous parasite which may give rise to severe disease, and to this little known remedy for trichuris, and especially that more work may be done on this juice with a view of isolating the active principle.

The difficulty of getting Leche de Higueron and my abrupt departure for the United States to enter the service in 1917 prevented me from amplifying this series and from investigating numerous questions which arose in connection with the work.

## SUMMARY

1. *Trichuris trichiura* is not a harmless parasite but frequently gives rise to severe or even fatal disease.

2. We find in the literature no specific treatment.

3. Chenopodium does not remove this parasite.

4. Leche de Higueron offers a safe and hopeful means of treating this disease.

5. This juice possesses a slight vermicidal action on ascaris and ankylostoma.

6. In this series of cases, this treatment caused the passage of trichuris in 57 per cent of cases.

I wish to acknowledge my thanks to Drs. Wm. Deeks, Urueta, Rodriguez, Fernandez, Lynn, and Lambert of the United Fruit Company Medical Department for their assistance and many courtesies shown me during the prosecution of this work.

# MALARIA IN EASTERN CUBA

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The Province of Oriente, comprising the entire broad eastern end of Cuba, is comparatively unknown to the world at large and its medical problems are rarely brought to the attention of the profession.

During one year, September, 1920, to August, 1921, the writer had the opportunity to study the health problems of one of the largest sugar plantations in Cuba. This plantation is situated on the lowlands and foot hills south and west of Nipe Bay. The climate is semi-tropical. Temperatures are only rarely below 60°F. or above 95°F. The mean temperature is close to 80°F. all the year. The winter months are cool with occasional heavy rains. Frequent local showers occur during the greater part of the year, especially near the mountains. The summer and autumn months are generally warm and dry.

The population is largely migratory and varies considerably during the year, being probably less than 9000 during the last months of 1920 and above 16,000 during the early part of 1921. Of these some 40 per cent are Haytians, about 25 per cent Jamaicans, and 5 to 10 per cent Cubans. The remainder is made up from the various smaller West Indian islands, China, India, Europe, and America.

The great majority of the Haytians work in the cane fields and live in groups of twenty to fifty in barracones. Some of these shelters are closed on the ends and one side while others are open on both sides. Many of them are in close proximity to anopheles breeding places along railroads and streams.

The Jamaicans are chiefly employed in transportation, construction and development work. This brings them in close proximity to swamps, pools, and sluggish streams where anopheles abound.

The Cubans are variously employed. Most of them live in the towns and are thus less exposed to infection.

In order to determine the actual situation in regard to malaria and other diseases, a complete consecutive record was kept of all patients admitted to Preston hospital during twelve months September, 1920, to August, 1921. This hospital serves the entire plantation. The records include about 16 per cent surgical cases. On admission blood, stool, and urine of every patient

TABLE 1

| MONTH | BLOODS EXAMINED | TOTAL MALARIA | TERTIAN | QUARTAN | ESTIVO-AUTUMNAL | CRESCENTS |
|---|---|---|---|---|---|---|
| September | 224 | 76 | 27 | 1 | 48 | 28 |
| October | 236 | 82 | 12 | 2 | 68 | 7 |
| November | 401 | 223 | 22 | 1 | 200 | 24 |
| December | 410 | 262 | 23 | 1 | 238 | 19 |
| January, 1921 | 403 | 158 | 25 | 2 | 138 | 20 |
| February | 511 | 135 | 14 | 0 | 126 | 15 |
| March | 448 | 135 | 15 | 2 | 119 | 20 |
| April | 353 | 181 | 18 | 0 | 163 | 24 |
| May | 513 | 321 | 25 | 0 | 296 | 33 |
| June | 684 | 391 | 39 | 6 | 350 | 50 |
| July | 674 | 318 | 47 | 6 | 265 | 28 |
| August | 304 | 176 | 29 | 4 | 143 | 22 |
| Total | 5161 | 2458 | 296 | 25 | 2154 | 290 |
| Per cent | 94.8 | 47.6 | 5.7 | 0.5 | 41.7 | |

was examined as far as practicable. The blood examination was made or verified personally by the writer in all but about 5 per cent of cases. Thin smears were used in all routine work.

Table 1 shows the monthly distribution of the various types of malaria. Crescents are included under estivo-autumnal but are also listed separately to show the relative frequency of fresh infections and carriers of the estivo-autumnal type of malaria during the year.

Figure 1 is a graphic representation of the chief points in table 1. September and October are the end of a prolonged dry season. Most of the anopheles breeding places were dry and fresh infections accordingly few. November and December were wet with an abundance of anopheles breeding places throughout cane field and bush. The result was numerous heavy fresh infections. Several factors account for the marked drop during

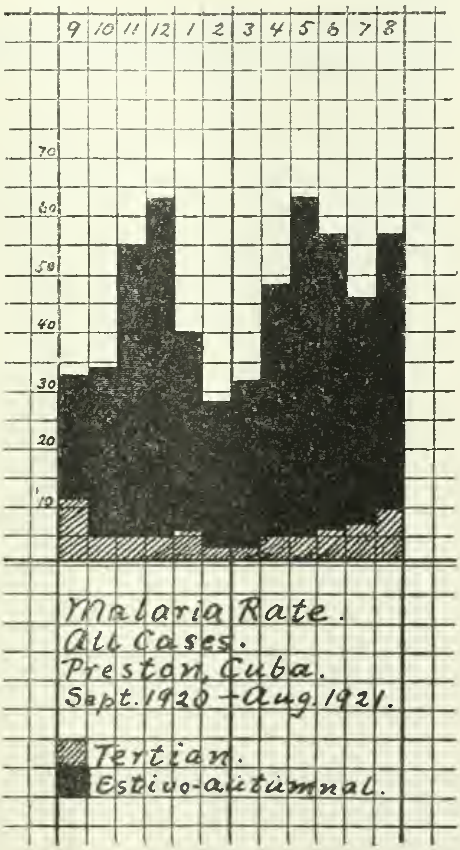


Fig. 1

January, February, and March. The temperature was sufficiently low to retard mosquito development somewhat. Several thousand new and relatively malaria free laborers came to the plantation from Hayti. The proportion of pneumonia and other respiratory diseases was high, and quinine prophylaxis was effectively carried out in certain sections. During April, May, and June conditions were very favorable for anopheles breeding, and there was an increasing tendency on the part of the laborers to avoid the bi-weekly dose of quinine. The result was a marked increase in new infections especially among the Haytian cane cutters.

In table 2 the Haytians, Jamaicans, and Cubans have been grouped separately. This brings out an interesting point in

TABLE 2

| MONTH | HAYTIAN | | | JAMAICAN | | | CUBAN | | |
|---|---|---|---|---|---|---|---|---|---|
| | Number examined | Tertian | Estivo-autumnal | Number examined | Tertian | Estivo-autumnal | Number examined | Tertian | Estivo-autumnal |
| September | 126 | 17 | 28 | 43 | 6 | 11 | 17 | 0 | 0 |
| October | 59 | 2 | 12 | 130 | 7 | 48 | 14 | 0 | 3 |
| November | 49 | 5 | 16 | 264 | 14 | 160 | 24 | 1 | 2 |
| December | 75 | 4 | 34 | 259 | 16 | 166 | 28 | 0 | 8 |
| January, 1921 | 155 | 4 | 27 | 157 | 14 | 90 | 26 | 3 | 10 |
| February | 345 | 2 | 61 | 96 | 7 | 48 | 30 | 0 | 6 |
| March | 293 | 4 | 81 | 76 | 7 | 29 | 31 | 1 | 2 |
| April | 230 | 7 | 123 | 76 | 9 | 23 | 22 | 1 | 7 |
| May | 366 | 15 | 233 | 84 | 7 | 46 | 24 | 1 | 8 |
| June | 442 | 27 | 243 | 105 | 5 | 50 | 41 | 0 | 10 |
| July | 411 | 23 | 165 | 119 | 12 | 50 | 48 | 0 | 11 |
| August | 182 | 17 | 97 | 56 | 4 | 20 | 15 | 0 | 5 |
| Total | 2733 | 127 | 1120 | 1465 | 108 | 741 | 320 | 7 | 72 |
| Per cent | 96.5 | 4.7 | 41.0 | 93.7 | 7.4 | 50.6 | 96.4 | 2.2 | 22.5 |

The quartan parasite was found 18 times in Haytians and 5 times in Jamaicans.

view of the employment of these groups during the year. Most of the Haytian laborers were left unemployed when the cane season ended about the first of October. Several thousand went back to Hayti, but a large number remained wandering about mostly in or near the towns, where they were less exposed to anopheles.

During the following four months, October to January, the Jamaican laborers were largely employed in construction and new development work, such as railroad building, pipe line construction, wood cutting. This involved considerable exposure not only to mosquitoes but to such debilitating influences as poor food and insufficient protection against rain and wind.

Late in January cutting and grinding of sugar cane was started again. About that time five thousand or more Haytians came

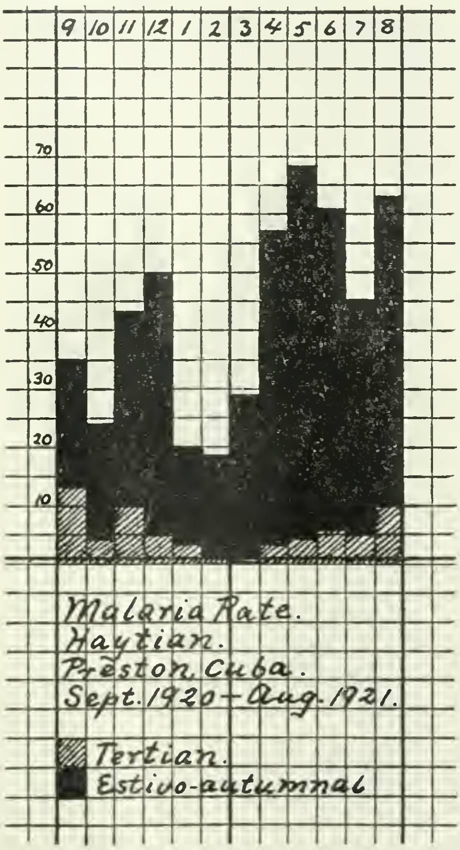


Fig. 2

over from Hayti. They all went out in the fields to cut cane. At the same time large numbers of Jamaicans were withdrawn from the outlying districts to be employed in transportation and other work in which they were much less exposed.

The result is plainly evident in figures 2 and 3 which show the Haytian and the Jamaican malaria rates during the year.

Table 3 gives a summary of the year as a whole. It will be seen that the percentage of infection is very much lower for the Cuban patients. This may be accounted for by the fact that most of the Cubans lived in the towns and therefore were largely cared for in the clinics and at their homes, thus leaving a greater

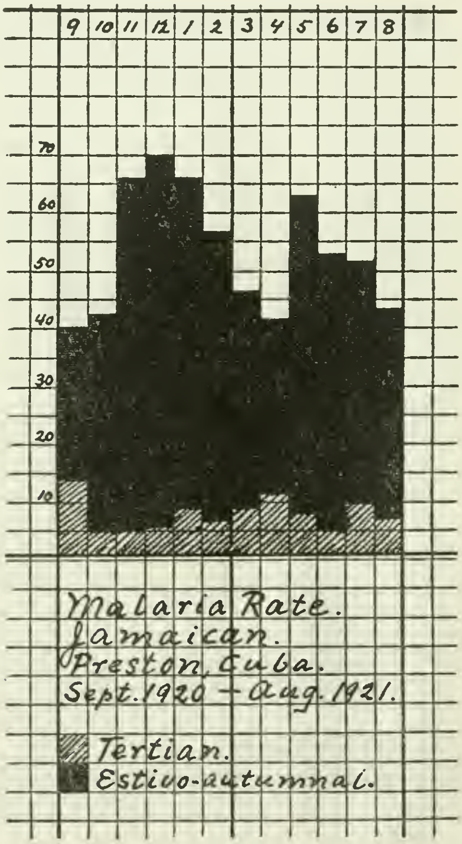


Fig. 3

proportion of non-medical cases among those admitted to the hospital.

From the foregoing it would seem that malaria was responsible for nearly 50 per cent of the morbidity on the plantation. However, the actual proportion should be put somewhat higher.

Many patients had had quinine shortly before entering the hospital and as a result showed no parasites in the blood, although they were suffering from the immediate consequences of malaria. Moreover, 87 per cent of the malaria cases were of the malignant or estivo-autumnal type which frequently shows few parasites, or none at all, in the circulating blood.

It is not necessary to go into the symptomatology except to emphasize the great multiplicity of symptom complexes in estivo-autumnal malaria. Attention may also be called to its

TABLE 3

| SEPTEMBER, 1920 TO AUGUST, 1921 | TOTAL | HAYTIAN | JAMAICAN | CUBAN |
|---|---|---|---|---|
| Admissions | 5453 | 2830<br>51.9% | 1564<br>28.7% | 332<br>6.1% |
| Bloods examined | 5161<br>94.8% | 2733<br>96.5% | 1465<br>93.7% | 320<br>96.4% |
| Positive bloods | 2458<br>47.6% | | | |
| Tertian | 296<br>5.7% | 127<br>4.7% | 108<br>7.4% | 7<br>2.2% |
| Quartan | 25<br>0.5% | 18<br>0.66% | 5<br>0.34% | 0 |
| Estivo-autumnal | 2154<br>41.7% | 1120<br>41.0% | 741<br>50.6% | 72<br>22.5% |

relation to hookworm. During the early part of the year it was frequently found that certain cases of malaria did not clear up and enter upon the usual rapid convalescence. Very often it was found in such cases that a hookworm infestation had been left untreated, and proper treatment quickly brought about the desired result. In view of that fact an effort was made through the rest of the year to diagnose and treat all cases of hookworm within twenty-four hours after admission unless there was evidence of acute pulmonary or renal diseases. The result obtained was very gratifying.

The routine treatment used in most cases was thorough catharsis and 15 grains of quinine in acid solution three times a day for five days. It is based on the extensive experience of Deeks and others in the Canal Zone. In grave cases 15 grains of quinine in sterile solution made up to 10 cc. with normal saline were given intramuscularly every four hours. The same dosage and preparation was also frequently used intravenously This method is very convenient, and it is safe provided at least five seconds be allowed for each grain injected. Too rapid injection is apt to cause a mild convulsion.

Preventive measures were instituted under the direction of Dr. E. J. Scannell along the lines worked out in Panama. A marked improvement was evident especially in the town areas. But the outlying districts still remain a problem. Quinine prophylaxis was tried but the result was hardly commensurate with the expense.

The economic aspect of the malaria situation on plantations in Eastern Cuba needs to be more fully realized by those concerned. Buildings and quarters for laborers should not be placed without the approval of the sanitary expert. The sanitary squad should precede the various construction gangs. And all should have safe quarters to resort to at night. If the actual cost of inefficiency and losses due to malaria could be calculated, it would be found much greater than the cost of efficient prevention. Furthermore, the time has come when far-seeing industrial leaders begin to see that ultimate success depends as much on the welfare and efficiency of the many that work as on the few that supervise.

# A COMPARISON OF THE NUMBER OF HOOKWORM OVA IN THE STOOL WITH THE ACTUAL NUMBER OF HOOKWORMS HARBORED BY THE INDIVIDUAL[1]

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The relation between the number of hookworm ova in the stool of an individual and the actual number of hookworms harbored in the intestines is not constant. In a previous communication (1), we reported experiments in which many individuals were found negative by the routine microscopic test and yet yielded large numbers of hookworms on treatment.

One criticism of this study was that the routine microscopic examination of feces as carried out in field hookworm posts is subject to errors for which the microscopist himself is not responsible. For example, when one distributes a number of specimen tins to illiterate individuals of the same family, certain errors in collection of the stools are almost sure to occur because the patients cannot read their own names on the tins and the specimens therefore become mixed. Thus, though the microscopic examinations are carefully made, the reports of the microscopist are not correct because of a mistake in collection of the specimens.

The following experiment was planned with the object of determining the relation between the number of hookworm ova in the stools and the actual number of hookworms harbored by a group of individuals in which the possibility of extraneous error

[1] The studies described in this paper were made under the auspices of the Laboratory of Hygiene, Faculty of Medicine and Surgery of São Paulo, and were carried out during the progress of a joint campaign for relief and control of hookworm disease conducted by the International Health Board of The Rockefeller Foundation, the government of the State of São Paulo, and the Federal Government of Brazil.

was reduced to a minimum. We desired to study not only the cases reported as negative by the microscope but the positive cases also.

To secure satisfactory results in such an experiment, three factors are desirable: (1) an accurate microscopic technique and a microscopist experienced in hookworm field work; (2) extreme accuracy in the collection of specimens of feces; and (3) the removal of *all hookworms* from those cases in which microscopic examination of the feces has been made.

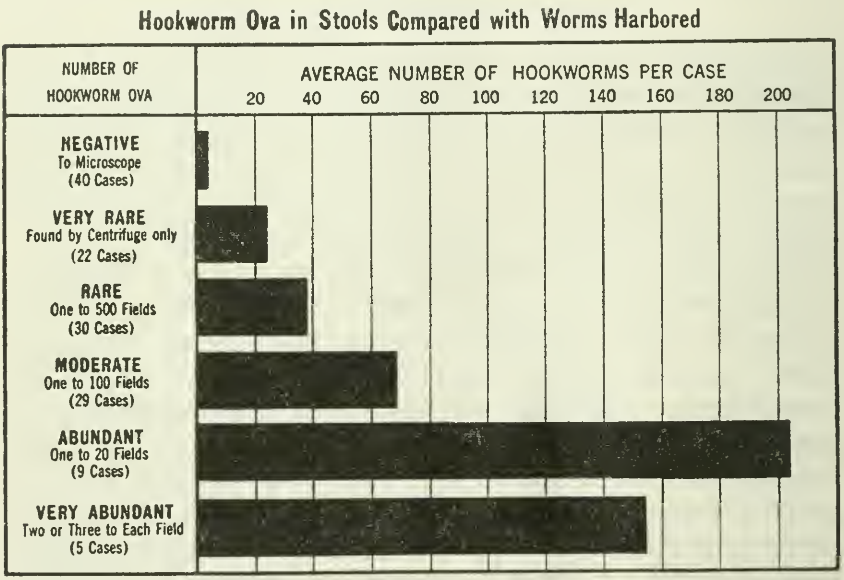


FIG. 1

1. *Technique and choice of microscopist.* The technique used was the method described in detail by Howard (2). Three large slides were made directly from each specimen and in case all three were negative the specimen was centrifuged and re-examined. The movable stage was used in examining the slides. The microscopist chosen was the best of those who have been working with the field units in Brazil. For the past three years he had devoted his entire time to the microscopic examination of feces and had developed an accuracy and rapidity of technique that was almost phenomenal.

The positive cases were classified in the five following general groups, in accordance with the number of ova in the stools:

(1) *Very rare* ova—found only on centrifuging the specimen.

(2) *Rare* ova—only one or two in the three slides examined directly; i.e., one ovum per 500 microscopic fields.

(3) *Moderate* numbers of ova—an average of one to ten ova on each slide, or one ovum to every one hundred microscopic fields.

(4) *Abundant* numbers of ova—one or two being found every time the microscopist crossed the slide laterally with the movable stage; roughly, one ovum every twenty microscopic fields.

(5) *Very abundant* numbers of ova—one to three being found in every microscopic field.

This rough classification gives only approximate results, but for purposes of comparison it is a fair index of the number of ova in the specimens examined.

*2. Collection of the feces.* The tins were distributed in the evening, collected the following morning, and examined within twenty-four hours. Care was taken to guard against error in collection of specimens.

*3. Accuracy in removing all hookworms harbored.* Within three days after the microscopic examinations were made, all cases, negatives and positives, were given a massive test treatment of chenopodium as described by Darling and Smillie (1). All stools were saved for forty-eight hours and the hookworms picked out, counted, andclassified. Thus we were able to learn how many hookworms had been harbored by each individual.

*Results.* There were 135 completed cases, harboring an average of thirty-two worms each. Female and male hookworms were found in almost equal numbers. Ancylostomes and necators are grouped together, since differentiation of the ova in the stools is practically impossible. The microscope showed a 70 per cent positive infection. The treatment test, however, showed an 83 per cent infection. These results are in close accord with our previous findings, and prove that even with very careful technique the microscope fails in a certain per cent of all cases examined—

usually 8 to 12 per cent. Table 1 gives the average number of hookworms harbored by each group of cases.

TABLE 1

*Average number of hookworms harbored by various groups, classified in relation to the number of ova in the stool*

| NUMBER OF OVA | NUMBER OF CASES | AVERAGE NUMBER OF HOOKWORMS PER CASE | PER CENT OF CASES HARBORING 10 HOOKWORMS OR MORE |
|---|---|---|---|
| Cases negative to microscope | 40 | 2.5 | 5 |
| Cases positive, very rare ova | 22 | 23.0 | 50 |
| Positive cases, rare ova | 30 | 38.0 | 70 |
| Positive cases, moderate numbers of ova | 29 | 68.0 | 73 |
| Positive cases, abundant numbers of ova | 9 | 201.0 | 100 |
| Positive cases, very abundant numbers of ova | 5 | 153.0 | 100 |

This table shows that when we consider *general averages*, there is a definite relation between the number of hookworm ova in the stools of a group of infected individuals and the number of hookworms actually harbored by them. When we consider *individual cases*, however, and not *general averages*, we find a great variation, as is shown in table 2.

TABLE 2

*Minimum and maximum number of hookworms harbored by the individuals of various groups studied, in relation to the number of ova in the stool*

| NUMBER OF OVA | NUMBER OF HOOKWORMS HARBORED BY INDIVIDUALS OF EACH GROUP | |
|---|---|---|
| | Minimum | Maximum |
| Negative | 0 | 28 |
| Very rare | 1 | 168 |
| Rare | 1 | 202 |
| Moderate | 1 | 563 |
| Abundant | 41 | 540 |
| Very abundant | 23 | 429 |

Table 2 illustrates several interesting points. It shows that an individual may harbor as many as 28 hookworms and yet his stool may give a negative microscopic result. An individual may present a stool specimen in which the hookworm ova are so rare as to be found only by the centrifuge method and yet he may be harboring as many as 168 hookworms. On the other hand, an individual may harbor only one female hookworm, and yet the microscopic examination of his stool will show considerable numbers of ova—an average of one ova to every 100 fields. These cases are exceptions and not the rule—as is shown by the general averages of table 1—but they do occur frequently, for we found several of them in our small series of 135 cases.

Nineteen of the forty cases which were negative by the microscopic test yielded hookworms on treatment, with a total of 104 worms. Of these worms sixty were females and thirty-four males. In one case male worms only were harbored, thus reducing the microscopic error to eighteen cases. It would seem at first glance that a failure by the microscope in eighteen out of forty cases was a most unsatisfactory result, but this failure is only relative, for the actual number of hookworms harbored by the cases diagnosed as negative was insignificant.

*Discussion.* This series of 135 cases, though small in number, is of value because all the microscopic examinations were made by the same individual, a highly trained microscopist, working with standard methods. They show that there is a general relation between the number of ova in the stools and the number of hookworms harbored. The results also show conclusively that in an individual case no conclusions can be drawn from a single examination of the stools as to the number of hookworms harbored. One individual may have abundant ova and harbor only twenty-three hookworms; another may have so few ova in the stools that they are found only after long and careful search, and yet be harboring large numbers—150 to 200 hookworms.

It is obvious that no matter how carefully done, the routine microscopic examination of a single specimen of feces, under the conditions which obtained in this study, cannot be relied upon as an absolute index as to whether an individual is or is not infected with hookworms. Does this mean that the use of the microscope as a means of diagnosing hookworm disease in the field posts should be discarded?

This question may be answered by considering the relative failure of the microscope in our series. In a previous study (3) I have set an arbitrary number of ten hookworms harbored as an insignificant infection, and of no consequence to the individual. Using this number as an index, we find that of those cases diagnosed as negative by the microscope only two were relative failures (table 1). We may consider this a very satisfactory showing. It is interesting to note that twenty-four individuals, or 25 per cent of the cases diagnosed as positive by the microscope, also harbored less than ten worms.

Let us imagine that this group of 135 cases had been examined and treated in the routine way by the field post laboratory. Only two cases harboring more than ten worms would have escaped treatment, while twenty-four positive cases harboring less than ten hookworms each would have received treatment for a few hookworms which were doing them an insignificant amount of harm. Therefore microscopic examination of the stools, though slightly fallible in individual cases, is nevertheless a convenient method for estimating the relative degree of hookworm infection in a *group*. A small per cent of cases harboring hookworms will escape diagnosis and treatment; a larger per cent will receive vigorous treatment for a few hookworms that are not doing them serious harm.

The results of these experiments are suggestive in relation to preliminary hookworm surveys of new fields. In making a hookworm survey of a new field the fact that interests us most is not the per cent of individuals *infected with hookworms*, but the per cent of individuals who have *hookworm disease*. This information can be determined most accurately by the worm count method; that is, by treating considerable numbers of people and counting their worms. The worm count method is a tedious and difficult process, however, and cannot be adopted as a routine procedure. If, after examining a much larger group of cases than the present series, we shall find that there is a definite and constant relation between the number of hookworm ova in the stools and the number of hookworms actually harbored, it will then be an easy matter to formulate a simple standard routine microscopic method of estimating ova in the feces of—let us say—2,000 individuals of a given community, the results of which would give us an approximate index as to the *degree* of hookworm infection of that community. I believe that the 135 cases here reported are too small a series from which to draw broad conclusions. The results are suggestive, however, and stimulate further study of the problem.

## CONCLUSIONS

1. When the cases were considered in groups there was a definite relationship between the number of ova in the stools and the number of hookworms harbored.

2. When the cases were considered individually, a trend toward such a relationship was noticeable, although the number of ova in the stools frequently gave no trustworthy index to the number of hookworms harbored.

3. The present investigation, involving only a small number of cases, suggests that a further study, dealing with a much larger number of cases, may eliminate statistical irregularities and have the very desirable result of establishing a fairly constant and direct correlation between ova in the microscopic field and the parasites in the intestine.

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# THE TERTIAN CHARACTERS OF QUOTIDIAN AESTIVO-AUTUMNAL FEVER

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In my paper on (1) Experimental Inoculation of Malaria by Means of *Anopheles Ludlowi*, the opinion was expressed that *Plasmodium falciparum* possesses inherently both tertian (or subtertian) and quotidian tendencies, as well as its well known tendencies to cause fever of the irregularly remittent or continued type.

The opinion was based on the study of two uncomplicated experimental cases inoculated with mosquitoes reared from larvae and infected with a pure strain of *Plasmodium falciparum*. Quinine was withheld for a period and temperatures taken every hour.

The initial paroxysms were tertian in time, the subsequent ones quotidian. The essential tertian character of the paroxysm, however, was never lost.

It is a painful and a serious matter to withhold quinine from very ill patients. Consequently when it was seen that temperatures were rising angrily the infection was checked. The observations therefore were confined to periods of four and six days only, but the time was sufficient to permit the development of a febrile course which lead to the opinion expressed above.

On account of their acute illness and the imminent danger of pernicious symptoms manifesting themselves, patients are dosed with quinine without delay. There consequently arise few opportunities for observing the types of temperature curves in *Plasmodium falciparum* infections.

### TEMPERATURE CURVE IN TERTIAN AESTIVO-AUTUMNAL FEVER

Craig (2), who has been a close student of malaria, has described in a recent publication some of the characteristics of the temperature curve in what may be termed the classical types of infections with *Plasmodium falciparum* or those types described by Italian investigators. He has also published some charts of quotidian fever which will be analyzed. He says:

> The temperature rises rapidly to 102°, 103° F. or higher. Following this rapid rise there occur slight oscillations in the temperature covering several hours, during which time it may fall from 0.5 to 1.°F. This period of oscillation is followed by a distinct fall or pseudo-crisis the temperature generally dropping from 1.5° to 2° or even 3° and this fall in the temperature is often mistaken for the true crisis.
>
> However the temperature again rapidly rises often to a height greater than that attained during the initial rise and then falls rapidly to normal or even below normal.

Craig notes also that "when the pseudo-crisis is very marked the temperature may fall to almost normal, and in these cases the temperature curve may resemble that due to the quotidian subspecies, there being apparently a quotidian rise in temperature." He states "that the actual febrile period in this type of infection is much longer than it is in infection with any other species of Plasmodium covering practically the greater portion of forty-eight hours."

This is often true, but "when the pseudo-crisis is very marked," the actual duration of fever is much diminished and in my experimental cases lasted as short a period as six or ten hours.

In severe infections the temperature may be continuous. Dosage and tolerance play a part in malarial infection as they do in other infections, for all grades of fevers are encountered from the severe or pernicious irregularly continued type to a milder tertian or quotidian form. In my experimental cases the duration of time of elevated temperature was shorter in the initial paroxysms when parasites were sparser in the peripheral blood.

Infections by *Plasmodium falciparum* of the tertian type are often characterized by a pronounced remission which breaks the continuity of the fastigium.

Tertian periodicity is best shown when either the first or second rise is abortive.

Marchiafava Bignami and Craig have named some of the essential parts of the curve in the tertian paroxysm as follows:

1. The initial rise
2. The period of oscillation
3. The pseudo-crisis
4. The precritical rise
5. The true crisis

But as the decline in temperature is often more suggestive of lysis than crisis and as some attention must be paid to other parts of the febrile wave, I have in mind for description and analysis the following points:

1. The first rise
2. The first crest
3. The first decline
4. The first trough
5. The second rise
6. The second crest
7. The second decline
8. The second trough

Under favorable circumstances certain features of the temperature curves become conspicuous.

The rise of temperature is usually more abrupt than the decline.

The temperature does not abruptly fall at the end of the paroxysm but usually takes some eight to sixteen hours. This gives to the curve of the second decline a more or less convex appearance and in some cases this line is broken by small shelves in which the fall of temperature is arrested.

The remission of temperature between the first and second crests varies greatly in extent from less than a degree to 2 or 3 or more degrees and sometimes reaching normal or subnormal. But usually never reaching so low a point as is attained by the fall at the end of the paroxysm. The bottom of the first trough therefore is usually higher than the lowermost point in the second trough, which point marks the end of the paroxysm and indicates its tertian periodicity.

The first or second crest may be abortive or subliminal. In subject 1, text figure 1, of my experimental cases, the second crest of the first paroxysm is abortive, the temperature rising to only 0.4° above normal. In subject 3, text figure 3, the second crest of the first paroxysm is abortive while in the second paroxysm, the second crest is subliminal and remains quite below 98° F., but hourly temperature records show that it is nevertheless a crest. It is in this graph that the tertian character of the paroxysm is best shown; this is due to the relative prominence of the first crest in each of the first two paroxysms.

Tertian periodicity may be fixed by the station of either one of the crests. That is to say, the first crest will tend to recur every other day at a certain hour. The second crest on every other succeeding day will tend to correspond with another certain hour, thus in Craig's chart III, the top of the first rise occurs at 21 o'clock (9 p.m.) every other day, i.e. 23rd, 25th, and 27th. In chart II there is a tendency for the first crest to occur every other day at 21 o'clock (9 p.m.) on the 24th, 26th, and 28th. The second crest tends to occur every other day from 12 to 15 o'clock on the 25th, 27th, and 29th.

The second trough is wider than the first and serves to mark tertian periodicity, for the lowermost point of this trough corresponds with a certain hour every other day.

It must be noted that while there is a tendency for all the first crests to synchronize with one another they do not synchronize with the second crests. First and second crests are usually quite independent of each other in the hours of their occurrence.

One of the minor shocks experienced by students of malaria is that sporulation and temperature do not always correspond with text book schedules; they do not always promptly occur at intervals of 24, 48, and 72 hours. In practice one observes a good deal of acceleration or anticipation and retardation.

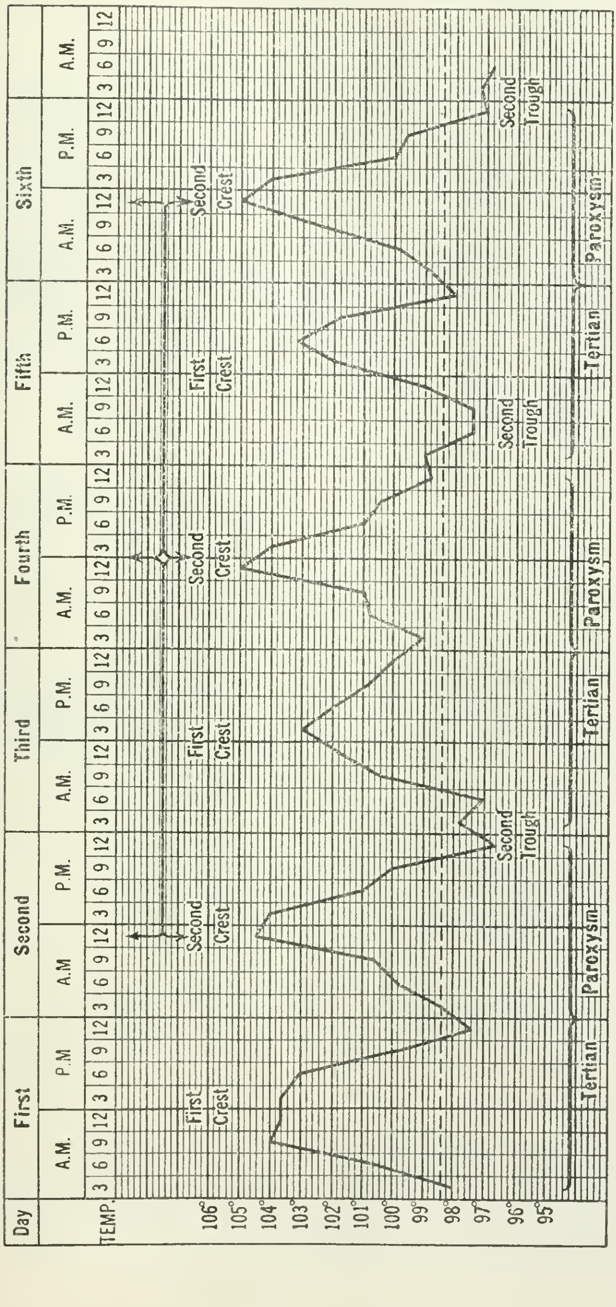


FIG. 1. The chart is a reproduction of Craig's chart VI—Temperature curve quotidian aestivo-autumnal malarial fever, but with indications on the graph of the crests and trough.

Note, that there are three tertian paroxysms.

The second crests display a tertian periodicity recurring every other day at 12 o'clock. The first and third second troughs synchronize. The second one is retarded.

In subject 3 the occurrence of three events was as follows:

| FIRST CREST | SECOND CREST | SECOND TROUGH |
|---|---|---|
| 16th day 23 o'clock | 17th day 18 o'clock | 18th day 9 o'clock |
| 18 " day 21 o'clock | 19 " day 18 o'clock | 20 " day 8 o'clock |
| 20 " day 19 o'clock | 21st day 18 o'clock | 22nd day 8 o'clock |
| 22nd day 15 o'clock (quinine) | 23rd day 18 o'clock (quinine) | 24th day 8 o'clock |

In subject 3 while the second crest remains fixed at 18 o'clock the first crest occurs earlier on each successive alternate day. This acceleration of the time of occurence of the first crest increases the width of the gap between the first and second crest and gives the graph a more distinct quotidian appearance.

The three events in subject 1:

| FIRST CREST | SECOND CREST | SECOND TROUGH |
|---|---|---|
| 15th day 18 o'clock | 16th day 16 o'clock | 17th day 4 o'clock |
| 17 " day 16 o'clock | 18 " day 19 o'clock | 19 " day 7 o'clock |
| 19 " day 13 o'clock (quinine) | 20 " day 16 o'clock (quinine) | 21st day 4 o'clock (quinine) |

Apparently second crest and second trough appear to be better fixed than first crest. This is not always the case for in Craig's chart I, II, and III, the first crest is more constant.

| | FIRST CREST | SECOND CREST | SECOND TROUGH |
|---|---|---|---|
| Case I.. | 17th day 20 o'clock | 18th day 12 o'clock | 18th day 8 o'clock |
| | 19 " day 20 o'clock | 20 " day 8 o'clock | 20 " day 16 o'clock |
| | 21st day 16 o'clock | 22nd day 12 o'clock | 23rd day 8 o'clock |
| | 23rd day 20 o'clock | 24th day 16 o'clock | 26th day 8 o'clock (quinine) |
| Case II. | 24th day 21 o'clock | 25 " day 15 o'clock | 26 " day 6 o'clock |
| | 26 " day 21 o'clock | 27 " day 12 o'clock | 28 " day 6 o'clock |
| | 28 " day 21 o'clock | 29 " day 12–15 o'clock | 30 " day 9 o'clock (quinine) |
| | 30 " day 18 o'clock | 31st day 6 o'clock | |
| Case III | 23rd day 21 o'clock | 24th day 15 o'clock | 25 " day 9 o'clock |
| | 25th day 21 o'clock | 26 " day 9 o'clock | 27 " day 3 o'clock |
| | 27 " day 21 o'clock | 28 " day 12 o'clock | 28 " day 21 o'clock (quinine) |
| | 29 " day 18 o'clock | 30 " day 9 o'clock | |

In these three tertian charts of Craig's it is evident that the first crest is the better fixed of the two.

Some of the irregularity or lack of synchronism noted is due to inherent irregularity of the Plasmodium; some of it would have disappeared had temperatures been recorded oftener than every three or four hours.

It is evident that one of the crests in malignant tertian fever exhibits a better tertian time periodicity than its fellow. Sometimes this is the first crest, at other times it is the second crest.

The fixed or constant crest preserves the tertian periodicity of the paroxysm and gives the impression that part of the febrile wave is due to a tertian liberation of toxin, protein or melanin and partly due to unbalanced heat regulation.

The heat regulation factor is so complicated that it does not precisely correspond with the evident tertian periodicity of sporulation as indicated by one of the crests.

*Width in hours measured from crest to crest*

| | TROUGH 1 | TROUGH 2 | INTERVAL BETWEEN SECOND TROUGHS |
|---|---|---|---|
| Subject 1 | 22<br>27<br>28 av. 25.6 | 24<br>18 av. 21 | 51<br>45 av. 48 |
| Subject 3 | 21<br>23<br>25<br>29 av. 24.5 | 27<br>25<br>21 av. 24.3 | 47<br>48<br>48 av. 47.6 |
| Craig I | 16<br>12<br>20<br>20 av. 17 | 28<br>37<br>32 av. 32.3 | 44<br>64<br>44 av. 50.6 |
| Craig II | 18<br>15<br>18 av. 17 | 24<br>33<br>27 av. 28 | 48<br>51 av. 49.5 |
| Craig III | 18<br>12<br>15<br>15 av. 15 | 30<br>36<br>30 av. 32 | 42<br>42<br>45 av. 43 |

Useful information may be obtained by noting the duration of time between the first and second crests and between the second and first crests, that is the first and second troughs.

The actual duration of the paroxysm may be ascertained by noting the time interval between the lowermost points of successive second troughs.

In my experimental cases of tertian aestivo-autumnal fever the first trough is a little wider than the second while in Craig's I, II, and III, the first trough is always narrower and more shallow than the second trough. Yet the duration of the paroxysm as marked by the lowermost point of the second troughs is approximately 48 hours in Craig's and my cases.

With some of these points in mind, Craig's quotidian aestivo-autumnal charts may be analyzed.

## TEMPERATURE CURVES IN QUOTIDIAN AESTIVO-AUTUMNAL FEVER

It is seen at first glance that chart VI is distinctly tertian in its general appearance. In fact it might be regarded as being more tertian than quotidian for the second crest corresponds with 12 o'clock on alternate days while the first crest neither synchronizes with 12 o'clock nor with other crests of the first crest series. This is as is shown above a characteristic of tertian aestivo-autumnal fever. Moreover, the first trough never reaches so low a point as the second trough does, which latter marks the end of a tertian paroxysm.

The greater depth of the second trough in this chart is a characteristic of tertian aestivo-autumnal fever.

Tertian characteristics can be detected in chart V also. It is made up of $3\frac{1}{2}$ tertian paroxysms. The first peak represents the second crest of a paroxysm not fully recorded on the chart. Peaks 2 and 3 represent respectively first and second crests and so on.

The second troughs dipping below the line of normal temperature and marking the end of paroxysms occur with tertian periodicity, that is at 3 a.m. on the 3rd, 5th, and 7th days.

The convexity of the second decline may be noted and compared with tertian charts.

All of the crests synchronize with 12 o'clock giving the chart a pronounced quotidian appearance, nevertheless tertian characters are present.

In chart IV there would seem at first to be no tertian characteristics, but the eye catches the convexity of the second decline. Searching for the lowermost troughs, the second, fourth and sixth troughs appear to be slightly lower than the others. This would seem to divide the chart into $3\frac{1}{2}$ paroxysms. Timing the troughs, it is seen that the second trough corresponds with 6 o'clock (6 a.m.) on the 27th, 29th and 31st days. Certainly a tertian periodicity, while the tertian time correspondence of the second trough is most precise. The quotidian crests are not so happily disposed, for they do not all correspond with a certain hour as they probably should if the plasmodia sporulate in twenty-four hours. But we note as in tertian aestivo-autumnal fevers that there is a tendency for certain crests to correspond with a certain hour, but not with each other. For example—in chart II (tertian fever) the first crests show a tendency to correspond with 21 o'clock while the second crests correspond with 12 to 15 o'clock. So in this chart, no. IV of quotidian fever the first crests have a tendency to correspond with 18 o'clock reaching it on the 25th, 27th and 31st days, missing it on the 29th.

The second crests show a tendency to correspond with 15 o'clock, reaching it on the 26th, and 30th. For some reason the first and second crests are disturbed on the 28th and 29th days, being anticipated in time, six and three hours. By analysis even this apparently unpromising chart has revealed sufficiently well-marked tertian characters.

In these charts we are struck by the fact that the quotidian charts resemble the tertian charts in the time correspondence of crests and troughs and that they differ chiefly in the depth of the first trough.

There is a gradual deepening of the first trough and a concomitant appearance of the quotidian character or periodicity as we pass from tertian to quotidian charts in the following order: Nos. I, III, II, VI, V, IV. These charts may be still further examined with regard to time of occurrence of crests and troughs and the duration of the first and second troughs.

| | FIRST TROUGH | SECOND TROUGH | INTERVAL BETWEEN SECOND TROUGHS |
|---|---|---|---|
| Craig IV.... | 25th day 18 o'clock<br>27 " day 18 o'clock<br>29 " day 12 o'clock | 26th day 15 o'clock<br>28 " day 12 o'clock<br>30 " day 15 o'clock | 27th day 6 o'clock<br>29 " day 6 o'clock<br>31st day 6 o'clock |
| Craig V..... | 3rd day 12 o'clock<br>5th day 12 o'clock | 4 " day 12 o'clock<br>6 " day 12 o'clock | 3rd day 3 o'clock<br>5th day 3 o'clock<br>7 " day 3 o'clock |
| Craig VI.... | 1st day 9 o'clock<br>3rd day 15 o'clock<br>5th day 18 o'clock | 2nd day 12 o'clock<br>4th day 12 o'clock<br>6 " day 12 o'clock | 2nd day 24 o'clock<br>5th day 6 o'clock<br>6 " day 6 o'clock |

While the periodicity in these charts is quotidian it is not any more regular than is the periodicity of the crests in tertian aestivo-autumnal fever, and we note a lack of synchronism between the successive crests that is those designated first crest and second crest.

Width in hours of first and second troughs measured from crest to crest, and interval between lowermost points of the second troughs.

| | FIRST TROUGH | SECOND TROUGH | INTERVAL BETWEEN SECOND TROUGHS |
|---|---|---|---|
| Craig IV.... | 21 hours<br>18 hours<br>27 hours av. 22 | 27 hours<br>24 hours<br>27 hours av. 26 | 48 hours<br><br>48 hours av. 48 |
| Craig V..... | <br>24 hours<br>24 hours av. 24 | 24 hours<br>24 hours<br>27 hours av. 25 | <br>48 hours<br>48 hours av. 48 |
| Craig VI.... | 27 hours<br>21 hours<br>18 hours av. 22 | 27 hours<br>30 hours<br>— hours av. 28.5 | <br>54 hours<br>42 hours av. 48 |

There is decided lack of uniformity when the first and second troughs are compared. The second trough is decidedly wider than the first trough as in tertian aestivo-autumnal fever, and it can be observed that while there is a lack of uniformity between the two troughs, there is a remarkable uniformity in the intervals between the lowermost portions of successive second troughs. This interval is forty-eight hours and corresponds closely with the interval seen in tertian aestivo-autumnal fever.

There seems to be greater uniformity to the points of lowest temperature, than to highest (crests) for it can be seen that the lowermost points of the first troughs are also separated uniformly by a time interval of forty-eight hours.

A final comparison can now be made between the various time intervals and time periods of the troughs in the three sets of charts and the points already referred to above may be noted. In this table the duration of time of the two troughs and the length of time interval between second troughs are averaged in each instance from the number of cases. The average duration of the troughs in quotidian fever instead of being 24 hours are 22.5 and 26.2 for first and second troughs which is strongly, suggestive of tertian time division of the parts of the paroxysm.

| | DURATION IN TIME | | |
|---|---|---|---|
| | First trough | Second trough | Interval between second troughs |
| | *hours* | *hours* | *hours* |
| Craig: Charts I, II, III average of three cases | 16.2 | 30.7 | 47.5 |
| Craig: Charts IV, V, VI average of three cases | 22.5 | 26.2 | 48.0 |
| Darling: Experimental cases 1 and 3 average of two cases | 25.0 | 23.0 | 47.8 |

## CONCLUSIONS

Malignant tertian or aestivo-autumnal malaria caused by *Plasmodium falciparum* may exhibit irregular, continued, tertian or quotidian fever curves.

These different curves may depend to some extent on dosage and tolerance but when temperatures are taken every hour or two under favorable circumstances a tertian character or periodicity may be detected in certain cases.

The tertian characters of special interest are:

Tertian periodicity of one or other of the crests, the first crest may be the most constant one.

Tertian periodicity of the second trough or lowest point reached by temperature after the paroxysm.

Quotidian fever may be found to have tertian characters when the periodicity of crests and second troughs is ascertained.

Three charts of quotidian aestivo-autumnal fever published by Craig as being caused by a subspecies, *Plasmodium falciparum Quotidianum* Craig, 1909, are analyzed and are shown to possess tertian characters.

On account of the inherent difficulties in differentiating some malarial plasmodia, absolutely, by microscopic methods and in view of the above findings, I feel that I am justified in repeating the opinion expressed before (1):

"That the creation of a specific plasmodium to account for clinical forms of aestivo-autumnal malaria having a quotidian periodicity is probably unwarranted."

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(1) Darling, S. T.: Jour. Exp. Med., 1920, xxxii, 313.
(2) Craig, C. F.: The classification and differential diagnosis of the aestivo-autumnal malaria plasmodia. Am. Jour. Trop. Med., 1921, **1**, 57.

## BOOK REVIEWS

*Sanitary Entomology, the Entomology of Disease, Hygiene, and Sanitation.* Edited by WILLIAM DWIGHT PIERCE, Consulting Entomologist, U. S. Department of Agriculture. Boston, Richard G. Badger, (1921). 518 pp., 28 pls., 88 figs. in text. $10.

Interest in sanitation resulting from the desire of entomologists of the United States to contribute to the efficiency and success of the Allied armies in the World War is responsible for this book. It originated as a mimeographed text in 1918, sent out to over 500 members of a voluntary class of entomologists aspiring to prepare themselves for sanitary service along entomological lines. The work is a coöperative one, the contributors all being members of the staff of the Bureau of Entomology, United States Department of Agriculture, with the single exception of Dr. H. A. Ballou, Imperial Entomologist, Barbados, who contributes the chapter on "Flies and Lice in Egypt." Dr. W. D. Pierce is the editor of the entire work and the contributor of 19 of the 35 chapters dealing with such subjects as How insects can carry or cause disease, necessary steps to prove insect transmission of disease, the needs of entomological sanitation in America, the seriousness of insect-borne diseases to armies, the relations of climate and life to medical entomology, the diseases borne by, and the life histories of the non-biting flies, the control of the housefly and related flies, diseases transmitted by, and biological notes on the bloodsucking flies, diseases transmitted by mosquitoes, mosquito control, diseases borne by lice, fleas, cockroaches, the bedbug and other bloodsucking bugs, and by mites and ticks, insect poisoning, and a tabulation of diseases transmitted by insects. Dr. Pierce collaborates with Mr. C. T. Greene in a chapter on the biology of mosquitoes and with Mr. R. H. Hutchison in an account of the life history and control of human lice. Dr. B. H. Ransom writes a critical and informing chapter upon the relation of insects to the parasitic worms of vertebrates. Mr. F. C. Bishopp treats of the control of flies in barn yards, pig pens and chicken yards, of the causes, prevention and treatment of myiasis, the life history and control of fleas, and the biology, habits and control of ticks. Mr. J. L. Webb discusses the biology and habits of horse flies, and Mr. S. H. Lamson deals with the lice affecting domestic animals. Mr. A. N. Caudell writes on cockroaches and Mr. E. W. Laake recounts the rather repulsive relations of insects to the packing house industry.

This book is invaluable to all workers in tropical sanitation because of the relatively larger significance of insects to disease in warmer climates as compared with that in the cooler ones. The tropics favor the rapid multiplication of insects, their persistence throughout longer periods of the year, their prevalence in great numbers because of the abundance of vegetation and animal life upon which they depend. Insects loom large in the tropics also because of the low stage of development of hygiene and sanitation among tropical peoples, especially as regards the use of human excreta in agriculture and resulting pollution of soil and water, which combined with irrigation prove ideal conditions for multiplication of man's worst insect foes, the fly and mosquito. This book is the most comprehensive compilation of much that has been written on the relations of insects to disease, has extensive bibliographies, especially of the American work, and is full of valuable suggestions for the sanitarian, epidemiologist, pathologist, bacteriologist, protozoologist and helminthologist, whose fields it necessarily overlaps to varying degrees.

As a compilation covering so large a field and prepared under the stress of a great emergency, it has the faults of its qualities. In the present state of progress in investigation, and of literature and bibliographies, with the disruptions attendant upon the war, it is an almost superhuman task to critically review the field covered by this work, and much more so for a group of entomologists alone to attempt it. The authors have had the coöperation of Dr. Ransom in his critical contribution on the relations of insects to the helminth infections of vertebrates but their work lacks such contributions from the bacteriologist, protozoologist, and epidemiologist, and is therefore at times uncritical in the fields of these specialists.

The mass effect of the vast amount of detailed evidence that insects may mechanically for a time carry the active or encysted stages of organisms which are etiological factors in disease, or be their facultative or obligatory hosts, is so great that even the biologist, much more the novice in sanitation, may be inadequately impressed by the fact of the widespread occurrence of normal parasites among insects and also of the fact that the spores, cysts, eggs and larvae of the disease-producing organisms of vertebrates may be harbored not only by insects, but also by other animals in contact with excreta, offal, and polluted soil, such as the sow bugs, earthworms, robins, gulls, pigs and rodents. Furthermore, the *relative sanitary significance of all such carrier action* is of fundamental importance in preventive medicine. At the best, it is difficult in the present stage of our knowledge in these fields to attain the scientifically correct perspective of such relative significances, and the reader of such a compilation as this must be on his guard to segregate the important from the unimportant, the proven from the hypothetical, and the possible, but as yet merely suggestive, from the erroneous. The mere fact that data, conclusions, inferences, or a mere hypothetical suggestion has once appeared in print is no scientific justification for repeating it. Error rides a fleet horse, truth follows afoot. The inclusion in the table of diseases transmitted by insects of eczema and the unqualified statement that it is transmitted by the direct attack of *Pediculus corporis* is a case in point, and no amount of general prefatory demurrer of responsibility justifies the perpetuation of this error *without correction*.

The user of the work must not rely upon the bibliographies as complete or even representative. For example, Hart's (1895) careful account of Tabanidae of the Illinois River is omitted in the bibliography of the horse flies. Minchin's (1915) epoch making investigation of *Trypanosoma lewisii* in the rat flea is omitted in that of diseases transmitted by fleas, and the crowning act of omission is that of Schaudinn's (1902) most fundamental discovery of the life cycle of *Plasmodium* in the mosquito. Incidentally there is no reference of methods of mosquito control at Panama, or to the work of Ross or Watson or Herms in this important field. Laveran's (1917) critical discussion of insect transmission of leishmanioses is apparently unknown to the writers as is also the discovery in California of a trypanosome in the kissing-bug, closely allied to that of Chagas found in *Triatoma* in Brazil and reputed to be the cause of Brazilian infantile trypanosomiasis.

While it is true that the mere presence in the digestive tract of the fly of active forms, spores, cysts or ova of human parasites render the fly a *potential* menace to the health of man, it does not follow, until proved by experiment that the menace is an actual one. For example, the work of Wenyon and O'Connor (1916) and of Root (1920) has shown that cysts of protozoans pass through the digestive tract of the fly in a viable state (as shown by eosin staining). We still await proof, however, that such parasites will later excyst and are still uninformed as to the relative *sanitary* importance of water or air borne cysts, fly borne cysts, rodent carriers, and the dirty hand of the food handler, as the medium of infection in human intestinal amoebiasis and flagellosis.

As a piece of book-making, some features call for criticism. Editing has not eliminated some unfelicitous phrases, such as "entomology sanitation." The date of the book, which the user is certainly entitled to know, is omitted from the title page and preface and is found only in the statement of copyright. Some of the illustrations, especially the half tone plates, are inexcusably indistinct and a few of them, as for example plate 9 "Carcass partly destroyed by larvae of the American screw-worm fly," have so little scientific or practical value that they ought to have been omitted so as to reduce the already large cost of the book. Many of the otherwise excellent diagrams of life cycles are so labelled and so reduced in reproduction as to bring some of the lettering to the size of 4-point type, a condition readily avoided by forethought in location of labelling and with very little increased demand for space. There is no correlation between the pagination of the preface (pp. i–xxvi) and that of the text proper (p. 20). The bibliographies vary in the matters of inclusion of and translation of titles, in citations, and very much in completeness and scope.

Notwithstanding these minor defects, the book will be a useful addition to the library of every one interested in sanitation and preventive medicine and should stimulate interest in this very important field of applied entomology.

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# TRANSACTIONS OF THE AMERICAN SOCIETY OF TROPICAL MEDICINE, SEVENTEENTH ANNUAL MEETING HELD AT HOT SPRINGS, ARKANSAS, NOVEMBER 14 AND 15, 1921

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# PRESIDENTIAL ADDRESS[1]

JOHN M. SWAN

*Rochester, New York*

In calling this, the seventeenth, annual meeting of the American Society of Tropical Medicine to order, I wish to express the pleasure that I feel, in common with all of our members, in holding the meeting conjointly with the annual gathering of the Southern Medical Association. Those whom you have chosen to manage the affairs of the Society have for several years had this intimite relationship in mind and, indeed, the two societies would have met together in 1918 had it not been for the pandemic of influenza which made such demands on the medical profession that it was thought wise to abandon the meeting altogether. I wish, with the consent of the Council, to invite the members of the Southern Medical Association to attend our sessions and to take part in our discussions.

The problems that have interested us since the foundation of the Society are the problems that interest you as practitioners in the southern portion of the United States. Your land is not situated within the tropics; but the entire United States south of the thirty-ninth parallel of latitude has a subtropical climate and is exposed, and will be more and more exposed as commerce increases, to all the tropical epidemic diseases. Indeed Baltimore, Philadelphia and New York have had epidemics of yellow fever and are open to plague, or would be were it not for that efficiently watchful sentinel, the United States Public Health Service. The problems which these diseases present, however, are spasmodic, and even in cities as far south as New Orleans and Galveston, not urgent. Malaria, on the other hand, is a con-

[1] Delivered at the seventeenth annual meeting of the American Society of Tropical Medicine, held at Hot Springs, Arkansas, November 14 and 15, 1921.

stant menace, not only in the tropics but also in all subtropical climates and in many communities within the temperate zone.

It is impossible to estimate the economic loss due to malaria; but it is appallingly large. In the Anderson-Cottonwood Irrigation district in Shasta County, California, Gray found that approximately one-half the population had malaria in 1918; the total cost to the district was estimated at $10,400 or $31.70 per family, $14.05 per sick person, or $7.66 per person. The estimate did not take into account the deaths, the labor loss among casual workers, losses due to inability to handle crops at the proper time, losses due to vacant property or losses due to depreciation of property. Large as it is, it might be accepted and the progress of the communities in which it is present would continue, thanks to the ability of the human will to overcome obstacles. The loss is, however, preventable. Since the discovery of the plasmodium by Laveran, in 1880, the researches of the host of malaria students, among whom four former presidents of this Society, Gorgas, Thayer, Craig and Bass, occupy illustrious positions, have made the facts of the etiology, pathology, clinical course, diagnosis, treatment and prophylaxis of malaria matters of common knowledge. Malaria is a disease the course of which is known and is easy of detection; the treatment of which is, in the great majority of cases, simple; the prevention of which has been repeatedly demonstrated to be possible, and the eradication of which has been repeatedly successfully attempted. Therefore, the control of this infection is a goal eminently worth striving for. There are four factors in the campaign for malaria control that will occupy the attention of those engaged in the work: (1) the reporting of cases in the acute stage of the disease to the health authorities; (2) the treatment of patients in the acute stages of the infection; (3) the detection and treatment of carriers; (4) the destruction of anopheles mosquitoes, not only as adult insects, but also by abolishing their breeding places.

The first essential in the reporting of acute cases of malaria is to have an accurate diagnosis. To this end every physician who practices in a malarial country should be able to stain a specimen of blood for the plasmodium and to recognize the organism in the stained specimen. It will no longer suffice for a diagnosis to be made merely because the patient has fever. A recent writer in the *Journal of Tropical Medicine and Hygiene* says: "Fever is such a commonplace of tropical practice that it does not always receive the attention that it deserves. Malaria is considered a safe diagnosis for any fever which is not acute and the origin of which is uncertain;" and Leathers has said that at least 25 per cent of the diagnoses of infectious diseases is incorrect.

It has been said, and it undoubtedly will be said that it will be impossible to have cases of malaria in the acute stage of the disease reported and that it will be impossible to get an accurate report of carriers. Such statements have been made about every disease that is now reported as a matter of course, including gonorrhea and syphilis. It is not impossible to obtain reports, and accurate reports, of any disease once the attempt is made in earnest.

The treatment of the acute attack of malaria is comparatively simple. It is known that quinine in solution in the blood serum will kill the plasmodium in its sporulating stage, on account of its property as a protoplasmic poison. The difficulty in the treatment arises from the fact that the plasmodium reproduces by two methods: the asexual and the sexual. It is the sexual form of the organism, the gametocyte, that escapes destruction by quinine. It is this form of the parasite that is retained in the capillary blood spaces of the bone marrow and the spleen, perhaps of the liver, and possibly of the other viscera, which later assumes the asexual method of reproduction and produces the clinical relapses.

It is for the destruction of these forms; these gametocytes, that the treatment has been too frequently prematurely discontinued. The standard treatment of malaria developed by Bass and his coworkers is to be recommended as the method for destroying the plasmodium in its human host, sporocyte and gametocyte, and so relieving the community of its carriers.

In relation to the problem of the carrier it must be remembered that children are subject to malaria, as are adults, and that the disease occurs also in infants. Two cases of tertian malaria in infants under six months of age were reported by Bloom in 1918. A parallel may be drawn between this disease and yellow fever, which is propagated in its endemic foci by cases in children; in whom its manifestations are usually irregular.

A great deal has been written about the destruction of anopheles mosquitoes. It can be done; it has been done. In 1915 I referred in a paper read at the meeting of this society held in San Francisco, to the work of Ross, in Mauritius. Ross estimated that for an expenditure of 0.36 rupee or about 11.6 cents per head of population per annum a place like Mauritius should expect to have its malaria morbidity and mortality very much reduced. In the last six years the cost of everything has increased. Recent work in the southern States has been done at a cost of 80 to 85 cents per capita. This cost includes the original outlay for drainage which will not reappear in the continuation of the work for subsequent years and which might be charged to general agricultural improvements. Gray, in the paper already referred to, estimates that in the district in which his study was made a charge of $31,000.00 might be expected for the various control measures for a 3 year period; but he adds that $12,000.00 of this should be deducted for agricultural drainage and should not be charged against malarial prophylaxis. Then he adds: "These figures show and the experience of other districts proves that it is economically cheaper to control malaria than to suffer from it." So that for three years an outlay of $19,000.00 for malarial prophylaxis with an annual expenditure of $3,800.00 after that would almost rid of malaria an area of 32,000 acres with a population of 1300.

The United States Public Health Service, the International Health Board and the Health authorities of ten southern states are at present engaged in an attack on the malaria problem which I have no doubt, will eventually result in the reduction of malaria to its very lowest point, if it does not abolish it. The organization within the United States Public Health Service is known as the Malaria Field Investigations with headquarters at Memphis, Tennessee, directed by Surgeon L. D. Fricks, assisted by Dr. M. A. Barber and senior sanitary engineer J. A. LePrince. The following problems are now engaging the attention of this organization: The longevity of anopheles mosquitoes; The viability of malaria parasites in mosquitoes; The blood picture of malaria; The relation of domestic animals to the transmission of malaria; Observations on the dispersion of anopheline mosquitoes; Winter activities of anopheline mosquitoes; Observations relative to early seasonal transmission of malaria; Observations on seasonal prevalence of different anopheles species; Larvicide experiments; Rice field investigations.

In 1920 a total area of 192 square miles was under control with a population of almost 200,000. This year malaria surveys have been made in 118 urban communities in ten different states and from these surveys 25 towns have been selected for new malaria control demonstrations; an area of 75 square miles with a population of 70,000. Furthermore, investigations are being made as to the possibilities of malaria control in rural districts in Virginia, North Carolina, Georgia and Alabama, the county being used as the unit in which to work.

The medical departments of the Army and the Navy are engaged in the same work in the more restricted fields furnished by their individual responsibilities. It seems to me that we may look forward to the time when malaria in the continental United States will be under control.

South of the United States, between the Tropic of Cancer and the Tropic of Capricorn there lie the countries of Central America, of South America and of the West Indies. The sanitary problems in these countries must be solved before the commercial, agricultural, engineering and mining enterprises can succeed. It seems to me that this is the field for the future endeavor of our country; not in the sense of exploitation; but in the sense of constructive coöperation. It appears to me that there is urgent need for the establishment in the United States of a clearing house for the problems of the tropics. An institute, if you please, in which physicians and nurses may be instructed in the problems that they will meet in the tropics and from which they may be supplied to the administrative areas in which they are needed. In which physicians returning from the field, where they have had time only for the application of information already at their disposal, may learn of new facts and new methods for the application of old facts. In which the questions arising in the field may be sorted out and distributed for solution to various coöperating organizations: pathological and bacteriological laboratories; botanical and zoological laboratories; parasitological laboratories both for plants and animals, entomological laboratories and other scientific workshops. From which information may be sent to the field: In short a regulating center for the entire range of tropical questions. Such an Institute ought to interest the 29,000 physicians in the southern states, and all those who have interest in the tropics, as well as the physicians, scientists and business men of the tropical portion of the western hemisphere.

Within the next few years we may expect to see the inauguration of the Gorgas Memorial Institute, which will serve as a stimulus to the study of the problems of Tropical Medicine in this hemisphere. The Republic of Panama, through its President, Dr. Porras, has contributed the site for the Institute and proposes to contribute a large sum of money for construction and equipment. The Institute will be erected on the Bay near the new Santo Tomas Hospital. Articles of incorporation have been approved by the President of Panama, and a charter, which will be registered in Panama, has been granted under the Laws of the State of Delaware. It is proposed to secure an endowment fund of $5,000,000. Among the Trustees of the Institute are The Surgeon General of the Army, The Surgeon General of the Navy, The Surgeon General of the Public Health Service, Rear Admiral Braisted, M. C., U. S. Navy, Retired, Mr. John Bassett Moore, The President of the Republic of Panama, The Minister of Public Health of the Republic of Panama, Dr. Franklin Martin, and Dr. Leo S. Rowe.

It is interesting to know that the Trustees of the Boston City Hospital have recently authorized the organization of a service for the diagnosis and treatment of cases of tropical disease including certain parasitic and infectious diseases rarely seen in Boston and more common in foreign countries. This service is to be directed by Dr. George Cheever Shattuck, who will assume the duties of Assistant Professor of Tropical Medicine at the Harvard Medical School. The Broad Street Hospital, in New York City, has also organized a service with instruction for ship physicians.

Another way in which the problem of instruction might be handled is for three or four of the smaller medical schools to combine forces and employ a man who would spend a portion of the time of each college year in the instruction of the senior class in each of the colleges of the group. Two months in each of four schools with a daily lecture, demonstration, or ward visit ought to be productive of good results.

Gentlemen: I have been a member of the American Society of Tropical Medicine since its organization in 1903: its Assistant Secretary from its organization until I was elected Secretary in 1907, and its secretary from that date until 1917. It is a matter of deep regret to me that I was obliged to miss the meetings of 1917 and 1919. In electing me to the office of President you have conferred upon me the highest honor in your power: an honor that I shall always remember with grateful appreciation.

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## REPORT OF THE SECRETARY FOR 1920–1921

Owing to the fact that the last annual meeting of the Society took place in April, 1920, this report covers the activities of the Society for a period of nineteen months. Upon invitation and after due consideration of the Council it was decided to hold the present meeting, representing the seventeenth annual session of the Society, in conjunction with the meeting of the Southern Medical Association. The duties of the Secretary during the past year have been taken up, for the most part, with general correspondence. In January, 1921, the first number of The American Journal of Tropical Medicine was issued, with Major Henry J. Nichols, our recently retired President, serving as Editor. This venture was launched in great part under the patronage of the Society and its success, from a journalistic standpoint, has now been fully established. Thanks are due to the publishers, Williams & Wilkins, of Baltimore, as likewise to the editorial board, for their untiring efforts in bringing to a successful fruition a long cherished ambition on the part of our membership. It will become necessary at the present meeting to establish some fixed status, both professional and financial, between the Journal and the Society. The transactions for 1920 have been issued within the past week, entailing a comparatively small additional outlay above the subscription price of $4.00 per annum for the Journal. This represents volume 12, of our transactions, the first to be published since 1917. Since the last annual meeting we have suffered irreparable loss in the death of two of our most distinguished members, namely General W. C. Gorgas, and Dr. Isadore Dyer. The President has appointed special committees to draw up suitable resolutions expressing the keen loss we have sustained, which will be presented at the present meeting. Resignations have been submitted from the following active members and are hereby presented to you for your action: Drs. C. C. Pierce, and Joseph Sailer. At the last annual meeting the dues for corresponding members was assessed at $3.00 per annum, and it pleases me to report that in no instance was objection raised to this step on the part of this body of our membership. For reasons apart, the following corresponding members have tendered their resignations: Drs. A. Castellani, E. S. Goodhue, C. W. Daniels, W. H. Parks. The present number of applications for membership is the largest in our history, indicating a renewal and reawakening of interest in the purposes for which the Society was organized. The President, during the past year appointed a special committee on new membership, composed of Drs. Nichols, Butler, and Ransom, who will submit a report passing upon the qualifications of the applicants. The membership roll at the present time stands as follows:

| | |
|---|---|
| Active Members | 107 |
| Corresponding Members | 11 |
| Honorary Members | 27 |

It will be your duty at the present meeting to elect the following new officers for the coming year: President, first vice-president, second vice-president, secretary, assistant secretary, treasurer.

The term of Dr. George Dock as Councillor has expired and his successor must likewise, be appointed at this meeting. During the year the Secretary has received a number of invitations for the next annual session from commercial bodies situated in various cities. These have been courteously declined as the 1922 session is fixed to take place in conjunction with the Triannual meeting of the American Congress of Physicians and Surgeons, in Washington, D. C., May 2–3, 1922.

## REPORT OF THE TREASURER FOR 1921

I hereby submit the following report of the financial status of the Society from the period April 14, 1920 to November 6, 1921.

*Receipts*

| | |
|---|---|
| Balance in bank as per check book April 14th, 1920 | $292.68 |
| Total membership dues for 1920 | 91.20 |
| Total membership dues for 1921 | 475.12 |
| Sale of 1920 transactions | 5.00 |
| Total | $864.00 |

*Expenditures*

| | |
|---|---|
| Sign painting for 1920 meeting | $4.00 |
| Stamps | 5.00 |
| Lantern for 1920 meeting | 15.00 |
| *New Orleans Medical and Surgical Journal* | 250.00 |
| Tulane University Press—Program 1920 | 10.00 |
| Stamps | 3.00 |
| *New Orleans and Surgical Journal*—printing Presidential address | 4.40 |
| Stamps | 5.00 |
| Williams & Wilkins, American Journal Tropical Medicine | 214.00 |
| Stenographer fee | 25.00 |
| Stamps | 5.00 |
| Tulane University Press—Stationery | 10.00 |
| Total exchange on checks | 2.00 |
| Total | $553.20 |

| | |
|---|---|
| Balance on hand November 14th, 1921 | $310.80 |
| Library Fund | 30.83 |
| Total resources at present date | $341.63 |

S. K. Simon,
*Secretary-Treasurer.*

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## MINUTES OF THE ANNUAL MEETING

The seventeenth annual meeting of the Scientific Session of the American Society of Tropical Medicine was called to order at 9.45 a.m. Monday, November 14th, 1921, in the Eastman Hotel, Hot Springs, Arkansas. President John M. Swan presided and in addition to the Secretary, Dr. Sidney K. Simon, the following members were in attendance: Drs. Bass, Siler, Dock, Nichols, Deaderick, Shattuck, Guthrie, Graves, Boyd, Lemann, Levy, McLean and Lynch. A number of guests were also present.

The President read an address entitled "Malaria Control." At its conclusion the following resolution was presented to the Society by Colonel J. F. Siler, and upon motion was unanimously carried:

*Whereas* it is proposed to establish on the Isthmus of Panama an Institute of Tropical Medicine as a memorial of the life and the work of one of our former presidents, William Crawford Gorgas, Major General M. C. U. S. A. and formerly Surgeon General of the Army; *Therefore be it resolved* that the American Society of Tropical Medicine cordially and heartily endorses the establishment of the proposed memorial, and be it *further resolved* that the retiring president appoint five members of the Society to coöperate with the Memorial Institute and in every way possible to further the accomplishment of its objects.

Dr. Norman T. McLean then presented a paper of "Public Health Problems of the Southern Countries," which was discussed by Drs. Guthrie, Nichols, Litterer (Nashville), Lanford, (New Orleans), Deaderick, Swan and McLean.

Dr. Reynolds Hayden, not being present in person, a synopsis of his paper entitled "A Review of the Sanitary and Public Health Work in the Dominion Republic Under the United States Military Government of Santo Domingo," was presented by Dr. Swan.

The paper of Dr. O. J. Mink, "The Medical Department in the Virgin Islands," was read by title.

Dr. Henry J. Nichols, read a paper entitled "The American Journal of Tropical Diseases." It was moved by Dr. Simon that the Society express its thanks to Major Nichols for his efforts in promoting the interests of the newly launched American Journal of Tropical Medicine. Carried.

The papers of Drs. Bailey K. Ashford entitled "Resumé of Cases of Sprue Treated According to the Conception that the Disease is a Mycosis Superimposed Upon a Deficiency of Certain Food Elements," and of Dr. Karl F. Meyer on "Recent Studies on the Bacteriology of Undulant or Malta Fever," were both read by title. The final paper of the first day session, was read by Dr. M. D. Levy, dealing with "The Treatment of *Trichomonas intestinalis* Infections." This paper was discussed by Drs. Simon, Swan, Lynch, Litterer and Levy.

The following contribution from Dr. A. C. Stevenson, on "The Incidence of a Leptospira in the Kidneys and of Parasites in the Intestines of 100 Wild Rats Examined in England," was read by title.

The second session of the scientific program was called to order on Tuesday, November 15th, at 9.15 a.m. with the President and Secretary in their respective chairs. The first paper presented was by Dr. C. C. Bass, "Studies on Inoculation of Experimental Animals with Malaria," and was discussed by Drs. Nichols, Lynch, and Bass.

Dr. Shattuck read a paper entitled "Typhus Fever with a Review of the Newer Methods of Diagnosing Typhus Fever." This was discussed by Drs. Graves, Wilson (Charleston, S. C.), Levy, Boyd, Siler and Shattuck.

The next paper, "Filariasis and its Relation to Other Tropical Lymphopathies," by Dr. R. Ruiz Arnau; in the absence of the essayist, was read by title.

Dr. M. L. Graves presented a paper on "Systemic Blasomycosis. Report of a Case with Illustrations." The following participated in the discussion: Drs. Fontaine and Haase, (Memphis), Echols (Milledgeville, Ga.), Kilpatrick (Mobile, Ala.), and Graves.

The paper of Dr. Richard P. Strong and Dr. George C. Shattuck, entitled "Etiology of Phagedenic Ulceration and Granuloma Inguinale," was read by Dr. Shattuck and discussed by Dr. Lynch and himself.

The following papers were read by title: "A Case of Paget's Disease Associated with Carcinomatous Infiltration of the Breast of a Male Native of the Sudan" by R. G. Archibald. "Some Observations on the Distribution of Botulism" by Karl F. Meyer. "Investigations Regarding the Etiology of Pellagra," by Monroe A. McIver and Mr. Douglas M. Gay.

An address on the life and work of the late General William C. Gorgas, was presented by Lieut. Col. J. F. Siler. The President announced that a similar tribute to the late Dr. Isadore Dyer, prepared by Dr. John B. Elliot, New Orleans, would be read by title and printed in the JOURNAL.

At the conclusion of the scientific program, a short general meeting was held during which the report of the Council was read, and the various recommendations contained therein were adopted. Adjourned.

## MINUTES OF THE COUNCIL MEETING OF THE AMERICAN SOCIETY OF TROPICAL MEDICINE, ANNUAL MEETING, 1921

The Council met in the Eastman Hotel, Sunday evening, November 13, 9 p.m. The following members of the Council were present: Drs. Swan, Siler and Simon. Drs. Henry J. Nichols and C. C. Bass were present by request. The reports of the Secretary and Treasurer were ordered accepted as read. Under the head of unfinished business, the Treasurer presented the record of an unpaid account amounting to $55.00, which represented the various expenses incidental to the campaign for new members conducted at the request of the Council by Dr. Damasco Rivas. This was ordered paid.

The resignations of Drs. Joseph Sailer and C. C. Pierce, as active members were accepted. The following corresponding members also resigned during the year and their resignations were ordered accepted: Drs. A. Castellani, C. W. Daniels, E. S. Goodhue, W. H. Park. Dr. A. Castellani was elected to honorary membership.

The Membership Committee for the ensuing year was requested to canvass the present list of honorary members for the purpose of making corrections and offering possible suggestions at the next annual meeting.

The following resolution was presented by Major H. J. Nichols, editor of the American Journal of Tropical Medicine, and after discussion was adopted:

1. That the Council confirm the action of the Editor of the American Journal of Tropical Medicine in entering into a contract with the publishers, Williams & Wilkins Company, Baltimore, Md., by which the Society becomes owner of the Journal and a member of the Coöperative Scientific Publishing Association.

2. That the Council be authorized to act for the Society in matters relating to the management of the Journal.

3. That the net proceeds coming from the JOURNAL be devoted to the expenses of the JOURNAL and of the Society and shall be divided into a fair proportion for each purpose, the final decision of the exact proportion to be determined by the Council. It is understood that the publishers will receive $4.00 a year for each active and corresponding member.

It was likewise moved and carried that the Editor of the JOURNAL be made ex-officio member of the Council.

The Treasurer reported that he had dropped the following members during the year for non-payment of dues: Drs. Barlow, Converse, Herzog, Garrison, Henson, Harris, Miller, Wright.

The following were recommended for election to active membership: Drs. J. E. Acker, C. H. Barlow, W. W. Cort, Reynolds Hayden, R. H. Hegner, Norman T. McLean, R. E. Noble, Lewis J. Petritz, Elliot C. Prentiss, Edward W. Reed, J. M. Root, F. F. Russell, E. E. Simon, W. H. Taliafeno, George C. Dunhan, F. J. St. John. Dr. Thomas W. Jackson was ordered reinstated to active membership upon the payment of back dues.

The Auditing Committee composed of Drs. M. D. Levy and Mark F. Boyd reported the accounts of the Treasurer in good order. Their report was ordered accepted.

The following officers were recommended by the Council to the Society for the coming year:

*President*, VICTOR C. HEISER, New York.
*First Vice-president*, GEORGE C. DOCK, St. Louis.
*Second Vice-president*, SIDNEY K. SIMON, New Orleans.
*Secretary*, BRAYTON H. RANSOM, Washington
*Assistant Secretary*, ALLEN J. SMITH, Philadglphia.
*Treasurer*, BRAYTON H. RANSOM, Washington
*Councillor to serve for five years*, K. F. MEYER, San Francisco.

The next meeting of the Society will be held in Washington, D. C., May 2, 1922, in conjunction with the Triannual Congress of Physicians and Surgeons. Adjourned.

S. K. SIMON,
*Secretary-Treasurer.*

# LIST OF MEMBERS

*December 31, 1921*

## ACTIVE MEMBERS

Ackert, J. E. ...Kansas State Agric. Coll., Manhattan, Kans.
Amesse, J. W. ...520 Metropolitan Bldg., Denver, Colo.
Ammerman, Chas. C. ...1026 Murray Hill Ave., Pittsburg, Pa.
Anders, James M. ...1605 Walnut St., Philadelphia, Pa.
Arnau, Ramon Ruiz ...San Juan, Porto Rico
Ashford, Bailey K. ...2 San Cristobal, San Juan, Porto Rico
Baetjer, Walter A. ...Johns Hopkins Hospital, Baltimore, Md.
Barker, Lewellys F. ...1035 North Calvert St., Baltimore, Md.
Barlow, C. H. ...Shaohsing Christian Hospital, Shaohsing, China
Barrett, Harvey P. ...1915 Park Drive, Charlotte, N. C.
Bass, C. C. ...1551 Canal St., New Orleans, La.
Bates, L. B. ...Ancon, Canal Zone
Beall, Khleber H. ...1703 Lamar St., Fort Worth, Texas
Bel, George S. ...Hibernia Bank Bldg, New Orleans, La.
Blue, Rupert ...U. S. Public Health Service, Washington, D. C.
Bonney, Sherman G. ...203 Metropolitan Bldg., Denver, Colo.
Boyd, John C. ...1621 22nd St. N. W., Washington, D. C.
Boyd, Mark F. ...International Health Board, 61 Broadway, New York, N. Y.
Butler, Chas. S. ...Naval Medical School, Washington, D. C.
Carter, H. R. ...U. S. Public Health Service, Baltimore, Md.
Clark, Herbert C. ...Ancon, Canal Zone
Cole, Rufus ...Rockefeller Hospital, 66th St. and Ave. A., New York, N. Y.
Coplin, W. M. L. ...606 South 48th St., Philadelphia, Pa.
Cort, W. W., School of Hyg. & Pub. Health, Johns Hopkins Univ., Baltimore, Md.
Craig, Chas. F. ...Army Medical School, Washington, D. C.
Creel Richard H. ...3716 Keokuk St., Washington, D. C.
Darling, S. T., International Health Board, 61 Broadway, New York, N. Y.
Darlington, Thomas ...27 Washington Square N., New York, N. Y.
Deaderick, William H. ...Dugan-Stuart Building, Hot Springs, Ark.
Dock, George ...611 W. Jefferson Ave., St. Louis, Mo.
Dunham, E. K. ...Bellevue Hospital, Medical College, N. Y.
Dunham, George C. ...Surgeon General's Office, U.S.A., Washington, D. C.
Duval, Charles W. ...Medical School, Tulane University, New Orleans, La.
Elliott, John B., Jr. ...Audubon Building, New Orleans, La.
Fenton, Thomas H. ...1319 Spruce St., Philadelphia, Pa.
Furbush, C. L. ...1501 Spruce St., Philadelphia, Pa.
Futcher, T. B. ...3 W. Franklin St., Baltimore, Md.

Martinez, I. Gonzalez....................P. O. Box 753, San Juan, Porto Rico.
Graves, M. L.............American National Insurance Bldg., Galveston, Tex.
Guthrie, Clyde G.........................................Indiana, Pa.
Guthrie, J. Birney....................Maison Blanche Bldg., New Orleans, La.
Hall, Maurice C.......U. S. Bureau of Animal Industry, Washington, D. C.
Harris, Seale..........................Empire Building, Birmingham, Ala.
Hatch, J. Leffingwell................50 East 50th St., New York, N. Y.
Hayden, Reynolds..............Medical Corps, U. S. Navy, Annapolis, Md.
Hegner, R. W.
School of Hyg. & Pub. Health, Johns Hopkins Univ., Baltimore, Md.
Heiser, Victor G....International Health Board, 61 Broadway, New York, N. Y.
Hiatt, Houston B.......................................High Point, N. C.
Hitchens, A. Parker..............Army Medical School, Washington, D. C.
Hopkins, Ralph............................124 Baronne St., New Orleans, La.
Houghton, Henry S.........Peking Union Medical College, Peking, China.
Hume, Edward H...................Hunan Yale Hospital, Changsha, China.
Igaravidez, P. Gutierrez..............................San Juan, Porto Rico.
Jackson, Thos. W...................Department of Health, Harrisburg, Pa.
Johns, Foster M.............................1551 Canal St., New Orleans, La.
Johnson, Francis B...Medical College of South Carolina, Charleston, S. C.
Kofoid, C. A.........................University of California, Berkeley, Calif.
Krauss, William... ................Physicians' Laboratory, Memphis, Tenn.
Leidy, Jos...............................1319 Locust St., Philadelphia, Pa.
Lemann, Isaac Ivan.....................3523 Prytania St., New Orleans, La.
Levy, Moise D...............................1402 Avenue E, Galveston, Tex.
Leys, James F...........................U. S. Naval Hospital, Newport, R. I.
Long, John D.................U. S. Public Health Service, Washington, D. C.
Ludlow, Clara S...........U. S. Army Medical Museum, Washington, D. C.
Lynch, Kenneth M.........................4105 Live Oak St., Dallas, Tex.
McCaw, Walter D..................Army Medical School, Washington, D. C.
McConnell, Guthrie...............2601 Hampshire Road, Cleveland, Ohio
McCoy, George W.
Hygienic Laboratory, U. S. Pub. Health Serv., Washington, D. C.
McElroy, John B..................Central Bank Building, Memphis, Tenn.
McLean, Norman T...............Medical Corps, U. S. Navy, Newport, R. I.
McLester, James S.......................3917 Cliff Road, Birmingham, Ala.
Matas, Rudolph......................2255 St. Charles Ave., New Orleans, La.
Meyer, Karl F.
Hooper Found. for Med. Research, 2nd E. Parnassus Ave., San Francisco, Calif.
Mink, O. J........................Naval Training Station, Great Lakes, Ill.
Moore, John T.....................Kress Medical Building, Houston, Texas.
Nichols, Henry J...................Army Medical School, Washington, D. C.
Noble, R. E.........Assistant Surgeon General, U.S.A., Washington, D. C.
Osterhout, Paul...... ................148 Dunning Ave., San Antonio, Tex.
Petritz, Louis J...... .......................................Mound, La.
Prentiss, Elliott C...... .. ...............................El Paso, Tex.
Querens, P. L.........................Cusachs Building, New Orleans, La.
Ransom, Brayton H...........Bureau of Animal Industry, Washington, D. C.

Reed, Edward U............U. S. Naval Medical School, Washington, D. C.
Rivas, Damaso, McManes Laboratory, Univ. of Pennsylvania, Philadelphia, Pa.
Root, F. M., School of Hyg. & Pub. Health, Johns Hopkins Univ., Baltimore, Md.
Rosenau, M. J........................Harvard Medical School, Boston, Mass.
Rucker, W. C.........................2131 Bancroft Place, Washington, D. C.
Russell, F. F.....International Health Board, 61 Broadway, New York, N. Y.
St. John, J. H.......................................Ancon, Canal Zone.
Seemann, William H......................1551 Canal St., New Orleans, La.
Shattuck, George C.......................205 Beacon St., Boston, Mass.
Siler, Joseph F.....................Medical Corps, U. S. A., Washington, D. C.
Simon, C. E., School of Hyg. & Pub. Health, Johns Hopkins Univ., Baltimore, Md.
Simon, Sidney K......................3439 St. Charles Ave., New Orleans, La.
Skinner, Henry................................P. O. Box 281, Narberth, Pa.
Smith, Allen J., McManes Laboratory, Univ. of Pennsylvania, Philadelphia, Pa.
Snow, William F.........................105 West 40th St., New York, N. Y.
Stitt, Admiral Edward R.....Surgeon General, U. S. Navy, Washington, D. C.
Strong, Richard P.......Harvard University Medical School, Boston, Mass.
Swan, John M..............................457 Park Ave., Rochester, N. Y.
Talbot, Paul T...............Maison Blanche Building, New Orleans, La.
Taliaferro, W. H.
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Tasker, Arthur N.......................1519 Webster St., Washington, D. C.
Thayer, W. S..............................406 Cathedral St., Baltimore, Md.
Todd, John L..........................McGill University, Montreal, Canada.
Tyzzer, E. E...............Harvard University Medical School, Boston, Mass.
Van Wart, Roy M.....................3431 Prytania St., New Orleans, La.
Wade, H. W........................University of the Philippines, Manila, P. I.
Walker, Ernest L.
Hooper Foundation for Medical Research, San Francisco, Calif.
Weis, Jos. D.........................3431 Prytania St., New Orleans, La.
White, C. Y............................1808 Diamond St., Philadelphia, Pa.
White, J. H..........................1720 17th St. N. W., Washington, D. C.
Whitmore, Eugene R................1335 H. St. N. W., Washington, D. C.
Wood, Edward J.......................201 Chestnut St., Wilmington, N. C.
Zeiler, A. H...............1003 Pacific Mutual Building, Los Angeles, Calif.

## CORRESPONDING MEMBERS

Charles, R. Havelock........9 Manchester Square W. 1, London, England.
Goodhue, W. J..................................Kalaupapa, Molokai, H. I.
Kudo Rokusaburo.......................University of Illinois, Urbana, Ill.
Lebredo, Mario G...........................................Havana, Cuba.
Liston, W. Glen................c/o Indian Medical Service, London, England.
Mackie, F. Percival.......................c/o Grindlay & Co., Bombay, India.
Pareja, Weneslao.................................... Guayaquil, Ecuador.
Pedreso, Alexandrino............................. .Sao Paulo, Brazil.
Perry, Allan. ..................Colombo Medical College, Colombo, Ceylon.
Rogers, Leonard....................24 Cavendish Square, London, England.
Stanton, A. T.
Institute for Medical Research, Kuala Lumpur, Federated Malay States.

## HONORARY MEMBERS

Agramonte, Aristides..................University of Havana, Havana, Cuba.
Calmette, A..............................Pasteur Institute, Paris, France.
Castellani, A...... ................ 15 Harley St., W. 1, London, England.
Chagas, Carlos......... . Oswaldo Cruz Instituto, Rio de Janeiro, Brazil.
Choksy, M. H...............Arthur Road, and Martha Hospital, Bombay, India.
Cofer, L. E.................................563 Park Ave., New York, N. Y.
Flexner, Simon......................Rockefeller Institute, New York, N. Y.
Grassi, Battista......................... . The University, Rome, Italy.
Guiteras, John. .....................University of Havana, Havana, Cuba.
Howard, L. O...............U. S. Department of Agriculture, Washington, D. C.
King, W. W..........................American Consulate, Trieste, Italy.
Kitasato, S.......Kitasato Institute for Infectious Diseases, Tokyo, Japan.
Kolle, W..........Koch's Institute for Infectious Diseases, Berlin, Germany.
Laveran, A............ ................ ....Pasteur Institute, Paris, France.
Liceaga, Eduardo....................... . ..........Mexico City, Mexico.
Manson, Patrick............The Sheiling, Clonbur, County Galway, Ireland.
Martin, Chas. J.
Lister Institute of Preventive Medicine, Chelsea Gardens, London, England.
Montizambert, F.
Office of the Director General of Public Health, Ottawa, Canada.
Nuttal, Geo. H. F...............Cambridge University, Cambridge, England.
Ogata, M..............................University of Tokio, Tokio, Japan.
Paltauf, R..........................University of Vienna, Vienna, Austria.
Ross, Ronald G.....36 Harley House, Regents Park, London N. W., England.
Roux, E....................................Pasteur Institute, Paris, France.
Stiles, Chas. Wardell....Hygienic Laboratory, U. S. P. H., Washington, D. C.
Stockman, Ralph........................The University, Glasgow, Scotland.
Trotter, E. E...........................................Honolulu, H. I.
Ward, Henry B..........................University of Illinois, Urbana, Ill.
Welch, Wm. H......... ............Johns Hopkins University, Baltimore, Md.
The Surgeon General..............................U. S. N., Washington, D. C.
The Surgeon General... ..........................U. S. A., Washington, D. C.

# PUBLIC HEALTH PROBLEMS OF THE SOUTHERN COUNTRIES[1]

N. T. McLEAN

*Commander (M. C.), U. S. N.*

At the American Medical Association meeting in Atlantic City in June, 1919, Dr. Juan Guiteras of Havana presented a paper with this title, on which it was my privilege to open the discussion. I was impressed with the clearness with which Dr. Guiteras pointed out the vital differences between the work of the medical man in temperate climates, as compared with his work in the tropics. Manson in the introduction to his work on "Tropical Diseases" well states the title he chose was one more convenient than accurate. When, on the request of your President, I began the preparation of this present paper, it struck me that the title used by Dr. Guiteras was a most convenient one.

While this paper will deal almost entirely with my experiences as Chief of the Public Health Service of the Republic of Haiti during the years 1917–18–19–20, it is my aim to point out the desirability of cooperation between the medical profession and the health authorities, if rapid progress is to be made. This is not peculiar to Haiti, or to the tropics, but as was pointed out by Dr. John D. McLean, the Chairman of the Section on Preventative Medicine and Public Health of the American Medical Association at the recent session in Boston, is one of the big medical problems at the present time. In Haiti or any similarly undeveloped country, however, the leadership should be in the hands of the trained, disinterested governmental organization rather than in the hands of the poorly trained and unorganized medical profession. Care should be taken, however, to keep such a health organization free from political influences

[1] Read before the seventeenth annual meeting of the American Society of Tropical Medicine, Hot Springs, Ark., November 14, 1921.

as well as from the misdirected hobbies of the victims of environment and tradition.

In September, 1915, the United States and Haiti arranged a treaty between the two countries, which was finally, after numerous modifications, put into effect during 1916. In one of the provisions of this treaty (Article 13), it was agreed that the United States would assist Haiti in bettering her health conditions. In view of the magnitude of this work, it was, after much discussion, very wisely decided by the State Department, that no details be placed in Article 13 of the treaty but only the general statement relative to improving the public health, or as used in the treaty, the French words "d'Hygiene Publique." In December, 1916, having been detailed by the Navy Department for duty with the State Department as Sanitary Engineer of Haiti, in accordance with this treaty, I took up the work of organization. The pioneer work of the Army Medical Corps in Panama offered me valuable suggestions but that work was done under military control and it soon impressed me that another basis along more diplomatic lines was necessary for this new work in Haiti. The laws of Cuba proved themselves to be most valuable in studying out and arranging an organization for her sister Republic, Haiti. The differences between the political situation in Cuba and in Haiti however, precluded full adoption at the moment, of many of Cuba's well based laws and regulations. After considerable study of the situation therefore, I came to the conclusion that the most feasible plan for Haiti was to arrange and effect such laws and regulations as were necessary under the direct control of the treaty official, planning that upon expiration of the treaty, this work would be continued with the mere change in title of "Sanitary Engineer" to "Minister of Public Health." The experiences of the past years have demonstrated the wisdom of this course, and it is now hoped that when the treaty expires in 1935, Haiti will have so far advanced that a competent Haitian will be available to take the portfolio of this important branch of her internal government. The experience in Cuba pointed conclusively to the desirability of centralization, and I am fully convinced that in small countries, and especially tropical countries, centralization is the only efficient method of handling the public health.

The only existing legislation in Haiti relative to public health or quarantine prior to the enactment of the treaty above mentioned, was that relating to the Jury Medicale. This Jury Medicale system had been originally inherited from France and was a most comprehensive series of legislative acts, but lacked any organization to make them effective. The Central Jury governed the Senior Local Juries; the Senior Local Juries governed the Local Jury, and the Local Jury was finally placed in direct control of each locality. All were political appointments, changed frequently owing to innumerable revolutions and consequent change of political parties. The appointments carried no salary and the only remuneration was the amount to be obtained by graft. The office was most frequently used as a means to work off political and personal grudges. No other organization had ever been attempted and no finances had ever been intelligently legislated toward the work of this Jury Medicale. The quarantine laws of the Republic were a separate and distinct variety of legislation, each port being a law unto itself. The result was that no real quarantine organization existed in any place and that except in sporadic instances, which were conspicuous by their infrequency, was any attempt made to better the health conditions of the Republic. As a result, aboriginal conditions were found even in the largest city—Port-au-Prince. One writer describing his entrance to Port-au-Prince (which by the way is one of the most beautiful harbors in the world), well stated, that the stench of the city was distinctly noticeable to the traveler many hundred yards off shore, and this welcome frequently changed the mind of the prospective visitor as to his landing.

Taking office in the capitol in January, 1917, it was September of the same year before the new department actually took over the functions for which it was created. In that month the skeleton organization which had been operating under the control of the military forces of the United States, was abandoned, and the new Public Health Service inaugurated. Street cleaning had from the beginning, occupied most of the time of this skeleton force mentioned, and this work became at once, one of the most active of the new organization. It was, as usually is the case, almost impossible to obtain finances from the government to carry on this work and only the most insistent demands of the Sanitary Engineer finally obtained a small monthly appropriation. After much labor with the National Assembly, the President, and the Cabinet, the law on public health was finally passed and approved by the President on February 26, 1919. This law was purposely condensed into the most comprehensive, organic type of law possible, leaving all of the details of regulation to be handled by the enactment of such decrees (the authority to issue which was contained in the Law itself), as might from time to time be found necessary. The eighteen-month period of the work preceding the passage of this law, was by no means a lost period as many valuable lessons were learned, especially in the handling of the Haitian problem. All activities referring to the public health, were included in the original law, excepting only the one regarding the regulation and control of the practice of medicine. I frankly admit that this practice has a direct bearing on public health, and in many instances on its mortality, but I was forced to believe that it was better to leave the medical profession alone, and limit the new department to public health work, rather than excite the antagonism of the Haitian profession. I regret that I am unable to admit that Dr. McLean, to whom I referred previously, is right in his contention that "The medical profession has too long permitted the laws dealing with health to be interpreted entirely by a public health executive." In highly developed countries like the United States, the Doctor may be absolutely correct but in primitive countries such as Haiti, such a move would be most disastrous. Only by centralizing governmental control can successful development progress, and this centralization must be continued for years. Such portions of the laws relative to the Jury Medicale as referred to the practice of medicine were therefore purposely left intact, and as a result the practice of medicine in Haiti today, undoubtedly is, and will continue to be for some time, a weird performance, especially in the country districts.

The ex-kaiser is credited as once having made a very true remark. It was to the effect that the Haitian race is aboriginal African with a very thin veneer of French civilization. The truth of this simile is well recognized by one who knows Haiti. The spectacular, bombastic, and erotic, appeals most markedly to the African race and the slightest veneer of education, or I might possibly say civilization, is frequently made grotesque through its misapplication, by a gentleman of color and means. The Haitian doctor is a scholar of no mean attainment, but always writes "shotgun" prescriptions of the pronounced type, having no ability to apply his theoretical training. He must always parade all he knows on every possible occasion, in a pompous, and vain glorious manner.

It would have been impossible to affect any Haitian law on Public Health methods, had it not been for the pioneer work of Cuba, and Panama. The Haitian governing class was quick to recognize the fact that something had to be done in order to keep Haiti on the map commercially, and as health as a commodity, is well recognized by all maritime nations, they were not adverse to legislation, looking toward their freedom in commercial affairs. With them, however, legislation was one thing, and the carrying out of the provisions when enacted, a totally different one. Haiti was represented at the International Sanitary Convention of Paris, 1907, but did not ratify this Convention, and had taken absolutely no steps toward future ratification.

I have endeavored to make as short as possible an introduction as to the development of the service in Haiti, and hope that the reasons for the apparent slow development have been made sufficiently plain in the foregoing remarks.

The organization of Public Health Service of Haiti may be said to have been effected on the 26th day of February, 1919, about thirteen months after I took office. Three divisions were created to handle the work, i.e., Division of Sanitation, Division of Hospitals and Charities, and Division of Quarantine. Under the Division of Sanitation was placed all branches of the work that ordinarily falls to a board of health, together with street cleaning, garbage removal, the construction, maintenance and operation of incinerators, public water closets, the control of abattoirs, control of foodstuffs, and such examination of foods as could ordinarily be done in the limited laboratory facilities at our disposal. Inasmuch as all of this was primarily created, this organization passed through considerable of an evolution during the four years of my control. It was found advisable and the plan now in operation is to have in each municipality one trained naval medical officer as the Public Health Officer, of that municipality. While his work may primarily be sanitation, and almost invariably is, he is also supervisor, if he does not actually run, the local government hospital, and is directly in charge of the quarantine work at that port.

Under the Division of Hospitals and Charities, active work was begun first in Port-au-Prince, toward the development of a real hospital. The institution now known as the City General Hospital, Port-au-Prince, which is a free hospital, was formed from the amalgamation of the Military and Women's Hospitals, both of which had previously been maintained more as almshouses than as hospitals. The condition of all of the hospitals throughout the country was such that no native voluntarily entered these institutions except to die. The most violent prejudice existed against applying for treatment, let alone becoming an inmate of any of them. It took a great deal of persuasion and more or less force, at the beginning, to get patients to enter. As usual, the education of the general public, soon changed this, and today the question of finding room enough for needy applicants is the vital one.

As Haiti is without drug or chemical supply houses of any size, one of the first steps necessary was to organize a medical storehouse from which the necessary supplies were issued to the various hospitals throughout the Republic. It will be remembered that during this period of time, the World War had upset the commercial world and it was extremely difficult to obtain supplies of any kind. Through arrangements with the Navy Department, the Naval Medical Supply Depot at Brooklyn finally solved this great difficulty.

Haiti being without the war zone, suffered markedly from lack of attention. Late in 1915 and early in 1916, the American Red Cross had allocated a few thousand dollars to Admiral Caperton, Commander of the American Forces, with which foodstuffs were purchased and given away to the starving native of Port-au-Prince. This proved most pernicious, as the Haitian never helps himself if he gets food without work. It was stopped in February of 1916. From then, until the visit of Colonel Swan representing the American Red Cross, in 1919, absolutely nothing was obtained from philanthropic America except through the benevolence of certain Americans who having seen the awful situation, offered their own funds to assist insofar as they were able. As a result of Colonel Swan's visit, arrangements were made whereby the Red Cross sometime later, assisted us in procuring a permanent staff of trained nurses to replace the Navy nurses who had inaugurated a school for native nurses. Colonel Swan also arranged for the American Red Cross to assist in the erection of a home for these native women while in training. I understand, however, that it was impossible to meet the conditions attached to this assistance, and that the project has fallen through.

Hospitals without nurses of any sort was the rule. Certain French Sisterhoods maintained a type of assistance at a few of the larger of the so-called hospitals. While these nuns did everything they possibly could for the needy, yet as they were not trained nurses, and had no previous training in the care of the sick, it can be readily seen that their efforts were humanitarian only. Further as the rules of their order obliged them to retire for their devotional services within the walls of their convents by 6 p.m., and not to appear again until after early morning mass, it will be further appreciated that in the very sick cases, their assistance was of no value whatsoever.

After great difficulty, thirty-three young women of fairly good families, and a reasonable amount of education, were induced to enter a school for the training of native nurses. Of this original class, the first graduation took place in June of this year, about fifty per cent having made good. Your President, I know, agrees with me in feeling that of all the work the so-called American occupation has done in Haiti, none can compare with this for permanent and lasting benefit to the Haitian nation. These recent graduates are the first leaven of modern personal hygiene that Haiti has ever had. Being Haitian, their influence reaches farther than that of any foreigner, no matter how able. And, while their training is below that of the recognized trained nurse of the United States, they at least teach the Godliness of cleanliness in the treatment of the sick.

The Haitian treatment of, I might say any disease, is at the present time the treatment that we have all read of with amusement if not horror in old volumes on the practice of medicine in the middle ages.

Voodooism is, I believe, best defined as the practice of superstition. The native African is a strong believer in this practice. His Haitian successors have increased the scope of the practice by the careful adjustment of their local practices to suit the times. The Roman Catholic Church has for years maintained missions in Haiti, and as one of the older Fathers of the Order of San Luis De Gonzague told me one day, "The Haitian has taken the spectacular features of my church and interwoven it skilfully and cleverly with the most diabolical variety of Voodoo worship. Now and then where a Baptist missionary has been located, they have added to the combination the practice of immersion." Had Mrs. Baker Eddy visited Haiti, undoubtedly a large cult of Christian Scientists would have been founded, with Voodooism interwoven.

The mass of the Haitian population (conservatively estimated at 90 per cent) are so absolutely ignorant of the fundamentals of personal hygiene that a kindergarten basis of sanitary education has to be established, in order to reach them at all. They urinate and defecate wherever nature's call happens to find them. They obtain their drinking water from any stream or pond that may be handy. Their clothes for work day use are made from flour, cement or coffee sacks, filthy beyond description, while their Sunday and holiday garments are very carefully washed and laundered. These, however, are only used on state occasions.

Foodstuffs that are dropped on the ground are brushed free from the sand, by the hand, and consumed as if nothing had happened. Ordinary cooking utensils are unknown. The 5-gallon kerosene can furnishes a family with all that is necessary for culinary purposes. Knives and forks are rarely to be found in the interior districts. The five fingers which are ordinarily found on the unmutilated human, supply the place of spoons, cups or other utensils which we consider necessary. They cook with pieces of wood, over loosely laid stones; no stoves, no gas, no electricity—except in the larger cities. Charcoal is preferred. From this brief outline of their habits, it will be readily seen that after a child passes the nursing stage it feeds itself on what it finds, without regard to any variety of infection. As a result, all kinds of worm infections are the rule. Hook-worm was found in about 75 per cent of all of the applicants for the native constabulary, created at the time of the treaty.

Large families are the rule, and unmoral rather than immoral conditions exist. Very few recorded marriages take place amongst the masses, publicly declaring themselves man and wife being sufficient. Fidelity of the female, generally speaking, is the rule. The male, however, is permitted to have as many families as his means permit. The only restriction apparently being that in Haiti as elsewhere, no two families can be peacefully accommodated in the same abode. As a result, in the small villages the leading citizen is frequently the husband and father of as many as five establishments, all of whom apparently live in peace and concord in the same village.

Years ago I was impressed with the belief, which I think is common to most medical students, if not practitioners, that in the aboriginal races, the women very rarely suffer from any of the well recognized gynecological affections so frequently found amongst our women. This is untrue in all of the tropical countries I have had experience in. On the contrary, a large proportion of the women are found to be suffering with all types of uterine displacements, abnormal growths, and deformities in general. Not having had the education or benefit of surgical knowledge to any extent, many of these women go through life with conditions which the normal American woman would immediately have remedied. As an example of this, I remember a case in the Isle of Guam in 1906 where one of my colleagues called me in consultation on a confinement case. A prolapsed and elongated cervix extended externally from the vagina to within approximately 6 inches of this woman's knees. Birth was accomplished by an extra high forceps with the entire forearm inserted in this cervix, and after the puerpurium, operative treatment removed four and a half pounds of excess tissue. In Haiti, cancers of all varieties, ovarian tumors of enormous size and all types of displacements are constantly found. Cancer of the breast is by no means infrequent. In view of the fact that modern civilized ideas have not affected the Haitian, most women nurse their children for a long period, in some instances up to thirty months. A well fixed belief exists in the masses that pregnancy will not take place if lactation is continued. They fail to appreciate the fact of frequent pregnancies in nursing women, which should undermine this belief.

The great infant mortality is between two and five years. As might be expected, the main cause in mortality is from gastrointestinal disturbances. Banana bellies are the rule. The children are brought up without clothes of any kind to about the age of seven or eight when a rag of some type generally appears around the waist. Early puberty is of course the rule, and it is not infrequent to find a girl of fourteen or fifteen in a pregnant state.

The long years of constant revolution has had its effect on the stature of the two sexes. The females have, during the past century, gradually increased in stature, and the males have decreased. As the men were pressed into military service wherever found, it became the rule for the women to do all of the marketing, and town purchasing, leaving the husbands and sons in the country, where they did a little farming, but usually loafed, leaving all of the work to the women. The anticipated result of this was that the males gradually left the work to the females and loafed around the hill country. This has produced two different types of male Haitians, i.e., the "city" and the "country." The city male is a fairly good common laborer; the countryman has to be taught, but is the more painstaking laborer after he has been taught. The countryman is, however, very shy and easily frightened, both by the idea of work and the conditions of housing, consequent upon all large enterprises. If you endeavor to bring your laborers to barracks of any type, you immediately have trouble, but if you allow them to live with their wife and family, singular or plural as the case may be they form a very happy and contented force for labor. If one knows how to handle them, they are a most docile and obedient race. If irritated, they are ferocious to the last degree, and are easily swayed by prejudice, and superstition. The wise administrator however, can use both of these factors to gain his ends and can frequently combat Voodooism by this means. The average laborer, is from lack of proper food, physically unable to carry or undertake a real hard day's work. For generations they have lived on an almost strictly vegetable diet—stewed plantain with a little grease, and either fish or vegetable added, has been the staple diet. Early in the development of the Port-au-Prince division of street cleaning, we found that while the laborers were willing enough, they were physically unable to carry out the task alloted to them. When the question of increasing wages began to make itself felt, we decided that in place of paying a higher daily wage, that we would inaugurate a daily meal. A type of soup kitchen was constructed and from it, at noon each day, a nutritious meal was served to all of the laborers.

The low cost of all native products and our ability as a governmental department to import without duty such foodstuffs as were not available and deemed necessary, made it possible for us to do this at a maximum of $.07 per laborer per day. That $.07 proved to be an excellent investment. Our laborers from being the poorest of the poor, gradually became a selected class. The various commercial organizations were not slow to appreciate this lesson, and by giving a better meal were able to seduce from us, a large number of their foreman. If it were possible to carry this work into all of the communities, the physical resistance of the native to disease would undoubtedly be greatly increased.

A peculiar pathological condition which might be termed epidemic, is, and has been found in the native prisoners. This condition has been considered as a pseudo beri-beri, by some and by others as a distinct pathological entity. Lieutenant Commander W. L. Mann (MC), U. S. N. published a preliminary article on this condition, using the title "Edema Disease." This article was published in the *Journal of the American Medical Association*, November 20, 1920. This problem offers a most interesting field for research work.

*Venereal disease.* The close commercial and educational association of Haiti with France has, as might be expected, kept constantly alive a fresh influx of gonorrheal and syphilitic infections. As this association has existed for generations, a syphilitic infection has gradually extended throughout the country. As no treatment was available for the early stages, the usual "survival of the fittest" elimination took place, and as a result, at the present time we find about 90 per cent positive Wassermann's with very little evidence of active syphilitic infection. Gonorrhea has worked its usual habit, and a large number of blind beggars are found in all parts of the country. In view of the heavy syphilitic infections, many of the tropical ulcers originally charged to the country, are being found to be of a syphilitic origin and yield readily to treatment.

*Leprosy.* Approximately six hundred lepers are known to be in the country. They are ordinarily the beggars of the country roads, and live an existence only, as they are shunned by their own in all ways.

*Yellow fever.* While the stegomyia mosquito is to be found in all parts of the country, yellow fever has not been epidemic in Haiti for many generations. Since the time of the treaty no cases have been found. Evidently the reason for Haiti's freedom from this scourge was due to its commercial isolation.

*Smallpox.* An epidemic of smallpox ravaged the country in the middle eighties. From that time to 1920, no smallpox occurred and no vaccination took place. Although the danger of this situation was constantly before me, I was unable to obtain funds sufficient to even begin a general vaccination of the natives of the Republic. Since my departure, smallpox entered the country at the port of Aux Cayes, and spread rapidly throughout the entire country. As usual, in such cases, the epidemic in assuming alarming proportions, forced the authorities to appropriate sufficient funds for combating its spread. The reports of the total number of cases are not yet available, but at Port-au-Prince, it is estimated that there were at one time over six thousand cases. Active vaccination was of course begun, but as usual under such conditions, the epidemic ran itself through the susceptible mass. I understand that the epidemic is now well under control and that general vaccination is being carried on throughout the entire Republic. It is hoped that this epidemic will impress the Haitian authorities with the wisdom of making sufficient yearly appropriations, not only to combat epidemic disease, but for the proper purchase of public health. The State of New York has a most excellent motto placed on its letterheads to the effect that "Public Health is Purchasable, and within limits, each community can decide how much it desires."

*Health in general.* The educated Haitian claims that his country is a remarkably healthy one. Investigation of these statements which are frequently made, however, shows that he bases them on the fact that of a family of twelve to fourteen, he expects to raise four or five. In view of the high birth rate, the excess in mortality was not noticed. The climate is unquestionably a very excellent one. In most sections of the country the rains even during the rainy season, take place mostly at night so that the rule is a brilliant sunshine throughout the major part of the year. A kind Providence had provided the native with a natural method of sanitation, to which should be ascribed, such good health as Haiti had. As practically all of the thickly settled districts are hill-side ones, with high mountain backgrounds, extending to the sea or river levels, the heavy night rains flushed the contaminated surface of the ground following which, a bright tropical sun effectually sterilized the remainder.

It is a peculiar fact that different from all other tropical and subtropical countries, Haiti has no bird scavengers. Turkey buzzards are unknown. The story is that earlier generations of Haiti ate them up. Be that as it may, it is a known fact that an importation of these birds from the neighboring island of Jamaica took place about eleven years ago, under the direct supervision of a prominent Haitien, who had the sole monopoly for the importation of turkey buzzards. Some two hundred were imported. Within a few weeks none remained. Strange that it may seem, I could not find any records of an epidemic of gastro-intestinal diseases or increased death rate, so it is evident that the Haitien's digestive organs are thoroughly resistant to buzzard meat.

With sewers, paved streets, proper water closets, and the other developments of civilization, Haiti bids fair to be one of the most healthful of all tropical or subtropical countries. Given a moderate financial backing for a few years under proper administration, the public health of Haiti can easily be brought into the class of Panama.

During the fiscal year of 1920, the actual amount spent per person in the City of Port-au-Prince was \$.75. It can be readily seen that \$.75 per annum per capita cannot purchase much public health. During this same year, 59,000 house visits were made in this same city. These visits could not be classified as inspections in the sense of an American inspection, but more as a visit of instruction, showing the householder where to erect a water closet, how to screen his water receptacles, how to clean his yard, and in general the most elementary hygienic instruction. Follow-up visits will be necessary for many years. An amusing illustration of the necessity for follow-up visits, occurred in the city of Gonaives. One of my assistants was assigned to this city as the Public Health Officer. He was young, very active and intensely interested in his work, and on one of my inspections of the city took me to a certain well-to-do native's property to show me what an excellent type of water closet this native had readily consented to build. On our arrival at the closet in question, my assistant was somewhat chagrined to find the door padlocked, and the owner and key missing. On a later inspection I inquired about the developments and in our conversation my assistant told me that the joke was on him. He had investigated this particular case and had found that while the native was more than interested, and willing to comply with the Law and construct this closet, he had no intention of allowing any person to use it, and required a summons to the Police Court before he could be forced to open it for the use for which it was intended.

Finally, I am confident the salvation of the future health of Haiti is in a great measure, now in the hands of the trained nurses who are conducting the school for the training of native nurses. The dissemination of a rudimentary knowledge of personal hygiene can most effectively be carried on by these young women. I feel confident that my successors in Haiti will recognize this if they have not already recognized it and will devote much effort toward increasing the scope of this school.

# REVIEW OF THE REORGANIZATION OF THE SANITARY AND PUBLIC HEALTH WORK IN THE DOMINICAN REPUBLIC UNDER THE UNITED STATES MILITARY GOVERNMENT OF SANTO DOMINGO

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The Dominican Republic is located in the West Indies, occupying the eastern two-thirds of the Island of Haiti, between Cuba and Porto Rico. The country has an area of about 20,000 square miles, about five times the size of Porto Rico or as large as the States of New Hampshire and Vermont combined. The people, about 800,000 in number, are a mixture of Spanish, Indian, and African, the negro element predominating and are noticeably Spanish in language, traditions and customs. The greater portion of the people are illiterate, the smaller number of educated people comprising the professional and political classes. The capital and largest city, Santo Domingo, has a population of about 27,000.

Owing to the failure of the Dominican government to observe its treaty obligations and the menace of unsettled conditions, both to foreigners and to the Dominican people themselves, due to revolutions, the United States government, in May, 1916, found it necessary to direct its naval authorities to occupy the country and to restore and maintain order. The present military government was established in November, 1916, with Captain (later Rear Admiral) H. S. Knapp, U. S. Navy, as the military governor. A cabinet of United States naval and marine officers was created in order to administer the affairs of the Dominican government departments but Dominicans were continued in all subordinate positions as far as practicable. The Dominican judiciary retained their functions. The proclamation of occupation states that the military occupation was undertaken with no idea of destroying the sovereignty of the Republic, but on the contrary, was designed to give aid to the country in returning to a condition of internal order. Measures are now being taken to restore the government to the Dominicans.

## REVIEW OF SANITARY CONDITIONS AT THE TIME OF AND IMMEDIATELY FOLLOWING THE ESTABLISHMENT OF THE MILITARY GOVERNMENT

At the time of the occupation, sanitary and public health activities in the country were found to be almost entirely lacking, except in the largest cities and in these they were very inefficient. A sanitary law was in existence, but it was inadequate and very weakly enforced. With few exceptions, none of the administrative bodies provided for by the sanitary law were even appointed and those appointed were not functioning. The law governing the practice of the medical professions was better administered, but this too was not well enforced.

Shortly after the establishment of the military government, the position of chief sanitary officer was created by executive order and filled by a naval medical officer who was given general supervision over the administration of the public health laws, but no actual personal authority. So far as possible, all the personnel required by law was appointed with the idea that the laws in question should be administered by the Dominicans under the general supervision and instruction of the chief sanitary officer. These conditions continued until the summer of 1918. During this time, but little more than the most elementary sanitation was accomplished. That more was not done during this period was entirely due to the lack of appropriations and the inertia or even passive resistance of the Dominican authorities, both sanitary and municipal.

Inasmuch as the organization of a public health service for the country was not included among the purposes specified for the establishment of the military government, it was decided that explicit authority from Washington was necessary before the military government could expend any large amount of money for this purpose. Accordingly, the subject was referred to Washington, and the whole matter of proceeding with the reorganization of the sanitary and public health work in a systematic and comprehensive way was approved by Washington before it was actually commenced.

### IMPROVED SANITARY CONTROL

In August, 1918, in view of the unsatisfactory record of the preceding year and a half, the apparent impossibility of obtaining satisfactory results from the administrative bodies provided by law, and the evident necessity of having central control with an active and responsible head to the public health organization of the country, the military government decided to abandon its former policy of leaving matters of sanitation and public health practically in the hands of the Dominicans. The real reorganization of the sanitary and public health work of the Republic dates from that time. Pending the promulgation of a new law on the subject, a series of executive orders was issued modifying existing law and giving more authority to the chief sanitary officer and naval medical officers stationed throughout the country. Better results were soon apparent, but because of the inertia and non-coöperation of the municipal authorities, the desired improvement in conditions was only very gradual. Various necessary sanitary regulations covering the most important needs of the country as a whole were promulgated, however, and efforts made to secure the interest and active support of the various municipalities.

### NATIONAL SANITARY ORGANIZATION

On January 1, 1920, a new sanitary law governing sanitation, public health and the practice of the medical professions became effective, all previous legislation on these subjects being annulled. This law created a new and independent government department, called the department of sanitation and beneficence, and centralized the administration of public health affairs in the secretary of sanitation and beneficence. Under the military government, this position is filled by a naval medical officer.

Briefly, the law is written in four chapters:

Chapter I deals with the creation of the department, its organization, administration and finance, formulation of a sanitary code, administration of public institutions for the care of the sick, establishment of a district organization, compulsory vaccination, legal abolition of prostitution, and control of venereal disease.

Chapter II regulates the practice of the medical professions and trades, including the manufacture, distribution, exchange, sale and dispensing of drugs and poisons. These matters are placed under the jurisdiction of the sanitary department, except the professional examinations of applicants for license to practise medicine, dentistry or pharmacy, which examinations are conducted by the University of Santo Domingo. Provision is made for the sale by merchants, under certain restrictions, of patent medicines and certain specified common drugs.

Chapter III established a national quarantine service under control of the sanitary department, and includes the necessary provisions of law for maritime quarantine.

Chapter IV provides for the enforcement of the sanitary law and the sanitary code.

Detailed sanitary regulations are provided by the sanitary code. This code comprises the usual requirements of such legislation and has the effect and force of law. For the purposes of the sanitary code, the communities of the country are divided into four general groups according to population, and the requirements of the code are graded accordingly.

## PRESENT ORGANIZATION OF THE SANITARY DEPARTMENT

The department is under the direction of the secretary of sanitation and beneficence, who is a member of the cabinet. The powers of the secretary are extensive and perhaps somewhat arbitrary. They are definitely outlined by law, however, and are necessary under existing conditions. They greatly aided the rapid establishment of an efficient department, and are essential to its proper maintenance and progress.

Acting in an advisory capacity to the secretary is the national public health council. This council acts upon all sanitary regulations formulated by the secretary or originating within its own membership. Such regulations, when approved and promulgated by the executive power, form the sanitary code and have the effect and force of law. The council is composed of five Dominicans, at least two of whom must be physicians.

Within the department proper are various divisions, as follows:

1. Division of vital statistics, transmissible diseases and quarantine.
2. Division of sanitary engineering.
3. National laboratory.
4. Division of registration and accounts.

These divisions are organized as in any modern health department and are charged with the administration of those portions of the law pertaining especially to them.

The entire personnel of the division of vital statistics is Dominican. The first national vital and morbidity statistics of the Republic were compiled for the last nine months of 1919. Because of inability to obtain proper reports from the country at large, the statistics for 1919 are rather inaccurate. Those for 1920 are much better. The quarantine service functioned well from the beginning. The average Dominican quarantine officer does not make an excellent inspector, but carries out the letter of the law explicitly and shows rapid improvement.

After much difficulty, an American sanitary engineer was obtained and placed in charge of the division of sanitary engineering. The work of this division is very important and has been extremely difficult because of the untrained local personnel and a public not only ignorant of but strenuously opposed to the majority of its requirements. The entire personnel of this division is American and Porto Rican as no competent Dominican was available.

Standard plans were made and distributed throughout the country illustrating the department's requirements regarding latrines, septic tanks, markets, etc. In order that local plumbers might be properly educated for their work and to enable them to pass the examination for license required by law, a night plumbing school was organized and carried on for the last three months of 1920. An illustration of the attitude of the people toward this work is shown by the fact that notwithstanding a very complete advertisement of the reasons for the school and the fact that only a nominal charge to cover cost of material would be made to students, the attendance was very poor.

The national laboratory was started with an entire Dominican personnel. It later became necessary to obtain the services of an American as chief of the laboratory and of another American as chemist. Dominican subordinates were retained. Unfortunately, the majority of Dominican medical students are very slow to appreciate or understand modern laboratory work. The work done was along the lines of the usual public health laboratory but the results were very disappointing from the departmental point of view because of the lack of interest by native practitioners and medical students.

For the purposes of sanitary administration, the country is divided into eleven sanitary districts. Each district is in charge of a district sanitary officer immediately responsible to the secretary of sanitation. Under each district sanitary officer are a varying number of communes or municipalities in charge of communal sanitary officers. These district and communal sanitary officers have direct charge of all sanitary and public health work within their jurisdiction. Municipal sanitation is subject to the general sanitary law and code, though individual "Ayuntamientos," or city councils, may adopt local sanitary regulations not in conflict with the sanitary code.

The majority of the district and all communal sanitary officers are Dominicans. While these were admittedly not the best men obtainable for these positions, the idea of the military government was to organize and train a Dominican sanitary department in order that the department might function efficiently after the government was returned to the Dominicans. To this end, it was necessary to appoint absolutely untrained natives to practically all subordinate positions, and train them. This was an extremely difficult proposition as the necessary intelligence and executive ability were rare among the people who would take the positions. As a result, much wasted effort and many changes were necessary before a reasonably efficient personnel was obtained. ·This training is a difficult problem with the personnel available and required much patience and perseverence. It was carried on through personal instruction by general inspectors and by departmental bulletins. Results were sometimes very good, but at other times sad and even ludicrous. With some few notable exceptions, the average native sanitary officer was inclined to think himself king of his community and had to be held down with a strong hand. As with the other departments of the government, very few native subordinates could be found who would interpret the law intelligently or reasonably and explanation in the most minute detail was frequently necessary. These difficulties were multiplied by the fact that the great majority of the people as a whole had little knowledge of or desire for modern sanitation or public health.

The average Dominican, however, is a very reasonable person, particularly when he realizes that the question at issue is really for his own well-being. The sanitary officers have markedly improved during the past two years and will continue to improve. The general public is gradually absorbing some public health education. The great need of the sanitary department, however, remains a trained personnel.

Violations of the sanitary law may be punished either by being submitted directly to the court having jurisdiction or by administrative fines imposed by the secretary. The court procedure is almost invariably very slow and the administrative fine is preferred for the majority of minor violations, by both the people and the department. Administrative fines have been limited to the amount imposed by law and in no case could they exceed one hundred dollars. If the accused did not pay his fine within a specified time, the case would automatically be taken to court. If convicted, the court was required by law to impose twice the sum of the administrative fine. These administrative fines speeded up justice to a marked degree and considerably enhanced the prestige of the sanitary officer.

## FINANCE

The financial situation as regards sanitation and the public health has improved remarkably during the period of the occupation. So far as can be ascertained, only about $30,000 was appropriated from all sources in 1916 for this work, about three cents per capita. In 1920, exclusive of new construction, $492,750, about sixty-four cents per capita, was appropriated for this purpose. During 1921, because of diminished revenues, the total appropriations for this work have had to be considerably reduced. Exact figures are not at present available. A very important method of financing this work is the requirement of law that municipalities shall appropriate from ten to fifteen per cent of their annual incomes for sanitation, public health and charity. All public funds for this work are expended under the direction or supervision of the sanitary department.

## TRANSMISSIBLE AND PREVENTABLE DISEASES

There are no statistics available from which an even fairly accurate comparison between former and present conditions can be made. The universal and voluntary testimony of many persons well acquainted with previous conditions testifies to the greatly improved sanitation and public health of the country. Both doctors and laity voluntarily testify that cases of disease have greatly decreased, particularly contagious diseases. Infantile mortality rates are universally stated to have been lowered through a diminished amount of intestinal diseases among children. Comment has been made upon the fact that there appeared to be more children about the streets than in former years.

The first national vital statistics were compiled by the sanitary department for the last nine months of 1919. These figures were admittedly inaccurate owing to the absence of an adequate registration law. Unreliable statistics are largely due to failure to register births and to inaccurate statements as to the causes of death. During 1919, 11.3 per cent of reported deaths were given as "cause unknown."

The statistics collected in 1919 show the gross unstandardized death rate to have been 14.26 per thousand, and in 1920, 11.67 per thousand. The infantile mortality rate for 1920 was 66. The figures for 1919 are so inaccurate that they cannot be considered for this purpose. The figures for 1920 are more accurate. The first national census has just been completed. This, with the experience of the past two years, should result in fairly accurate statistics in the future.

This infantile mortality rate is low and particularly so when the almost criminal ignorance of so many of the mid-wives and mothers in the Dominican Republic is considered. It will be seen from these figures that there is practically no chance for the sanitary department to make any startling showing in the reduction of the death rate. The reduction of the infantile mortality and reduction of the incidence of disease with its accompanying economic loss must be the main points of attack. Control of infantile mortality is being brought about by the compulsory use of antiseptic umbilical dressings supplied by the sanitary department free or at a minimum cost, by schools for and licensing of mid-wives, and by regulations governing the production and sale of milk. The death rates are low but cannot be compared with those of previous years as figures are not available, except in a few scattered localities.

The chief preventable diseases, in what is believed to be the order of relative importance, are as follows: 1, Venereal disease, 2, malaria, 3, uncinariasis, 4, tuberculosis, 5, yaws.

Venereal disease is given first place because of the general and high incidence of same in an active state and the great number of people suffering from its after effects, either congenital or acquired. Estimates by supposedly competent observers place the incidence of syphilis at about 70 per cent of the population. Surveys made at prisons have shown about 50 per cent of syphilitics among the inmates. Throughout the country are numbers of mentally deficient persons whose condition is almost certainly due to syphilis.

After protracted consideration of the matter, including a trial of the so-called restricted districts and legalized prostitution, it was decided to make the practice of prostitution illegal, and in 1920 the sanitary department inaugurated a vigorous anti-venereal campaign along the lines of similar work in the United States. At first, because of a lack of understanding of the new law and of the requirements of the department, there was a wide-spread protest from the people generally and from many municipal authorities. There was a general fear of a return to the old wide-open towns which had existed prior to the occupation. After the new legislation had been in effect for a year, considerable difference in results was found in different localities. In those areas where there was active and intelligent coöperation between the health and police authorities, open prostitution was practically eradicated and venereal disease greatly diminished. Where the police authorities did not so coöperate, there was an increase in clandestine prostitution and venereal disease. The people have generally accepted and are now believed to favor the new legislation. Results to date show that there are no real grounds for the contention that such legislation is impracticable with tropical or Latin races. As elsewhere, the results depend entirely upon the authorities in charge of the administration of the law. The effacement of prostitution was neither expected nor obtained. The same difficulties encountered elsewhere were encountered here but intensified because of poor police and lack of adequate hospital and dispensary facilities. With the development of the hospitalization and dispensary system proposed by the sanitary department and fairly adequate police coöperation, the anti-venereal campaign should prove successful in Santo Domingo. The real anti-venereal problem in that country is whether this work will be effectively continued under a native administration. At present, this seems rather doubtful.

Malaria is endemic in many parts of the country but enforcement of anti-mosquito measures has diminished the incidence of same to a considerable extent. Reported cases for 1920 were about 40 per cent less than for 1919. There are no extensive swampy districts nor bad malaria regions in Santo Domingo. Because the majority of the towns are rural communities and the country population very scattered, the control of malaria there is largely a question of controlling the house water supply. This is very difficult in a country where the great majority of houses obtain their water supply from cisterns, tanks, barrels, etc., where the sanitary personnel is inadequate, and where the people generally fail to appreciate the necessity of mosquito control work. Fortunately but few Anopholes mosquitoes are found in the cities.

Hookworm disease is very generally distributed through the country. Upon invitation of the military government, the Rockefeller International Health Board made a hookworm survey of the Dominican Republic in the summer of 1920. The result of this survey gave an estimated infestation of 52 per cent of the population as a whole. Some parts of the country are much more heavily infested than others. The north central part shows an infestation of 70 per cent, while the arid western portion had only 12 per cent.

A very interesting result of this survey was that the haemoglobin tests of some 600 cases gave an average haemoglobin index of 77. The average index in the heavily infested north central region was 68. This fully bears out the observation made by Dr. Stitt that the clinical effects of hookworm infection are much less in the black race than in the white. A great majority of Dominicans have a high percentage of negro blood. Compared with other countries having a corresponding hookworm infestation, hookworm patients in the Dominican Republic show very few clinical effects. This is particularly noticeable when the Dominicans are compared with their neighbors, the Porto Ricans.

Notwithstanding the absence of clinical effects, the incidence of hookworm in the Republic is sufficient to constitute a serious problem and is undoubtedly a considerable economic burden. The sanitary department is endeavoring to control this disease by prevention of soil pollution and, so far as is practicable with the available funds, by dispensary treatment of patients.

Tuberculosis is an ever-present problem here, as elsewhere. The average native of the tropics has but little resistance to this disease and his living conditions are against him. As yet it has been impracticable to do any real anti-tuberculosis work in Santo Domingo. Provision for hygenic house construction and improved living conditions is made in the sanitary code. The existent hospitals, dispensaries and municipal physicians render what help they can. A tuberculosis sanitarium was contemplated by the sanitary department, but the idea had to be abandoned for lack of funds.

Yaws exist to a considerable extent in the Republic and causes great economic loss. On the suggestion of Dr. John M. Swan and at the request of the Military Government, the Harvard University School of Tropical Medicine sent an expedition headed by Dr. R. W. Sellards to Santo Domingo in June, 1920, for the purpose of investigating and treating yaws. This expedition established two small field hospitals and conducted an extensive campaign of investigation and treatment of the disease. In addition, the sanitary department provided free treatment for yaws in several of its dispensaries. The people showed great interest in and appreciation of this work, many yaws patients riding horseback ten, twenty, and even thirty miles to obtain treatment. Altogether 2500 cases of yaws were treated during the last six months of 1920.

As is well known, yaws is a disease which lends itself readily to dispensary treatment. Cases were treated by both the intravenous and intramuscular administration of neosalvarsan. With the personnel available, the sanitary department found intramuscular injections to be more satisfactory. The average native practitioner available for this work could not be depended upon to give either a satisfactory or safe intravenous injection. All cases received from one to three injections, depending upon the severity of the disease. All cases were cured and none suffered from abscess formation. Everything considered, this was an excellent record and one that can only be really appreciated by those acquainted with the difficulties under which the work was performed. During the early summer of 1921, the yaws cases treated by the Harvard expedition and the sanitary department during 1920 were checked up to discover possible recurrences. So far as could be discovered, there have been no recurrences or new infections amongst these patients, six to eight months after stopping treatment and living where many were exposed to yaws. In addition, four volunteers from the cured yaws patients were inoculated with scrapings from an active yaws lesion. They were carefully watched for four months but none developed yaws. A volunteer control case with a negative history of yaws was inoculated with the same scrapings and developed characteristic yaws by the end of three weeks. Of course, it is difficult to draw conclusions from such a small series of cases, but it appears that there is an apparent immunity produced by yaws, even after cure by neosalvarsan, or that the affection remains without any apparent clinical manifestation and the patient is, therefore, not susceptible to reinoculation. An interesting coincidence of the treatment of yaws by the sanitary department was the comparatively large number of cases of apparent gangosa who came for treatment. The clinical manifestations were identical with the text book illustrations of this disease. The frequency with which these cases gave a history of yaws was very suggestive of a relationship between the two. These cases of apparent gangosa were found to respond rapidly to treatment with neosalvarsan. This would appear to indicate that gangosa is only tertiary yaws. The relationship between these two diseases is now being further investigated by Doctors Hager and Houghton of the navy, now working with the sanitary department.

## HOSPITALS

The hospital situation of the Republic was considerably improved during the past year. Prior to that time there were only seven charity hospitals in the country, five of these being most inadequately supported by local lotteries and subscriptions.

The government considerably increased the facilities of the old Dominican Military Hospital in Santo Domingo City and established a training school for native nurses there. The American Red Cross rendered material and greatly appreciated assistance in this work, as well as in connection with the Seibo Hospital, established by the Dominican Chapter of the American Red Cross. The government has practically completed a leper colony about fifteen miles from Santo Domingo City. Plans were also made to construct a new and very much needed government insane asylum but it was never started because of lack of funds.

In addition, after the reorganization of the lotteries previously mentioned, all charity hospitals and orphanages supported by these funds were placed under the general supervision of the department of sanitation, and were required to obey its regulations for their proper administration. The amounts available for each institution were considerably increased by the reorganization of the lottery and were allotted in accordance with the needs of the institution in question, upon recommendation of the Secretary of Sanitation. The Juntas or Boards previously administering the institutions continued this work if they so desired, but they were required to administer them in accordance with the department's regulations. If these regulations were not complied with, no allotment of funds was paid the institution in question.

Under this plan, the charity hospital capacity of the Republic was more than quadrupled in a year. The working bed-capacity of these hospitals was increased from approximately 100 for the entire country to about 450. This number of course, could be greatly increased in case of emergency. In addition, much new and modern hospital equipment was provided. The orphanages were improved to a certain extent, but not as much as the hospitals. American doctors and nurses were provided for two of these hospitals for the purpose of introducing more modern methods and training the local personnel. These improvements were brought about with practically the same funds as those that had been previously theoretically available for this purpose.

In addition to the above mentioned completed improvements, the department planned the completed hospitalization of the country so far as charity hospitals were concerned, as well as a system of dispensaries. This additional plan has had to be at least temporarily abandoned for lack of funds.

## PRACTICE OF MEDICINE

The practice of medicine, and for that matter dentistry and pharmacy in the Republic, has been and is still in a rather chaotic state. There is approximately only one doctor for every 8700 of the population. Outside of the forces of occupation, there are very few foreigners practicing medicine in the country. The majority of practitioners are graduates of the University of Santo Domingo. Some few of these have taken post-graduate courses abroad. The majority of such courses, however, lasted only a few months each. The standards of the medical profession there, are those of any backward country. Until recently, the practice of the various forms of witchcraft flourished in the country districts and also existed among the poorer classes in the cities.

The University of Santo Domingo examines the professional qualifications of foreign graduates desiring to practice in the Republic. Its own graduates are licensed to practice upon graduation, and take no examination corresponding to that of our state boards. The medical course at the University is five years, but most inadequate. All teaching is didactic. There is no dissection and no laboratory worthy of the name. Practically all clinical instruction is obtained from private practitioners in their offices and is entirely dependent upon the initiative of the student. For the past two years, attempts have been made by the sanitary department to provide regular hospital clinical instruction for senior students, but the University faculty would not make this compulsory and attendance was at a minimum. As a matter of interest, and to give a comparison with our own medical schools, one instance is quoted where a graduate of this University, after considerable coaching, was admitted to the second or sophomore class in a class A medical school in the United States. Except to contribute to local pride the University does more harm than real good as a medical school. So long as it continues as at present, the country can hope for little improvement in the general grade of its medical practitioners. As may be readily imagined, the average graduate of the University is comparatively ignorant and may even be considered rather dangerous to his patients, as he thinks that he has a first class medical education and acts accordingly. These remarks apply also to the dental and pharmaceutical schools. Under present conditions in the Republic, there is little if any hope for the ultimate betterment of the University. Were it entirely discontinued, the would-be medical practitioner would be forced to go abroad for his professional education, to the greater good of himself, his prospective patients and his country.

The few graduates of the University prefer the larger cities and towns, and it is almost impossible to get them into the country. As a result, it was found necessary to "authorize" a limited number of non-graduates to practice medicine, dentistry, or pharmacy, as the case might be, in places where there no graduates. This is an admittedly poor system, but slight medical care is perhaps better than none, in spite of the old saying that "a little learning is a dangerous thing."

## THE FUTURE OF SANITATION AND PUBLIC HEALTH WORK IN THE DOMINICAN REPUBLIC

Real sanitation and public health work in the Dominican Republic is largely in the future. There has been no past worthy of mention, and only a good start has been made for the present.

The sanitary department has been organized, has adequate legislation under which to act, and during the last two years has made considerable progress. From a condition of practically no sanitary organization, a well-functioning organization has been built up, one that is daily securing results. While much is still to be desired, the present sanitary organization has been stated by competent observers to be securing general results equal to those of the much older sanitary departments of Porto Rico and Cuba.

The great need of the department is a trained personnel. This can not be too strongly emphasized. The existing laws are enforceable but because of the lack of a trained personnel and the ignorance of the majority of the population, are not yet being efficiently enforced. It must be remembered that the organization is but three years old and the results obtained to date are all that could be reasonably expected. The future effectiveness of the department depends upon overcoming this lack of a trained personnel. Because of lack of funds and difficulty of travel, it has been impracticable to conduct a school of sanitary inspectors. At present, training is being accomplished through an elementary text book for inspectors, published by the department, frequent departmental bulletins, and frequent inspections and instruction by an American inspector. These methods are gradually securing results and the work of the local inspectors has been much better during the past year than before. Strangers arriving in Santo Domingo are apt to think that little real sanitation has been accomplished; but they are ignorant of previous conditions. As yet, the department has had but little time to attempt any real public health education. Its own personnel had to be educated first. Such public health education as has been attempted has been almost entirely by means of pictures, posters and personal instruction by sanitary officers. This is necessary on account of the very high percentage of illiteracy in the country. The public schools give elementary instruction in sanitation and hygiene along lines similar to those followed in the public schools in the United States. This will help eventually.

Because of the short time in which any attempt at real health work has been in progress, and because of the almost universal public illiteracy and ignorance, but little real appreciation of this work is yet shown by the public. The average Dominican, however, seems to be receptive to public health teaching, and good results can be obtained as soon as they understand the object in view. In my opinion, and speaking for the good of the Dominicans themselves, as well as for the future of the sanitary department, the time has not yet arrived, and will not arrive for some time to come, when this work can be safely turned over entirely to the Dominicans. Outside assistance will be essential for some years if the good beginning already made in the sanitation of this country is to continue, and real results finally obtained.

If the existing sanitary laws of the Republic are not continuously and vigorously enforced, and if the present young but promising sanitary department is not properly supervised and supported, the work of the past few years in this respect will have been wasted. If the present work is continued and at all adequately supported, the results obtained should be excellent and lasting.

# THE MEDICAL DEPARTMENT IN THE VIRGIN ISLANDS[1]

O. J. MINK

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When the Danish West Indies were transferred to the United States in 1916 the name "The Virgins" with which Columbus christened them over four hundred years ago was revived and they became "The Virgin Islands of the United States." Only a portion of the Virgin Islands were involved in the transfer, the remainder being the property of Great Britain. The Virgin Islands of the United States comprising three principal islands and many small islands are located about 50 miles east of Porto Rico. The larger islands are St. Thomas, St. John and St. Croix.

The Danish Government organized the Danish West Indies into two municipalities or states each governed by its own Colonial Council whose acts were valid when approved by the Danish Governor who acted for both municipalities. The authority in medical matters was vested in the Danish Governor but this authority he detailed to two officers in each municipality who were known as the Chief Municipal Physician and the Chief Sanitation Officer. When the islands were transferred to the United States and the government became American the Danish organization was continued. At this time the Governor added to his staff a medical aide. The medical aide is the head of the Medical Department and is the only medical officer whose duties are not limited to a single municipality. The office of the Medical Aide is the final repository of all vital statistics for the Virgin Islands. As the organization is identical in both municipalities it will be necessary to speak only of St. Thomas and to mention those points in which St. Croix differs.

The municipality of St. Thomas and St. John commonly called

[1] Read by title at the seventeenth annual meeting of the American Society of Tropical Medicine, Hot Springs, Ark., November 14, 1921.

St. Thomas comprises the island of St. Thomas and the island of St. John and a number of very small islands, many containing only a few acres. The two large islands are about one mile apart. The population is about 11,000, one-tenth of whom live in St. John. The Medical Department of this municipality is divided into the Sanitation Department and the Department of the Sick, the former in charge of the Chief Sanitation Officer and the latter in charge of the Chief Municipal Physician. The Chief Municipal Physician has as his medical assistants a number of medical men designated municipal physicians, one of whom is located in the island of St. John. A hospital with the capacity of 100 beds is located in St. Thomas and a large out-patient department is maintained. A school for native nurses has been maintained at the hospital for about three years. This school for instruction has produced very competent graduates who in time will no doubt be able to entirely take over the work of the American nurses. A municipal dentist under this department cares for the teeth of the school children.

Funds for the department of the sick are appropriated annually by the Colonial Council to be expended under the direction of the Chief Municipal Physician. The purchasing officer of the hospital known in Danish days as the inspector is by law the local registrar who records birth and death certificates and issues burial permits.

The work of the sanitation department, in charge of the Chief Sanitation Officer covers a wide field. The most laborious duty is the night soil removal but in addition there is mosquito control, study of infectious diseases, examination of food products and control of water supplies. Night soil removal probably offers one of the most difficult problems for the small town sanitary officer. In the Danish days only the better families could afford privies. The great mass of the people were accustomed to use the most convenient receptacle, which was carried to the harbor and emptied after night fall. Less energetic individuals allowed the receptacle to stand in the yard indefinitely or threw the contents into the street. The first step in relieving this condition was the installation of a suitable container for each family in which the family night soil was placed. The first containers were 5 gallon gasoline tins which were replaced later by special galvanized iron cans. The filled cans were collected nightly and clean cans distributed by the night soil carts. The cans were emptied and cleaned at a station located on the beach several miles from town. The carts were later replaced by trucks. In 1920, one section of the town was piped for a salt water flushing system and "Family joint toilets" each capable of caring for a dozen families were installed. Due to the corrosive action of salt water on the ordinary toilet fixtures the "Family joint toilets" are made of concrete, with a copper flushing bucket which flushes the toilet at regular intervals according to the adjustment.

Mosquito control is so intimately connected with the control of water supplies that the two may well be considered together. The water supply of the Virgin Islands is obtained with a few exceptions by collecting rainfall from the roofs or from small artificial water sheds and stowed in cement or metal cisterns, barrels, tubs, or any obtainable receptacle. The exceptions are an occasional mountain spring and a number of shallow brackish wells. The wide variety of containers used for storing water makes the problem of controlling mosquitoes a very difficult one. Three methods are used, screening containers, surface oiling and stocking with mosquito fish. Screening and oiling are of value within limits, but are expensive and need constant supervision. Usually the property owner after considerable trouble and expense says "Oh well, put in the fish." Before fish are placed in closed cisterns, screens must be installed to admit light as without light the fish will not survive. The examination of food products includes the manner of preparation and of sale. Milk is the most important food product handled and offers quite a difficult problem. As the milk must be handled without ice it is no small problem to supply the consumer with a clean product. The sanitation officer is materially assisted by the universal custom of boiling milk before using. Abattoirs are the property of the municipality and are under the supervision of the Sanitation Department. The study of infectious diseases includes the detection of cases and contacts and the methods to prevent spread of infection. In addition to the common infectious diseases must be added tropical infections, particularly hook worm, malaria, leprosy, dengue and filariasis. Surveys have shown that a high percentage of the people without other symptoms harbor adult filaria. Hook worm surveys do not indicate much hook worm infection except among the colony of poor whites. During the past winter, the presence of plague in Porto Rico made it necessary to start trapping and examining rats. Malaria is infrequent and fully 90 per cent of the cases are imported from neighboring islands. This department also has charge of revaccination and the administration of typhoid prophylaxis which is universal in the islands. At the request of the Department of Education, the Sanitation Department has just completed an examination of all school children. The funds for the Sanitation Department are appropriated annually by the Colonial Council.

The municipality of St. Croix has an organization similar to that described. The Department of the Sick handles two sixty-bed hospitals, one in Christiansted and one in Fredericksted. In addition to these hospitals it maintains and manages one insane asylum with 40 beds and a leper colony of 100 beds located at Richmond. The work at the leper colony has taken on added interest during the past year due to the institution of treatment with the split products of chaulmoogra oil. The results from this treatment are very promising.

The medical administration of the Virgin Islands since the change of sovereignty has achieved many important results among which the most important are:

1. Marked reduction on infant and general mortality rate.

2. General administration of typhoid prophylaxis and the disappearance of typhoid as mortality and morbidity factor.

3. The disappearance of pellagra.

4. Improvement in general sanitation especially in connection with night soil collection and mosquitoes.

5. Preservation of accurate mortality, morbidity and birth statistics.

6. Relief of the deformities resulting from filariasis.

7. Improvement of conditions in the production, and distribution of food products.

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# THE AMERICAN JOURNAL OF TROPICAL MEDICINE[1]

HENRY J. NICHOLS

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*The American Journal of Tropical Medicine* is now completing its first year in a condition which is fairly satisfactory to the editor and to the publishers. It has apparently also been acceptable to its readers. As is well known, American workers in tropical medicine have wanted and needed a journal for some time. Our population, our resources, our history and our prospects have all seemed to warrant it. A journal somewhat on the same lines was conducted in New Orleans for a short time a few years ago. It was discontinued, but only for personal reasons and not because there was no place for it.

The existence of a journal reduces itself to a question of manuscript and money. The present journal was established after an offer of a strong publishing house to undertake the financial risk. The editor considered this offer an opportunity that should not be missed. An Advisory Editorial Board was formed, made up of representative workers in tropical medicine in all parts of our country and its dependencies. A tentative arrangement was made with the Council to have the journal the official organ of the American Society of Tropical Medicine and a start was made. The results have justified the belief in the possibilities. The members of the Advisory Board have given loyal support. Manuscripts have been received in sufficient quantity and quality to fill the regular numbers and with material coming from the annual meeting of the Society of Tropical Medicine, it is safe to say that there will be no difficulty from this point of view. This year there have been contributions from American workers in various places in the United States, Panama, Hawaii,

[1] Read at the seventeenth annual meeting of the American Society of Tropical Medicine, Hot Springs, Ark., November 14, 1921.



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Cuba, Santo Domingo, Brazil and Peru—a fairly representative geographical distribution.

The publishers also have a fairly good subscription list which while not large enough as yet to make the journal self-supporting is growing and in the publishers' opinion will support the journal inside of two or three years.

The journal is planned as a medical journal, that is, as a journal of applied science rather than as a journal of the basic sciences themselves. However, as science and practice are so closely related and interdependent, no sharp line is being drawn, provided the contributors keep in mind the medical necessities of life.

The American experience in tropical medicine has been largely an official or semi-official one and it is natural that the home of the journal should be in Washington. At present it is at the Army Medical School and can continue there, in spite of inevitable changes of personnel, as the teaching of tropical medicine is a part of the official work of the School and the management of the journal can be regarded as a semi-official duty and an asset in teaching. It may be desirable to rotate its management among other branches of the Government Service, but Washington has distinct advantages as its permanent home. Along these lines the *Journal* can attain a position worthy of the past accomplishments, and present and future possibilities of America n tropical medicine.

In connection with the project of making Washington the home of the *Journal*, the Army Medical Museum is also a suitable place for the home of pathological collections of tropical medicine. This project is explained by the Curator in an accompanying article.

The *Journal* now receives the following exchanges, which are distributed on request to the members of the Advisory Editorial Board:

*English*

Journal of State Medicine
Bulletin, Tropical Diseases Bureau
Annals of Tropical Medicine and Parasitology
Review of Applied Entomology

Medical Science (Abstracts and Reviews)
Indian Journal of Medical Research
Transactions of the Royal Society of Tropical Medicine and Hygiene
Journal of Tropical Medicine and Hygiene

*French*

Archives Des Institute Pasteur De L'Afrique Du Nord
Revue de Medicine et Hygiene Tropicales
Bull. Soc. Path. Exotique

*Italian*

Lo Sperimentale
Annali d'Igiene

*Spanish*

Archivos de Medicine
Cirugia y. Especialidades

*Portuguese*

Arquivos de Instituto Bacteriologico

*Peruvian*

Anales de University Facultad de Medecine de Universitad de Lima
La Crinica Medica

*Dutch*

The Tijdschrift voor Vergellijkende Geneeskunde etc.

*German*

Archiv fur Schiffs und Tropen-Hygiene

*American*

Journal of Parasitology
Chemical Abstracts
Journal of Philippine Islands Medical Association
Transactions, Medical Society Isthmus of Panama

The *Journal* will also publish book reviews on suitable subjects. The question of abstracts has been considered, but the Bulletins of the Tropical Disease Bureau are so complete that it seems undesirable to attempt anything in this line. The subject of personal notes has also been considered and they will be incorporated as soon as practicable. Editorials may also be added. It is expected to publish abstracts in Spanish at the end of each article.

In relation to the Society, the *Journal* should be owned by the Society. It should publish the transactions of the annual meeting. The Council should have a deciding voice in the management. Membership dues should include a subscription to the *Journal*. Any returns from the *Journal* should be distributed to pay for expenses of Society and *Journal* in a fair ratio, to be determined by the Council.

In asking support of the *Journal*, the Editor is asking for a recognition of the needs of the individual worker and of organizations for such a journal and of the advantages of maintaining one.

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# SECTION OF TROPICAL MEDICINE, ARMY MEDICAL MUSEUM, WASHINGTON, D. C.[1]

G. R. CALLENDER

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The collections of the Army Medical Museum illustrating those diseases commonly considered as tropical, and including particularly insect borne diseases and those due to animal parasites, are being grouped together as covering most of the diseases of special interest to students of tropical medicine. The intention of this new arrangement is to so place this material that it may be more easily studied as a group with the idea that those interested will avail themselves of the opportunity to study it and that becoming interested they will assist the museum by making additions. In spite of the fact that many of our states, the territory of Hawaii and our island possessions are tropical or sub-tropical, pathological specimens illustrating the so-called tropical diseases are relative rarities in the museums of the United States. It is believed that it is a proper function of the American Society of Tropical Medicine to see that this condition is remedied and this note is presented with a view to offering a method of solution of the problem. The Army Medical Museum hopes in the near future to so combine its activities with other museums and pathological departments that a general exchange system may be inaugurated of benefit to all concerned, while at the same time maintaining in its own collections adequate material for the study of any group of diseases, no matter how unusual they may be. In some instances it probably will be impossible to gather sufficient material for general distribution, but it is believed that practically all conditions can be represented at the Medical Museum in Washington.

[1] Read at the seventeenth annual meeting of the American Society of Tropical Medicine, Hot Springs, Ark., November 14, 1921.

The present collection contains quite a few specimens illustrating this group of diseases, most of which have been contributed by special boards of army medical officers appointed for duty in the tropics in connection with special problems of the Medical Department. The yellow fever board, headed by Major Walter Reed, is perhaps the first of these groups to contribute and some twenty-five or thirty specimens of the organs of yellow fever victims were added to the collections at that time. A board for the study of tropical diseases in the Philippine Islands has contributed the greater part of this collection which includes some 150 mounts of leprosy, many specimens illustrating dysentery and a few specimens of mycetoma, filariasis, etc. These collections include also examples of the insects transmitting disease as well as animal parasites. Some of the diseases of interest in this group are not represented at all, and others by too few specimens to be of much value. This deficiency can be easily remedied by those having access to such material. Several men have promised to aid by sending in such material for the collection, among them Dr. Chagas of Brazil who has promised specimens illustrating Chagas' disease or South American trypanosomiasis of which the collection now has no examples.

Specimens should preferably be sent after going through the Kaiserling process or may be shipped after hardening in 10 per cent formalin for one to three days, according to the density of the specimen. On receipt they are prepared, photographed, histological material made and the gross specimen mounted. The descriptions, clinical notes and histological slides are filed. Those furnishing specimens may have copies of photographs, both gross and microscopical, returned if they so indicate. The clinical notes, descriptions, etc., are extremely valuable, many specimens depending for their greatest interest on those clinical features which can only be preserved if adequate histories and recorded physical examinations are forwarded with the specimen, the idea being to carry on into the future the lesson it has taught the person who has collected it and who has had opportunity to observe the case.

The museum maintains a general collection and is always glad to receive pathological specimens of all varieties. It is hoped that the members of the American Society of Tropical Medicine will coöperate in making the collection on tropical diseases adequate in every way and will use it freely. The collections are open for study to physicians from 9 a.m. to 4 p.m. Microscopes are available and permission to use the histological material and consult the record files can be obtained from the Curator, accommodations being available to those who desire to make extensive studies.

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# THE TREATMENT OF TRICHOMONAS INTESTINALIS INFECTIONS[1]

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The treatment of any flagellate infection immediately brings up the question as to whether or not the flagellate to be treated is pathogenic to the host. Among the common intestinal flagellates found, we note the Trichomonas, Giardia, Chilomastix, Cercomonas and Waskia Intestinalis, in about the order named. Of these only the Giardia is more or less universally accepted as having definite pathogenic qualities.

The frequency of Trichomonas infections varies considerably, judging from the reports of various observers. Lynch found 20 per cent of his patients infected following a saline purge, Barlow reporting 25 per cent and Castellani about the same percentage. McNeil reported 5 per cent of patients from this clinic in 1917 harboring the flagellate but his examinations were not preceded by the usual purge. Kofoid and Swezy found only 0.1 per cent in 2400 cases of military patients from overseas and 0.5 per cent in 576 Home Service men. Pringault in 943 stool examinations found only 0.6 per cent infections. We have found 20 per cent of our cases infected, the saline purge being given in all cases.

All of the cases in this latter series have given a history of diarrheal attacks at some time, and in several instances mucus and some blood were also present in the evacuations. Woodcock described the Trichomonad stool as loose or thin diarrheal, containing sometimes a little mucus and scattered pus cells, the diarrhea being troublesome, chronic, and often resisting all

[1] Read at the seventeenth annual meeting of the American Society of Tropical Medicine, Hot Springs, Ark., November 14, 1921.

treatment. Barlow thinks that the increase of numbers of Trichomonads in the stool is the result and not the cause of the diarrhea. Bahr has also stated that there is no evidence that the Trichomonas is pathogenic, concluding that its presence in the diarrheal stool is only accidental. On the other hand, Emerson states that they are now to be considered pathogenic, and the adequate cause of even a severe diarrhea. Kofoid and Swezy have adopted Wenyon's cautious conclusions that the Trichomonas may at least in some cases cause diarrhea, an opinion also held by Castellani. Escomel is more emphatic in his support of the contention that the Trichomonas is pathogenic, reporting a large epidemic in Arequipa, Peru, from a contaminated water supply. In this monograph he mentions four cases of hepatic abscess, due, so he states, entirely to the Trichomonad.

In an excellent critical review of all the intestinal flagellates, Haughwout quotes extensively from the researches of Hadley to show that in some instances the Trichomonad may assume definite pathogenic qualities. Hadley reports finding Trichomonads in and beneath the mucosa and submucosa of the ceca of turkeys, believing that they enter through the goblet cells of Lieberkuhn's glands, being forced in by the peristaltic movements of the intestines or pushing their way into the cells similarly to the Trypanosomes. Haughwout believes that the axostyle of the Trichomonads may serve as a borer to break through the surface of the epithelial cells and that then the rapid undulatory movements of the flagellate serve to force it into or between the cells. He thinks that "we should abandon as our criteria of pathogenicity or non-pathogenicity, the presence or absence of blood and pus in the stools" and suggests among the possible effects that may be produced by these organisms the following:

1. The production of anti-growth vitamines or growth inhibiting substances as suggested by Gibson in 1918 with the Ascaris.
2. The production of substances definitely toxic.
3. Unfavorable effects upon the host through the liberation of the products of metabolism of the parasite.
4. Mechanical irritation of mucous surfaces by the parasites when present in large numbers.

5. Interference with absorption in the intestines through the adherence of large numbers of parasites to the surface of the epithelium, as in the case of the Giardia.

6. Actual invasion and destruction of the tissues with all its concomitants and seqeulae.

He presents the interesting theory that changed conditions in the host, probably chemical changes originating in the cells and body fluids of the host, may substitute tissue parasitism for lumen commensalism in the case of the flagellates.

It is conceivable that such a change might take place as a result of the effect of the products of metabolism of the parasite upon the host. As such might be considered the practically constant marked hypochlorhydria which is common in the majority of protozoon diseases of the intestine, and which we have noted in all our cases of Trichomonas infections. As a result of this hypochlorhydria or as an accompanying result of the effect of the flagellates we have noted also almost an entire absence of bile in the feces, using Schmidt's bichloride test.

Working with specimens from this clinic, Boyd in 1918 reported the cultivation of the Trichomonas in fecal suspensions in physiological saline. In a subsequent paper, published in 1919, he states that he found certain specimens of feces unsuitable for the purpose of making suspensions. These unsatisfactory suspensions in which the organisms will not grow are characterized by an acid reaction to litmus and an intense bile staining of the saline above the fecal sediment. The suspensions in which a good growth was secured were neutral to litmus and the supernatant saline was colorless or only tinged slightly yellow.

Using these observations as a working hypothesis and having in mind the theories expressed by Haughwout regarding the chemical changes originating in the cells and body fluids of the hosts, we have formulated a plan of treatment in which we have hoped to counteract the hypochlorhydria and the acholic condition of the intestinal contents, believing that if we could so influence the functions of the host as to produce an excessive concentration of bile in the intestinal contents a media would be produced inimical to the growth and reproduction of the Trichomonas. Our treatment has consisted of the following:

The usual preliminary saline purge and liquid diet having been given, calomel gr. $\frac{1}{10}$ is ordered every twenty minutes until ten doses have been taken, this to be repeated daily for four days each week for four weeks. Dried ox-gall gr. V–XXV in capsules is given t. i. d. after meals in addition to Dil. HCl. M. XX–XL. The HCl and ox-gall are given daily during the entire month. If an examination of the stool following a saline purge at the end of this time shows Trichomonads present, the treatment is repeated. It is our practice to repeat the treatment at least once.

Owing to the natural tendency for the flagellates to disappear from the stools for varying periods and to reappear later, it is rather difficult to determine definitely when a cure has been secured. Three of our cases which we have been able to observe closely over a period of four months have remained free of flagellates, although recently one of these cases returned with many organisms again present in the stool. This patient, a negro woman, had been living in the country, drinking water from shallow wells, and it is very probable that a reinfection resulted from a contaminated water supply, the most common source of infection as noted by Escomel, Rhamy and Metts, and others.

Our past experiences in treating Trichomonas infections, wherein we have used methylene blue, thymol, emetin and the arsphenamine products, would make us hesitate to proclaim the treatment outlined above as the treatment par excellence. We realize also that the number of cases observed is entirely too few to serve as the basis for any broad conclusions. However, in the group of cases which we have treated, three have remained free of flagellates for four months, a length of time sufficient we think to justify our conclusion that these patients were cured as a result of the measures employed. The fact that this treatment appears to be based upon physiological grounds, and the ease with which its details are carried out, we believe entitle it to an extensive trial.

I wish to acknowledge the assistance of Dr. E. Roe in the above study.

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# THE INCIDENCE OF A LEPTOSPIRA IN THE KIDNEYS AND OF PARASITES IN THE INTESTINES OF ONE HUNDRED WILD RATS EXAMINED IN ENGLAND

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*Wellcome Bureau of Scientific Research*

A good deal of work has been done on the presence of *Leptospira icterohemorrhagiae* in the kidneys of wild rats since the first descriptions by the Japanese in 1916, and its incidence all over the world in this situation is now practically proved. There have been two contributions to the subject as it affects England: by Coles in November, 1918, and Foulerton in March, 1919. Coles working in the Bournemouth district with the microscope alone found the organism in 9 out of 100 rats examined, while Foulerton in the London area by inoculation of guinea-pigs found 4 affected rats out 101. Coles unluckily does not mention the period of the year in which his examinations were made, and Foulerton, commencing his examinations on July 12, examined 82 rats before finding 3 positive out of a batch of 12 on November 5. He afterwards, on November 15, found another positive in a batch of 7. From this and the evidence of Ch. Nicolle and G. Blanc, and Ch. Nicolle and Ch. Lebailly in Tunis, he suggests a seasonal incidence in the winter. In a later paper Blanc corrects his earlier view, and points out that possibly locality is more important than season.

As a systematic examination of rats for another purpose was going on in the Bureau, and it had already been found by inoculation of guinea-pigs that a fair proportion were infected with *Leptospira icterohemorrhagiae*, it was thought well to carry out a systematic examination of rats at different periods from those in which Foulerton made his observations.

Up to the present I have examined 100 rats in two batches of 50, the first period extending between February 2 and March 15, the second from May 2 to June 22, and I am now commencing a third series, which will coincide with part of the time in which Foulerton worked.

As I had demonstrated the parasite easily by Giemsa-stained smears and Levaditi-stained sections of the kidney in some of the cases which had been proved positive by inoculation, I adopted these methods of examination; the frequent non-virulence of the parasite and the not infrequent immunity of guinea-pigs would have made the use of a large number of these animals in each case necessary if the inoculation method had been used.

These two staining methods gave practically identical results. In only one case were they different and in this the sections showed the parasite while the smears did not. The kidney was the organ chosen, as in the earlier attempts I had been unable to demonstrate the parasite in other tissues. In the second group of 50, examinations were made by smears alone.

Of the 100 rats all but 10 came from the London district and only 4 were specimens of *Mus rattus*.

As far as inoculation results went the only guinea-pig inoculated from a positive rat in the first batch failed to take the disease, but in the one case in the second batch the result was positive.

The results are as follows:

| | RATS EXAMINED | RATS FOUND POSITIVE | PER CENT |
|---|---|---|---|
| First batch, February 2–March 15 | 50 | 12 | 24 |
| Second batch, May 2–June 22 | 50 | 18 | 36 |
| Totals | 100 | 30 | 30 |

All the positive rats except one came from the London district, and that one from Hampshire, but outside these series positive cases were found by inoculation from rats from Cheshire and Kent.

In 52 of these 100 cases the urine was examined by the dark backgound method, this number being that of those rats that had urine in the bladder when post-mortemed. Out of these cases

18 were found to be positive by the staining methods, but the leptospira was only demonstated in the urine in 9. The only figures of incidence that I have seen that are comparable to these are those of Ido, Hoki, Ito, and Wani, who working microscopically found 32.4 per cent.

In the smears the organism was found singly and in coiled masses both large and small. In fact the masses are sometimes so large and dense that it is only by examination of their periphery that their nature can be made out. In sections the convoluted tubules, often those near the suface of the kidney, are seen to be affected, masses of the organism appearing to block the lumen, lying in hollows between projecting cells or lining the lumen with one end free, almost giving the appearance of a ciliated epithelium. They can also be seen in small numbers in the cells of the tubules. The reactions of the organism when stained by Levaditi's method (Dobell's modification) are not at all constant. Organisms in the same section of tubule may be black or any shade of brown, though when in the cells they are generally dark. As the penetration of the reagents to a spot of this size must be equal, some difference in the parasites may be responsible for the varying color. Size, I think, has something to do with it.

The numbers shown above prove that a very large proportion of rats are infected, and the probability is that the rate of incidence is really much higher. It would be a mere chance if one found the organism in a kidney when only one or two tubules were affected, and they are only affected for a short part of their length. My examination of each smear was not very prolonged and I seldom examined more than one.

It is difficult to say whether the presence of the organism has any pathological effect on the rat, though one is struck on examining sections by the number of changes one observes, when compared with what is probably the normal kidney as seen in the white rat. At least 75 per cent of the kidneys show changes of a definitely pathological character. Marked dilatation of the tubules, giving a cystic effect and once associated with the presence of leptospira in them, areas of infiltration by lymphocytes and polymorphonuclears, great enlargement of many of the renal epithelium cells and often of the cells themselves, together with the presence of casts, were the commonest changes observed. Whether these changes are the result of the presence of the leptospira or of some of the numerous bacilli which are present in many cases one cannot say. None of the rats examined, however, appeared gravely ill, the bodies of all being well nourished.

There seem to be two points to be deduced from the above:

1. That there may be a high incidence of a leptospira, probably *Leptospira icterohemorragiae,* in rats in an area where the disease is practically unknown. The high rate of incidence shown by the Japanese was correlated with the area being one where the disease was endemic.

2. That it is very unlikely that the incidence is greater during the winter months. In the second batch of cases in early summer the number of rats affected was 50 per cent greater than in the later winter months. I do not consider the figures large enough, however, to give a definite pronouncement.

With regard to the intestinal protozoa, I am surprised to find the rate of incidence so low, but I am afraid my examinations were slight, as I only examined one specimen from each animal. As is well known, fairly frequent examinations on different dates are required before any really adequate idea of the intestinal fauna can be obtained. I give the results for what they are worth, dividing them into two batches as before, and also the percentage of incidence in 400 rats over a period of thirteen months.

| | BATCH 1 | BATCH 2 | AVERAGE PER CENT OF TWO BATCHES | PER CENT IN 400 RATS 13 MONTHS |
|---|---|---|---|---|
| | *per cent* | *per cent* | *per cent* | *per cent* |
| Entamoeba muris | 12 | 24 | 18 | 17.25 |
| Trichomonas | 12 | 24 | 18 | 19.0 |
| Coccidia | 24 | 20 | 22 | 23.75 |
| Giardia | 10 | 12 | 11 | 7.0 |
| Octomitus | | 2 | 1 | 2.5 |
| Chilomastix | | 2 | 1 | 1.75 |

There here again appears a tendency for an increase of protozoa in the early summer months. That the average percentage of the two batches is a fair sample of the year is seen by comparing the last two columns.

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## DESCRIPTION OF PLATE

Fig. 1. Photomicrograph of Section of Kidney of Wild Rat Stained by Levaditi's Method

showing tubule infected by *Leptospira icterohemorrhagiae*. The black lining of the tubule is composed of the leptospira. Below the infected tubule is a healthy tubule for comparison. × circa 1000.

Fig. 2. Photomicrograph of Smear from Kidney of Wild Rat

showing *Leptospira icterohemorrhagiae*. The oval in the left hand top corner is a coiled-up leptospira. × circa 3000.

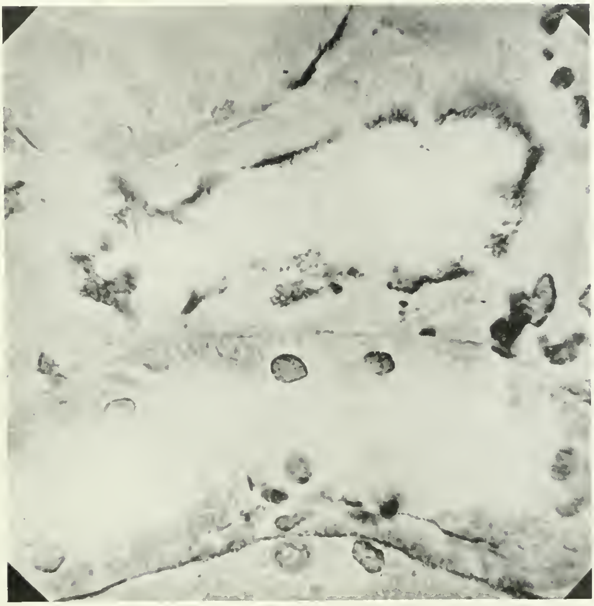

Fig. 1

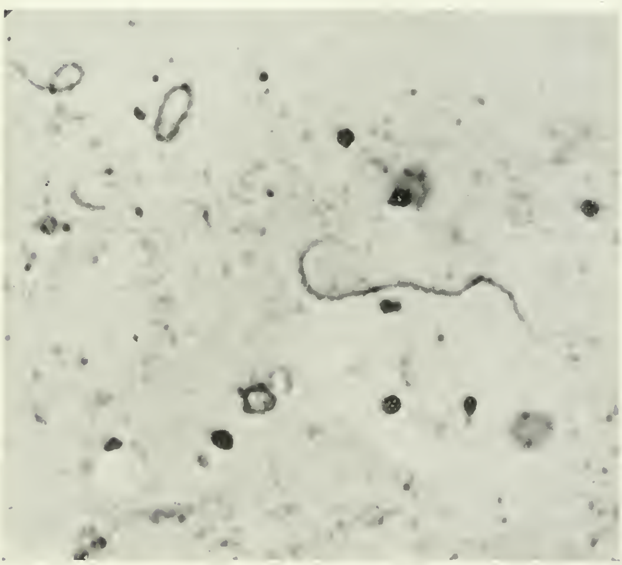

Fig. 2

# CORRESPONDENCE

December 30, 1921.

*The Editor, The American Journal of Tropical Medicine,*
Army Medical School, Washington, D. C.:

In the November, 1921, issue of The American Journal of Tropical Medicine, in a paper entitled "The Tertian Characters of Quotidian Aestivo-Autumnal Fever" Dr. Samuel T. Darling endeavors by an analysis of the charts published in my paper in the same journal, in March, 1921, and entitled: "The Classification and Differential Diagnosis of the Aestivo-Autumnal Malaria Plasmodia," to prove that the quotidian cases of malaria there reported were really instances of infection with the tertian aestivo-autumnal plasmodium. Darling calls attention to what he regards as the tertian characteristics of the charts of quotidian aestivo autmnal that are shown and from these characteristics concludes "That the creation of a specific plasmodium to account for clinical forms of aestivo-autumnal malaria having a quotidian periodicity is probably unwarranted."

I believe that any unprejudiced observer who studies the charts of quotidian aestivo-autumnal malaria reproduced in my paper will admit that they are as typical of a quotidian fever as anything that we meet with in clinical medicine and while, by following Darling's method, it is possible to trace his so-called "tertian characters" in Chart VI, one must leave a great deal to imagination to trace any evidence of a tertian character in Chart IV or even in Chart V. If these are not charts of a quotidian fever certainly such a fever cannot be illustrated by a chart. The same "tertian characters" could be as easily demonstrated, by Darling's method, in charts of a quotidian fever due to the benign tertian plasmodium or to septic infections, in many instances.

However, the claim of the sub-specific status of *Plasmodium falciparum quotidianum* is not based upon the character of the temperature chart, as this is only of secondary importance, but upon distinct differences in morphology which can be recognized by anyone who is expert in the differentiation of the malaria plasmodia. These differences are carefully described in my article and photomicrographs accompany it which illustrate the principal differences. That Dr. Darling does not admit the sub-specific status of this plasmodium is due, I am sure, to not having observed it in his experience, as it is a comparatively rare species as compared with *Plasmodium falciparum* and does not occur at all in many malarial regions.

As regards the argument of Darling that the charts of quotidian aestivo-autumnal malaria published in my paper are atypical examples of the temperature curve in infection with the tertian aestivo-autumnal plasmodium, it may be stated that each quotidian rise in temperature was accompanied by the usual signs of a malarial paroxysm in each case, i.e., there was a distinct daily chill followed by the temperature and terminating in the usual sweating stage. If these daily paroxysms, typical in character of a malarial infection, and accompanied by a plasmodium in the blood differing in morphology from that of the usual aestivo-autmnal plasmodium, does not constitute sufficient evidence for the creation of a distinct sub-species, one is at a loss to know what data are necessary for this purpose. In my many years of experience with malarial infections I have never observed an aestivo-autumnal infection showing the tertian curve so characteristic of the tertian type, in which before the pre-critical rise, or, as Darling calls it, the "second rise" there was a definite chill, followed by fever and sweating, while the initial rise, or the "first rise" terminated in sweating and a decline to below normal of the temperature. Unfortunately the chill is not indicated in every instance on the charts but in most of them it is indicated, and it is a fact that where the chill was not sufficiently marked for entry it occurred, as shown by Charts IV and V, at the time of the initial rise in temperature. In other words, the chill was least marked at the very time that it should have been present, while a definite chill occurred before the pre-critical or "second rise," if we accept Darling's interpretation of the charts, and it is well known that a chill does not occur at this time in cases of tertian aestivo-autumnal infection.

It should be remembered that it is not claimed that the quotidian aestivo-autumnal plasmodium is a distinct *species* of plasmodium but that it is a *sub-species* of the tertian plasmodium and it would be but natural, if this be true, that in both morphology and in clinical symptoms, it showed some resemblance to the species from which it had its origin. However, it is certain that the slight "tertian characters" noted by Darling in the charts published in my paper are of little value as evidence against the sub-specific status of this parasite, in view of the occurrence of the definite quotidian malarial paroxysms and the presence in the blood of the patients of a plasmodium having the characteristics described in my paper and which are those typical of this variety of the aestivo-autumnal malaria plasmodium.

Chas. F. Craig.

# YELLOW FEVER IN PERU

## EPIDEMIC OF 1919 AND 1920[1]

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### INTRODUCTION

It seems proper to give the relations of the writer of this paper to the epidemic to which it refers:

He left New York in February, 1920, as a member of the Yellow Fever Commission of the International Health Board of the Rockefeller Foundation, to join Gorgas, its chief, at Lima. He stopped at Payta, to investigate the yellow fever reported to be at Piura, the town. Fever was reported at Payta also before he landed and was, indeed, present as a beginning epidemic. At Payta he met Hanson, then Director of the Campaign against Yellow Fever and Plague, en route to Lima, but saw him only a couple of hours—talking mainly about plague, also present as a general and virulent epidemic. He, the writer, had no authority here, but the sanitary inspectors, being old Canal Zone men, asked for advice in a number of matters. He did not feel justified, however, in advising them to change fundamentals such as to cease the isolation of the sick and fumigation of houses. When Hanson returned on April 3, this was discontinued.

About the time he had finished his investigation, Gorgas informed him that he, Gorgas, had accepted a position as "Sanitary Advisor" to the Peruvian government, but (on account of his projected African trip) could not go on duty until January 1, 1921, and asked the writer to substitute him until that time. To this he agreed. He remained in Peru assisting Hanson until the end of April, when he had to return to the States on official

[1] Prepared for the seventeenth annual meeting of the American Society of Tropical Medicine, Hot Springs, Arkansas, November 14–15, 1921.



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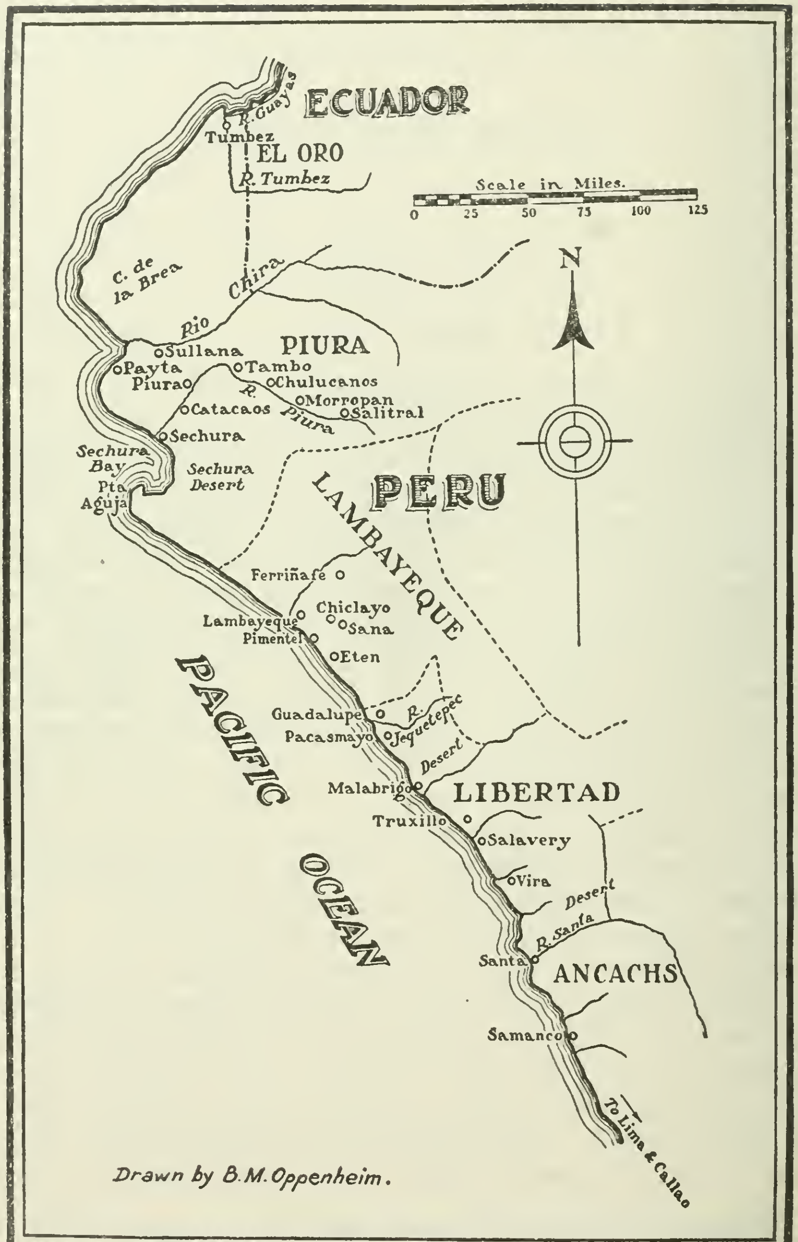
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Pimentel
Eten
PACIFIC
OCEAN
Guadalupe
R. Jequetepec
Pacasmayo
Desert
Malabrigo
LIBERTAD
Truxillo
Salavery
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Desert
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Samanco
To Lima & Callao
Drawn by B. M. Oppenheim.

business. Staying only a few days he returned to Peru in June. Finding the conditions in Piura were decidedly unsatisfactory and that Hanson was to be kept at Lima for work in that vicinity, he, with the approval of the President, took direct charge of the epidemics in the north—yellow fever and plague—as a field officer. There was no other way to carry out his own advice.

Hanson developed typhoid fever in latter August—of which the writer did not hear until the end of October.

After December 31, 1920, his status was that of a volunteer, assisting in diagnosis and advising with the President, with Hanson and with the health authorities on the conduct of the campaign against the yellow fever, which had developed in Lambayeque.

## EPIDEMIC OF 1919 AND 1920

In June, 1916, a Commission of the International Health Board of the Rockefeller Foundation, of which Gorgas was chairman and myself a member, made a survey of the yellow fever situation in South America. On the West Coast we found Guayaquil to be sharply infected with yellow fever. This town, for a number of years, had been a permanent focus of infection from which the disease had been communicated from time to time, frequently up the coast toward Panama; much less frequently down the coast into Peru and almost continuously to the towns and haciendas up the rivers (the Guayas and Daule) and on the Guayaquil and Quito Railroad.

An epidemic from this source had just been completed in Buenaventura—spreading to Cali and some smaller towns in Colombia. Esmeraldas, also to the north, had reported yellow fever the previous year, when also there had been reports, neither confirmed nor investigated, of fever at Tumaco.

Nevertheless, these places were evidently infected from Guayaquil and the infection in them would quite certainly be self-limited. The Peruvian coast seemed, and at that time was, clear of infection.

After the elimination of Panama, Guayaquil then was clearly the sole point of permanent infection on the West Coast of South America; a permanent focus itself and a source, directly or indirectly, of infection to all other ports of the West Coast in which climatic, or what is the same thing here, biologic, conditions allow yellow fever to propagate itself. The other ports on this coast when infected had in the past always cleared themselves spontaneously from yellow fever. Guayaquil then was evidently the key-point on this coast.

Moreover, with the then existing trade-routes—there being no direct communication between the ports of the West Coast of South America and any port suspected of being infected with yellow fever, all such trade going by Balboa—the elimination of yellow fever from Guayaquil would not only free the whole Pacific Coast of South America from yellow fever, but, as long as the present routing of ships continued, do so in perpetuity. It was thus doubly a key-position and the elimination of yellow fever therefrom extremely desirable.

This was arranged for and it was purposed to begin the work in the early part of 1917. The imminence of war prevented this and it was not begun until the summer or fall of 1918, when Connor took charge of the work for the International Health Board. His success was complete. Yellow fever quarantine was removed from Guayaquil in August, 1920, and might have been safely removed ten months earlier.

In the meantime, however, in the early part of 1919, yellow fever had gone from Guayaquil via Tumbez or Payta—the former most probably—to Peru. There Hanson, formerly assistant chief sanitary officer of the Canal Zone, but then engaged for malaria control work by the Peruvian government, found it in the summer of 1919 at a number of places in the department of Piura, which, with Tumbez, is the most northern department of Peru. At Piura, the town, he developed an attack himself, a severe one, but recovered.

The fever died down in the cool weather of July and August of 1919 and Gorgas, who visited Piura in the fall, considered it as practically extinct. In the department of Tumbez it was—

doubtless from the exhaustion of human material. In that of Piura it was not, and with the advent of hot weather it recrudesced and, before it was done, spread to practically every town and village on the coastal plain in the department. The department of Piura is somewhat larger than Massachusetts and Connecticut. There are no roads: a railroad from Payta to Piura, and a short one from Piura to Catacaos. Travel otherwise is by horse-back or burro, carrying one's water. Goods go by pack animals, burros, also carrying water.

It was reported in Payta, La Huaca, Miraflores, Sojo, Sullana, Piura, Catacaos, Muñuela, Vice, Bella Vista, Sechura, Tambo Grande, Chulucanos and Morropon—places of from 1500 to 40,000 inhabitants, in most of which I saw cases myself, and in some haciendas. It was quite an epidemic. I have reports of 496 cases and 152 deaths, and the reporting was extremely imperfect. There were probably over 250 deaths and from 4000 to 5000 cases. The last case, a doubtful one, died September 18, 1920, at Chulucanos.

Obviously, this outbreak in Peru would prevent the ultimate result aimed at by the elimination of yellow fever from Guayaquil, i.e., the permanent freedom from this disease of the Pacific coast of South America without further sanitary effort.

Confined to the departments of Tumbez and Piura it would quite certainly die out spontaneously within, say, two and a half years, but left alone it would as certainly extend south by overland travel to the rice country of Chiclayo and its environment and to the populous sugar district of which Trujillo is the center. By sea the whole coast of Peru was threatened, and yellow fever has in the past extended to Callao and Lima as a virulent epidemic.

True, in the past such epidemics in Peru have always been self-limited, that in Lima and Callao lasting, as I recollect it, into the third year. Yet whether this would be so again may be a question. The increase of population since that time and, more important still, the increased intercommunication with the consequent increased movement of people susceptible to yellow fever, made me very doubtful of it. The unit of the cotton, rice and sugar districts, the departments of Piura, Lambayeque and Libertad, seemed as liable to form a permanent focus as is Yucatan with its small towns and sisal plantations. It is well to remember that Rio freed itself spontaneously from yellow fever once, possibly twice, but on subsequent infection did not do so.

Besides the possibility of forming a permanent focus on this coast, there was the risk of re-introducing the disease into Guayaquil, now free of it, rendering it necessary to continue the expensive Stegomyia control (to prevent its propagation if introduced) until the threat from Peru was removed. A second campaign for a reinfected Guayaquil had been economically and politically impossible. To me then, the situation seemed serious enough when I landed at Paita on March 3, 1920, or rather as soon as I could look over and appreciate the situation.

### *The epidemic itself*

As usual the disease failed of early report in many, indeed in most, places. In the beginning, it was usually found after it was well established.

On the other hand, and especially in the fall of 1920, several epidemics reported as yellow fever were found to be iufluenza or malaria and one was bubonic plague. This last was on the divide between the Amazon and the Pacific Ocean; propagated apparently by guinea-pigs.

### *Mortality*

The death rate was low. There were two local reasons evident for this: First there was considerable negro blood, in the towns especially, and second the fever was practically confined to people under twenty years of age. The combination of these factors would markedly tend to a low mortality.

For the second factor, I will say that yellow fever in a native-born adult was extremely rare. I saw none. Among adults born elsewhere—North Americans, Europeans, and people from other parts of Peru—it was common and of ordinary severity. Quite certainly there had been a general epidemic in this country about twenty years ago. This was confirmed by inquiry, although, I think, not of record.

I have said that the death rate was low. One would not think so from some of the reports. One place gave "cases, 14; deaths, 12." Here most of the cases were "found dead" and diagnosis made from post-mortem appearances. Many cases were hidden and many more simply not reported.

In one place, Payta, the conditions for observation were unique: First, the place was small, 3000 people; second, absolutely free from malaria of local origin, and, indeed, from sickness of any kind except plague and yellow fever; third, the yellow fever hospital was popular among the peones; fourth, owing to a series of lucky recoveries when he first arrived, the reputation of the writer as a therapist in yellow fever received, certainly an "unearned increment" and he was taken to see nearly all of the sick. The result was that I think nearly half of the sick were seen by a physician. I feel sure few were hidden, after, say, March 14, and that erroneous diagnosis was reduced to a minimum.

Payta gives 130 cases, 18 deaths (of those who died 4 were born elsewhere) and from Payta I feel like taking my death rate. In other places "casos escondidos" were the rule, many being first seen when dead.

*Management of the epidemic*

In Piura, Tamarinda, Payta, and a few other places, this was by attempting the control of both hosts, human and insect; by isolation of the sick man (in hospital when available); and fumigation of his, and the adjacent premises, and also by control of Stegomyia breeding.

The stegomyia work was pressed, and was properly done, but, in my judgment, that for the sick man, except in so far as it helped him and lessened the number of attacks in his family, had better have been omitted, as involving a waste of both time and money. The *shortening* of the epidemic, by putting all of one's force on elimination of stegomyia breeding places had, I think, saved more (although not the same) lives than fumigation of his premises, especially, as on account of the open construction of the houses, this was difficult.

That this was done was due to a great extent to the fact that Hanson, "Director of the Campaign against Plague and Yellow Fever," had three sanitary inspectors from the Canal Zone, two of whom had done, or seen, similar work in Panama, in 1905, and who simply followed and induced him to follow the methods there used. Hanson, an excellent man, had had no experience with yellow fever until he found himself in this epidemic and followed recognized authority.[2] All the local authorities too were *urgent* for isolation and fumigation. When Hanson returned from Lima on April 3, this was discontinued everywhere and all reliance placed on anti-stegomyia work. This was the only method used in Morropon, Tambo Grande, Chulucanos, etc., where the epidemic was discovered after this date.

Payta gave some interesting information on the length of life of Stegomyia in nature. Rapid and thorough work against Stegomyia breeding was instituted here in early March and on March 13, this was so well controlled that the number *produced* thereafter would not be sufficient to propagate yellow fever. There was no apparent diminution of cases, rather an increase of *reported* cases for, say, two or three weeks, but a rapid drop after April 14, and the last case occurred April 24. Obviously, if my postulate be admitted, all cases after March 13 were infected by Stegomyia already in flight prior to that date, which were thus living and effective, infecting the case developing April 24. This agrees fairly with the results of the work of Converse at Iquitos and that of Connor in Guayaquil. It is more definite than either, as Payta was small and the breeding quickly and completely controlled. In consequence of the intense dryness, the fierce heat at mid-day and the high winds, the average life of stegomyia in nature should be less in Payta, as seemed to be the case, than in Guayaquil or Iquitos. Yet they did breed very freely and were abundant indoors.

Except for the La Brea oil country, no attempt was made to limit travel in the department; it would have been useless to have done so.

[2] Gorgas recommended isolation and fumigation with control of stegomyia breeding places at the same time for the sanitation of Guayaquil, in his report of 1913.

### *Terrain and water supply*

Except in the irrigated valleys of the Chira and Piura Rivers, the department of Piura west of the foothills of the Cordilleras is desert, absolute desert—table lands and small mountains. This irrigated district is rather densely populated in towns and villages, not single farm houses. In one town, Piura, water is supplied to some of the better class houses in pipes by privately owned wind-mills or hand pumps. In the others it is brought from the river by hand or in small kegs on the backs of burros. Here the oil tin is much in evidence.

Two settlements of importance are not on the rivers: the oil districts of La Brea and Payta. The former are under foreign management and as soon as the fever was announced, were protected from the rest of the province by a quarantine, the more easily made efficient by the paucity of land communication with the rest of the department, and, more efficaciously, by an anti-stegomyia campaign begun somewhat later. They escaped infection. Their water supply is distilled from sea water.

Payta, originally a fishing village, and to an extent one yet, is the port of the department of Piura. Its water supply had been through a two-inch pipe from the river Chira, about 17 miles distant. It had broken down and when the epidemic begun about 90 per cent of the water used was brought in in tank cars and sold by measure to the people. That piped in was distributed the same way, as the water works was a private corporation. Water here was *exceedingly* scarce, at times not enough being furnished for cooking and drinking.

### *Method of control of Stegomyia breeding*

This scarcity of water everywhere greatly complicated the problem of stegomyia control: First the water jars were rarely emptied—in Payta never—they were not willing to lose the even small amount left over from the last filling; second, the water was nearly always turbid. It was turbid in the river in the hottest part of the year, January to April, inclusive, and became more so in the containers from their being rarely emptied, the sediment remaining in the bottom of the jar. This last condition rendered inspection of water unusually difficult. Stegomyia is a bottom feeder and on being disturbed always goes at once to the bottom and even with electric torches, the batteries of which were difficult to renew, we simply could not see them at the bottom of the turbid water. Add to this that (*a*) the containers were always in the darkest part of the house, (*b*) 90 per cent had the upper parts so broken that it was hard to cover them even with a cloth, impossible any other way; (*c*) the favorite container, except in Payta was the *botija*, an earthenware jar about 5 feet high, with a sharp point set about 16 inches in the earth floor of the house. They held about 15 or 20 gallons. There were some of them in Payta, but not so many, not water enough to justify them. (*d*) The social standing of a household apparently depended on the amount of water they kept on hand and especially on the *number* of containers in which it could be distributed. This was not true of Payta, respectability by this criterion being too difficult of attainment.

Nor could we generally empty the water out in the street, even if it were breeding stegomyia. It was costly everywhere, in labor or money and in Payta unattainable.

We resorted then to *straining the water through cloth:* both as an inspection, the larvae being found in the last part of the water, and as freeing it from larvae. If larvae were found, the container was rinsed and scrubbed out two or three times with the cloth and the rinsing water thrown away. In Payta we strained the rinsing water again and gave it back to the householder.

This was slow work and, except for very small amounts of water, we soon changed. If a sudden dip on the surface along the sides of the *botija* yielded no larvae, a dip was made from the bottom with a long handled dipper and if this was positive or we had other reason to suspect the water it was slowly poured out into another vessel—each gang carried water buckets—waving one's hand over the surface all the time to keep the stegomyiae at the bottom. All was thus emptied except about the last foot or 18 inches and if we had not found larvae this was examined for them either by dipping from the bottom or by straining. Frankly, I think we missed no larvae of sanitary importance by this method and it was *very* much quicker than straining all in the container.

We attempted to use a long handled dipper made of fine wire gauze, to hold the larvae and let the water through, for the "bottom dipping." It was not successful; the gauze was not fine enough, nor was any kind of cloth or net covering satisfactory. It would have been an excellent addition to our armamentarium with finer gauze and enabled us to negative breeding in many a *botija* without the loss of time in emptying it. Larvae so small as to pass through, say, no. 30 or 40 gauze, would not develop into imagoes before the next inspection.

Except in Payta, we held ourselves free to empty water known to contain larvae out in the street, hence much time could be saved if the first surface or bottom dip showed them. In point of fact, if the quantity was considerable, we rarely did so, never except with a frequent offender, pouring off all we could without getting stegomyia into other vessels and throwing away only that at the bottom. In Payta during the scarcity of water, none was ever thrown away. It was too scarce.

I must add here that ultimately the government of Peru took over the waterworks at Payta and, under the administration of the Foundation Company, a decent supply of water was finally brought in with *free distribution* at a number of stations in the town. The value of this in the control of stegomyia can scarcely be overestimated.

In addition to the difficulties enumerated, resulting from physical conditions, there were a number due to social customs. For instance, the people had the habit of locking the doors of their houses and going off into the country for weeks at a time, leaving water in their houses, to which we could have access only after application *in each case* to the *alcalde.* Frequently also the door was locked, the family being in the street or gone to some neighboring *fiesta.* In either case we called at a house three days in succession and if no one was in applied to the *alcalde* for a policeman to open for us. Except in Payta—the Paytenses stayed at home—the average of "casas cerradas" was about 8 per cent of which one-third required help from the *alcalde.*

Troublesome too in the beginning was the feeling of the upper classes that they were exempt from any legal obligation. Fortunately, as they kept more water on their premises, they found that—unlike plague—yellow fever was, if anything, more prevalent among them than among the peones and as fatal. Three such deaths and two other very severe cases occurring in Payta removed most of the opposition to stegomia control among the upper class there.

The little hospital, an extremely crude affair, was popular among its cliéntèle and several patients presented themselves for readmission with pretended relapses. This was a potent factor in getting cases reported. There were few "casos escondidos" in Payta, except in the beginning.

This work was kept up until December 30. Many places were known to be free from fever long before that time, but they were in open communication with others infected, or suspected of infection—a death occurred at Chulucanos on September 18—and this was judged advisable, in the case of some necessary, to prevent reinfection.

*The results*

In spite of the difficulties, the stegomyia control was good; in the key-points, Payta, Sullana, Piura, Catacaos and Chulucanos, it was very good. In Payta the stegomyia index, i.e., the percentage of the number of *containers* with larvae to the number of *premises* examined, fell as low as $\frac{1}{6}$ per cent. Connor, on one or two days inspection in Payta, found *no* stegomyia and suggested that we continue the work to see if they could be absolutely eliminated. In early July, when this index was less than one per cent, I recommended the removal of maritime quarantine against Payta, as being *non-infectable,* although in open communication with infected towns. Passengers from such towns were allowed free pratique after a stay in Payta. Later this privilege was extended to Piura and Sullana. For Catacaos, with a population of 40,000, scattered and mobile—they were 90 per cent Indians—I was afraid to ask it. The index was low enough, but the difficulty of identification of a man as living there was too great. Chulucanos—10,000 people—and the rest of the valley of Morropon were not sufficiently under my own eye. I felt reasonably sure of its safety on December 30, but stegomyia control was kept up there to the middle of March, six months from the last case, a doubtful one. I felt quite certain that it was unnecessary, but it was little costly and was insurance. To be consistent, stegomyia control should have been kept up in all places in open communication with this district, but this had been a heavy expense and the travel from this valley to the rest of the department is very small until well after the middle of March.

During 1920, Drs. Noguchi and Kligler, from the Rockefeller Institute, were with us from March to May, inclusive. They isolated *Leptospira icteroides* from cases of yellow fever at Morropon, vaccinated a number of people and used the curative serum for the same organism in a few cases of yellow fever, among whom was Kligler himself.

This work, however, is for the Institute to report.

### *Extension of epidemic*

It is necessary to return to a description of the topography of the seat of the epidemic. See the accompanying map.

To the north the spread of the fever was limited by high mountains and a country very sparsely inhabited or uninhabited. To the east by the foot hills of the Cordilleras. Stegomyiae were not found on the upper reaches of the Chira or in the foot hills west and southwest of Morropon; water being abundant and readily accessible, there was little stowage of it in these places. This country was then "non-infectable." Stegomyiae were in abundance in Salitral, about 800 inhabitants, but no fever was reported there, the only place of any size of which this was true.

To the south the country is desert from 45 to 75 miles to the irrigated valley of which Chiclayo is the center in the department of Lambayeque. This was decidedly more populous than that of Piura and abounding in stegomyia—the very home of the *botija!* South of this, and separated by a narrow desert, less than 20 miles wide, lay the Department of Libertad, of which

Trujillo is the center. This is a large and very populous department, the center of the sugar industry of Peru and unquestionably infectable. Trujillo is the second or third city in Peru. There are many towns and the large haciendas, which are numerous, are themselves towns, one having 8000 people in a single settlement, and there are several of 5000 or 6000.

Obviously, it was all important to limit the spread of the epidemic; to prevent its spread across the desert to the south—it was limited by natural conditions in every other direction. On my arrival I earnestly pressed this as of prime importance—far more so than measures for the elimination of the fever in Piura. This without them would ultimately disappear from exhaustion of material—"failure of the human host." I could not assert the same of a well established epidemic in Chiclayo and the Trujillo districts and it would certainly cause a heavy mortality.

There was, of course, a "Cordon Sanitaire" of soldiers between the two provinces, but what I proposed was stegomyia control in that part of the Province of Lambayeque in direct communication with that of Piura.

The travel to the south was mainly from Sechura, Catacaos and Sullana. Spite of the desert, this travel, on horseback or burro, was considerable and I feared it. It was purposed then by stegomyia control work in the towns south of the desert most threatened by this travel to render them uninfectable to yellow fever should it be introduced. I pressed this even if it should be necessary to stop work in Piura, although the prompt extinction of the fever there was also of the greatest importance in the protection of Lambayeque.

This plan met with little favor from the Peruvian authorities. They relied on their Cordon Sanitaire and were unwilling to spend money against yellow fever where it did not exist. However, by the influence of Hanson, this work was begun at Chiclayo in April or May, under experienced men (an Assistant Director and a former Canal Zone sanitary inspector). On my visit to Lima in latter July, it was reported as highly successful and progressing satisfactorily. In the meantime, the work of eliminating the fever in the north was pressed by myself, both for its own sake and as a means of removing a danger to the rest of Peru.

In point of fact, a little after this time the work in Lambayeque was stopped altogether and the allotment therefor, as I was long afterwards informed by the chief sanitary officer of Peru, was "used for other necessities." In December an epidemic of "haemorrhagic malarial fever" was reported in Ferreñafe, a town of 8000 people in the northern part of Lambayeque. About the middle of January this was pronounced yellow fever by Dr. Quiroz. Some days later, Hanson and I found an extensive epidemic, past its acme and from two and a half to three months from its introduction. A few days later we saw it in the towns of Lambayeque and in Chiclayo and it doubtless existed in a number of others as no systematic search was made to find cases.

The epidemic of 1921 was begun. It unquestionably came from the north—the history is from Catacaos in July, 1920. It could easily and certainly have been prevented by stegomyia control in Lambayeque in 1920 and at less than five per cent of the cost of eliminating it, without counting the loss of life it has caused.

## EPIDEMIC OF 1921

It is not my intention to give the history of the epidemic of 1921, yet a few words on the *plan* of its control and the initial measures therefor seem proper.

As compared with our condition in 1920 we possessed some advantages: We had a number of men partly trained and a few well trained and reliable. Nor were the lessons of the previous year altogether lost on those with whom we worked. The futility of the Cordon Sanitaire was recognized. Not less plain was the demonstration of the elimination of yellow fever from the Department of Piura by stegomyia control and its recrudescense after the cool season where this measure had *not* been taken.

As soon as it could be arranged, Hanson, who had purposed to leave Peru in June, was placed by the President in absolute charge of all yellow fever work, including maritime quarantine. The International Health Board agreed to furnish funds in assistance to the Peruvian government. These were immediately available, dependable and, if necessary, themselves sufficient. These two factors were the fundamentals of the campaign and also gave us a very great advantage over 1920.

Before this, as soon as the conditions in Lambayeque were apparent, stegomyia control was begun at the principal key-points of that Department, without regard to their being infected or not, for the purpose of preventing the extension of the fever further south. That this lessened the amount of fever in these places was true and was a good thing; nevertheless, *our prime object* was as stated above. Beginning in these places soon after or before the disease was introduced it did lessen the fever markedly, so much so that, in one place at least, it caused disbelief in the nature of the disease "because it did not spread enough for yellow fever." Where this work could not be done there was no such complaint. Against advice, both fumigation and stegomyia control were used at Ferrenafe. It was too late to do any work here, a waste of money and time to attempt, and both time and money were badly needed elsewhere.

During and following a rapid inspection (by Hanson and the writer) of the southern part of Lambayeque and of Libertad to Trujillo and Salaverry, stegomyia control was organized under local agencies in both Departments to be taken over or supervised by Hanson's men as soon as they could be placed there. Special attention was paid to the towns and large haciendas nearest, and on both sides of, the narrow desert in the south of Lambayeque, it being a natural barrier to travel and hence to the extension of infection. The chance was, however, that the disease had already passed this barrier. Infection had existed for many months in Lambayeque; and, although at first in a district from which there was extremely little travel southward, recently it had invaded other places, as Chiclayo, of which this could not be said. Moreover, owing to an absolute interdiction of sea-travel by the health authorities from the time yellow fever was announced, a considerable amount of it had been diverted to the overland route. Normally, when the ports are open, travel this way is small. There was the usual sanitary cordon across this route.

Our design in this work was to so reduce the stegomyia index at strategic points, ports, centers of travel and large towns, that yellow fever would not spread in them if introduced; and also to reduce this index as much as possible by local agencies everywhere.

We scarcely hoped to accomplish the first completely before fever was introduced, but as our index at any place approached the desired figure the danger of the spread of infection from that place diminished both by its lessened amount and its shorter duration there.

Our best men, from the Piura epidemic, were placed in charge of such places and three sanitary inspectors were brought from the Canal Zone as supervising inspectors. Two of them had been with us in 1920 and were familiar with Peruvian conditions.

As much supervision as possible was to be given to the work done exclusively by local agencies, and later Hanson found we could give enough to be of great value, especially to that at some large haciendas which were under good discipline and intelligent management.

The district to be covered by this work was to include all of the Department of Libertad to the desert in the south, across which there was little travel. Restrictions on travel by sea, easily safeguarded, were to be reduced to the minimum necessary, so as not to divert any to the land route. If necessary later the work would be carried further south into the Department of Ancash.

A medical inspection by men with knowledge of yellow fever, from the experience of last year, was arranged for the territory exposed to infection—to be extended later on the coast as far as Callao.

Naturally, the work as outlined for the south had to be instituted again in certain places in Piura, lest the infection it had bestowed on Lambayeque should be returned to it. This was easy, as first we had an organization and fairly trained men, and second, in some places there had been so much fever that we considered them uninfectable from lack of susceptible people. In all, the lowered number of such people—by those immunized in 1920—made the work of protection easier.

A large quantity of Noguchi vaccine, *Leptospira icteroides*, was furnished by the Rockefeller Institute to be used not only for individuals exposed to infection, but on the large scale to, if possible, immunize communities against infection, just as the cow-pox vaccine is used to limit the spread of smallpox. Our dependence, however, in the limitation of spread of the fever was control of stegomyia breeding places.

The writer left Peru in March, reaching New York in April, and it will be for Hanson to tell the tale of this epidemic. Yellow fever, as was expected, developed in Libertad, most probably introduced before our measures to prevent it were begun, but not before they were able to control and prevent any serious epidemic, even in Trujillo. There were some severe ones in Lambayeque to the east and north where stegomyia control was not possible, nor was that at Ferrañafe mild.

The writer has kept in touch with the work as closely as the distance allows and the information received to date, October 31, leads him to believe that yellow fever has *not* extended beyond the limits under stegomyia control and that by the end of the year it will be eliminated from that district.[3] If so, Peru and the whole Pacific coast of South America will be free from yellow fever and we can hope, and indeed believe, free forever.[4]

[3] Of its extinction we can scarcely be sure until the end of the present hot season; although if nothing shows, under a decent inspection service, by January 1, 1922, we will feel quite easy.

[4] Hanson has this year greatly developed the use of fish in water-containers, depending on it to the exclusion of other methods, and with brilliant success. The same is true, I do not know if to the same extent, in the work in Mexico and Central America. This method was made known to us in Peru by Connor, in the fall of 1920. It had doubtless been valuable in our work in 1920 had we known of it, but had been less generally applicable in Piura than to the South.

This method for Stegomyia control was first used in Cuba, tentatively by the sanitary department, in 1905, on the suggestion of Major Kean (M. C. U. S. A.) and on a large scale by McMillan at Camaguey in 1908 (1). Apparently, however, it was not generally known until after its use by Connor in his yellow fever cam-

## SUMMARY

1. In 1916, when the survey by the Rockefeller Foundation was made, Guayaquil was the key to the yellow fever situation of the West Coast of South America. It was a permanent endemic focus, from time to time infecting the coast both north and south of itself.

The elimination of yellow fever from Guayaquil *at this time* would have eliminated it from this entire coast and probably in perpetuity. It was therefore planned.

2. This was postponed on account of the war and before it was accomplished yellow fever had been introduced (in early 1919) from Guayaquil into northern Peru, where it spread rather widely during that year and the next, threatening both to reinfect Guayaquil, now free of it, and to spread into the populous districts to the south where there was a good chance of its forming a more or less permanent focus.

3. In the campaign against this epidemic the ultimate dependence was exclusively on the control of Stegomyia by elimination of their breeding places, isolation of the sick and fumigation of infected premises being disregarded.

4. This was pressed only at certain places of strategic importance, *key places*, and little attention paid to outbreaks elsewhere. The prime object was to *prevent further extension of infection* rather than the elimination of that already existing, except as a means to prevent extension.

5. It was urged that the same measures—Stegomyia control—be extended to healthy places in the south exposed to infection, *key places*, so as to render them incapable of propagating yellow fever should it be introduced.

This was not done efficiently, reliance being placed on a military Cordon Sanitaire and the natural defence furnished by a waterless desert about 60 miles wide to the south.

paign in Guayaquil in 1919 (2). It is now in general use and is by far our most satisfactory means of Stegomyia control; where applicable, and it usually is, our sheet anchor!

The use of the "millions" in the water-barrels of Barbadoes greatly antedates the above and, as Boyce pointed out, *its effect* is Stegomyia control. Yet it would scarcely be fair to claim priority for this: its purpose being entirely different.

6. Yellow fever was eliminated from the northern department, where the above campaign was undertaken, the last (doubtful) cases occurring in September, but passed the Cordon Sanitaire and was found in epidemic form in Janurary, 1920, well to the south, where it had been some months.

7. General outline of plan of campaign for 1921, now being carried on by Hanson.

8. Importance of this work: It should free the entire Pacific coast of South America from yellow fever—and permanently.

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# STUDIES ON INOCULATION OF EXPERIMENTAL ANIMALS WITH MALARIA[1]

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Malaria has been transmitted from man to man by direct blood inoculation in so many instances that no detailed account is required here. All that is necessary is to inject blood containing asexual parasites either subcutaneously or, preferably, intravenously. The incubation period varies with the number of parasites injected, but is usually from one to two weeks. Even less than one drop of blood is sufficient to infect (Mannaberg). If animals were as susceptible as man, we would expect similar methods of inoculation to be successful in infecting them, followed by multiplication of the parasites accompanied by symptoms of the disease.

Deaderick (1) names the following lower animals which have been inoculated with malaria without results: horses, mules, dogs, monkeys, rabbits, mice, guinea-pigs, hedge-hogs, bats, wolves, cats, pigeons, doves, magpies, screech-owls, turtles, frogs and lizards.

Mannaberg (2) states that inoculation of malaria blood into animals (monkeys, rabbits, horses, foxes, dogs, cats, guinea-pigs, mice, doves, etc.) has all been negative. He also directs attention to the fact that there is no animal known which is affected by malaria in the same way as the human being, although many have hematozoa which somewhat resemble malaria plasmodia.

Knowles (3) injected 10 cc. of a mixture of equal parts citrate solution and blood containing "malignant tertian rings and crescents," into the abdominal wall of each of two monkeys (*Macaccus rhesus*). The animals remained well and daily ex-

[1] Read at the seventeenth annual meeting of the American Society of Tropical Medicine, Hot Springs, Ark., November 14, 1921.

aminations of the blood for the next twenty-three days were negative.

He later inoculated a hanuman monkey (Sp. *Semnopithecus entellus*) with 2 cc. blood containing crescents only, mixed with 10 cc. of citrate solution. The animal was etherized and inoculated by exposing the femoral vein and injecting the mixture intravenously. Twenty-three hours afterward the animal was quite ill; coma and prostration developed and death followed forty-eight hours after the injection. Blood specimens collected twenty-three, twenty-seven, forty and forty-four hours after injection contained large numbers of plasmodia. These resembled somewhat the malignant tertian parasite, according to Knowles, but he did not think they were connected in any way with the crescents only which were injected. It is inconceivable that they could have multiplied to this extent in so short a time. Although only 2 cc. of blood were injected, the heart blood at autopsy showed the majority of erythrocytes to contain these plasmodia, some two to the cell.

Apparently it happened that a monkey that was already infected with plasmodia of some other kind was used for experiment without previous examination of the blood. Knowles believes this plasmodium may be specific for this particular species of monkey and proposes the name *Plasmodium semnopitheci*.

Two other monkeys (*Macaccus rhesus*) were injected intravenously with blood containing crescents mixed with an equal amount of citrate solution. The results were negative as shown by blood examination over a period of fourteen days. It is noteworthy that crescents only were injected in these two monkeys. There is no conclusive evidence that this form reproduces even in man and it is doubtful whether the inoculations would have been successful, even if the animals inoculated were susceptible to infection with malaria.

Mesnil and Roubaud (4) succeeded in transmitting benign tertian malaria to a chimpanzee in 1917. The same authors (5) in 1920 described eight experiments including the successful one in 1917, in which citrated blood infected with benign tertian parasites in four and *Pl. praecox* in four, was injected into two chimpanzees, and two experiments in which these animals were bitten by infected *A. maculipennis.* All were negative except in one case in which citrated blood containing parasites was injected. Ten days after the inoculation with *Pl. vivax,* the parasites appeared in the blood and were present for a period of ten days, after which no more parasites were found.

This appears to be the only successful inoculation of experimental animals with malaria. On account of the many unsuccessful attempts to inoculate the chimpanzee for one successful attempt and on account of the difficulty and expense of obtaining and working with these particular animals, this report does not offer much encouragement to those who desire to study malaria in experimental animals.

In spite of the previous unsuccessful efforts of others to inoculate experimental animals, it seemed worth while to try again, approaching it in a somewhat different way. Although the efforts I wish to report were also unsuccessful, information was obtained which sheds additional light upon the possibility or rather impossibility of transmitting malaria to the particular animals experimented with.

Two things were done that have not been done previously in connection with the efforts to transmit the infection. One was to make malaria cultures from the same blood with which the inoculations were made in order to prove that the plasmodia injected were viable. The other was to make cultures of the plasmodia from the same blood used in the inoculations, in serum from the particular animals in place of the human serum usually employed in cultivating them. The object of this was to determine whether the plasmodia could grow in the presence of the serum of these animals. Since malaria plasmodia grow well in vitro in the presence of human serum, we may assume that they would also grow in vitro in the presence of the serum of any animal that is susceptible to infection.

A total of three guinea-pigs, four rabbits and one monkey (*Macaccus rhesus*) was inoculated, the monkey being inoculated two different times. The blood for inoculation was obtained from patients in the New Orleans Charity Hospital. It was drawn from the median basilic vein with an all-glass, dry syringe, run into a defibrinating tube in which the proper amount of 50 per cent aqueous solution of dextrose had previously been placed to make the blood contain 0.5 per cent of the sugar. It was at once defibrinated by stirring with the defibrinating rod. It was then transported to the laboratory and kept at room temperature until the inoculations were made and cultures were put up. The animals were inoculated first and the remaining blood was used for the cultures afterwards, making sure that the plasmodia inoculated into the animals were as viable as those planted in the cultures.

The necessary blood for the culture experiments was drawn from the animals just before the inoculations were made. In each instance sufficient of the 50 per cent dextrose solution was added to make the blood contain one-half per cent of dextrose. The animal bloods were immediately defibrinated in exactly the same manner as in the case of human blood for malaria cultures.

Blood for this purpose was drawn from the guinea-pigs from the heart direct, from the rabbits from an ear vein and from the monkey from a vein in the hind leg. The injections were made into these same parts, usually through the same needle before it was withdrawn and always directly into the blood stream.

The cultures were examined after twenty-four hours' and forty-eight hours' incubation at 37°C.

Blood specimens were collected from the animals and examined twenty-four hours and forty-eight hours after inoculation. Further blood examinations were made at intervals of two to five days during the observation period.

The following table shows some of the details of the inoculations and corresponding cultures and also the results:

| ANIMAL | DATE OF INOCULATION | AMOUNT OF BLOOD | KIND OF PLASMODIA | GROWTH OF PLASMODIA IN CULTURE IN HUMAN SERUM | GROWTH OF CULTURE IN ANIMAL SERUM | DURATION OF OBSERVATION | RESULTS |
|---|---|---|---|---|---|---|---|
| | | cc. | | | | | |
| Guinea-pig.... | 10/22/20 | 1.5 | Falciparum very many rings only | Good | None | 29 | Ring form parasites found (several) in blood 24 hours after inoculation None afterward |
| Rabbit........ | 10/22/20 | 2.0 | Falciparum very many rings only | Good | None | 12* | Negative |
| Rabbit........ | 9/14/20 | 1.5 | Falciparum rings and crescents | Good | None | 43 | Negative |
| Rabbit, 1 month old.. | 9/14/21 | 1.5 | Falciparum rings and crescents | Good | None | 43 | Negative |
| Guinea-pig, 10 days old... | 9/14/21 | 0.25 | Falciparum rings and crescents | Good | None | 43 | Negative |
| Monkey (Macaccus rhesus | 9/14/21 | 2.0 | Falciparum rings and crescents | Good | None | 58 | Negative |
| Rabbit........ | 9/29/21 | 1.0 | Falciparum very small rings, many crescents | Good | None | 26 | Negative |
| Rabbit........ | 9/29/21 | 2.0 | Falciparum very small rings, many crescents | Good | None | 26 | Negative |
| Guinea-pig.... | 9/29/21 | 1.5 | Falciparum very small rings, many crescents | Good | None | 1 | Died, result of blood being injected into pericardial sac |

| ANIMAL | DATE OF INOCULATION | AMOUNT OF BLOOD | KIND OF PLASMODIA | GROWTH OF PLASMODIA IN CULTURE IN HUMAN SERUM | GROWTH OF CULTURE IN ANIMAL SERUM | DURATION OF OBSERVATION | RESULTS |
|---|---|---|---|---|---|---|---|
| | | cc. | | | | | |
| Guinea-pig.... | 9/23/21 | 1.0 | Falciparum very small rings, many crescents | Good | None | 23 | Negative |
| Monkey (Macaccus rhesus† | 9/29/21 | 1.25 | Falciparum very small rings, many crescents | Good | None | 43 | Negative |

* This animal died sixteen days after the inoculation during my absence from the city and was destroyed without examination through misunderstanding. It cannot be said that he may not have died from malaria.

† This is the same monkey inoculated 9/14/21.

In one guinea-pig inoculated with a relatively large amount of blood containing very many *falciparum* ring form parasites, the parasites were found in considerable numbers twenty-four hours after inoculation but not later. These parasites did not seem to have grown in size, and did not stain well. One got the impression from studying the stained specimens that there was something wrong with them. No motility could be made out in fresh blood preparations.

The parasites in the corresponding culture in human serum grew well, some of them having reached almost complete development in twenty-four hours and practically all of them had passed the ring stage at the time the rings only were found in the guinea-pigs' blood.

The corresponding culture in this guinea-pig's serum showed ring forms only resembling in every way those found in the pig's blood. No growth whatever took place in the culture.

Barring this one exception in which parasites were found twenty-four hours after inoculation, no parasites were found in any of the experimental animals.

The parasites in the cultures in human serum made from the same blood immediately after the inoculations, grew well in each instance, showing absolutely that the parasites injected were living and viable. They were kept until complete segmentation had taken place. The parasites in the corresponding cultures in serum from the different animals made at the same time failed to grow in any instance. This furnishes additional evidence that these particular animals are resistant to malaria infection.

## SUMMARY

1. In three different sets of experiments four guinea-pigs, five rabbits and one monkey (*Macaccus rhesus*) were inoculated directly into the blood stream, with blood containing *P. falciparum.*

2. The plasmodia were proved to be living and viable at the time they were injected into the animals, by the fact that cultures put up at the same time grew and segmented.

3. The animals remained apparently well and repeated blood examinations extending beyond the incubation period of malaria in man failed to show plasmodia in any of the animals except in one guinea-pig twenty-four hours after the inoculation. These plasmodia did not seem to have grown, although those in the corresponding culture in human serum had practically all grown beyond the ring stage found in the animal.

4. The plasmodia in cultures in serum from the different animals failed to grow, although those in the corresponding cultures in human serum grew in the usual way.

## CONCLUSIONS

The experiments furnish additional evidence that these particular animals, guinea-pigs, rabbits and monkeys (*Macaccus rhesus*) are resistant to human malaria and tend to support the conclusion of other workers, that they are not susceptible to infection.

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# PHOTODYNAMIC ACTION OF EXTRACTS OF VARIOUS GRAINS WITH SPECIAL REFERENCE TO PELLAGRA[1]

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## INTRODUCTION

Ordinarily the clinical symptoms of a disease are sufficient to distinguish the infectious processes from the metabolic disorders. Nevertheless, some remarkable errors have occurred. For example, beriberi was at one time classed without question among the infectious diseases. Eijkman's (1) demonstration in Java that polyneuritis gallinarum is due to a dietary deficiency has furnished the starting point for an intensive study of the essential accessory dietary factors. Goldberger (2) has pointed out that many pellagrins live on an unbalanced diet and he has met with marked success in the eradication of pellagra from institutions by simply improving the diet. In spite of these results, there is still much confusion regarding the etiology of pellagra. Many authorities agree that the disease is a dietary deficiency; others hold that it is an infection; another school of investigators regard pellagra as an expression of photodynamic action. Indeed in some of the European literature it is considered as definitely established that pellagra is a photodynamic disease (3). It is with this last view that the present paper is concerned.

The supporters of the photodynamic theory base their arguments in large measure on the rather dangerous process of reasoning from analogy supplemented by a comparatively small amount of experimental evidence. Photodynamic effects in biology were

[1] Read by title at the seventeenth annual meeting of the American Society of Tropical Medicine, Hot Springs, Arkansas, November 14–15, 1921.

first described accurately by Raab (4). This observer noticed that certain fluorescent dyes killed paramoecia promptly in the ordinary diffuse light of the laboratory but were without action in total darkness. The subject of photodynamic action was subsequently developed rapidly in Europe. A wide range of effects were described but it was found that the process could be transferred only with considerable difficulty from the test-tube to the animal body. However, the hypothesis of photodynamic production of disease is extremely attractive and it has been countenanced by many investigators of the theory of photodynamic action.

## PHOTODYNAMIC ACTION IN DISEASE

The most definite indication of spontaneous photodynamic disease is found in buckwheat poisoning of animals. Many observers have noticed that sheep, swine, cattle, and other domestic animals are poisoned by buckwheat under certain conditions. When white or light colored animals are exposed to the light after eating any part of the plant which contains fluorescent pigment, inflammation of the ears, nose, and eyelids occurs, the animals sicken and occasionally die. Prompt recovery occurs if they are removed from the bright sunlight.

The adherents of the photodynamic theory assume that corn pigment and sunlight play a similar rôle in the production of pellagra. Emphasis has been placed upon the occurrence of pellagra in the south where sunlight is more abundant and where corn frequently affords an important article of diet. Clinically it has been observed that the cutaneous lesions of pellagra are exacerbated by exposure to light.

Experimentally, Raubitscheck (5) reports that white mice fed on corn and exposed to the diffuse light of the laboratory develop inflammation of the ears and the tips of the tail and die within a few weeks whereas control animals kept in total darkness remain in good health. Corn from which the pigment had been extracted produced no ill effects. These results have been confirmed by Horbaczewsky (6). Lode (7) reported that symptoms were produced only by yellow and not by white corn. In our own work we have not yet succeeded in confirming these apparently very simple experiments. Moreover we have not found any experimental demonstration that corn contains a fluorescent pigment which possesses photodynamic action. According to the consensus of opinion the fluorescence of a substance possesses only a casual relationship to its photodynamic action. However, virtually all of the photodynamic substances are fluorescent and this property therefore furnishes a very practical guide in searching for materials that are photodynamically active. The following experiments have been conducted to determine whether corn and other grains contain pigments which fluoresce and possess photodynamic action.

Preliminary tests with yellow corn showed that the problem had three aspects, namely, the isolation of the pigment, the tests for fluorescence, and the test for photodynamic action.

### PREPARATION OF CORN PIGMENT

For these experiments a bright yellow field corn was selected and ground to a rather fine meal. It seemed desirable to separate the pigment from the starch and oil of the grain but no attempt was made to secure a chemically pure preparation of the corn pigment. It was found that the oil dissolved rather readily in carbon tetrachloride and that only traces of the pigment were taken up by this solvent. Accordingly corn meal was placed in an extraction thimble with a reflux condenser and treated for several hours with carbon tetrachloride. The meal was then dried at 55°C. for twelve hours to remove the carbon tetrachloride and the extraction was continued in the thimble with methyl alcohol for five hours. The alcoholic solution was bright yellow in color and on cooling a small amount of white precipitate was deposited. This was filtered off and discarded. The filtered solution was found to contain 0.4 gram of extractives per 100 cc.

### FLUORESCENCE

This yellow alcoholic solution did not possess any obvious fluorescence in ordinary light. In determining fluorescence one encounters the difficulty of differentiating this phenomenon from the Tyndale effect due to fine particles in suspension. Dr. E. L. Chaffee of the Department of Physics kindly suggested the following plan and provided specially tested color screens necessary for carrying it out. A small oblong box (12 by 6 by 4 inches) with black inner walls is constructed with a partition 4 inches from one end. Three apertures are provided, a slit, *A* (0.5 inch) is cut in the side of the box to admit light into the small compartment, a similar slit, *B*, is cut in the center of the partition, and a wide opening, *C* (3 by 3 inches) is made in the end of the large compartment for the convenience of the observer. Ready access to the small compartment is gained by means of a lightproof hinged cover.

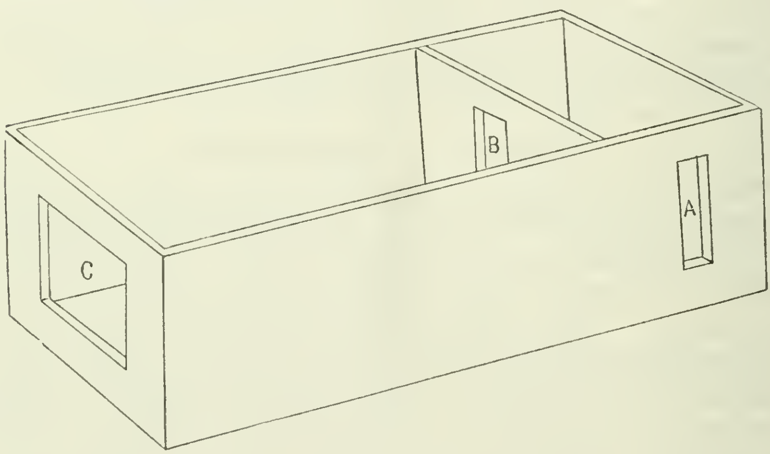


Fig. 1

The solution to be tested is placed in the small compartment in front of the slit, *B*, illuminated through *A*, by colored light, for example by a beam from an arc light, passing through a blue glass. If eosin is illuminated by a blue beam, the observer will see a bright green light emitted from the red solution. This change in color of the light from blue to green affords virtual proof of fluorescence. Further confirmation of fluorescence may be obtained in the following manner: A combination of glasses is selected such as blue and red which when placed one on top of the other do not permit any visible light waves to pass through them. Then with the blue glass at aperture *A*, if the solution under investigation is still visible through the red glass at the opening, $C$, this means that fluorescence is occurring since the original blue light can not pass through the red glass. This apparatus proved satisfactory in testing for fluorescence. Indeed it was sufficiently delicate to detect the very slight fluorescence of ordinary glass. Hence in examining solutions for traces of fluorescence it was necessary to use quartz containers. Obviously no quantitative measure of the intensity of fluorescence was obtained. However, it has been found that the photodynamic activity of a substance is not quantitatively proportional to the intensity of its fluorescence.

The alcoholic solutions of corn pigment were tested with a blue screen and emitted a yellowish red light. A combination of blue and orange screens was selected which permitted the passage of only a small amount of light from the arc lamp. The solution of corn pigment illuminated by the blue light was plainly visible through this orange screen, thus giving additional proof of the fluorescence of the pigment.

The fluorescence of a given substance is frequently influenced by the solvent which is used. The alcoholic extracts of corn pigment when diluted with physiological saline formed a suspension which showed no demonstrable fluorescence with this apparatus. In occasional instances it has been reported that photodynamic action has been obtained with non-fluorescent dyes. Also it has been frequently noted that the degree of photodynamic action is by no means proportional to the degree of fluorescence (8).

## PHOTODYNAMIC ACTION

After establishing the fluorescence of corn pigment in alcoholic solution, tests were made to determine whether it possesses photodynamic action. Hemolysis of washed corpuscles furnishes a simple and delicate test for such action. Indeed, if a given substance failed to produce effects in vitro it would seem superfluous to look for any action in vivo.

The insolubility of corn pigment in water complicates the use of this pigment in hemolytic work. Moreover the suspensions of the pigment which result in diluting the alcoholic solution with physiological saline are rather unstable. A finely divided opalescent suspension was obtained by adding 20 parts of physiological saline warmed to about 50°C. to 1 part of the alcoholic extract, at room temperature, thus giving a final dilution of alcohol much too dilute to cause hemolysis of itself. This suspension was usually stable for several hours at 37°C. Occasionally precipitation occurred within thirty minutes thus invalidating an entire series of experiments. Serial dilutions from this suspension of pigment were then prepared by the addition of saline. These suspensions in 1 cc. quantities were mixed with 1 cc. of 2 per cent washed sheep cells in ordinary glass test-tubes 14 mm. in diameter. A duplicate set of tubes was prepared and wrapped in tinfoil for protection from the light. These two sets were then incubated in a water bath at 37°C. exposed to direct sunlight.

As with many photodynamic substances, the corn pigment exhibited considerable activity in total darkness but this was definitely increased by exposure to sunlight.

## EXTRACTS OF OTHER GRAINS

For comparison with corn, extracts were made of buckwheat, rye, wheat and oats, omitting the preliminary extraction with carbon tetrachloride. There was not sufficient oil in these grains to interfere with the preparation of the emulsions of the pigment. The alcoholic extracts were fluorescent in each instance. The saline suspensions, however, showed no demonstrable fluorescence but were active photodynamically. Although it was not possible to carry out all the experiments on hemolysis at the same time, the reported results were all obtained under uniform conditions of sunlight; that is, the experiments were carried out during the early summer months, at approximately the same time of day, and during periods of continuous sunshine when no haze in the sky was visible to the naked eye. The relative strength of the pigments from various grains was compared with chlorophyll and eosin. The results are reported in the following table:

*Photodynamic hemolysis with extracts of grass, eosin, and various grains*

| EXTRACT OR SOLUTION | WEIGHT OF EXTRACTIVE | TIME REQUIRED FOR COMPLETE HEMOLYSIS | |
|---|---|---|---|
| | | Light | Dark |
| | *mgm.* | | |
| Corn | 1–500 | 30 min. | 40 min. |
| | 1–1000 | 45 min. | 1 hr. 45 min. |
| | 1–1500 | 1 hr. 30 min. | 3 hrs. |
| | 1–2000 | 2 hrs. | 4 hrs. 30 min. |
| | 1–2500 | 4 hrs. 30 min. | None in 5 hrs. |
| Buckwheat | 1–2500 | 10 min. | 12 min. |
| | 1–5000 | 12 min. | 15 min. |
| | 1–7500 | 45 min. | 3 hrs. |
| | 1–10000 | 1 hr. 30 min. | Partial in 4 hrs. |
| | 1–12500 | 2 hrs. 15 min. | None in 4 hrs. |
| Grass | 1–1000 | 7 min. | None in 2 hrs. |
| | 1–2000 | 15 min. | None in 2 hrs. |
| | 1–3500 | 18 min. | None in 2 hrs. |
| | 1–4500 | 21 min. | None in 2 hrs. |
| | 1–5500 | 30 min. | None in 2 hrs. |
| Rye | 1–1000 | 1 hr. 45 min. | 1 hr. 45 min. |
| | 1–2000 | 3 hrs. 45 min. | None in 6 hrs. |
| | 1–2500 | 4 hrs. 15 min. | None in 6 hrs. |
| | 1–3500 | 5 hrs. 30 min. | None in 6 hrs. |
| | 1–4500 | Partial in 6 hrs. | None in 6 hrs. |
| Wheat | 1–1000 | 1 hr. | 1 hr. 15 min. |
| | 1–2000 | 1 hr. 15 min. | 1 hr. 30 min. |
| | 1–3500 | 2 hrs. 30 min. | 5 hrs. |
| | 1–4500 | 3 hrs. 10 min. | None in 6 hrs. |
| | 1–5500 | 4 hrs. | None in 6 hrs. |
| | 1–6500 | 5 hrs. | None in 6 hrs. |
| | 1–7500 | 5 hrs. 30 min. | None in 6 hrs. |
| Oaten | 1–1500 | 5 min. | 5 min. |
| | 1–3000 | 5 min. | 8 min. |
| | 1–4000 | 7 min. | 10 min. |
| | 1–5500 | 10 min. | 20 min. |
| | 1–7000 | 15 min. | 30 min. |
| | 1–8500 | 20 min. | 40 min. |
| | 1–10000 | 35 min. | 1 hr. 5 min. |
| | 1–11000 | 45 min. | 1 hr. 45 min. |
| | 1–12500 | 1 hr. | 4 hrs. |
| | 1–14000 | 1 hr. 40 min. | 5 hrs. |
| Eosin | 1–2000 | 1 hr. | None in 1 hr. |
| 5 per cent methyl alcohol | | Very slight in 5 hrs. | None in 5 hrs. |

From this table it is seen that the extract of corn possessed an activity of the same order of magnitude as eosin, wheat and rye, but several times weaker than extracts of grass, buckwheat and oats. The extracts from the buckwheat and oats contained a considerable amount of chlorophyll or chlorophyll-like pigment which might readily explain their well-marked activity.

## SUMMARY

1. Alcoholic extracts of the pigment of yellow corn, rye, oats, and buckwheat possess fluorescent properties.

2. Aqueous suspensions of these pigments produce photodynamic hemolysis in vitro.

3. These data are not inconsistent with the theory of photodynamic action in pellagra. Obviously these experiments cannot be regarded as offering any substantial support of this theory unless successful experiments in animals are obtained.

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# SYSTEMIC BLASTOMYCOSIS[1]

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*Galveston, Texas*

On April 6, 1911, there was admitted into my service at the John Sealy Hospital at Galveston, a negro, Joe Bardy, from Kingsville, Texas. He was a brakeman on the Brownsville Railroad and brought a letter to me from Drs. M. E. and Amy B. Miles. The letter stated that he was referred because of an unusual and obscure infection and requested my assistance in diagnosing and treating the disease.

The patient was thirty-nine years of age, appeared quite ill, somewhat emaciated and weak.

*Family history.* Negative.

*Previous illness.* Yellow fever in childhood, rheumatism affecting the joints twelve years before, Neisserian infection several times, the last attack being eight months previously.

*Habits.* Were usual to his race and station and he was a heavy consumer of alcohol in the form of whiskey, beer and gin.

*Present illness.* Three months before he had observed a warty projection on the forehead just above the left eye. It was not painful and the patient called it a "seed wart"; and as it was not troublesome, the patient paid no attention to it with the exception that he picked it a time or two with a pin and subsequently a little pus exuded from the papillomatous growth. About the same time he began to suffer with headache, severe and constant, and lasting for one month. He thought he had fever during this time and was unable to keep at work all of the time.

One month after his illness began, abscesses appeared; two coming upon the neck, one on each side in the supra-clavicular fossae, one preceding the other about one week. They were

[1] Read before the seventeenth annual meeting of the American Society of Tropical Medicine, Hot Springs, Arkansas, November 14–15, 1921.

painless. Others followed in a few days; one on the abdomen, three on the foot and later several upon the head and chest, appearing at intervals of several days. None of these abscesses ever disappeared or ruptured spontaneously and, when lanced, they continued to discharge, never healing. During this period the patient lost about twenty-five pounds in weight, became weak in the legs and stiff in the hips.

*Physical examination.* A medium sized negro, emaciated, with rapid pulse and respiration, but without cough or expectoration. On admission his temperature was 99.8°F., pulse 136, respiration 32. The temperature was irregular and intermittent with a maximum of 103.2°F. in the evening and a minimum of 98°F. in the morning during the next eight or ten days. The pulse rate was disproportionately high, ranging from 108 to 168 with respiration ranging from 30 to 42. Four abscesses about the size of a small hen's egg were present on the body. They were soft and elastic—one in the epigastrium, one in the right hypogastrium and two on the forehead. Two deep undermined, dirty, discharging abscesses presented above the clavicles on each side of the neck and extended down to the sterno-clavicular articulations. A thick, yellow, odorless pus was being discharged. This condition had continued since the lancing of these abscesses after their first appearance a few weeks before. The same condition obtained in two abscesses upon the left foot.

Careful examination of the chest at that time revealed no lesion of the heart or lungs, although the heart was growing progressively fast and feeble and the respiration was rapid and at times difficult. Severe sweats occurred at night. Neither cough nor expectoration occurred during his illness.

On April 14, two days before his death and eight days after his admission, further examination of the chest was made with the following notation:

Crepitant râles, diminished vesicular breathing, slight increase in bronchial note on expiration and dullness on percussion over the base of the right lung posteriorly. Respiration clear and no dullness obtainable over the right lung anteriorly and in the upper lobe. The left lung appeared clear. The heart's action was very fast but neither arrhythmia nor murmurs were present. Early on April 16, fine pleural friction and crepitant râles were found in the lower lateral and posterior


Fig. 1

aspects of the left chest, diminished vesicular breathing, with a broncho-vesicular note, and my impression was that pleurisy and beginning consolidation were occurring in these areas. On the right side extension of râles to the mid-axillary area with bronchial breathing and increased percussion dullness and vocal resonance clearly indicated the increase of the consolidated area of the right lung.

No further examination was made and the patient was not seen again. His death occurred at 7:00 p.m. April 16, with a temperature of 95.2°F., respiration shallow, 60 to 70, and pulse recorded as 154, with labored breathing and delirium.

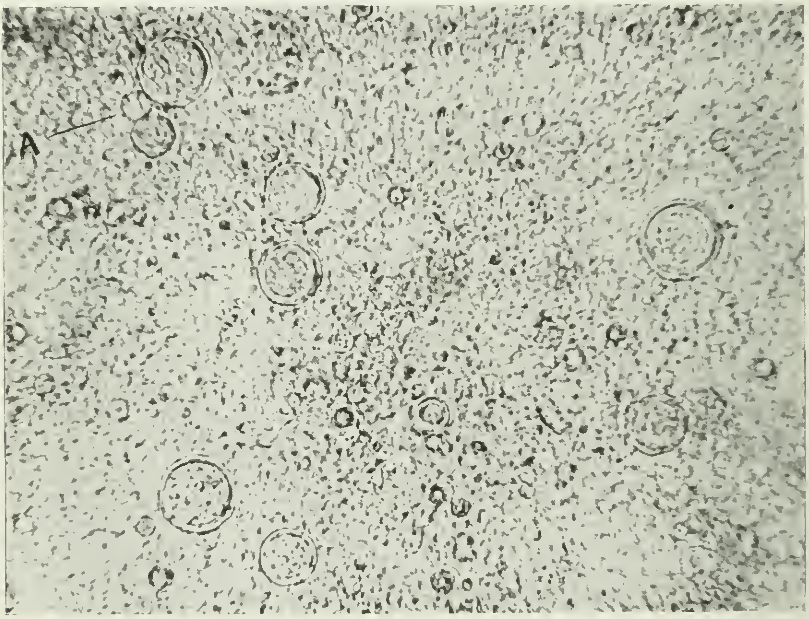


Fig. 2. Blastomyces in Pus from Chest Wall. A = Budding Form

*Laboratory examinations.* Were reported as follows:

On the day of admission, April 6, 6 cc. of thick yellowish white pus from two of the unopened abscesses on the body were withdrawn and this material was sent to the laboratory for examination and culture with especial reference to blastomyces. The latter was reported as positive during the day and subsequently cultured and photographed in the various forms and tissues, seen in accompanying illustrations.

April 7, 1911. Blood count was as follows:

| | | |
|---|---|---|
| Hemoglobin | 65 | per cent |
| Red cells | 3,470,000 | |
| White cells | 18,000 | |
| Polys | 86 | per cent |
| Lymphocytes | 6 | per cent |
| Large mononuclears | 1.5 | per cent |
| Eosinophile. | 4.5 | per cent |

April 15, 1911. Blood count was as follows:

| | | |
|---|---|---|
| Hemoglobin | 70 | per cent |
| Red cells | 3,500,000 | |
| White cells | 12,400 | |
| Polys | 82.5 | per cent |
| Lymphocytes | 8.5 | per cent |
| Large mononuclear | 2 | per cent |
| Transitional | 1.5 | per cent |
| Eosinophile | 1.0 | per cent |
| Basophile | 5.0 | per cent |

The *urine* was negative except for a high specific gravity, a trace of albumen and a few casts, hyaline and granular. Two blood cultures were negative.

His illness was progressive and proceeded rapidly to a fatal termination. The post mortem was made on April 17 by Prof. J. J. Terrell and I quote from his protocol the following distinctive findings:

*Post Mortem. Inspection of thorax.* Left lung adherent by loose adhesions to the external wall and strongly at the apex. Projecting into the pleura but not invading it, at the level of the fifth, sixth and seventh ribs in the mid-axillary line, is a rounded mass projecting 2.5 cm. and over this area the lung is loosely adherent.

The right pleural cavity has an excess of fluid. Pericardium is smooth and glistening, cavity contains about 50 cc. of clear fluid. Auricles are filled with black clot with some of lighter color. Ventricles contracted, almost empty, very little epicardial fat. Heart valves normal, heart muscle red with slight streaking of lighter color not too friable.

*Left Lung.* Adherent as before described, crepitance diminished throughout, no definite areas of consolidation, in feeling over the surface of the pleura it feels as though grains of sand or grit and this on close inspection shows a number of grayish areas beneath the pleura, on cut section of the lung great numbers of little grayish areas of consolidation are scattered throughout even through the depth of the tissue these do not seem to have any definite relation to the bronchi and vary from the size of a pin-point to the size of a pin-head.

*Right lung.* On the right side the lung is very much the same save that the middle lobe of the lung is absolutely studded with little areas mentioned before, the lung otherwise has the same description as its fellows.

*Microscopical examination*

*Lung.* The lung throughout the sections show numerous areas in which the air spaces have been supplanted by a proliferation of the connective tissue and epithelioids in which lie numerous giant cells mostly of the Langhan's type, and in these areas one finds numbers of connective tissue epithelioids, some of which are elongating into fibroblasts and there are a few lymphocytes; however there is no definite arrangement of these into zones. In the giant cells and occasionally in the tissue round about are to be found blastomyces which show up as a lightly stained rim with granular center, the latter taking the nuclear stain to a slight degree. The air spaces round about this are full for the most part either of a catarrhal exudate which consists of swollen epithelia with granular débris, or of precipitated protein material, or else the latter makes up almost the entire exudate in the air spaces. Sometimes in these air spaces numerous blastomyces are to be found. At no time in the stained sections are we able to demonstrate absolutely that there is budding of the blastomyces although numerous examples are found lying side by side, at times one decidedly smaller than the other, but even here the capsules seem to be distinct in each and not fused together. Practically this same appearance shows in all the sections of the lung, whether they were fixed in absolute alcohol, Orth's fluid or Zenker's, although the latter when deep hematoxylin stain is used seems to give the best picture.

*Diagnosis:* Blastomycotic granulomata of the lung.

*Kidney.* No increase in the intertubular connective tissue, slight increase in the thickness of the Capsule of Bowman, Glomerules are filled with blood and there is some excess of blood in the adjacent vessels. The epithelium of the convoluted tubules is swollen, fused, granular, frayed, nuclei too few or too pale, seeming to take the red stain at times somewhat. Occasionally in the tubules fine vacuoles are found which are not infrequently lined up toward the basement membrane. The lumens of the tubules are often fused shut, but at times closed up with granular débris. As one approaches the medulla these features change somewhat. There is much infiltration of the intertubular connective tissue with small lymphocytes, the epithelia show a fair amount of vacuolation of the cytoplasm, although the nuclei re-

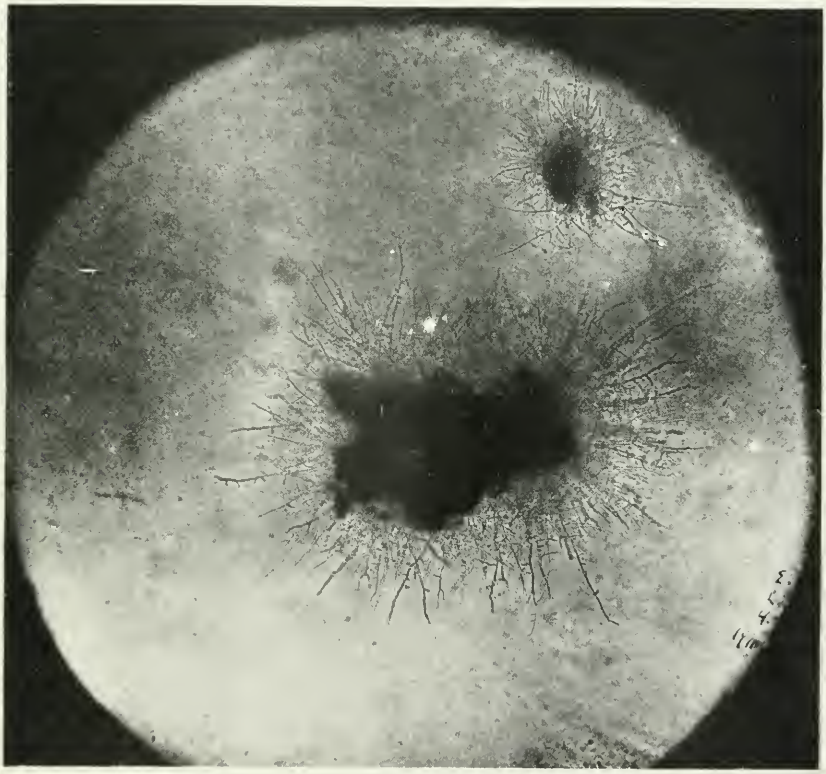

Fig. 3. Radiating Branched Hyphae; Young Colonies on Agar Plate

main they are somewhat distorted in shape by shrinkage. Occasionally tube casts are found. No evidence of blastomyces are found.

*Diagnosis:* Acute interstitial nephritis with distinct fatty change.

The character of this illness was suggested by a previous case of local blastomycosis with a similar verrucous growth in multiple form on the head of a patient of one of my surgical colleagues about 1910. This case was purely local and was cured by surgical means. The papillomatous growth in the forehead of my patient, designated by him as a "seed wart," was to superficial appearances the same sort of growth as that of the case of 1910.

Our premortem diagnosis was blastomycosis, systemic infection, septic pneumonia right and left lungs, acute nephritis.

In the light of the post-mortem examination we felt somewhat humilated that the recognition of the pneumonic areas in the lungs was not made earlier in the disease, although the absence of cough and expectoration and pronounced pulmonary signs was confusing. The disease must have been present in the lungs at the time of admission and before, although the gross evidence was lacking and no well marked clinical picture of pulmonary disease was present and the further fact that we were dealing with an infection unfamiliar to us.

The literature available to us at the time was the able monograph of Dr. H. T. Ricketts (1) on "A new mould fungus as the cause of three cases of blastomycosis or oidiomycosis of the skin."

A very exhaustive review of the subject of systemic blastomycosis with critical survey and summary of twenty-two cases by Montgomery and Ormsby (2) in the Archives of Internal Medicine and an illuminative article with report of a case by Fontaine, Haase and Mitchell (3) in the Archives of Internal Medicine in August, 1909.

Since the death of my patient a number of similar cases have been reported in American and foreign literature. In the Journal of the American Medical Association, Dr. Robert T. Morris (6) of New York, detailed the history and delayed diagnosis of a patient, a Texas physician, who contracted this disease while dissecting a body with blastomycetic dermatitis in Chicago and who subsequently went to London and was operated for abscess of the liver, leaving a foul discharging sinus without recognition of the character of the disease. The diagnosis was established a few days before his death in New York by examination of the pus from an abscess.

In Dr. Morris' article he asserted that the disease is not so rare but must pass unrecognized in many portions of the country.

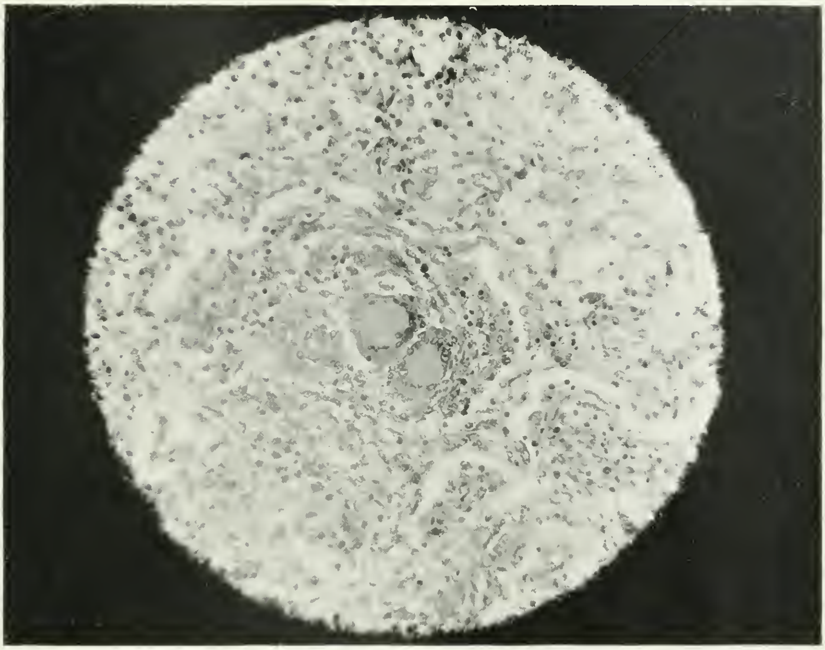

FIG. 4. FOCUS IN LUNG SHOWING GIANT CELLS

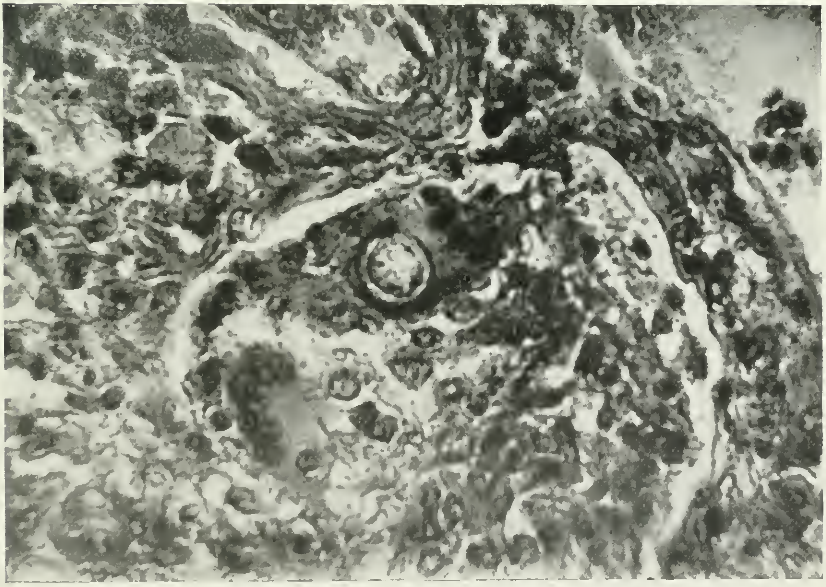

FIG. 5. SINGLE ORGANISM IN GIANT CELL IN LUNG

It is quite possible that sporadic cases do occur and that they may pass on to death without recognition; but I believe his conclusion is open to serious doubt as to the frequency of systemic infection of blastomycosis, as it appears to be a rare disease, having about the same incidence in cases so far reported in the literature as progressive lenticular degeneration or Wilson's disease, in both of which something over thirty cases are now of record.

All cases by no means present the same complexes. Recent reports by Washburn (4), Sihler, Peppard and Cox (5), detail instructive cases, and in the case of the latter, none of the ordinary dermal or sub-dermal lesions appeared; but an ulcer of the stomach, showing blastomycetes in the wall and with lesions in the liver with recurring ascites and with involvement of other viscera. This report, with photographs of patient, organisms and pathological tissues, is herewith presented, not because it contains anything new; but because it has never been published and may be of some value in refreshing the memories of the physicians of the south concerning this interesting disease.

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# A CASE OF PAGET'S DISEASE ASSOCIATED WITH CARCINOMATOUS INFILTRATION OF THE BREAST OF A MALE NATIVE OF THE SUDAN

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The case, which forms the subject of this paper, was under the care and treatment of Dr. John M. McCleery, American Mission, Doleib Hill, Malakal, and I am indebted to him for the material sent for histopathological examination, as well as for the photographic figures 1 and 2 and the notes on the clinical history of the case.

The patient was that of a male, approximately thirty-five years of age, a native of the Southern Sudan, who came to the American Mission for treatment. This mission station is about 500 miles south of Khartoum, and obtains a number of patients from the various Nuer, Dinka and Shilluk tribes who frequent that district.

On examination, the patient was found to have a large indurated ulcerated area involving the lower part of the right nipple. The ulcer had existed for a period of nearly a year and was relatively painless. There was no previous history of trauma connected with the lesion.

The lymphatic glands in the right axilla were enlarged (fig. 2) and of a hard consistency. The left breast and axilla were not involved.

The patient was kept under observation for a period of six weeks pending the histopathological diagnosis of a small portion of the ulcerated area which was removed. During this time, the ulcer was treated on ordinary surgical lines with suitable dressings and showed little or no improvement, and the lymphatic glands in the axilla increased in size and showed a tendency to become adherent to each other. The general condition of the patient showed no apparent ill effects.

The small portion of the ulcerated area removed for histopathological diagnosis was suitably fixed and sections cut and stained by different methods.

For descriptive purposes, the portion of tissue sent for examination may, with advantage, be divided into two areas:

1. A small area external to the margin of an ulcer in which the layers of the epidermis, showing pathological changes, were more or less intact.

2. An area representing the ulcer.

*1. The area external to the ulcer.* Here the stratum corneum and the rete mucosum showed some thickening; the cells of the rete were enlarged and swollen and the majority had lost their prickle arrangement owing to the intracellular edema present. In the rete and also subjacent to it, there were large oval or round cells which showed rather a pale staining or vacuolated cytoplasm with a dense staining nucleus—the so-called Paget cells (fig. 4).

In the subjacent corium, there was a dense cellular infiltration consisting chiefly of plasma cells and lymphoid cells in fibrous tissue (fig. 3). In this particular area, there was no evidence of cancerous infiltration.

*2. The area corresponding to the ulcer.* Here the stratum corneum, and the greater part of the rete mucosum, had disappeared as the result of desquamative ulceration. In the corium, at the base of the ulcer, there was a round celled inflammatory infiltration; while, subjacent to this, the tissue was invaded by columns of cancer cells arranged irregularly, some in the form of processes with the cellular elements actively proliferating, and invading the surrounding tissue (fig. 6) while, in other parts, the alveolar arrangement of the cancer cells could be seen (fig. 5), the various alveoli being separated by oedematous fibrous tissue. Sections stained by Gram's method showed no evidence of a mycosis.

## REMARKS

The histopathological changes noted in the sections leave no doubt as to the malignant nature of the growth; unfortunately, it was not possible to obtain any lymphatic glands for histopathological examination. The patient would not submit to a complete operation being carried out, and eventually returned to his district. The case appears worthy of record as it represents two points of more than usual interest: (1) the existence of Paget's disease of the nipple in a male breast (2) its association with a carcinoma of the breast, in a male native, aged thirty-five years.

It would be speculation to hazard an opinion as to whether the carcinoma was primary or secondary to the ulceration of the nipple area. It is well known that Paget's disease and carcinoma are comparatively common concomitant conditions in the female breast, but it has been a controversial point whether the carcinoma is secondary to the superficial ulcerative lesions, or whether the latter are a direct result of lymphatic obstruction by means of cancer cells.

In the literature available, the writer has been unable to find any record of Paget's disease being recorded in the male breast, although it has been recorded in areas other than the mammary gland.

Hartzell, in his classical book on diseases of the skin, refers to the fact that of eighteen cases of extra mammary Paget's disease collected in 1910, no less than nine were situated on the external genitalia and five of these were situated on the glans penis. Hartzell also states the interesting fact that in 75 per cent of all the cases of Paget's disease of the nipple, the right breast was affected as was the case recorded in this paper.

As regards the Sudan, cancer is more prevalent than is commonly supposed, and it has been the writer's experience from various histopathological examinations carried out in these laboratories during the past thirteen years that the disease is not a rare entity, and that neither race nor creed are exempt from it. Growths and tumors of fungal origin (mycoses) are common; simple tumors similar to those seen in Western races are equally common; while sarcoma, epithelioma and carcinoma are not infrequent.

## EXPLANATION OF PLATE

Fig. 1. Illustrates the area of the right breast involved.

Fig. 2. Illustrates the enlargement of a lymphatic gland at the anterior border of the axilla.

Fig. 3. Section showing the exfoliated epidermis and the increase in depth of the rete layer with Paget's cells, and the round cell and plasma cells, and the round cell and plasma cell infiltration in the corium. $\times$ 100 diameters.

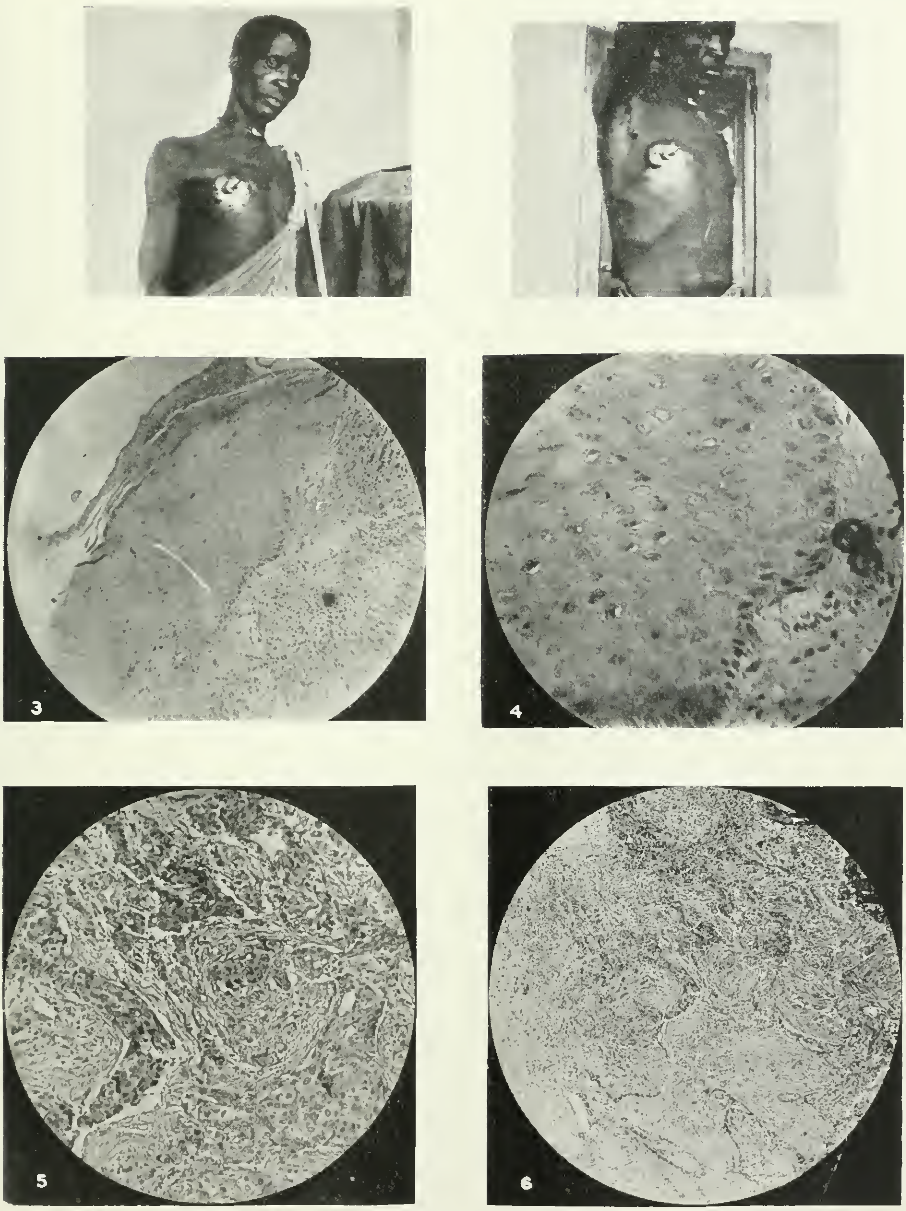
Fig. 4. Section showing cells in the rete. $\times$ 310 diameters.

Fig. 5. Section showing alveolar arrangement of cancer cells.

Fig. 6. Section showing cancerous infiltration.

Figures 1 and 2 are from photographs kindly sent by Dr. John M. McCleery, American Mission, Doleib Hill, Malakal.

R. G. ARCHIBALD



# OBSERVATIONS ON THE CONCEPTION THAT SPRUE IS A MYCOSIS SUPERIMPOSED UPON A STATE OF DEFICIENCY IN CERTAIN ESSENTIAL FOOD ELEMENTS[1]

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## INFECTION BY MONILIA PSILOSIS

The writer has had to date over one thousand cases of typical sprue in the Island of Porto Rico. The cases were studied in four periods:

1. A purely clinical series, 1908–1913.
2. A clinical series, checked upon by mycological study of tongue, scrapings and feces, 1914–1917.
3. A clinical series, checked upon by serologic study of patients' blood, 1920.
4. An unfinished series, 1921.

The work upon the statistical data is not yet complete, but in general it can be stated that of 350 cases in the first two series, of which about one-half received in treatment one-sided diets, there were 29 deaths, 4 of which were due to complications. In these cases sugar of commerce and cereals were prohibited but the treatment was, in general, that recommended in standard works of that epoch on tropical medicine.

In the 1920 series there were 348 cases of typical sprue and only 2 deaths. In this series the treatment was uniform and consisted of a liberal balanced diet, less sugar of commerce and cereals, as well as of pancreatin and other digestants, and, in about one-third of the cases, specific *Monilia psilosis* vaccines.

This diet, which was devised by the writer to conform to the taste and markets of the Island, is as follows:

[1] Read by title at the seventeenth annual meeting of the American Society of Tropical Medicine, Hot Springs, Arkansas, November 14–15, 1921.

*Breakfast*
Two eggs, soft boiled or poached.
Fruit: oranges, grape fruit, bananas, pears and apples.
Coffee and milk sweetened with saccharin.

*Noon meal*
Soup with fresh vegetables.
Fish fried in good fresh butter, or ham omelette, or soft boiled eggs.
Boiled filet of beef in a buttered saucepan and rapidly seared.
Fresh garden vegetables, preferably boiled or baked:

| | | | |
|---|---|---|---|
| Egg plant | Okra | Carrot | Cabbage |
| Chayote | Spinach | String beans | Tomato |
| Yautía | Paw-paw | Squash | |
| Plantain | Ñame | Amarillo (large ripe plantain banana) | |

Lettuce salad with good oil and lemon juice.
Fresh fruit.
Coffee with milk sweetened with saccharin.

*At 4 p.m.*
A glass of milk and some fruit.

*Evening meal*
As at noon.

*At bedtime*
A glass of milk.

*Prohibited*
All sugar of commerce and articles sweetened therewith.
All cereals including bread, crackers, rice, meals, and patent "breakfast foods" containing bran and other cereal derivations.
Beans and potatoes.

A 5-grain capsule of pancreatin is administered one hour and another two hours after each one of the three principal meals.

All of the cases of sprue under treatment in these series are not included, but only those which could have been clinically recognized as typical by any practitioner in the tropics. In other words they were not mere "laboratory cases."

The 1921 series bids fair to equal or surpass the hopeful results of 1920.

As will be imagined, each of these series contained a large number of patients suffering from the varied ailments and diseases, medical and surgical, of this Island.

In order to establish some basic factors in our conception of the nature of this disease, let us analyze the entire number comprising the second and third series.

*Second series, 1914–1917*

There was a total of 456 assorted cases, in all of which mycologic study of tongue scrapings and feces was made.

The results are as follows:

| CLASSIFICATION | CASES | PERCENTAGE IN EACH GROUP POSITIVE FOR MONILIA P. |
|---|---|---|
| Clinical sprue | 225 | 75.0 |
| Varied and vague gastrointestinal disturbances | 72 | 2.8 |
| Cases clinically negative for sprue | 150 | 0.7 |
| Cured cases | 9 | 0 |
| Total | 456 | |

In 199 clinical cases of this series the complement deviation test (González-Michel) was applied in 88 cases and found positive in 85 or 96.5 per cent, while in the same 88 cases the mycological study was positive in only 72.2 per cent. This is the connecting link between this and the next series.

*Series of 1920*

In this series 601 cases were serologically tested. Of these 385 were positive and 216 negative. Of the total number of 601, 348 were typical clinical cases of which 312 were positive serologically, or 90 per cent.

One hundred and two were cases of gastro-intestinal disorder too vague to merit a positive clinical diagnosis of sprue, but possessing a history sufficiently suggestive to put them under suspicion. Of these, 63 or 61.7 per cent were found to be positive by the complement fixation test.

One hundred and fifty-one were clinically free from any suspicion of sprue at the time of examination and ten were serologically positive, but four of these gave a previous history of sprue, leaving a legitimate 4 per cent positive.

Thus by combining these two series we find:

Of 1057 assorted cases subjected to laboratory methods for evidence of infection by *Monilia psilosis:*

573 were typical cases of sprue of which 501 were positive by mycologic or serological examination, a percentage of 87.4.

174 were cases of vague gastro-intestinal disorder impossible to negative for incomplete sprue. Of these, 37.3 per cent proved positive in the laboratory.

301 cases without a sign or symptom of sprue, a few healthy individuals, and the rest suffering from some other definite medical or surgical disease. Of these, 3.8 per cent were positive by laboratory methods but two were mycologically positive only and were carriers, and four were cases which had probably suffered from sprue. Thus the real percentage for this group is 1.6.

No discussion of *Monilia psilosis* as a pathogen, or even as a separate species, will be here attempted; the evidence is too voluminous and the writer is preparing an extensive work on the disease in all of its phases. Attention is invited, however, to the fact that a culture of *Monilia albicans* sent from the Hague by Dr. Elders, on differential media, especially by biochemic and morphologic study, has turned out to be so completely different from *Monilia psilosis* as to impress even those who are not mycologists in recognizing it as a separate and distinct species.

It is also well to bear in mind that a Monilia suggesting *Monilia psilosis*, or alleged to be identical therewith, has been reported in cases of sprue from India, Ceylon, the Dutch West Indies, China, West Africa, Arabia and the southern part of United States.

The writer himself has verified it in Cuba, Santo Domingo and in a case from India.

### *Deficiency in certain food elements in Porto Rico*

The population of Porto Rico, numbering about 1,300,000 souls, are sociologically divided into two great groups, the rural and the urban. Not less than 500,000 of these form the class of agricultural laborers, poor people who are limited to a wage running from 35 cents a day in coffee plantations to 75 cents or a dollar in sugar estates and tobacco plantations. As the money crops are sugar, tobacco and coffee, the Island is small and the population dense, it has been considered more economical to consume cheap foods, imported from other countries to form the bulk of the poor man's dietary, piecing out the ration with fruits and vegetables which until recently were abundant in a wild or semi-cultivated state. The tendency toward a dependence upon a foreign market for the bulk of the food has increased steadily as sugar has increased in money value, reaching its culmination during the Great War when the fabulous prices brought by this product drove all but the staid old tobacco and coffee planters into a feverish scramble to increase its output. The result was that plantain groves and vegetable patches were swept away to make room for cane. Then came the unprecedented fall in sugar values from 23 to $3\frac{1}{2}$ to 4 cents a pound and the result can be imagined, especially as tobacco and coffee fell with it.

Before the War these 500,000 lived mainly upon a diet of rice, beans, dried codfish, plantains and such fruits and vegetables as were locally at hand. Today they live on codfish, rice, beans and, mainly, tubers, with such fruits, plantains and other vegetables as can be irregularly obtained. But the alarming tendency at present is toward more and more rice, and an inferior quality of rice at that, polished and imported. The peasant that has plantains now, sells them and buys this grain which, bulk for bulk, and in calorie value, is greater. His chickens, eggs and milk are generally sold in the town, but at times are an irregular source of food in his home. Beef is rarely a part of the fare of these people as will be seen when we reflect that towns of from 3000 to 5000 inhabitants kill one beef a week only. Very little of that meat reaches the country population, double or treble the urban, especially when one considers the price of meat and the hours of toiling over villainous and at times dangerous paths to reach the town. Besides, the country dweller does not crave meat. Most of them do not like it or cannot digest it. The years of a traditional dietary, fashioned for their humble condition when they were bound to the soil, have produced a true habit for the alimentary elements to which they have become accustomed. Bread they rarely used to obtain; now much more frequently.

From a fairly intimate knowledge of the food habits and limitations of the Porto Rican peasant it is felt that he is living in a state of marked nutritional unbalance. The effects thereof are most striking in a deficiency complex which may be instantly recognized by those who are alive to the phenomena produced by food deficiencies.

An analysis of this dietary and the physical condition of the agricultural laborer of Porto Rico reveals:

1. A marked deficiency in fresh animal proteins and in the fat-soluble A vitamine.
2. A probable deficiency in certain mineral constituents.
3. A bare sufficiency of B-substances, a balance easily disturbed when the bean and fresh vegetable constituents are considerably reduced.
4. A sufficiency of water-soluble C-substances.

This food deficiency spells physiologic glandular deficiency. We should therefore not be surprised to find the pallor, the mental hebetude and the thousand and one functional aberrancies which one has united in the term "effect of the tropics."

It would be hopeless to attempt to analyze or even list all of these abnormal conditions. But some of the outstanding ones merit attention, such as:

1. The very prevalent pigmentation of the skin, especially of the forehead, the malar prominences, and around the lips.
2. The dry atrophic skin and tendency to mycotic affections, particularly of the legs.
3. The prevalent pyorrhea and early caries of the teeth.
4. The frequency of nasal catarrh, bronchitis, and, in children, adenoids and hypertrophy of the tonsils.
5. Obscure lymphopathies.
6. Low blood pressure, a tendency to palpitation and irregularity of the heart, and dyspnea.
7. Chilliness and an abnormal dependence on stimulants such as coffee, "tonics," and hot foods. (Alcoholism has never been a vice of much menace in Porto Rico.)
8. A tendency to anaphylaxes, urticaria and edema.
9. The extreme prevalence of myalgias, neuralgias and neuritis, as well as of occipital headache.

10. The mental apathy, difficulty in concentration of attention and loss of memory for details.

11. The frequency of hystero-epilepsy coming on after puberty, and queer spastic conditions often observed in women who become chilled after toasting coffee, or in men who become overexerted in the midst of excitement, such as that of extinguishing a fire.

12. The frequent dysmenorrhea or scanty and irregular menstruation.

13. The flatulent acid dyspepsias with inflation of bowels and constipation.

14. The chronic asthenia and rapid fatigue on sudden demand for efforts out of the ordinary.

15. Above all, the waxy sallowness with puffy features which so readily deepens into actual anemia upon the advent of infections like uncinariasis, malaria, tuberculosis, and others.

These signs and symptoms are so inextricably confused with actual disease, such as uncinariasis, on the one hand, and physical causes, such as over-exertion, lack of sleep, chilling, etc., on the other, that one is not authorized to conclude that these ills of the Porto Rican peasant are alone dependent upon physiologic glandular deficiency, but it is believed that we are enabled to conclude that food deficiency has at least laid the foundation for a breakdown in the glandular apparatus under the strain of their monotonous daily life, infections, bad hygiene, and poverty.

It is also as evident that such a physiologic glandular deficiency courts widespread infection, once the conditions for propagation are favorable, notably of tuberculosis, which until now has not effected a substantial foothold. It is therefore a powerful predisposing factor to serious infections.

In this condition the "jíbaro" or poor country laborer, works not alone from necessity, but also from a strict sense of duty and a simple hearted devotion to his family. But he instinctively realizes his limitations. He knows that there is something that prevents a sudden expenditure of energy, so he works deliberately and at low speed, and that something, it is believed, is largely a reduced output of internal secretions, not to mention the decrease in function of vital organs whose defect is more clearly in evidence.

In this condition, definite infections work with deadly effect. We only have to ask ourselves the question, why did Necator americanus, a practically universal parasite of the "jíbaro," kill 7369 in 1898, and in the fiscal year 1900–1901, 11,895? For the very simple reason that in August of 1899 one of the most destructive hurricanes that ever visited the Island swept over the mountains of Porto Rico, destroying both the coffee, the source of the daily wage, and the wild fruits which furnished the bulk of the peasants' fresh food. In the deplorable state of malnutrition that followed, in which they were fed for six months by the United States, *Necator americanus* converted 5500 cases of chronic invalidism into a fatal anemia.

These things are well-known here in Porto Rico. The disappearance of a large part of the native fruits and vegetables to make room for more cane has gradually produced artificially the same physiologic deficiency in the laborer as was suddenly produced by the hurricane of 1899.

It will be remembered that the principal opposition to considering *Necator americanus* as the principal cause of Porto Rican anemia in the period 1900–1906 was based on the well-known malnutrition of the laborer, an argument not lightly brushed aside and one which we ourselves were compelled to admit as a predisposing cause in our final report ("Uncinariasis in Porto Rico," Senate Document 808, Government Printing Office, 1911).

Thus, although the fare of our jíbaro approximates, if it does not actually reproduce, that consumed by the pellagra sufferers of the Southern States, and although the same likeness exists to the hypothetic deficiency which Elders considers the probable cause of sprue, *nevertheless pellagra and sprue are extremely rare diseases among these country laborers!*

With regard to pellagra, some 20 cases have been found in 20,000 examined by the writer, and these cases, for the most part, in the better conditioned of the masses we cover by the term "country laborer." This immunity may be due to the B-substance in the bean and fruit and vegetable component of their ration, but if we understand Goldberger's position, it is not the deficiency in this substance that produces pellagra.

As to sprue, food deficiency alone as a cause of the disease seems still less possible. In 1913, of 10,140 country laborers and their families studied by us in an expedition of the Institute of Tropical Medicine to the country districts of the mountain town of Utuado, only 11 positive and 19 suspicious cases were seen and most of these hailed from the town of Utuado. In a conversation with Dr. Hill of the Rockefeller Foundation, who is working in Quebradillas on uncinariasis, he informed me that he had seen only two cases of sprue among 8000 of a similar class of people in 1920–1921. The towns, on the other hand, for these same periods have rendered over a thousand cases.

If there is one fact which positively needs no discussion in the complex question of the etiology of sprue, it is that the higher we ascend in the social scale in Porto Rico the more cases of sprue we see. This, however, does not negative the self-evident observation that sprue is frequently, perhaps usually, preceded by a deficiency in the complete protein molecule, B-substance and certain minerals, notably calcium and phosphorus.

Most of the Porto Rican cases present a history of having eaten little meat and an excess of vitamine-less carbohydrates. The point is, however, that the deficiency and its syndrome are far more marked in the country laborer who rarely suffers from sprue, than in the well-to-do town dweller who has the disease.

These facts are in complete accord with observations of writers on this subject the world over. Sprue is a disease of towns and of the better classes of society; it is not usually a disease of the poor and underfed.

But within the classes of society that suffer most from sprue, it seems to be more a matter of food habits of the individual than of the food available to the individual that brings food deficiency into prominence as a predisposing factor. If we make a careful study of the individual diet of the victim of sprue we very soon come to the conclusion that food deficiency in certain elements and excess in others is a very frequent predisposing cause and that a deficiency syndrome as frequently seems to antedate the familiar sprue picture.

Most of our cases eat far too small an amount of meat and are often lacking in B-substances and mineral constituents of a balanced diet but then, on the other hand, many cannot consistently be considered to have a defective dietary. Some of the worst cases are in wealthy gourmands; the most of the better conditioned to all intents and purposes eat exceedingly varied diets.

Moreover, there are acute cases of sprue in newcomers to the Island, usually Americans, in whom it would be begging the question to assert the presence of a food deficiency. There have also been cases who after a brief visit to the tropics have returned to the hearty diet of our Northern cities and have developed sprue.

In a summing up, therefore, let us recognize this food deficiency as a frequent predisposing cause, let us even recognize a deficiency syndrome as a common prologue of the drama, but let us not lose sight of another strong predisposing factor, namely, the enrichment for *Monilia psilosis* of an acid medium in the human intestine by excessive quantities of vitamine-less cereals and sweets.

Let us now turn to the application of the conception that sprue is a mycosis superimposed upon a food deficiency.

No matter what theory we may entertain as the cause of sprue, one fact stands out with startling vividness: A cure depends more upon the complete abstraction of sugar of commerce and vitamine-less carbohydrates from the dietary than upon any other combination of therapeutic factors. This is more firmly fixed in the minds of our patients who have experienced the immediate relief such a diet gives, than in our own, for almost without exception the ingestion of the prohibited articles will precipitate a bout of sore tongue, gas and diarrhea, one or all, in the patient who had been previously doing well. The exception must be made, however, of certain cases in marasmic cachexia who have been cured of their *infection* by *Monilia psilosis* but who are in a state of physiologic ruin, of a starvation of tissues. Such cases are treated by Northern practitioners by a liberal diet, including sugar and cereals, and, of course, they often gain enormously in weight and are cured. Conclusions drawn from such cases are fallacious.

In the matter of the impropriety of permitting cereals and sweets in sprue, the great mass of literature extant is again almost uniformly corroborative.

## CONCLUSIONS

1. Typical sprue is most frequently preceded by a physiologic glandular deficiency recognizable by a deficiency syndrome in which pallor, lassitude, mental hebetude and gastro-intestinal derangement are prominent.

2. In this condition there is a marked reduction in the output of the digestive glands, particularly of the pancreas and intestinal glands.

3. This results in a change in the reaction and composition of the intestinal contents which brings about a high acidity.

4. In this state *Monilia psilosis,* which is a pathogen, finds a medium in which it can colonize and produce the typical picture we know as sprue.

5. In a minority of cases, sprue occurs in those in whom food deficiency plays no evident part and in which the disease seems to come by sheer force of infection, but it is justifiable to suppose that some other factor has diminished the output of the digestive glands to permit the successful implantation of the Monilia.

The same train of events seems to occur in thrush, whose cause is universally recognized to be Oidium, or, as it is now more frequently termed, *Monilia albicans.*

Thrush is usually a disease of marasmic infants and the senile, as it is also an intruder in the gastro-enteritis of avitaminous babies. Upon this marasmus, or avitaminosis with gastro-enteritis, a rapid colonization of the organism occurs in a favoring acid medium which ends in a violent membranous inflammation of the tongue and the primae viae.

The organism of thrush, as well as that of sprue, usually appears to find no propitious medium for colonization save in debilitated states, principally due to food deficiency.

When one considers the claim to specific rank of *Monilia psilosis* by comparison with the acknowledged chaotic state of mycologists regarding the proper classification, even the unity of species, of *Monilia albicans*, the frequency and consistency with which overwhelming infection of active cases of tropical sprue by *Monilia psilosis* occur, and the mass of laboratory, clinical and epidemiologic evidence too wearisome to recount that speaks for the pathogenicity of the latter organism in this disease, it seems not too much to exclaim:

If *Monilia psilosis* be not accepted as the direct cause of tropical sprue, why continue to consider its near relative, *Monilia albicans* the cause of thrush!

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# FILARIASIS AND ITS RELATION TO OTHER TROPICAL LYMPHOPATHIES[1]

R. RUIZ-ARNAU

It is not my purpose on this occasion to deal with filariasis in itself, but mainly with its relation to other lymphatic conditions in tropical countries. There exists, in fact, a close connection, from a pathogenic viewpoint, between the various lymphopathies of warm countries, and it is my deliberate opinion that this has not been given due consideration.

In 1916, I published a work devoted to the peculiar action that the climatic factor performs upon the people living in said countries, and discussed therein other writers' views on the subject (1). I find however, that despite such contributions, certain erroneous concepts are still prevalent among physicians in and out of the tropics, and it is for that reason that I presently wish to insist upon some fundamental ideas on the matter.

It is not my desire now to treat such an important subject fully, since I have done so in the work already mentioned, but simply to confine myself exclusively to two of the different lymphopathic processes I have referred to.

The *recurrent lymphangitis of warm countries* is usually still described mixed up with other lymphatic conditions very common there, and this notwithstanding the far-reaching researches made by Le Dentu (2), Le Dantec (3), Dufougeré (4), Clarac (5), etc., to mention just a few. This lymphangitis is not always a mere symptom of filariasis, as many claim; but it may also be a condition apt to be met with clinically, and this really is often the case, as an absolutely independent form, and of different nature, from any other analogous processes. I share the opinion of Dufougeré, of La Martinique, that recurrent lymphangitis may

[1] Read by title at the seventeenth Annual Meeting of the American Society of Tropical Medicine held at Hot Springs, Arkansas, November 14, 1921.

exist without elephantiasis, or, rather, without any infestation by filaria, even though it is hard to conceive the existence of elephantiasis in a patient who has not been previously and repeatedly attacked by lymphangitis; but since I have dwelt upon this fact several years ago, I will not attempt now to further explain my opinion. Suffice to say that to regard all tropical patients with recurrent lymphangitis as necessarily of filarial origin is but a great mistake.

We should, of course, not only suspect, but firmly insist on the presence of filarial infestation in each and every case of real elephantiasis, that is, pachydermic, but we must not do the same in every case of recurrent lymphangitis not accompanied by such a state, as is frequently done. Even in many cases of true elephantiasis it is impossible to detect any embryo in the blood although it appears to have been a common view that the condition is always filariasic. From now on we have at our disposal a new and efficient procedure for the investigation of filaria embryos which we did not have before, namely, that of Rivas' concentration method (6), and I presume that such a technical improvement will prove rather useful to clear up the problem.

Though in the simple recurrent lymphangitis of the tropics may be found, by mere coincidence, a vestige of the Bancroft's parasite, still in all my experiences, which cover a period of over twenty years in Porto Rico, and during which time I have dealt with many cases, I have never had the opportunity to discover any such traces. The results of my findings have always led me to consider as totally independent from one another the endemic simple lymphangitis, which develops a simple chronic edema, and the lymphangitis complicating filariasis, which ingrafts itself repeatedly during the course of chronic elephantiasis.

Finally, there exist two different processes: one purely infectious, the other parasitical associated with infectious outbreaks of acute lymphangitis.

There is yet a clinical element common to both that is, in my opinion, what has brought on so much confusion; I refer to the phenomenon of recurrence. The severity of the attacks and the recurrent character of the lymphangitis, as well as those other processes localized or not in the lymphatic system and so frequently present in those countries, are linked, rather than to circumstances derived from the biology of the causative organism, to another factor dependent, on the contrary, on the patient himself. This pathogenic factor, to which I made special reference in the beginning, is absolutely free of any infectious or parasitic action, and originates in a number of physiopathologic modifications in persons exposed to the permanent influence of the hot climate.

Such a condition of predisposition in people living in the tropics was long ago recognized by writers, especially by A. Corre (7), a prominent French author who named it *lymphatexy*. But due to the discovery of filaria and the remarkable works of Manson on the unity of the different clinical manifestations of human infestation by said parasite, the medical attention was for a long time diverted towards considering exclusively the aggressive nematod, and to such extent as to neglect entirely that peculiar lymphatic state accompanying and underlying the tropical lymphopathies. This situation still prevails, and it leads to the confusion of the two etiological factors, the parasitic and the climateric, thus creating an obstacle to exactly appreciate what corresponds especially to one or the other in determining the lymphatic processes in tropical countries. In my quoted work I had the opportunity to present the results of my research on the subject carried on in several hospitals in San Juan, Porto Rico. There were about 540 cases on record besides all those not recorded and observed in my private practice. From these sources of observation, mainly clinical, and on individuals kept under the proper conditions to detect and follow step by step the slow influence of the torrid climate on them, I was able to disclose the pathogenic relation in many cases which differed in their clinical appearances. Such study led me to the conclusion that not only is this pathogenic factor a reality, but that it does not originate in a special condition of the *contents* of the lymphatic system, the lymph, as Corre thought, but in the *container*, that is to say, the walls of the white vessels. Such a condition is mainly a state of permanent relaxation of the latter, which in turn is caused by the insufficiency of their involuntary muscular fibers due to the constant influence of the climate. This is what I have termed the *third factor* in the morbidness of warm countries. In view of the vagueness of the term lymphatexy, I have proposed a more determinate and precise conception, and a term more in harmony with modern physiopathologic attainments. It is understood that the over-exertion first, then the fatigue, and lastly the functional insufficiency of the small and delicate involuntary muscular fibers will bring the lessening if not the total loss of their contractile power. Consequently, the walls of the white vessels expand in a larger or lesser degree, according to the possible intervention of other various weakening circumstances, such as a constant vertical position, fatigue of the striated muscles, lessening of activity in the circulation of the blood, etc., all of which are important factors in delaying the course of the lymph. This delay or stasis, which could be called simply climateric or hygrothermic lymphectasy, is in fact a permanent state in the inhabitants of tropical climates, requiring some time to establish itself in individuals coming from extratropical countries: diminishing and even disappearing as soon as a person, native or not, moves to a cold climate. In many persons this condition, which I have chosen to call *primary tropical lymphectasy*, so as to distinguish it from that lymphatic ecstasy of the tropics secondary to inflammation or to mechanical obstruction of the white vessels (as by filaria), is latent during all their lives, whether it is because they are well adapted to it, or because the different causes named above do not operate on them. But in others, numerous also, it manifests itself under different aspects and distinct localizations, due to the same circumstances, thus creating the *substratum* in which is often ingrafted although not always, the infection or the infestation which causes, with its sequel of phlogosis, obstruction and secondary expansion of the lymphatic vessels, the clinical manifestations characteristic either of the lymphangitis or the filariosis.

To this preëxisting lymphectasy are due not only the frequency and intensity of lymphangitis in the tropics, but also, and above all, its recurrent character. Indeed, the three forms of the primary lymphectasy (radicular, reticular and ganglionic) present themselves with a recurrent type, linked with the change of season in the torrid zone, and perfectly pure, that is, free from the presence of infection or infestation, and with a thorough apyretic course. I will add that such facts are better detected in individuals who, by special circumstances (mode of living, place or residence, etc.), are protected from all living etiological influences, but who are, on the other hand, subject to other elements connected with the climateric and seasonal action.

Dwelling now exclusively on filariasis I will state that this conception of a previous pure lymphectasy is the only one that enlightens certain points still rather obscure or not well explained in the history of that disease. For instance, it is evident that the different regional localizations of the adult worm explain in a satisfactory manner the different clinical manifestations of filariasis, but fails to give full explanation, for example, to the following question put by Audin, of Hayti, in 1900:

"Why is it that cervical adenolymphoceles and lymphangiectasies of the head and neck do not occur as often as those of the extremities, bladder, and genitals?"

Yet, the interpretation made from the standpoint of the primary lymphectasy of the results obtained from recent investigations related to the biology of the Bancroft's parasite, seems to give us a solution, not only to this question alone, but also to many other problems still under consideration.

The preëxisting lymphectasy, which is more or less latent in the pendent regions of the body, and which in itself facilitates the infection by the germs of simple endemic lymphangitis, also favors the access of the larvae of the nematod, just as the secondary lymphectasy, caused by the adult parasites, accentuates the intraganglional extagnation of the lymph so propitious for a rapid procreation of the worms which, like all parasites, in order to perform this important function for the perpetuation of their species, always seek those conditions most favorable for perfect quiet. The evacuation of their uterus should be more frequent and much earlier when the lymphatic current is slower in that ganglion or group of ganglia infested with the parasite.

The filaria larvae, which the mosquito deposits on the skin of the individuals of the tropics, find not only spots but vast regions which will later become their permanent dwelling-places and which will also offer similarly favorable conditions, although less intense, than those which the adult must create for its own benefit and the greater security of its progeny. Let us remember, by the way, that according to Fülleborn (8), the filaria larvae do not penetrate the human body through the opening made by the mosquito bite, but that they spread along the surface of the skin, finding for themselves an entrance through which they lively penetrate. The dryness or humidity of the skin, he adds, plays a very important rôle; if the skin is dry, it is certain death for the larvae, while if damp, it enables them to live long enough to be able to penetrate.

The primary lymphectasy conveying with it a great reduction of the normal resistance in the walls of the lymphatic system and especially in its roots, which is more accentuated along the most pendent parts of the body, seems to be the factor actually responsible for the prevailing infestation of said regions.

It is likewise better understood now why it is that in patients attacked with filariasis, in whom the lymphectasy is more clearly shown, as in elephantiasis, for instance, the embryo is very seldom found in the peripheral blood, and this because the condition for procreation in them is eminently good; the filaria lays prematurely large eggs which obstruct the lymphatics, instead of light embryos which are susceptible of easily passing to the sanguinous current.

It is just now the occasion to insinuate an important variation of the formula proposed by Manson (9) to synthesize the development of the tropical elephantiasis. The hypothetical injury affecting the filaria assumed by him should be substituted by the fact, real and permanent, of the primary lymphectasy, more noticeable in the organic regions mentioned, which not only favors the parasitic oviparity in the patient infested, but the periodical outbreaks of complicating lymphangitis.

Thus is also explained the infrequency of acute attacks in individuals suffering from filariasis who have moved into a cold climate, where the pure tropical lymphectasy lessens and finally disappears. It is the opposite with those filarial patients who return to the tropics, especially in summer, for the outbreaks are more frequent and severe then. This again gives suitable explanation of the fact that individuals not born in the tropics require a long stay there to contract the disease.

In closing, I wish to state that as Manson attained the etiological unity of all clinical and so varied manifestations of filariasis, so could be established the pathogenical synthesis not only of the latter, but of all genuine tropical lymphatic diseases, by recognizing what belongs by rights in their determinism not to the possible aggressive germ or parasite, but to the human body thus attacked, or in other words, by attributing to the causative elements the only part that they strictly play in determining the said morbid conditions in intertropical countries.

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# In Memoriam

# MAJOR-GENERAL WILLIAM CRAWFORD GORGAS[1]

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Since the last annual meeting of this Society, it has suffered the loss of its most illustrious member, Major-General William Crawford Gorgas.

General Gorgas will be known to future generations as the Great Sanitarian of his age. History will emphasize the fact that he applied practically, on a large scale, the knowledge of the transmission of yellow fever by one particular species of mosquito which fact had been so thoroughly and so completely demonstrated by the Board of Medical Officers of the United States Army headed by Walter Reed; that through his initiative as a practical sanitarian yellow fever was banished from Cuba in an astoundingly short period of time; that his broad vision, comprehensive knowledge and practical application of the sanitary principles required in the prevention of disease made possible the construction of the Panama Canal. At the time of his death he was waging a contest with yellow fever in its final remaining strongholds in South and Central America. There is no doubt but that the plans initiated by him will be carried to a successful conclusion, and that even we, during the span of our lives, may witness the complete extermination of yellow fever from the world.

A very striking but not generally known series of coincidences in which yellow fever played a part, have occurred in the last two generations of the Gorgas family. In 1853, the father of William Crawford Gorgas, Josiah Gorgas, was placed in command of the Mount Vernon Arsenal near Mobile, Alabama. The surgeon of the arsenal at that time was a Dr. Gayle, a native of

[1] Read at the seventeenth annual meeting of the American Society of Tropical Medicine, Hot Springs, Arkansas, November 14–15, 1921.

Mobile. Soon after Lieutenant Josiah Gorgas took command of the Mount Vernon Arsenal, the city of Mobile was visited by a severe epidemic of yellow fever, and the sister of Dr. Gayle, Miss Amelia Gayle, left Mobile to remain with her brother at Mount Vernon Arsenal during the continuation of the epidemic. Lieutenant Josiah Gorgas met Miss Gayle during this visit, the acquaintance ripened into love and they were married in December, 1853. It will thus be seen that the occurrence of an epidemic of yellow fever was instrumental in bringing together a couple whose son was to play such a dominant rôle in the eradication of yellow fever from the Western Hemisphere. Passing on to the next generation, we find that General Gorgas, at that time a first lieutenant and assistant surgeon in the medical corps of the army, was ordered to Fort Brown, Texas, in the midsummer of 1882. Yellow fever was then epidemic in a nearby town, Brownsville, Texas, and cases soon began to occur at Fort Brown. A few days after his arrival he was called to treat professionally Miss Marie Doughty, who was visiting her brother-in-law, Captain William J. Lyster. Miss Doughty was suffering from yellow fever and her life hung in the balance for several days. Finally, however, she rallied and recovered and during her convalescence Dr. Gorgas was stricken with yellow fever. Miss Doughty and Dr. Gorgas resided in adjoining officers' quarters during their convalescence and saw a great deal of each other. This was the beginning of an acquaintanceship which culminated three years later in their marriage.

As a result of his experience with yellow fever in the early days of his career as a medical officer, General Gorgas became intensely interested in the then mysterious disease, and his future career was greatly influenced thereby.

William Crawford Gorgas, the son of Josiah Gorgas and Amelia Gayle Gorgas, was born at Mobile, Alabama, on October 3, 1854. His education as a young boy was obtained in a private school in Richmond, Virginia, and continued at the University of the South, Sewanee, Tennessee, from which he was graduated in 1875 with the degree of Bachelor of Arts. He graduated in medicine from the Bellevue Hospital Medical College, New York

City, in 1879, and served as an interne in Bellevue Hospital, New York, during 1878–1880. During the last year of his interneship he took the examination for admission to the medical corps of the United States army, receiving his commission in that corps on June 16, 1880. His first assignment to active duty was at Fort Clarke, Texas. In the midsummer of 1882, he was transferred to Fort Brown, Texas, and immediately after his arrival had his first professional experience with yellow fever. Not only did he treat cases of the disease occurring locally but was himself stricken with it. His studies in connection with yellow fever were interrupted, temporarily, by his transfer to Fort Randall, Dakota, in the fall of 1884.

He was promoted to the grade of captain on June 16, 1885. On September 15, 1885, he was married to Miss Marie Cook Doughty of Cincinnati, Ohio.

His transfer to Fort Barrancas, Florida, permitted a resumption of his study of yellow fever, in which he was so intensely interested. He remained at Fort Barrancas, Florida, until the outbreak of the Spanish-American War, except for an eighteen months' tour of duty at Fort Reno, Oklahoma.

At the outbreak of the Spanish-American War in 1898, he was appointed a major and brigade surgeon of volunteers, and received his promotion to the grade of major in the medical corps of the regular army on July 6, 1898. He went to Cuba on the hospital ship *Relief*, landing at Siboney, and served in Cuba throughout the Santiago campaign.

He organized and was in command of the yellow fever hospital established at Siboney and was invalided to the United States after the occupation of Santiago by reason of a severe malarial infection. After convalescence, he returned to Cuba, was appointed chief sanitary officer of Havana and held that position from 1898 to 1902.

It was providential for Walter Reed and his coworkers that General Leonard Wood and General Gorgas were the directing heads of governmental affairs for Cuba and public health affairs for Havana, respectively, when their investigations of the etiology of yellow fever were undertaken. The broad vision and sympathetic understanding with which these two officials were so well endowed gave assurance of the highest degree of support and coöperation. The investigations of the Reed board were quickly crowned with success and on February 6, 1901, Walter Reed and his coworkers were able to announce to the world, in a paper read before the Pan-American congress in session in Havana, that they had demonstrated definitely and conclusively that yellow fever was transmitted by the *Aedes aegyptus* mosquito (generally known as *Stegomyia fasciata*), the possibility of which had first been suggested by Dr. Carlos Finley of Havana in 1881.

The actual demonstration of the method of transmission of yellow fever permitted the chief sanitary officer, Major-General Gorgas (then major) to put into effect logical measures for its prevention and control. The records of the comprehensive manner in which the active anti-mosquito campaign was planned, the energy with which it was prosecuted, the difficulties encountered and surmounted, and the brilliant results attained, constitute one of the most fascinating chapters in the history of preventive medicine. Within a period of three months yellow fever, which was known to have been epidemic in Havana almost continuously since 1620, was entirely eliminated, the last case having been reported on September 28, 1901.

In the net that was spread, primarily for the destruction of the yellow fever-transmitting-mosquito in the various stages of its life cycle, large numbers of malaria-bearing mosquitoes also became entangled with the result that malarial fevers which had for centuries been the cause of much sickness and death in Havana, were greatly reduced. Special measures applicable to the eradication of malaria transmitting mosquitoes were also introduced with the result that eventually malarial fevers became a negligible factor in the morbidity and mortality statistics of Havana. The importance of this work can best be appreciated when we learn that during the thirty-year period, 1871 to 1900, inclusive, an average of 399 individuals died in Havana each year of malaria. The smallest number of deaths, 101, occurred in 1885, and the largest, 1907, occurred in 1898. After 1901, when the anti-mosquito campaign was in full sway, there was a very rapid and marked decline in the death rate from malaria. The average number of deaths occurring each year during the eleven-year period, 1902 to 1912, inclusive, was only 28 and in 1912 only 4 deaths were reported.

On completion of his work in Cuba, General Gorgas was assigned to duty as chief surgeon of the Department of the East with headquarters at Governors Island, New York Harbor, where he remained until March 1, 1904. He was then appointed chief sanitary officer of the Isthmian Canal Commission, the construction of which, as an American undertaking, was begun about May, 1904.

The magnitude of the problem confronting him may well be realized when it is remembered that at the time the French, under de Lesseps, undertook the construction of the Panama Canal in 1880, the Isthmus of Panama was known to be one of the plague spots of the world. In the course of nine years of construction activities under the French régime, 22,189 laborers died of disease, mainly yellow fever, malaria and dysentery. The official death rates of the French company, 65 per 1000 per annum, failed to include many of the deaths occurring on the line of the canal and in the cities of Colon and Panama, and competent observers, on the ground at that time, estimate that the losses during the period of construction under French control more nearly approximated 250 per 1000 per annum. While the true rate can never be determined it certainly was considerably in excess of 65 per 1000 per annum.

The records disclose many instances in which 75 per cent or more of concrete groups of employes newly arrived from France lost their lives from disease within a period of two to three months after landing on the Isthmus.

This, very briefly, was the situation which confronted General Gorgas on his arrival in Panama. It was his responsibility and his task to convert this plague-spot into a healthy region; to reduce the death rate from disease from the appalling ratio obtaining under the French régime (65 per 1000 per annum, official) to that prevailing in communities in the United States under enlightened sanitary supervision (20 per 1000 per annum);

to so reduce the morbidity rates from disease as to assure efficiency and expedition in construction; and to initiate such general sanitary measures as would permit the families of employes to reside indefinitely on the Canal Zone and in the cities of Colon and Panama in comfort and without detriment to their health.

The completely successful manner in which he accomplished all these seemingly impossible things is a matter of history. A few cases of yellow fever occurred in 1904 and a rather sharp epidemic in 1905. In May, 1906, the last case of yellow fever occurred on the Isthmus. In 1906 the admission rate for malaria was 821 per 1000 per annum. This rate was very rapidly reduced and in 1913 was only 76 per 1000.

During the nine-year period of construction under French auspices the number of employes constantly engaged in construction averaged approximately 10,000, the losses from disease and other causes being made good by replacements from France and elsewhere. During this nine-year period slightly in excess of 22,000 employes died from disease.

The American force of employes constantly engaged in construction during the period 1904 to 1913 (approximately nine years) averaged approximately 33,000. During this nine-year period the number of deaths from disease was only 4000. Had the average number of employes constantly engaged in construction work under the French régime been the same as during the American régime (33,000) and had their death rate been the same as actually existed at that time, they would have lost by death from disease 72,600 men.

The general death rate was reduced by 1910 from a maximum of 49.94 per 1000 per annum to 21.18.

After 1906 one could live in Panama with equal assurance of being guarded against preventable diseases as if living, for example, in New York, London, or Paris.

The work of General Gorgas in Panama is by far the greatest object lesson in disease control and prevention ever witnessed by the world.

From 1904 to 1907 the department of sanitation, administered by General Gorgas, functioned as a branch of the department of government and sanitation. On March 1, 1907, President Roosevelt, appreciating the importance of this phase of the problem of construction of the Canal and recognizing the phenomenal results attained, appointed General Gorgas a member of the Panama Canal Commission and head of the department of sanitation.

The outstanding results attained by General Gorgas in Panama soon became the common property of educated peoples throughout the world with the result that the Canal Zone became a Mecca for the sanitarians of the nations of the earth.

While serving in Panama invitations to advise in matters of sanitation were extended him by nations and by corporations and two of these invitations he accepted.

He spent about two months in Guayaquil, Ecuador (December, 1913, to January, 1914), on the invitation of the President of the Republic of Ecuador.

A general sanitary survey of Guayaquil was carried out and recommendations made for improvements in sanitation, more particularly for the prevention of yellow fever and plague. Steps were taken by the government of Ecuador to put these recommendations into effect. In 1916, General Gorgas again visited Guayaquil as a member of a commission sent down by the International Health Board of the Rockefeller Foundation, and arrangements were perfected to wage the fight against yellow fever with renewed vigor. As a result of the work initiated in 1913 and further augmented in 1918 and 1919, yellow fever has been exterminated and health conditions in Guayaquil compare favorably with those of other tropical cities of equal size.

In October, 1913, General Gorgas sailed for South Africa, on invitation from the chairman of the chamber of mines, Johannesburg, Transvaal, for the purpose of making inquiry into housing and other conditions that might perchance be responsible for the excessive death rate from pneumonia prevailing in mine laborers recruited from the tropical regions of Africa. While engaged in this investigation, General Gorgas was appointed surgeon general of the United States army (January 16, 1914), with the rank of brigadier-general, arriving in the United States in the latter part of March, 1914, to assume the duties of his office. He served as surgeon-general of the army from the date of his original appointment in January, 1914, until his retirement for age in accordance with existing law on October 3, 1918.

It was his responsibility to direct the organization of the medical department and the entire medical profession of this country for the World War. The efficiency with which this stupendous undertaking was carried to a successful conclusion is a matter of common knowledge and will be still more thoroughly appreciated when the passage of time permits its proper evaluation.

General Gorgas was a member of the board of directors of the Rockefeller Foundation and after his retirement from the army in 1918, became the director of the Yellow Fever Commission of the International Health Board. It was his hope and dream that yellow fever might be banished from the world before his retirement from active professional work. With this in view he spent the greater part of 1919 and the early months of 1920 in Central and South America organizing campaigns against this disease in its few remaining strongholds on the Western Hemisphere.

In May, 1920, he sailed for Europe en route to the West Coast of Africa to investigate the status of the disease in that region and to advise as to the necessary preventive measures to assure its eradication. While en route to Africa he was taken ill in London on May 31, 1920, and died at 1:30 a.m. on July 4, 1920.

His distinguished services to humanity were recognized by governments, institutions and scientific bodies in various parts of the world.

The appreciation of the people of the United States for the monumental work in disease prevention accomplished by Major-General Gorgas (then Major Gorgas) in Cuba was expressed by the Congress in an Act of March 9, 1903, promoting him to the grade of colonel in the medical corps of the army.

In recognition of the distinguished services rendered his country as a member of the Panama Canal Commission and in charge of its department of sanitation, he received the thanks of the

Congress of the United States on March 4, 1915, and as further evidence of grateful appreciation for his eminent services he was promoted to the grade of major-general on the same date.

For especially meritorious services rendered during the World War he was awarded the Distinguished Service Medal by the President of the United States. Among the foreign decorations awarded him were: Cross and Star of Knight Commander of the Order of St. Michael and St. George, by the King of England; Commander, Legion of Honor, by the French Government; Grand Cross of the Order of the Crown of Italy, by the King of Italy.

General Gorgas was awarded honorary degrees by many universities, including Doctor of Science (D.Sc.) from eight universities in this country and abroad, and the degree of Doctor of Laws (LL.D.) from five universities.

For his eminent and notable services to humanity in the application of science for the public welfare he was awarded a number of special medals, including the Mary Kindsley Medal of the Liverpool School of Tropical Medicine, Medal of the National Academy of Sciences, the Dawson Medal of the University of the South, the Buchanan Medal of the Royal Sanitary Institute, London, and the Harkin Medal of the Royal Institute of Public Health, London.

Scientific societies in various parts of the world showed their appreciation of his achievements by conferring on him honorary or associate fellowship or membership.

He was president of the American Medical Association in 1910, and president of this Society during the same year.

Soon after his death it was proposed that a permanent memorial be erected in his honor. This movement assumed concrete form when Dr. Belisario Porras, President of the Republic of Panama, proposed the establishment of a research institute in the Republic of Panama to be known as the "Gorgas Memorial Institute." Plans for the establishment of such an institute are now well under way, the details of organization have been completed, a charter has been secured, and the Republic of Panama already has presented a plot of land for the erection of the Institute and a large fund for the establishment of the Institute.

A memorial service was held in his honor in the Hall of the Americas, Pan-American Union, Washington, D. C., on January 16, 1921, under the auspices of the Southern Society of Washington. This service was participated in by high officials of our government and diplomatic and other representatives of many other nations. The addresses and messages presented at this service have been published by the United States government for preservation in its archives (Senate document No. 390, 66th congress, 3rd session).

The personality of General Gorgas was so well portrayed by the Honorable Newton D. Baker, former Secretary of War, in an address delivered at the Gorgas Memorial Service held in Washington, that the following quotation from his address is deemed particularly appropriate:

. . . . Those who are to speak of General Gorgas in a personal way will doubtless describe his genial and gracious manners, his courtesy and considerate treatment of all with whom he came in contact. I prefer to dwell upon the youthfulness of his spirit. If indeed, as was the fact, he was born in one age and lived into another, he became the adopted child of the younger age and was as elastic as any youth in it, both in his appreciation of the things that were new and practical and his acceptance of the better for the things with which he had once been accustomed.

It was appropriate that he should die on foreign soil, for he had become a citizen of the world. It is appropriate that his remains shall lie here, for this was his country; and in all this country there is not a fitter place to set up his final tent than Arlington, once the home of the commander under whom his father fought, now the Westminster Abbey of America's heroic military dead, overlooking the capital of the nation which he served. I like to think that his death was as he would have wished it to be—on the battle field; not, it is true, in a shell-torn no man's land, but pressing forward with his face to the front, seeking still to pursue and conquer the enemies of human happiness and health; retired, but not resting; full of years, but still full of energy; almost unaware of the laurels he had won, in his eager impatience to render further service to his fellowmen. Physician and Soldier—he fought a good fight and won the only kind of victory that counts; he added years to the length of human life; he freed countless multitudes from sickness and premature death he served his generation and won a place in the lasting memory of all mankind; and withal, he was a modest gentleman—this Physician, this Soldier.

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# ISADORE DYER[1]

JOHN B. ELLIOTT, JR.

*New Orleans*

Isadore Dyer was born in Galveston, Texas, November 2, 1865, and received his early education at private schools in that city. From 1880 to 1884, he attended the Bellevue High School, Bellevue, Virginia. He entered the Sheffield Scientific School of Yale University in October, 1884, and graduated with the degree of Bachelor of Philosophy in 1887; studied medicine for one year at University of Virginia and while there helped to found "Corks and Curls," an annual which has a national reputation; entered the Medical Department of Tulane in November, 1888, and graduated in May, 1889.

From January, 1890, to June, 1892, he studied in New York City and was an interne in the New York Skin and Cancer Hospital from December, 1890, to June, 1892, and then spent several months in Europe, returning to Tulane in October, 1892, to become lecturer on skin diseases in the Tulane Medical Department, and in March, 1893, was appointed professor of diseases of the skin in the New Orleans Polyclinic.

In 1894 Dr. Dyer commenced his life work in the study of leprosy, founding the Louisiana Leper Home and becoming president of its board of control. From this date articles appeared from his pen yearly, studying this subject from its every aspect until he made for himself an international reputation and was the recognized authority on this subject in this country.

While devoting himself to his specialty in college and private work, Dr. Dyer always made time to further medical education in his adopted city and state; he became the moving spirit of the New Orleans Polyclinic in 1895; then president, successively, of

[1] Read by title at the seventeenth annual meeting of the American Society of Tropical Medicine, Hot Springs, Arkansas, November 14–15, 1921.

the parish and state societies. In these different offices he showed executive ability, clear judgment and a happy faculty of stating things in concise and convincing language and it soon became evident to every teacher in Tulane Medical College that, when their beloved Dean Chaille retired, Isadore Dyer must be the logical successor and so, in 1908, nominated by Dr. Chaille, he was unanimously elected dean and came into his real life work which was only to be relinquished at his death.

It can be said without fear of contradiction that the success of the Medical Department of Tulane University was the one absorbing interest of his life; his every work, whether local or national, was for the advancement of his college; no labor was too arduous, if, by it, he could add prestige and standing to his university. As chairman of the committee on medical education of the Association of American Medical Colleges and later, its president, he was always in the forefront as an advocate of higher medical education and increased requirements, though he knew full well what sacrifices it meant for his college and himself.

In 1914, he founded and edited with Wellman "The American Journal of Tropical Diseases and Preventive Medicine" which in 1916 merged with the New Orleans Medical and Surgical Journal, of which, he had already been co-editor since 1896.

Dr. Dyer realized that Tulane, the largest of the extreme southern colleges, was the logical place to promote the study of tropical diseases and the work of Bass has proved his unerring judgment.

As a first lieutenant in the medical reserve corps, United States army, he served in Texas in 1916 and again as major, in 1917 was president of the medical reserve corps examining board. In 1918, he was ordered to Washington in the surgeon general's office and was honorably discharged in December, 1918.

No student or alumnus can ever forget how ardently Isadore Dyer urged every Tulane man to volunteer for service whether at home or abroad and was the prime mover in the organization of the Tulane Medical Unit.

Dr. HOWARD BENJAMIN CROSS

## DR. HOWARD BENJAMIN CROSS

Howard Benjamin Cross, eldest son of Mr. and Mrs. John K. Cross, of Waukomos, was born July 31, 1889, near Conway Springs, Kansas. In childhood he moved with his parents to Lamont, Oklahoma, where he later received his public school education. Later he entered the Tonkawa preparatory school. After graduation he taught two terms in a rural school near Lamont. In 1911 he entered the University of Oklahoma, from which he graduated in 1915, receiving the degree of Bachelor of Science. He taught biology in the Southwestern State Normal at Weatherford one year and zoölogy as assistant to Dr. Lane, University of Oklahoma, for three years. He was a graduate student at the University of Chicago and Johns Hopkins University, receiving the degree of Doctor of Philosophy from the latter institution in June, 1921.

In 1918 he enlisted in the United States army and was sent to Baltimore to assist in the work of the Johns Hopkins Army Medical School.

In April, 1921, Dr. Cross began a special study of the yellow fever organism at The Rockefeller Institute for Medical Research under Dr. Noguchi.

On November 23, 1921, he was sent by the International Health Board to Vera Cruz, Mexico, to help in the blotting out of the yellow fever plague. Dr. Cross fell a victim of the disease and died December 26, at Vera Cruz. By order of President Obregon of Mexico special services were held at both Vera Cruz and Mexico City, at which the Mexican government, the various health organizations, and members of the medical profession paid the highest tribute.

Both the Mexican government and the International Health Board sent special representatives to accompany the remains to its final resting place, in Enid, Oklahoma.

## SOCIETY NOTICES

### 1922 Meeting of the Society

The eighteenth annual meeting of the American Society of Tropical Medicine will be held May 2 and 3, 1922, at the Hotel Washington, Washington, D. C., in conjunction with the twelfth triennial congress of American Physicians and Surgeons. Announcements as to details of the meeting of the Society and of the Congress will be duly mailed to members. Titles of papers received later than March 31 will not appear on the printed program.

The meeting this year promises to be of unusual interest and also affords an excellent opportunity for members to attend the meetings of a considerable number of other national medical societies which together with this Society constitute the Congress, namely, American Ophthalmological Society, American Otological Society, American Neurological Association, American Gynecological Society, American Dermatological Association, American Laryngological Association, American Surgical Association, American Climatological and Clinical Association, Association of American Physicians, American Association of Genito-Urinary Surgeons, American Orthopedic Association, American Pediatric Society, American Association of Pathologists and Bacteriologists, and American Society of Tropical Medicine.

Delegate from the Society to the Executive Committee of the Congress:

Dr. W. S. Thayer, Baltimore, Maryland.

Alternate: Dr. H. J. Nichols, Washington, D. C.

Member of the Society on the Committee of Arrangements of the Congress:

Rear-Admiral E. R. Stitt, Washington, D. C.

Communications for the Society should be sent to the Secretary, P. O. Box 131, Pennsylvania Avenue Station, Washington, D. C.

## Foreign Membership in the American Society of Tropical Medicine

Inquiries have recently come to the Secretary of the American Society of Tropical Medicine regarding certain applications for membership presented at the annual meeting of the Society in 1919 on behalf of a considerable number of non-residents of the United States. These applications were largely the result of efforts of a membership committee appointed at the annual meeting in 1917. There was no report of the committee in 1918 as the Society did not meet that year because of the influenza epidemic. The committee during the two years of its existence notwithstanding the disturbances of the war, kept actively at work and communicated with a large number of medical men interested in or likely to be interested in tropical diseases, both in the United States and abroad. A rather long list of prospective members was thus assembled and presented to the Society. In many instances, however, the committee had not yet been able at the time of the meeting to arrange, in final form for the consideration of the Council of the Society, certain data relative to prospective members that are required in accordance with custom before names are presented for election. Also, some of the prospective members had not had an opportunity of replying in a definite manner to the committee's communications prior to the meeting as to whether they wished their names proposed for membership. Action by the Society on the committee's list was therefore postponed. Additional reason for this postponement was found in the fact that through an error or oversight on the part of the Council rather than on the part of the committee there was some uncertainty as to what was intended, in the case of many of the persons whose names were proposed, with reference to their membership status. The Council in its instructions to the committee had overlooked the fact that under the by-laws of the Society only regular physicians and scientists interested in the study of tropical diseases who are citizens of the United States can legally be elected to active membership. The Council also overlooked the fact that the by-laws limit the number of active members to 200. In view, however, of the attendant circumstances, when it is remembered that during the anxious years of 1917 and 1918 the members of the Council were so busy with other important matters that it was quite impossible for them to give proper attention to the affairs of the Society, this lack of due regard to details of the by-laws is not surprising nor altogether inexcusable.

Since the 1919 meeting, owing to the stress of the early reconstruction period following the war, to continued unavoidable distractions of the attention of the officers of the Society, and to various other conditions, no effective action has been taken toward securing the membership of the persons listed in the committee's report. At the present time on account of incompleteness in the records now in the possession of the Society, proper consideration of the report in question, so far as concerns individual cases, seems no longer practicable. It is therefore suggested that persons with the qualifications for membership who desire to join the Society at this time as corresponding members irrespective of whether their names were in the 1919 list that has been mentioned, send their applications to the Secretary either directly or through their colleagues already members of the Society.

To explain briefly the matter of foreign membership for the information of those not familiar with its details, it may be stated that regular physicians and scientists not residents of the United States who have contributed to the knowledge of tropical diseases are eligible for corresponding membership. The limitations in the by-laws as to the number and citizenship of active members do not apply in the case of corresponding members. Corresponding members have all the rights and privileges of active members except the vote and the holding of executive offices. The American Journal of Tropical Medicine, the official journal of the Society, goes without additional cost to all members (active and corresponding) who pay dues. The dues are fixed annually by the Council but may not be increased beyond $5.00 without approval by the Society at its annual meeting.

It is believed that in the present improved position of the Society, especially with respect to its publications, persons engaged in the field of tropical medicine in Latin America and elsewhere abroad, who possess the qualifications for corresponding membership, will derive considerable benefit from membership in the Society. Moreover the closer relationship which may thus be brought about between the present members of the Society and their colleagues in various countries, can not fail to help in the advancement of knowledge of tropical diseases, the main purpose for which the Society was founded. It will in many ways tend to promote the general welfare of the Society and increase its usefulness.

In order that loss of time and further correspondence in gathering necessary information concerning the qualifications of prospective members may be avoided, it is requested that applicants for corresponding membership and members sending in applications on behalf of their colleagues supply the data referred to below even in cases in which the Council might be supposed to be fully informed concerning the professional status and other qualifications of the person proposed for membership:

1. The name of the prospective member should be exactly stated and an adequate address given.

2. In accordance with the custom of the Society the application should be indorsed by or references given to two members of the Society from whom information concerning the qualifications of the prospective member can be obtained.

3. A brief statement of the professional education of the prospective member should be made, naming institutions attended, and degrees received, with the dates. Other data also may be given to show his status as a regular physician or scientist.

4. It should be shown that the prospective member has contributed to the knowledge of tropical diseases. This may be done by the submission of published papers, or of bibliographic references.

5. Professional positions held, present and past, should be noted.

B. H. Ransom, *Secretary*,
American Society of Tropical Medicine, P. O. Box 131,
Pennsylvania Ave. Station,
Washington, D. C.

*March 1, 1922.*

## Socios Extrangeros de la American Society of Tropical Medicine

Al Secretario de la American Society of Tropical Medicine se le han hecho, recientemente, varias preguntas acerca de ciertas solicitudes de entrada en la Sociedad procedentes de un numero de personas sin residencia en los Estados Unidos y las cuales fueron presentadas durante la asamblea anual de la Sociedad en 1919. Estas solicitudes se debieron al resultado directo de los esfuerzos realizados por el comité de socios nombrado durante la asamblea anual del 1917. Durante el año 1918 no de recibió ningún informe de dicho comité debido a que la Sociesad no pudo reunirse por motivo de la entonces reinante epidemia de influenza. El comité durante sus dos años de existencia, no obstante las perturbaciones de la guerra, continuó su trabajo activamente y estableció correspondencia con un alto numero de médicos, ya interesados, o con probable interés en las enfermedades tropicales, tanto en los Estados Unidos como en el extrangero. Se compuso, pues, una lista algo larga de individuos que podrían llegar a ser miembros y fué presentada a la Sociedad. Al reunirse la Sociedad en asamblea anual, sin embargo, no le fué posible al comité, en varios casos, tener listos y en forma completa ciertos datos que la costumbre requiere de los candidatos y los que debe considerar el Concejo de la Sociedad antes de ser sometidos a elección. Ademas, con anterioridad a la asamblea, varios de los individuos capaces de poder llegar a ser miembros aún no habian tenído la oportunidad de contestar definitivamente a las comunicaciones del comité en las que se les requería si deseaban o no que sus nombres fueran propuestos como socios. La Sociedad al no poder actuar debidamente sobre la lista, se vió precisada a posponer el asunto. Otra razón adicional que motivó esta decisión se debió al hecho de que, por mediación de un error o equivocación, no por parte del comité, sino del Concejo, en el caso de varios individuos no se sabía con fijeza lo que exactamente se intentaba con referencia al status de aquellos en la Sociedad. El Concejo, al transmitir sus instrucciones al comité, se olvidó del hecho de que el reglamento de la Sociedad prescribe que solamente médicos titularmente capacitados y otros hombres de ciencia, quienes sean ciudadanos de los Estados Unidos, pueden ser legalmente electos miembros de la Sociedad. El Concejo asi mismo pasó por alto de que el reglamento exíge que el número de miembros activos no exceda de 200. Considerando, sin embargo, las circunstancias acompañtes, como fueron los perplejos años del 1917 y del 1918, que obligaron a dichos miembros a considerar otras cuestiones de suma importancia—cohibiéndoles, por lo tanto, de prestar debida atención a los asuntos de la Sociedad, las faltas de cumplimiento de detalles reglamentarios arriba mencionados, no causan extrañeza y son realmente excusables.

Desde la asamblea del 1919 no se ha podido hacer nada efectivo tendente a la admisión como socios de las personas cuyos nombres contiene el informe del comité. Entre varias razones esto se ha debido en gran parte al peso del periodo reconstructivo subsiguiente a la guerra y así mismo a importantes cuestiones que inevitablemente han distraído la atención de los directores de la Sociedad. Actualmente, lo incompleto de los informes en posesión de la Sociedad, en lo que a casos individuales se refiere, evita la debida consideración y pone al asunto lejos de ser factible. Se sugiere, por lo tanto, que aquellas personas debidamente competentes y calificadas que deseen asociarse, sin importar si sus nombres aparecen o no en la lista ya mencionada, envíen sus solicitudes al Secretario, ya directamente o por mediación de colegas miembros de la Sociedad.

Para beneficio de aquellos que no estén familiarizados con los requisitos de admisión de socios extrangeros, los siguientes datos brevemente explican sus detalles. Son admisibles aquellos médicos titularmente capacitados y otros hombres de ciencia, sin residencia en los Estados Unidos, quienes hayan contribuido al desarrollo de los conocimientos de las enfermedades tropicales. Las restricciones que reza el reglamento tocante a ciudadanía y limitación del número de miembros activos, no son aplicables a los socios correspondientes. Los miembros correspondientes tienen todos los derechos y privilegios de los miembros activos, excepto el voto y la tenencia de puestos ejecutivos. The American Journal of Tropical Medicine, órgano oficial de la Sociedad, se envía sin costo adicional, a todos los miembros de la Sociedad—tanto activos como correspondientes, que pagan la cuota anual de socio. La cuota se fija anualmente por el Concejo pero no puede exceder la cantidad de cinco dólares a menos que la Sociedad, en asamblea anual, no decida lo contrario.

Es de creerse que la posición avanzada que hoy ocupa la Sociedad, especialmente en lo que respecta a sus publicaciones, sean de considerable beneficio a todos aquellos individuos, tanto de la América Latina como de otros paises extrangeros, interesados en el campo de la Medicina Tropical. Adémas, el establecimiento de relaciones íntimas entre los miembros de la Sociedad y sus colegas de países extrangeros, no puede tener otro resultado sino el mutuo progreso y desarrollo del conocimiento de las enfermedades del trópico—para el cual proposito la Sociedad fué establecida. Su utilidad y properidad serán, de la misma manera, altamente favorecidas.

Para evitar pérdida de tiempo y correspondencia acerca de los informes requerídos y calificaciones de aquellos individuos que puedan llegar a ser miembros, se manifiesta que las solicitudes como socios correspondientes—ya vengan directas o por mediación de miembros—suministren los datos abajo consignados—aún en aquellos casos en que se suponga que el Concejo ya esté informado del status profesional y calificaciones de las personas propuestas:

1. El nombre del indivíduo capaz de llegar a ser miembro con su dirección y señas adecuadas.

2. De acuerdo con las costumbres establecidas por la Sociedad, la solicitud deberá ser endosada por dos miembros, o referencias hechas de dos miembros, de la Sociedad, quienes puedan suministrar datos tocante a las calificaciones y competencia de la persona referida.

3. Una breve reseña recitando la educación profesional, instituciones que se han atendido, y títulos recibídos con sus fechas. Debe aqui mismo informarse acerca de la reputación y consecuencia del individuo como médico u hombre de ciencia.

4. Debe demostrarse si el indivíduo capaz de llegar a ser socio ha contribuído al conocimiento de las enfermedades tropicales. Esto podria hacerse enviando copias de artículos publicados o referencias bibliográficas.

5. Puestos profesionales que haya ejercido, presentes y pasados, y fechas de los mismos.

B. H. RANSOM, *Secretary*,
American Society of Tropical Medicine, P. O. Box 131,
Pennsylvania Ave. Station,
Washington, D. C.

*Marzo 1 de 1922.*

# OBSERVATIONS ON THE MICROFILARIA OF FILARIA BANCROFTI

WILLIAM L. McFARLAND

*New York*

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Infections with *Filaria bancrofti* are supposed to have been introduced in Charleston, South Carolina, by a cargo of negro slaves from a filarial district on the West Coast of Africa. In the same manner the infection must have been materially increased if not actually introduced in the northern portions of South America, in Central America, and in the West Indian Islands. The existence of filarial infection in the West Indies was, according to Manson (1) first recognized by Demarquay. In later years Manson, also Daniels (2), have stated that such infections occur in all the West Indian Islands and in those portions of the Western mainland already mentioned, and Ashburn (3) has given evidence of the prevalence of the condition in one island by finding microfilaria in the bloods of 12 per cent of the mounted battalion of the Porto Rico Provisional Regiment. During 1915 those interested in the subject were given food for thought by Johnson's (4) statement that in an examination of 400 individuals in Charleston South Carolina, principally routine hospital cases, he had found microfilaria in the bloods of 19.25 per cent. To Charleston as an endemic center, attention has again been drawn by the recent survey of Francis (5) in that and other cities of the South Atlantic and Gulf states. In the opinion of Francis transmission of the filarial infection here considered requires mass infection, large numbers of microfilaria in the peripheral circulation, and mass mosquito biting, to insure passage into a new host of one or more male and female organisms. The infrequent combination of these factors he considers responsible for the limitation of heavy infection to Charleston in the district covered by his survey and questions. Francis' conclusion regarding transmission is probably correct but with the increasingly restless movement of labor elements and *Culex fatigans* as a common household mosquito in many parts of the South, mass individual infection and mass mosquito biting must be from time to time associated, hence it is advisable that filariasis and its endemic centers be kept in mind by physicians practising in the South and by those treating patients who have resided in filarial areas. The methods and results here given are for such value as they may be to investigators of filarial infection, the pathological possibilities of which are as yet undetermined.

During the spring of 1918, the staff of the Board of Health Laboratory in the Panama Canal Zone was called upon to examine several hundred thick blood smears for malarial plasmodia. As microfilaria of *Filaria bancrofti* had shortly before been found in the blood of an Ançon Hospital ward patient the malarial survey with its promised amount of material suggested a simultaneous filarial survey with possibly some transmission experiments. The survey was begun but never completed and transmission experiments could not be undertaken as that particular malarial work was soon discontinued and a press of laboratory routine allowed no time for research which required systematic daily attention. However, at that time and during succeeding months it was possible to record examinations of the bloods of 1124 individuals and an hourly count for twenty-five hours on the blood of one individual. Over half of the first 500 smears were examined by Dr. Oscar Teague, then Director of the Laboratory, and he also collaborated in the twenty-five-hour count with many helpful suggestions and an equal share of the labor.

The first series of 25 ward patients had blood from finger or ear, drawn between 11:00 p.m. and 1:00 a.m., into small tubes containing 1 per cent sodium citrate in normal salt solution. Some of the tubes were kept at room and others at ice box temperature until the following morning when the citrate solution was pipetted off and the blood run onto slides and examined with a one-sixth objective for motile organisms. They were all negative though reëxamined. From 10 ward patients, blood was drawn in the same manner at 7:00 a.m. and examined within three hours, one positive being found who was afterwards used for the twenty-five-hour count. The method of drawing blood at midnight or midday in this manner and keeping it at ice box temperature until examined will probably give a higher percentage of positives than any other for the following reasons: periodicity, retention of motility Fulleborn (6), quantity of blood examined, facility and certainty of recognition of organism. When blood was kept at room temperature microfilariae rapidly whipped themselves into a state of inactivity from which they did not seem to revive, though the degree of heat was by no means tropical in the generally accepted sense of the term. This was at variance with the observations of Johnson, who found motility to be retained for ten and one-half days at room temperature in Charleston and suggests for the Northern organism a difference possibly due to long continued climatic influence on the host.

During the malarial survey 522 thick smears were examined. These smears were made between 3:00 a.m. and 7:00 a.m., at the primitive camps of laborers engaged in brush cutting. (This class of labor was recruited entirely from the blacks and mixed breeds. The men lived in rough huts and were at all times freely exposed to mosquito biting.) The first 18 were treated with a solution of 1 cc. of hydrochloric acid in 50 cc. of alcohol, then stained with Loeffler's alkaline methylene blue. Neither the solution for removing haemoglobin nor the stain were satisfactory, for smears made under such conditions are so covered with fine hairs, fibres, etc., that unless thoroughly laked or so stained as to clearly bring out the microfilaria many mistakes are likely to occur, as did in this series where 6 cases at first thought positive were found on repeated examination to be negative. Search for microfilaria in unlaked or partially laked thick smears is an almost hopeless undertaking no matter what stain has been used and while von Exdorf's tenchique is not mentioned the examination of unlaked preparations may have been one of the factors responsible for his statement to Francis that he found no microfilaria in 13,000 thick smears taken in various southern states.

In casting about for a better method smears were laked in 2 per cent acetic acid, then treated with a weak alkali and stained with Loeffler's blue but the results were not satisfactory. As some workers had recommended laking in tap water it was tried and found to answer the purpose admirably. Carbol fuchsin, haemotoxylin, and other text book stains were experimented with but none of them could be made to give more than a hazy outline of the body and all failed to clearly define the cell column and V-spot, so as a matter of convenience Loeffler's blue was used as a stain in examination of 504 of the 522 smears from brush cutters, the smears having been first laked in tap water. Of these 12 were positive.

As the stain was still unsatisfactory text book methods were again tried and new stains tested. Eventually it was found that a saturated alcoholic solution of methylene blue could be relied upon to bring out the body lines with great distinctness, and stain the cell column sharply, thus defining the V-spot.

The remaining 556 bloods were from ward patients in the Ançon and Santo Tomas hospitals, thick smears being made between 7:00 a.m. and 8:00 a.m., at the former and 7:00 p.m. and 8:00 p.m. at the latter institution. These smears, kept until time permitted their examination, were laked in tap water until the films were free of color, they were then flooded with a saturated alcoholic solution of methylene blue for about a minute, washed in tap water and searched wet or dry with a one-sixth objective. The process is simple, rapid, and economical as a number of preparations can be handled at once, timing is not necessary, and stain can be poured from treated to untreated preparations. The films can be quickly examined and there is no possibility of mistaking anything else for the clearly defined microfilaria. This series gave 21 positives.

There were amongst the last 556 patients a group of 100 Porto Rican soldiers with 5 positives, and a group of 100 Panamanian prostitutes with 2 positives, the latter group being examined night and day. Not one of the 34 positive cases was under observation or treatment for any condition which has been attributed to filariasis. In the bloods of one or two cases of elephantiasis no microfilaria could be found nor could any be demonstrated in the numerous sections of lung tissue removed at routine autopsies. The absence of pathologic conditions attributable to filariasis in the 34 positive cases is not in accord with the findings of Johnson who noted such conditions in 25 per cent of his 77 carriers. On the other hand Croll (7) says that not one of the 11.5 per cent cases of filarial infection, found in a routine examination of the bloods of 4000 adults at the Brisbane hospital, showed symptoms of filariasis nor were they aware of the fact that they were hosts of such a parasite. Croll states, however, that while about 10 per cent of the population of Southern Queensland have microfilaria in the blood and cases of filarial lymphangitis, chyluria, and filarial adenitis are only occasionally seen and elephantiasis is unknown, that cases of hyrocele, lymphocele, and deep intramuscular abscess of obscure origin are notably prevalent though microfilaria can rarely be found in the blood.

Counts for a period of twenty-four hours have been made by several investigators at intervals of two hours or more. The most recently published are those of York and Blacklock (8) who in a series of two hour counts not only charted the number of microfilaria in peripheral and venous blood but were able to gradually reverse the periodicity by changing hours of rest from night to day. The chart here given shows hourly counts for a period of twenty-five hours. For making such counts, into each of two graduated pipettes 0.02 cc. on blood from finger or ear was drawn and mixed with an equal quantity of 1 per cent sodium citrate in normal salt solution. After thorough mixing the pipette contents were discharged, each on a separate slide, protected with large vaseline rimmed cover slips and counted immediately with the aid of one-sixth objective. To prevent activity being retarded by pressure a few grains of very fine sand were so placed that they would mix with the blood and act as supports for the cover slips. The patient, a mixed breed, was under observation and treatment for malaria. He said that he had been born in Panama City and had never been out of the country.

| HOUR | NUMBER MICROFILARIA PER CUBIC CENTIMETER PERIPHERAL BLOOD | HOUR | NUMBER MICROFILARIA PER CUBIC CENTIMETER PERIPHERAL BLOOD |
|---|---|---|---|
| *March 26, 1918* | | | |
| 9:00 a.m. | 300 | 10:00 p.m. | 275 |
| 10:00 a.m. | 175 | 11:00 p.m. | 1175 |
| 11:00 a.m. | 125 | 12:00 midnight | 500 |
| 12:00 noon | 100 | *March 27, 1918* | |
| 1:00 p.m. | 25 | 1:00 a.m, | 825 |
| 2:00 p.m. | 0 | 2:00 a.m. | 695 |
| 3:00 p.m. | 50 | 3:00 a.m. | 825 |
| 4:00 p.m. | 25 | 4:00 a.m. | 800 |
| 5:00 p.m. | 25 | 5:00 a.m. | 550 |
| 6:00 p.m. | 275 | 6:00 a.m. | 360 |
| 7:00 p.m. | 500 | 7:00 a.m. | 350 |
| 8:00 p.m. | 330 | 8:00 a.m. | 400 |
| 9:00 p.m. | 575 | 9:00 a.m. | 325 |

All charts agree in fixing the maximum number of microfilaria in the peripheral circulation of day workers as occurring at about midnight. The variation of one to three hours between this and the charts of Smith and Rivas (9), York and Blacklock and others may be accounted for by change in hours of rest incident to hospital or other confinement during observation, technical error, etc. They all indicate that you may reasonable expect to find microfilaria in thick smears made about 7:00 a.m. or 8:00 p.m.

Reserve should be exercised in basing conclusions regarding local conditions on data collected from sources materially influenced by a constantly shifting foreign population, from those portions of Panama under direct supervision of "The Health Department of the Panama Canal" (10) the mortality list of 1918 being contributed to by 57 countries and islands. In addition due allowance must be made for the varying and contradictory replies of blacks and mixed breeds to questions concerning their places of nativity and their wanderings. With these facts in mind the small number of examinations here presented may be summarized as follows:

| CLASS | NUMBER EXAMINED | NUMBER POSITIVE | PER CENT POSITIVE |
|---|---|---|---|
| Brush cutters | 522 | 12 | 2.2 |
| Hospital patients: | | | |
| A. General | 402 | 15 | 3.7 |
| B. Porto Ricans | 100 | 5 | 5.0 |
| C. Prostitutes | 100 | 2 | 2.0 |
| Total | 1124 | 34 | 3.0 |

*Nationality of positives*

| | |
|---|---|
| Barbados 1 | Jamaica 1 |
| Hayti 1 | Panama 3 |
| India 1 | Porto Rico 5 |
| St. Kitts 1 | |

Answers could not be obtained from the remaining 20 as they had quit work, left the hospitals, etc.

It would appear that the only manner by which one could ascertain whether or not filariasis was a condition introduced in Panama from other parts of the world would be thorough examination of some of the isolated Indian tribes who avoid contact with any people except their own. Even to them such an infection might have been brought by the occasional wanderer who after testing the questionable pleasures of civilization returned to his hunting grounds. However, with a constant ebb and flow of people from known endemic centers and conditions outside the sanitated areas admirable for the transmission of such infection, it is reasonable to assume that filariasis will gradually increase in Panama. The figures here given represent a minimum of the percentage of infections.

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# THE EFFECT OF EMETINIZED BLOOD AND SERUM FROM MAN AND CAT ON PATHOGENIC ENTAMOEBAE IN STOOLS

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It has been conclusively demonstrated (1) that emetine hydrochlorid is not particularly toxic when applied directly to pathogenic entamoebae within the time limit of one to two hours. Inasmuch as emetine will generally abolish entamoebic dysentery in man, but has no effect on the same infection when transferred to cats, Dale and Dobell (2) have pointed out that emetine acts upon the host rather than upon the parasite.

We have undertaken to investigate the possibility of reproducing this reaction outside of the body by, first, mixing emetine with blood and serum from man and cat, and second, by injecting man and cat with therapeutic doses of emetine, withdrawing blood after absorption, and then applying these various mixtures to pathogenic entamoebae in stools.

The entamoebae for the first set of observations were obtained from a young white man who developed bloody painful dysentery on the Western Front in 1918 and who has several times been partially treated within the past two years.

The blood and emetine mixtures were made by adding to whole blood equal amount of a 4 per cent sodium citrate solution to which emetine hydrochlorid, 1:500, had been added. To the serums of cat and human blood was added an equal amount of a 1:200 emetine solution. Equal parts of each of these mixtures and the dysenteric stool were stirred vigorously on slides and observed under cover glasses for approximately an hour. Dilutions were made with distilled water. Controls were still active after two hours.

TABLE 1

*Dilutions*

| BLOOD EMETINE MIXTURES | EMETINE | CITRATE | BLOOD OR SERUM | TIME OBSERVED | EFFECTS |
|---|---|---|---|---|---|
| | | | | *minutes* | |
| *A*. Citrated-emetinized human blood (from) the dysenteric, plus feces, equal parts | 1:2000 | 1:100 | 1:4 | 5 | Disintegrating |
| | | | | | All gone |
| | 1:4000 | 1:200 | 1:8 | 60 | 20 per cent sluggish 80 per cent quiet |
| | 1:6000 | 1:300 | 1:12 | 30 | Sluggish |
| | | | | 60 | Quiet, many gone |
| | 1:10,000 | 1:500 | 1:20 | 100 | Quiet, many gone |
| | 1:20,000 | 1:1000 | 1:40 | 55 | Active |
| *B*. Citrated-emetinized cat blood plus feces, equal parts | 1:2000 | 1:100 | 1:4 | 65 | Dead, may gone |
| | 1:4000 | 1:200 | 1:8 | 10 | Very active |
| | | | | 60 | Very active |
| | 1:6000 | 1:300 | 1:12 | 34 | Sluggish |
| | | | | 60 | Half quiet, half sluggish |
| | 1:10,000 | 1:500 | 1:20 | 50 | Active |
| | 1:18,000 | 1:900 | 1:36 | 50 | Sluggish |
| *C*. Emetinized human blood serum (from the dysenteric) plus feces | 1:800 | | 1:4 | 45 | All quiet |
| | 1:2400 | | 1:12 | 65 | Active |
| | 1:4000 | | 1:20 | 45 | Sluggish |
| *D*. Emetinized cat blood serum plus feces. | 1:800 | | 1:4 | 50 | All quiet |
| | 1:2400 | | 1:12 | 60 | Active |
| | 1:4000 | | 1:20 | 60 | Active |
| *A*. Repeated after emetinized blood had stood 20 hours | 1:2000 | 1:100 | 1:4 | 65 | All gone |
| | 1:4000 | 1:200 | 1:8 | 64 | Very active |
| | 1:6000 | 1:300 | 1:12 | 63 | Very active |
| *B*. Repeated after emetinized blood had stood 20 hours | 3:2000 | 1:100 | 1:4 | 58 | All gone |
| | 1:4000 | 1:200 | 1:8 | 70 | All quiet |
| | 1:8000 | 1:400 | 1:16 | 53 | All quiet |
| *C*. Repeated after emetinized serum had stood 20 hours | 1:800 | | 1:4 | 64 | Active |
| | 1 1600 | | 1:8 | 61 | Active |
| *D*. Repeated after emetinized serum had stood 20 hours | 1:800 | | 1:4 | 73 | Active |
| | 1:1600 | | 1:8 | 65 | Sluggish |
| *E*. Emetinized blood serum (from a diabetic) plus feces, equal parts | 1:800 | | 1:4 | 80 | Sluggish |
| | 1:2400 | | 1:12 | 80 | Active |
| | 1:4800 | | 1:24 | 70 | Active |
| | 1:11,200 | | 1:56 | 73 | Active |

Both the dysenteric patient's blood and blood from a diabetic were used. The observations were repeated the next day after the emetine blood mixtures had stood at 28°C. for five hours, and then in the ice box for fifteen hours.

The semi-liquid stools, every drop of which swarmed with active entamoebae, contained very little mucus, a small amount of fecal material, and blood microscopically. About 10 per cent of the entamoebae contained one or two red blood cells; there were no old very large organisms engorged with red cells. Burroughs, Wellcome and Company emetine was used.

TABLE 2

| A. Dilutions human emetinized blood | Time started | Time observed | Remarks | Dilutions emetinized citrated cat blood | Set | Observed | Remarks |
|---|---|---|---|---|---|---|---|
| 1:4 | 2:38 | 3:00<br>3:47 | All quiet or dead<br>All dead | 1:4 | 2:40 | 3:20<br>3:45 | Motile<br>Motile |
| 1:8 | 2:43 | 3:10<br>3:46 | Non-motile<br>Disintegrating | 1:8 | 2:44 | 3:24<br>3:45 | Quiet and disintegrating<br>Disintegrating |
| 1:16 | 2:47 | 3:12<br>3:46 | Sluggish<br>Motile | 1:16 | 2:48 | 3:25<br>3:40 | Quiet<br>Motile |
| 1:32 | 2:50 | 3:14<br>3:45 | Sluggish<br>Motile | 1:32 | 2:51 | 3:26<br>3:50 | Sluggish<br>Motile |
| 1:64 | 2:52 | 3:15<br>3:50 | Motile<br>Motile | 1:64 | 2:53 | 3:28<br>3:54 | Quiet<br>Motile |
| 1:128 | 2:54 | 3:16<br>3:35 | Quiet<br>All faded | 1:128 | 2:55 | 3:29<br>3:53 | Sluggish<br>Motile |
| 1:256 | 2:56 | 3:20<br>3:55 | Sluggish<br>Motile | 1:256 | 2:57 | 3:30<br>3:59 | Sluggish<br>Motile |

As may be seen from table 1, human blood and serum mixed with emetine had no more effect than cat blood and serum similarly mixed. Having failed to note any difference in effect between human and cat blood, mixed with emetine outside the body, we next tried the effect of blood withdrawn from man and cat two or three hours after therapeutic doses of emetine. The entamoebae were secured from a half grown kitten experimentally infected. An emulsion of stool in 0.9 per cent NaCl solution was made and the supernatant fluid after settling was used to avoid mucus. The man selected was a chronic case of entamoebic dysentery of ten years standing, weighing 115 pounds. He had never before been given emetine. He was given one grain daily for eight days, entamoebae disappearing from the stools after the fourth day, and two hours after the eighth dose blood was withdrawn and mixed with equal parts of 0.5 per cent sodium citrate solution. At the same time a 3-pound cat, experimentally infected with entamoebae, was given 0.05-grain emetine by hypo and after three hours blood was withdrawn and added to equal parts of 0.5 per cent sodium citrate solution; the cat blood was laked at once. Entamoebae rapidly disintegrated in undiluted blood as noted by Dale and Dobell (2).

These observations show that citrated blood of man and cat withdrawn after therapeutic doses of emetine have no effect on entamoebae in stools within an hour in dilutions weaker than 1:8.

Conclusion: Emetinized human blood is no more toxic for entamoebae in stools than emetinized cat blood within the time limit of one hour.

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# AN EXPERIMENTAL INVESTIGATION OF THE SUPPOSED POISONOUS QUALITIES OF THE GRANARY WEEVIL, *CALENDRA GRANARIA*

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There are current many unsubstantiated opinions concerning supposedly poisonous insects. A striking illustration of this is afforded by the literature relative to the granary weevil, *Calendra granaria*. In view of the fact that no experimental work has been done which supports the theory that this beetle is poisonous, the subject of this paper was suggested by Dr. W. A. Riley as one worthy of study, and to him the writer is very grateful for advice and many helpful suggestions.

It was found that, meager and unsupported as are the data concerning it, the belief is widespread that the granary weevil may be used as a substitute for the official blister beetle, *Lytta* (*Cantharis*) *vesicatoria*. It is well known that these beetles and closely related forms belonging to the family Meloidae contain a substance, cantharidin, which is highly toxic when ingested and an active vesicant when it is applied to the body surface. The belief that *Calendra granaria* is as efficient a vesicant as the true blister beetle is not a recent one, but there is no experimental evidence which supports this belief.

## LITERATURE REVIEW

The first note relative to this subject was published in 1827 by Mitouart and Bonastre, from a report before the pharmaceutical section of the Académie Royale de Médecin. They cite experimental work by Peneau, a pharmacist at Bourges, who noted that besides causing incalculable injury to wheat, the weevil, *Calendra granaria*, was thought to be the cause of colic produced from eating bread made from flour from infested wheat.

After crushing the fresh insects in sweet almond oil and applying them to the skin, Peneau claimed that in five hours a "lively irritation" resulted, somewhat less strong than that produced by a plaster of cantharides. He also mentioned the presence of gallic acid in the weevils. This finding, however, is of no importance in this connection, since the writer has determined by experiment that a strong solution of gallic acid bandaged on for six to eight hours has no effect.

The commissioners of the Academy repeated Peneau's experiments with crushed weevils, and failed to note any appreciable irritation on the skin from such an application. They also tried distillation with water and obtained only a pale and inert liquid which, treated with alcohol and ether, has a styptic or astringent taste. This property they found to be very well marked, but nevertheless the solution was not strong enough to cause irritation of the tongue, lips or pharynx.

Some months later Henry and Bonastre (1827) carried out analytical experiments on the granary weevils to endeavor if possible to isolate some principle analogous to that in cantharides, which Peneau seems to have indicated. Their most careful analysis resulted in separating out eleven substances, not one of which bears any relation to cantharidin. To quote:

> In order to once more assure ourselves if the weevils were vesicating, we made a powder of them in the fresh state and formed two blister plasters with the paste. These two plasters were applied on two subjects, one robust, vigorous and middle aged, the other very young and more delicate; they have produced neither burns nor rubefacience in the space of twenty-four hours. We have thus confirmed the experiments of our colleagues.

Wm. Mills (1835) published a note which seems to indicate that other observers agree with Peneau that these weevils may possess some of the properties of cantharides. While in Madeira Mr. Mills was making some rather intensive observations on the oviposition habits of Calendra, and in his report included the following statement:

An old medical gentleman assured me that he considered the wings and crustaceous parts of the weevil so heating to the system as to be almost as injurious as cantharides taken internally on a slow scale. And when we consider the quantity of bread which is imbued with them in warm climates, it is decidedly worth attending to for the sake of a purer food.

We find this statement quoted later by Walsh and Riley (1869) in an article entitled "Poisonous Flour."

In this same article Walsh and Riley also say:

We have recently been informed by Dr. W. D. Hartman of West Chester, Penn., that "in the South this beetle has been used successfully as a substitute for the Spanish Blister-beetle (Cantharides), and with this advantage over the foreign insect, that it does not cause strangury, to escape from which," as Dr. Hartman further observes, "is a very great and important item in the formation of a blister." We are not informed how the above discovery came to be made in the Southern states, but infer that it was probably from the great scarcity there of the imported Spanish fly, during the late war, in consequence of the rigid stringency of the blockade of their sea-ports.

Furthermore, we are told in this same article that there is no doubt but that great numbers of this weevil are often ground up into flour, and although the legs, snouts and elytra are probably removed by the bolting cloth, a considerable portion of the body will be gound fine enough to be incorporated in the flour that we use every day. Thus, if the number of weevils were large, the flour would be poisonous, "for we know now that these weevils have nearly the same medicinal properties as Spanish flies, and Spanish flies, as is notorious, are even in comparatively very small doses, a most violent and dangerous drug to take internally, and when swallowed in larger doses are a deadly poison."

The writers also suggest that several cases of poisoning from flour from a certain mill in New York might be attributable to weevils in the flour rather than lead, as was then concluded.

Thus it seems that Walsh and Riley have accepted without question the views of the unknown "medical gentleman of Madeira" and of Dr. Hartman to the extent of stating that "we know now that these weevils have nearly the same medicinal properties as Spanish flies." We find no record of their having tested out this property or analyzed the beetles in any way.

In "Insects Injurious to the Household," 1914, Herrick has repeated almost verbatim this statement from Walsh and Riley, adding that "so far as the author is aware, however, the granary weevils are not generally used for that purpose at present."

Riley, 1922, briefly reviews the literature on the subject, and reports negative results from the ingestion of the dried beetles.

## PROPERTIES OF CANTHARIDIN

The physiological effects of cantharidin are two-fold. The application of cantharidin, or any substance containing it, to the surface of the body causes rubefacience, or in larger amounts, blistering. Vesication is sometimes accompanied by a leucocytosis which is so striking, according to Kobert (1906) as to have greatly reduced the therapeutic use of Spanish fly.

Internally the effect of cantharidin is severely toxic, and no antidote for it has been discovered. Quoting from the United States Dispensatory (twentieth edition) "it is a powerful irritant, with a peculiar direction for the urinary and genital organs." Dissection of mammals which have ingested it reveals inflammation, or sometimes ulceration, of all mucous membranes with which it comes in contact.

With the foregoing literature under consideration, the experimental work on *Calendra granaria* was begun.

## PREPARATION OF MATERIAL

The writer's thanks are due to Dr. R. N. Chapman of this University, who furnished a culture of barley which was very heavily infested with the weevils, and from which all the specimens were collected.

After being separated from the grain, the weevils were killed by heat, to obviate the possibility of any insecticide entering into the subsequent reactions. They were then dried in a hot chamber at 60°C. until they were sufficiently brittle to be pulverized, and the dry powdered insects were bottled and used when desired to make the various preparations.

The experiments were of three types: namely, feeding experiments in which rats, mice, chickens, frogs and a rabbit were used; vesicating experiments with the writer as subject in all but a very small number of trials; and subcutaneous inoculations using rats and mice.

## FEEDING EXPERIMENTS

In these experiments the insects were fed either dry in capsules; moistened to a paste with distilled water, or extracted with distilled water and the clear solution used. In every case control preparations, made from powdered Chinese blister beetles (various species of Mylabris) were used under identical conditions.

### *1. Experiment on a rabbit*

A young rabbit was fed 100 Calendra in a capsule, and observed closely for a week. During this time the only noticeable symptoms were restlessness and lack of appetite, which might easily be explained by its close confinement while under observation. At the end of the week the rabbit was fed 350 more Calendra making a total of 450, but it showed no ill effect whatever.

A check with Mylabris was not used in this experiment because the effect of cantharides on rabbits is very clearly outlined by Lissonde (1869). Briefly, a rabbit may be killed by 0.025 mgm. of the principle, cantharidin, which would be contained in 0.4 gram of cantharides. "It would succumb not because of organic lesions, but because of a general action on the vital functions." The symptoms present are stupor, trembling limbs, partial paralysis, bloody saliva, death in convulsions in approximately four hours.

### *2. Experiments with rats*

1. Three half-grown white rats in good condition were each fed 0.260 gram of powdered Calendra. Close observation extending over ten days showed no unnatural reaction at any time, so the rats were not dissected.

2. A rat from the same litter and kept in the same cage as those in the foregoing experiment was fed 0.250 grams of powdered Mylabris. It immediately began to show symptoms of illness; there were no strong convulsions but a constant convulsive shivering. It crouched down in a corner of the cage, and its condition remained the same for the rest of the day. The next morning the rat was dead, and dissection showed a condition similar to that observed later in the mice, namely a deeply inflamed body cavity, intense inflammation of the entire alimentary canal, and lungs congested and collapsed. No effect was observed on the reproductive organs or kidneys.

### 3. *Experiments with mice*

1. Three adult white mice were fed 35, 40 and 100 Calendra administered in two feedings two days apart. The closest observation showed that they were wholly unaffected. On the other hand a mouse which had received 25 beetles died two days later, without any observed symptoms. This mouse was dissected immediately, but showed no unusual inflammation or other gross pathological condition. By way of comparison, the mouse which had ingested 100 beetles was killed and dissected but it likewise showed no abnormality. There is every reason to suppose that the death of the one which had been fed 25 beetles was due to other causes.

2. Two adult white mice were fed approximately 0.5 gram Mylabris in enough distilled water to facilitate feeding. Almost immediately convulsions began which increased in severity until the mice were unable to stand, and the convulsive tremors were coming at intervals of two seconds. This continued for sixty-five minutes, when they were noticeably exhausted, and the gasping for breath slower and weaker. At the end of one and one-half hours they were both dead, and were dissected immediately. For comparison a normal unfed mouse from the same cage was dissected at the same time. There was a marked contrast exhibited; the poisoned mice showed a distinctly darker and congested appearance of the viscera, the intestinal lining was highly inflamed as far as the powdered insects had passed, the stomach was distended with gas, and the lungs collapsed and congested.

### *4. Experiments with chickens*

1. Fifteen young chickens approximately three weeks old were divided into three lots of five each (by markings) and were all kept in the same pen. Group 1 was fed 0.5 gram Calendra each, group 2 fed 0.5 Mylabris, and group 3 was kept as control. In all cases the ground insects were mixed with distilled water and administered with a large pipette. None of the chicks showed any ill effect following the feeding, but on the following day one from each lot was killed and dissected. They all were similar and normal so far as could be observed.

2. One week later the four remaining chickens in each lot were fed as before, but no reaction could be observed. Dissection of one from each group showed no abnormality.

Kobert (1906) states that some birds are immune to cantharidin poisoning which would probably explain the above results. It is reported by Kobert, however, that the flesh of the birds which have eaten cantharides is poisoned, and will cause the characteristic symptoms if it is eaten by a mammal.

### *5. Experiments with frogs*

1. Six half-grown *Rana pipiens* were each fed 25 Calendra. They showed no effect and the feeding was repeated in two days. In twelve days one frog died, but dissection showed no abnormal condition; its death was probably due to lack of food, since this individual was much smaller than the others. The remaining five frogs were killed and dissected at the end of the fourteenth day, and seemed wholly unaffected.

2. Five adult frogs were each fed 0.5 gram of Mylabris, and the dose repeated in eight hours. Twelve hours later two had died, whether from the effects of the insects, or due to injury from handling in feeding, it was not possible to determine. The remaining three were fed repeatedly in 0.5 gram doses until each had ingested 3 grams, and yet none showed any ill effect.

3. The powdered insects passed through the alimentary canal so rapidly (four to five hours) and were somewhat difficult to administer, so that it was thought advisable to try an aqueous

extract. Five-tenths gram Mylabris was macerated in 4 cc. distilled water at 60°C. for forty-eight hours. One frog received 3 cc. of this extract every day for one week and remained unaffected.

Vezien (1860), Meynier (1893), Kobert (1906) and others have mentioned the immunity of frogs from cantharidin poisoning, which serves to substantiate the above results.

In summarizing the ingestion experiments, there seems to be no evidence which would justify the opinion that "these weevils have nearly the same medicinal properties as Spanish flies."

## VESICATING EXPERIMENTS

The preparation of all materials and solutions used in the experiments to determine the effect of *Calendra granaria* on the skin, was governed by methods indicated by various chemists and pharmacists. Robiquet (1810) and Brettoneau (1813) who discovered cantharidin, employed boiling water followed by boiling alcohol and ether. Carpenter (1831) boiled the insects in sulphuric ether, while Wolff also employed ethereal extraction. Warner (1856) evolved a method useful in quantitative extraction of cantharidin which makes use of boiling water, boiling alcohol and ether. According to Mortreux (1864), Dragendorff (1867), and Beguin (1874) the use of carbon disulphide with the above reagents yields a purer product. Fahnestock (1879) and Goossens (1881) used processes in which chloroform is the solvent; Galippe(1876) and Greenish and Wilson (1898) employed acetic ether and acetic acid as the solvent. The fact that cantharidin is soluble in most oils, such as clove, almond, olive, cedar, turpentine, etc. is well known and included in all discussions of its properties.

The solvents used in the writer's experiments were, therefore, alcohol, chloroform, ether, acetic acid, acetic ether, water, clove, cedar and almond oil. The control preparations of true blister beetles were made from various species of Mylabris as before. The method of applying the solutions was similar to that employed by Fabre (1916) in his experiments on urticating insect larvae, namely that a moisture proof, air tight bandage be used. The solutions were soaked up with pledgets of absorbent cotton or folded lens paper, applied to the inner arm, wrist or finger and covered with an oiled silk or rubber bandage, which was in turn covered with a gauze bandage.

1. Five-tenths gram powdered weevils macerated in 3 cc. distilled water for one week. The extract was filtered off and applied on cotton. After twelve hours there was no effect on the skin.

1a. The check preparation with Mylabris in distilled water was bandaged on and the dressing removed in two hours because of the intense pain. Immediately a large full blister formed.

2. Five-tenths gram Calendra boiled in 4 cc. distilled water down to 2 cc. This fluid applied to the wrist for eight hours had no effect.

2a. The check preparation with Mylabris caused a blister in three hours.

3. Three hundred Calendra macerated in chloroform thirty-six hours filtered, evaporated to a few drops and applied on lens paper. After eight hours there was not the slightest effect.

3a. The check preparation with Mylabris caused a blister in six hours.

4. Some powdered Calendra was macerated in ether for one-half hour (Carpenter, 1831) then distilled; the distillate was poured back and the process repeated three times. The yellowish fluid left after the last distillation was applied on lens paper. No effect was noted after twelve hours.

4a. The control solution of Mylabris produced a blister in three hours.

5. Three grams Calendra were mixed with 2 cc. cedar oil and kept at 55°C. for one hundred-twenty-eight hours. Filtered and applied, there was no effect after twenty-four hours of application.

5a. The control solution of Mylabris produced an exceedingly large blister at the end of the three and one-half hours.

6. Five-tenths gram Calendra was macerated in acetic ether for one week. Soaked in absorbent cotton and applied for eight hours, there was no effect on the skin save a slight redness which was subsequently proved to be caused by the acetic ether alone.

6a. The control preparation with Mylabris caused a blister in four hours.

7. Five-tenths gram Calendra was macerated in 95 per cent alcohol for one week. The clear yellowish fluid resulting caused no effect on the skin after twelve hours of application.

7a. The check solution with Mylabris caused a blister to form at the end of five hours.

8. A "vinegar" was made of acetic acid, alcohol and Calendra (United States Dispensatory) and bandaged on the arm. Burning and inflammation immediately resulted, but it was subsequently proved to be due to the acetic acid alone. No blister or other permanent reaction was observed.

8a. The control preparation caused redness, and after being bandaged on for six hours a large blister formed.

9. Five-tenths gram Calendra was macerated in oil of bitter almond for one week, filtered and bandaged on. There was a great deal of burning which was afterwards proved to be caused by the oil. No blister formed after twelve hours.

9a. The control solution with Mylabris caused a blister to form in six hours.

10. Ten fresh *Calendra granaria* were ground to a coarse paste in pure glycerine (Stokes, 1914) and bandaged on the arm. Not the slightest reaction occurred after twenty-four hours of application.

10a. An equal amount of Mylabris in glycerine caused a blister to form in seven hours.

11. Five fresh Calendra were bruised and rubbed on the skin of the inner arm and allowed to dry there. No effect was noted.

11a. One fresh blister beetle, *Meloe angusticollis* was rubbed on the arm. After drying, redness began to develop and in three hours became intensified until a small blister appeared.

By way of summarizing the experiments on the vesicating power of the granary weevil, the evidence that they possess no such property is without contradication so far as the writer's experiments have been carried out. Without exception, the control preparations with Mylabris caused vesication, and since the materials used were the best solvents of cantharidin, it seems to follow that *Calendra granaria* possesses no cantharidin. If vesication ever resulted from the use of this species, which is at least doubtful, if not actually impossible, the causative agent was probably contained in the reagents used, and not in the insects themselves.

### SUBCUTANEOUS INOCULATION

The solutions used in inoculating were prepared by mixing one gram of dried insects (Calendra or Mylabris) with 8 cc. of distilled water, and boiling down to 4 cc. The resulting fluid was then diluted to 8 cc. with a salt solution of double isotonic strength, making the final product isotonic. In this way the writer hoped to make a solution which would preclude so far as possible a reaction of the subject to the fluid itself, and any effect on the animal might be attributed directly to the insects used. A control solution of the same concentration without insects was made up at the same time. The three solutions were then sterilized in an autoclave, and injected with a sterile hypodermic syringe.

#### *1. Experiments with mice*

1. One adult white mouse was inoculated subcutaneously with 1 cc. of the Calendra solution. The closest observation showed no abnormal reaction in the two weeks following inoculation.
2. A mouse inoculated with salt solution at the same time remained unaffected.
3. A third mouse was injected with 1 cc. of Mylabris solution, and immediately began to breath convulsively. In a few minutes it lay stretched out, motionless except for convulsions of increasing frequency. In one and one-half hours the mouse was dead.

#### *2. Experiments with rats*

1. Four young white rats were each inoculated with 2 cc. of Calendra solution. They continued to be active and showed no unfavorable reaction at any time during the following two weeks.
2. Five rats inoculated with salt solution at the same time were likewise unaffected.

3. Four rats from the same litter were each injected with 2 cc. of Mylabris solution. They did not regain their normal activity following inoculation as the other animals did, but lay stretched out breathing convulsively. In one and three-fourths hours one rat was dead, and a second one lying on its side with strong muscular spasms of the hind legs. The twitching increased until the whole body was in constant convulsions, and death occurred two hours after inoculation. The other two rats died shortly after with the same symptoms.

They were all immediately autopsied, together with one from the Calendra and one from the salt solution group. The last two mentioned showed a slight redness at the site of injection, with the surrounding tissues somewhat distended with fluid, but no inflammation; all the other organs seemed normal.

This picture was in strong contrast to that presented by the four Mylabris-injected rats. There was a great deal of inflammation both where the needle punctured the skin and in the surrounding tissues. The most notable feature however, was that the entire area was congested with a clear yellowish jelly similar to coagulated blood serum, and adhering closely to the body wall. It might be described as a subcutaneous blister, approximately 3 cm. in diameter. None of the organs seemed affected; the poison probably acted too quickly to allow of penetration to all parts of the body before the heart action was stopped.

## CONCLUSION

In the light of the foregoing facts and experimental data, the writer considers it justifiable to conclude that the granary weevil contains no cantharidin, and cannot be used as a substitute for the blister beetle, nor is there any evidence to indicate that it is responsible for cases of poisonous flour.

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# A DEATH CAUSED BY ASCARIDES

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In the course of the International Health Board's campaign against hookworm disease in the Republic of Panama, on August 26, 1921, in the village of El Pilon in the District of Montijo, Province of Veraguas, a baby girl twenty-two months of age died under the following conditions:

At 6:00 a.m. she was given ½ minim of the oil of chenopodium, and two hours later a dose of Epsom salts. There were no disagreeable symptoms in evidence at this time, but because the salts did not produce results within two hours, the microscopist who treated the child gave her a saline enema. In the resulting evacuation there were eighteen ascarides. In the movements which followed, innumerable ascarides were expelled.

About 5:00 p.m. the little girl became very weak. Several masses formed in her abdomen, and ascarides came from her mouth and nose. Many ascarides collected in her throat and some of them must have blocked the larynx, for her respiration ceased. In spite of all efforts to save her, the child died at 8:30 p.m. Ten hours after her death a scarides were still issuing from her mouth.

The statements of the microscopist are fully corroborated by the parents of the child and several neighbors. One man who sought to make capital out of this sad accident to the detriment of the campaign was fined ten days of arrest by the alcalde, although he denied the statements attributed to him. The parents of the child have continued to bring their other children for treatment and the campaign in that district has not suffered in the least from this occurrence. The people of the village are convinced that the ascarides were responsible for her death and not the medicine.

There was no irregularity whatever in the method of administration of the treatment, the dose was easily within the limits of safety, and there was no other cause to which her death could be attributed than the accumulation of ascarides in her throat.

# BLASTOCYSTIS SPECIES IN CULTURE

## A PRELIMINARY COMMUNICATION

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Blastocystis is a cell occurring in the feces and intestine of man and other animals about which considerable confusion has existed for a number of years. It is very often associated with intestinal protozoa and has been described in relation to one or another as a stage of encystment or degeneration by several parasitologists.

In 1915, the writer obtained the cell in culture in ascitic fluid but at the time confused it with a trichomonas cyst. Later, after recognizing it as the Blastocystis of Alexieff (1911), report was made of its prevalence and some of its characteristics in the intestinal content and feces in South Carolina (Lynch, 1917). Following a personal communication in November, 1919, with Dr. H. P. Barrett of Charlotte, North Carolina, in which it was learned that he had obtained blastocystis in culture in liquid human blood serum, further cultivation was attempted with some rather interesting results concerning the nature of the organism and its manner of reproduction. Specimens from this work along with drawings and photographs of different phases of the cell formed a part of an exhibit in the scientific exhibit section of the American Medical Association in Boston, June 6, 1921.

Since that time Barret (1921) has published a report of his method of cultivation. His best cultures were obtained in human blood serum, inactivated and diluted 1:10 with 0.5 per cent sodium chloride solution. Barret states that "budding, as described by Alexieff, and binary division" are the methods of multiplication of the cell, both processes having been observed in all cultures and the cell retaining its original form after twenty-five successive transfers in artificial culture media. He further states that in the examination of hundreds of preparations "the so-called multiple division form of Alexieff, pictured by Wenyon and O'Connor (1917), has been encountered on only two occasions." He made no attempt to classify different strains although the gross appearance of organisms from different individuals suggested that several may have been encountered. Just what Barret has called budding is not clear since in Alexieff's description (1911), as I read it, no process of budding occurs except that concerned in his "multiple division" form and that Barret says he encountered only twice.

In the study under present consideration several different body fluids in addition to blood serum have been used successfully. The media upon which Blastocystis has grown readily includes the fluid from an ovarian cyst, several peritoneal transudates of fairly high albuminous content, and liquid human blood serum. These have been used in various strengths from the pure state to dilutions of 1:10 or even 1:20 in sodium chloride solution of 0.5 per cent and 0.9 per cent. While these media will all grow Blastocystis readily some of the cells grow best in strong solutions and some in diluted solutions. Whether this is governed by the strain or by other factors such as the bacterial content of the culture or the degree of exposure to air is not clear at the present. No cultures have been obtained in a number of attempts to plant the cell on such solid media as Loeffler's blood serum, nutrient agar, and Saboraud's sugar agar, or in beef broth, although it is indicated that anaerobic cultures might be successful on solid media since the cell grows in liquid media at the bottom of the tube and exposure to air is rapidly destructive.

In cultures three methods of reproduction have been encountered; fission, peripheral gemmation, and endosporulation, and, while mixed cultures have been obtained, out of the material and observations from many cultures from different individuals there have emerged three distinct types.

The first of these apparently reproduces only by fission. It has grown well on various strengths of blood serum and ascitic fluid and is easily transplanted during activity in the culture. In the process of fission there occurs an equal division into two or, less commonly, into four or, more rarely, into six or even eight, similar cells. It appears that the process may start anew in the daughter cells before primary division is completed, thus giving not uncommon figures of incompletely divided cells some of which are smaller than the others. At times division into two of unequal size occurs and this may be looked upon as single budding but the process appears to be no different to that producing daughter cells of equal size. The process of division into more than two cells is comparable to Alexieff's multiple division and it is probable that it is the same. The mucilagenous envelope or matrix surrounding the cell is perfectly plain at times and is demonstrable in some stained specimens, especially in the most prolific cultures, but in some it is not made out. As Alexieff interprets and pictures this form there is division into a definite number of small secondary cysts within the primary and then a disintegration of the primary capsule to liberate them. It appears in the cultures of this study that this type is better described by the term multiple fission and that when the mucilagenous envelope is to be made out it is pushed outward by the new cells and when they break away from each other it is carried along and continues to envelope them. In fact, this matrix seems to be a secretion of the cell. It does not seem that there is any difference in the process of multiplication whether two or more cells are formed, but Alexieff divides the cycle of reproduction into two distinct phases, one of binary division and the other of multiple endogenous sporulation. It is noted that Alexieff places a question mark along with his figure of this stage, and because of the fact that he was not dealing with cultures and the possibility that these two processes may be the same it is thought best to tentatively identify this first type of this study with Blastocystis enterocola (Alexieff, 1911). Brumpt (1912))gave the name Blastocystis hominis to the species in man, which, according to him, reproduces only by fission. It is consequently impossible to differentiate this first type from Blastocystis hominis and Blastocystis enterocola and Blastocystis hominis must, for the present, be considered synonymous. If this type should be differentiated from Blastocystis enterocola, then Blastocystis hominis will become reinstated, whereas it is otherwise displaced.

The second type reproduces by fission and multiple peripheral gemmation and furnishes the most common cell encountered. There seems to be no gross difference between the process of fission here and in the first case. Gemmation, in which daughter cells are budded from the surface, varying in number from few to many, regular and symmetrical or irregular and assymetrical, may occur while fission is still in progress but is usually later. The buds are short and blunt, long and finger-like, of large and lobose, and are projected from points at the surface where nuclei and apparently material from the central reserve body have been collected. At times the number is so great as to be uncountable. The buds contain all the elements of the cell, they are pinched off from the surface and may be well differentiated before they are free. This process is not to be confused with the multiple division form of Alexieff or the multiple fission of the first type, although kinship may be established between the two by the occasional single bud seen in the first.

The third type reproduces by fission and apparently a process of endosporulation. The process of formation of spores within the body of the cell seems to be fairly complicated and apparently results from a collection of the divided material into a number of globules, among which a process of fusion takes place with apparently a reduction in number. The spores seem to have not matured before they are liberated by disintegration of the parent cell but to undergo further development afterward. There are several phases of this stage that are not clear at his time, among which is the suggestion of sexual conjugation.

Thus far there are certain features common to the different types, such as the gross appearance in feces and the processes of fission and budding. There are certain differences between the forms such as the large size of the budding forms as compared to the fission and sporulating forms, and the optimum strength of the culture media, which may be more apparent than real and may depend on environment or other circumstance not concerned with specific differences. The main difference upon which the types are based at the present stage of study and upon which a specific differentiation is proposed is the manner of reproduction. Elaboration of the study is in progress and as soon as certain data which are apparently in hand but which must be subjected to thorough critical study are established it is contemplated to report the details of structure and other considerations of the proposed species.

It is proposed at the present time that there are three distinct species of Blastocystis from the intestine of man in this study, as determined by the method of reproduction in culture. The first of these, i.e., that reproducing by binary division and multiple fission, is tentatively identified, as before stated, with Blastocystis enterocola (Alexieff, 1911) with the reservation that should the processes of multiple division of Alexieff and that of this study be differentiated certainly, the first species of this study will become identified as Blastocystis hominis (Brumpt, 1912) which name is under the first hypothesis a synonym and becomes displaced.

The seond type, reproducing by fission and multiple peripheral gemmation, it is proposed to name Blastocystis gemmagina,n.sp, and the third, reproducing by fission and endosporulation, Blastocystis sporogina, n.sp.

Appreciation is hereby expressed for valuable suggestions received from Prof. C. W. Stiles of the United States Public Health Service and from Prof. Allen J. Smith and Prof. Damaso Rivas of the University of Pennsylvania concerned with the naming of these species.

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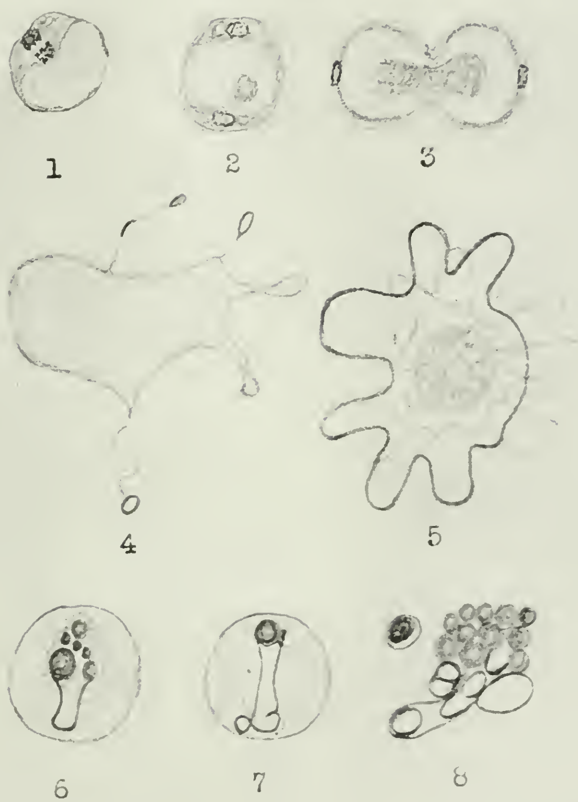
## EXPLANATION OF PLATE

### Drawings of Specimens of Blastocystis from Cultures of Different Types

Figures 1, 2, 3, specimens from culture of the first type, Leishman's stain showing division of the cell, possibly mitotic.

Figures 4 and 5, large budding forms from cultures of the second type. Fresh unstained specimens.

Figures 6, 7, 8, fresh unstained specimens from cultures of the third type showing the formation and liberation of spores.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# A NOTE ON CERTAIN COPROZOIC ORGANISMS IN CULTURES FROM MAN

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In culture work with the so-called intestinal parasites danger of error and introduction of confusion exists from the likelihood of obtaining free-living organisms, ingested with food and water, which may pass through the intestine of man alive, although not growing there. From time to time new "intestinal parasites" have been thus encountered and described, adding to the confusion already existing.

The writer in recent cultivation experiments with intestinal protozoa and Blastocystis has encountered several forms which it is well to be informed about in this sort of work, some of which may be confused with Blastocystis. Those which it has been necessary to differentiate are probably of the fresh water algae and they must always be taken into consideration in cultivation of this organism as there are several which are apparently similar to certain forms of Blastocystis that may be reasonably expected to pass through the intestine at times.

Fortunately it appears that not many of such organisms grow well at body temperature and when they have been observed it was rather as individuals than growing cultures.

Figure 1 of the accompanying illustrations shows a body encountered now and then which evidently belongs to the Diatoms, it bearing a structure similar to several of them, although the writer is not sufficiently familiar with these plants to identify it with certainty. As the organism was seen it was about thirty by fifty microns in size, the shell was doubly contoured and of a yellowish-green refractive cast, as were also the internal longitudinal structures. The cross striations were very fine lines.

Figures 2, 3, and 4, represent bodies seen fairly frequently which resemble *Gleocystis vesiculosus* Nageli. The inner body was highly refractive, and two or four cells were frequently present within the thick envelope, the membrane of which was thin.

Figures 5, 6, 7, and 8, represent different stages of an unidentified organism, probably also belonging to the algae, which occurred in several cultures. The body of the organism was ovoid and showed rather large refractive granules clinging to the rim, the center being grossly granular. The body lay within a colorless transparent material surrounded by a thick refractive shell.

1 2 3 4

5 6 7 8

The organism was expelled from the shell through a rupture at one end, the expulsion being very rapid. The broken shell remained as seen in figure 7. The surrounding matrix swelled considerably after being released and became rounded. It then collapsed, shriveled and disintegrated, leaving the body free as in figure 8. Under further observation the refractive granules became larger and the rim thicker, leaving the organism much as it was originally. No further development took place.

# TYPHUS FEVER IN BOSTON AND A REVIEW OF THE NEWER METHODS OF DIAGNOSING TYPHUS[1]

GEORGE CHEEVER SHATTUCK

*From the Service for Tropical Diseases of the Boston City Hospital*

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## I. INTRODUCTORY

At a time when cases of typhus were being found among immigrants recently arrived in New York, and when it was feared that a serious outbreak of typhus might develop in Boston, it seemed

[1] Read in part at the Seventeenth Annual Meeting of the American Society of Tropical Medicine at Hot Springs, Arkansas, November 14–15, 1921.

desirable to study the records of the Boston City Hospital for the preceding ten years in order to ascertain how many cases of typhus had been diagnosed there during this period, whether any cases of typhus had been overlooked, and to determine the principal diagnostic difficulties relating to typhus in Boston.

The number of patients admitted to the medical wards during the ten-year period under consideration was estimated roughly at 45,000 and the number of case-records looked over was probably not less than 7000.

About 70 cases, or roughly 1 per cent of the 7000, were found to have had eruptions more or less suggestive of typhus, and 44 of these records were selected for careful study. The cases so selected included all those in which a diagnosis of typhus seemed to require serious consideration and besides these, there were added to the group examples of what seemed to be clear cases of pneumonia, influenza and other diseases in which an eruption suggestive of typhus had been observed.

By further selection, the group of 44 cases was reduced to 14. The data regarding these cases have been published more fully in another place (1). In 4 of the cases, the hospital diagnosis was typhus; in 5 others, a diagnosis of typhus would probably have been justified; and in 5 more, this diagnosis might perhaps have been correct.

On the basis of the estimated total of medical cases admitted during the ten-year period, the proportion of typhus diagnosed is slightly less than 1 case per 10,000. Failure to diagnose typhus seems to have occurred in the proportion of from 1 to 2 cases per 10,000. If this be true, the actual occurrence of fairly typical typhus cases during the past ten years was at the rate of from 2 to 3 cases per 10,000 admitted, but if any considerable number of atypical cases suggestive of typhus were in fact typhus, the figure should be higher.

The epidemiological aspect of the question requires serious consideration because, should typhus begin to spread in Boston, the recognition of mild or atypical cases in their early stages would assume serious importance and the problems of differential diagnosis would be much the same as those encountered in the study of the hospital records.

The diagnosis of typhus may present great difficulties because of the frequency in non-typhus cases of rashes more or less suggestive of the exanthem of typhus and because the exanthem of typhus may be very slight, transient or atypical.

It would seem that a considerable number of diseases may be associated with a rash more or less resembling that of typhus or that typhus might pass under one of these diagnoses and escape recognition. A list of such diseases follows:

1. Typhoid and para-typhoid
2. Febricula, or fever of unknown cause
3. Dermatitis medicamentosa.
4. Measles.
5. Sepsis.
6. Cerebro-spinal meningitis.
7. Influenza.
8. Food-poisoning.
9. Lobar pneumonia.
10. Bronchopneumonia.
11. Bronchitis.
12. Pleurisy.
13. Acute alcoholism with pneumonia

The difficulty of satisfactory diagnosis in cases having unusual types of eruption has been further borne in upon me during the past six months of service at the hospital where I have been examining cases having eruptions of doubtful nature.

Four such cases were particularly interesting. One patient, with a scattered petechial eruption showing elements of various sizes, proved to have staphylococcus septicaemia. In a second case, in which there was a maculo-papular rash, largely petechial in character, it was believed that arsphenamin had been administered prior to admission to the hospital and that the rash was attributable to this drug. The third case showed a generalized, profuse, rose-pink exanthem over the body and limbs. There were no petechial elements. Food-poisoning seemed the most probable diagnosis. The fourth case ran a course of fever very like that of a moderately severe case of typhus. The eruption came late and resembled in appearance the rose-spots of typhoid. Bacteriological and serological tests were all negative and the patient was discharged without a satisfactory diagnosis. Other cases could be mentioned to illustrate the problem. The Weil-Felix reaction was performed in several cases with negative results.

It is now generally accepted that the older methods of diagnosis are inadequate for the recognition of atypical cases of typhus fever. This is doubly true when such cases occur sporadically and it follows, conversely, that typhus is difficult to exclude in cases of doubtful nature having features suggestive of typhus.

Consequently, in a large community which may be exposed to a possible outbreak of typhus, the newer methods of diagnosing the disease should be known as widely as possible and should be applied in all doubtful cases.

Since 1915, the literature on typhus fever has become very voluminous. A review of what seem to be the essential facts of importance for diagnosis, follows.

## II. REVIEW OF LITERATURE

### *1. The typhoid group and the Widal reaction in typhus*

A striking fact is that the old question of whether typhoid and typhus are separate entities was raised again in 1915 by Spät (2) working in the war area of Eastern Gallicia. He published two articles in 1915 purporting to show that typhoid cases occasionally occur which are clinically identical with typhus, and he concluded that the cases of supposed typhus in Gallicia were in reality typhoid fever. Rosenberger (3) came to the same conclusion. About this time, Weil and Spät (4) reported a few cases of "clinical typhus" from the same area and stated that, after repeated attempts, typhoid or paratyphoid bacilli were obtained from the blood or from the stools. They add that they had had little clinical experience with typhus and that the cases may have been less typical of typhus than they had supposed. The most probable explanation would seem to be that both diseases coexisted in some of these cases, that some were in reality cases of typhoid or paratyphoid resembling typhus, and that others were typhus in carriers of typhoid bacilli. The relations of the Widal reaction to typhus were not then known and the proteus reaction described below had not yet come into general use.

In 1919, a case of typhus was reported by Putter and van der Reis (5) in which, at autopsy, typhoid bacilli were obtained from the blood. They believed the patient was a carrier of typhoid bacilli.

It is generally conceded now that the Widal test is frequently positive in typhus in the dilution of 1:50 and less often in dilutions of 1:400 or even higher. It is believed that this may result in some instances from a combination of the two diseases and in other instances from the agglutinins existing in the blood as a result of a previous attack of typhoid fever, from antityphoid inoculation, or perhaps that the patient is a carrier of typhoid bacilli, evidence of a previous attack of typhoid being lacking.

It is known that in the course of typhoid fever in previously inoculated persons, the curve of agglutination as shown by the titer of the reaction shows a progressive rise and fall. During the war in Europe, this curve was believed to be diagnostic for typhoid in men who had previously been inoculated against it and who were at the time suffering from a continued fever clinically like typhoid.

Provided that such a rise in agglutinating power of the serum against the typhoid bacillus does not occur in a case of suspected typhus having a positive Widal reaction, the result would point to typhus rather than typhoid. Conversely, a diagnosis of typhoid rather than typhus might be made if the curve of agglutinins should show such a rise.

Unfortunately, evidence on the behavior of the Widal titer in typhus is conflicting. Walko (6) asserts that the Widal test in typhus fever in persons who have previously been inoculated against typhoid shows, in his experience, a moderate and constant titer; and that when a regular rise occurs in the titer from a low figure such as 1:100 this is a point of great importance in favor of a diagnosis of typhoid.

Weil and Felix (7) on the other hand, had a contrary experience. They affirm that the serum of persons *previously inoculated against typhoid* fever shows, in the course of *typhus*, a marked increase of agglutinating power against the typhoid bacillus; and moreover, that when the inoculation was given so long ago that the Widal reaction had disappeared, it may return again. They found that in inoculated subjects retaining a positive Widal reaction, the agglutinating power of the serum for typhoid bacilli increases in 53 per cent of cases and that it returns after having been lost in 33 per cent. These writers are supported by Starkenstein (8), who has published curves showing the increase of titer for the Widal test in typhus.

Weil and Felix (9) found no constant relation between the proteus reaction and the Widal reaction in typhus. They further stated that a positive Widal reaction never occurs in typhus unless "influenced." Apparently they meant produced by a previous attack of typhoid, by inoculation, or by the presence of the typhoid bacillus, the patient being a carrier. They found the reaction positive in about 18 per cent of uninoculated persons in Eastern Gallicia and attributed these reactions to saturation of the population with typhoid.

The findings of Werner and Leoneanu (10) are of special interest in relation to those of Weil and Felix on this point. They found a much higher percentage of positive Widal tests in an *unvaccinated* population which was *not saturated* with typhoid. Taking the dilution of 1:50 for the standard, they had 75 positive results in 140 cases or 53 per cent. With 1:100 as the standard, they still had 42 per cent of positive reactions and 23 of these showed agglutination at 1:200 and 8 at 1:400. They quote the findings of others to support their views and reach the conclusion that a positive Widal reaction in typhus is not necessarily due in any way to the typhoid bacillus, but that it is a para-agglutination reaction due to the near relationship of proteus to the typhoid-colon group. Wolbach (11) and his associates found agglutinations of from 1:200 to 1:1600 in 15 cases of typhus and from 1:25 to 1:100 in 27 cases. One case only gave a history of previous typhoid, and two cases and perhaps other patients had received inoculations; but in most of their cases no explanation was found for the agglutinating power of the serum. It was considered due, probably, to the propensity of typhus sera to show non-specific agglutination.

In brief, the occurrence of positive Widal reactions in uncomplicated typhus has been maintained by numerous observers. Whatever the right explanation for a positive Widal may be in an individual who is suspected of having typhus, it is clear that great weight cannot be attached to a positive Widal test as evidence against typhus even when the titer of the Widal shows progressive increase and decrease in the course of the disease. To neglect a positive reaction entirely, however, might result in failure to recognize cases of double infection, the occurrence of which there is no reason to doubt.

Neither is there reason to doubt that pure cases of typhoid may show an erruption of petechial character very like that of typhus (Herrnheiser, 12). Walko (13) pointed out that typhoid fever at autopsy may show petechial hemorrhages on the dura and on the pleura as in typhus. As an aid to diagnosis in such cases it might be found that the eruption had appeared later in the disease than it usually does in typhus and that there were repeated crops of spots. The exanthem of typhus shows progressive changes, but it does not recur in crops.

Like typhoid, the paratyphoids have proved stumbling blocks to diagnosis and for similar reasons. Walko (14) who observed 222 cases of paratyphoid A and 323 of paratyphoid B, emphasizes its protean picture. He says that the roseola in paratyphoid may show a rapid spread and a hemorrhagic change like that of typhus, but that there are frequent crops of spots in paratyphoid and that the exanthem first appears about the end of the first week. In typhus it develops between the third and the fifth day of illness.

Sterling and Sterling (15) present further evidence on the occurrence of positive Widal reactions in typhoid and paratyphoid.

### 2. *The proteus reaction of Wilson, Weil and Felix*

The proteus reaction is similar in principle to the Widal reaction except that the true relationship of the proteus bacillus to typhus fever and the cause of the reaction are in doubt. It is generally accepted that the proteus bacillus is not the cause of typhus so that the reaction cannot be considered in the usual sense specific.

The reaction is performed macroscopically by mixing a suspension of a particular strain of B. proteus called X19 with serial dilutions of the serum to be tested. A positive reaction is shown by clumping of the bacilli.

*1. Technic of proteus reaction.* Weil and Felix at first performed the proteus reaction using strains of proteus called X and X2. These strains were not so highly agglutinable as the X19 discovered subsequently and positive results were not obtained so uniformly in typhus as was the case after X19 came to be used. This strain was first recommended in 1916 by Felix (16). In any review on the proteus reaction it is important to recognize this fact and not to confuse the results obtained by the use of different strains of proteus.

The original description of the reaction seems to have been published in a bulletin for field surgeons of the Austrian army in 1915. This publication is not readily available, but the method was again described by the above-mentioned writers (17) as follows: A culture on an agar slant of proteus X19 from one to three days old was washed off with from 1.5 to 2 mils of normal salt solution and emulsified by shaking. One drop of the emulsion was added to each of a series of test tubes containing dilutions of the serum to be tested each made up to 1 mil with salt solution. The dilutions recommended for routine work were 1:25, 1:50, and 1:100. When these were strongly positive, dilutions of 1:200, 1:500 and 1:1000 were similarly treated. The tubes were then placed in the incubator. Although not clearly stated by the writers, their practice seems to have been to leave the tubes for two hours in the incubator and to take the final reading after a further period of six to eight hours at room temperature. To determine the exact titer limit, however, the readings were taken after fourteen hours. A tube containing 1 mil of normal salt solution and 1 drop of the emulsion was used as a control. Positive reactions were often recognizable after from twenty to thirty minutes in the incubator. Because the clumping was often fine and especially so near the titer limit, the use of a handlense was advised.

The culture, says v. Gutfeld (18) should be from one to three days old and kept preferably for twenty-four hours in the incubator and for a day or two longer in the ice-box. Many minor modifications of technic and differences in the length of time allowed to elapse before making the reading have been advised by different writers.

*2. Technical errors.* These include errors due to loss of agglutinability of the culture, increased agglutinability, and errors of technic. Weil and Felix (19) emphasized the point that Proteus X19 will retain its agglutinability unchanged for long periods, if not indefinitely, when grown always on *strictly neutral agar.* Should the culture become contaminated, the organism can be isolated again on the Drigalski-Conradi medium, transferred back to neutral agar, and after half a dozen subcultures will have regained its agglutinability. The least trace of acidity in the agar reduces agglutinability. This statement is confirmed by Bijlsma (20). Weil and Felix further state that excessive inoculation of the tubes diminishes agglutinability and that the reaction may be inhibited in the concentrated dilutions of 1:25 and 1:50 but positive in higher dilutions and that normal sera give positive reactions commonly in the dilution of 1:25, and that incomplete reactions occur less often at 1:50.

Wolff (21) has discussed sources of error in detail. He believed that positive errors may come from the agglutinins of normal serum or from those present in other diseases, and especially in paratyphoid. He recommended reading the test after two hours in the incubator without waiting for a further period at room temperature because on long standing false positives may develop. He considered a positive result in the dilution of 1:200 the best standard for diagnosis.

Wolff pointed out that negative errors may result from diminished agglutinability of the culture or from the presence of traces of corrosive sublimate, phenol, formalin, sodium, or sodic hydrate which greatly reduce agglutinability.

Schiff (22) stated that diminution or failure of agglutinability may be due to insufficiency of sugar in the medium and that after continued growth in the presence of an excess of sugar, spontaneous agglutination may occur.

Van der Reis (23) confirmed the work of Schiff to the extent that the quantity of sugar in the medium was shown to have an influence on agglutinability, but he did not obtain spontaneous agglutination even with high concentration of sugar.

*3. Significance of titer.* Weil and Felix (24) believe that a *complete* reaction at 1:50 after 8 hours is "certainly specific" and that for early diagnosis *a strong reaction at 1:25 after a previous negative* "can be considered specific." A marked increase of titer a day or two later then confirms the diagnosis of typhus.

Weil and Felix (25) state that the test is positive at some stage in 100 per cent of typhus cases and that in 75 per cent it is positive on the fourth day. In the other 25 per cent it comes on the sixth or seventh day. The reactions which come late are found in the lightest or in the most severe cases and the titer in them does not exceed 1:200 or 1:500.

Ordinarily, the titer of the reaction rises until the beginning of defervescence at which time it usually reaches dilutions of from 1:1000 or 1:5000. It may run up occasionally to 1:10,000 or even 1:50,000.

After defervescence, the titer falls rapidly at first and then gradually, the reaction generally disappearing after several months. Reactions of from 1:25 to 1:100 were usually found three to four months after typhus. Sometimes the reaction persisted for a year.

*4. Nature of the proteus reaction.* To discuss fully the question of the nature of the proteus reaction would exceed the limits of this paper, but a few observations in regard to it require passing mention. Weil and Felix have adhered to the opinion that the reaction between X19 and typhus serum is "specific" but they claim no etiological relation for the organism. Weil (26) thinks it probable that "specific" strains of proteus are constantly present in typhus. He says that an artificial immune serum prepared from X19 does not distinguish it from proteus of group III and that only the serum of typhus patients is suitable for recognition of this strain.

Felix (27) pointed out that differences in the behavior of typhus patients' serum as compared with immune sera produced artificially, indicate the presence of two antigens only one of which is active in the sera of patients. This question is further discussed below under the head of O and H forms.

Numerous authors have reported a tendency of typhus serum to agglutinate various organisms. This subject was discussed by Felix (28) with regard to the Plotz bacillus, the typhoid and paratyphoid bacilli, saprophytic proteus, B. coli and related organisms, micrococcus melitensis and Csernel's typhus organism. The fact that none of these organisms clump regularly with typhus serum seems to him to a high degree conclusive that agglutination with X races is "specific" for typhus. Few, if any, other writers on the subject hold the view that the proteus reaction is a specific reaction.

The question was later discussed by Weil (29) and in 1920 Weil and Felix (30) stated that the typhus agglutination with X19 comes only from the "specific receptor of the cause and is in the immunological sense specific" and that the etiological significance of Rickettsia and the production of agglutination with X19 stand together.

Epstein (31) has made a valuable contribution to the subject and Wolff's (32) article is interesting.

The nature of the reaction has been well discussed by Wilson (33) from another standpoint. He advanced the hypothesis that under the stimulus of typhus fever some bacterium, a normal inhabitant of the intestine, produces agglutinins for itself and group agglutinins for numerous other organisms and especially for P. X19, P. X2 and for various members of the colon-typhoid group.

*5. O and H forms of X19.* Further studies of the nature of the agglutination with P. X19 were prosecuted by Weil and Felix. In 1917 they (34) observed in old cultures of X2 and of X19 that colonies could be isolated which grew without the formation of "breath." These they called the O forms and the others the H forms.

In 1920 Weil and Felix (35) recommended the use of O forms only for the proteus reaction.

Meanwhile they had published an article showing that O and H receptors are found in all ordinary proteus races (36) and another stating that the double type of receptor found in the proteus group is also present in paratyphoid B (37). The receptors, they say, show the characteristics found by Sack and Braun. They found that immune sera prepared from the H forms behave like those produced with the ordinary emulsions which are almost entirely composed of H forms, i.e., they precipitate the ordinary emulsion by the production of *large* flocculi and agglutinate as well the saprophytic proteus races of group III. The immune sera prepared from the O form, on the other hand, agglutinate both the O form and the H form in fine clumps as does the serum of typhus patients. As is true of the serum of patients, immune sera prepared from the O form does not agglutinate the saprophytic races of group III.

Fixation tests show that the O form has but one receptor, the specific one, whereas the H form has two, namely, the specific and the "substance" receptors. The last is identical with the corresponding receptor of the saprophytic races of group III.

The agglutinin prepared artificially against O forms is less resistant to heat than is that for H forms. The agglutinin in the sera of typhus patients behaves like the artificially prepared O agglutinin and this complete correspondence indicates that the O form of X19 occurs principally in cases of typhus. The conclusion requires confirmation by cultivation.

The subject of O and H races has been extensively investigated by Epstein (38) and by Rotky (39). It was discussed as well by Schiff (40), Schiff and Northrop (41), and by Michaelis (42). Variants of P. X were discussed by Weil (43) and by Epstein (44).

*6. Interpretation of the proteus reaction.* As has already been said, Weil and Felix claim that the reaction performed with X19 is positive at some stage of the disease in 100 per cent of cases of typhus fever. Other authors who have used the test extensively for undoubted cases of typhus have put the percentage nearly as high. In fact, it is difficult to find in the literature isolated cases of typical typhus in which the test has remained negative throughout the febrile period. Some of the reported negative results are based on one or more tests made relatively early in the disease. On the other hand, the aggregate number of cases of clinical typhus in which the test has been positive is very large.

The interpretation of positive tests in cases in which the diagnosis of typhus could not have been made on clinical grounds is difficult. For example, there are cases of so-called typhus without eruption in which the diagnosis rests partly on association with cases of undoubted typhus and partly on positive proteus reactions, the symptoms being very mild and atypical. Cases of this sort apparently occur most often in children. Atypical cases with positive reactions were reported by Popper (45), Bardachzi and Barabás (46), by Brohm (47), by Rosenberg (48), by Löwy (49) and by Ciuca and Bancheriu (50). Such cases are of great epidemiological importance.

Positive proteus reactions may be found when typhus is combined with some other infection. Cases of this sort have been reported by Brauer (51) and by Rosenberg (52).

Confusing positive tests have been observed in typhoid by Sterling and Sterling (53) who obtained agglutination up to 1:200 in 2 cases and by Werner and Leoneanu (54) who obtained one positive in typhoid at 1:100 and one at 1:200. Mühlens and Stojanoff (55) report a case of relapsing fever in which the proteus reaction was positive at 1:100 and similar findings have been reported for typhoid by Sterling and Sterling (56) and for paratyphoid by Wolff (57) and by Rosenberg (58) and by the latter for dysentery, and for malaria by Seyfarth (59).

If the reactions which are explainable on the ground of mixed infection and those resulting probably from a previous attack of typhus with a persisting proteus reaction be excluded, few of the reported cases of proteus reaction positive in other diseases would remain.

Seyfarth suggests that a latent proteus reaction due to former typhus may perhaps return in the course of another infectious disease as has been shown to be the case with the Widal reaction.

Normal sera frequently give positive reactions at 1:25, and incomplete reactions at 1:50 are not unusual. There are those who believe that normal sera can give reactions sufficiently complete in higher dilution to be confusing. Wolff (60) believes that normal sera may give slight reactions in dilutions above 1:50 particularly after long standing.

The reactions of normal sera remain at a constant level in repeated tests whereas those of typhus show a rising titer as the disease progresses. As a counterpoise to the comparatively small number of equivocally positive reactions, it should be stated that very large numbers of cases including normal individuals and a great variety of diseases have given definitely negative results.

Epstein and Morawetz (61) found the proteus reactions reliable when applied to serum from the cadaver. The reaction was obtained in the urine in the presence of albumen but not otherwise by Ballner and Finger (62) and others have obtained it in the cerebro-spinal fluid (see below).

*7. Proteus reaction with preserved cultures.* A good deal has been written on the use of killed cultures and preserved suspensions of P. X19 for diagnosis. Cultures have been killed by heat, by alcohol, by formalin, and by phenol. The subject has been discussed by Csépai (63), by Reinhardt (64), by Fairley (65) and by many others. The method has value where bacteriological work cannot be undertaken.

*8. Summary of proteus reaction.* (*a*) The majority of recent writers agree that the proteus reaction is positive at some stage in very nearly 100 per cent of cases of typhus. It has very seldom been positive when typhus fever coexisted with other disease or when a previous attact of typhus could be definitely excluded.

(*b*) The dilution to which a positive reaction should be accorded diagnostic importance has been placed by different observers at from 1:50 to 1:200.

(*c*) When the significance of a positive reaction is doubtful, the test should be repeated in two days to see if the titer remains constant or is rising. A marked rise of titer may be considered a sure indication of typhus.

(*d*) If the test is to be reliable it would seem necessary to check the agglutinability of the culture of P. X19 from time to time by testing it against the serum of a man or animal having typhus infection. Adequate control tests should always be performed when making use of the reaction.

*9. Conclusions.* As with other laboratory tests, clinical evidence should be considered in the interpretation of the findings.

The following points should not be lost sight of: (*a*) A previous attack of typhus, perhaps unrecognized, may occasionally result in the persistence of a positive proteus reaction for at least a year. (*b*) Mixed infection with various other diseases may occur. (*c*) There seem to be very mild forms of typhus of short duration in which the eruption is very transient or absent entirely. (*d*) Such cases seem to be relatively common among children. (*e*) Normal sera may cause incomplete agglutination up to 1:100. (*f*) Positive reactions which have not been satisfactorily accounted for have been observed rarely in various diseases. (*g*) In the severer and in the milder types of typhus, the reaction may be expected to come late and not to reach the usual high titer. (*h*) It is probably safest to read the result of the test after 2 hours in the incubator. (*i*) Incomplete reactions should be disregarded. (*j*) Caution should be observed in the interpretation of positive results in titers below 1:200. (*k*) A marked rise of titer in the course of a fever is important confirmatory evidence of typhus. (*l*) The absence of such a rise would tend to exclude typhus.

### *3. Pathology*

*Typhus in man.* Little has been added to knowledge of the gross pathology of typhus and no macroscopic lesion characteristic of typhus has been demonstrated. The contrary is true of the histopathology. In this field, lesions have been found upon which a diagnosis can be based with confidence.

The characteristic pathology was first described by Fraenkel (66) and his work was confirmed and amplified by many other writers. Fraenkel (67) later reported a case in which the vascular changes were still recognizable in the excised skin of a convalescent patient eight weeks after defervescence. A most interesting and comprehensive description of the pathology has just been published by Wolbach (11) and the reader is referred to this article for full information on the subject.

It is important to emphasize the fact that characteristic changes in the walls of the smaller arterioles of the skin and in their neighborhood can be demonstrated by histological examination of bits of skin excised either during life or after death. It is believed that such findings are more reliable for diagnosis than any other evidence procurable during life. The only lesions closely resembling those found in typhus, according to Wolbach, (11) have been demonstrated in Rocky Mountain spotted fever. Wolbach thinks it true that the lesions occurring in the central nervous system of typhus are pathognomonic for this disease.

The vascular lesions consist of exfoliation of the intima leading sometimes to thrombosis, of infiltration of the vessel wall and of minute nodular foci of cellular infiltration in the neighborhood of the smaller arterioles. Vascular changes may be found in the internal organs, and in the central nervous system where characteristic nodules and capillary hemorrhages occur. These lesions are most numerous in the mid-brain.

Vascular lesions have been described in the heart, the kidneys and the muscles, and myocardial degenerative lesions are common. In a general way, typhus may be regarded as a system disease of the arterioles, and on that basis the symptoms which characterize the disease are explainable.

The characteristic lesions are believed by Wolbach to be constantly present in all typhus cases except very early or very late in the disease. Fraenkel's observation, above mentioned, indicates that the vascular changes may still be recognizable after several weeks of convalescence.

Additional references on the subject of pathology in typhus may prove useful (68).

Habetin (69) calls attention to reported cases which seem to show that typhoid fever may occur without the usual lesions and may thus obscure the diagnosis. Inasmuch as cases of supposed typhus have been reported which apparently harbored the typhoid bacillus as carriers, the soundness of Habetin's contention is open to question. References to such cases are given under section I, entitled the "Typhoid group and the Widal reaction in typhus."

*Typhus in animals.* In the monkey and the guinea-pig experimental infection with typhus fever produces lesions similar to those found in man. Wolbach describes the lesions. He believes that characteristic lesions are constant in the brain of the guinea-pig but that they may be scattered and few in number so that sections from various parts of the brain should be carefully examined.

Doerr and Kirschner (70) recommend intraperitoneal inoculation of the guinea-pig for diagnosis. They say that the characteristic lesions are most numerous in the medulla and that they are present on the sixth day, soon after the appearance of the specific fever.

In an article just published, Olitsky (71) describes non-specific or pseudo-reactions closely resembling the lesions of typhus. These non-specific reactions, he says, can be produced by means of various substances. He warns against the danger of confusing such changes with the lesions of typhus.

The lesions in the guinea-pig have been described by Löwy (72) and by Friedberger (73).

*Diagnosis by pathology.* (*a*) Bits of skin excised during life or after death from cases of typhus show vascular changes of great value for diagnosis.

(*b*) Microscopic lesions occurring in the central nervous system of man and of guinea-pigs seem to be pathognomonic for typhus.

(*c*) Intraperitoneal inoculation of the guinea-pig and subsequent microscopical examination of the mid-brain may be resorted to for diagnosis.

### *4. Less important aids to diagnosis*

*1. The blood picture.* Daniélopolu (74) has shown that there is a certain relation between the white-count, the severity, and the stage of the disease. Others have observed an increase in the younger forms of the neutrophilic leucocyte, a large proportion of which may show immature forms of the nucleus. These changes have been described by Reichenstein (75) and by McIver, one of Wolbach's associates (11). Schilling (76) thinks the blood picture suggestive for diagnosis when other diseases giving similar pictures can be excluded.

Granules of doubtful nature seen in the leucocytes were described by v. Prowazek and were found by Lipschütz (77) as well. They were scarce and were not constantly present. There have been similar findings by others. Stempell (78) describes inclusions demonstrated by microphotography with ultra-violet light.

In the present state of knowledge it is believed that the most valuable evidence for diagnosis that can be obtained from the blood picture in typhus is the absence of leucopenia. The white-count is nearly always normal or increased in typhus, whereas in typhoid leucopenia is a very constant finding.

2. *Cerebro-spinal fluid.* The most extensive published observations on the cerebro-spinal fluid in typhus are those of Daniélopolu (74). He found the intra-spinal pressure frequently somewhat increased. The fluid was often clear, but occasionally slightly cloudy, and sometimes xantho-chromatic. When the color is slight, the fluid he says should be examined immediately after withdrawal.

There is nearly always a cellular reaction which seems to run parallel in degree to the severity of the case. Counts of from 5 to 300 cells per cubic millimeter were observed.

In the light cases, lymphocytes only are found during the first week, but later, mononuclear cells of larger size, and cells resembling plasma cells appear. The lymphocytes persist for a time after defervescence, but meanwhile the larger forms disappear in these cases. In cases of moderate severity the reaction is similar but more intense and more prolonged.

Hypertoxic cases show a more intense cellular reaction of the same kind at first but later in the disease polymorphonuclear leucocytes and red cells appear. The fluid is slightly cloudy, yellowish in color and contains much albumen. In such cases, the reaction of Noguchi performed with buturic acid is nearly always positive.

Daniélopolu's work confirms and amplifies the findings of earlier writers on the subject. There are interesting articles by Heuyer (79) and by Rothacker (80).

Heilig (81) described bodies resembling seal-rings which he found attached to leucocytes and to small mononuclear cells in the cerebro-spinal fluid. He says that they were not found in malaria and that they are pathognomonic for typhus.

*3. The Weil-Kafka reaction,* which depends upon the presence of a hemolysin in the cerebro-spinal fluid, was originally discovered by its authors in cases of acute meningitis and in progressive paralysis. Weil (82) subsequently obtained it in typhus fever and this observation was confirmed by Soucek (83) who found it present almost without exception even in mild cases.

Starkenstein and Zitterbart (84) found both the proteus and the Widal reactions strongly positive in the cerebro-spinal fluid of typhus cases. This, they say, is in contrast to the findings in typhoid.

*4. Complement fixation.* Tests have been tried for diagnosis by a number of writers. Their results have been almost uniformly discouraging. Fairley (85) states that no immune body for P. X19 is formed in the blood of typhus patients. Studies of the subject have been made by many writers, among them Papamarku (85) who tried three kinds of antigen, namely, P. X19, extracts of lice containing Rickettsia, and alcoholic extracts of the organs of typhus patients (87). His attempt to make a satisfactory antigen from the Plotz bacillus failed.

There is doubt as to the significance of a positive Wassermann test in typhus fever. Some writers have maintained that P. X19 could be substituted for the ordinary antigen in making the Wassermann test. Jablons (88) and Grysez (89) give different views on this subject.

*5. The "clouding reaction."* Weltmann (90) observed that, when to typhus serum was added 10 parts of normal salt solution, marked cloudiness developed in the serum. He found that nearly all sera showed a precipitate on standing, but that in typhus sera the cloudiness was so much more marked as to be distinguishable. The reaction generally appeared toward the end of the second week and persisted for a day or two after the temperature became normal. He found the reaction constantly in typhus and absent in controls and recommended the method for diagnosis (91).

Epstein and Morawetz (92) obtained Weltmann's reaction in 6 per cent of controls and state that it was permanently absent in 16 per cent of typhus cases. Sampietro (93) says that

Weltmann's reaction is neither constant in typhus nor specific. Another disadvantage, according to Dünner (94), is that it does not ordinarily appear before the end of the second week.

*6. The anaphylactic reaction.* Csernel (95) isolated a bacillus from the blood of typhus cases with which he sensitized guinea-pigs. Anaphylactic shock was then produced in these animals when inoculated with typhus blood. Csernel recommends the procedure for diagnosis.

*7. Skin reactions.* Friedberger and van der Reis (96) injected killed cultures of P. X19 subcutaneously and intracutaneously. In cases of typhus no reaction resulted, but in normal individuals and in other diseases, marked redness, pain and fever were produced. Van der Reis (97) published a second article on early diagnosis by means of this test. I have found no testimony confirming their results.

Lipschütz (98) observed hemorrhage at the margin of a wound in a case of typhus. He then found that by scarification of the skin, a hemorrhagic reaction was produced which appeared within twenty-four hours and reached its maximum in forty-eight hours. The occurrence of the reaction was attributed to the vascular changes and to diminished coagulability of the blood. The reaction varied considerably in degree and was less constant in children than in adults. The test was recommended for diagnosis, but Schwoner (99) points out that hemorrhagic skin reactions can be produced by slight trauma such as pinching the skin in scarlet fever, measles and septic conditions.

*8. Dietsch's congestion test.* Dietsch (100) has recommended artificial congestion as an important and almost specific means of diagnosis for typhus. When a tourniquet has been placed on the arm for the purpose of puncturing a vein, numerous petechiae appear on the the distal part of the arm. The phenomenon is attributed to the changes in the smaller blood vessels. A similar reaction has been observed in scarlet fever and less often in measles after taking the blood pressure. The method was long ago recommended for the diagnosis of scarlet fever but has been practically discarded for this purpose because the reaction has been found frequently in many other conditions such as measles, sepsis, and cerebro-spinal fever. By means of Dietsch's test, reactions have been obtained in typhus several weeks after defervescence. Observations bearing on the subject have been recorded by Simecek (101), Schwoner (102), Fraenkel (103) and Feinmann (104).

Dietsch's test may be used to distinguish typhus from typhoid fever and perhaps for retrospective diagnosis as well.

9. *Wiener's color reaction* (105) was tried by Dreist (106) who simplified it a little. Dreist's technic was as follows: To 1 mil of urine were added 10 drops of a 10 per cent solution of potassium permanganate and then Jenner's stain drop by drop. On adding the third or fourth drop of stain an intense green color develops in typhus cases whereas in other diseases a blue color appears. The reaction is no longer obtainable after defervescence.

Dreist confirms Wiener's claims and recommends the reaction strongly for early diagnosis. Rothacker (107) says that when performed with *fresh urine* the reaction has shown itself absolutely reliable in many hundred cases.

Wiener's reaction seems to have attracted little attention, but to be deserving of further trial.

### 5. *Miscellaneous observations*

A brief review of some of the diagnostic methods above described was published by v. Gutfeld (108).

Kollert and Finger (109) tried a number of tests of minor significance and obtained no important results.

Zuelzer (110) asserts that in the prodromal and early stages of typhus, both liver and spleen are enlarged and that this fact may be of diagnostic value for persons who have been exposed to typhus provided that malaria, scarlet fever and syphilis can be excluded.

Supposedly characteristic notches in different parts of the temperature curve of typhus were described by older writers. Grober (111) describes such a notch on the second or third day and Lipschütz (112) points to a sag in the middle of the curve. It is my impression that variations of this kind in the temperature curve of typhus may be noticeably frequent in certain groups of cases but that no one of these variations of temperature is broadly characteristic of typhus.

Conjunctival changes, supposed to have diagnostic value, were described by v. Chiari (113). He says that at first there is congestion only. When the exanthem develops, bluish-red elongated spots of irregular shape make their appearance particularly in the conjunctival sack. Hemorrhagic changes appear there earlier than on the skin and may develop when the exanthem on the skin has passed without becoming hemorrhagic.

Kyrle and Morawetz (114) describe cases in which swelling and necrosis of some of the papules occurred at a stage when the rash would ordinarily be subsiding.

That all cases of typhus peel more or less is stated by v. Höffern (115). Bran-like scaling of the skin was observed especially on the abdomen and near the anterior superior spine of the ilium, and less often on the limbs and face. Desquamation begins from three to six days after defervescence, but may be delayed for two weeks. It may be questioned whether or not the use of delousing solutions may have had an influence in producing the desquamation observed.

The "hard rubber" sign, which Brauer recommended for diagnosis, consists in the observation that when the skin is stroked with the finger a mark results from the rubbing up of small white scales. Pichler (116) says the sign is found also in typhoid, and in pregnant women without fever, and that "deloused skin" shows it particularly well even in persons who have not had typhus. Consequently, he considers the sign of no diagnostic value.

## III. CONCLUSIONS IN BRIEF

1. The small number of cases of typhus and of probable typhus found in the records of the Boston City Hospital covering the period of the past ten years, points to the conclusion that the typhus problem there has not been significant from the diagnostic standpoint. Nevertheless, the potential epidemiological significance of typhus and particularly of atypical cases requires that all cases of possible typhus be studied with the greatest care in order to arrive, if possible, at a satisfactory diagnosis.

2. Under the head of possible typhus are included a considerable group of cases having eruptions or temperature curves suggestive of typhus.

3. This group is composed of two classes of cases: first, undiagnosed infections; and second, diagnosed infections in which the diagnosis is not adequately supported by facts when recent advance of knowledge is taken into consideration.

4. Careful investigation of all cases in which typhus might seem a possible diagnosis would perhaps show that typhus fever is in reality more common in Boston than it appears to have been in recent years.

5. A Widal reaction positive in the dilutions generally used for diagnosis is commonly present in typhus fever and, therefore, it is not, per se, an obstacle to the diagnosis of typhus.

6. The proteus reaction of Wilson, Weil and Felix is not an infallible, but a very valuable aid to diagnosis.

7. The proteus reaction to be of value must be adequately controlled. Not only should controls be performed with the test, but it would seem necessary from time to time to check with known typhus serum the agglutinability of the culture used for the test.

8. For interpretation of the results of the test, all known facts regarding it should be borne in mind and clinical evidence should be taken into consideration.

9. Probably the surest means of diagnosing typhus fever during life is by means of histological examination of excised bits of skin.

10. Pathological changes developing in the guinea-pig after inoculation with material containing the virus of typhus are believed to be constant but may be difficult to demonstrate.

11. Somewhat similar lesions due to other causes may perhaps lead to error. Guinea-pig inoculation may be used for diagnosis.

12. The point of greatest importance for diagnosis in the blood picture is the almost constant absence of leucopenia in typhus and its nearly constant presence in typhoid.

13. The cerebro-spinal fluid shows an increase of cells which may be slight or marked. Failure to recognize this fact may lead to erroneous interpretation of the findings. Other changes usually found in this fluid are less important.

14. Wiener's color reaction is very easily performed and seems to warrant further trial.

15. Other tests and diagnostic points have not been shown to have considerable value.

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# THE RELAPSING FEVER SPIROCHETE OF PANAMA

## EVIDENCE TO SHOW THAT IT IS A DISTINCT SPECIES

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The July, 1921, number of the AMERICAN JOURNAL OF TROPICAL MEDICINE contained an article entitled "Relapsing fever in Panama" by Bates, Dunn and St. John, in which it was shown by human experimentation that relapsing fever in Panama is transmitted by the human tick, *Ornithodorus talaje*. The same article contains tabulations of results obtained by inoculating white rats, white mice and monkeys, *Macaccus rhesus*, with the Panama relapsing fever spirochete; also a short account of its measurements and appearance in cultures. The data at that time was insufficient to determine the identity of the spirochete under study. Since then the work presented in this paper, mostly in the form of tables, has been completed and is offered as evidence that the Panama strain of the relapsing fever spirochete is a distinct species of the relapsing fever spirochete, if these spirochetes may be divided into species.

In this work comparative studies have been made of *S. obermeieri*, *S. novyi*, *S. kochi*, *S. duttoni* and the Spirochete of Panama, by inoculating white rats, and white mice which had recovered from each of these infections with the Spirochete of Panama; by inoculating white mice which had been hyperimmunized against each of these infections with Spirochete of Panama; and by ascertaining the effect of immune serum of each of these spirochetes upon each spirochete, both by dark-field examination and by animal inoculation. The first two tables are given simply to show the average blood picture in normal clean animals inoculated with the different spirochetes.

TABLE 1

*Blood findings in clean white rats inoculated with the various relapsing fever spirochetes*

| Days | S. OBERMEIERI | | | | | | S. NOVYI | | | | | | S. KOCHI | | | | | | S. DUTTONI | | | | | | S. OF PANAMA* | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Rats | | | | | | Rats | | | | | | Rats | | | | | | Rats | | | | | | Rats | | | | | |
| | 3 | 13 | 43 | 83 | 183 | 33 | 84 | 74 | 494 | 404 | 94 | 194 | 2 | 12 | 42 | 72 | 82 | 432 | 11 | 41 | 91 | 441 | 491 | 161 | 293 | 306 | 309 | 311 | 312 | 444 |
| 1 | + | + | + | 0 | + | 0 | + | + | + | 0 | + | + | + | 0 | 0 | 0 | + | 0 | + | + | 0 | 0 | 0 | + | 0 | 0 | 0 | 0 | 0 | + |
| 2 | + | + | + | 0 | + | + | + | + | + | + | + | + | + | 0 | 0 | 0 | + | 0 | + | + | 0 | 0 | + | + | + | + | + | 0 | + | + |
| 3 | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 0 | + | + | 0 | + | + | + | + | + | 0 | 0 | 0 | + |
| 4 | 0 | + | + | + | 0 | + | + | + | + | + | + | + | 0 | + | + | + | + | 0 | + | + | 0 | + | + | + | 0 | 0 | 0 | + | 0 | 0 |
| 5 | 0 | 0 | + | + | 0 | + | 0 | + | 0 | 0 | 0 | 0 | 0 | + | + | + | 0 | 0 | 0 | + | + | + | + | 0 | + | 0 | 0 | 0 | 0 | 0 |
| 6 | 0 | 0 | + | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | + | + | 0 | 0 | 0 | 0 | 0 | 0 | + | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7 | + | 0 | + | + | + | 0 | 0 | + | 0 | 0 | + | 0 | 0 | 0 | + | 0 | 0 | 0 | 0 | 0 | 0 | + | + | 0 | + | 0 | 0 | + | 0 | 0 |
| 8 | + | + | + | + | + | 0 | + | + | 0 | 0 | + | 0 | + | 0 | + | + | + | + | + | + | + | + | 0 | 0 | + | 0 | 0 | 0 | 0 | 0 |
| 9 | + | + | + | + | + | 0 | + | + | + | 0 | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 0 | 0 | 0 | 0 | 0 |
| 10 | + | + | + | + | + | + | + | 0 | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 0 | 0 | 0 | 0 | 0 |
| 11 | 0 | 0 | 0 | + | 0 | + | 0 | 0 | + | + | 0 | + | 0 | + | + | + | 0 | + | + | + | 0 | + | + | + | 0 | 0 | 0 | 0 | + | + |
| 12 | 0 | 0 | + | + | 0 | + | 0 | + | + | 0 | + | + | 0 | + | 0 | 0 | + | 0 | 0 | + | 0 | + | 0 | 0 | 0 | 0 | 0 | + | 0 | 0 |
| 13 | 0 | + | + | 0 | 0 | 0 | 0 | + | + | 0 | + | 0 | 0 | + | + | + | + | + | 0 | 0 | + | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 14 | | 0 | + | 0 | + | + | 0 | 0 | 0 | 0 | + | 0 | 0 | 0 | 0 | + | + | + | 0 | 0 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 15 | | 0 | 0 | 0 | 0 | + | + | 0 | 0 | 0 | + | 0 | 0 | 0 | + | + | 0 | + | 0 | + | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 16 | | 0 | 0 | | 0 | + | + | 0 | 0 | 0 | 0 | + | 0 | 0 | + | 0 | 0 | + | 0 | + | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 17 | | + | + | | 0 | + | 0 | 0 | 0 | 0 | 0 | + | 0 | 0 | + | 0 | | + | | + | 0 | 0 | 0 | | 0 | 0 | 0 | 0 | 0 | 0 |
| 18 | | 0 | 0 | | 0 | + | 0 | 0 | 0 | 0 | 0 | + | 0 | 0 | 0 | 0 | | | | + | 0 | | 0 | | 0 | 0 | 0 | 0 | 0 | 0 |
| 19 | | 0 | 0 | | 0 | 0 | 0 | 0 | 0 | | 0 | + | 0 | 0 | 0 | 0 | | | | 0 | + | | 0 | | 0 | 0 | 0 | 0 | 0 | 0 |
| 20 | | 0 | 0 | | 0 | 0 | 0 | 0 | 0 | | | | + | + | 0 | 0 | | | | 0 | + | | | | 0 | 0 | 0 | 0 | 0 | |
| 21 | | 0 | 0 | | 0 | 0 | 0 | 0 | 0 | | | | 0 | + | 0 | 0 | | | | 0 | 0 | | | | 0 | 0 | 0 | 0 | 0 | |
| 22 | | 0 | 0 | | 0 | 0 | 0 | 0 | 0 | | | | 0 | + | 0 | 0 | | | | 0 | 0 | | | | | | | | | |
| 23 | | 0 | 0 | | | 0 | 0 | 0 | 0 | | | | 0 | 0 | 0 | 0 | | | | 0 | 0 | | | | | | | | | |
| 24 | | 0 | 0 | | | 0 | 0 | 0 | | | | | 0 | 0 | 0 | 0 | | | | 0 | 0 | | | | | | | | | |
| 25 | | 0 | 0 | | | 0 | 0 | 0 | | | | | 0 | 0 | 0 | 0 | | | | + | + | | | | | | | | | |
| 26 | | 0 | | | | 0 | 0 | 0 | | | | | 0 | 0 | 0 | 0 | | | | 0 | + | | | | | | | | | |
| 27 | | 0 | | | | 0 | 0 | 0 | | | | | 0 | 0 | 0 | 0 | | | | 0 | 0 | | | | | | | | | |
| 28 | | 0 | | | | 0 | 0 | 0 | | | | | 0 | 0 | 0 | 0 | | | | 0 | 0 | | | | | | | | | |

* Also see table 8 on page 202 of article, "Relapsing fever in Panama," above referred to.

0 = No spirochetes found in 600 fields.

+ = Slides positive for spirochetes.

TABLE 2

*Number of spirochetes found in rats' blood in different types of relapsing fever*

| DAYS | S. OBERMEIERI | S. NOVYI | S. KOCHI | S. DUTTONI | S. OF PANAMA |
|---|---|---|---|---|---|
| 1 | 24 | 3 | 600 | 10 | 0 |
| 2 | 2,240 | 30 | 120,000 | 7,200 | 4 |
| 3 | 7,200 | 15,000 | 60,000 | 120,000 | 600 |
| 4 | 6 | 4,800 | 0 | 30,000 | 0 |
| 5 | 0 | 20 | 0 | 15,000 | 0 |
| 6 | 0 | 0 | 0 | 0 | 0 |
| 7 | 0 | 6 | 0 | 0 | 0 |
| 8 | 3 | 60 | 3 | 10 | 0 |
| 9 | 40 | 600 | 40 | 4,800 | 0 |
| 10 | 1,200 | 0 | 1,200 | 30,000 | 0 |
| 11 | 0 | 0 | 0 | 3,000 | 0 |
| 12 | 0 | 3 | 0 | 6 | 0 |
| 13 | 3 | 10 | 3 | 0 | 2 |
| 14 | 0 | 0 | 0 | 0 | 0 |
| 15 | 0 | 0 | 0 | 1 | 0 |
| 16 | 3 | 0 | 3 | 3 | 0 |
| 17 | 1,200 | 0 | 1,200 | 3 | 0 |
| 18 | 0 | 0 | 0 | 0 | 0 |
| 19 | 0 | 0 | 0 | 0 | 0 |
| 20 | 0 | 0 | 0 | 0 | 0 |
| 21 | 0 | 0 | 0 | 0 | 0 |
| 22 | 0 | 0 | 0 | 0 | 0 |
| 23 | 0 | 0 | 0 | 0 | 0 |
| 24 | 0 | 0 | 0 | 3 | 0 |
| 25 | 0 | 0 | 0 | 0 | 0 |
| 26 | 0 | 0 | 0 | 0 | 0 |
| 27 | 0 | 0 | 0 | 0 | 0 |
| 28 | 0 | 0 | 0 | 0 | 0 |
| 29 | 0 | 0 | 0 | 0 | 0 |
| 30 | 0 | 0 | 0 | 0 | 0 |
| 31 | 0 | 0 | 0 | 0 | 0 |

Numerals = Number of spirochetes found (or computed) in 600 fields.
0 = No spirochetes found in 600 fields.

## IMMUNE SERUM REACTIONS

*Method used for obtaining spirochetes for agglutination reaction*

An infected rat is bled at a time when the peripheral blood shows many spirochetes, usually on the second or third day of infection. About 2 cc. of the blood is immediately transferred in unmodified

TABLE 3

*Results obtained by inoculating white rats and white mice which had recovered from a typical infection with Panama relapsing fever spirochetes; with S. obermeieri, S. novyi, S. kochi, S. duttoni and S. of Panama*

| DATE | S. OBERMEIERI | | | | S. NOVYI | | | | S. KOCHI | | | | S. DUTTONI | | | | S. OF PANAMA | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Rats | | Mice | | Rats | | Mice | | Rats | | Mice | | Rats | | Mice | | Mice | |
| | 3 | 13 | A1 | B1 | 4 | 14 | A3 | B3 | 2 | 12 | A2 | B2 | 1 | 11 | A4 | B4 | A5 | B5 |
| *1921* | | | | | | | | | | | | | | | | | | |
| December 11 | + | + | 0 | 0 | 0 | + | + | + | + | 0 | + | + | + | + | + | + | 0 | 0 |
| December 12 | + | + | + | + | 0 | + | + | + | + | 0 | + | + | + | + | + | + | 0 | 0 |
| December 13 | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 0 | + | 0 | 0 |
| December 14 | 0 | + | 0 | + | + | + | 0 | 0 | 0 | + | 0 | 0 | 0 | + | 0 | + | 0 | 0 |
| December 15 | 0 | 0 | 0 | 0 | + | 0 | D | 0 | 0 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| December 16 | 0 | 0 | 0 | 0 | + | D | | D | 0 | + | 0 | + | 0 | 0 | 0 | 0 | 0 | 0 |
| December 17 | + | 0 | 0 | 0 | + | | | | 0 | 0 | 0 | 0 | + | 0 | 0 | 0 | 0 | 0 |
| December 18 | + | + | 0 | D | D | | | | + | 0 | + | 0 | + | + | 0 | 0 | 0 | 0 |
| December 19 | + | + | + | | | | | | + | + | + | + | + | + | + | + | 0 | 0 |
| December 20 | + | + | 0 | | | | | | + | + | 0 | 0 | + | + | + | 0 | 0 | 0 |
| December 21 | 0 | 0 | 0 | | | | | | 0 | + | 0 | 0 | D | + | + | D | 0 | 0 |
| December 22 | 0 | 0 | D | | | | | | 0 | + | 0 | + | | 0 | 0 | | 0 | 0 |
| December 23 | 0 | + | | | | | | | 0 | + | 0 | + | | 0 | 0 | | 0 | 0 |
| December 24 | D | 0 | | | | | | | 0 | 0 | + | + | | 0 | 0 | | 0 | 0 |
| December 25 | | 0 | | | | | | | 0 | 0 | 0 | + | | 0 | 0 | | 0 | 0 |
| December 26 | | 0 | | | | | | | 0 | 0 | 0 | D | | 0 | 0 | | 0 | 0 |
| December 27 | | 0 | | | | | | | 0 | 0 | 0 | | | D | 0 | | 0 | 0 |
| December 28 | | 0 | | | | | | | 0 | 0 | 0 | | | | 0 | | 0 | 0 |
| December 29 | | 0 | | | | | | | 0 | 0 | 0 | | | | + | | 0 | 0 |
| December 30 | | 0 | | | | | | | + | + | + | | | | + | | 0 | 0 |
| December 31 | | 0 | | | | | | | 0 | + | 0 | | | | + | | 0 | 0 |
| *1922* | | | | | | | | | | | | | | | | | | |
| January 1 | | 0 | | | | | | | 0 | + | 0 | | | | 0 | | 0 | 0 |
| January 2 | | 0 | | | | | | | 0 | 0 | 0 | | | | 0 | | 0 | 0 |
| January 3 | | 0 | | | | | | | 0 | 0 | 0 | | | | + | | 0 | 0 |
| January 4 | | 0 | | | | | | | 0 | 0 | 0 | | | | 0 | | 0 | 0 |
| January 5 | | 0 | | | | | | | 0 | 0 | 0 | | | | + | | 0 | 0 |
| January 6 | | 0 | | | | | | | 0 | 0 | 0 | | | | + | | 0 | 0 |
| January 7 | | 0 | | | | | | | 0 | 0 | 0 | | | | + | | 0 | 0 |
| January 8 | | 0 | | | | | | | 0 | 0 | 0 | | | | 0 | | 0 | 0 |
| January 9 | | 0 | | | | | | | 0 | 0 | 0 | | | | 0 | | 0 | 0 |
| January 10 | | | | | | | | | 0 | 0 | 0 | | | | 0 | | 0 | 0 |
| January 11 | | | | | | | | | | | 0 | | | | 0 | | D | 0 |
| January 12 | | | | | | | | | | | 0 | | | | 0 | | | 0 |
| January 13 | | | | | | | | | | | 0 | | | | 0 | | | 0 |
| January 14 | | | | | | | | | | | 0 | | | | 0 | | | 0 |

TABLE 3—*Concluded*

| DATE | S. OBERMEIERI | | | | S. NOVYI | | | | S. KOCHI | | | | S. DUTTONI | | | | S. OF PANAMA | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Rats | | Mice | | Rats | | Mice | | Rats | | Mice | | Rats | | Mice | | Mice | |
| | 3 | 13 | A1 | B1 | 4 | 14 | A3 | B3 | 2 | 12 | A2 | B2 | 1 | 11 | A4 | B4 | A5 | B5 |
| *1922* | | | | | | | | | | | | | | | | | | |
| January 15 | | | | | | | | | | | 0 | | | | 0 | | | 0 |
| January 16 | | | | | | | | | | | 0 | | | | 0 | | | |
| January 17 | | | | | | | | | | | 0 | | | | 0 | | | |
| January 18 | | | | | | | | | | | 0 | | | | 0 | | | |
| January 19 | | | | | | | | | | | 0 | | | | 0 | | | |
| January 20 | | | | | | | | | | | 0 | | | | 0 | | | |

\+ = Positive for spirochetes.
0 = No spirochetes found in 600 fields.
D = Died.

Control inoculations into two clean rats and two clean mice were followed by typical infections in each case.

TABLE 4

*Results obtained by inoculating white rats, hyperimmunized against Panama relapsing fever spirochetes, with S. obermeieri, S. novyi, S. kochi, S. duttoni and S. of Panama*

Fifteen white rats which had recovered from a typical infection with the Panama strain, were inoculated at three day intervals with heavy doses of the same organism. On the eighth day following the last inoculation, their blood having been free from spirochetes on all eight days, they were inoculated as follows:

| DATE | S. OBERMEIERI | | | S. NOVYI | | | S. KOCHI | | | S. DUTTONI | | | S. OF PANAMA | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Rats | | | Rats | | | Rats | | | Rats | | | Rats | | |
| | 467 | 497 | 483 | 425 | 466 | 460 | 479 | 480 | 478 | 419 | 496 | 459 | 475 | 484 | 427 |
| *1922* | | | | | | | | | | | | | | | |
| February 5 | + | + | + | 0 | 0 | 0 | + | + | + | + | + | 0 | 0 | 0 | 0 |
| February 6 | + | + | + | + | + | + | + | + | + | + | + | + | 0 | 0 | 0 |
| February 7 | + | + | + | + | D | + | + | + | + | + | + | D | 0 | 0 | 0 |
| February 8 | + | 0 | + | D | | + | + | + | 0 | + | + | | 0 | 0 | 0 |
| February 9 | D | 0 | 0 | | | 0 | 0 | 0 | 0 | + | 0 | | 0 | 0 | 0 |
| February 10 | | 0 | 0 | | | + | 0 | 0 | + | + | 0 | | 0 | 0 | 0 |
| February 11 | | + | + | | | + | + | + | + | 0 | + | | 0 | 0 | 0 |
| February 12 | | + | + | | | + | + | + | 0 | 0 | + | | 0 | 0 | 0 |
| February 13 | | + | + | | | + | + | + | 0 | 0 | + | | 0 | 0 | 0 |
| February 14 | Smears discontinued on all but the Panama set | | | | | | | | | | | | 0 | 0 | 0 |
| February 15 | | | | | | | | | | | | | 0 | 0 | 0 |
| February 16 | | | | | | | | | | | | | 0 | 0 | 0 |

\+ = Positive for spirochetes.
0 = No spirochetes found in 600 fields.
D = Died.

Control inoculations into clean rats were positive in each of the above series.

condition to 10 cc. of sterile ascitic fluid. The tubes are then allowed to stand for from two to six hours. The clear fluid from above and around the clot is then transferred to a centrifuge tube and centrifuged. The upper three-quarters of the fluid is then discarded; the remainder is rich in spirochetes and is used for agglutination purposes. 0.15 cc. of the spirochete suspension is mixed with an equal amount of undiluted immune serum and cover slip preparations are examined at ten-minute intervals by dark-field illumination.

*Preparation of immune serum*

A rat or monkey is inoculated with a given strain of the relapsing fever spirochete. After recovery from a typical course of the disease, it is given three or more massive inoculations of the same strain at three-or four-day intervals. If following the last inoculation blood films of peripheral blood are negative for a period of ten days, the animal is bled and the serum separated, tested and stored in sterile containers for future use.

At first we used dilutions of the immune serum but the results were so much more satisfactory with the undiluted serum that we discontinued the use of the dilutions.

*Discussion of agglutination results*

The occurrence of some irregularity in the results obtained in the agglutination tests warrants a short description of the effect of each immune serum upon each type of spirochete studied.

*S. obermeieri.* Obermeier immune serum caused immediate cessation of movement and agglutination of this organism, and beginning lysis in about twenty minutes. Novy immune serum caused cessation of movements and in one instance good agglutination and in two others little or no agglutination. Koch immune serum 72, gave good agglutination while Koch immune serum 152, although capable of killing *S. kochi* in one hour, had no harmful effect upon *S. obermeieri.* Dutton serum, unless highly potent, caused only slowing of movement. Panama serum caused no slowing of movements and was without harmful effect on this organism.

*S. novyi.* Novy immune serum caused immediate cessation of movement only poor agglutination of this organism. Obermeier, Koch and Dutton serum also caused cessation of movement of the Novy spirochete. Immune sera prepared from two different strains of the Panama spirochete had no effect upon the Novy spirochete.

*S. kochi.* The results obtained with this spirochete were slightly irregular. With its own immune serum it was rendered lifeless but the process was a slow one. Obermeier and Novy serum had the same effect upon it, in addition Novy serum caused fair agglutination. Dutton serum in one of the tests rendered the spirochete apparently lifeless but in another had no effect upon it. Normal serum and Panama serum had no effect upon this spirochete.

*S. duttoni.* One lot of Koch immune caused quick and beautiful agglutination of this spirochete; two other lots of Koch immune serum caused immediate cessation of movement but did not cause agglutination. Obermeier, Novy and Koch immune sera also caused cessation of movement but little or no agglutination. Two immune sera prepared from the Panama spirochete were without effect on this spirochete.

*S. of Panama.* The most marked and spectacular agglutination occurred when this spirochete was mixed with its own immune sera. Cessation of movement was almost instantaneous and agglutination complete in ten minutes. The clumps formed were unusually large. Strong Obermeier, Novy, Koch and Dutton immune sera had no effect upon this spirochete.

The above results show that a very close relationship exists between the four spirochetes of Obermeier, Novy, Koch and Dutton. A hyperimmune sera prepared by the method above described does not suffice to distinguish these strains. The Panama strain is, serologically, unrelated to any of these strains.

*Summary of results obtained by incubating spirochetes with immune serum*

The results as shown by dark-field examination and by animal inoculation were practically the same.

TABLE 5

*Effect of immune sera on spirochetes as shown by dark-field examination*

| TIME IN MINUTES | SERUM OBERMEIER | | | SERUM NOVY | | | SERUM KOCH | | | SERUM DUTTON | | | SERUM PANAMA | | | NORMAL SERUM |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 143 | 173 | 183 | 74 | 74 | 494 | 72 | 72 | 152 | 141 | 91 | 151 | 456 | 456 | 30 | |
| *S. obermeieri* | | | | | | | | | | | | | | | | |
| 10 | * | | | * | – | | – | | | – | | | – | | | – |
| 20 | | ++++ | | * | | | | | | | | | | | | – |
| 30 | +++ | | * | +++ | | – | ++ | ++ | – | – | | ** | – | | – | – |
| 40 | | | | | | | | | | – | | | | | | |
| 50 | | | | | | | | | | | | | | | | – |
| 60 | +++ | | ** | +++ | +– | ** | +++ | +++ | – | * | | ** | – | – | – | – |
| | | 143 | | | | | | | | | | | | | | |
| *S. novyi* | | | | | | | | | | | | | | | | |
| 10 | – | | | – | | ** | – | | | – | | | – | – | – | – |
| 20 | – | | – | – | | | – | | – | – | | ** | – | – | – | – |
| 30 | ** | | | ** | | | – | | | ** | | | – | – | – | – |
| 40 | | | * | | | +– | | | ** | | | | | – | – | |
| 50 | + | + | | +– | +– | | * | * | | + | + | + | – | – | – | – |
| 60 | + | | ** | +– | | +– | * | | ** | + | | + | – | – | – | – |
| *S. kochi* | | | | | | | | | | | | | | | | |
| 10 | – | | | – | | | – | – | | – | | | – | | | – |
| 20 | | | | | | | | | | | | | | | | |
| 30 | ** | | ** | * | | ** | – | | ** | – | | ** | – | | – | – |
| 40 | | | | | | | | | | | | | | | | |
| 50 | | | | | | | | | | | | | | | | |
| 60 | +++ | | | +– | ** | | ++ | ++ | ** | – | | | – | | – | – |

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *S. duttoni* | | | | | | | | | | | | | | | | |
| 10 | | − | | | − | | | | | | | | | | | |
| 20 | | | | | | | | | | | | | | | | |
| 30 | + | ++ | | +− | − | | + | * | | − | ++++ | | − | − | | − |
| 40 | | | | | | | | | | | | | | | | |
| 50 | | | | | | | | | | | | | | | | |
| 60 | + | | ** | +− | +− | ** | + | * | ** | + | | ** | − | − | − | − |
| *S. of Panama* | | | | | | | | | | | | | | | | |
| 10 | − | | − | − | | − | − | | − | − | | − | ++++ | | ++++ | − |
| 20 | − | | − | − | | − | − | | − | − | | − | | | | |
| 30 | − | | − | − | | − | − | | − | − | | − | ++++ | | ++++ | − |
| 40 | − | | − | − | | − | − | | − | − | | − | ++++ | | ++++ | − |
| 50 | | | | | | | | | | | | | | | | |
| 60 | − | | − | − | | − | − | | − | − | | − | ++++ | | ++++ | − |

*Interpretation of symbols*

−, No change in the normal movements of the spirochetes.
*, Slowing of the movements of the spirochetes.
**, Cessation of the movements of the spirochetes without agglutination.
+−, Cessation of the movements with slight agglutination.
+, Cessation of the movements with poor agglutination.
++, Cessation of the movements with fair agglutination.
+++, Cessation of the movements with good agglutination.
++++, Cessation of the movements with extreme agglutination.

TABLE 6

*Effect of immune serum upon spirochetes as shown by animal inoculation*

Spirochetes incubated with immune serum for 60 minutes before inoculation.

| DATE | SERUM OBERMEIER (183) | | SERUM NOVY (494) | | SERUM KOCH (152) | | SERUM DUTTON (151) | | SERUM PANAMA (30) | | NORMAL SERUM | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mouse A6 | Mouse B6 | Mouse A8 | Mouse B8 | Mouse A7 | Mouse B7 | Mouse A9 | Mouse B9 | Mouse A10 | Mouse B10 | Mouse A11 | Mouse B11 |
| *1922* | | | | | | | | | | | | |
| *S. obermeieri* | | | | | | | | | | | | |
| February 14 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| February 15 | 0 | 0 | 0 | | 0 | 0 | 0 | 0 | 6 | 4 | 1 | 0 |
| February 16 | 0 | 0 | 0 | | 0 | 0 | 0 | 0 | 600 | 2400 | 18 | 24 |
| February 17 | 0 | 0 | 0 | | 0 | 0 | 0 | 0 | 0 | 0 | 600 | 20 |
| February 18 | 0 | 0 | 0 | | 6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| February 19 | 0 | 0 | 0 | | 30 | 120 | 0 | 0 | 0 | 0 | 0 | 0 |
| February 20 | 0 | 0 | 600 | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| February 21 | 0 | 0 | 120 | | 0 | 0 | 0 | 0 | 8 | 9 | 0 | 0 |
| February 22 | 0 | 0 | 0 | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| February 23 | 0 | 0 | 10 | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Mouse A24 | Mouse B24 | Mouse A26 | Mouse B26 | Mouse A25 | Mouse B25 | Mouse A27 | Mouse B27 | Mouse A28 | Mouse B28 | Mouse A29 | Mouse B29 |
| *S. novyi* | | | | | | | | | | | | |
| March 11 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| March 12 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | 60 | 70 | 0 | 0 |
| March 13 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | 350 | 900 | 600 | 80 |
| March 14 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | 0 | 0 | 720 | 150 |
| March 15 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | 0 | 0 | 40 | 20 |
| March 16 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | 0 | 0 | 6 | 6 |
| March 17 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | 0 | 10 | 0 | 20 |
| March 18 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | 10 | 0 | 6 | 0 |
| March 19 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | 40 | 0 | 40 | 0 |
| March 20 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | 0 | | 60 | 0 |
| | Mouse A30 | Mouse B30 | Mouse A32 | Mouse B32 | Mouse A31 | Mouse B31 | Mouse A33 | Mouse B33 | Mouse A34 | Mouse B34 | Mouse A35 | Mouse B35 |
| *S. kochi* | | | | | | | | | | | | |
| March 20 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 60 | 50 | 30 | 30 |
| March 21 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 200 | 4800 | 200 | 60 |
| March 22 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1800 | 20 | 0 | 0 |
| March 23 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| March 24 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| March 25 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 30 | 0 | 0 | 0 |
| March 26 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 20 | 0 | 0 |
| March 27 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 10 | 30 | 5 |
| March 28 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 2 | 50 | 12 |
| March 29 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

TABLE 6—*Concluded*

| DATE | SERUM OBERMEIER (183) | | SERUM NOVY (494) | | SERUM KOCH (152) | | SERUM DUTTON (151) | | SERUM PANAMA (30) | | NORMAL SERUM | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mouse A18 | Mouse B18 | Mouse A20 | Mouse B20 | Mouse A19 | Mouse B19 | Mouse A21 | Mouse B21 | Mouse A22 | Mouse B22 | Mouse A23 | Mouse B23 |
| *1922* | | | | | | | | | | | | |
| *S. duttoni* | | | | | | | | | | | | |
| March 8 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 8 | 5 | 0 |
| March 9 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 180 | 240 | 1200 | 240 |
| March 10 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1200 | 2600 | 300 | 300 |
| March 11 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| March 12 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| March 13 | 0 | 4 | 0 | 0 | 5 | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| March 14 | 0 | 100 | 0 | 0 | 40 | 0 | 0 | 0 | 1 | 0 | 5 | 0 |
| March 15 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | 12 | 0 |
| March 16 | 0 | 0 | 0 | 0 | 12 | 0 | 0 | 0 | 100 | | 100 | 0 |
| March 17 | 0 | 0 | 0 | 0 | 2200 | 12 | 0 | 0 | 0 | | 10 | 12 |
| March 18 | 0 | 0 | 0 | 0 | 600 | 300 | 0 | 0 | 0 | | 0 | 0 |
| | Mouse A12 | Mouse B12 | Mouse A14 | Mouse B14 | Mouse A13 | Mouse B13 | Mouse A15 | Mouse B15 | Mouse A16 | Mouse B16 | Mouse A17 | Mouse B17 |
| *S. of Panama* | | | | | | | | | | | | |
| February 17 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| February 18 | 0 | 0 | 0 | 0 | 6 | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| February 19 | 20 | 30 | 90 | 3 | 20 | 30 | 30 | 40 | 0 | 0 | 210 | 60 |
| February 20 | 0 | 0 | 0 | 60 | 0 | 0 | 0 | 0 | 0 | 0 | 20 | 0 |
| February 21 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 60 | 0 | 0 | 0 | 0 |
| February 22 | 0 | 3 | 0 | 0 | 2 | 0 | 0 | 3 | 0 | 0 | 0 | 0 |
| February 23 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| February 24 | 0 | 0 | | | | | | | 0 | 0 | 0 | 4 |
| February 25 | 0 | 0 | | | | | | | 0 | 0 | | |
| February 26 | 0 | 0 | | | | | | | 0 | 0 | | |

Numerals = Number of spirochetes found (or computed) in 600 fields.
0 = No spirochetes found in 600 fields.

*S. Obermeieri* was killed by incubating with serum Obermeier and Dutton but not by incubating with Panama and normal serum. The incubation period in animals was delayed when it was incubated with Koch and Novy sera.

*S. novyi* was killed by incubating with Obermeier, Novy, Koch and Dutton sera but not by incubating with Panama and normal sera.

*S. kochi* was killed by incubating with Obermeier, Novy, Koch and Dutton sera but not by incubating with Panama and normal sera.

*S. duttoni* was killed by incubation with Dutton and Novy sera, but not by incubation with Panama and normal sera. The incubation period in animals was delayed when it was incubated with Obermeier and Koch sera.

*S. of Panama* was not injured by incubating with Obermeier, Novy, Koch, Dutton or normal sera but was killed by incubating with Panama serum.

## EXPERIMENTS TENDING TO PROVE THE PANAMA RELAPSING FEVER SPIROCHETE TO BE A SINGLE SPECIES

### *Origin of strains*

*Strain A.* Spirochete obtained from relapsing fever patient in Ancon Hospital, H. C. (Hosp. no. 236908).

*Strain B.* Spirochete obtained from relapsing fever patient in Ancon Hospital, J.T.B. (Hosp. no. 237060).

*Strain C.* Spirochete obtained from naturally infected ticks brought from Arraijan.

*Strain D.* Spirochete obtained from relapsing fever patient in Ancon Hospital, J. M. (Hosp. no. 243588).

### *Strain A protecting against strain C*

March 26, 1921. Rat 300 received an intraperitoneal injection of citrated blood from relapsing fever patient, H. C. A typical infection developed in the rat which lasted for eleven days. For twenty-one days following the last appearance of the spirochete in the blood stream the blood films were uniformly negative.

April 27, 1921. Rat 300 received an intraperitoneal injection from rat 362. Rat 362 contained an average of one spirochete in every ten fields examined. The spirochete used to infect rat 362 was strain C.

Blood films from rat 300 were uniformly negative for spirochetes for a period of twelve days following this latter inoculation while control rats developed a typical infection.

*Strain B protecting against strain C*

March 3, 1921. Rat 293 received an intraperitoneal injection of citrated blood from relapsing fever patient, J. T. B. A typical infection developed in the rat which lasted for ten days. For ten days following the last appearance of spirochetes in the blood of the rat the films were uniformly negative for spirochetes (600 fields examined). No films examined for a period of five days thereafter.

March 27, 1921. Rat 293 received an intraperitoneal injection of blood from rat 362. Rat 362 contained an average of one spirochete in ten fields at the time of the injection. The spirochete used to infect rat 362 was strain C.

Blood films from rat 293 following this latter inoculation were uniformly negative for a period of twelve days following the inoculation (600 fields examined daily). Control rats developed typical infections.

*Strain B protecting (partially or completely) against strain D*

Monkey 68 was infected with Panama relapsing fever spirochetes by experimentally infected ticks. This spirochete was originally obtained from J. T. B., a relapsing fever patient in Ancon Hospital and one of a party that had been infected at Arraijan. The spirochete passed through three white rats and the ticks used in this experiment. Monkey 68 became positive May 16, 1921.

Monkey 318 was infected with spirochetes originally obtained from the same patient (J. T. B.) but which had been passed through three white rats and one wild rat. Monkey 318 became positive May 25, 1921. Both monkeys had a typical infection.

About seven months later, January 21, 1922, these two monkeys were inoculated with Panama strain obtained from B. S., a relapsing fever patient in Ancon Hospital. This strain had been passed through several white mice prior to the inoculation. The blood citrate mixture used for the inoculation contained two spirochetes in five dark fields. Monkey 318 failed to show spirochetes for the following seventeen days while monkey 68 became positive three days following the inoculation but instead of the usual two or three paroxysms characterizing the infection in monkeys there was but one.

TABLE 7

*Blood findings in two monkeys inoculated with strain D*

The monkeys had been infected with and recovered from strain B infection.

| | DAYS | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 |
| Monkey 68 | 0 | 0 | 1 | 0 | 600 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Monkey 318 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Numerals = Number of spirochetes found (or computed) in 600 fields.
0 = No spirochetes found in 600 fields.

*Strain D protecting (partially or completely) against strain E*

On February 1, 1922, four white rats that had received three injections with spirochetes of strain D were inoculated with citrated blood from J. M. (strain E), a relapsing fever patient in Ancon Hospital who probably contracted his infection at a point remote from Arraijan. Table 8 showing the blood film findings following the inoculation is given below.

TABLE 8

*Blood findings in four white rats inoculated with strain E*

These rats had been infected with and recovered from a strain D infection.

| | DAYS | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
| Rat 460 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Rat 470 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Rat 474 | 0 | 6 | 6 | Died | | | | | | | | |
| Rat 477 | 0 | 3 | 6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Control 177 | 0 | 8 | 6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Numerals = Number of spirochetes found (or computed) in 600 fields.
0 = No spirochetes found in 600 fields.

*Strains B and D protecting against strain E*

February 9, 1922, monkeys 68, 318 and 67 received subcutaneous inoculation from rat 177. Rat 177 was originally infected with strain E from the blood of patient J. M. Monkey 68 had previously passed through an infection by strain B and had manifested an immunity to strain D. Monkey 67 was used for the control. The blood findings following the inoculations are given in table 9.

TABLE 9

*Blood findings in monkeys inoculated with strain E*

The monkeys had previously recovered from strain B infection and strain D inoculation.

| | DAYS | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| Monkey 68 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Monkey 318 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Control 67 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 120 | 50 | 6 | 10 | 20 | 25 | 0 |

Numerals = Number of spirochetes found (or computed) in 600 fields.
0 = No spirochetes found in 600 fields.

## SUMMARY OF EXPERIMENTS TENDING TO PROVE THE PANAMA RELAPSING FEVER SPIROCHETES TO BE A SINGLE SPECIES

Rats which had recovered from infections, one with strain A and the other with strain B, were protected from infection by strain C.

Two monkeys which had passed through an infection with strain B, seven months later demonstrated in one instance a partial immunity and in the other a complete immunity to strain D.

Four white rats which had recovered from infection with strain D were inoculated with strain E. Two showed immunity to to strain E and two were not immune to strain E.

A monkey which had recovered from infections with strains B and D and a monkey which had recovered from infection with strain B showed immunity against strain E.

## *S. carteri*

We were unable to obtain a live strain of *S. carteri* to use in this work but from the descriptions of this spirochete given in the literature the possibility of its being the same as the Panama spirochete may be considered as extremely remote.

## CONCLUSION

The spirochete of relapsing fever in Panama is a distinct species, variety or strain as compared with *S. obermeieri*, *S. novyi*, *S. kochi*, *S. duttoni*, and, we feel we may safely add, *S. carteri*.

Relapsing fever in Panama is, in all probability, due to one species variety or strain of the relapsing fever spirochete, namely, the one described above under the heading of Panama spirochete or spirochete of Panama.

We desire to take this opportunity to tender our thanks to Dr. F. G. Novy, Professor of Bacteriology at the University of Michigan Medical School, Ann Arbor, Michigan, for furnishing us with living strains in rats of the relapsing fever spirochetes of Obermeier, Novy, Koch and Dutton which were used in this work.

We also wish to thank Mr. Carl G. Brown, technician at this laboratory, for the personal interest he has taken in this work and for examining a great many of the blood films.

# TRANSACTIONS OF THE AMERICAN SOCIETY OF TROPICAL MEDICINE, EIGHTEENTH ANNUAL MEETING, HELD AT WASHINGTON, D. C., MAY 2 AND 3, 1922

# MINUTES OF THE ANNUAL MEETING

The eighteenth annual meeting of the American Society of Tropical Medicine was called to order at 9 a.m., Tuesday, May 2, 1922, at the Hotel Washington, Washington, D. C., with Vice-President George Dock in the chair. The first session for the reading of papers followed by a business session at 11:45 a.m. was attended by 37 members and visitors.

In lieu of the presidential address, not delivered owing to the absence abroad of the President, the Act'ng President, Dr. Dock, opened the program with the following remarks (here given in abstract):

The annual meeting of the American Society of Tropical Medicine recalls the great contributions by American physicians to Tropical Medicine. The names of Sternberg, Reed and Gorgas are most outstanding, but the large number of others, many of whom are still alive and active, cannot be forgotten. Not less important are the great works in tropical sanitation, carried out by American students of tropical disease. Cuba, the Isthmus of Panama and the Philippines are striking examples of what can be done by the application of scientific discoveries to sanitation. The program prepared for this meeting shows the wide interest and activity of the members. But there are other phases of the situation that seem in need of further work. There still seems to be a tacit belief on the part of the citizens and even many members of the medical profession who are not personally engaged in tropical disease problems that tropical diseases are something foreign and distant, though we know that a very large part of what should be the richest and most productive part of the country is the seat of several important tropical diseases. The need of enlightenment on this subject is part of the general need of dissemination of scientific knowledge. This is beginning to receive the attention of publicists and I feel sure that anything we can do as a body or individually will be well worth while. There is something I think should be seriously considered as a means of stimulating interest and attention, viz., the publication of a thorough, expert and impartial set of abstracts of all articles in periodicals in the United States on Tropical Disease, still better to include the Western hemisphere, with authoritative reviews of books on the subject. I recognize the work now done by several abstracting journals, but I believe better and more work would be stimulated, and the importance of the subject more clearly recognized, if the work was more centralized. The abstracts should include all, and should be short or long according to the importance of the original. Criticism should be freely used. The rapid increase of experts should furnish reviewers and abstracters who could subdivide the material and deal with it promptly and competently. I think the history of the Centralblatt movement shows the value of such a scheme, which should appeal to workers, publishers, and, if necessary to get financial aid, to philanthropists and patriots.

A paper presented by Dr. John M. Swan on "A contibution on the question of the leucocyte formula in malaria" was discussed by Drs. Bass, Carter, N. Barlow, J. B. Guthrie and Craig.

A paper presented by Dr. C. C. Bass on "Some observations on the effect of quinine upon the growth of malaria plasmodia in vitro" was discussed by Drs. Craig and Swan.

A paper presented by Dr. Stewart R. Roberts on "Influence of malaria on the circulation" was discussed by Drs. J. B. Guthrie, Wood, Bass, Butler, Swan and Dock.

A paper presented by Dr. E. R. Whitmore on "The action of light in the production of relapse in malaria" was discussed by Drs. N. Barlow and Carter.

A paper was presented by Dr. Ernest L. Walker on "Contributions to the bacteriology of leprosy. I. The diphtheroid in leprosy."

A paper by Dr. Damaso Rivas on "A contribution to the pathology of leprosy" was read by title.

A paper by Dr. Bailey K. Ashford on "Beri-beri in the garrison at San Juan, Porto Rico," was read by title.

A tribute by Dr. E. J. Wood to "Sir Patrick Manson: the father of tropical medicine" was presented to the Society. At the close of the reading of this paper, the audience at the suggestion of the chairman, rose as an expression of reverence for the memory of Sir Patrick Manson and of appreciation for his great accomplishments in extending the knowledge of tropical diseases.

At 11.45 a.m. a business session was held during which the reports of the Secretary and Treasurer, and the minutes of the Council meeting, were read and approved, the various recommendations of the Council as contained in the minutes of its meeting of May 1, 1922, were adopted, and the ballot of the Society was cast for the 55 new active members and 5 new corresponding members listed in the minutes of the said Council meeting.

The second session for the reading of papers was called to order at 9 a.m., Wednesday, May 3, 1922, at the Hotel Washington, Washington, D.C., with the newly-elected President, George Dock in the chair. This session was attended by sixty members and visitors.

A paper presented by Dr. J. C. Parham on "The relation between syphilis and yaws as observed in American Samoa" was discussed by Drs. Butler, Nichols, Reed, Welch and Dock.

A paper presented by Dr. W. M. Kerr on "Should gangosa be removed from the nomenclature of tropical medicine?" was discussed by Drs. Nichols, Butler and Carter.

A paper presented by Dr. Kenneth M. Lynch on "Cultivation of Trichomonas from the human mouth and vagina and from urine" was discussed by Drs. Kofoid, Simon, Bass and Dock.

A paper presented by Dr. C. A. Kofoid on "Geographical distribution of hookworm infection in the United States detected in army recruits" was discussed following the reading of the next paper.

A paper presented by Dr. W. W. Cort on "A graphic analysis of certain factors in hookworm control" was discussed in conjunction with the preceding paper by Drs. Craig, Bass, Nichols, Kofoid, Carter, Butler and Dock.

A paper was presented by Dr. M. C. Hall on "Carbon tetrachloride as an anthelmintic."

A paper presented by Dr. George C. Shattuck on "Incidence of tropical diseases in Massachusetts" was discussed by Drs. Simon, Kofoid, Butler, Cort, Dock and Lynch.

A paper presented by Dr. Tomas Cajigas on "Complement fixation in malaria" was discussed by Drs. Bass, Tasker and Whitmore. The following papers were then read by title:

"A study of the intestinal protozoa of children and adults in Washington," by E. R. Whitmore.

"Statistical summary of work on human intestinal parasites in California, covering about 15,000 examinations," by C. A. Kofoid.

"The hookworm index and mass treatment," by Samuel T. Darling.

"Porto Rico as a field for the study of tropical hygiene," by R. W. Hegner.

"A new and rapid laboratory method for the diagnosis of intestinal parasites," by Damaso Rivas.

The Society adjourned *sine die* at 12:45 p.m.

## REPORT OF THE SECRETARY, MAY 1, 1922

Although I was elected to the office of Secretary in November, 1921, circumstances prevented my actively taking up the work until after January 1, 1922. Thanks however, to the continued interest of the former Secretary, Dr. Simon, and his kindly assistance and that of Major Nichols, together with the help of other members of the Society with whom I have been in touch, it has been possible for me during the brief time I have been in office to become familiar with and to administer the affairs of the Secretary's office with much less difficulty than I would have otherwise experienced.

My principal activities have been along the line of miscellaneous correspondence; collecting, as secretary of the membership committee, a list of prospective members; preparing a statement concerning the status of a list of prospective foreign members that was presented to the Society in 1919 and sending copies of this statement to the persons on this list, a copy of which was kindly furnished by Dr. Rivas; arranging the program of the 1922 meeting; and as Treasurer, collecting the annual dues.

The Society has lost by death a distinguished honorary member, Sir Patrick Manson, who died April 8, 1922. Dr. E. K. Dunham, an active member, died April 15, 1922. There have been no other death losses in the Society's membership that have come to my attention. I would, however, call attention to the following death losses among members prior to the last meeting that appear not to have been noted in the Society's published reports:

Dr. D. E. Salmon, an honorary member, died in 1914; Dr. Maximilian Herzog, an active member, erroneously included among those mentioned in the minutes of the last council meeting as having been dropped for non-payment of dues, died in 1918; Prof. Raphael Blanchard, an honorary member, died February 7, 1919; Sir Pardey Lukis, a corresponding member, died in 1919.

Numerically the membership lists now stand as follows:

| | |
|---|---|
| Active members | 110 |
| Corresponding members | 11 |
| Honorary members | 29 |

Active members are delinquent in the payment of dues as follows:

| | |
|---|---|
| 1918 (paid in part), 1919, 1920, 1921, 1922 | 1 |
| 1920, 1921, 1922 | 2 |
| 1921, 1922 | 2 |
| 1922 | 16 |

Corresponding members are in arrears for dues as follows:

| | |
|---|---|
| 1920, 1921, 1922 | 6 |
| 1921, 1922 | 1 |
| 1922 | 2 |

There are the following officers to be elected: President, two Vice Presidents, Secretary, Assistant Secretary, and Treasurer. The term of Dr. C. L. Furbush as Councillor expires this year and his successor for a term of five years should be elected.

The question of the time and place of the next meeting should be given consideration. The Society has received invitations from commercial organizations in St. Louis and New York to meet in their respective cities.

A report of the Treasurer is appended.

B. H. Ransom,
*Secretary.*

## REPORT OF THE TREASURER JANUARY 5, 1922 TO MAY 1, 1922

On receiving the funds and records of the Treasurer's office from the former Treasurer, January 5, 1922, I found that the following transactions had occurred since the last audited report of the former Treasurer, as shown by records now in my possession.

*Receipts*

| | |
|---|---|
| Balance in bank, November 9, 1921 | $310.80 |
| Membership dues | 64.00 |
| Total receipts | $374.80 |

*Expenditures*

| | |
|---|---|
| Exchange on checks | $0.05 |
| Transfer of funds to new Treasurer, December 20, 1921 | 374.75 |
| Total Expenditures | $374.80 |

Since assuming charge of the Treasurer's office I have received and expended money and have incurred liabilities on the Society's account as shown by the following summary:

*Receipts*

| | |
|---|---|
| From former Treasurer (deposited with McLachlen Banking Corporation, Washington, D. C., January 5, 1922 | $374.75 |
| Membership dues (arrears prior to 1919) | 10.00 |
| Membership dues (1919) | 4.00 |
| Membership dues (1920) | 28.00 |
| Membership dues (1921) | 68.00 |
| Membership dues (1922) | 445.49 |
| Total receipts | $930.24 |

*Expenditures*

| | |
|---|---|
| To Williams and Wilkins for publications: | |
| Subscriptions, volume 1 of JOURNAL | $214.00 |
| Transactions sixteenth Annual Meeting | 40.78 |
| Expenses of office of Secretary-Treasurer: | |
| Printing and stationery | 19.00 |
| Post office box rent to June 30, 1922 | 3.82 |
| Postage | 14.00 |
| Parcel-post | 1.11 |

| | | |
|---|---|---|
| Telegram | $0.68 | |
| Trip of Secretary to Baltimore | 2.00 | |
| Mimeograph supplies | 8.15 | |
| Exchange on foreign check | .31 | |
| Registration of Secretary at Congress of American Physicians and Surgeons | 5.00 | |
| Miscellaneous: | | |
| D. Rivas, membership campaign 1919 | 55.68 | |
| J. E. Ackert, refund a/c overpayment of dues | 1.00 | |
| Total expenditures | $365.53 | |
| Balance May 1, 1922 | | $564.71 |
| Library Fund (not yet in hands of present Treasurer) | | 30.83 |
| Credited by Williams & Wilkins (cancelled subscription volume 2 of JOURNAL) | | 4.00 |
| Total Resources, May 1, 1922 | | $599.54 |

*Liabilities*

| | | |
|---|---|---|
| To Williams & Wilkins for publications: | | |
| Subscriptions to volume 1 of JOURNAL | $16.00 | |
| Subscriptions to volume 2 of JOURNAL | 428.00 | |
| Transactions 17th Annual meeting (partial statement) | 21.00 | |
| Reprints (Society notices for Secretary's use) | 7.25 | |
| Total liabilities, May 1, 1922 in bills rendered | $472.25 | |
| Net visible resources, May 1, 1922 | | $127.29 |

*Uncertain assets*

| | | |
|---|---|---|
| Dues of 21 active members in arrears | $141.00 | |
| Dues of 9 corresponding members in arrears | 66.00 | |
| Total dues in arrears | 207.00 | |
| If all active members in arrears pay their dues, additional subscriptions to the JOURNAL will cost the Society | 99.00 | |
| If all corresponding members in arrears pay their dues, additional subscriptions to the JOURNAL will cost the Society | 64.00 | |
| Total charges against dues in arrears, if and when paid | $163.00 | |
| Total possible additions to resources during 1922, if all dues in arrears are paid | | $144.00 |

B. H. RANSOM,
*Treasurer.*

We have examined the accounts of the Treasurer and found them correct to April 27, 1922.

J. BIRNEY GUTHRIE,
NATHAN BARLOW,
*Auditing Committee.*

## SUPPLEMENTARY STATEMENT OF TREASURER

In order that unnecessary loss to the Society and embarrassment in meeting financial obligations may be avoided, it has been suggested to the Council for approval that, following a common custom in other societies, statements be mailed about December 1 of the membership dues for the following year, so that members, except those in very distant places or away from home, will have ample opportunity to pay their dues before the first number of the next volume of the official Journal of the Society is issued. Under this arrangement no member would be placed on the mailing list to receive that volume of the JOURNAL until after his dues had been paid. Members paying their dues in proper season would receive the Journal as issued and without delay. Members suspended from the mailing list would receive back numbers of the JOURNAL and be restored to the regular mailing list as soon as their dues were paid, without incurring any penalty except delay in receiving the JOURNAL and possible failure to receive certain issues on account of the supply having been exhausted.

## MINUTES OF THE COUNCIL MEETING

The Council met at 7 p.m., May 1, 1922, at the Hotel Washington, with the following present: Doctors Butler, Siler, Ransom, members of the Council, Doctors Dock, Nichols, and Simon, advisory members, and Dr. Swan, past president.

Doctor Swan on behalf of the Committee of the Society appointed to cooperate with the Gorgas Memorial Institute of Tropical Medicine, consisting of Doctors Lambert, Meyer, Elliott, Thayer and Shattuck, reported that the committee had recently begun work but would have no definite report to make at this meeting. The committee was continued.

The following amendments to the By-Laws submitted to the Council in March, 1922, of which notice was mailed to members April 20, were adopted.

The provision in Article I of the By-Laws limiting the number of active members shall be amended to read as follows:

The number of active members shall be limited to 300. (This change raises the limit from 200 to 300.)

Articles II of the By-Laws shall be amended to read as follows:

The dues shall be fixed each year by the Council, but shall not be increased beyond $5.00 without approval by the Society at its annual meeting.

Active members shall pay the regular dues.

Corresponding members shall pay dues as determined by the Council but not exceeding the regular dues.

Honorary members shall be exempt from dues.

(This change authorizes the Council to establish dues for corresponding members as well as for active members, not exceeding $5.00 annually in either case.)

It was voted to continue the publication of annual volumes of the Transactions of the Society and the Treasurer was authorized to fix a price at which they are to be sold.

The Council approved the action of the Treasurer in accepting the sum of £1.7.0 from the Secretary of the International Society of Tropical Medicine in settlement of the share of contributions made by the American Society of Tropical Medicine to the Society in question, which has been disbanded and whose funds are being returned to the contributors.

Doctor Swan at his suggestion was authorized to make arrangements concerning the transfer of the Library Fund to the present Treasurer. Doctor Swan was also authorized to make a suitable disposition of the files of various periodicals which have accumulated in his hands as exchanges sent to him during his service as Secretary.

The Treasurer's report was read and approved subject to approval by an audit committee.

No change was recommended in the present arrangements for the custody of various archives and other property of the Society now in charge of Doctor Smith, Assistant Secretary.

Major Nichols was appointed a committee of one to investigate the question of the transfer of some or all of the archives and property in question to other quarters if such a transfer should become desirable.

The resignations of Doctor W. A. Baetjer, and Doctor W. M. L. Coplin, active members, were accepted. The resignations of Doctor Henry Skinner, in 1920, Colonel W. P. Chamberlain, in 1916, Doctor A. W. Sellards, in 1917, Doctor Charles P. Emerson, in 1919, Doctor Walter Brem, in 1919, and Doctor W. E. Musgrave, in 1919, tendered at various times but not apparently heretofore noted in the minutes as accepted, were ordered accepted as of the dates given above. Corrections were ordered made in the last minutes of the Council of typographical errors made in the names of the following members elected at the last meeting: J. E. Ackert, R. W. Hegner, Louis F. Petritz, Elliott C. Prentiss, Edw. U. Reed, F. M. Root, C. E. Simon, W. H. Taliaferro, George C. Dunham, J. H. St. John.

The name of Doctor John L. Todd who has been carried on the published lists as an active member, was ordered transferred to the list of corresponding members.

Doctor Alexander Lambert was ordered reinstated as an active member dating from Jauary 1, 1922. Doctor Nathan Barlow who was dropped from the rolls on account of a lack of proper address due to war service, was ordered reinstated on payment of accrued dues.

The Secretary was authorized to consult American honorary members with a view of securing their concerted action toward shortening the honorary list, in order that the Society might develop a policy of occasionally electing to honorary membership distinguished foreign workers in the field of tropical medicine without swelling the list beyond the limit of twenty, it being recognized that an honorary list, if very long, loses its significance as an honorary list.

The following were recommended to the Society for election as active members: James E. Ash, Robt. P. Bigelow, F. C. Bishopp, Theodore Bitterman, Wm. C. Boeck, George R. Callender, Philip P. Calvert, J. H. Chambers, Asa C. Chandler, M. E. Connor, E. C. Cort, Wesley Cintra Cox, E. C. Faust, William D. Fleming, Alvis E. Greer, John E. Guberlet, Henry Hanson, J. Harper, Frank G. Haughwout, Allan G. Heard, Jesse Bundren Helm, Fred. E. Herzer, M. E. Higgins, Rae E. Houke, Wm. McC. James, W. M. Kerr, George R. LaRue, A. L. Levin, Randolph Lyons, Theo. C. Lyster, A. C. McKenney, Ward J. MacNeal, Chas. H. Manlove, Henry G. May, Kent Churchill Melhorn, J. C. Michael, J. C. Parham, E. Peterson, David J. Prather, Lee Rice, Wm. A. Riley, L. J. Roberts, Stewart R. Roberts, P. S. Rossiter, Wilbur A. Sawyer, Edwin W. Schultz, Benjamin Schwartz, R. E. Scott, Wilson G. Smillie, Frank Smithies, Oscar Teague, Wilbur F. Thomson, W. W. Watkins, Richey Laughlin Waugh, D. H. Wenrich.

The following were recommended to the Society for election as corresponding members: E. Escomel (Peru), Juan Iturbe (Venezuela), L. E. Migone (Paraguay), R. Robles (Guatemala), Luis Zanotti-Cavazzoni (Paraguay).

It was the sense of the Council in conformity with the spirit of the By-Laws and the purposes of the Society that the Membership Committee in its recommendation of prospective active members be actuated by the policy that the Society welcomes to active membership, within the limits of number set by the By-Laws, any regular American physician or scientist (that is, who is a citizen of the United States) of good professional standing, who is believed to be genuinely interested in the study of tropical diseases, his fitness having been investigated by the Membership Committee in cooperation with other members.

The Membership Committee (Nichols, Butler and Ransom) was continued.

The suggestion of the Treasurer relative to mailing statements of dues about December 1, for the ensuing year and of suspending members from the subscription list of the Journal until dues were paid, was approved.

The dues of active members for 1923 were fixed at $5.00, the dues of corresponding members elected at this meeting for 1922 at $4.00, the dues of corresponding members for 1923 at $4.00. It was provided that honorary members wishing to receive the official Journal might secure it on the payment of the same dues as corresponding members.

The following were recommended to the Society for election as officers and councillors:

*President*, George Dock
*First Vice-President*, Sidney K. Simon
*Second Vice-President*, Joseph F. Siler
*Secretary*, Brayton H. Ransom
*Assistant Secretary*, Allen J. Smith
*Treasurer*. Brayton H. Ransom
*Councillor for five years*, Kenneth M. Lynch
*Councillor for one year*, George C. Shattuck

It was voted to hold the annual meeting in 1923 at the time and place of the meeting of the American Medical Association.

B. H. Ransom,
*Secretary.*

# A CONTRIBUTION TO THE QUESTION OF THE LEUKOCYTE FORMULA IN MALARIA[1]

JOHN M. SWAN

*Rochester, New York*

In a paper by W. Broughton-Alcock in the Journal of Tropical Medicine and Hygiene, May 16, 1921, based on the examination of the blood of 28,270 soldiers returned to London from various parts of the tropics, the following conclusion is drawn: "The outstanding conclusion to be drawn from these tables is that a relative increase of large mononuclear cells is not a constant factor in latent malaria, even when the most reliable diagnostic clinical sign, an enlarged spleen, is present, and the clinical diagnosis of latent malaria is clear."

It occurred to me that the publication of the differential leukocyte counts of the specimens of malarial blood in my possession might add something to the information at hand concerning the question of the leukocyte formula in malaria. The material is scanty, and has been accumulated since 1906. I have made all the counts, and, unless otherwise stated 500 leukocytes were counted in each instance. The origin of the material is indicated by the following numerical reference table:

[1] London School of Tropical Medicine, 1906
[2] Philadelphia Polyclinic, 1905–1910
[3] St. Mary's Hospital, Philadelphia, 1908
[4] U. S. Naval Hospital, Philadelphia, 1907–1909
[5] Dr. M. Y. Pope, Monticello, Arkansas, 1908
[6] Rochester, New York, 1912–1922
[7] Dr. L. W. Roe, Mobile, Alabama, 1907
[8] Dr. Paul Osterhout, Bocas del Toro, Panama, 1908

Incidentally there is the indication of a method of determining the number of parasites to the cubic millimeter of circu-

[1] Read at the eighteenth annual meeting of the American Society of Tropical Medicine, May 2–3, Washington, D. C.

TABLE 1

*Benign tertian cases*

| NUMBER | POLYMORPHONUCLEAR PERCENTAGE | LYMPHOCYTE PERCENT-AGE | LARGE MONONUCLEAR PERCENTAOE | EOSINOPHILE PERCENT-AGE | BASOPHILE PERCENT-AGE | MYELOCYTE PERCENT-AGE | KIND OF PARASITES |
|---|---|---|---|---|---|---|---|
| [1] 0.1 | 69.6 | 23.2 | 5.4 | 1.6 | 0.2 | | Very numerous small rings, presegmenting forms, rosettes and gametocytes |
| [1] 0.2 | 63.0 | 13.8 | 22.8 | | 0.4 | | Full grown parasites and gametocytes 139 to 100 leukocytes |
| [1] 0.3 | 77.4 | 9.6 | 11.0 | 1.8 | 0.2 | | Small rings, rosettes and gametocytes 248 to 100 |
| [1] 0.8 | 46.3 | 23.7 | 30.0 | | | | Small rings, rosettes and gametocytes 50 to 10 leukocytes* |
| [1] 0.9 | 49.6 | 7.6 | 42.6 | 0.2 | | | Small rings. 166 to 100 leukocytes |
| [1] 0.10 | 64.6 | 20.6 | 14.4 | | 0.2 | 0.2 | Large and small rings, 46 to 100 leukocytes |
| [1] 0.11 | 32.8 | 35.8 | 27.4 | 2.0 | 1.4 | 0.6 | Rings and gametocytes. 75 to 100 |
| [1] 0.15 | 51.6 | 41.2 | 6.2 | 0.6 | | 0.4 | Rings and gametocytes. 28 to 100 |
| [1] 0.16 | 61.2 | 14.2 | 6.6 | 18.0 | | | Large rings and gametocytes |
| [1] 0.24 | 31.0 | 42.0 | 4.0 | 23.0 | | | Few rings† |
| [1] 0.26 | 59.6 | 34.4 | 4.8 | 1.0 | 0.2 | | Gametocytes, moderate number |
| [2] 0.27 | 32.0 | 51.0 | 15.0 | | 2.0 | | Large rings and gametocytes† |
| [3] 62 | 65.2 | 12.4 | 22.2 | | | | Pigmented rings 26 to 500 leukocytes |
| [2] 132 | 57.4 | 37.2 | 5.0 | 0.2 | 0.2 | | 24 to 500 leukocytes |
| [2] 149 | 77.0 | 10.4 | 11.8 | 0.6 | 0.2 | | Few parasites |
| [2] 214 | 73.2 | 15.4 | 10.6 | 0.4 | 0.4 | | 177 large and small rings and gametocytes to 100 leukocytes |
| [2] 247 | 73.6 | 7.8 | 17.8 | 0.2 | 0.4 | 0.2 | 43 rings and gametocytes to 10 leukocytes |
| [4] 260 | 54.4 | 12.8 | 27.2 | 5.4 | 0.2 | | 12 to 100 leukocytes |

* 350 leukocytes counted.

† 100 leukocytes counted.

TABLE 1—*Continued*

| NUMBER | POLYMORPHONUCLEAR PERCENTAGE | LYMPHOCYTE PERCENTAGE | LARGE MONONUCLEAR PERCENTAGE | EOSINOPHILE PERCENTAGE | BASOPHILE PERCENTAGE | MYELOCYTE PERCENTAGE | KIND OF PARASITES |
|---|---|---|---|---|---|---|---|
| [2] 263 | 51.0 | 19.4 | 26.8 | 2.4 | | 0.4 | 18 half grown rings to 100 leukocytes |
| [2] 269 | 64.6 | 11.8 | 21.4 | 2.2 | | | 1 gametocyte to 500 leukocytes |
| [5] 275 | 35.2 | 57.2 | 6.8 | 0.6 | | 0.2 | Gametocytes |
| [5] 277 | 88.0 | 8.4 | 3.0 | 0.6 | | | Full grown parasites and rosettes |
| [5] 278 | 83.4 | 8.6 | 7.8 | | 0.2 | | Small unpigmented rings |
| [4] 324 | 66.4 | 12.4 | 20.8 | | 0.4 | | 5 parasites to 500 leukocytes |
| [4] 325 | 46.2 | 19.4 | 31.8 | 1.2 | 0.4 | | 2 parasites to 500 leukocytes |
| [4] 336 | 53.0 | 16.0 | 30.6 | 0.2 | 0.2 | | 22 small rings and gametocytes to 100 leukocytes |
| [5] 446 | 65.4 | 17.8 | 16.6 | | 0.2 | | 73 small rings and gametocytes to 100 leukocytes |
| [6] 451 | 61.4 | 33.6 | 3.0 | 1.2 | 0.8 | | None |
| 451a | 58.0 | 34.4 | 6.0 | 1.6 | | | 4 to 500 leukocytes |
| 451b | 82.6 | 12.4 | 4.8 | 0.2 | | | 18 to 500 leukocytes |

lating blood. If the number of leukocytes per cubic millimeter is known and the number of parasites to 10, 100, or 500 leukocytes is known; a proportion will determine the number of parasites per cubic millimeter of blood and so give an idea of the degree of infection.

In examining one of the slides a red cell was found in which there were two parasites; one becoming converted into a gametocyte and the other forming a rosette.

In all there are recorded sixty-eight differential counts in 55 cases: 28 cases of benign tertian malaria; 10 cases of estivo-autumnal malaria; 3 cases of quartan malaria; 11 cases of malaria in which parasites had disappeared from the peripheral blood; and 3 cases in which examinations were made before the occurrence of clinical malaria; during malarial paroxysms, and at varying periods after the paroxysms had ceased.

TABLE 2

*Estivoautumnal cases*

| NUMBER | POLYMORPHONUCLEAR PERCENTAGE | LYMPHOCYTE PERCENTAGE | LARGE MONONUCLEAR PERCENTAGE | EOSINOPHILE PERCENTAGE | BASOPHILE PERCENTAGE | MYELOCYTE PERCENTAGE | KIND OF PARASITES |
|---|---|---|---|---|---|---|---|
| [1] 0.4 | 24.2 | 33.8 | 39.8 | 1.4 | 0.6 | 0.2 | 30 small rings and crescents to 100 leukocytes |
| [1] 0.6 | 58.8 | 11.8 | 28.0 | 1.4 | | | 28 small rings and crescents to 100 leukocytes |
| [1] 0.7 | 58.0 | 30.8 | 10.8 | 0.4 | | | 5 crescents to 500 leukocytes |
| [1] 0.21 | 74.6 | 15.0 | 10.4 | | | | Crescents |
| [2] 63 | 60.2 | 11.2 | 26.6 | 1.6 | 0.4 | | 70 crescents to 100 leukocytes |
| [4] 239 | 46.0 | 20.8 | 30.4 | 1.6 | | 1.2 | 7 rings and crescents to 500 leukocytes |
| [2] 248 | 63.0 | 26.0 | 10.0 | 0.6 | | 0.4 | Large rings and crescents |
| [7] 283 | 45.8 | 30.6 | 23.4 | 0.2 | | | Small rings and crescents |
| [7] 284 | 74.8 | 13.0 | 11.8 | 0.4 | | | Crescents |
| [8] 329 | 70.4 | 14.6 | 14.8 | 0.2 | | | 43 small rings and cresents to 100 leukocytes |

TABLE 3

*Quartan cases*

| NUMBER | POLYMORPHONUCLEAR PERCENTAGE | LYMPHOCYTE PERCENTAGE | LARGE MONONUCLEAR PERCENTAGE | EOSINOPHILE PERCENTAGE | BASOPHILE PERCENTAGE | MYELOCYTE PERCENTAGE | KIND OF PARASITES |
|---|---|---|---|---|---|---|---|
| [2] 264 | 62.6 | 16.2 | 16.4 | 4.4 | | 0.4 | 59 half grown rings to 500 leukocytes |
| 264a | 67.4 | 23.0 | 4.2 | 4.8 | | 0.6 | 1 gametocyte to 50 leukocytes |
| [5] 280 | 48.2 | 34.4 | 16.0 | 1.0 | | 0.4 | Rosettes and gametocytes |
| [2] 368 | 50.6 | 27.4 | 20.2 | 1.2 | 0.4 | 0.2 | 125 medium sized rings to 500 leukocytes |

Ten per cent is accepted as the high normal percentage of large mononuclear leukocytes in the peripheral blood. On this basis there was an increase of the large mononuclear leukocytes in the peripheral blood in thirty out of forty-four counts in cases with malarial parasites in the blood; or 68.1 per cent. In cases without malarial parasites in the peripheral blood there were 7 in which there was an increase of the large mononuclears, out of twelve counts: 58.3 per cent. In the cases that were counted before malarial paroxysms were observed, during malarial paroxysms, and after the paroxysms had ceased; twelve counts were made; there was a large mononuclear increase at the time of paroxysm in two; slight in one (11.6); large in the other, (33.2 per cent). In the third case there was no increase. This patient was also suffering from sprue.

TABLE 4

*Cases with no parasites in the peripheral blood*

| NUMBER | POLYMORPHONUCLEAR PERCENTAGE | LYMPHOCYTE PERCENTAGE | LARGE MONONUCLEAR PERCENTAGE | EOSINOPHILE PERCENTAGE | BASOPHILE PERCENTAGE | MYELOCYTE PERCENTAGE | KIND OF PARASITES |
|---|---|---|---|---|---|---|---|
| [1] 0.13 | 43.8 | 47.8 | 6.6 | 1.8 | | | |
| [1] 0.14 | 45.4 | 38.6 | 15.6 | 0.4 | | | |
| [1] 0.29 | 51.0 | 41.8 | 4.6 | 2.2 | 0.4 | | |
| [1] 0.30 | 63.8 | 31.6 | 2.2 | 2.0 | 0.4 | | |
| [1] 0.31 | 45.8 | 36.4 | 16.0 | 1.8 | | | |
| [2] 76 | 47.0 | 44.0 | 7.0 | 2.0 | | | |
| [2] 108 | 50.8 | 24.0 | 19.6 | 3.2 | 1.2 | 1.2 | |
| [2] 200 | 74.4 | 12.0 | 11.4 | 2.0 | 0.2 | | |
| 200a | 70.0 | 5.8 | 19.4 | 3.6 | 1.2 | | |
| [5] 276 | 44.6 | 48.4 | 6.6 | 0.2 | 0.2 | | |
| [5] 279 | 45.6 | 9.4 | 34.6 | 9.8 | | 0.6 | |
| [4] 326 | 51.0 | 27.0 | 20.8 | 0.8 | 0.4 | | |

A large mononuclear increase, therefore, is constant in malaria neither in the acute stage of the disease nor in carriers. But if in a suspected case of malaria or of recent malaria there is an increase of the large mononuclear leukocytes, it seems reasonable to assume that the patient has or has had malaria.

TABLE 5

*Cases examined during absence of parasites: in which clinical malaria subsequently developed with parasites in the peripheral blood. All benign tertian*

| NUMBER | POLYMORPHONUCLEAR PERCENTAGE | LYMPHOCYTE PERCENTAGE | LARGE MONONUCLEAR PERCENTAGE | EOSINOPHILE PERCENTAGE | BASOPHILE PERCENTAGE | MYELOCYTE PERCENTAGE | KIND OF PARASITES |
|---|---|---|---|---|---|---|---|
| [2] 295 | 76.8 | 10.2 | 12.2 | 0.8 | | | None. Infection in Panama. |
| 295a | 57.6 | 6.6 | 33.2 | 2.0 | 0.4 | 0.2 | 69 rings to 500 leukocytes. Nineteen days later during a paroxysm |
| 295b | 74.4 | 8.8 | 16.0 | 0.2 | 0.4 | 0.2 | None. Fourteen days later; paroxysms ceased |
| [6] 741 | 69.2 | 26.2 | 2.2 | 2.2 | 0.2 | | None. Infection in the Dominican Republic |
| 741a | 72.8 | 21.2 | 4.8 | | 0.2 | 1.0 | 25 small rings and gametocytes to 100 leukocytes. Thirty-four days later during a paroxysm |
| 741b | 69.6 | 17.6 | 9.2 | 2.6 | 1.0 | | None. Five months later |
| 741c | 64.6 | 28.0 | 3.6 | 2.6 | 1.2 | | None. Four months later |
| 741d | 71.4 | 19.6 | 5.6 | 2.2 | 1.2 | | None. Ten months later |
| [6] 983 | 66.0 | 27.8 | 3.4 | 0.6 | 0.6 | 1.6 | None. Infection in Haiti |
| 983a | 68.2 | 26.4 | 4.6 | 0.6 | 0.2 | | None. Three months later, no paroxysms |
| 983b | 57.2 | 29.8 | 11.6 | 0.6 | 0.8 | | 87 medium sized rings and a few gametocytes to 100 leukocytes. Forty-four days later during a paroxysm |
| 983c | 68.4 | 24.5 | 4.6 | 1.0 | 0.6 | | None. Forty-two days later |

SUMARIO

Este artículo informa el resultado del contaje leucocítico diferencial de cincuenta y cinco casos de malaria mediante el exámen de sesenta y siete muestras de sangre obtenídas de los mismos. Se llega a la conclusión, por lo tanto, de que en malaria—ya sean casos agudos o portadores de la enfermedad—no existe un aumento constante de los mononucleares grandes. Sin embargo, si existiese un aumento de los leucocítos mononucleares grandes en casos ya sospechosos o de malaria reciente, es muy razonable asumir de que el paciente tiene o ha tenído malaria.

# SOME OBSERVATIONS ON THE EFFECT OF QUININE UPON THE GROWTH OF MALARIA PLASMODIA IN VITRO[1]

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Experiments were undertaken in 1921 to find out how quinine would affect malaria plasmodia in vitro, with the hope that it might throw some light upon its mode of action upon the plasmodia in man. Unfortunately, the work was interrupted before much definite information was obtained and it has not been resumed. The little information obtained, although not conclusive, indicates that there is a direct protoplasmic poisoning effect upon the parasites.

A concentrated (15 per cent) stock solution of quinine dihydrochloride in 0.85 per cent sodium chloride solution was prepared. The desired amount of quinine was added to the blood containing plasmodia by means of very small measuring pipettes.

The blood was obtained from a patient who had a very heavy *Plasmodium falciparum* infection and had not taken any quinine. Ten cubic centimeters of blood were drawn from the median basilic vein in the usual way, 0.5 per cent of dextrose (in 50 per cent solution) was added and the blood was defibrinated in the usual way for cultivation of malaria plasmodia. This blood containing plasmodia was used in the following three experiments:

Experiment M 49. To 2 cc. defibrinated dextrose blood containing plasmodia 0.005 cc. of the 15 per cent solution of quinine dihydrochloride was added (This corresponds to about 2 grams or 30 grains to the total volume of blood of a 150-pound man.)

Another tube of 2 cc. of the same blood was put up at the same time for a control. Both tubes were placed in the incubator and examined after five hours' incubation and again after a total of twenty-nine hours.

[1] Read at the eighteenth annual meeting of the American Society of Tropical Medicine, May 2–3, Washington, D. C.

The plasmodia in the control tube grew well in the usual way. Most of them were decidedly larger at the end of the five-hour period and some had grown out of the ring form and begun to produce pigment. By the end of the twenty-nine hour period many of them had reached full maturity and had completely segmented. It was an unusually good culture.

In the tube to which the quinine was added no growth whatever had taken place after five hours' incubation. Some of the parasites had shrunken into much smaller ball-shaped bodies in place of the usual ring forms. Most of them stained very poorly. A few stained much darker than plasmodia usually stain.

By the end of the twenty-nine-hour period little evidence of the plasmodia could be recognized. Faint shadows only could be found. They had lost their ability to take up the stain and evidently were dead.

*Experiment M 53.* Quinine was added to 2 cc. of the blood containing plasmodia as in Experiment M 49. After allowing it to stand for about twenty minutes the cells were thrown down with the centrifuge. The serum was carefully pipetted off and added to the cells obtained by centrifugalizing another tube containing the same amount of the same blood, to which no quinine had been added. This made a suspension of cells containing plasmodia in serum removed from a blood to which quinine had been added and had been allowed to become fixed or absorbed during a period of twenty minutes.

At the end of five hours most of the parasites retained their normal appearance and staining reaction. A few were shrunken and none appeared to have grown in size. There was definite difference in the appearance of these plasmodia as compared with those in the control tube.

Upon examination at the end of the twenty-nine hour incubation period, most of the parasites were pale or unstained and none showed evidence of growth, whereas those in the control tube had grown in the normal way.

This experiment indicates that some of the quinine is held in solution by the serum and that it is not all quickly taken up by the blood cells or removed from the serum. The fact that the plasmodia were not so badly injured as they were in experiment M 49 above and also in the following experiment M 54, indicates that more quinine is taken up and held by the cells than by the serum.

*Experiment M 54.* To the cells containing plasmodia in Experiment M 53 from which the serum was removed twenty minutes after the quinine was added, the serum from the untreated tube was added. After five hours' incubation the condition of the plasmodia was practically the same as was noted in Experiment M 49. After twenty-nine hours only a few shadows of plasmodia could be made out. They were dead and had not grown at all.

This experiment indicates that quinine in the blood is taken up within a period of twenty minutes by the cells or by the plasmodia to sufficient extent to prevent their growth and to finally kill the plasmodia.

These experiments were repeated as nearly as possible with two other bloods, each containing falciparum plasmodia. The results were essentially the same. In one instance, experiment M 67 corresponding to experiment M 53 above, the parasites appeared quite well after a period of four hours and looked as if they might grow. They were all dead, however, by the end of thirty hours.

## CONCLUSIONS

Perhaps no definite conclusions should be drawn from so few limited experiments. However, the results obtained show that quinine in therapeuic proportions prevents the growth of malaria plasmodia in vitro, and, in fact, kills them.

## RESÚMEN

Se acepta generalmente que la acción de la quinina en la malaria es la de un veneno protoplásmico, mediante una afinidad especial de aquella por los plasmodias de la enfermedad.

Hemos hecho ciertos experimentos con el objeto de determinar si la quinina, añadida a los cultivos de los plasmodias en cantidades correspondientes a las dosis terapéuticas humanas, obstaculiza o no su crecimiento o si los destruye.

A una cantidad de sangre que contenia *P. falciparum* le fué añadida una solución concentrada de di-hidroclorido de quinina y puesta seguida en la incubadora. No sólo no se desarrollaron en lo más mínimo—sino que cinco horas más tarde todas habían muerto. Aquellas contenidas en el tubo de gobierno se desarrollaron; muchas llegando a su madurez dentro de un período de veintinueve horas.

Otros experimentos nos dieron a saber que, veinte minutos despúes de haber sido añadida la quinina a la sangre, ambos, células y suero aún contenían suficiente cantidad de quinina para prevenir el desarrollo de los plasmodias.

Los experimentos fueron repetidos dos veces y los resultados fueron siempre idénticos.

La información obtenida prueba lo correcto de la opinión generalmente aceptada que la quinina actúa como veneno protoplásmico directo con afinidad especial para los plasmodias de la malaria.

# CONTRIBUTIONS TO THE BACTERIOLOGY OF LEPROSY[1]

## I. THE DIPHTHEROID IN LEPROSY

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The presumptive causal organism of leprosy, the acid-fast *Bacillus leprae*, was discovered in leprous lesions by Hansen in 1871. Although subsequently numerous attempts have been made to cultivate this organism and repeated claims of success have been made, bacteriologists are at the present time extremely skeptical that *Bacillus leprae* has ever been grown on artificial media. If this skepticism be justified, no other bacterial organism has so long resisted all attempts at artificial cultivation.

Nevertheless, competent bacteriologists have cultivated repeatedly certain more or less acid-fast bacteria from the lesions and organs of lepers. If we exclude organisms that have been encountered only occasionally in the cultures, of which many are obviously contaminations, the bacteria that have been cultivated more or less constantly from lepers are of two types, namely: First, partly acid-fast diphtheroids, first cultivated by Bordoni-Uffreduzzi (1), in 1887; and second, chromogenic acid-fast bacilli, first cultivated by Clegg (2), in 1909, in symbiosis with amoebae and cholera vibrios. This paper is concerned exclusively with the partly acid-fast diphtheroid organisms.

The literature records the following cultivations of these partly acid-fast diphtheroids from the lesions and organs of lepers: Bordoni-Uffreduzzi (1), in 1887, from the bone marrow of a leper, on glycerinated peptone blood serum; Babes (3), in 1889, from various organs of twelve lepers, on glycerinated blood serum and plain

[1] Read at the eighteenth annual meeting of the American Society of Tropical Medicine, May 2 and 3, 1922, Washington, D. C.

agar; Gianturco (4), in 1889, from a non-ulcerating cutaneous nodule of a leper, on glycerine agar; E. Levy (5), in 1897, from a non-ulcerating leprous nodule, on glycerine agar streaked with human blood; Spronck (6), in 1898, from a skin tubercle and from the bone marrow of two cases of leprosy, on neutral glycerinated potato medium; Czaplewsky (7), in 1898, from nasal secretions and discharges from a throat ulcer of a case of leprosy, on inspissated glycerinated sheep's blood serum; Shibayama (8), in 1899; Teich (9), in 1899, from nasal secretions, incised and excised nodules of five cases of leprosy, on glycerine agar streaked with human blood; Baranikow (10) in 1899, from early nodules of two cases of leprosy, on media made from human brain and from transudates; Kedrowski (11), in 1901, from incised follicles and excised nodules of three cases of leprosy, on placental extract agar; F. Levy (12), in 1902, four times in glycerine veal broth and on slabs of red beet; Klitin (13), in 1905, from excised nodules of four cases of leprosy, on various media; Bayon (14), in 1911, from an excised nodule of a leper, on placental extract agar and on horse serum maltose agar to which was added ground up smegma bacilli; Williams (15), in 1911, from non-ulcerating nodules of an unstated number of lepers in Persia and India, on "lemco" glucose agar; Ophüls (quoted by Wolbach and Honeij (16); and Wolbach and Honeij (17), in 1914, from an excised epitrochlear lymph gland of a case of leprosy, on ascitic fluid dextrose agar.

The literature records that, from 1887 to 1914, at least 16 bacteriologists cultivated partly acid-fast diphtheroids 46 + times from various tissues and organs of 40 + cases of leprosy in different parts of the world. How many others have cultivated such organisms and discarded them as secondary invaders or as contaminations, because they did not conform completely in morphology and staining with *Bacillus leprae* in the tissues, will probably never be known. Since 1914, owing to the doubts that have arisen over the identity of these cultural organisms, interest has declined and the literature contains no further references to attempted cultivations of *Bacillus leprae.*

It is admittedly difficult to identify with certainty bacteria cultivated by the earlier bacteriologists, owing to imperfect descriptions of these organisms; but the diphtheroid cultivable from leprous lesions possesses cultural, morphological and tinctorial peculiarities which are so striking and characteristic that they can not readily be overlooked or confused with those of other diphtheroids. These characteristics are briefly: Gray colonies with an elevated, whitish center and a serrated border from which secondary colonies may arise; large size and extreme pleomorphism of the bacilli; the formation of arthrospore-like bodies; and acid-fast staining of granules, segments or whole organisms. An examination of the descriptions by the authors quoted, made in the light of these peculiar characteristics and of my own experience with cultivations from leprous lesions, make it reasonably certain that most, if not all, of them have isolated one and the same diphtheroid organism from leprosy.

The first purpose of my investigation was to substantitate, if possible, the more or less constant cultivability of a pleomorphic, partly acid-fast diphtheroid from leprous lesions. The material for this investigation was obtained from lepers confined in the San Francisco Isolation Hospital. These lepers were under treatment with intramuscular injections of esters of chaulmoogric acids. As difficulty was constantly experienced in persuading these patients to continue the intramuscular injections, it was not considered advisable to further antagonize them by repeated biopsies. Consequently, the material used for this cultural study was obtained chiefly from nasal ulcerations and occasionally from open leprous lesions of the skin. In a few cases aseptic incision of non-ulcerating leprous nodules was performed.

The routine procedure with the contaminated leprous material, collected on sterile swabs, was to add a little sterile saline to the tubes, rub up the material on the swabs in the saline and plate this saline suspension in three dilutions on glycerinated veal broth agar. These plate cultures were incubated at 37°C. With experience, it was possible to identify with a hand lens the colonies of bacteria ordinarily developing in these plate cultures. The suspected diphtheroid colonies were examined in stained smears unter the microscope and the diphtheroid colonies transplanted on glycerine agar slants for further study. The material taken aseptically from non-ulcerating nodules was inoculated directly on slants of various media.

In 312 cultivations from the nose and open skin lesions of 16 lepers, four types of diphtheroids have been encountered, which can be distinguished from one another by colony characters, carbohydrate fermentations, morphology and staining peculiarities. The distribution of these four types in the last 164 cultivations, with reference to the number of cultivations from each patient, the type and progress of the disease and the presence or absence of acid-fast *Bacillus leprae* in the nasal secretions, is shown in table 1. The first 148 cultivations are not included in this table, because the plate cultures were not incubated sufficiently long to secure the development of visible colonies of diphtheroid IV.

TABLE 1

*Types of diphtheroids cultivated from nasal secretions of lepers*

| PATIENT | TYPE OF DISEASE | PROGRESS OF DISEASE | ACID-FAST BACILLI IN NASAL SECRETION | TOTAL NUMBER OF CULTIVATIONS | DIPHTHEROID TYPE I ISOLATED TIMES | DIPHTHEROID TYPE II ISOLATED TIMES | DIPHTHEROID TYPE III ISOLATED TIMES | DIPHTHEROID TYPE IV ISOLATED TIMES |
|---|---|---|---|---|---|---|---|---|
| Abdul | Tubercular | Advanced | + | 6 | 3 | 2 | 2 | 3 |
| Anman | Tubercular | Advanced | + | 20 | — | 12 | — | 3 |
| Bemat | Tubercular | Advanced | + | 15 | 1 | 7 | 5 | 3 |
| Dan | Tubercular | Advanced | + | 13 | — | 6 | — | 5 |
| Fong | Anesthetic | Moderate | 0 | 7 | 2 | — | — | — |
| Frank | Tubercular | Moderate | ± | 11 | 2 | 4 | — | — |
| Garcia | Macular, anesthetic | Early | 0 | 3 | 1 | — | — | — |
| George | Tubercular | Moderate | ± | 2 | — | 1 | — | — |
| Kim | Mixed | Moderate | ± | 18 | 1 | 3 | — | — |
| Luey | Mixed | Moderate | ± | 8 | 5 | 5 | — | — |
| Lum | Anesthetic | Moderate | 0 | 8 | 3 | 1 | — | — |
| Silva | Tubercular | Advanced | + | 14 | 6 | 2 | 2 | 2 |
| Tony | Tubercular | Advanced | + | 18 | 1 | 7 | 2 | 10 |
| Wong | Tubercular | Moderate | 0 | 6 | — | 2 | — | — |
| Yat | Tubercular | Moderate | ± | 15 | 1 | 9 | 1 | — |
| Total | | | | 164 | 26 | 61 | 12 | 26 |

The essential characters of these four types of diphtheroids are as follows. Cultural characteristics not noted are those common to the diphtheroid group.

### DIPHTHEROID I

Colonies on glycerine agar well developed after forty-eight hours' incubation; small, moist, circular, elevated with a central boss; light gray and translucent. None of the carbohydrates are fermented. Bacilli rather short, of medium thickness, cylindrical or with tapering ends, occasionally slightly clubbed. Organisms stain uniformly or with a single unstained cross-bar; Gram-positive; non-acid-fast. This diphtheroid has been cultivated from the nasal secretions of lepers independently of the type or progress of the disease and of the presence or absence of *Bacillus leprae* in the secretions. The characters of this diphtheroid identify it as the well known pseudo-diphtheria bacillus of Hoffmann (18), or *Corynebacterium pseudo-diphthericum* Eberson (19), and a common habitant of the throat and nasal passages of man in health and disease.

### DIPHTHEROID II

Colonies on glycerine agar well developed after forty-eight hours' incubation; thin, flat, moist, translucent, dirty gray in color. Dextrose, lactose, saccharose and maltose fermented vigorously, glycerine slightly, with the production of acid but no gas. Bacilli medium length to long, slender, cylindrical, swollen in the middle or clubbed. Organisms stain segmentally or with polar granules; Gram positive; non-acid-fast, but many of the bacilli are of a polychromatic (reddish-purple) color after staining by the acid-fast method. This diphtheroid was the one most frequently encountered in the cultures from the nose and open skin lesions of lepers. Like diphtheroid I, it was cultivated from both early and advanced cases of all types of leprosy and independently of the present of acid-fast bacilli in the secretions, although it appears to have a predilection for ulcerative lesions.

### DIPHTHEROID III

Colonies on glycerine agar more rapidly growing, larger and more elevated than diphtheroid II; convex, cream to pale salmon colored. Carbohydrate fermentations are the same as diphtheroid II, except that lactose is fermented feebly. Morphology and staining similar to diphtheroid II. This diphtheroid differs but slightly from type II, except in the very distinct colony characteristics. Diphtheroid III has been cultivated from the nasal secretions of only a few cases of leprosy.

Diphtheroid II and III do not correspond to any hitherto adequately described species and are not included in Eberson's (19) classification of the diphtheroid group. Morphologically and in staining both types are indistinguishable from the diphtheria bacillus, but differ from it in colony characters, carbohydrate fermentations and pathogenicity. They are perhaps identical with some of the diphtheria-like organisms inadequately described in the recent extensive literature on the bacteriology of war wounds. I have cultivated diphtheroid II from non-leprous chronic ulcers.

### DIPHTHEROID IV

Colonies on glycerine agar, recognizable in the first cultural generation only on the fourth day of incubation, or later; variable within certain limits; typically of medium size, gray, with an elevated, whitish center and an irregular serrated or lobulated border from which secondary colonies may arise. Dextrose and maltose fermented vigorously, saccharose and glycerine feebly and sometimes evanescently, with the production of acid but no gas. Bacilli extremely pleomorphic; characteristically large, but size variable; coccoid to long, occasionally streptothricoid; clubbed or irregularly swollen; segmented, often appearing as short chains of coccoid elements of variable size; some of the segments may become much swollen, stain intensely and become detached as arthrospore-like bodies. Organisms stain with ordinary aniline dyes segmentally and show metachromatic granules; Gram positive; partly and variably acid-fast, especially in the first cultural generation. Acid-fast staining is frequently restricted to certain segments, large spore-like granules or to the clubbed ends, and may be lost in subsequent transplants of the organism.

This diphtheroid has been cultivated from the nose of only advanced cases of tubercular or mixed leprosy, showing many acid-fast *Bacillus leprae* in the nasal secretions. Cultures from early cases and of the anesthetic type of leprosy, of which the nasal secretions contained no acid-fast bacilli, have been consistently negative. Moreover, patients, who had been long under treatment with the esters of chaulmoogric acids with improvement of symptoms and diminution or total disappearance of acid-fast bacilli from their nasal secretions, were either negative for diphtheroid IV or this diphtheroid could be cultivated only during the earlier stages of the treatment. In addition to the 26 isolations of this diphtheroid from the comtaminated material from the nasal secretions of lepers, it was also cultivated in pure culture once in three attempts, from material obtained by asceptic incision of leprous nodules.

Diphtheroid IV cannot be identified with any of the adequately described diphtheroids cultivated by Frankel and Much (20), Billings and Rosenow (21), Negri and Mieremet (22), Buntin and Yates (23), Hine (24), Bloomfield (25), Fox (26), Torry (27), Neubauer (28) and others in their extended studies of the bacterial flora of lymphatic glands and other tissues of man in health and diseases other than leprosy. On the other hand, this diphtheroid does possess the characteristic colonies, extreme pleomorphism and partial acid-fastness of the diphtheroid that has been cultivated repeatedly since Bordoni-Uffreduzzi (1887) to Wolbach and Honeij (1914) from leprous lesions.

Having substantiated the claims of previous investigators that a pleomorphic, partly acid-fast diphtheroid can be cultivated repeatedly from open as well as non-ulcerating leprous lesions, I have next directed my efforts to discover a possible saprophytic source of this diphtheroid, as bearing on its parasitism and etiologic relation to leprosy. Passing over the unproductive cultural investigations of normal nasal secretions, chronic ulcerations and external sources, I would direct attention to the bacteriology of smegma praeputii.

Microscopic examination of a smear preparation of smegmal secretion, stained with carbol fuchsin, decolorized with acid and counterstained with methylene blue, shows two types of microorganisms, staphylococci and bacilli. The bacilli, however, present the greatest diversity of form, including coccoids, rods of various length and thickness, diphtheroids, short filaments and branching forms, giving the impression of a very diverse bacilliform flora. This impression is further emphasized by the fact that some of the bacillary forms are acid-fast and retain the carbol fuchsin, while others are stained by the methylene blue. The acid-fast forms are predominantly the more slender rods of uniform thickness, but careful search will disclose an occasional coccoid, diphtheroid or streptothricoid form that is partly or wholly acid-fast.

If some of this smegmal secretion be cultured in proper dilutions on glycerine agar plates, it will be found that from this apparently diverse bacterial flora only colonies of staphylococci and of a diphtheroid develop on the plates. The diphtheroid colonies are slow growing, gray, with an elevated, whitish center and serrated border. The diphtheroids are large and extremely pleomorphic, much segmented, develop in old cultures arthrospore-like bodies and frequently show acid-fast granules or segments. They ferment dextrose, saccharose, maltose and glycerine.

What is the relation of this cultivable diphtheroid to the apparently diverse bacilliform flora of smegma praeputii? The most obvious conclusion might be that this diphtheroid is the only one among several species that is able to grow on glycerine agar. On the contrary, a consideration of the transitional stages in morphology and acid-fastness between the different bacillary types in smegma, the cultivability of this diphtheroid from smegmal secretions after treatment with Petroff's sodium hydroxid solution or antiformin, and the fact, that it can become completely acid-fast on a special medium, as will be discussed in a succeeding paper, leads me to believe that this diphtheroid is the cultural stage of a very pleomorphic, facultative acid-fast bacillus, the so-called *Bacillus smegmatis*.

A review of the literature on the bacteriology of smegma praeputii supports this conclusion. Czaplewski (29), Laser (30), Frankel (31) and Neufeld (32) were able to cultivate only one kind of bacillus from smegma. Although the acid-fastness of this bacillus was not lost in all cases in the first cultural generation, it quickly and almost completely disappeared when the cultures were transplanted to fresh media. Weber (33) observed that cultures of the smegma bacillus retained their acid-fastness on a culture medium containing lanolin. Gillert and Smitt (34) cultivated a diphtheroid from smegma, after antiformin treatment, which was in no case acid-fast. Hartmann (35) was able to cultivate only a pleomorphic diphtheroid from smegma praeputii treated with antiformin. This diphtheroid was not acid-fast; but, if some fatty material such as lanolin was spread over the slide and slightly warmed before making the preparation, the greater proportion of the bacilli stained acid-fast. Hartmann concludes that this pleomorphic diphtheroid, resistant to antiformin, is probably *Bacillus smegmatis;* and that the acid-fastness of this organism is not an inherent property, but is the result of the protective action against acids of the coating of fatty smegmal secretions.

Whether or not we accept the conclusion that the diphtheroid cultivable from smegma praeputii is *Bacillus smegmatis* is immaterial for my purpose, since in either event the essential fact remains that this diphtheroid from smegma possesses cultural, morphological, biochemical and tinctorial characteristics which are apparently identical with those of the diphtheroid cultivable from the lesions and organs of lepers and considered by some authors as the cultural form of *Bacillus leprae.*

## SUMMARY

1. The pleomorphic, partly acid-fast diphtheroid of Bordoni-Uffreduzzi and other authors can be cultivated more or less constantly from nasal and other open lesions of lepers, as well as from non-ulcerating leprous lesions.

2. This diphtheroid differs in its large size, extreme pleomorphism, peculiar colonies, carbohydrate fermentations and

partial acid-fastness from all diphtheroids from other sources adequately described in the literature.

3. A search for the possible saprophytíc source of this diphtheroid from leprous lesions has disclosed that it is apparently identical with a diphtheroid cultivable from smegma praeputii, which is probably a cultural form of the pleomorphic and facultative acid-fast *Bacillus smegmatis.*

SUMARIO

1. El difteroide pleomórfico y parcialmente ácido-resistente descríto por Bordoni-Uffreduzzi y otros autores, puede cultivarse, con más o menos constancia, de las lesiones nasales y abiertas de los leprosos. Asi mismo de lesiones sin ulcerar.

2. Este difteroide difiere de los otros difteroides de diversos orígenes ya descritos en la literatura médica, por su tamaño grande, pleomorfismo, peculiaridad en su formación de colonias, fermentación de carbohidratos y ácido-resistencia parcial.

3. Una indagación del orígen posiblemente saprofítico de este difteroide de lesiones leprosas, nos hace creer que es aparentemente idéntico con el difteroide cultivable que se obtiene del smegma preputii. Este último es probablemente una forma cultural del pleomórfico y ácido-resistente-facultativo *Bacillus smegmatis.*

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# BERIBERI IN THE GARRISON AT SAN JUAN, PORTO RICO[1]

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The first indigenous cases of beriberi in the history of Porto Rico seem to have proceeded from United States draft troops recruited from this Island in 1918. At no time, even to the present, has this diagnosis figured in civil mortality records, nor has it been made, apparently, by any physician of the island. In fact, when the first cases were reported by Dr. Pedro Gutiérrez of the Institute of Tropical Medicine, then a captain in the medical corps for war service, the Medical Association of Porto Rico was united in sustaining that it had never before been placed in evidence as a cause of morbidity and some members expressed the opinion that the polyneuritis described might have been due to impure alcoholic intoxicants.

Only upon three occasions in the history of medicine here had beriberi been a topic for discussion: Once when Dr. W. W. King and the writer in 1902 reported a severe case of uncinarial anemia simulating beriberi but rapidly cured by thymol; on another occasion, in 1906 when some dozen cases of oriental beriberi in Philippine sailors, taken from a ship en route to the East and treated in the military hospital, were exhibited by the post medical officer to the civil profession in San Juan; and once when the disease appeared for the first time suddenly in the early winter of 1918 in Camp Las Casas where draft troops were in training and a board of medical officers, of which Dr. Gutiérrez was a member, was appointed to examine into the cause of the epidemic of polyneuritis. The following is a condensed statement of facts in that report:

[1] Read by title at the eighteenth annual meeting of the American Society of Tropical Medicine, May 2 and 3, Washington, D. C.

There were 60 cases of polyneuritis investigated. The first manifestations of the diseases were numbness in the legs, beginning over the shins, then extending to the calves, and finally, over the thighs, to the lower abdomen. This numbness at times affected the upper extremities, beginning in the finger tips and extending even to the arms. Numbness was a symptom in 47 cases. Pain with tenderness was first noticed in the calves in practically every case. The peroneal group of muscles was involved next in frequency and in order. Of the muscles of the thigh the quadriceps were first and most severely affected, the hamstring muscles next; the adductor group last. Intense pain was caused by pressure over these affected muscles but the large nerve trunks revealed no great tenderness.

Only one-third of the patients had pain in the hands and in these only the thenar eminences were markedly tender. The flexor group in the forearms was the most sensitive to pressure, when the forearm was involved.

Slight edema was noted in one-third of the cases, as a rule noticed in the ankles. There were two cases of moderate anasarca which disappeared, as did edema of the ankles, on rest in bed.

The urine in these cases was negative for albumin.

In over half the cases areas of partial anesthesia were demonstrated. This was most frequently made out over the shins but was also found in other parts of the leg. The feet, abdomen and thighs were next affected in order named, with at times a few such areas in hands and forearms. Hyperesthesia was found in nine cases.

The digestive tract for the most part escaped without indications of involvement. Some form of cardiac involvement was noted in only 12 cases and consisted chiefly of tachycardia and enlargement of the heart.

The patellar reflexes were absent in 26 cases and diminished in 26 more. Romberg's sign was present in 46 cases. Korsabow's syndrome was absent.

Two patients were admitted with acute dyspnea. They presented anasarca with a rapidly progressive pulmonary edema, tachycardia with feeble pulse, and dilatation of the heart. Their extremities were cold and they were cyanotic. Apnea and death supervened in less than twenty-four hours after admission.

In only 22 of the 60 cases was the neuritis confined to the legs; in 15 the thighs and abdomen were involved. Ataxia was noted in 42; atrophy of muscles affected in 6.

In 9 the symptoms developed a week before admission to hospital; in 17, two weeks before; in 22, three weeks before; in the rest up to 60 days before.

### TREATMENT

"In view of the fact that the majority of cases began to improve immediately when placed upon a high protein diet . . . . it is recommended that a highly nitrogenous diet be instituted."

Gutiérrez reported: (1) that the average hemoglobin was 72.6 per cent; (2) in 12 cases, a percentage of 38.7 per cent small mononuclears; (3) absence of albumin in the urine of 39 (but of these, 39 per cent had hyaline and 15 per cent granular casts); (4) in 90.5 per cent ova of *Necator americanus* were found; (5) in 13, swabs from the throat revealed nothing of note; (6) in one case the spinal fluid showed 3 leucocytes and 14 erythrocytes.

There was one autopsy as follows:

Body well developed and in rigor mortis. Edema of lower extremities. Face cyanotic. Edema of lungs and moderate pleural effusion. Pericardium contained about 2 ounces of fluid. Heart markedly dilated. Liver slightly enlarged but apparently normal. Pancreas normal as were stomach and intestines. Spleen slightly diminished in size. Kidneys, slightly congested. Brain and cord, no macroscopic changes. Cerebrospinal fluid clear. Cultures from heart and lungs at autopsy negative.

With regard to the diet of the draft soldiers during the war the following facts were elicited in an investigation practiced in four companies.

1. Polished rice was a staple article of diet during September, October and November, 1918.

2. It was served on an average of twice a day in that period.

3. There was a deficiency in fresh vegetables owing to local conditions.

4. The only vegetables served in large quantities were potatoes and the different varieties of beans.

5. A large amount of canned meats and vegetables were used, particularly by the company which yielded the majority of the cases.

On questioning of the patients suffering from this polyneuritis it was discovered that those affected were rice eaters and consumed the full rice component daily. Most of the men did not eat the meat component and those who did ate sparingly of it.

On calculation from a mass of data in that report I have deduced that 1000 men in the camp consumed, for September, October and November, 1918, on an average per man per day:

| | *pounds* | | *pounds* | | *pounds* |
|---|---|---|---|---|---|
| Rice | 0.45 | Fresh meat | 0.64 | Yams | 0.03 |
| Red beans | 0.092 | Potatoes | 0.3 | Sweet potatoes | 0.04 |
| White beans | 0.069 | Oranges | 0.1 | Sago | 0.35 |
| Peas | 0.06 | Bananas | 0.07 | Alligator pears | 0.03 |
| Spanish beans | 0.067 | Onions | 0.03 | Yautia (tuber) | 0.04 |

While Dr. Gutiérrez considered these cases to be due to some form of beriberi, the finding of the board limits itself to recommending measures to control the extension of a polyneuritis due to nutritional errors but fails to conclude specifically that this polyneuritis was beriberi.

Thus far the polyneuritis prevailing among the troops had not been officially designated beriberi.

## HISTORY OF THE DISEASE IN THE GARRISON AT SAN JUAN

Upon discharge of draft troops and reëstablishment of the regimental post of San Juan in 1919, the incoming post medical officer found 9 cases of polyneuritis in the station hospital which had remained over from the cases occurring in the training camp. From that time to July, 1921, he took up 26 new cases from the garrison. One of these men died in 1919 in a crisis marked by tachycardia and apnea. From the very beginning of his incumbency the post medical officer recognized in official communications that a large number of the sick of the post were incapacitated due to an ill-balanced ration and certain errors in preparing food, classifying these sick in two groups.

1. Those suffering from diarrhea and enteritis.

2. Cases of polyneuritis "due to a diet deficient in active nutrient principles (i.e., vitamines)."

He recommended the use of more meat, fruit and fresh vegetables and the substitution of undermilled for highly milled rice. He called attention to the actual messing conditions prevailing in the garrison at that time (November, 1919) as follows:

| COMPANY | RICE, UNPOLISHED; AVERAGE PER DAY IN OUNCES | FRESH BEEF, PORK AND CHICKEN; AVERAGE PER DAY IN OUNCES |
|---|---|---|
| A | 6.24 | 5.28 |
| B | 7.04 | 4.64 |
| C | 6.59 | 8.48 |
| D | 7.84 | 5.92 |
| E | 5.92 | 5.76 |
| F | 6.24 | 5.28 |
| G | 5.76 | 6.08 |
| H | 5.28 | 4.80 |

The principal comments upon the letter of the post medical officer, which was opened to company commanders for discussion, were as follows:

1. The period for which the post medical officer had made his calculation of rice and beef consumed was not representative of the actual average conditions.

2. Rice is a favorite staple and it is consumed in larger quantities than any other food by Porto Rican troops. Its reduction would cause serious dissatisfaction among them.

3. Meats and fats are not so needful in the tropics and rice should be allowed "to the maximum permitted by regulations as it is easily digested, never causes gastrointestinal disorder, has a high food value and is extraordinarily well adapted to climatic condition" in preservation, handling, etc. "From 60 to 80 per cent of the hard agricultural labor done in this country during the last century has been energized by rice."

4. Rice is the only article always on hand. Unavoidable delays in transportation of beef from the States would cause temporary shortage in the ration if not met by the issue of an extra amount of rice, for the cost of eggs, fruit and vegetables in sufficient amounts to meet this shortage would exceed the 25 per cent allowance for exceptional articles.

No definite conclusion or action was really possible without a more definite diagnosis, as that of "polyneuritis" still prevailed. Not only was there a very reasonable belief among civilian physicians in San Juan that the disease might be due to some intoxication from alcoholic impurity, or mineral poison, but the soldiers themselves had formed a theory of their own, i.e., that this paralysis was due to walking on cold cement floors, in bare feet, exposure to wet and fatigue in marches and sudden chilling. They were not at all worried at the fears expressed by some officers that it might be due to infected barracks, even when certain supposed foci were white washed and painted and the men were put out on the parade ground in tents. They had talked it all over among themselves and were calm and even lofty in the confidence they had placed in their conclusion. Above all was the tradition of the entire Porto Rican people, that the ration of the American soldier, alone, converted the pale "jibaro," or countryman, into a fine looking, husky male of whom they were justly proud.

The real reason for the hesitancy of all medical officers, who had previously come in contact with this polyneuritis, in designating it beriberi was that treatment by Vedder's pericarp, withdrawal of rice, feeding with fresh vegetables, yeast vitamines and the employment of all therapeutic and dietetic agencies known to be successful in treating beriberi were generally a failure, or, at best, only partially successful in treating this polyneuritis of Porto Rico.

Before making radical changes in the ration here and in order to prevent so many discharges for disability on account of polyneuritis, the Commanding General, Second Corps area, ordered an investigation and I was designated upon recommendation of my chief for this duty in July, 1921. The situation at that time, July 5, 1921, was as follows:

Twenty-four men throughout a period of two years had been discharged for disability on account of polyneuritis, not to speak of pensions for those among the draft soldiers of 1918, and the majority were still reported to be disabled for any active labor.

Ten were hospitalized with polyneuritis and most of them, all fine looking young soldiers, were hardly able to walk.

Before I could lay out a plan for my investigation I was suddenly called to autopsy one of them who had died with tachycardia and apnea.

### THE DIETARY OF TROOPS DURING THE PRESENCE OF BERIBERI IN PORTO RICO

From only companies A and D and the Howitzer Company, was it possibly to secure accurate menus with weighed quantities of all food from June 1 to June 10, 1921, inclusive. The quantities in these menus were consolidated and grouped as per following table. The average number of men fed per day in each company was: Company A, 102; Company D, 72.9; Howitzer Company, 92.7.

The Vitamine Manual, by Professor Walter H. Eddy, (Williams and Wilkins Company, 1921, Baltimore) gives the following relative values in B-substances (American standards) based in a classification with a maximum of ++++:

| | |
|---|---|
| Beef and pork | 0 |
| Eggs | ++ |
| Potatoes | +++ |
| Onions | +++ |
| Cabbage | +++ |
| Sweet potatoes | ++ |
| Bananas | + |
| Grape fruit | +++ |
| Oranges | +++ |
| Beans | +++ |
| Bread, white | + (?) |
| Oats | +++ |
| Canned milk | + |
| Cheese | + |

In conformity with this estimate, and excerpting from the actual diets for the period June 1 to June 10, inclusive, for 3 typical

| | Pounds per man per day | | | |
|---|---|---|---|---|
| | Company A | Company D | Howitzer Company | Average |
| *Fresh animal food:* | | | | |
| Meat | 0.53 | 0.59 | 0.36 | 0.493 |
| Eggs | 0.027 | 0.011 | 0.02 | 0.0193 |
| Pork | | 0.055 | 0.1 | 0.077 |
| Total | | | | 0.5893 |
| *Fresh vegetables:* | | | | |
| Potatoes | 0.73 | 0.9 | 1.25 | 0.96 |
| Plantains | 0.002 | 0.027 | 0.11 | 0.045 |
| Gandules | 0.021 | | | 0.021 |
| Yautia | 0.024 | 0.05 | | 0.037 |
| Onions | 0.05 | 0.1 | 0.06 | 0.07 |
| Cabbage | | | 0.016 | 0.016 |
| Pumpkins | | 0.031 | | 0.031 |
| Sweet potatoes | 0.01 | 0.27 | 0.08 | 0.15 |
| Total | | | | 1.33 |
| *Fruit, fresh:* | | | | |
| Pineapples | | 0.05 | | 0.05 |
| Oranges | 0.05 | | | 0.05 |
| Grape fruit | 0.06 | | 0.51 | 0.285 |
| Bananas | 0.08 | 0.03 | 0.14 | 0.08 |
| Total | | | | 0.465 |
| *Legumes:* | | | | |
| White beans | 0.064 | 0.1 | | 0.082 |
| Red beans | 0.096 | 0.1 | 0.05 | 0.079 |
| Garbanzos | 0.08 | | 0.035 | 0.057 |
| Total | | | | 0.218 |
| *Cereals:* | | | | |
| Rice | 0.42 | 0.4 | 0.21 | 0.343 |
| Bread | 0.56 | 0.75 | 0.8 | 0.703 |
| Macaroni | 0.01 | 0.02 | 0.035 | 0.0216 |
| Vermicelli | | 0.02 | | |
| Oat meal | 0.004 | 0.0027 | 0.014 | 0.0033 |
| Corn flakes | 0.014 | 0.01 | | 0.012 |
| Flour | 0.004 | 0.007 | 0.09 | 0.005 |
| Corn meal | | 0.015 | 0.03 | 0.022 |
| Cream of wheat | | | 0.016 | 0.016 |
| Total | | | | 1.1259 |

| | POUNDS PER MAN PER DAY | | | |
|---|---|---|---|---|
| | Company A | Company D | Howitzer Company | Average |
| *Fats:* | | | | |
| Olive oil | 0.004 | 0.004 | 0.012 | 0.0066 |
| Butter | 0.035 | 0.027 | 0.027 | 0.0293 |
| Lard | 0.12 | 0.06 | 0.071 | 0.0836 |
| Total | | | | 0.1195 |
| *Sweets:* | | | | |
| Sugar | 0.2 | 0.23 | 0.31 | 0.246 |
| Jam | 0.011 | | | 0.011 |
| Syrup | 0.004 | 0.0015 | | 0.0027 |
| Ice cream | 0.022 | 0.0055 | 0.005 | 0.0108 |
| Total | | | | 0.2705 |
| *Preserved animal food:* | | | | |
| Canned milk | 0.14 | 0.1 | 0.15 | 0.13 |
| Canned beef | 0.04 | 0.03 | 0.025 | 0.0316 |
| Canned salmon | 0.021 | | 0.06 | 0.0405 |
| Ham | 0.033 | 0.004 | 0.02 | 0.019 |
| Sausage | 0.008 | | 0.03 | 0.019 |
| Codfish | 0.04 | 0.03 | 0.03 | 0.033 |
| Bacon | 0.046 | 0.027 | 0.033 | 0.035 |
| Chipped beef | | | 0.03 | 0.03 |
| Cheese | 0.002 | | 0.004 | 0.003 |
| Total | | | | 0.3411 |
| *Canned fruits and vegetables:* | | | | |
| Tomatoes | 0.051 | 0.077 | 0.08 | 0.0693 |
| Peas | 0.013 | 0.087 | | 0.05 |
| String beans | | | 0.025 | 0.025 |
| Sweet corn | | 0.04 | | 0.04 |
| Peaches | 0.011 | 0.01 | | 0.01 |
| Cherries | | 0.01 | 0.02 | 0.015 |
| Total | | | | 0.2093 |
| *Dried fruits:* | | | | |
| Raisins | 0.002 | 0.004 | 0.004 | 0.003 |
| Apples | | 0.003 | 0.04 | 0.0215 |
| Prunes | | 0.0135 | | 0.0135 |
| Total | | | | 0.086 |
| *Beverages:* | | | | |
| Coffee | 0.1 | 0.07 | 0.09 | 0.124 |

companies, we have per man per day, 0.961 pound of food containing +anti-neuritic vitamine (bread 0.703, bananas 0.08, plantains 0.045, canned milk 0.13, cheese 0.003); 0.1693 pound containing ++ (eggs 0.0193, sweet potatoes 0.15); 1.7413 pounds containing +++ (all of the fresh vegetables, excepting plantains and sweet potatoes, all of the fresh fruits save bananas, and all the legumes and oatmeal).

Thus of a total amount of 4.7926 pounds of food per man per day, there is, roughly, 25 per cent with a + and 30 per cent with a +++ content of B-substances or anti-neuritic vitamines. Due allowance must, of course, be made for waste in preparation, etc., but if this were even 25 per cent the proportion would remain the same.

To check on the preceding tables, I requested that as full a statement as possible be secured from companies A, B, C, E, F and C as to the amount of food issued by the commissary in the period January 1, to April 30, 1921.

The following is a consolidated statement therefrom:

| | POUNDS PER MAN DAILY | | | | | |
|---|---|---|---|---|---|---|
| | Company A | Company B | Company C | Company E | Company F | Company G |
| Rice | 0.5 | 0.5 | 0.51 | 0.45 | 0.54 | 0.41 |
| Beans | 0.09 | 0.16 | 0.13 | 0.09 | 0.08 | 0.08 |
| Potatoes | 0.73 | 0.63 | 0.72 | 0.58 | 0.46 | 0.63 |
| Onions | 0.09 | 0.09 | 0.12 | 0.14 | 0.13 | 0.12 |
| Fresh meat | 0.35 | 0.27 | 0.68 | 0.35 | 0.37 | 0.35 |

The following amounts of fresh vegetables and fruits were consumed in January and April, 1920, by these same companies. The amounts are only approximate:

| | POUNDS PER MAN DAILY | | | | | |
|---|---|---|---|---|---|---|
| | Company A | Company B | Company C | Company E | Company F | Company G |
| Plantains | 0.10 | 0.035 | 0.15 | 0.17 | 0.17 | 0.14 |
| Bananas | 0.048 | 0.0 | 0.036 | 0.065 | 0.046 | 0.078 |
| Oranges, grape fruit, etc. | 0.25 | 0.37 | 0.15 | 0.23 | 0.23 | 0.15 |
| Fresh vegetables | 0.21 | 0.061 | 0.355 | 0.15 | 0.22 | 0.20 |
| | 0.608 | 0.466 | 0.691 | 0.615 | 0.666 | 0.568 |

Thus, comparing the menus in June with the ration in January–April, we find a daily consumption in pounds per man as follows:

| | AVERAGE PER MAN PER DAY IN JUNE, 3 COMPANIES | AVERAGE PER MAN PER DAY JANUARY–APRIL, 5 COMPANIES |
|---|---|---|
| | *pounds* | *pounds* |
| Rice | 0.343 | 0.48 |
| Beans | 0.218 | 0.105 |
| Potatoes | 0.96 | 0.625 |
| Onions | 0.07 | 0.115 |
| Fresh meat | 0.493 | 0.395 |
| Fresh fruit and vegetables, 2 months | 0.765 | 0.602 |

The ration, therefore, in June seems to be richer in anti-neuritic substances than that in the period January to April inclusive. As it was in the latter period or shortly thereafter that the most of the cases under consideration developed, it seems to be more than a coincidence that at that time the food was less rich in protecting substances.

Hence, it is quite impossible for the writer to condemn the ration of the Porto Rican troops on the ground that it does not contain sufficient anti-neuritic vitamines. What does happen is that certain men, from an inordinate appetite for rice to the exclusion of vitamine-rich food, stuff themselves with this article which has not sufficient protective substances, and disturb thereby their vitamine balance. In addition to this, there is a physiological, perhaps congenital, deficiency in their glandular apparatus from babyhood, due to starvation of high value animal proteins, a deficiency which becomes a disaster when sudden demands for thyroid and adrenalin secretion are made in the shape of normal military training. These military exercises are, for the recruit, severe work, and thus we have, with a continuance of a prejudice against meat, and perhaps an inability to digest it, plus a continuance of the rice eating habit, an increased demand for sudden exertion without nutritional preparation therefor, a breakdown, and—beriberi or some complex thereof.

There is only one way to insure against beriberi in this regiment and that is to issue *only* under-milled rice, for such individuals as above described will persist in following their alimentary bent, no matter what vigilance is employed.

The two complementary measures to be adopted are:

1. Lectures to the men on food and the necessity for more meat and less rice.
2. The establishment of vegetable gardens.

## ANALYSIS OF RICE CONSUMED BY PORTO RICAN TROOPS AND EXPERIMENTATION ON FOWLS

The United States Government Chemist, Mr. McGee, reports sample examined on July 20, 1921, to contain an ash of 0.45 per cent and 0.16 per cent phosphorus pentoxide, and states that the germ had been entirely removed. This rice was probably quite old and bears evidence from the packer's sign, of having been sent over seas during the world war. On December 6, 1920, a previous sample of rice was found to contain 0.40 per cent of ash, pentoxide of phosphorus not reported.

The rice in use in June was fed to fowls with boiled water, as an exclusive diet and paralysis of both legs was produced in three of six of them after the usual period.

## THE NATURE OF THE CASES OF POLYNEURITIS SEEN IN THE POST OF SAN JUAN

There were ten new cases seen in the post and two old cases, one discharged for his disability, and one of doubtful nature discharged shortly after his enlistment during the war.

A tabulated statement giving details of these cases follows.

The rest of the men, save the last two, were patients in the military hospital and I personally took their histories and made physical examinations of them throughout a period of days.

All of these men were questioned alike and were seen frequently by me thereafter to date of their discharge. Not only this, but they have since continued to come to me voluntarily for treatment and many long interviews have been had with them in their native tongue.

The last two men in the table were looked up and studied apart, as they had already been discharged. Most of them had noticed their symptoms about the same time and all told about the same story. In fact, the startling similarity and simplicity of the clinical picture in each case was the most striking feature.

### THE TEN CASES IN THE HOSPITAL

All save one were recruits of a few months' service, were apparently healthy countrymen when enlisted, and had lived at home on country food, rice, beans, fresh tropical vegetables and fruits, codfish and occasionally fresh meat. Two of them were athletes and the man who died was reputed to have been the strong man of the regiment, but their complexion was pasty and although their weight was above the average they did not have firm healthy flesh. Half of them came from one company, but in the cases which had preceded this investigation, and which had been already discharged, the surgeon informed me that practically all companies were represented. Only the history of the fatal case is incomplete owing to his sudden death before it could be taken in conformity with the table. Only one of nine ate meat with a relish; all of the rest confessed that they disliked it or that it "fell heavy in their stomachs" and that they "filled up on rice" and other things.

Practically all stated that after short marches and other military exercises in the spring they had noticed a gradual pain and weakness in the calves of the legs, followed by swelling and anesthesia thereof. Finally the weakness and inability to "manage themselves" became so disabling as to force them to put themselves on sick report.

In none was there fever, nor further digestive derangement than loss of appetite, nor urinary phenomena.

When examined, one by one, they all showed alterations in gait. Most of them shuffled in with more or less difficulty; some had to be helped in. Foot drop was evident but, while there was no spasticity, all save one complained of more or less painful cramps in the legs on leaving their beds in the morning, which disappeared after exercise.

The pain was generally in the calf of the leg, was often severe and deep, and was relieved by rubbing. All complained of numbnesss in the legs, which were "not much use any more." The sense of cutaneous touch and pain by pin prick was usually lost from the knee down, as was also the sense of heat and cold, but deep pressure was somewhat painful. Eight had, or had had, slight edema in the legs, ankles and feet, but generally over the lower third of the leg. It was very slight to the observer but the men made a great deal of the symptom and insisted upon its prominence.

Romberg's symptom, marked incoördination, and gross tremor of the muscles of thigh and leg on standing in a fixed position were prominent signs. The pupillary reflex was normal. The knee jerks were usually abolished but in one case they were distinctly increased. In another man, in one leg, the knee jerk was abolished, while in the other it was increased with also ankle clonus. In one man the knee jerks appeared to be normal. In four, muscular atrophy was clearly evident. In five, a history of pronounced palpitation of the heart was complained of, but the blood pressure in three of these was normal. There were a few stray symptoms here and there which had no bearing on the subject and which may be summed up by the expression "physiologic deviations from the normal." The digestive, respiratory and genito-urinary systems were apparently unaffected. There had been no fever, and, save in one case, no headache. Backache was rare. Five had Tinea cruris which is said to be very common throughout the regiment. The course of the disease was almost colorless. Observed for about three months they all remained about the same as when first seen despite a treatment consisting of a diet poor in cereals and sugar and rich in B-substances, including Vedder's pericarp and yeast. The diet consisted mainly of animal proteins, fresh vegetables and fresh fruits. The therapeutic agents used in all were a combination of thyroid, suprarenal and testicular extracts, and calcium lactate.

I was sent for to see one of these men who was reported to be dying a few days before beginning this medication. I found him practically pulseless at the wrist, with 180 beats (estimated by auscultation of the heart), blue, cold, semi-conscious and apneic. He had been taken suddenly ill while a patient in the hospital with palpitation of the heart, and had rapidly gone from bad to worse. The man seemed to be *in extremis* but I ordered an intravenous transfusion of normal saline solution with 30 drops of adrenalin solution, 1:1000, and by the afternoon he was up and about, apparently as well as ever. In general, however, the men improved by imperceptible stages up to the point of their discharge several months later, but all remained more or less paralyzed and helpless for any active labor.

On the day the order reached me to make this investigation I was informed by telephone of the sudden death of one of the men. He had been in the state of the others above described for some time and suddenly expired with the same picture as that presented by the soldier who was so ill with cardiac palpitation. The autopsy was performed by me ten hours later and the following was found:

*Case of private*

This man, who was reputed to be one of the strong men of the regiment, was taken gradually with the same symptoms as recounted for all of the rest and appeared at sick call, June 29, 1921, with weakness, heaviness and pain in legs, a shuffling gait, anesthesia, and loss of heat and cold sense below the knee. He had the same monotonous symptomatology as the rest of the cases of polyneuritis then in the hospital until about 6 p.m., July 12, when he was seized with alarming tachycardia and asthenia, became cyanotic and apneic, and died at 1.30 a.m., July 13, or seven and one-half hours later. Man was kept on ice until time of *biopsy.*

*Autopsy (10 a.m. July 12)*

An unusually well-developed, muscular man in rigor mortis. Weight 175 pounds; stature 67 inches. Upon opening the peritoneum about two quarts of clear, lemon-tinted peritoneal fluid was recovered. There was no meteorism of the bowel.

On opening the pleurae 140 cc. of bloody fluid was recovered and from the pericardium 150 cc. of a clear serum.

A pre-mortem clot was found filling the right auricular and both ventricular chambers.

The tricuspid orifice admitted three fingers; the mitral, two. There was relative stenosis of the aortic valve, but no vegetations on any of the valves.

The epicardiac fat was increased and fatty degeneration of the muscle, particularly at the apex and posterior surface, was clearly noted and extensive. The weight of the heart was 103 grams. The thickness of the left ventricular wall was 1 cm.; of the right, 3 to 4 mm.

*Lungs.* Apparently normal, crepitation good in all parts. No signs of previous tuberculosis but some bronchial glands were enlarged.

*Liver.* No adhesions; weight 1400 grams. Perihepatitis visible on posterior surface and areas of fatty degeneration in right and left lobes. Gall bladder moderately full, containing 25 grams of dark green bile. No calculi, evidence of inflammation, nor obstruction in the ducts.

*Spleen.* Normal size; weight 100 grams; apparently normal.

*Pancreas.* Weight 100 grams. Acute congestion of whole gland with hemorrhagic areas in head.

*Kidneys.* *Right,* weight 130 grams, capsule completely adherent, cortical layer atrophied. *Left,* weight 135 grams, cortical layer atrophic, capsule not so adherent.

*Stomach.* Contains 50 grams of a grayish yellow liquid. The mucous membrane of the fundus was somewhat congested.

*Intestines.* Normal.

*Appendix.* Normal; no adhesions.

*Bladder.* Empty and contracted.

*Suprarenal glands.* Atrophic, entirely degenerated and cystic.

*Hemolymph glands.* Hypertrophic, but separate the one from the other, not conglomerate.

*Brain.* Normal. Gelatinous exudate in the vicinity of the precentral gyrus giving appearance of an old pachymeningitis. The lesions are symmetrical on both sides of the brain but there was no congestion around these lesions. Osteoporosis of right parietal bone.

*Summary of histologic findings*

*Lungs.* Chronic passive congestion, edema, anthracosis, foci of broncho-pneumonia and acute pleuritis.

*Heart muscle.* Extreme fragmentation of myocardial fibers, fatty degeneration and edema.

*Spleen.* Atrophy of lymph follicles, fibrosis and marked pigmentation.

*Kidneys.* Chronic passive congestion and slight cloudy swelling.

*Adrenals.* Atrophy, edema and marked pigmentation of cortex. Fatty, vacuolar and cystic degeneration of the medulla.

*Liver.* Hemorrhagic foci, fatty infiltration, abundance of nonsideral pigment.

*Gastric mucosa.* Hyperemia.

*Duodenum.* Same as stomach.

*Jejunum.* Same as stomach.

*Pancreas.* Chronic passive congestion, hemorrhagic foci.

*Mesenteric ganglia.* Hypertrophy fibrosis, edema and follicular atrophy.

*Tracheo-bronchial nodes.* Edema, anthracosis, chronic passive congestion.

*Hemo-lymph nodes.* Hypertrophy, edema, excessive pigmentation.

*Testicle.* Chronic passive congestion.

*Case records*

| | AGE | MONTHS OF SERVICE BEFORE ONSET OF DISEASE | MODE OF ONSET |
|---|---|---|---|
| 1 | 21 | 3 | Pain in lumbar region, dizziness and loss of appetite. Legs heavy and painful. Stumbling gait. |
| 2 | 21 | $5\frac{1}{2}$ | Cramps in legs. Began suddenly. |
| 3 | 24 | 6 | Began gradually. Pain lumbar region and legs which were also weak and edematous. |
| 4 | 24 | 54 | Began gradually, with pain and edema of feet, weakness in the legs and stumbling gait. |
| 5 | 22 | 1 | Began gradually. Pain in both lower extremities; legs were weak and "would not work right." |
| 6 | 29 | 2 | Began gradually with pain in knees, wrists and back. Weakness and edema of legs. |
| 7 | | | Began gradually with pain, cutaneous anesthesia, weakness and edema in legs. |
| 8 | | 2 | Began gradually with cutaneous anesthesia which crept upward from toes. Pain and weakness in legs. |
| 9 | | 10 | Began suddenly with cutaneous anesthesia of legs, pain followed soon thereafter. |
| 10 | 22 | 6 | Began gradually with weakness and pain in legs. |
| 11 | 21 | 10 | Began gradually with numbness and swelling of legs. |
| 12 | 37 | $\frac{1}{6}$ | Five days after enlistment took a shower bath while perspiring and "felt pins and needles in his feet." Later, pain in calves of legs which became stiff. Discharged in ten days. |

| | GAIT | PAIN | CRAMPS LEGS | NUMBNESS LEGS | ANESTHESIA | EDEMA |
|---|---|---|---|---|---|---|
| 1 | Stumbling, shuffling. | Much in legs. | Yes | Yes | Yes, legs. | Yes, legs and ankles. |
| 2 | Shuffling. | Much in legs. | Yes | Yes | Yes, partial, especially feet and hands. | Yes, legs. |
| 3 | Stumbling, shuffling. | Legs, feet and back. | Yes, severe | Yes | Complete, legs. | Yes, feet and legs. |
| 4 | Stumbling, shuffling. | Yes | Slight | Yes | Complete, legs. | Yes, feet and legs. |
| 5 | Shuffling with cane. | Much in legs. | Yes | Yes | Yes, legs. | Yes, legs. |
| 6 | Stumbling. | Waist, knees, back. | Yes, severe | Yes | Yes, complete. | Yes, legs. |
| 7 | Stumbling. | Yes, legs. | Yes | Yes | Yes, legs. | Yes, legs. |
| 8 | Stumbling. shuffling. | Yes, legs. | Yes | Yes | Yes, legs. | Yes, legs. |
| 9 | Slight uncertainty gait. | Yes, legs. | Yes, left leg. | Yes, especially left leg. | Yes, left leg. | No |
| 10 | Shuffling. | Yes, legs. | Yes | Yes | Yes, legs. | No |
| 11 | Stumbling, shuffling. | Yes, legs. | No, but muscles of calves are stiff in morning. | Yes | Yes, legs. | Yes, legs. |
| 12 | Stumbling, shuffling. | Yes, legs. | Yes | Yes | Yes, legs. | No |

*Cerebral cortex.* Hyperemia of the pia, lymphangiectasia, (region of gross lesions).

*Cerebellum.* Hyperemia.

*Spinal cord.* Normal.

*Sciatic nerve.* Fatty degeneration at the periphery and some of the external bundles of the nerve trunk.

These histologic studies were made by our pathologist (Institute of Tropical Medicine), Dr. Torregrosa, who also assisted me at the autopsy.

| | ROMBERG | KNEE JERK | MUSCULAR ATROPHY | CIRCULATORY SYSTEM | REMARKS |
|---|---|---|---|---|---|
| 1 | Marked | Increased | No | | Dizzy. Recommended 40 per cent disability. |
| 2 | Marked | Diminished | Yes | | Recommended 25 per cent disability. |
| 3 | Marked | Abolished | Yes | No palpitation | Recommended 30 per cent disability. |
| 4 | Absent | Abolished | Yes | Palpitation B.P. 125 S | Recommended 40 per cent disability. Dizzy. |
| 5 | Slight | Left almost abolished, right retarded. | No | | Began with feeling as though great toes were immersed in very hot water. Recommended 40 per cent disability. |
| 6 | Marked | Left increased; right delayed | Yes | Palpitation | Recommended 25 per cent disability. |
| 7 | Slight | Left increased; right abolished; ankle clonus on left. | No | Palpitation B.P. 128 S 88 D | Recommended 12.5 per cent disability. |
| 8 | Marked | Normal | No | Palpitation B.P. 124 S 76 D | Babinski positive-slight. Recommended 25 per cent disability. |
| 9 | Absent | Right, normal; left retarded. | No | Nearly died of tachycardia | |
| 10 | Absent | Diminished and retarded. | No | Palpitation | Died of cardiac asthenia. |
| 11 | Marked | Abolished | Yes | Palpitation, heart | Is a cripple and walks with difficulty with a cane. |
| 12 | Marked | Normal | Yes | He once thought he was going to die of palpitation | Draft soldier of 374 Infantry. Discharged in ten days after enlistment. Has been practically paralyzed for ten months. |

*Notes*

*a*. All had a mixed diet at home before enlistment and a small quantity of meat two or three times a week, generally boiled in soup.

*b*. All showed and confessed to a positive aversion to meat in substance as furnished in the army, with the exception of one man who ate liberally of it.

*c*. In all, save one man, there was partial paralysis of the lower extremities with a feeling of heaviness and, lowering of power in the legs.

*d*. In all, numbness in legs was a source of constant complaint.

*e*. In all, there was complete loss of the heat sense in legs.

*f*. In all, save one, the pupillary reflexes were normal.

*g*. In none was there fever nor, save in one, headache.

*h*. In all, the digestive tract seemed normal. Only three complained of loss of appetite.

The third point of view of company commanders merits a brief comment for it expresses a time worn theory elaborated in temperate climes that in practice is believed to account for a large part of the physiologic deficiency in tropical people the world over, and a certain part of their propensity to certain pathologic states and susceptibility to pathogens which colonize best in relatively devitalized tissues and in media abnormal to a healthy individual but propitious for these organisms. The old theory is based on the point of view that food to the human being is what coal is to the machine, that rice is the ideal food because it gives the highest degree of energy with the least amount of heating of the machinery. But when this theory took the center of the stage the vital principles in food were not considered, nor was the necessity for a protein molecule with a complete set of amino-acids. The part played by the thyroid and suprarenals in the government of nutrition, and especially for the nutritional control of the highly specialized organs and tissues, was little appreciated. The value of rice is unquestioned as a source of *cheap energy*, but a predominance of this article of diet with a reduction in meat tends to produce a physiologic diminution in the products of the glandular system and an ever increasing difficulty in converting the starch into bihexoses through a deficiency in maltase, a ferment which the digestive glands should supply; a difficulty in breaking up fats by lipase, a glandular product which shares in the deficiency; and finally a serious difficulty in digesting meat and the protein molecule in general, which becomes the prey of pathogenic bacteria and undergoes putrefaction. The result is a labored digestion, a hyperacid intestine full of gas, and the familiar deficiency syndrome of the tropics, languor, pasty complexion, neuralgias, neuritis and other nervous disorders.

The argument that 60 to 80 per cent of the hard work done in in this country has been energized by rice falls to earth when we reflect that the wage of the laborer is low partly because he is unable to work at the 100 per cent *rate of speed* set by the northern meat-eating races, and that these same laborers double their physical efficiency *when they eat* the food set before them by the United States Army, and even quite equal these races.

It is not a moral issue; it is a physical one. Laborers here are not lazy nor indolent; they are either sick of hookworm disease or mal-nourished and incapable of further effort without more vital food—or, which is generally the case in the interior—are suffering from both conditions.

Previous to 1919, in the outbreak of polyneuritis among the draft troops, the only recommendation made by the board was "that a highly nitrogenous diet be instituted."

Long before this, when the writer started out upon the campaign against the anemia of Porto Rico in company with Drs. Gutierrez and King, although we were trying to prove that the ill health of the laborer was due to the hookworm, we had to recognize that the people were mal-nourished and that this contributed to the intensity of their anemia.

And even before us, from time immemorial, the well known writers of Porto Rico have been lamenting the fact of an ill-balanced dietary among the working classes: the Spaniards clamoring for more meat for the people. And this is at the bottom of the whole question. It is not merely a deficiency in

B-matters but also a deficiency in the proteins of high value, which latter brings about, especially, a physiologic deficiency of the glandular system.

As a result of the recommendations of the surgeon for an under-milled rice, 5000 pounds were shipped here in August, 1921. This rice was examined by the iodine test and found to apparently contain from 90 to 95 per cent of its pericarp. The chemical composition was reported as follows:

| | |
|---|---|
| Moisture | 10.06 |
| Ether extract | 1.88 |
| Ash | 1.16 |
| Crude fiber | 0.96 |
| Phosphorus pentoxide | 0.43 |

It was recommended by the Surgeon that 50 per cent of this rice and 50 per cent of the polished rice on hand be issued to the troops in San Juan. Under the rate of issue then advised each man would receive 0.27 pounds of rice per day, 60 per cent of which would be under-milled.

In addition to these measures the investigating officer, Colonel Ashford, requested permission to speak to the men on the danger of excess in rice eating and of an insufficient amount of meat. The men were assembled by battalions and the talks given in the Spanish language with the apparent result that the consumption of meat in the companies notably increased thereafter. From the beginning of the investigation recommendation was made that all issue of rice be stopped to see the effect on the case incidence. This was done for the month of August but on September 9 further recommendation was made that a 50 per cent rice allowance be permitted.

### GENERAL HYGIENIC AND SANITARY CONDITION OF THE POST

Having been the post surgeon myself from 1908 to 1913, I can say with a considerable degree of certainity that no good reason exists for involving the sanitation or general hygiene of the post in this question. Nevertheless, although I had only a few months before made a long and careful inspection of every part of the post for the purpose of recommending measures for its adequate rat-proofing against plague, then epidemic in San Juan, I repeated such part of this inspection as seemed to bear on questions raised by lay observers.

### *1. Infection*

The charge has been made, and with semblance of reason in the past, that all cases of beriberi originated in the old "yellow-fever barracks" near the large Ballajá *barrack*. This is overthrown in the present outbreak as cases have occurred in companies A, B, C, E, F, G and K, some of which were never quartered in these barracks.

It is also true that the first cases of beriberi ever seen in Porto Rico were some hospitalized on the military post in 1906 near these barracks. These patients were removed from a ship from the Orient to the military hospital by the Public Health Service with which a contract to treat its patients was then in force.

These facts are cited to prove the infectious nature of beriberi by those who are thus persuaded.

It is also striking, that before 1918, in the eighteen years of life of this regiment, this polyneuritis never presented itself. I can testify to the five years immunity therefrom when I was post surgeon (1908–1913) and yet the country lad was the same. But in reality the conditions since 1917 have been totally different. Before, much more fresh food was consumed in the regiment. It was cheap and abundant. In 1917, the price of sugar rose to fabulous figures and there was a scramble for the cane fields. The production of garden truck has suffered to such a startling extent that today, and for the last three years, only the wealthy could afford it and often they could not obtain fresh vegetables because there were none. The country-man himself changed his ration thereby, and began to eat more rice and less plantains, which were selling for 6 cents apiece. Whereas before he secured his plantains for nothing or for a mere song, now he finds that by selling a plantain or two he can get enough rice for the day and piece out the rest of his ration with sweet potatoes and vautía (another tuber).

This also changed the dietary of the troops and fresh vegetables became an expensive luxury, as they are today. So that, whereas the peasant who enlisted ten years ago found rice, beans and fresh vegetables in the Army just as he had had at home, today he finds rice and beans but practically no fresh vegetables. If, as has been suggested, this recruit will not eat meat nor anything but what he can pick out of our ration that conforms to what he used to eat in his home, a relative insufficiency in anti-beriberi factors must be admitted and can be the only explanation for the continued presence of the disease in the garrison on the accepted etiology of the disease.

There remains, however, the curious fact that the troops at Cayey have never been known to have this polyneuritis. Moreover it is cool and damp there for six months of the year, two conditions which the soldiers consider causal. But as a matter of fact, more fresh vegetables enter the Cayey dietary. It is a country post where vegetables are more plentiful and much cheaper and they also have a small post garden.

### *2. Dampness*

As we have seen, the men themselves all firmly believe that walking on the cold cement floor of the barracks without their shoes causes the disease. Such are the floors in the lower story of the Ballajá barracks and those of the "yellow-fever barracks."

In a careful re-inspection of these barracks absolutely no reason of a sanitary nature could be found to justify the suspicion of their being "a focus of infection." The floors, however, are cold, and susceptibility to cold is marked in this island. No amount of scientific argument will suffice to prevent the good housewife in Porto Rico, who can do so, from buying slippers for her children and obliging them to wear them, for, she says, "If they do not wear them they are always sneezing and coughing." Part of this fear of barefootedness is due to the notoriously poor health of the country laborer twenty years ago, through whose feet the embryos of *Necator americanus* entered to produce, later, the anemia of the island. The explanation was not known then but the connection between barefootedness and ill health had been established.

Nevertheless, it is well to consider a possible predisposing factor in the precipitation of neuritis in an individual just on the edge of an explosion of the beriberi syndrome. It is a fact that many of these cases date their first symptoms from a soaking while they were overheated and that cold, even cool baths, a slight current of air, a kicking off of the covers at night, results in vague rheumatoid or neuritic pains in those presenting a more or less clear deficiency syndrome.

### *3. Preparation of the food*

The kitchens were carefully inspected in company with the commanding officer. They were clean and orderly and the food was abundant and well served but the excess of rice and grease and paucity of fresh food is very noticeable. The food is even too greasy for some of the troops and the weakened digestion of some of these men will not tolerate it. One of the patients stated that three quarters of what the soldiers eat is rice with beans the latter cooked from four to five hours, but that while his company (E) "feeds well" it has had more cases than any other. He stated that fresh vegetables are served once a week and potatoes now and then.

The abhorrence of the islander for "carne muerta," or "dead meat," as they term refrigerated animal food furnished the garrison, is an obsession, and people here are as much enslaved by their dislike for the idea, as our Northerners who spurn the freshly killed, or "live meat" of the island.

There is no legitimate ground for complaint, however, that the food is badly cooked, nor badly prepared. It is delicious for those who like good Spanish cooking, and only lacks more fresh vegetables and roast meat. It is rather reluctantly admitted that it is too greasy because the palate of most men here requires much more grease than that of continental troops. Seasoning with chorizo, onion, garlic, etc., merely caters to the crowd taste and, as I learned in observation of English kitchens at the front, a good company mess sergeant must be a good caterer to be a popular non-commissioned officer.

### *4. Water*

The water was examined for mineral poisons and found free. It was discovered in the course of the investigation that access was had by the men to the old Spanish cistern water. This, too, was examined and found free of lead or other mineral poison.

### *5. Clandestine alcoholic beverages*

Men have confessed to taking a "nip of rum" when they could get it but this is far from common and not possible to continue with regularity. Moreover, the civilian population drinks a far greater amount of a very bad quality of rum and yet civilian morbidity records and the personal experience of civilian physicians with whom I am in constant daily relation are absolutely negative. As a matter of fact, knowing the country boys of Porto Rico, I am as positive as it is possible to be that they were telling me the truth. While nine absolutely denied having taken rum, the tenth man cheerfully admitted it but said that his supply was irregular and never made him sick. None of the cases presented a single sign of alcoholism.

### *6. General habits of the men*

It would be difficult to find a better disciplined body of men in Porto Rico than these soldiers, nor a cleaner, more self-respecting one. No vicious, nor unhygienic habits can be dragged out to explain the presence of polyneuritis.

## DISCUSSION

The diagnosis of "some form of beriberi" needs a few words of explanation. The peculiarity of these cases lies in that under treatment by abundant quantities of anti-neuritic vitamine they do not usually become cured in a reasonable time. There seems to be little doubt that a food deficiency symptom-complex exists in those cases, resembling, if not identical to, beriberi. Poisons (impure alcohol and minerals) can be ruled out as far as the evidence goes. So can syphilis, malaria, pellagra, nephritis, influenza and cerebro-spinal meningitis. I have never seen anterior poliomyelitis in an adult but there is rarely a history of fever in the cases under investigation, nor do the sensory phenomena accompany that disease, nor is the onset nor the clinical course the same. Myelitis should give some loss of control over bladder and rectum. Locomotor ataxia, aside from other signs, gives the Argyll-Robertson pupil. There is no obtainable history of an intoxication by any definite substance. Moreover, the men attacked confessed to eating an excess of a rice which was found later to contain but 0.16 per cent of phosphorus pentoxide and the disease disappeared on prohibiting the use of this rice. Not only this, but one autopsy reveals only such a pathologic picture as is described for beriberi, on gross and histologic examination. The records in the examination show that ten were negative for syphilis by the Wassermann and only one by other tests; the records of the other were not taken. Three were examined by the complement deviation and mycologic tests for sprue and were negative. The urinalysis showed no involvement of the kidney. The ova of *Necator americanus* were reported as being present in ten but there was no clinical evidence of uncinariasis whatsoever. If to all of this, we add the evidence of the board for the investigation of polyneuritis in Camp Las Casas in 1918 and the positive statement by Dr. Gutierrez, who was a member of that board and who examined the twelve cases now under consideration, that the two groups were suffering from identically the same syndrome, which he considers with me to be a form of beriberi, we can hardly escape the conclusion that no other diagnosis is warranted.

The accepted etiology of beriberi is a deficiency in water-soluble B-vitamines but the ration of the companies from which these men proceed certainly does not seem to lack in these protective substances. It *is* high in rice and low in fresh meat and fresh vegetables. There is not enough of a difference in the dietaries of these companies to explain a predominance of beribri in one company over another. No one infectious agent has been proved to accompany beriberi and the only reasonable explanation in accord with the currently accepted etiology of the disease seems to be as has been already foreshadowed in the body of this paper but which should be again repeated.

The men of this regiment are, in the main, country lads used to a monotonous diet of *highly milled* rice, beans, fresh vegetables and fruits, and codfish. They are protein-starved all their lives (lack of the complete protein molecule) and hence, according to McCarrison's experiments and those of others, are living in a state of physiologic glandular deficiency in which the nervous system is particularly mal-nourished. The people work slowly and deliberately throughout the day but instinctively avoid a rapid expenditure of energy for which the output of their glands of internal secretion is insufficient. They enlist and the majority change their habits of alimentation and eat the full army ration, thus enabling them to meet the sudden demand for relatively lively exercise for shorter periods in the course of their normal military training. This military training is by no means severe and is, according to the colonel commanding the Post, less than that required of our continental troops. But for the recruit who is in a state of physiologic deficiency it is severe. If this recruit, therefore, persists in trying to pick out of the ration only such articles as he has been accustomed to eat in his country home, he is reduced in the main to rice, as there is less of beans and vegetables than he formerly secured. Such persons should suffer from a relative deficiency in B-substances, plus poverty in protein of high value, which sustains their glands and their nervous systems in a state of physiologic degradation. The syndrome related in previous pages is believed to be the resultant of these two factors. If there is an infective agent working as an exciting cause it has not been discovered and should therefore be eliminated from any practical consideration.

## CONCLUSION

1. The polyneuritis in question is some form of beriberi, probably a combination of the beriberi syndrome plus a physiologic deficiency in the glandular system due to chronic protein starvation from relative deficiency in food containing the complete protein molecule.

2. The condition has been self-induced in certain men who, with a ration containing a sufficiency of protective substances, have

elected to satisfy their appetite by eating inordinate quantities of highly milled rice containing only 0.16 per cent of phosphorus pentoxide, at the expense of food containing protective vitamines.

3. The dietary of the Porto Rican troops, although protective against beriberi when eaten as served, contained too high a proportion of rice and fat and too little fresh meat and fresh vegetables.

4. The treatment has been based on super-feeding of substances rich in antineuritic vitamines and the complete protein molecule, by hospital treatment and the use of endocrinic therapy, and by change of environment through furloughs to the patients' home.

5. It is not practicable to purchase undermilled rice locally as the insular production is extremely small and scattered.

7. These conclusions are based on the accepted etiology of beriberi. If there be any infective agent involved it has not been discovered, nor is there any scientific ground for such an assumption.

8. The suggestion has been made that men presenting themselves for enlistment without normal knee jerks be rejected. I do not concur with this measure if it would exclude otherwise healthy appearing individuals, as the physiologic deficiency above referred to is extremely common condition, well known here to be overcome in a short time by proper feeding and exercise. In other words, I do not consider that retarded knee-jerks, without other signs, in the average applicant for enlistment in Porto Rico, is a precocious diagnostic sign of the beriberi syndrome, although I do believe it to be a sign of physiologic deficiency.

## RECOMMENDATIONS FOR PREVENTION

1. All rice issued Porto Rican troops should be under-milled and contain at least 0.43 per cent of phosphorus pentoxide. There will always be men here who will eat inordinately of rice in spite of vigilance.

2. Lectures should be given officers and men on the danger of eating too little meat and an excess of vitamine-less carbohydrates.

3. Vigilance should be exercised directly by the proper authority in each company at mess tables to prevent one-sided individual diets.

4. The surgeon of the post should keep a weekly bulletin demonstrating the kind and quantity of food being consumed in each company from menus with actual or approximate weights furnished by company commanders. This, should act as a barometer of safety in preventing outbreaks.

5. A large vegetable garden to furnish these troops is considered to be one of the best means to insure against future outbreaks.

The conclusions and recommendations as a result of this investigation were accepted by the commanding officer of the post and vigorously turned to practical application. The end-product will be seen in the following letter by the present post medical officer.

In reflecting upon the significance of this communication it should be added that since September of 1921 no new case of beriberi has developed and apparently a neat yearly sum has been saved to the treasury in pensions for what promised to be an expensive disease.

Office of the Surgeon,
Post of San Juan, P. R.
March 21, 1922.

From: The Surgeon,
To: Colonel Bailey K. Ashford, M.C.,
Subject: Ration of Troops, Post of San Juan, P. R.

1. In compliance with verbal request, March 20, 1922, for a brief history of recent improvement in the health of troops resulting from better feeding, the following report is submitted:

2. (*a*) On December 1, 1921, it was recommended that each organization maintaining a mess, be required to render daily menus, specifying each article of food, and the quantity of same, as well as the number of rations drawn. As a result of this recommendation, on December 7, 1921, each organization began rendering these reports. Each menu contained 4 columns; one for the article of food; one for the gross quantity; one for quantity in ounces per man; and one for vitamine value. The latter two columns were filled in by the surgeon. At the end of the month the total amount consumed by each organization of certain staple articles of food, was checked against a statement furnished by the quartermaster, with a view to ascertain the correctness of the menus. In making this check it was found that many organizations were consuming less than 75 per cent of their

ration allowance in fresh beef or potatoes, and several times their allowance in rice (undermilled) and beans, plainly indicating that the Porto Rican soldier, if allowed, will favor rice and beans to the exclusion of other foods.

(*b*) According to the menus, the average amount of food consumed per man per day with the B++ vitamine value according to Eddy's Vitamine Manual was as follows:

Company A, 52.9 oz., 42.2 per cent of which contained B++ vitamine.
Company B, 73.9 oz., 50.8 per cent of which contained B++ vitamine.
Company C, 81.7 oz., 38.5 per cent of which contained B++ vitamine.
Company D, 57.8 oz., 46.5 per cent of which contained B++ vitamine.
Company E, 85.4 oz., 46.8 per cent of which contained B++ vitamine.
Company F, 70.7 oz., 48.4 per cent of which contained B++ vitamine.
Company G, 72.7 oz., 39.8 per cent of which contained B++ vitamine.
Company H, 72.9 oz., 38.8 per cent of which contained B++ vitamine.
Company I, 73.3 oz., 43.7 per cent of which contained B++ vitamine.
Company K, 68.2 oz., 43.9 per cent of which contained B++ vitamine.
Service Company 70.3 oz., 45.3 per cent of which contained B++ vitamine.
Headquarters Company, 54.9 oz., 28.3 per cent of which contained B++ vitamine.

The approximate proportion of articles furnishing the B++ vitamine was as follows:

| | *per cent* |
|---|---|
| Potatoes, fresh; Potatoes, sweet | 70 |
| Beans | 10 |
| Fresh fruits and vegetables | 20 |
| | 100 |

(*c*) The variation in the quantities per man and the vitamine value can be explained by the fact that some messes often furnished bananas or plantain instead of potatoes. This would increase the quantity and not the vitamine value. Other organizations frequently served oranges and grape fruit which would increase both the quantity and vitamine value. Others again consumed more than the ration allowance in potatoes, thereby greatly increasing both quantity and vitamine value.

(*d*) Inasmuch as potatoes furnish 70 per cent of the B++ vitamine and if the consumption of this article is materially reduced without a proportionate increase in fresh fruits or vegetables, the command would soon be on a diet that would produce beriberi.

(*e*) In checking the menus it was noted that in several organizations breakfast was frequently light during the month of January. Companies E, F, and K averaged $8\frac{4}{10}$ ounces per man with an average caloric value of 686. Many of these breakfasts were as low as 5 or 6 ounces, and some as high as 24 ounces with a proportionate caloric value.

3. During the early part of January, a report embodying the above information was rendered the commanding officer and a meeting of all officers was called to discuss the food question with the surgeon with a view to improving the menus.

At the end of January another analysis was made of the menus for the preceding month, and it was found that the average amount consumed per man per day for the Post was 82 ounces, 49 per cent of which contained B++ vitamines. Practically all organizations drew less than 60 per cent of their fresh beef allowance, exceeded their potato allowance by 30 per cent and drew practically five times their allowance in rice (undermilled) and beans. The high vitamine value was due largely to the excess in potatoes and the large amount of citrous fruit. Rice has been limited to one meal a day, with an average of five ounces per man.

4. The menus for February and March have shown about the same quantities consumed, with the same vitamine value, and a gradual improvement in the method of preparation and variation.

5. As a result of the improved ration of the post, sick call has been reduced from between 50 and 60 men daily, to an average of 10. The actual number of sick in hospital and quarters during the months of December, 1921, and January, February and March, 1922, as compared with the same months of the previous year, is as follows:

| MONTH | YEAR | MEAN STRENGTH OF COMMAND | AVERAGE NUMBER PATIENTS, H & Q. |
|---|---|---|---|
| December | 1920 | 1260 | 43.18 |
| January | 1921 | 1155 | 49.25 |
| February | 1921 | 1257 | 51.33 |
| December | 1921 | 1170 | 13.40 |
| January | 1922 | 1196 | 18.50 |
| February | 1922 | 1200 | 11.33 |

6. The entire command has shown a marked improvement in general appearance. Seventy-eight men from various organizations, selected at random, have gained an average of 2.13 pounds in weight per man per month.

7. These results can not be attributed entirely to food as there are several other factors to be reckoned with, such as, improved sanitation, close supervision of sick call, careful attention to details of treatment of all sick in hospital and quarters.

(Signed) George E. Atwood,
*Captain, Medical Corps.*

## DISCUSIÓN

El diagnóstico "una forma del beri-beri" (que aparece en el artículo) requiere una breve explicación. La peculiaridad de estos casos gira en el hecho de que bajo tratamiento con cantidades abundantes de vitamína anti-neurítica éstos no responden curándose despúes de un período razonable. No se tiene la menor duda de la presencia de un complejo-simtomático traído por deficiencias de alimentación que se parece, sino no es en realidad idéntico, an el del beri-beri. Los venenos, como el alcohol im-puro y los minerales, no manifiestan la más leve evidencia an su favor y por lo tanto se descarta su consideración. Así mismo eliminamos a la sífilis, malaria, pellagra, nefrítis, influenza y meningitis cerebro-espinal. Aunque nunca he visto poliomielitis anterior en un adulto, puedo asegurar que en los casos aquí investigados rara vez se ha obtenido historia de fiebre. Tampoco a aquella enfermedad acompañan los fenómenos sensorios que aquí vemos, ni es el arranque ni el curso clínico el mismo. La mielitis debe manifestar falta de dominio sobre la vejiga y el recto. La ataxia locomotríz nos dá la pupila de Argyll-Robertson-además de ciertas otras indicaciones. No es posible obtener datos que imputen una intoxicación por medio de sustancias precisas. Además, los soldados afectados confiesan haber comído un exceso de arroz el cual más tarde se averiguó que sólo contenía 0.16 per cent de pentóxido de fósforo. Al prohibirse el uso de este arroz, la enfermedad desapareció. No solamente esto, sino que de todas las autopsias, menos una, se revela un cuadro patológico que bajo exámen grueso e histológico, es el mismo que se describe para el beri-beri. Otros exámenes nos demuestran a diez con Wasserman negativo y solamente uno da un resultado por otro método de análisis. A tres se les examinó la deviación de complemento y micología de *sprue* siendo todos negativos. Los urinálisis no demostraron affección del riñón. Los huevos de Necator Americanus se me informa fueron encontrados en diez casos pero sin evidencia clínica de uncinariasis. Si a todo esto añadímos el resultado de la investigación practicada por la Junta para la Investigación de la Polineuritis en el Campamento Las Casas en 1918, y la declaración explícita del Dr. Gutierrez (que fué uno de los miembros y examinó los doce casos que aquí sometemos á nuestra consideración) que los dos grupos presentaban idénticos síndromes—síndromes que tanto él como yo creemos una forma de manifestación del beri-beri—hemos llegado a la decisión de que no es justificable hacer otro diagnóstico sino el de beri-beri.

La etiología del beri-beri es, según hoy generalmente se acepta, una deficiencia de las vitaminas-B, solubles en agua. Las raciones consumidas por los soldados de las Compañias afectadas no parecen carecer de estas sustancias protectivas. En las raciones predomina el arroz muy por encima de los vegetales y carmes frescas. No existe diferencia marcada en los regímenes alimenticios (dietas) de estas Compañías que esclarezca el porqúe en nuestras Compañía prevalezca mas el beri-beri que en otras. Aun no se ha demostrado ningún agente infeccioso que acompañe con regularidad a esta enfermedad. La unica explicación razonable es la que ya ha sido brevemente mencionada en el curso del artículo y que deseo repetir a continuación:

Los soldados de este Regimiento son, en su mayoría, jóvenes campesinos acostumbrados a una dieta que consiste de arroz *muy molido,* habichuelas, vegetales, frutas frescas y bacalao. Toda su vida han vivído en medio de una carencia de proteínas (falta completa de la molécula protéica) y por lo tanto, de acuerdo con los experimentos de McCarrison y otros, presentan un estado-de deficiencia glandular fisiológica en el cual el sistema nervioso está malnutrido. Estas gentes trabajan sosegada y delibe radamente a través del día y—debido a que la acción de sus glándulas de secreción interna es insuficiente—instintivamente evitan el desgaste rápido de energías. Al alistarse en el ejército la mayoria cambia su hábito de alimentación al consumir la ración militar en su totalidad. Esto les habilita para cumplir con las exigencias de la vida militar, a que han ingresado de súbito, durante periodos cortos de su instruccion. Esta instrucción no es severa. Segun la opinión del Coronel Comandante de la Plaza se les exíge mucho menos que a las tropas continentales. Pero para el recluta en estado de deficiencia fisiólogica cualquier cosa es severa. Si este mismo recluta, a pesar de esto, persiste en seleccionar de la ración aquellos artículos que estaba acostumbrado a comer en su casa del campo, terminará por no tocar nada mas que arroz. Tampoco puede consumir con liberalidad, como antes lo hacía, habichuelas y vegetales, pues la ración militar limita la cantidad de estos artículos. Tales individuos seran presa de una deficiencia en sustancias-B, mas una carencia de proteínas de gran importancia, todo lo cual les mantiene el sistema nervioso en un estado de degradación fisiologica. El síndrome ya mencionado en páginas anteriores, se cree sea el resultante de estos dos factores. Si existiese un agente infeccioso que actúe como incitante de la enfermedad, este aún no se ha desubierto, y debe por lo tanto eliminarse de consideraciones prácticas.

### CONCLUSIONES

1. La polineurítis en discusión es una forma de beri-beri—probabemente una combinación del síndrome del beri-beri con una deficiencia del sistema glandular debido a un estado crónico causado por falta de proteínas en dietas cuyas moléculas protéicas son relativamente deficientes.
2. Este estado fue auto-inducido, instigado por ciertos individuos en sí mismos, quienes, teniendo a su alcance una ración con suficiencia de sustancias protectivas, eligieron en vez de tales alimentos, satisfacer las tendencias de su apetito comiendo cantidades excesivas de arroz muy molido que arroja un análisis de sólo 0.16 per cent de pentóxido de fósforo.
3. El régimen alimenticio de las tropas puerto-rriqueñas, aunque resguarda o proteje del beri-beri según se preparan para la mesa, contiene una proporción muy alta de arroz y muy poca cantidad de carne y vegetales frescos.
4. El tratamiento ha tenído por base la super-alimentación con sustancias ricas en vitaminas anti-neuríticas y también poseyendo la molécula protéica completa. Esto ha requerido ingreso en el hospital, uso de la terapia endocrina y cambio de ambiente mediante licencias temporales que permitían a los pacientes pasar temporadas en sus propios hogares.
5. La compra de arroz parcialmente descascarado o trillado en la isla es una imposibilidad pues la producción es casi insignificante además de ser muy esparcida.
6. Estas conclusiones se fundan en la etiología aceptada del beri-beri. Aún no se ha podido demostrar un agente infeccioso, ni es posible desde un punto de vista científico asumir tal cosa.

### RECOMENDACIONES PREVENTIVAS

1. Todo el arroz que se expida para el consumo de las tropas puerto-rriqueñas, deberá haber sido solamente parcialmente

molido (descascarado) y deberá así mismo contener por lo menos un 0.43 per cent de pentóxido de fósforo. No obstante esto y la vigilancia que se pueda ejercer, siempre se encontrarán individuos aquí que coman arroz desmesuradamente.

2. Por medio de conferencias se debe explicar, tanto a los oficiales como a los soldados, el resultado peligroso de comer muy poca carne y un exceso de carbohidratos sin vitaminas.

3. Las personas que ejerzan mando sobre las Compañías deberán, directamente, vigilar los comedores con el fin de evitar que ningún soldado consuma ninguna parte de la ración con mayor y marcada parcialidad que otras.

4. El jefe médico de la guarnición deberá expedir un boletín semanalmente en el que se demuestre la clase y cantidad de alimentos que cada Compañía consuma. Esta información debe tener por base las cantidades pesadas, exactas o aproximadas, que rindan en informe los comandantes de Compañía. Esto servirá de barómetro que permita mantenerse o girar dentro de los confines de la seguridad para evitar brotes de la enfermedad.

5. Una huerta grande, que pueda abastecer con una suficiencia de hortalizas a estas tropas todo el tiempo, será la mejor medida preventiva que se puede tomar en contra de la enfermedad en el futuro.

# THE RELATION BETWEEN SYPHILIS AND YAWS AS OBSERVED IN AMERICAN SAMOA[1]

J. C. PARHAM

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All medical men are familiar with the various clinical pictures in the human being that result from infection by the *Treponema pallidum;* far fewer are acquainted with the clinical picture that results from infection by the *T. pertenue* and of this latter number the majority hold that there is no relation between the two treponemata just mentioned, other than a morphological one; in other words, that syphilis and yaws are separate disease entities. A careful survey of the literature of the past and present reveals few champions of the unity of the diseases under discussion.

Observations made by the author during a tour of duty of two and one-half years in American Samoa have tended to discount the belief expressed by most workers in tropical medicine and seem to point to the original unity of yaws and syphilis. While the clinical pictures presented by the two diseases are not exactly parallel, it is contended that they show no greater variance than should be anticipated when the many clinical types of other protozoal diseases, malaria, the Leishmaniases, etc., are recalled.

At this point it may be well to briefly discuss the geographical location and history of the Samoan Islands and people. These islands lie between the parallels 13 and 15 south latitude and in longitude between the 169th and 173rd meridians west. They are essentially tropical.

Prior to the late war the islands of Upolo, Savaii, Apolima and Manona of the group were German Colonies. Apia in Upolo has always been the principal seaport and it is seldom that the

[1] Read at the eighteenth annual meeting of the American Society of Tropical Medicine, at Washington, D. C., May 2 and 3, 1922.

flags of many nations are not seen displayed on the merchantmen loading or discharging therein. It is a typical south sea port and as such under German control, offered for the amusement of the sailor ashore grog shops and women of easy virtue galore.

The earliest recorded contact established between Samoans and Europeans occurred in 1722, two hundred years ago, when they visited by three Dutch ships under Roggenwein. French explorers followed in 1768 and again in 1787. In 1791 the British war vessel, Pandora, visited the Islands. The London Missionary Society established missions in all of the islands shortly after its initial venture in 1830. The United States exploring expedition, under Lieutenant Chas. Wilkes, United States Navy, made the first scientific investigation in the islands in 1830. This expedition was composed of six vessels—a considerable fleet and large personnel for those days. Surveys were made of all of the islands and we are justified in believing that, on account of the amount of work accomplished, together with the friendly attitude and very pleasing personality of the Samoans, considerable intermingling and intercourse took place between the surveying parties and the inhabitants.

As early as 1850, England, Germany, and the United States were represented by commercial agents in Apia and great rivalry occurred between the agents of the countries represented in developing trade, acquiring land, and cultivating friendly relations with the natives.

Since 1900, six islands of the group, with a population at this time of 5679, have been wards of the United States Government with a naval officer as governor and naval medical officers entirely responsible for the health and sanitation of the inhabitants. The distances separating the islands of the group are not too great to permit of free intercourse among the natives.

Ethnologically, the Samoans are Polynesians, probably the finest physical specimens of their race. There is nothing about them to suggest the negro.

It was among those people that my observations were made. As health officer of the only port of entry in American Samoa, every incoming vessel carrying natives was boarded and every native carefully examined before pratique was given. The genitalia of the men were always carefully inspected for evidence of gonorrhea, a quarantinable disease in Samoa. During the performance of this duty several hundred natives were examined monthly but without finding any venereal lesions resembling syphilis. As attending physician to the native hospital for the period of two and one-half years, during which an average of 120 out-patients were examined weekly, no cases of venereal infection other than a rare gonococcus infection were found.

In 1914, a campaign looking to the eradication of yaws was inaugurated. In prosecuting this campaign the writer made a tour of the eastern district of the Island of Tutuila with a population of 3226 at that time. The chiefs of all villages were notified in advance as to the day the inspecting party would arrive and were required to have all hands present. Examinations were checked against the official census returns of the village concerned and thus none escaped. Not a case of venereal disease of any nature was found. To recapitulate: the Samoans have been in contact with Caucasians since 1722. Since 1850, contact has been intimate. No cases of syphilis were seen during a period of two and one-half years service in a hospital which was the only source of medical treatment for a population of over 7000 people. Physical examination of over 3000 Samoans during a period of six weeks failed to disclose evidence of syphilis. It is believed that the facts cited justify the conclusion that the Samoan is not capable of infection by the Treponema pallidum, at any rate by the strains of treponemata that cause syphilis, as we know it in the Caucasian.

The absence of syphilis in the Samoan has been noted on numerous occasions. However, it appears that it has not been accorded the significance it merits. Is not this immunity a very unusual and striking departure from the history of other people of the human race? Is not the immunity from syphilis enjoyed by the Fijian most unusual? Is it not a matter of far more than passing significance that yaws with which nearly 100 per cent of Fijians and Samoans are afflicted in childhood, and which cannot be distinguished by serologic or therapeutic tests from syphilis, affords entire and complete immunity in the human race from syphilis? Various authors refer to Charlouis' experiment of successfully inoculating a native suffering from typical yaws with syphilis and state that there have been many instances of the development of yaws naturally and by inoculation in those affected with syphilis. But Charlouis' experiment was done in 1881, when diagnosis was dependent upon clinical and therapeutic criteria alone—a very insufficient basis for scientific observation.

Surely, as opposed to the great mass experiment just recorded, we cannot consider the few isolated instances of yaws and syphilis that are recorded in the same individual. Considering the great difficulty of differentially diagnosing syphilitic lesions of the skin, I submit that it is unscientific to attempt to differentially diagnose syphilitic and framboesial lesions which are alleged to have occurred in the same individual.

Textbooks on tropical medicines, by authors who hold to the duality of the two diseases, present contrasting tables which set forth the diagnostic differences between yaws and syphilis. Careful study of such tables forces the conviction that often times our predessors' statements are swallowed whole, even in the light of authoritative evidence to the contrary; for instance, the monotony of framboesial eruptions. Manson-Bahr (1) himself an advocate of the duality of the diseases, states that as in syphilis the eruption may be very pleomorphic; it may be a roseola or consist of macules with desquamation resembling a squamous syphilide. Castellani (2) describes the cutaneous lesions thus:

The general eruption develops as follows: minute roundish papules, the size of pin-heads, appear on various parts of the body; some papules soon show a yellow point or minute yellow crust at their apex. Most the papules remain of practically the same size for many weeks, and disappear, leaving occasionally some furfuraceous patches: others become larger, several often coalescing, and frequently acquiring a dark areola in natives, a reddish one in Europeans. Some of the larger papules increase in size, and develop into the characteristic large granulomatous nodules covered with a crust, honey-yellow or brownish, formed of desiccated secretion. In the majority of cases—within three or six months in children, and six to twelve months in adults—the granulomata dry up, shrink, and disappear, leaving dark hyperpigmented spots, or occasionally pigmented areas, on their site, which are most persistent. Though the framboetic granuloma is the characteristic eruption of the secondary stage, there are during this stage other types of eruption or framboesides—papular, scaly, and occasionally ulcerative. An average ordinary case will present at the same time several typical framboesiform granulomata, numerous small reddish papules with the epidermis intact, other papules which have become moist and are covered by a tiny yellow crust, several furfuraceous patches here and there, and spots of increased pigmentation at the place of previous granulomata. Occasionally some granulomata break down, and large irregular ulcers form, presenting in their center reddish papillomatous masses, which in our experience do not usually heal spontaneously. At times in the latter period of the secondary stage peculiar roundish or irregularly outlined whitish patches are present, especially on the back and arms, with a nutmeg-grater-like surface. On closer observation these patches are seen to consist of numerous hard, conical papules, containing in their center an epidermic plug, which is easily removed, leaving a depression in the papules. Sometimes the plugs are spiny, and in this case the eruption closely resembles lichen spinulosus.

Surely the skin lesions of yaws as described by Manson-Bahr and Castellani cannot be designated monotonous in type.

Neurologists are of the opinion that there is a strain of the *pallidum* that has predilection for the nervous system and for this reason one case of syphilis develops general paresis or tabes while another does not; less than one-half of one per cent develop tabes (3). On the other hand, in Algiers where a high syphilic percentage obtains and where there is reason to believe the disease has been present since the sixteenth century, tabes is practically unknown. Noguchi (4) in cultures of *T. pallidum* noted certain definite morphological differences. He states that the lesions caused in the testicle of a rabbit differ according to the variety inoculated and consist of a diffuse or nodular orchitis. He aptly remarks that this is a highly important distinction and if maintained by the study of larger numbers of specimens of the *T. pallidum*, it is capable of throwing light on certain important clinical features of syphilis in the human being.

These facts seem to indicate strikingly that the clinical manifestations of syphilis are modified by stains of the organism, by the resistance of the infected individual, or by other factors as yet unknown. Of these, the former appears to be the predominating and we find one strain attacking vessels and joints with skin manifestations, another the nervous system, and one attacking chiefly the skin as happens in yaws.

Referring to the contrasting tables again, we find that the absence of involvement of the central nervous system in yaws is mentioned as a point of differentiation. But Harper (5) states that tabes and general paresis are found among the Fijians, who are free from syphilis as are the Samoans. He further states that aneurysm and gangosa occur among the Fijians. From this it appears that one more contrasting point must henceforth be deleted from the tables.

It is stated that yaws is not hereditary. Butler (6) who has observed yaws extensively in the Phillippine Islands states that he has repeatedly found in children whose parents admitted or showed evidence of having had yaws, that the Wassermann reaction was positive. He describes such conditions in children who have not had yaws, as deformity of the skull, pustular eruptions, enlargement of the spleen, etc., and illustrates his article with the picture of a mother with yaw-like lesions upon her body and her two months' old child who, to use his words, looks like the original "little old man." This child had stomatitis, an undetermined eye condition and an eroded irritated condition of the skin around the anus—a picture that is classical in its portrayal of hereditary syphilis in a child.

A differential point always mentioned is that the primary lesions in yaws is almost always extragenital. With this there is no argument, but among the natives in whom I have observed yaws, the genitalia were the only portions of the body that were not exposed to the trauma of the bush and that were always kept covered and thus protected from the yaws-conveying fly and other infectious contacts. When a disease changes its usual method of transfer, it is often the case that it also changes its infection rate or virulence, or both. This was noted in the milder type of smallpox from inoculation as against that acquired naturally. It is perhaps best exemplified in plague as transferred in the usual way by the flea, and plague transmitted by droplet infection, which latter practically always assumes the pneumonic form. Again, when a disease which responds to a specific drug is allowed to go untreated, the course of the disease and its immunity reactions are considerably modified, Thus malaria, if untreated, will ultimately develop for those infected a tolerance to the presence of the parasite, so that though infected the individuals do not have symptoms. In my opinion, the lack of ancestral treatment, combined with the difference in personal habits, explains the clinical (framboesial) habitus of syphilis in these natives. When they take on European habits, clothing, and treatment, then tropical yaw-begins to appear more and more as ordinary syphilis. Yaws may briefly be defined then as "stone age syphilis." At any rate, in human beings it seems to immunize to syphilis, and if this observation is correct, the last differential point supporting the duality theory falls to the ground. It seems that it would not be asking too much to request the supporters of duality to explain the extensive unstaged experiment which has been going on in Samoa for two hundred years. If the natives do not have syphilis then why do they not have it? They must be immune to it. The only known protection against syphilitic infection is the actualpresence of *Treponema pallidum* in the body at the time the infecting contact is made, and since contact between Samoans and Caucasians has existed for two hundred years, the conclusion is drawn that the Samoan is protected from syphilis by infection with the *T. pertenue*, which is doubtless a strain of the *T. pallidum.*


RESÚMEN

El autor ofrece observaciones de un período de dos años y y medio, acerca de la frambesia tropical (yaws) en los Samoanos Manifiesta que entre la mayoría de los investigadores de la medicina tropical se expresa la opinión de la existencia de dualidad entre la frambesia y la sífilis. Tal observación está muy en

desacuerdo con los hechos notados en Samoa. Despúes de hacer un breve relato de la posición geográfica e historia de las islas de Samoa y sus habitantes, nos demuestra que en 1722, hace doscientos años, se estableció por primera vez el contacto entre Samoanos y europeos—el que ha sido íntimo desde el 1850.

Ejerciendo el puesto de Oficial Sanitario del único puerto de entrada de Samoa y así mismo de médico a cargo de un hospital de nativos, que es el único medio para el tratamiento de una población de más de siete mil almas, se le ofreció al autor la oportunicampaña que tenía el fin de eradicar la frambesia de la isla. En dad de poner bajo su observación miles de nativos durante una ningun caso se notó la menor indicación de sífilis. Aunque existen oportunidades abundantes para la infección sifilítica, las manifestaciones familiares que vemos en los Caucásicos no existen entre los Samoanos. Parece pues, que el habitante de Samoa no es capaz de infectarse con el *Treponema pallidum;* por lo menos con aquellas razas microbianas que ya conocemos como causantes de la enfermedad. Aunque ya otros también han notado que la sífilis no existe en Samoa, a esa enfermedad sin embargo, nos dice el autor, no se le ha dado toda la significación que merece. El experimento de Charlouis, al cual se hace mucha referencia cuando se trata de la dualidad de la sífilis y la frambesia tropical (yaws), se llevó, a cabo en 1881 cuando, segun es sabido , la diagnosis se efectuaba sobre la base del criterio clínico y terapéutico. Tal criterio, de tal manera, es base insuficiente sobre la cual formular observaciones científicas. Los que creen en la dualidad de las dos enfermedades ofrecen cuadros de contraste sinópticos en los cuales los puntos contrastados no pueden ser comprobados. Un punto, por ejemplo, es la monotonía de las erupciones frambuésicas. Manson-Bahr y Castellani nos dicen haber notado amplia variedad de lesiones.

La rareza de infección frambésica en los órganos genitales la atribuye el autor al hecho de que entre los Samoanos los mencionados órganos son la única parte del cuerpo que recibenabrigo y por lo tanto, además de protección infecciosa, no reciben el trauma de los matorrales. El autor manifiesta que aquellos que mantienen la dualidad de las dos enfermedades deben explicar el porqué de la falta de manifestación después de los experimentos naturales que han tenido lugar en Samoa desde hace doscientos años. Si los indígenas no tienen sífilis, porqué no la tienen? Deben ser immunes a ella; y además, la unica condición conocida que produce inmunidad en un individuo, es la presencia actual del *Treponema pallidum* en el momento de verificarse el contacto infectivo.

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## DISCUSSION BY C. S. BUTLER

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I may arrange my remarks under several headings as follows: A. Things we know about yaws, B. matters about which we are uncertain, C. some suggestions.

Under A we know that:

1. *Treponema pertenue* is morphologically identical with *Treponema pallidum.*

2. That the framboesial gumma (i.e., the uncomplicated tissue reaction to *T. pertenue*) is like that of syphilis.

3. That the serum of yaws patients is immunologically identical in its reactions with that of syphilis. 4. That symptomatically yaws is so similar to certain types of syphilis that they are clinically undistinguishable. 5. That yaws is usually not a venereal disease. 6. That if differences exist (i.e., if there are separate viruses) that these differences cannot be worked out upon animals other than man.

7. That yaws is inoculable and contagious and that it is occasionally venereal in origin.

8. That the older investigations (such as those of Charlouis, made before bacteriology and serology were developed) prove nothing to the modern investigator except that yaws like syphilis

is a contagious and inoculable disease and that it is curable by mercury and iodide of potassium.

9. That the typical framboesial skin lesion uncontaminated by other organisms than *T. pertenue*, is a pathological impossibility.

10. That the tests which we consider as absolutely diagnostic of syphilitic disease in a Caucasian are not considered as valid when applied to a negro or a Malay suffering from yaws (Dark-field, Wassermann and therapeutic tests and pathology).

11. That yaws is *limited* to the tropics and that ordinarily only dark skinned races show its typical strawberry lesions. Such limitation is unparallelled by any other contagious and inoculable disease.

B. Matters about which we are uncertain.

1. Why it is that among native peoples yaws is mostly a disease of childhood? In the absence of a better explanation it would seem that that given by Dr. Parham offers a reasonable line for investigation. According to the excellent paper of Moss and Bigelow at least 25 per cent of 1046 cases of yaws were under five years of age. This is at least eight years before sexual life begins and if yaws and syphilis are the same it offers a chance for investigation as to whether this may explain why yaws is so rarely hereditary. It ceratinly seems logical to attribute its rarity as a venereal disease in part to this fact, since tertiary and latent syphilis are rarely commnicable and rarely transmitted to the offspring.

2. We do not know why places like Santo Domingo and Haiti have so much yaws and so much syphilis and yet places in constant communication with them like Porto Rico, the Virgin Islands and Cuba have little or no yaws in other words why yaws seems to have died out in those Caribbean islands which are the furthest advanced in European habits and customs. If yaws is an entity and breeds true it should not die out when no means are taken to stop it. Also we don't know why yaws stops at the outskirts of cities like Manila and Santo Domingo City. It is a sylvan disease not an urban one. This is *most* remarkable.

3. We do not know why those who have worked with yaws in tropical islands have failed to figure in the large percentage of

syphilis (varying from 10 to 50 per cent) in their studies of the disease called yaws. Thus Hispaniola is given as the home of syphilis by some and of yaws by others and neither group seems to believe that there is any of the alternate disease on the ground to be reckoned with.

C. Some suggestions.

1. We should find out, in places more or less isolated (such as Guam or Samoa) what it is that is giving an apparent immunity *in human beings*, to syphilis. If it is yaws *that is* doing it, then there is only one answer to the question, what is yaws?, for the only thing which prevents people from acquiring syphilis is the actual presence of *Treponema pallidum* in their bodies. The idea of 12,000 people (anywhere in the world) running along for twenty years (as at Guam) and none of them acquiring syphilis is too preposterous for enlightened medical men to seriously contend. It *cannot* be so. The epidemiology of syphilis will guide us to the light in this.

2. It seems to me that we are not much further along in this matter than was Sydenham three hundred years ago who said:

> The lues venerea was introduced into Europe A.D. 1493, from the West Indies, it being, before that time, unknown even by name. Hence the disease is usually considered as endemic to the American colonies. In my mind, however, it is rather referable to the coast of Guinea, or to some portion of the Negro country thereabout. This I think because many of my countrymen have told me that, in slave-ships, even before they have reached America, the disease breaks out—also that it breaks out with the natives in the country itself, and *that* independent of any previous unclean intercourse. Indeed, in some cases, it afflicts a whole family—men, women, and children. The disease that thus comes spontaneously is, in no respect, different from the true venereal lues. The symptoms, the pain, and the ulcers are the same—making allowance for the difference of climate only. The name, however, is different. The African disease is called the *yaws.*

It seems that we have been taking authority when we could have had fact. We have been relying upon animals to tell us the truth when we might have got it from man. In the interest of exactness and of simplicity in teaching, our ideas in this matter should be cleared up, for it is doubtful if there is *any* disease of tropical countries more damaging to the efficiency of the laboring classes than is syphilis. There is room for much constructive work in ridding the native populations of it.

If an extension of Dr. Parham's dictum may be suggested I would say that under stone-age conditions of sanitation, syphilis constitutes one of the exanthemata of childhood.

# SHOULD GANGOSA BE REMOVED FROM THE NOMENCLATURE OF TROPICAL MEDICINE?[1]

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In nearly all textbooks on tropical medicine one finds a section devoted to a condition termed gangosa—a word which has been employed on the Island of Guam for many years to designate a pathological condition characterized by a destructive ulceration of the palate, nose and pharynx. The term in late years, in Guam, has come to include cases of extensive ulcerations of the skin and underlying connective tissue, and nodular lesions of bone which have the gross appearance of syphilitic gumma, occurring coincidently with or independently of the naso-pharyngeal lesions and in mutually remote locations. During recent years knowledge of this condition has accumulated to such an extent that we have reached a point where we might profitably consider whether we are not justified in removing this term from the nomenclature of tropical medicine.

The etiology of the condition has been the subject of much controversy. Gangosa has been thought by some to be a manifestation of syphilis. By others it is thought to be a sequela of yaws. Some believe it to be a clinical entity.

Leys (1) first described those cases which present destructive lesions of the nose and throat, under the name of rhinopharyngitis mutilans. He, together with Mink and McLean (2), believed gangosa to be neither yaws nor syphilis, but a peculiar and independent local disease due to an undetermined specific infecting agent.

One, seeing the facial deformity produced by gangosa, for the first time, would at once think of untreated syphilis as the cause

[1] Read at the eighteenth annual meeting of the American Society of Tropical Medicine, at Washington, D. C., May 2 and 3, 1922.

of the condition, but the medical officers who served in Guam in the early days of American occupancy were led to believe that the condition was non-syphilitic because they found no manifestation of early syphilis among the natives. In fact some went so far as to believe that the native of Guam is immune to syphilis, which of course is absurd, as there is no such thing as a racial immunity to syphilis. They further attempted to rule out syphilis on the ground that apparently the condition did not respond to antisyphilitic treatment.

The disease was considered contagious and the cases were isolated for treatment in a special colony. The treatment used was that advised twenty years ago for chronic phagendenic ulcerations. In spite of conscientious treatment no marked advance was made in diminishing the number of cases, and those which did improve showed a marked tendency to relapse.

In 1910, partly on empyrical grounds and partly because he considered that gangosa bore the ear-marks of syphilis, Odell (3) the senior medical officer in Guam compelled each gangosa patient to take daily as much old fashioned mixed-treatment as his system would handle. This compulsory treatment was effective in time. Three hundred and thirty-eight cases of gangosa existed among a population of 11,000 in 1910.

In January, 1911, after many of the cases had been under mixed treatment almost one year, Crow found that out of 100 cases 85 per cent were positive to Emery's modifications of Wassermann's method. He also found that several blood relations (brothers and sisters of those afflicted, but showing no evidence of the disease) gave positive results.

Halton (4) while investigating frambesia, which is common among the natives of Guam, in September, 1911, found that this disease gave a positive reaction. He also determined that his control cases (apparently healthy natives) which gave a positive reaction had frambesia and those which gave a negative reaction had never acquired that disease.

Corroborating the work of Crow, Halton found that a large majority of the gangosas gave a positive reaction.

Salvarsan was first received in Guam in 1911, and it was soon found that this preparation was remarkably effective in both gangosa and yaws.

An examination of 2429 normal natives in Guam showed that nearly 74 per cent had contracted yaws, generally during childhood (5).

It was found that 83 per cent of the gangosas had had yaws prior to the first symptoms of gangosa.

Kindleberger (6) found that 69 per cent of gangosas gave a positive luetin reaction.

Baermann and Heinemann (7) working in Sumatra found the same to apply to yaws.

Gangosa was at one time thought to be limited to the Ladrone Islands, the Caroline Islands and the Marshall Islands, but cases of ulceration with naso-pharyngeal involvement have been reported from places located quite generally throughout the tropics. The majority of the cases investigated elsewhere than in Guam give positive Wassermann reactions and are readily healed by salvarsan.

As far as our present knowledge permits, it is fair to assume that tropical ulcerations of unknown etiology, giving a positive Wassermann reaction and responding readily to salvarsan or its newer derivitives have as an etiological factor either *Treponema pallidum* or *Treponema pertenue,* which are very closely allied organisms. In fact they are so near alike that competent observers cannot differentiate them morphologically.

The presence of these organisms in gangosa lesions has never been demonstrated in Guam, but in January, 1912, Rossiter (8) reported finding *Treponema pertenue* in smears from a gangosa lesion in a Samoan child. In Rossiter's (9) case the naso-pharyngeal ulceration was preceded by yaws.

Ferdinand Schmitter while working in the San Lazaro Hospital, Manila, reported two cases of gangosa, both of which gave positive Wassermann reactions and histories suggestive of yaws. In one of these treponemata with the tight spiral morphology of *Treponema pallidum* and *Treponema pertenue* were found.

Schmitter also reports a case of mutilating leg ulcer in a patient giving a history suggestive of yaws. Treponemata were found in the tissue about the margins of the ulcer.

The uniform likeness of the gangosa and leg ulcer cases made it appear to Schmitter that they are suffering from one and the same disease. Each gave a history of yaws, had a positive Wassermann, had the same type of treponemata in the ulcer margins and healed rapidly under salvarsan.

Schmitter found the same type of organism in a case of papulo-circinate yaws which subsided readily after the administration of salvarsan. In Manila, gangosa and circinate yaws are rare, although there is plenty of raspberry yaws. In Guam where the naso-pharyngeal lesions are common, papulo-circinate yaws is prevalent. This suggests to Schmitter that papulo-circinate yaws may be a separate variety of disease from framboesia or the ordinary raspberry yaws and that gangosa may constitute a late stage of papulo-circinate yaws.

Theoretically one might consider the treponemata causing papulo-circinate yaws a strain which might account for the preponderance of the naso-pharyngeal lesions in Guam as they were noted there in larger numbers than in any other part of the tropics in proportion to the population.

The advent of salvarsan sounded the death knell of gangosa. Recent reports from Guam indicate that only three or four new cases are encountered in a year. The natives have learned of the value of salvarsan and patients with the early lesions of the condition which used to terminate in extensive facial deformity, are brought at once to the hospital for treatment. Likewise patients with chronic ulcers which have been found to respond so readily to salvarsan, and children with yaws are brought to the hospital for salvarsan as soon as the condition is apparent.

The next generation will find Guam free from gangosa and will learn of it only from the textbooks of tropical medicine unless we remove the term from our nomenclature.

The question as to the exact etiology is still open to discussion. I believe no one will maintain that gangosa is a clinical entity. The fact that the condition gives a positive Wassermann reaction and responds so readily to salvarsan, points to the treponema as the causative agent.

A number of workers in tropical medicine from their observations have quite definitely come to the conclusion that yaws precedes the destructive naso-pharyngeal lesions and other mutilating ulcerations which have been called gangosa.

A great number of workers in the tropics have encountered evidence which has led them to believe that yaws and syphilis are distinct diseases, and there are those who believe them to be the result of strains of the same organism. On the other hand there are those who have become convinced of the unity of yaws and syphilis, and one could go on almost indefinitely discussing the pros and cons of the question of the unity and duality of yaws and syphilis, but the discussion would not be pertinent to this paper. The practical point to the clinician is that both these diseases, whether they are caused by the same organism, strains of the same organism or first cousins in the Treponema family, respond to salvarsan, and that under the influence of salvarsan, gangosa and a host of puzzling tropical ulcerations in patients giving a history of yaws and a positive wasserman reaction have ceased to exist. Therefore, it seems to me that the time has arrived when we should cease to employ the term gangosa, eliminate it from our literature where it merely serves to confuse, and to place the ulcerations which the term was employed to describe into the category of late syphilis or late yaws.

SUMARIO

El autor de este artículo reune la evidencia aducida por varios investigadores y llega a la conclusion de que el uso del termino "gangosa" debe cesar en la nomenclatura médica y de que las ulceraciones que se suponen dicho término describen deben ser puestas bajo la categoría de sífilis o frambiesia avanzada.

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Yours faithfully
Patrick Manson

# SIR PATRICK MANSON: THE FATHER OF TROPICAL MEDICINE[1]

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The death of Sir Patrick Manson in his seventy-eighth year will be regretted throughout the whole civilized world but especially in those vast tropical areas which either directly or indirectly have been so helped out of disease into health through his activities. In his earlier work he was a veritable torch-bearer making his own road as he went, for none had preceded him; but he carefully blazed the trail and now unknowingly or thouthtlessly every day in our work we travel that safe course laid out by him so many years ago unmindful of the difficulties and hardships which he met silently and alone. It matters not what branch of tropical medicine may interest us, we will not go far in it without seeing the wise part played in its early history and development by Sir Patrick Manson. His observations being made with the precision and accuracy which characterized all he ever did, remain in spite of the years, our safest guide.

A review of his life and work furnishes a striking example of the possibilities of real achievement of a single life. Probably no man of his period accomplished so much and certainly no single individual ever did a greater amount of real creative work—work, which in the truest sense, was original research and of a sort which proved to be of the most extraordinarily utilitarian character. There were few indeed of his contributions which were not immediately of the most far-reaching importance in the prevention and cure of parasitic or infectious disease. In the whole realm of medicine there was no truer scientist than Sir Patrick Manson but it is given to few to contribute always

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things having a direct practical bearing on the relief of man from disease: the final high aim of our profession.

It is a long flight from that time in 1877 when as a young man working alone in China he attracted attention to the *filaria sanguinis hominis* to the present time with its wealth of accomplishment in tropical disease study, and yet not a point made has escaped him though in recent years he could only play the part of a keen spectator at a game which he, himself, had started. It has been well said that his work evolved with the development of the microscope. In 1877 and until the final completion in 1879 of his observations on the life history of the *Microfilaria nocturna* his research was done with a one-sixth objective and yet with it he was able to work out the full development in the mosquito's body just as Laveran in 1880 discovered the parasite of malaria. In itself Manson's discovery of the mosquito as an intermediary in the transmission of filariasis was of comparatively small moment, but measured by its effect on other problems it must ever be regarded as one of the greatest of the epoch-making contributions. It was the first evidence of the part played by animal intermediaries in the transmission of disease from man to man apart from the question of the part the host may play in the development of the parasite. Almost at once Manson began applying the principle to Laveran's discovery and it was only a little later that he suggested the possibility of the mosquito as an intermediary in the transmission of malaria. His views on this subject soon became known as "Manson's hypothesis" and it was one of his younger associates and co-worker who was given the distinction of working it out. The story of Ronald Ross' work in India on this hypothesis with its difficulties, its discouragements and its final brilliant accomplishment needs no retelling here. Without detracting in the least anything of our debt to Sir Ronald Ross let us not be unmindful of the part that Sir Patrick Manson played in this great achievement. I have heard the story retold in Sir Patrick's presence and it seemed to me that "there was glory enough for all." It will be recalled that when Ross' difficulties seemed insurmountable the suggestion from Sir Patrick's laboratory made by Louis W. Sambon that the malaria of the sparrow and the culex as a possible intermediary be tested out and thereby many of the difficulties of the problem in man would be simplified. This is a striking illustration of the close touch and the sympathetic relationship between Manson and his pupils and associates scattered, as they soon were, throughout the greater part of the eastern tropics. It was as though he sat at a great switchboard directing, encouraging, setting straight and possibly curbing the precocious enthusiasm of those young men who looked to him always as their chief. Most of these men long ago became famous and their names are by-words to us but it is not likely that the great directing genius behind their efforts will be forgotten by them nor will they permit the part he played to be passed over in writing the history of this glorious period.

The discovery of Manson of the life history of *Microfilaria nocturna* was the first chapter in the conquest of the tropics; the discovery of the plasmodium of malaria by Laveran was the second chapter, and the work of Ross in India proving the anopheles to be the intermediary in the transmission of malaria was the third. The great principle set forth by Manson in his filaria discovery had begun to bear fruit; already to the far-seeing the breaking of the curse of the tropics was in sight. One by one the missing links in the chain were being rapidly added and diseases hitherto inexplicable became comparatively easy of solution.

The next scene in the strange drama was laid in the Pontine Marshes near Rome. Several of Sir Patrick Manson's younger co-workers were to be found there subjecting themselves to the experiment which put to the test the practical application of Sir Ronald Ross' discovery. Would they be able to live in mosquito-proof huts in this most pestilential spot and escape malaria was the burning question. In this group were Dr. Louis W. Sambon and Dr. George C. Low, who today are teachers in the London Tropical School. Not only did they live to tell the tale but they came out of the experiment in the pink of condition. With their experiment was seen the death of miasma and the old air-borne idea of the disease. Another link in the chain had been forged and today the application of the principle is so homely and so commonplace that even the most ignorant swamper accepts it without a doubt or a question.

During the Italian experiment numerous attempts were made to ship infected mosquitoes to London where Sir Patrick Manson awaited them for the next step in the experiment. Shipment after shipment were received with all mosquitoes dead. It was then that through the genius of Sambon an artificial spider's web was rigged up and the mosquitoes lighting in it reached London in safety. One day while observing a group of anopheles at rest in a spider's web swinging to and fro in the wind without being distrubed, Sambon conceived this brilliant idea which made possible an immediate trial in London of the next step.

The volunteer accepted for the experiment in London of allowing an infected mosquito to feed on the human subject in order to prove whether or not the disease actually could by this means be transmitted, was the son of Sir Patrick Manson, a young man then a medical student at Guy's. The story is so well known that its repetition to this audience calls for an apology but hearing it, as I did, from the actors in the original play added something to the tale which I had missed and which I wish it might be my privilege to pass on to you today. I have read the letters of the father on this occasion in which the experimental biting of the son by the infected mosquitoes is related, and an account of that anxious period of waiting (which gave to us the period of incubation of the disease) for the development of symptoms of malaria. Finally he records the occurrences of that great day when the typical chill appeared and parasites were found in the volunteers's blood. The story is told after a long hard day in the laboratory before the great man dared to rest, as though, there were danger of his omitting some important detail. One may well imagine the mixed emotions of the father watching the volunteer-son through a sharp illness which he, himself, had inflicted. Surely never before in literature was there such a blending of paternal affection and scientific zeal: a fine example to some of the misguieded zealots of the day.

There was no sham and no false pretense about Sir Patrick Manson as I knew him. His early difficulties, his mistakes, his ignorances and his lack of professional equipment to meet his problems were related in the frankest way and probably in no other way was he more helpful to the young fellow too sensitive of his own limitations and short-comings. One of the most amusing and yet one of the most helpful anecodotes with which Sir Patrick delighted me was the account of the first view he had of a human trypanosome at a time when that parasite had never been seen in the blood of man. The work in that field on the lower animals had made considerable progress and it was anticipated that very soon man would be found to harbor a similar parasite which would likely prove to be the casue of some definite disease process. In examining the blood of a man, home from a suspected region in Africa, what was thought to be a trypanosome was found. For hours with Dr. Sambon he searched for others but without success. Finally they decided to get more blood films. After a long search they found their patient in a London club enjoying a mild degree of alcoholic intoxication. Their request for more slides of blood did not meet with a sympathetic response but as the need was to them desperate the two zealous scientists persisted and finally succeeded though they did not tell me just what plan of attack they adopted. They then returned to the laboratory and worked throughout the whole night searching for more trypanosomes but without success. In the early dawn Manson went back over the original preparation and one may well imagine his chagrin when he detected that his precious trypanosome was only a mutilated blood platelet.

Such an account is in keeping with his teachings to students who seemed to him more prone to find malaria which did not exist than to fail to recognize its presence. He regarded this as one of the most frequent error in clinical microscopy.

On one of my visits I found the "grand old man" reading the last edition of Colonel Alcock's Entomology for Medical Officers which was just off the press. He was enthusiastic in his admiration of the fine pen sketches accompanying the descriptions. In the days when he had needed such a book, he told us, there was none to be had and he had been obliged to dig out for himself all he got. He then passed on to the question of medical education as it affected tropical disease study. Twenty-three years ago he had been instrumental in the establishment of the London School of Tropical Medicine. It was a simple need which had prompted him in this and little had he known to what an extent this School would develop nor the great part it was destined to play in the development of our knowledge of tropical diseases. His efforts had been stimulated by a very practical need for such training before young men from the English and Scotch medical schools and hospitals were sent to tropical posts far removed from experienced consultants and without even a speaking acquaintance with the diseases they were to combat. It was evident that he had not anticipated the development in a scientific way of the School as it is found today. The School was dear to him and he kept in close touch even with the details when he was kept to his room by sickness. At no time was there a new thing at the School with which he was not as conversant as the youngest enthusiast. Well do I recall his keen interest in the latest additions to the ever-growing knowledge of the life history of the Schistosomum. "Leiper tells me that the monkey drinking the cercaria-infested water shows marked irritation of the mouth indicating that at once penetration of the mucous membrane occurs just as when the native is infested while in the river drawing water" he told me and it was a type of the things which made his latter days full and happy. The schistosomiasis work done in Egypt during the War had been regarded as one of the momentous additions to modern medical knowledge. The part played by the snail, which had been suspected by his associates, was proven and one may readily imagine his proud interest in the work of his own people: men of the School which he had established to give primer knowledge to colonial officers. The School had not only fulfilled his wildest expectation but had become a power in scientific medicine, and chief among all the glory it had helped to win the war!

The accomplishments of the Tropical School during the war will be dealt with by those better able to do justice to it. We must not, however, overlook the superb part they played nor be unmindful of the additions added to medical knowledge by them. When we think of them let us always include in the front ranks Sir Patrick Manson who, while not there, played as great and as vital a part as the most active worker.

The stranger soon threw aside his reserve in the presence of Sir Patrick Manson. The obscure fellow seeing the great man for the first time after following his writings through many years, soon forgot his own insignificance and found himself telling Sir Patrick of his problems at home. I went to him with the perplexities of one of my fellows in North Carolina who wrote me to ask Sir Patrick Manson why he was having such poor success in that particular year (1920) with the treatment of hemoglobinuric fever. Sir Patrick discussed the specific need and told us of his past experience in just such circumstances. Even in his advanced years he had retained his mental elertness and it was obvious that he had sustained the closest familiarity with every phase of his branch of medicine from the time when he began his life work in Formosa, in Amoy and in Hong Kong until this day when all about him he could view not only the fruits of his own handiwork but that also of his students and followers who had been directed solely by him.

During my residence in London General Gorgas, on his way to wipe out yellow fever from its last lair in Africa, died. One of the most notable tributes ever paid by the British to one who was not of their own nation was accorded his memory. In him and his work they, with one accord, recognized the fourth and last chapter in the conquest of the tropics. He it was who had made the last stab of "the dragon which guarded the golden apples in the gardens of the Hesperides." There was no stint in their tribute to our leader nor did the ever-present element of jealousy enter in. On his bier, those of us near by, liked to believe that the wreath of roses lying there was that of Sir Patrick Manson. The planter of the little seed so long ago was paying tribute to one of his followers and most brilliant students, the man who had applied the discoveries of the great pioneer genius to the solution of the greatest problem of modern times.

What could more gloriously round out a man's life than to see the consummation of his conclusions as practically applied by the work of Gorgas in Panama! True it was, that between the inception of the idea of the part played by the insect intermediary in the transmission of disease by Manson, many had joined in the fight and the work of each one was essential for the completed whole. Those of us privileged to pay the last tribute to General Gorgas had very strikingly brought to us the realization of the part our chief and the British chief had played in the conquest of the tropics. Theirs was the first chapter; ours the last. Without theirs, ours could not have been. Without ours the real significance of the vastness of the life work of Sir Patrick Manson could not have been appreciated in this generation. Our debt to him is as great or greater than that of his own nation and it is but fitting that for all time his memory should be kept green by us and those coming after us. No single man ever added so much to our material prosperity and no man ever gloried more than he in our accomplishments.

# CORRESPONDENCE

## THE END OF THE INTERNATIONAL SOCIETY OF TROPICAL MEDICINE

*To the Editor of The American Journal of Tropical Medicine.*
From Professor G. H. F. Nuttall, Sc.D., F.R.S.,
Longfield, Madingley Road, Cambridge.

*Dear Sir:*—With a view to preventing misconceptions in the future, I would ask you to kindly publish the following communication in your JOURNAL:—

The International Society of Tropical Medicine was founded on September 27, 1907, on the occasion of the Fourteenth International Congress of Hygiene and Demography, Berlin, at an informal meeting attended by forty-two gentlemen representing Brazil, France, Germany, Great Britain, Holland, Italy and the United States. Provisional Officers[1] were chosen: Sir Patrick Manson was elected president by acclamation and the writer was chosen secretary-general and treasurer of the Society.

A meeting of the Committee of Management took place in London on July 27, 1908, followed by a conference at which Laws governing the International Society of Tropical Medicine were framed and adopted by delegates of the British, French, German and Dutch Societies of Tropical Medicine. A formal election of officers followed, Sir Patrick Manson and the writer being elected president and secretary-general respectively, whilst Professors A. Laveran and A. Plehn were chosen as vice-presidents.

As time proceeded, it became evident that the society was destined to disappoint its founders, it being recognized that sufficient opportunities for meetings were afforded at international congresses of medicine and hygiene. With the advent of the great war, the late president and the writer concluded that the best course to pursue would be to end the International Society and distribute its funds to the national societies which had mainly contributed to the International Society's funds.

*Financial statement.* At the meeting held in 1907, the sum of £7.18.0. was contributed toward clerical expenses by voluntary subscriptions, whilst at the meeting in 1908, £1.5.0. was subscribed for the same purpose including the printing of the Society's laws. Contributions to the funds of the International Society were subsequently received (1909–1912) from some of the national societies, this money being placed by the writer on deposit account in the name of the International Society with Barclay's Bank Limited, Cambridge.

The total amount received from all sources by the writer, with accrued interest added to January 1, 1921, amounted to £42.19.5. This amount, after deducting a small sum for clerical expenses, was distributed pro rata to the contributary societies as follows after they had signified their formal assent to the proposal sent to them on October 7, 1921.

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[1] For further particulars, see Journal of Tropical Medicine and Hygiene, October 15, 1907.

*Amount paid to each society*

| | £. s. d. |
|---|---|
| Société de Médecine et d'Hygiène Tropicales (Paris. Treasurer Dr. L. Dyé. Rec't. 22. V. 1922) | 16. 4.6 |
| Società Italiana di Medicina e Igiene Tropicale (Rome. Treasurer Prof. Levi della Vida. Rec't. 29. I. 1922) | 10.16.4 |
| Société de Pathologie Exotique (Paris. Treasurer Dr. Ed. Tendron. Rec't. 2. II. 1922) | 6.15.2 |
| Deutsche Tropenmedizinische Gesellschaft (Leipzig. Treasurer Dr. A. Meiner. Rec't. 22. IV. 1922) | 6. 4.2 |
| American Society of Tropical Medicine (Washington, D. C. Secretary-Treasurer Dr. B. H. Ransom. Rec't. 6. V. 1922) | 1. 7.0 |
| | 41. 7.2 |
| Reserved for clerical expenses | 1.12.3 |
| Total | £42.19.5 |

The funds of the International Society having been distributed in the manner above stated and receipts from the several secretaries of the societies mentioned being now in my hands, it devolves upon me as one of the two surviving officers to announce the end of the International Society of Tropical Medicine, greatly regretting that circumstances proved inimical to its development. Strangely enough this event has almost synchronized with the death of Sir Patrick Manson and Professor A. Laveran, the late society's most distinguished members.

I remain, Sir,

Yours faithfully,
(Signed) GEORGE H. F. NUTTALL,
Secretary-General and Treasurer of the International Society of Tropical Medicine.

# NOTICES

## MEDICAL WOMEN'S INTERNATIONAL ASSOCIATION

The second meeting of the Medical Women's International Association will be held at Geneva, Switzerland, from September 4 to 7, 1922. All members are urged to be present. Each society of medical women in the world is invited to send one eligible delegate and an additional delegate for every hundred members.

Interesting reports will be read by medical women from different countries and the constitution of the organization will probably be revised in accordance with the provisions under which it was adopted. Clinics in the different European cities may be visited en route. The attractions of travel in Europe are great this year. Practically all countries are accessible and the Passion Play will be on at Oberammergau during the entire summer.

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# CARBON TETRACHLORIDE AS AN ANTHELMINTIC[1]

MAURICE C. HALL

*United States Bureau of Animal Industry, Washington, D. C.*

Carbon tetrachloride was used to some extent in human medicine as an anesthetic and analgesic at one time, but for over fifty years has not been used as a drug. At the present time it is much used as a solvent for oils, fats, gums, rubber, sulphur, etc., as a fire extinguisher, a cleaning agent for clothing, etc., and as an insecticide. As an insecticide it is less toxic for insects than are carbon bisulphide or sulphur dioxid. It is distinctly less volatile than carbon bisulphide or chloroform, has a higher boiling point, and is much less soluble in water than are carbon bisulphide or chloroform. One part of carbon tetrachloride is soluble in 1250 parts of water at 25°C., whereas one part of chloroform is soluble in 161 parts of water at 22°C. and one part of carbon bisulphide is soluble is 526 parts of water at 25°C. The safety of the drug when introduced into the digestive tract is probably correlated at least in part with its low volatility and solubility.

Administered by inhalation carbon tetrachloride, according to Laffont, acts first on the brain and then on the spinal cord, producing reflexes indicated by active movements. The action of the heart and lungs ceases when the medulla oblongata is affected. In the first phase, that of excitation, there are tonic and clonic movements of a constant character, the heart beat is disordered and augmented, and the arterial pressure rises and then falls, the pupil of the eye being constantly dilated. In the second phase, that of insensibility, the heart beat is very fast, the pulse feeble and the arterial pressure low, the pupil reaching its maximum dilation. In the third phase, that of collapse, the pulse is very

[1] Read before the eighteenth annual meeting of the American Society of Tropical Medicine, Washington, D. C., May 3, 1922.

feeble, the heart beat slows, and finally respiration and heart beat cease; animals are rapidly revived by artificial respiration. Carbon tetrachloride does not affect the oxygen content of the blood. The safety factor in the administration of this drug may be increased by the preliminary administration of morphine. It is reported that frequent inhalations of the drug may cause headache, anemia, vomiting, dyspepsia of a toxic type, and ultimately a toxic jaundice. Veterinarians report that where the liquid drug is introduced into the lungs or the fumes are inhaled as a result of capsules breaking in the mouth in treating dogs and foxes, there is usually immediate collapse of the animal with a cessation of respiration, though the heart continues to beat; many animals are revived by artificial respiration under these conditions. As the vapor of carbon tetrachloride is very heavy, it would seem advisable to keep the head and chest of such an animal lowered in order to assist in mechanically clearing the lungs by permitting the vapor to flow down and out.

In using carbon tetrachloride as an anthelmintic care must be taken to secure a pure product. Among the impurities reported as occasionally present in carbon tetrachloride are carbon bisulphide and carbonyl chloride (phosgene). The editor of the *Lancet* in the number for February 25, 1922, states that Waller has noted that the toxicity of carbon tetrachloride is increased one-third by the presence of carbon bisulphide. This is probably not an exact statement, as the toxicity would be correlated with the amount of carbon bisulphide, as well as with its presence. Morse has reported that approximately twice as much of carbon tetrachloride is required to kill certain insects as is required of carbon bisulphide. The pure drug, introduced into the digestive tract, appears to be astonishingly safe for a number of the experiment animals on which it has been tried. Hall and Shillinger, in a paper now in manuscript, find that dogs will tolerate doses of 16 cc. per kilo and chickens will tolerate doses of 20 cc. per kilo, even where the animal receiving these doses has been given comparatively large doses of the drug a few days previously. As the therapeutic dose for removing hookworms from dogs is at the rate of 0.3 cc. per kilo of weight of animal, the safety factor for dogs is at least 53, the minimum lethal dose not having been ascertained. Monkeys are very tolerant of the drug and Lake has shown that they may be given large and repeated doses without showing evidence of injury or lesions due to the drug on postmortem examination.

Carbon tetrachloride was first proposed as an anthelmintic by the writer in 1921 on the basis of experiments to determine its efficacy against worms, especially hookworms, in dogs, and those results were brought to the attention of the medical profession with the suggestion that the drug deserved investigation as perhaps a useful drug for the removal of hookworms from man. The drug appears to be extremely effective in removing the blood-sucking strongyles, including hookworms of dogs, foxes, sheep and cattle, stomach worms of sheep and cattle, *Strongylus* of horses, etc. It is also of value in removing certain other nematodes, but more work is necessary to determine its relative efficacy in these cases. It is not of value in removing tapeworms. At the present time it is being tested as a drug for the removal of hookworms from man in various parts of the world, and the preliminary reports on this drug, where administered in capsules without purgation, are very encouraging as regards its safety and efficacy. No positive conclusions as to its safety can be reached, however, until a large number of tests are reported. Its apparent advantages are that it is a definite chemical, easily standardized, cheap, easily obtained, does not require a purgative, and is apparently more effective and safe than the drugs now in use.

The best mode of administration of carbon tetrachloride appears to be by means of ordinary hard gelatine capsules, so far as we know at present. The indicated dose for man, based on the dose for dogs, is 3 cc. Care must be taken that the drug does not enter the lungs, and as some individuals have difficulty in swallowing capsules and as hard gelatine capsules soften rapidly in the mouth and open easily on pressure, it is possible that a safer capsule might be devised which would be equally satisfactory as regards opening in the digestive tract. The ordinary soft gelatine capsules might prove satisfactory, but we have no published evidence in regard to this matter. Soft gelatine capsules open in the digestive tract more slowly than do the hard capsules and are hardened by some drugs, sometimes to the point where they fail to open at all. Experiments indicate that carbon tetrachloride loses some of its anthelmintic efficacy when administered in castor oil or when given in capsules and immediately followed by castor oil. As carbon tetracloride does not depress unstriated muscle and appears to increase peristalsis, at least to some extent, no purgation appears necessary with this drug. If purgatives are given, castor oil apparently should not be used except where patients are unable to swallow capsules, and a saline given three hours after the drug would perhaps be the best purgative for use after the administration of capsules.

Experiments show that the combination of carbon tetrachloride and oil of chenopodium is very effective against hookworms and also ascarids, and very good results were also obtained by the use of carbon tetrachloride and thymol. A problem arises in connection with the use of carbon tetrachloride and oil of chenopodium, and that is the matter of the use or avoidance of purgatives. Carbon tetrachloride apparently should be given without purgation, but chenopodium is constipating and more or less toxic and requires the use of purgatives to safeguard the patient. Whether the tetrachloride is sufficiently stimulating to peristalsis to offset the constipating effects of the chenopodium is an open question, and it is also a question as to how each of these two drugs will influence the solubility of the other in the digestive tract. If a purgative is necessary with this combination, probably it should be given at least three hours after the drugs. A combination of carbon tetrachloride and thymol is also very effective against hookworms and appears to be effective against tapeworms.

A matter on which information is very much needed at the present time is that of the amount of absorption and the mode of elimination of carbon tetrachloride. When given to experiment animals in very large doses the drug can be detected in the large and small intestine on shaking up the contents with water, the carbon tetrachloride separating out in discrete bubbles. It displays an anthelmintic efficacy against certain worms in the large intestine which indicates that it is only absorbed to a slight extent in its passage through the digestive tract and that it is largely eliminated in the feces. This assumption is supported by the absence of liver lesions or lesions of other viscera following the administration of large doses of the drug. However, the subject of the absorption and elimination of this drug is one which deserves attention. It is also desirable that more be ascertained in regard to the local and systemic effects of the drug when given by mouth. In very large doses, Dr. Shillinger and the writer find that it occasions some inflammatory reactions, usually not extensive or severe, in the digestive tract.

RESUMEN

El tetracloruro de carbono no ha sido usado como medicamento en la Medicina humana desde hace cincuenta años. Se usó hasta cierto punto una vez como anestésico y analgésico. Es esta substancia menos volátil, tiene un punto de ebullición más alto y es mucho menos soluble en agua que el di-sulfuro de carbono o que el cloroformo. Su seguridad como droga cuando se introduce en el tubo digestivo, está probablemente correlacionada con su baja volatixidad y solubilidad.

Administrado por medio de la inhalación el tetracloruro de carbono es venenoso y algunos investigadores informan que las frecuentes inhalaciones de la droga pueden causar dolor de cabeza, anemia, vómitos, dispepsia de tipo tóxico, y últimamente ictericia tóxica.

Cuando se use como antelmíntico debe investigarse la pureza del producto antes de administrarse. Cuando la droga en estado de pureza se introduce experimentalmente en el tubo digestivo de ciertos animales, hemos observado que no causa el más leve daño. Hall y Shillinger, en un artículo que está ahora en vías de preparación, demuestran que los perros toleran 1 cc. por kilo de peso y que los pollos pueden tolerar hasta 20 cc. por kilo aun cuando aquellos ya previamente habian recibído dosis comparativamente altas. Considerando que la dosis terapéutica que se requiere para remover los guzanos de uncinaria del perro es a razón de 0.3 cc. por kilo de peso del animal, el factor de seguridad que así se establece para los perros es de

por lo menos 53. La dosis letal minima para ellos aun no se ha averiguado. Los monos toleran muy bien la droga. Lake ha demostrado que a estos se les pueden administrar grandes y repetidas dosis sin la menor seña de daño o de lesiones visibles durante el exámen postmortem.

La droga es en extremo eficaz en la extirpación de los strongylus chupantes, incluyendo las uncinarias, guzanos intestinales del ganado, strongylus del caballo, etc. Tiene cierto valor en la destrucción de ciertos nematodes. No tiene ningún efecto, sin embargo, sobre la tenia. Los informes preliminares que se reciben de varias partes del mundo, acerca de su efecto en la extirpación de las uncinarias humanas, son en verdad muy halagadores. Las ventajas aparentes de este medicamento son: es substancia química definida, tiene tipo de normalidad que fácilmente se establece, es barato, es fácilmente obtenible, no requiere purgante y el hecho de ser más cierta y carecer del peligro de las otras en uso.

El mejor método de administración del tetracloruro de carbono es en cápsulas ordinarias de gelatina dura. Se debe evitar que la droga gane acceso al pulmón. Los experimentos indican que esta pierde su eficacia antelmíntica cuando se usa en combinación con el aceite de castor o cuando este último se dá inmediatamente después de las cápsulas. Como el tetracloruro no es depresor de los músculos lisos y parece aumentar la peristalsis hasta cierto punto, no se hace necesaria la catarsis. No obstante, en caso de usarse purgantes, un salino tres horas antes de la administración del tetracloruro sería lo más a propósito. El aceite de castor debe desecharse enteramente.

La combinación de aceite de quenopodio y de tetracloruro de carbono es muy eficaz en contra de la uncinaria y también de las ascárides. Igualmente resulta ser la combinación de tetracloruro y timol.

Un asunto que requiere investigación todavía es el grado de absorción y el modo de eliminación del tetracloruro de carbono. Cuando se administran grandes dosis a animales, experimentalmente, la presencia de la droga se hace demostrable en el intestino grueso y en el delgado. Esto se hace agitando el contenido de aquellos en agua en la que el tetracloruro se ve separarse en burbujas discretas.

Manifiesta este medicamento una eficacia tan poderosa en contra de ciertos guzanos del intestino grueso, que esto de por sí prueba que la absorción de la droga en su paso por el tubo digestivo debe ser leve y desde luego que la eliminación se efectúa vía las materias fecales. Tal suposición la juztifica el hecho de la ausencia de lesiones en el hígado u otras vísceras subsiguientes a la administración de grandes dosis de la droga.

# USE OF CARBON TETRACHLORID FOR REMOVAL OF HOOKWORMS IN HUMAN BEINGS

## A PRELIMINARY REPORT

G. G. HAMPTON

*The International Health Board, New York*

Received for publication June 26, 1922

In the *Journal of the American Medical Association* of November 19, 1921, Dr. Maurice C. Hall, Senior Zoologist, United States Bureau of Animal Industry, published an article on the use of carbon tetrachlorid for removal of hookworms in animals. He stated that the results of the drug were very gratifying and that practically all the worms harbored by the experimental animals were removed by one treatment. He recommended a dose of 0.3 cc. for every kilogram of live weight. Later on he gave to monkeys from two to five times that dose without noting any symptoms of injury. Dr. Hall himself took 3 cc. of carbon tetrachlorid in order to study subjectively its pharmaceutical effects. After taking this medicine he did his usual day's work and was not materially inconvenienced in any way.

With this information at hand it was thought advisable to test out the drug in Ceylon. Prisoners in the Kandy jail volunteered to take the medicine and reported for treatment on January 28. Dr. C. N. Leach administered the drug to a series of fourteen cases, ranging the dosages from 3 cc. to 10 cc. No unfavorable symptoms were noticed. One of the patients was later executed and at postmortem examination no hookworms were found in the bowels.

Another prisoner at the Kandy jail, awaiting execution, was microscopically examined and found positive to hookworm, Ascaris, and Trichocephalus. On February 12 he volunteered to take carbon tetrachlorid and 6 cc. of the drug in 25 cc. of water was administered by Dr. Leach one hour after midday meal (meal 11:30, treatment 12:30). The prisoner was seen again on February 25. He said that shortly after taking the medicine he had passed four large worms. These worms were also seen by the jail guards. The stools were not saved, however, but it is likely that the worms were ascarids. On February 26 another dose of carbon tetrachlorid was given by Dr. Hampton (6 cc., in water) at 7 o'clock in the morning on an empty stomach. No food was given until 8:30 o'clock. The prisoner was seen at 11:45 a.m. He said that he felt giddy and sleepy, but otherwise he was all right.

The prisoner was executed on March 2. A postmortem examination was made one hour after execution. No hookworms or ascarids were found. One Trichocephalus and eight Oxyuris were found in the sigmoid colon. The spleen was enlarged; the liver and kidneys appeared to be normal on gross examination. There were no petechial hemorrhages in the small intestine. The spleen, both kidneys, and sections of the liver and pancreas were removed and sent to the pathological laboratory for examination. Dr. L. Nicholls, Director, Bacteriological Institute, Colombo, reported on the specimens as follows:

> Sections of the kidney showed no signs of cellular degeneration.
>
> The spleen sections showed thickening of the capsule and a small amount of pigment. Probably the patient was a malarial subject.
>
> The liver sections showed no signs of fatty degeneration or any changes from normal.
>
> The pancreas sections showed advanced changes due to autolysis; apparently the tissue had not been fixed rapidly.

Further experiments were desired. The Heneratgoda Garden School consisting of twenty young men, ranging in age from eighteen to twenty-five, had just opened a session with new students. These students are selected from schools in various parts of the Colony and are given a scholarship to the Garden School in order that they may prepare themselves to be teachers. They are, accordingly, a selected group above the average in intelligence. They were approached on the subject of taking carbon tetrachlorid and, after the subject had been fully explained to them, they agreed to be examined, and, if infected with hookworms, to take the drug.

A preliminary microscopical examination was made of specimens of feces from each student and all were found positive to hookworm; in addition, eleven were positive to Ascaris: fourteen to Trichocephalus, and one to Oxyuris. Plain smears were first examined and then all specimens were examined by the salt flotation method. The same findings were recorded by both methods. Hookworm ova were abundant, many appearing in each microscopical field.

A day of treatment was arranged (February 25, 1922). There was no restriction as to work, play, or diet before treatment. Treatment was given at 6:30 a.m. before food had been taken. The dose was 3 cc. in one dose with water as a vehicle. No preliminary or post-purge was administered.

The usual morning meal consisting of *appas* (boiled rice-flour cakes), fruit, and tea with sugar and milk was taken at 7:30 o'clock. Immediately after the morning meal all the students worked in the garden as usual for two hours. They then went to the schoolhouse and did their regular routine school work. Thirteen reported a slight headache and giddiness; four claimed they felt burning or rather tingling sensations in the body; four had no symptoms whatever; and all admitted that the symptoms they felt were too slight to mention. Two of those treated had previously taken chenopodium and one had taken thymol; all three stated that they preferred to take carbon tetrachlorid. The headmaster stated that in his opinion the students were not inconvenienced at all by taking the treatment. He had seen two previous classes take chenopodium and found that they suffered considerable inconvenience at the time.

At 10:30 a.m., four hours after taking the treatment, sixteen of the students had been to stool once, four had been twice, one had been three times and four had not been at all. These four did not have a stool until the next morning. All stools passed for three days after treatment were collected and carefully searched for worms. A total of 719 hookworms (necators) and thirteen ascarids were recovered. The largest number of hookworms recovered from any one person was 161 and the largest number of ascarids was six. Hookworms were recovered from nineteen of the twenty patients and ascarids were recovered from six. No Trichocephalus were recovered. A prize was offered to the student passing the largest number of worms. This had the desired effect in securing a careful saving of all stools for three days.

Microscopical examination of fecal specimens ten days after treatment showed eighteen negatives and two positives to hookworm; indicating that 90 per cent were cured. Specimens were examined by the plain smear and by the salt flotation method. The two positive specimens contained very few hookworm ova; not more than two to the slide could be found. In the preliminary examination several ova appeared in each field with plain smears. See table at end of article for statistical data concerning these experiments.

*Economy and efficiency*

| | COST PER POUND | CEYLON DOSE | PURGE |
|---|---|---|---|
| | *shillings* | *cc.* | |
| Chenopodium | 30 | 1.5 | Magnesium sulphate. |
| Carbon tetrachlorid | 3 | 3.0 | None. |

One 1.5 cc. dose of oil of chenopodium gives microscopical cures in from 30 to 50 per cent of the patients treated, while one 3 cc. dose of carbon tetrachlorid gives microscopical cures in 90 per cent of the cases treated.

Experiments are now in progress in the Children's Hospital, Colombo, to determine a safe and efficient dose of carbon tetrachlorid for children.

## RESUMEN

Con el objeto de comprobar la eficacia del tetracloruro de carbono en la extirpación de uncinarias, de acuerdo con las investigaciones y recomendaciones de Hall, recientemente publicadas, Hampton ha experimentado con dos grupos de individuos, como sigue: Grupo 1. Catorce casos procedentes de una cárcel que se ofrecieron voluntariamente y a quienes se les

administraron dosis de la droga variando desde 3 cc. hasta 10 cc. Resultado: Ningunos síntomas desfavorables. Uno de los sujetos que estaba condenado a la pena capital fué examinado poco despúes de la ejecución y no se le encontró un solo guzano de uncinaria. Otro de los casos que esperaba ejecución, fué examinado al microscopio y se le encontró positivo para uncinaria, ascárides y tricocéfalos. El doce de febrero se le administró a este sujeto 6 cc. de tetracloruro en agua una hora después de almuerzo. Al verlo días después manifestó que poco tiempo después de haber tomado la medicina había evacuado cuatro guzanos grandes. Es probable que estos hayan sido ascárides. El veintiseis del mismo mes la misma dosis anterior le fué administrada a las siete de la mañana, en desayuno. A las 11 y 45 nos dijo que sólo había sentido mareos y soñolencia. Este prisionero fue ejecutado el día dos de marzo. Se hizo exámen post mortem una hora después. No se encontraron ni uncinarias ni ascárides. Exámen de los tejidos no reveló nada de particular.

El segundo grupo lo componían veinte estudiantes de una escuela normal de maestros. Edades de los sujetos variaban de 18 a 25 años. Procedían de diferentes localidades de la colonia. Un exámen preliminar de las materias fecales nos reveló que todos estaban infectados con uncinaria; once, con ascárides; catorce, con oxiuris. Los huevos de uncinaria eran abundantes. En día señalado se administró la droga, en desayuno, en dosis de 3 cc. en agua. No se dió purgante ni antes ni después. Resultado: trece, mareo y poco dolor de cabeza; cuatro, cosquilleos en el cuerpo; cuatro, ningunos síntomas. En general las sensaciones de malestar fueron muy leves y sin importancia. Todas las evacuaciones durante tres días fueron recogidas y examinadas. Se obtuvieron 719 guzanos (necator) y trece ascárides. El mayor numero de uncinarias recogidas de un solo indivuduo fué de 161. De ascárides, seis. Ningun tricocéfalo. Exámen fecal diez días después nos dió a 18 casos negativos y dos positivos lo que indicaba que 90 por ciento estaban curados. Se cree, por lo tanto, que dosis de 3 cc. en agua cura en 90 por ciento de los casos. La tabla adjunta dá detalles de importancia acerca de los casos estudiados.

| Case number | Preliminary examination and treatment | | | | | | | | | | | | | | Worm count and microscopical examination after treatment | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Name | Age | Home province | Hemo. Talq. | Malaria | | Spleen | Preliminary fecal examination | | | | Treatment | | Drug symptoms 4 hours after dose | Number of stools day of treatment | Worm count | | | | | | | | | | | | Total worms (3 days' stools) | | | | Fecal 3/8/22 examination (10 day interval) | | | | Remarks |
| | | | | | | | | | | | | | | | | First day | | | | Second day | | | | Third day | | | | | | | | | | | | |
| | | | | | History | Blood | | H | A | T | O | Date | Dose | | | H | A | T | O | H | A | T | O | H | A | T | O | H | A | T | O | H | A | T | O | |
| | | | | | | | | | | | | | cc. | | | | | | | | | | | | | | | | | | | | | | | |
| 1 | W. D. Kumudasena. | 21 | W. P. | 80 | – | – | Neg. | + | – | + | | 6.30 a.m., February 25 | 3 | "Giddy and headache slight 1 hour after dose" | 0 | 0 | | | | 2 | | | | 0 | | | | 2 | | | | – | – | + | | |
| 2 | J. P. S. Dissanayake. | 20 | W. P. | 80 | – | – | Neg. | + | – | – | | 6.30 a.m., February 25 | 3 | "Slight giddiness relieved after stool" | 2 | 1 | | | | 0 | | | | 11 | | | | 12 | | | | – | – | + | | Had 3 treatments chenopodium in 1921 |
| 3 | E. P. Wijeyatileke... | 21 | Sab. | 65 | – | – | Palp. | + | + | + | | 6.30 a.m., February 25 | 3 | "Giddy—eyesight blurred" | 0 | 0 | | | | 116 | 1 | | | 45 | | | | 161 | 1 | | | – | + | + | | |
| 4 | M. Nagalingam...... | 20 | W. P. | 70 | – | – | Neg. | + | + | + | + | 6.30 a.m., February 25 | 3 | "No symptoms" | 1 | 0 | | | | 38 | | | | 0 | | | | 38 | | | | – | + | + | | |
| 5 | D. B. Dedigama..... | 20 | Sab. | 80 | – | – | Neg. | + | + | + | | 6.30 a.m., February 25 | 3 | "Body tingling" | 1 | 0 | | | | 34 | | | | 8 | | | | 42 | | | | – | + | + | | |
| 6 | A. M. Perera......... | 22 | W. P. | 80 | – | – | Neg. | + | + | + | | 6.30 a.m., February 25 | 3 | "No symptoms" | 2 | 1 | | | | 37 | 1 | | | 7 | | | | 45 | 1 | | | – | + | + | | |
| 7 | D. L. Ranatunga.... | 19 | W. P. | 75 | – | + | Palp. | + | + | + | | 6.30 a.m., February 25 | 3 | "Slight headache and giddiness" | 1 | 0 | 1 | | | 83 | | | | 3 | | | | 86 | 1 | | | – | – | + | | |
| 8 | G. C. Weerasuriya... | 18 | S. P. | 70 | – | – | Palp. | + | + | – | | 6.30 a.m., February 25 | 3 | "Slight headache and giddiness" | 1 | 0 | | | | 1 | | | | 8 | | | | 9 | | | | – | + | + | | |
| 9 | E. W. J. Rambukewala.............. | 24 | C. P. | 80 | – | – | Neg. | + | + | – | | 6.30 a.m., February 25 | 3 | "No symptoms" | 2 | 9 | | | | 19 | | | | 5 | | | | 33 | | | | + | + | – | | |

| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 10 | K. D. Danister...... | 21 | S. P. | 75 | – | – | Neg. | + | + | + | | 6.30 a.m., February 25 | 3 | "Body tingling" | 1 | 0 | | | | 19 | 2 | | | 10 | 4 | | | 29 | 6 | | | – | – | + | | |
| 11 | K. A. Wanakulasuriya................ | 18 | S. P. | 75 | – | – | Neg. | + | + | + | | 6.30 a.m., February 25 | 3 | "Slight giddiness and headache 1 hour after dose" | 1 | 0 | | | | 2 | | | | 12 | | | | 14 | | | | – | + | + | | |
| 12 | S. D. Bastian........ | 18 | W. P. | 70 | – | – | Neg. | + | – | + | | 6.30 a.m., February 25 | 3 | "Slight headache body tingling ½ hour after dose" | 3 | 0 | | | | 3 | | | | 2 | | | | 5 | | | | – | + | + | | Had 2 treatments thymol, 1915 |
| 13 | N. B. S. Sumanasekera | 21 | S. P. | 80 | – | – | Neg. | + | + | + | | 6.30 a.m., February 25 | 3 | "Slight headache 1 hour after dose" | 1 | 0 | | | | 33 | 4 | | | 11 | | | | 44 | 4 | | | – | + | + | | |
| 14 | M. D. S. Gunatilake. | 21 | W. P. | 70 | – | – | Neg. | + | – | + | | 6.30 a.m., February 25 | 3 | "Burning in chest(?)" | 0 | 0 | | | | 0 | | | | 26 | | | | 26 | | | | – | + | + | | |
| 15 | D. J. Ranasinghe.... | 25 | W. P. | 70 | + | – | Palp. | + | – | + | | 6.30 a.m., February 25 | 3 | "Slight headache" | 1 | 0 | | | | 1 | | | | 7 | | | | 8 | | | | – | – | – | | |
| 16 | C. Herath........... | 19 | N.W.P. | 80 | + | – | Palp. | + | – | + | | 6.30 a.m., February 25 | 3 | "Slight headache and giddiness" | 1 | 0 | | | | 14 | | | | 4 | | | | 18 | | | | – | + | + | | |
| 17 | F. B. Petiyagoda.... | 22 | C. P. | 70 | + | – | Neg. | + | + | – | | 6.30 a.m., February 25 | 3 | "Slight headache" | 1 | 0 | | | | 9 | | | | 24 | | | | 33 | | | | – | + | + | | Had 1 treatment chenopodium, 1919 |
| 18 | G. P. Manual......... | 23 | W. P. | 70 | – | – | Neg. | + | – | – | | 6.30 a.m., February 25 | 3 | "No symptoms" | 1 | 0 | | | | 96 | | | | 12 | | | | 108 | | | | + | – | + | | |
| 19 | H. C. S. Wijesuriya.. | 22 | S. P. | 60 | – | – | Palp. | + | – | + | | 6.30 a.m., February 25 | 3 | "Headache and giddiness—slight" | 2 | 0 | | | | 0 | | | | 0 | | | | 0 | | | | – | + | + | | |
| 20 | G. A. Ratnavarathar | 23 | N. P. | 65 | – | – | Neg. | + | – | – | | 6.30 a.m., February 25 | 3 | "Giddiness and numbness of body" | 0 | 0 | | | | 0 | | | | 6 | | | | 6 | | | | – | – | – | | |
| | | | | | | | | | | | | | | | | 11 | 1 | | | 507 | 8 | | | 201 | 4 | | | 719 | 13 | | | | | | | |

# THE GEOGRAPHICAL DISTRIBUTION OF HOOKWORM INFECTION IN THE UNITED STATES, DETECTED IN ARMY RECRUITS[1]

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Examinations of recruits for hookworm in the army camps, conducted by the Medical Department of the United States Army during the late war, afforded unique opportunities of detecting the extent and distribution of infection by this human parasite. The distribution thus detected is not that of the infected population of the country as a whole, but rather that in a selected group of able-bodied men, most of whom had already run the gauntlet of one or more medical examinations, and were, at the time of our examination, in army camps on duty as able-bodied soldiers, or in some stage preparatory to this status. They therefore present to a considerable degree a selected group, since the obviously sick had been excluded.

The data also includes only males, presumably the sex most exposed to infection. Furthermore, the males included are not those of all ages, but only those of military age, the general body of which were between the ages of twenty-one and thirty, with certain numbers below twenty-one and above thirty. They represent a fair sample of able-bodied young men of the United States of Southern residence or exposure with but slight modifications due to selective factors and class of occupation. These selective factors would tend to modify somewhat the representation of classes most liable to infection, especially in some cases, such as agricultural exemptions, which tended to counteract the inclusion of the normal representation from agricultural districts in the hookworm area.

[1] Read at the eighteenth annual meeting of the American Society of Tropical Medicine, May 2 and 3, 1922, Washington, D. C.



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Not all of the states are represented equally in the data, since the orders of the Surgeon-General's Office covering these examinations provided only for the examination of men who entered the army from the hookworm area, or had resided there for six months or more, or who had formerly lived in that area but emigrated to other states of the Union. Percentages of infection therefore which appear for states other than those of the hookworm area are not representative of the normal population of those states but rather of a selected group of persons who have lived within the area of distribution of hookworm and thus have come within the possibility of exposure to infection by hookworm.

Our data therefore are fairly representative of the normal population of males of military age only for states of the hookworm area and only those males of military age who in other states might have acquired the infection by reason of Southern residence.

The total number of men examined for hookworm in the United States Army during the war and reported for inclusion in the medical statistics of the war was 501,472; of these 56,740 or 11.3 per cent were found to be infected with this intestinal worm, upon one examination as a rule. Had repeated examinations been made by the brine flotation method in all cases this percentage would have been increased, perhaps from 25 to 50 per cent. Unfortunately the army records did not permit the allocation of these men to the states of their birth, residence, or enlistment in most of the cases. This was feasible, however, in the case of 126,140 men. Infection in this group will now be examined. (See tabulations on pages 391–392.)

In order that the contrast between the different areas of the United States may be set forth in their relations, we have grouped the statistics under four heads: states in the hookworm area (16 and District of Columbia); the 10 states of northeastern United States; the 13 states of northern Mississippi Valley, or middle west; and 10 of the Pacific slope, including Alaska.

| STATE OF BIRTH | PER CENT POSITIVE | NUMBER POSITIVE | NUMBER MEN EXAMINED |
|---|---|---|---|
| *Hookworm infection in states in the hookworm area* | | | |
| Alabama | 29.4 | 656 | 2,223 |
| Arkansas | 6.4 | 787 | 12,292 |
| District of Columbia | 1.6 | 2 | 121 |
| Florida | 31.8 | 1,202 | 3,778 |
| Georgia | 32.6 | 1,265 | 3,872 |
| Kentucky | 16.3 | 376 | 2,301 |
| Louisiana | 27.3 | 2,010 | 7,348 |
| Maryland | 2.1 | 12 | 584 |
| Mississippi | 27.1 | 2,358 | 8,684 |
| Missouri | 1.8 | 41 | 2,326 |
| North Carolina | 27.1 | 3,402 | 12,558 |
| Oklahoma | 6.9 | 607 | 8,686 |
| South Carolina | 23.5 | 1,918 | 8,135 |
| Tennessee | 12.6 | 1,233 | 9,722 |
| Texas | 11.7 | 3,494 | 29,837 |
| Virginia | 6.7 | 65 | 969 |
| West Virginia | 3.7 | 36 | 972 |
| Total | 17.01 | 19,464 | 114,408 |
| *Hookworm infection in the middle west—Mississippi Valley* | | | |
| Illinois | 1.4 | 17 | 1,153 |
| Indiana | 1.7 | 10 | 582 |
| Iowa | 0.4 | 2 | 418 |
| Kansas | 0.8 | 3 | 354 |
| Michigan | 1.0 | 7 | 665 |
| Minnesota | 1.5 | 5 | 325 |
| Montana | 1.2 | 1 | 81 |
| Nebraska | 0.9 | 3 | 345 |
| North Dakota | 0 | 0 | 82 |
| Ohio | 3.5 | 45 | 1,277 |
| South Dakota | 1.6 | 1 | 63 |
| Wisconsin | 0.7 | 2 | 278 |
| Wyoming | 0 | 0 | 41 |
| Total | 1.69 | 96 | 5,664 |

| STATE OF BIRTH | PER CENT POSITIVE | NUMBER POSITIVE | NUMBER MEN EXAMINED |
|---|---|---|---|
| *Hookworm infection in northeastern United States* | | | |
| Connecticut | 1.5 | 4 | 265 |
| Delaware | 8.7 | 2 | 23 |
| Maine | 0.9 | 2 | 216 |
| Massachusetts | 1.1 | 9 | 813 |
| New Hampshire | 4.2 | 2 | 47 |
| New Jersey | 0.3 | 1 | 284 |
| New York | 0.7 | 11 | 1,479 |
| Pennsylvania | 0.3 | 4 | 1,074 |
| Rhode Island | 1.3 | 1 | 73 |
| Vermont | 1.1 | 1 | 84 |
| Total | .84 | 37 | 4,358 |
| *Hookworm infection in Pacific slope states* | | | |
| Alaska | .0 | 0 | 1 |
| Arizona | 3.1 | 4 | 128 |
| California | 2.0 | 11 | 527 |
| Colorado | 2.4 | 9 | 368 |
| Idaho | 2.7 | 1 | 38 |
| Nevada | 8.3 | 2 | 24 |
| New Mexico | 2.6 | 9 | 345 |
| Oregon | 2.4 | 2 | 81 |
| Utah | 3.2 | 2 | 61 |
| Washington | 2.1 | 3 | 137 |
| Total | 2.5 | 43 | 1,710 |

*Summary*

| | |
|---|---|
| Total number men examined | 126,140 |
| Total number positive | 19,640 |
| Percent infected | 15.5 |

The number of men examined, according to these tables, is 126,140 among 19,640 or 15.5 per cent were found to be infected by hookworm. The percentage of infection in the men outside the hookworm area owes its origin to two factors, the relative importance of which it is not possible, owing to the nature of the data, to disentangle from available records. These two factors are infection due to birth or residence in childhood or later life in states of the hookworm area, on the one hand, and to exposure in southern army camps or service on the Mexican border on the part of recruits in the army service in the years prior to the war, and service in army camps in the hookworm area for more than six months after the United States entered the war. Owing to the sanitary supervision in army camps, it is highly improbable that many cases of hookworm infection could have been acquired by men of the latter group during their period of army service. The inclusion of these two groups of men among those accredited to states outside the hookworm area undoubtedly has tended to decrease the percentage of infection reported for these states. Had the examinations been limited to men of southern birth or residence outside of army service, the percentage would possibly have been higher, because of the varying degrees of sanitary supervision during periods of residence and the tendency for many of these periods of residence to have been more prolonged than those of army recruits.

In view of these considerations, it is evident that the degree of suspicion of hookworm infection which attaches to persons of birth or residence in the hookworm area and subsequent migration to states outside of that area must be somewhat higher than that suggested by the percentages of infection here reported. Thus, for example, in the state of Illinois in which 1,153 men were examined, there were 17 men or 1.5 per cent found to be infected with hookworm. It happens that Illinois recruits at Camp Logan, Texas, who had been there for more than six months, were examined for hookworm and constituted a considerable proportion of the persons accredited to that state. In that camp, among 7,539 patients at the hospital 7.4 per cent were found to be infected, while in 4,807 men on duty in the 15th Division, the percentage was 2.4 per cent. This percentage is higher than that accredited to the state of Illinois, because of the infiltration into this camp of other recruits, largely from the hookworm area. It is impossible to disentangle the extent to which the 2.4 per cent among troops on duty in this camp was due to infections acquired during residence therein, or in like manner to determine in what degree the 1.5 per cent credited to the state of Illinois was due on the one hand to migration from the south into that state, and on the other hand, to local infection acquired by recruits born in Illinois and subsequently residing in the southern army camps. The presumptive evidence is against the acquirement of the infection in the camps, owing to the sanitary supervison of food and of latrines and the wearing of shoes. Only under the most exceptional circumstances, would a recruit be exposed to infection by contact with polluted soil or food or water.

Certain sources of error are inevitable in so large a mass of data as this, gathered under circumstances so diverse. These errors arise from varying methods of examination. Many of the examinations were made by the direct smear method, which is relatively less than 50 per cent effective as compared with the flotation or brine loop method (Kofoid and Barber, 1918). About half of the total number of examinations made were carried on under the supervision of either Major M. A. Barber or the writer, by comparable methods. They constitute therefore a coherent and comparable body of data. The remaining examinations were carried on under diverse supervision and varying methods and were subject to such differences in efficiency as are inherent in these diversities. All of the examinations are subject to errors arising from a single test. Repeated tests would undoubtedly have increased the number of infections perhaps as much as 30 per cent, and 10 per cent if examined by the brine loop method. The lighter infections by few worms are often overlooked or undetected in cases of a single examination only. The percentages of infection here reported fail to represent adequately he degree of infection prevalent, because of the fact that the group of men included are of the age in which infection acquired in childhood is gradually dying out, especially in these cases in which changes have ensued from rural to urban life and from barefoot days to those of the constant wearing of shoes. These changes cut off the opportunities for renewed infection, and combined with the dying out of worms from old age, tend to eliminate in the older men of the group the infection of earlier years.

Imperfect as these figures of necessity are, still they indicate that there is much to be done in sanitary supervision, no only in military camps, but by local and state boards of health, by educational agencies, by industrial organizations, and by other institutions interested in the improvement of the sanitary conditions and of the health and efficiency of the community.

The previous investigations of the incidence of hookworm and morbidity and mortality at Camp Bowie by Kofoid and Tucker (1921), and the investigations of these authors and subsequent ones, such as Myers (1921) and Waite (1921) on the relation of hookworm infection to intellectual efficiency and progress serve to indicate that hookworm infection is an incubus upon the health, education and industrial progress and efficiency of the community and state. There is approximately a 25 per cent reduction in intellectual alertness and efficiency in the case of hookworm infection.

The percentage of infection detected in the hookworm area is 15.5 per cent in 19,640 men. If these men, as our studies on the incidence of disease, have indicated, are more liable to be chronically and severely ill than those without the infection, there is ample justification in the interest of human efficiency, to say nothing of human welfare, for the continued interest and action by the community and by the state in the detection and elimination of these infections among the citizens. Furthermore, investigations by Myers and Waite clearly prove that hookworm infection is associated with intellectual inferiority and impedes and limits the intellectual development of the pupil and restricts his educational progress. Economy and efficiency in education call for sanitary inspection which will detect and eliminate hookworm infections among the children in attendance at the public schools. It is ideally possible by thorough-going and repeated inspection and eradication of the infection by the treatment of infected persons and by proper sanitation to so reduce hookworm infection in this country as to bring it within the group of relatively rare diseases and perhaps permanently to eliminate it from its present widespread relation to human health and efficiency. Once thoroughly done, it does not have to be again repeated, unless a new invasion of infection enters our civil population.

### SUMMARIO

De 507,000 reclutas examinados en los campamentos militares durante la última guerra, se obtuvo un 10 por ciento de infección por medio de la uncinaria. Enlos Estados del Sur es en donde la diseminaciónes mayor y más ponderosa, especialmente en Alabama (29 por ciento), Florída (32 por ciento), Georgia (33 por ciento), Louisiana (27 por ciento), Carolina del Norte (27 por ciento), Carolina del Sur (23 por ciento), Tennessee (13 por ciento) y Tejas (12 por ciento). Otro elemento infectado que existe en otras partes de los Estados Unidos consiste en reclutas de la región norte que habían residido en el sur y nativos del sur que vivían y se alistaron en el norte. El grupo procedente de los Estados de la región noreste presentaba una infección del 1 por ciento; del medio-oeste, 2 por ciento; de la falda del Pacífico, 2.5 por ciento. La uncinaria aumenta la incidencia y la severidad de otras enfermedades, generalmente, porque reduce la resistencia vital. Aumenta la mortalidad de pneumonías tal como lo demostró un estudio estadístico de la División 36 en el Campamento Bowie de Tejas. Baja, así mismo, la eficiencia intelectual de las víctimas. Un exámen de 15,000 hombres verificado por la Junta Psicológica demuestra que aquellos individuos afectados con uncinaria presentaban una clasificación mental reducida en un 25 por ciento de lo normal.

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# THE HOOKWORM INDEX AND MASS TREATMENT[1]

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## I. INTRODUCTION

In a previous paper (1) some suggestions for the mass treatment of hookworm infection were made, in which it was shown that the gravity of hookworm infection should be estimated by the method of worm counting which I and my colleagues have used so extensively in Malaya, Java, Fiji and Brazil.

It is unfortunate in some respects that we possess an easy microscopic method of detecting the presence of hookworm infection; for this has led us to think too exclusively in terms of "percentage of persons positive for ova," rather than in thinking in terms of number of hookworms harbored in the body of the infected person and of number of larvae infesting the soil. We have until recently neglected to a great extent these last two very important factors in hookworm infection.

Mere ascertainment of the presence of ova in stools does not give sufficient knowledge of the severity of the infection or the number of worms being harbored by the infected person. Using this rigorous method of diagnosing the infection, it was found that the microscopist might overlook from 4 to 23 per cent of the positive cases.

But of even greater importance is the information which the method gives us as to the widespread severity of the disease among the agricultural population in the tropical and subtropical

[1] Read by title at the eighteenth annual meeting of the American Society of Tropical Medicine, May 2 and 3, 1922, Washington, D. C.

This discussion is based on data collected in the Orient and Brazil with my colleagues, M. A. Barber, H. P. Hacker, M. A. Barnes, and W. G. Smillie, all of which has been the subject of report to the International Health Board, but only a portion of which has as yet been published.

lands where, as in Java, the average worm count or worm index of men reached the numbers 235 to 378, and in rural Brazil, 228.

It was shown that the percentage of persons infected, as ascertained by ova examination, was no indication of the number of worms harbored or of the number of worms removed by treatment; for whereas only 28 per cent of cases treated were found to have been cured or freed from infection by a first treatment, 90 per cent of the worms had been actually expelled; and when only 49 per cent of the cases had been cured by two treatments, 97 per cent of the worms of the group had been expelled.

All grades of infections are encountered in the endemic regions. In general, agriculturists are severely infected, while town-dwellers are lightly infected. It is more humane to treat these populations which are more highly infected and, in consequence, are suffering more severely from the disease.

Diagnosis by means of vermicide has revealed an incidence of 90 to 100 per cent infection in agricultural regions. The campaign is but slowly moving from village to village and millions of suffering humanity will never come within the reach of the activities of the present workers. When the rate of progress of the campaign is slow, re-infection from the still heavily infested soil will occur. Treatment not only removes the burden of worms which the people are carrying and reduces the number to a minimum but it can be made to remove most of the worms from *all* the people in a given district. This will immediately reduce the amount of soil infestation and only the lighter infections can result.

Hence the strategy of the campaign, whenever possible, should not be one of slow attrition but of massed attack so that new infections or re-infections cannot take place, or will be reduced to an irreducible minimum beyond which it is not possible economically to pursue the infection.

Essentially the problem in hookworm control consists in:

*a*. The installation of the latrines.

*b*. The expulsion of the hookworms harbored by a population by means of medication.

*c*. The prevention of soil pollution.

The essential problem is stated simply enough and no disease with which we are familiar presents less complicated features, on the biological side. It is merely necessary to remove the worms and prevent further soil pollution, from the lightly infected persons and those persons who have not yet come under treatment.

The administrative side of the problem is not so simply formulated. For the reason that:

*a.* Latrines cost money to construct, to erect. It is difficult to persuade administrators, planters, native people, and others of the necessity of constructing and of using them. It is frequently impossible to induce the people to install latrines in time to be of value at the strategic moment when they will be of greatest service in delimiting infection.

*b.* The campaign moves slowly from place to place, at its present rate, permitting a good deal of re-infection to take place. Until mass treatment is instituted and entire populations are treated in a wholesale manner, large numbers of persons continue to seed their environment. Much time is lost by treating only those people who are accessible and living in villages where the infection can be treated at a low per capita cost and where infection oftentimes is much lighter than among the people who work in the soil infested by themselves. A good deal of time is consumed by microscopic examination of feces, in districts where practically 100 per cent of the people are infected with helminths and where nearly 100 per cent of the people over twelve years of age are infected with hookworms—districts in which the use of the microscope for diagnosis might be dispensed with.

A difficult part of the problem is the educational and disciplinary one.

Age-old and time-honored tribal, religious and social customs have bred in certain people the practice of passing their dejecta in or near the water; for the tribal adat or law enjoins ablutions after the act.

Convenience determines that defecation shall be performed in the morning on the way to the spring for water or ablutions, in one of the many clean, shady, sequestered spots—any secluded place in fact—except the filthy, stinking, pit provided by the authorities.

It must be said, however, that some of the most severe hookworm infection to be encountered anywhere is that to be seen on tea, coffee and rubber estates where the coolies being unprovided with latrines, or even simple pits in the planted groves where they spend their working hours, use the shelter of the trees in the plantation, the soil of which becomes so polluted that re-infection is said to occur as fast as it is possible to remove the worms by treatment in small groups.

In discussing the problem of hookworm infection there are certain matters which may profitably be brought under review. The efforts of the International Health Board in coöperation with various local agencies in tropical and subtropical countries, and of certain tropical workers notably Schüffner, Vervoort and Baermann have led to the investigation of some of the factors concerned in the spread of hookworm disease and in its treatment and prophylaxis. These observations and investigations have been carried out in the field in a variety of climatic and environmental influences. The administrative schemes are being checked and controlled by observations made in many localities and by a variety of observers. Public health problems, particularly those having a biological basis, as in hookworm control should be worked out in this way in the region under consideration. Data obtained in European laboratories would hardly apply in Africa or India where the climatic conditions are so different. Malaria, for example, as it exists in the Southern States and as it is transmitted by the American anophelines, can hardly serve for the study of problems to be solved in Java where the species and environment are widely different and where the economic conditions of the people are so unlike those of the South.

Hence the necessity of checking or controlling administrative schemes, particularly those resting on processes not immediately evident to the senses, and of conducting research and investigation *in situ*.

The method of investigation of hookworm infection pursued by the Uncinariasis Commission to the Orient lead to the estimation of the worm content or index by counting the hookworms expelled from a very large number of persons.

In Java, the survey was made entirely by the method of diagnosis by vermicide and worm count.

The worm count method applied to several problems has yielded important information of greater value and of wider range of applicability than the other and less informatory method of estimating the degree of infection by microscopic examination of stools for ova.

Much clearer pictures of the nature of infection, the degree of infection, the correspondence between infection and anaemia, and the effects of soil, occupation, age, sex, and personal habits, have been obtained from worm-counts than from microscopic examination of stools.

More severe degrees of anemia are associated with infection in which *A. duodenale* predominate than when *Necator americanus* more exclusively are found when the number of worms is approximately equal.

The mere presence of ova in the stools gives no quantitative index of the degree of infection suffered by the host.

Whereas by means of a survey in which a representative sample of the population is taken, and their worms expelled and counted, it is possible to estimate the degree of infection of the individuals and the degree of soil infestation to which they are subjected.

Until the report of the Uncinariasis Commission to the Orient was published, there seemed to have been a general impression that there was no correspondence between the number of hookworms and the degree of anemia; this is because comparisons have been made with small number of cases—numbers too small to exclude the error due to small samples. When sufficiently large numbers are taken and averaged, it may be seen that the amount of anemia is proportional to the number of worms.

Such conditions as age, sex, pregnancy, hard labor, and underfeeding and the influence of natural resistance and of variable and inestimable amounts of malaria, so affect the hemoglobin content as to render comparisons difficult; but when specially selected homogeneous groups are studied, it is seen (2) that fewer worms are required to cause a given loss of hemoglobin in a child than in a woman, and fewer in a woman than in a man.

There is a steady loss of hemoglobin with an increasing number of worms. The rate of loss in the worm-groups over 100 is higher than it is in groups lower than 100. This is probably due to the host's ability to make good the losses due to a few worms. The smaller number of worms presumably has the same proportionate effect in causing loss of blood as has the larger number; but the effect of the former is masked and not readily measurable; for this reason, the loss of hemoglobin is understood to mean the measurable or evident effect of the infection and does not include any loss which can be compensated for by blood regeneration.

In an analysis of the cases from the Malay States, the average loss of hemoglobin is 4.3 points per case and the average number of worms is 53.1. Therefore the ratio of the loss of hemoglobin to the number of worms is 1:12.3. In Java, in a series of estimations made independently by another member of the Commission, it was calculated that the number of worms required to cause a loss of 1 per cent of hemoglobin in a man was 11 to 12; while in a boy, it was 7 to 8.

By means of these factors, it is possible, within wide limits, to calculate the amount of anemia in a community, due to hookworms, and that due to other causes, such as malaria by difference.

Thus it has been seen that the severity of the disease depends, not on the mere fact of infection, but upon the number of worms being harbored. It follows from this that we must concern ourselves, not merely with the fact of infection, but with the amount of infection. Heavily infected persons and heavily infested soils should receive preferred attention. The grades of infection or the worm-index of groups of individuals as influenced by age, sex, or by habits and environment, must be ascertained. This is readily obtainable by the method of worm-counting. It is more humane to treat those wretched persons who are suffering from the more severe infections than the more lightly infected ones. Agriculturists, who are carrying a burden of 200 or 300 hookworms, demand our attention before the lightly infected townspeople and mountaineers and others, who may harbor no more than 25 worms.

Not only is it more humane to treat the heavily infected persons first; but by this means, the corresponding heavily infested soil is treated as well; and a source of infection of great magnitude is removed. These people and their soils are veritable nests of infection, and nests of infection in any disease demand immediate attention.

While the worm index is of some value in estimating the degree of soil infestation and of exposure to soil infestation, it is highly desirable to know as much as possible about the behavior of hookworm larvae in the soil, particularly their longevity as influenced by temperature and moisture and their natural enemies in the soil.

## II. THE HOOKWORM INDEX

### *The index of infection in uncinariasis*

Uncinariasis, more than any other disease with which the health officer has to deal, can be expressed quantitatively; that is to say, the amount of the disease from which the patient is suffering, and the amount of the disease from which the community is suffering, can be ascertained and expressed quantitatively.

In the case of other diseases, the health officer has to depend on the incidence as reported, or on the mortality, or case-mortality rates of disease in order to be informed of the amount or severity of the disease in the community. This is true of typhoid fever, tuberculosis and measles, for example. In malaria, it is true, the epidemiologist receives some help from the splenic and endemic indices as well as from a determination of the sporozoite rate; and they enable him to tell, within wide limits, whether malaria is present, and whether it is mild or severe. But none of the tests convey as exact a quantitative idea of the amount of disease from which the individual or the community may be suffering, as in Hookworm infection when expressed in terms of worm-index.

Hookworm infection is slowly acquired from infested soil during all periods of life after the first year of life, chiefly, however, among bare-footed persons in the more active years. The number of worms that are harbored slowly increase from month to month, depending on the amount of exposure to polluted and infested soil, on the amount and intensity of soil infestation, and on the degree of individual resistance to infection. The barefooted population visit daily the polluted places, adding to the amount of hookworm infestation in the soil, and receiving, at the same time, from the infested spots or area, elements of infection, some of which—from time to time—succeed in reaching maturity in the intestinal tract of the human host.

The Uncinariasis Commission to the Orient from a very large series of observations showed that there is a correspondence between the number of hookworms harbored and degree of anemia. On account of individual variation and different conditions of *age*, sex, pregnancy, malaria, occupation, and underfeeding, as well as hard labor, etc., this correspondence is not always evident in individual cases, or in small numbers of cases; but when several hundred cases are bulked and averaged, the correspondence is unmistakable and striking.

The degree of infection from which a community is suffering, may be expressed by an index of a representative sample of the group, which is the average number of worms being harbored by members of the group in question—men, boys, women or girls; or of a group further influenced by occupation, as agriculturists working in self-polluted soil, or of town-dwellers, somewhat more protected from infection than agriculturists.

*The infective or worm-index of a group varies directly with the amount of exposure to infested soil*

Soil infestation is the result of a number of varied circumstances, and depends, in the first instance, on soil pollution by infected persons; and is secondarily influenced by humidity, temperature, rainfall, dryness, natural enemies of the larvae, etc. Actual amounts of soil infestation, we are in almost complete ignorance of; but the work of Baermann and of Cort will tend to remedy this defect.

As the infective index, or number of worms harbored, is reciprocal to the amount of soil infestation, and as it is an expression of the amount of exposure to infested soil, the worm-count will give us important information as to the opportunities for acquiring infection in any given district.

The striking differences in worm indices noted in various groups of Oriental and Brazilian people have led me to pay particular attention to the indices as influenced by age, sex, occupation, degree of exposure to pollution and racial customs, etc.

### *Sex and age*

Men are usually the most severely infected in regions of high endemicity; and this is due to the greater exposure to which they are subjected.

Indices among women exposed to heavily infested soil may be as high as those found among men. The highest index among Tamil men was 1063; while the highest among women was 1228; among boys 402; among girls 365. Sex does not appear to offer any protection whatever against infection. Whenever the lightly infected women of the village have to go out into the polluted gardens or fields to work where soil infestation is greater than in the village, they acquire indices of infection as high as those of the men.

Exposure to infested soil is progressive and the infection which results is cumulative. High indices do not, as a rule, occur at once in children. The first year of life is almost always exempt from infection; for contact with infested soil does not occur until the child can run about with his mates and visit the infested places where the children customarily defecate.

The worm indices of a group of Tamil children on a rubber estate in the F. M. S. showed the following interesting increase with their advancing age:

| | AGE | | |
|---|---|---|---|
| | 3 to 4 | 5 to 7 | 8 to 10 |
| Worm index | 57 | 89 | 123.5 |

A group of children of Eurasian parentage, partly protected and sheltered from infection and living in a school, not only showed a slight correspondence between age and worm index but they showed as well that the percentage of infected persons in the group was similarly correlated with age; that is, as age increased, more and more persons became infected and the infected persons harbored more and more worms.

| | AGE | |
|---|---|---|
| | 3 to 7 | 8 to 12 |
| Per cent infected | 47 | 71 |
| Worm index | 9 | 11 |

In the following tables the worm indices of 344 Javanese are given, analyzed according to age, sex and district.

Table 1 shows the number of cases and the average number of worms harbored by the group, or the worm index.

TABLE 1

*The hookworm index as modified by age, sex and locality*

| PLACE | MEN | | BOYS | | WOMEN | | GIRLS | |
|---|---|---|---|---|---|---|---|---|
| | Number of cases treated | Average number of worms | Number of cases treated | Average number of worms | Number of cases treated | Average number of worms | Number of cases treated | Average number of worms |
| All Batavia kampongs, town dwellers | 23 | 50 | 16 | 21 | 32 | 23 | 11 | 26 |
| Jail, Batavia | 109 | 79 | 0 | | 0 | | 0 | |
| Gebongelir, fishing village | 18 | 80 | 7 | 47 | 21 | 24 | 4 | 11 |
| Mountain villages. | | | | | | | | |
| Endil | 10 | 48 | 3 | 84 | 9 | 51 | 3 | 24 |
| Tjimatjam | 9 | 8 | 2 | 29 | 8 | 1 | 4 | 0.5 |
| Batak Highlands | 4 | 5 | 0 | | 0 | | 0 | |
| Agriculturists: | | | | | | | | |
| Kalimaru | 9 | 378 | 5 | 90 | 7 | 74 | 4 | 85 |
| Kebasekan | 9 | 235 | 4 | 150 | 9 | 162 | 4 | 26 |

The first group from the Batavia kampongs were native Malays. They are barefoot and enjoy some considerable measure of protection from infection. Many of them defecate in a latrine in the kabun or garden on the premises where they live. A few public conveniences have been provided by the authorities recently, where the feces are passed in septic tanks. However, large numbers of people defecate in the river-canal which runs through the city, and they use the ditches and drains which penetrate many of the streets. Gross evidences of feces were frequently observed in these drains (from which infectious material is carried out to sea) in the kampongs of the city. The indices here are typically those of persons partially protected.

The index of the men is 50; of boys 21; of women 23; of girls 26. This index represents an infection, for the greater part, derived from the soil of kampongs in the city; but a modicum is introduced from without in the persons of newly arrived immigrants from the country seeking work.

In spite of the constant influx of country people, the index in each kampong is well below that which is usually associated with manifestations of disease. The boys and girls are all born in the city and their indices are indications of the relatively slight opportunity for picking up infection in the city.

The inmates of the jail in Batavia brought all of their infection into the jail with them; for there were no opportunities for acquiring infection or re-infection inside its walls. The inmates represent a population which is slowly losing its hookworms by the natural process of old age of the worms.

This group will be discussed later.

The group at Gebongelir were fisher folk, although one or two of the men may have worked at agriculture in the village nearby. They represent villagers living in the country but not working the soil. They defecated in kabun latrines; and, to a less extent, in ditches and streams. The worm index of men is 80; of boys 47; of women 24; of girls 11.

The people of Endil, Tjimatjam and from the Batak Highlands of Sumatra were mountaineers living in little villages. They were agriculturists and cultivated rice. They defecated in the kabun latrine and in the streams. But the streams were mountain streams and had possibly not been polluted to the same extent as those at lower altitudes or at the sea level. These people as well as the mountaineer folk in Viti Levu Fiji had low indices for agriculturists.

Passing now to two typical agricultural villages in mid Java at the lower altitudes and at sea level, we find a people surrounded by paddies where rice and cane are intensively cultivated. The people defecate in little pits in the kabuns (back gardens); but there is some soil pollution there; for it was evident to the senses in inspecting the gardens. About half the people interrogated said they defecated in streams and ditches. The worm-indices of the men were 378 and 235; of boys 90 and 150; of women 74 and 162; of girls 85 and 26.

These indices are typical of the heavily infested agricultural districts in Java, where the people work in infested soil and presumably infested water.

In Brazil, somewhat similar indices obtained for rural populations. Men 228; boys 191; women 89 and girls 80.

The village of Kalimaro was only distant about one short mile from the fishing village of Gebongelir; yet, notwithstanding this, the indices were 2, 3, 4, and 7 times as great in the agricultural village as in the fishing village.

It is apparent that there is a considerable difference in their worm indices between the town-dwellers of Batavia and the agriculturists of mid Java; and this is an expression of the degree of soil pollution and of soil infestation occupation, and habits in the two locations.

But it has been observed that there is a considerable difference also between the indices of the sexes; and this can be brought out rather strikingly if the percentage composition of the worm-content of the four age-sex groups is shown.

In table 2, the percentage composition and proportionate number of the age-sex groups are shown. As 3 of the 4 kampongs of Batavia possessed no boys or girls in the treatment groups, they are excluded from the calculation of the totals. The proportionate numbers show that girls are usually less infected and have lower indices than women; women less than boys; and boys less than men. Taking an average of 6 kampongs from four types of localities with girls as unity, women had 1.7 times as many; boys had 4.4 times as many; men had 4.9 times as many hookworms as the girls.

TABLE 2

*The percentage composition of the worm content of a place—sample, in age and sex groups*

| PLACE | MEN | BOYS | WOMEN | GIRLS |
|---|---|---|---|---|
| Jaagpad* | 32.4 | 0 | 38.0 | 28.8 |
| Djmbatan Lima* | 15.9 | 61.5 | 22.4 | 0 |
| Sewah Besar* | 42.1 | 10.2 | 46.7 | 0 |
| Kramat | 49.7 | 34.3 | 3.6 | 11.7 |
| Tjimatjam | 21.2 | 74.6 | 2.7 | 1.2 |
| Endil | 23.3 | 40.3 | 24.7 | 11.5 |
| Gebong | 48.8 | 29.1 | 14.7 | 7.1 |
| Kalimaru | 59.7 | 14.2 | 12.2 | 13.4 |
| Kebasekan | 40.7 | 26.0 | 28.1 | 4.5 |
| Total | 243.5 | 218.8 | 86.2 | 49.6 |
| Percent composition | 40.6 | 36.4 | 14.3 | 8.2 |
| Proportionate number | 4.9 | 4.4 | 1.7 | 1. |

* The percentage not included in totals.

TABLE 3

*Relative numbers of hookworms harbored shown by proportionate numbers*

| PLACE | MEN | BOYS | WOMEN | GIRLS |
|---|---|---|---|---|
| Kabasekan | 8.8 | 5.6 | 6.1 | 1 |
| Kalimaru | 4.4 | 1.0 | 0.9 | 1 |
| Gebong | 6.8 | 4.0 | 2.0 | 1 |
| Endil | 2.0 | 3.5 | 2.1 | 1 |
| Kramat | 4.2 | 2.9 | 0.3 | 1 |

In table 3 the relative numbers of worms harbored by men, boys, women and girls are shown by means of proportionate numbers. In this table, only those villages were taken where the people harbored fair numbers of worms. In this way, the errors due to small numbers, are to some extent obviated.

Personal familiarity with the habits and customs of the natives, derived from residence near the native villages and from daily contact with them in their villages during the prosecution of hookworm and malarial surveys, leads me to believe that the figures of the foregoing table represent degrees of exposure to infection to which the different age and sex groups are subjected.

### *Race and occupation*

It is extremely difficult, if not impossible, to ascertain whether one race is more resistant to hookworm infection than another; for the reason that each race has a different personal hygiene and, to a great extent, follows somewhat different occupations—consequently, is exposed to different degrees of soil infestation.

Chinese mining coolies use small latrines, frequently passing their feces into a disused mine hole containing water. Chinese market garden coolies dilute their feces with water and, after standing a period, use it for fertilizing gardens.

Malays defecate into or near small streams but they bathe and cool their bodies often times with polluted water. Tamils will freely pollute the soil anywhere and the odor emanating from Tamil coolie lines is characteristically fecal.

The relative resistance of persons to infection cannot be ascertained by a mere determination of the percentage of persons disclosing ova in their stools. This must be in part ascertained by a determination of the number of hookworms harbored.

The worm count does give more information for, if two persons are exposed to the same amount of soil infestation, and one acquires 59 worms, and the other 239, the latter, it would seem, has the feebler resistance to infection. But we have no way to ascertain the degree of exposure to infestation to which the two persons have been subjected. For infection is very slowly acquired and many month-hours of exposure to infested areas are required before any notable number of worms is gained.

Even in a group of persons of the same race and habits and occupation, living in the same environment, and of the same age and sex, the amount of individual variation in the number of hookworms is very considerable.

All grades of infection were encountered in the three races dealt with in Malaya. The highest number of worms expelled from a Chinese was 1319; of a Malay or Javanese was 1139; and of a Tamil was 1063, (man) and 1228 (woman); a North Indian, 1003. Under conditions of soil infestation in the Orient where we worked, there would seem to be no racial difference in the ability of the different people to acquire severe infection of this grade.

Occupation and personal hygiene appear to determine the grade of infection to a very great extent. This is strikingly brought out in a comparison between the Tamils engaged in building roads and those engaged in handling night soil which they collect from the closets of the town of Kuala Lumpur, Federated Malay States. The night soil is collected daily in buckets, carried to a burial place, where it is placed in holes dug in the ground. The buckets are then washed in a neighboring stream, the shores of which are heavily polluted and infested with hookworm larvae. The burial place has been used for several years and, in all likelihood, is infested to an extraordinary degree. Over this soil, the men carry the buckets and acquire infection. Children accompany their parents to the grounds.

| | MEN | WOMEN | CHILDREN |
|---|---|---|---|
| | | *Road coolies* | |
| *WI | 102 | 53 | No cases |
| | | *Night soil coolies* | |
| WI | 165 | 82 | 39 |

*WI=Worm index.

The indices of the road coolies are much like those of the agriculturists; while those of the night soil coolies are decidedly higher. That the higher index is due to infection from handling night soil of Chinese, we may assure ourselves by noting that while the average number of *Ancylostoma duodenale* among road coolies is 1.69, that of the night soil coolie is 14.14, or about 8 times as great.

My colleagues and I have shown elsewhere (2) that Chinese harbor 16 to 30 times as many *A. duodenale* as the Tamils.

It will be shown later that the number of ancylostomes increases with the service years.

In these two groups the night soil coolies harbor 55 per cent more worms than the road coolies and they have also five times as many more ancylostomes. But this is not an extraordinary number considering the enormous amount of infectious material to which they are daily exposed. It would appear that natural bodily delimitation of infection is constantly taking place, due to some protective mechanism.

The effect of a better personal hygiene as practised by persons living in the towns is seen in noting the indices of women, clerks, police, shopkeepers, institutional children and European planters.

The persons enjoying a good protection are European planters, but a few men are no doubt infected when they walk barefooted to the bath or river.

In Fiji, the only Europeans infected were a few young men who had been born in Fiji and who as boys had gone barefoot about the plantation or village.

In Malaya, seven infected planters who had lived for many years in the tropics, had a worm index of 26, the number of worms ranging from 8 to 70.

Another well protected group were some Japanese women living in the Federated Malay States whose worm index was 12.4. This index is an indication also of the lighter infections usually harbored by town-dwellers.

A group of Sikh and Pathans from North India who had been living in the Federated Malay States for several years as police and watchmen and thus exposed to a minimum of infection had low indices.

| | MEN | WOMEN |
|---|---|---|
| WI | 8 | 2.5 |

The Eurasian population are usually of the kerani or clerk class and live in the cities well protected from soil infestation and dangers of infection. Their index was low.

| | MEN | CHILDREN |
|---|---|---|
| WI | 14 | 9.8 |

On the rubber estates Tamil women are found to be nearly as efficient tappers as the men; consequently, many of them are sent out into the planted area where the soil is infested. On the other hand, men are given work in the factory, handling the latex and preparing the rubber crepe. Here the chances of acquiring infection are minimized. The older children are also given employment outside at weeding. This tends to alter the usual type of ratio between the ages and sexes in regard to the worm index, and we find the women more highly infected than the men, and find the men even less highly infected than the children, as the following indices show:

| | WOMEN | CHILDREN | MEN |
|---|---|---|---|
| WI | 145 | 100 | 73 |

These indices point unmistakeably to the influence of occupation in exposing a sex and age group to unusual degrees of infection—degrees to which they would not have been exposed in the ordinary course of village life.

### *Malays living in the Federated Malay States*

*Malays born in the Federated Malay States.* These people are bare-footed agriculturalists. They are more cleanly than the Tamil estate coolies and defecate in or near the water. They do not spend so much time in the fields nor do they walk about so much as the Tamils. Consequently, they should have a lower worm index.

| | MEN | BOYS | WOMEN | GIRLS |
|---|---|---|---|---|
| WI | 93 | 49 | 43 | ? |

Malay men from Sumatra who had lived in the Federated Malay States several years and at times had been employed on rubber estates had an index of 89.

Javanese Malays, men who like the Sumatra Malays had lived in the Federated Malay States a few years and had worked on rubber estates, had an index of 132.

The index suggests that some of these worms had been brought with them from Java where the index is higher than it is in the Federated Malay States.

*Chinese living in the Federated Malay States*

The Chinese emigrants came to the Federated Malay States from town and country and they usually possessed an index lower than that of Tamils of Malays although a few men with very high indices entered the country.

A number of these emigrants examined at the quarantine depot, St. John's Island, had the following indices:

| | MEN | WOMEN | CHILDREN |
|---|---|---|---|
| WI | 32 | 55 | 10 |
| *Town-dwelling Chinese living in the Federated Malay States* | | | |
| WI | 36 | 26 | |
| *Rubber estate and mining Chinese coolies* | | | |
| WI | 65 | | |

*Tamils living in the Federated Malay States.* Most, if not all, these people came from Madras and were agriculturalists employed on rubber estates. Several groups of these people were examined at different times and places.

One group treated on estates after they had lived in the Federated Malay States for about six to eight months on rubber estates had the following indices:

| | MEN | BOYS | WOMEN | GIRLS |
|---|---|---|---|---|
| WI | 97 | 64 | 44 | 33 |

*Rural Fiji*

The Fijian autocthonous population of the archipelago was examined in two localities. In the first, a coastal district, the people have begun to use latrines to which they take kindly. But the index here is still high even among the well cared for chiefs. The index of nine men was 142; while the range of worms was from 14 to 444.

In the mountains everywhere the indices are lower than on the fluviatile river plains below and Fiji is no exception to this rule; for the index of 15 mountaineers at Nasoqo was:

| | MEN | BOYS | WOMEN | GIRLS |
|---|---|---|---|---|
| WI | 16 | 102 | 47 | 17 |

It is worthy of note that in Java and Fiji the mountaineer boys had a higher index than the men.

*Rural Brazil*

Men, women and children who work in the coffee fazendas go out into the groves and oftentimes spend the entire day gathering and cleaning the beans and caring for the trees. No latrines are provided for them in the planted areas and they void their excreta in the groves and gullies and in the woods nearby.

| | MEN | BOYS 8 TO 15 | WOMEN | GIRLS |
|---|---|---|---|---|
| WI | 228 | 191 | 89 | 80 |

*Rural Brazil—town-dwellers*

These people do nor go into the coffee groves nor do they work in the fields. They are shod, and use latrines. Some of this infection represents the modicum left over from the period when as children or adolescents, they went barefoot.

| | MEN | BOYS | WOMEN | GIRLS |
|---|---|---|---|---|
| WI | 6–33 | 14 | 12 | |

### *Altitude*

Three groups of mountain folk were examined:

| MEN | BOYS | WOMEN | GIRLS |
|---|---|---|---|
| *Sundanese Malays in the Preanger Java, where the indices were found to be as follows* | | | |
| WI Tjimatjan 8 | 29 | 1 | 0.5 |
| " Endil 48 | 84 | 51 | 24. |
| *Batak Malays from the Batak Highlands Sumatra* | | | |
| WI 5 | | | |
| *Fijian autocthons from the village of Nasquo Viti Levu Fiji* | | | |
| WI 16 | 102 | 57 | 10 |

The climate here is still tropical and there is no apparent reason for the lighter infections other than possibly the washing out of larvae to lower levels by the rains. Some unknown factor raises the index of the boys high above all other groups.

### *Influence of intensified soil pollution and soil infestation on the worm index*

In ascertaining the worm indices of Tamil coolies working on rubber estates, it was found that there was a difference on different estates.

In the hilly country of the Federated Malay States lower indices were the rule, whereas in the flatlands, higher counts were often encountered. The same was true of Java and Fiji Tamil children in the hilly country of the Federated Malay States had an index of 56; while the index of some of those of the flatlands was 145.

Not all of the flatland estates presented this evidence of intensified soil infestation. Indeed, on one estate the children had a much lower index than the children from the same but distant part of the plantation.

The difference between the indices of Batavia and those of the agricultural kampongs (Kalimaru) are undoubtedly due to the intensified soil pollution in the latter place.

### *Rate of acquisition of infection*

Infection is but slowly acquired. This needs special emphasis because the knowledge is of strategic value whenever it is desired to rapidly reduce infection and soil infestation by mass treatment.

The exact rate of acquisition of hook-worms is difficult to determine for the reason that the habits and occupations change in such a manner that the individuals are exposed to varying degrees of soil infestation. The total number of worms acquired per year in an agricultural district is more than the number acquired in a town.

Among the boys of an agricultural dessa in Java and among Tamil children in the rubber estates of the Federated Malay States perhaps 12 worms are acquired each year after the end of the first year. While in the City of Batavia where there is still some soil infestation, the annual worm increment is not above 2.5 up to about the ninth year.

Even where the conditions for acquiring infection are of the greatest intensity as among those night-soil coolies who are daily exposed to intense soil infestation, the acquisition of infection is held within limits as may be seen by noting the rate of acquisition of *Ancylostoma duodenale* by the coolies.

The night-soil coolies are pariahs and work continuously at this vocation for "Once a night-soil coolie, always a night-soil coolie." They constitute a caste living by themselves.

The average number of *A. duodenale* among the coolies who had worked but one year in the service was 1.6. As this is the normal ancylostome index of Tamil coolies, it seems that on the average no ancylostomes are acquired during the first service year. From the second to the fifth years inclusive, the Ancylostome index among the coolies is 14; and from the sixth to the tenth years, the ancylostome index is 21. The net gain in ancylostomes, therefore, cannot be more than 2 to 3 per year under the circumstances.

### *Rate of natural loss of hookworms*

The expression *net gain in worms* was used because the absolute number of worms acquired is more than the index actually records. For the reason that the average duration of life of the hookworm is about eight years. Consequently, a few worms are dropping out from year to year. Barber and Hacker determined this point in Pt. Swettenham. For among natural stools of infected coolies who were under observation to be treated later were detected single specimens of *N. americanus.*

An analysis of the average number of worms harbored by prisoners in the penitentiary at Batavia in relation to the length of time they had been in prison shows that there is a tendency for the number of worms to diminish as the length of time increases.

| LENGTH OF TIME IN PRISON | AVERAGE NUMBER OF HOOKWORMS PER MAN |
|---|---|
| Less than one year | 110 |
| One to five years | 80 |
| Five years or over | 45 |

Considering the worm indices encountered in Java, it seems likely that worms are lost at the rate of about 12 per annum, or about as fast as they may be acquired.

Hookworms, therefore, are being slowly lost as well as being slowly acquired at the same time. The index represents the difference between gains and losses.

Now, as worms are but slowly acquired, the strategy of rapidly reducing the worm content of a population so that the soil may be no longer seeded is evident. The slowness with which infection is acquired permits the attainment *of a population which is nearly worm-free, and is of little potential danger as a* factor in infesting the soil.

It may be inferred from this analysis of many worm counts made from a wide variety of persons engaged in different occupations in a number of locations that the worm index of a group—a representative group of persons, will convey important information to the health officer, as to the amount of hookworm infection and disease, and the degree of soil infestation to which members of the group are subjected.

The worm index is increased by age; it is modified by sex, by occupation, by race, altitude, climate, residence, etc., but such modifications as we have studied are due to differences in the opportunities for acquiring infection. Some of the differences met within the group may be due to individual differences in amount of exposure, or to individual resistance to infection. More research is required to elucidate this matter; but, in any case, the individual number is not desired by the sanitarian. He requires the index of the group.

Not the least important feature of these worm counts is the individual character of the worm indices in different places and among different groups, a fact not known fully until the Java survey had been made.

It is not only apparent that the indices of the kampongs of Batavia are lower—much lower—than the agricultural dessas of Mid Java and that the latter are higher than that of the neighboring fishing villages or of mountain villages; but it is evident that these indices being dependent on the degree of soil infestation, can be increased or diminished They can be increased by the introduction of immigrants more highly infected than the natives of the community; and they can be increased by increasing the amount of soil pollution and infestation in the community; that is by lowering the prevailing standard of community hygiene. On the other hand, these indices can be diminished by diminishing the number of hookworms and of hookworm larvae in the community.

The difference between Batavia kampongs and agricultural kampongs is largely due to the hookworm index of the population and of the hookworm larval index of the soil in the two locations.

The index of Batavia is characteristic of the people and their sanitary environment and the index will remain so until one or the other is changed.

No hidden or mysterious influence can alter them. So long as some Batavians defecate in the canals and drains, all the people will have a lower index than the people of an agricultural kampong who more thoroughly pollute and infest the soil with hookworm embryos.

One community puts more hookworm embryos into the soil than the other and it just as surely gets more back. The lightly infected community cannot become heavily infected because there are not sufficient larvae in the soil to raise the index of the people in question.

Our problem is to place a heavily infected population in the position of the lightly infected one so that it cannot acquire high indices.

## III. THE SITES OF POLLUTION AND INFESTATION

From the literature on the subject and from conversation, it would appear that erroneous notions are held in regard to the sites of pollution and the origin of infection. Hookworm larvae are not blown about by the wind; nor are they uniformly spread and scattered over the soil. In 1912, from my work with cultures, I said that infection was likely to occur from "fecal" puddles in polluted soil not dried by the sun; and Cort has found certain nests of infestation corresponding with this idea.

The nature of our research in the Orient and elsewhere made it necessary to investigate malaria as well as hook-worm. Research in malaria took us out into the field, forest and stream—everywhere out-of-doors, in fact, in order that the propagation areas of all species of anopheline larvae might be studied. The Oriental anophelines are found in a great variety of locations, and Orientals have a variety of places where they pollute, not only the soil, but the water. Consequently, in the search for anopheline breeding places, I observed the habits of Orientals and noted the sites of pollution in a great variety of locations.

In view of the results of our worm counts, and these observations on the sites of pollution, it is not difficult to understand why the worm index of certain villages and kampongs is low and that of others is high; and why workers in rubber, tea, coffee or other plantations should be more highly infected than the workers in the rubber factories and the town-dwellers.

This subject is worth pursuing and will yield important information. A great deal of what has been called racial immunity to hookworm infection will undoubtedly prove to be due to racial differences of personal hygiene. The difference between the infection rates in the Southern States among white and blacks may prove to be the result of whites tending to frequent nests of infection near the privies or barnyard; and the blacks spreading their feces over a wider area in different locations while at work which would result in light infection.

Persons living in rural communities who habitually pollute the soil appear to select certain special places—places where they will be secure from intrusion, sheltered from the wind, sun or rain. Sometimes the places are selected because of their convenience as being near their work or dwelling, or near water, as in the case of the Malays who perform ablutions after the act.

Whatever the spot or location of the place, or whatever the reason for selecting the place, it seems to be a rule that the practice of defecating in that peculiar and special place will become a fixed and permanent habit. It follows that there become certain spots or nests of pollution and of infestation. This is analagous to the habit of dogs of defecating and urinating in certain common places, as around trees and lamp posts.

The health officer must pay attention to the site or location of the latrines provided for coolies.

It will avail little if closets are built only in the neighborhood of the barrracks and lines, and not out in the fields and groves where those with the heaviest infections spend their working hours, and where most of the pollution occurs. Ignorant coolies cannot be expected to walk away from the barracks at night in the dark and use a filthy closet, often placed on the margin of a clump of trees. They will prefer to defecate in the grass near the barracks.

Moslems, Chinese, Tamils and others have habits peculiar to themselves. The Moslem Malays and Javanese of Indonesia by custom or tribal "adat" go to the water when they defecate; or if they cannot do this, they take a bottle of water to the "jam-pan" and after defecation in a pit closet, wash the anus and genitalia. In Java the women and men walk into the shallows of the stream and either squat over and in the water, or, as in Batavia, they stand on bamboo rafts and pass their dejecta into the river. So fixed is this custom that the expression for "going to the 'water closet'" is "pergi sungei," or "going to the river." In the homes of the Dutch and Dutch half-castes in Java as well as on the steamers plying between the ports of the Netherlands Indies, and in rooms occupied by Europeans in all the hotels, there is in the water closet a rack of water bottles to be used in the Oriental way for cleansing the parts after defecation and urination.

This widespread custom of ablutions and defecating into the water tends to pollute all the water courses. When I was working in Java, it was a common sight to see women and girls washing clothes in the drainage ditches or cement drains of the larger streets, and to see large masses of rice feces floating down the surface of the water of the drain. In the same drain nearby, other women could occasionally be seen washing rice for their daily meal.

By careful inquiry it was estimated that about one-half the native Javanese people, rural and urban, defecate in the rivers, streams, ditches, drains or irrigation channels—the same water course in which they wash their clothes, prepare their rice for cooking, and bathe their bodies.

The Javanese are all enthusiastic agriculturalists and their system of irrigation brings water down from the hills, conveying it from stream to rice paddies or sawahs, and thence by ditches to other sawahs to the lower levels.

So that water is constantly passing from polluted wayside streams or ditches to sawahs to be collected again and re-distributed to the sawahs below. The ditches and streams are constantly receiving pollution which floats and which is being conveyed to sawahs and to streams below. The men and larger boys prepare the soil in the sawahs for cultivation. When it is ready, the women enter and plant the rice sprouts. The men often work with plow and patjol up to their knees in mud and water for two-thirds of the daylight hours. Splashing about in the mud and water, their entire bodies become exposed to infection, assuming that the water of the sawah is infested. The younger boys herd the buffaloes, and this takes them into the streams and sawahs for water for short periods. Both sexes bathe in the water of the polluted litches. The indices of the men, boys, women and girls in the agricultural districts of Java correspond to the time spent in the presumably infested sources.

Chinese, in towns and villages, use some form of the pit or closet. In the cities, of course, the type depends on the method of conservancy used by the municipality; while in the country, the feces are saved and used for fertilizer. The mining coolie passes his feces into an unused mine-hole which usually contains water.

The Tamil will contaminate the ground beside his house. He has no compunction about passing his feces anywhere.

While motoring along the roads in the Federated Malay States, the location of the coolie lines or barracks could frequently be recognized some time before they were seen by the characteristic fecal odor emanating from them. This is due to the large amount of pollution which occurs in the immediate vicinity of the lines. Some of it is derived from children, but a large amount from adults as well. For, at night, they are afraid or disinclined to visit the frequently dirty or distant latrine provided by the authorities.

Ravines, or wooded, or otherwise, sheltered places near the lines become highly polluted. Coffee, tea, rubber, cane and other cultivated plants offer abundant shelter and are used by the coolies, at work in them, as places for defecation; in making inspections of latrines, it was common to find the path on each side with signs of recent and copious pollution, while the latrine itself showed no recent evidences of having been used.

In rural communities the world over, amongst all races, there still exists a good deal of soil pollution. This is because of the convenience of passing the stools wherever the individual may happen to be. In the South in certain sections, privies were only used by womenfolk, the men going to the woods or stable.

And where the white folks provided themselves with a "necessary," this was, under no circumstances, to be used by the negroes who worked about the house and garden. They perforce found a place in the bushes or nearby woods.

In the North and in Europe, soil pollution persists. Hedge rows in Ireland and glens in Scotland are still used for this purpose.

Certain spots protected from view of passers-by are used. In a village in Columbia, South America, it was customary for the people to walk out into a large clump of bushes standing about 1.3 meters high in a vacant place within the village. Then, after selecting a satisfactory spot, they would suddenly squat down out of sight and ease themselves. This place must have been highly infested for, on account of its convenience, it was much frequented.

In the Pearl Islands, Bay of Panama, the water used for household purposes had to be brought from a stream distant several hundred feet from the center of the village. It was the custom of the villagers to go for water early in the morning. A large path had been cleared to the stream which was bordered by woods. Into these woods, the people went in large numbers to pass their morning motion. The inclination of the land was such that the stream must also have received some pollution from this source.

In this village, as well as others in Panama, it was customary for the women after nightfall to carry out the dejecta passed in the houses during the day. Here the feces were thrown over into ravines which arose near the margins of the village.

Shore and stream margins are often used. In the coast villages as in Papua, the feces are passed along the shore, sometimes within reach of the tide.

Stream margins were commonly used by Tamils in the Federated Malay States.

Deep ditches are very frequently used by Malays. The ditches used for drainage on the rubber estates in Java and Sumatra are favorite places of resort by the coolies working the rubber.

The planted area, whatever it may be, becomes polluted. Coffee, tea and rubber, for example, are planted by the 1000 acres. On one estate in the Orient, there were 43,000 acres under cultivation and this required the daily labor of 21,000 coolies who spent the first part of the day in the planted area, going about from tree to tree. Each coolie, when the call comes, visits the place of his selection nearest at hand, for as he is at a considerable distance from his barracks, and as the desire to stool comes oftenest during the morning hours soon after food is taken or work begun, a great deal of pollution takes place among the trees. Evidences of some of this pollution, I have been acutely aware of in the drainage ditches and near small streams of water, when searching for malarial mosquito larvae.

Evidences of gross pollution do not last long in the tropics. Stools rapidly alter in physical character. This is due to the influence of rain and drying, and also to the activities of insects and microbiological changes.

The infestation of the soil and the dangers of infection continue after the stool as such has entirely disappeared, as Cort and his colleagues have shown.

## IV. THE LARVAL INDEX

Hitherto our knowledge of the biotics of hookworm larvae in the soil has been confined to the studies, and observations, of Looss and Leichtenstern and Perroncito, and to casual observations by some tropical workers.

We possess no exhaustive study of the biotics of the larvae in the soil made in a variety of locations and under sufficiently varied climatic conditions to enable us to say what the conditions of the survival in the outside world are. Most of the work has been done with cultures, in which the larvae are protécted from whatever gross enemies they may be subjected to in nature, and from inimical microbiological agents, such as bacteria, yeasts and molds, etc., as well as from adverse physical conditions such as drying.

Baermann (3) of Sumatra has recently undertaken the investigation of the spread of or transportation of larvae and the infestation of various points about the barracks of coolie quarters on rubber estates. And he has succeeded in estimating roughly the degree of infection in these places by means of larval counts.

He uses a simple apparatus. The soil sample is placed in a sieve; water is poured through into a funnel upon which the sieve rests. The larvae tend to displace downwards and are passed into funnel tube, thence into rubber tubing held by a pinchcock. The larvae are found in the lowermost point in the tubing, from which they may be drawn off into tubes or slides and examined under the microscope.

More recently Cort (4) and his colleagues have made some valuable studies of the longevity of larvae in the soil at Trinidad, and of the amount of migration possible to larvae. Baermann's technique, slightly modified to meet local conditions, was used in these experiments.

The information which it may be possible to derive from the use of Baermann's technique will be considerable. But if we learn nothing more than the longevity of the larvae in the soil, this in itself will be of the greatest value.

The health officer may not care to know particularly whether one particular ravine or field or ditch or barracks is more heavily infested than another; for he cannot put the infested place "out of bounds;" nor build a barbed wire fence around it. To him, every place beyond the latrine is out of bounds.

And his problem is to make everybody use the latrine or the place indicated and provided by the authorities. Coolies or other people who prefer to defecate out of bounds will merely select another place if they are prevented from using the customary one.

Cort and Payne have shown how larvae may be reduced in the soil of a cacao plantation by a combination of methods in which the soil pollution and infestation are reduced by educational methods and by treatment with vermicides.

Unfortunately, we cannot state how much of the reduction was due to each factor. But the method of ascertaining the reduction in larvae within a limited period in a strip of cane field when as many as 36 locations are sampled, is well shown.

Augustin found that after a period of twenty-one days a 90 per cent reduction in the number of larvae occurred in his migration experiments. As the cultures used were three to eight days old, this would make a period of 26 to 29 days after expulsion within which the majority (90 pe rcent) of the larvae had disappeared. He concludes that in the soil of Tropical Trinidad from May to September, a rapid deduction in the number of larvae occurs in soils of various types and the extent of their life is limited to about six weeks.

It may be thought premature to speak of a larval index until those now engaged on its determination have reported further; but it is a convenience to refer the larval index to its source and give it the same figure.

The larval index, LI. of 300 is that of a community whose worm index is 300. The worm index, WI, being based on some convenient group unit as: men, field workers, etc.

### V. THE NUMBER OF FEMALE WORMS HARBORED AND THE NUMBER OF HOOKWORM OVA EXPELLED

The worm index, as we have seen, is not only an index of the severity of the infection in a community but it discloses in no unmistakable manner the amount of soil pollution and infestation in a community and the degree of exposure of the people to it.

Connecting these two reciprocal phases of the infection—soil infestation and worm infection, are the number of female hookworms harbored and the number of ova expelled by them.

Data on this subject were collected by the Commission to the Orient in 1916 at Taiping, in some experiments carried on by Drs. Barber and Hacker.

Experiments were made on two confined groups of prisoners: one consisting of nine Chinese and Tamil men; the other of eight Tamil men—with the object of ascertaining the number of ova passed in measured amounts of feces from day to day and removed by brine flotation, and comparing this with the number of female hookworms removed by thorough vermicidal treatment.

From an examination of table 17 it can be seen that in general the number of ova counted in a unit volume of feces corresponds with the number of female worms harbored and expelled. The ova content of a specimen of feces from any given person was also fairly constant from day to day; for example, the successive daily stools of no. 208 contained in $\frac{1}{32}$ cc. 106, 158, 113, 110, and 107; while those of no. 44 contained 34, 22, 16, 27, 19 and 20. The method would therefore seem to yield sufficiently uniform results to warrant its use for estimating the number of ova passed.

The correspondence between the number of ova and female worms is not so close. There is a good deal of variability or range in the number of ova expelled per female hookworm harbored in a unit volume of feces. This is shown in the last column under "Ratio of female worms to ova," and is evidently an expression of the fecundity of worms of different ages in different hosts.

In the table the number of ova is estimated for 100 cc. of feces. In a series of stools measured approximately at the Quarantine Station, Federated Malay States, the quantity varied between 10 and 440 cc. in the usual morning stool.

The highest number of ova was counted in the case with the highest percentage and highest absolute number of *A. duodenale*. The case with the lowest output of ova had, as it happened, no *A. duodenale*. In other cases, there was no great amount of correspondence between ancylostomes and a higher yield of ova. *A. duodenale* is a larger nematode than *Necator americanus* and it may also have a larger yield of ova. The size of the ova in the two species is nearly the same. It is possible, therefore, that *A. duodenale* has a larger output of ova than *N. americanus*.

The tables show that while there is a correspondence between the number of worms and ova, the method of estimating the number of female worms from the ova would not be reliable for small numbers of cases except within wide limits.

When a large number of worms are being reviewed, it is not uncommon to find all ages represented in the specimens expelled by medication. We found a number of small immature forms as well as old defunct ones.

The proportion of "barren" worms was ascertained by Bass as follows: 7 per cent of 247 *Necator americanus* females contained no ova. He also examined 397 female *Necator americanus* and $9\frac{1}{4}$ per cent of these were "barren."

The correspondence between the female worms and ova is brought out in a correlation table in which the relation of ova to female worms is shown.

*Correlation table: Average number of ova in $\frac{1}{32}$ cc. of feces compared with number of female worms obtained by treatment*

| | Ova | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| WORMS | 0 TO 5 | 5.1 TO 10 | 10.1 TO 25 | 25.1 TO 50 | 50.1 TO 100 | 101.1 TO 150 | 150.1 TO 200 | TOTALS |
| 1 to 5 | 1111 | 1 (1) | (1) | | | | | 12 |
| 6 to 10 | 1 | 1 | | (1) | | | | 3 |
| 11 to 25 | | 11 | 1 (111) | | | | | 6 |
| 26 to 50 | | | 11 | 11 | 1 | | | 5 |
| 51 to 100 | | | 1 | | 0 | 1 | | 2 |
| 101 to 150 | | | 1 | 1 | 1 | | | 3 |
| 151 to 200 | | | | | 1 | | | 1 |
| 201 to 250 | | | | | | | 1 | 1 |
| Totals.. | 10 | 5 | 9 | 4 | 3 | 1 | 1 | 33 |

Worms

Figures enclosed in parentheses represent tests made on one day only, others were made on two or more days.

There is seen to be a correlation between numbers of ova and numbers of female worms, and while it is possible by this method to estimate within limits the degree of hookworm infection in a population, the method would be unreliable for a few cases except within very wide limits. Much more accurate results could be obtained by means of direct worm counts.

As there exists in large groups a correspondence between the number of hookworms harbored and the number of ova expelled, we have a basis for computing approximately the decrease in the larval index of the soil when the number of hookworms harbored in man is gradually reduced to a minimum as by present methods of campaign, or is suddenly reduced to a minimum as by a method of mass treatment carried out on a large group of the population.

## VI. REDUCTION OF HOOKWORM INFECTION AND OF SOIL INFESTATION BY MASS TREATMENT

By mass treatment is meant the administration of vermicide to large or small bodies of people—all the inhabitants of a community, village, district or neighborhood; all the inmates of a plantation, institution, or any other group of persons living on and polluting and infesting more or less the soil of one area. This treatment is carried out within a few days and without a previous microscopic examination of the stools of each and every person. But the index of infection is ascertained previously by examining a representative sample of the population, preferably by worm count.

Experience has impressed me with the need of expediting the hookworm campaign, particularly in those regions where very high indices occur and where real evidences of severe hookworm disease are to be found. As I have stated elsewhere, it is not the small number of hookworms being harbored by town dwellers in easily accessible places, but the 150 or more worms that are busy in the great mass of untreated humanity, with which we should at first concern ourselves.

In conducting a campaign sometimes a notable number of persons in every treated community do not receive treatment.

*Relation between number of ova expelled per diem and number of hookworms harbored*

| Race | Daily number of ova counted in $\frac{1}{32}$ cc. | | | | | | | Average | Ancylostoma | | Necator | | Total worms | | Total hookworms | Percentage of ancylostomas among female worms | Daily number of ova per female worm basis of 100 cc. soft feces per day | Ratio of ova to female worm average $\frac{1}{32}$ cc. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1st day | 2nd day | 3rd day | 4th day | 5th day | 6th day | 7th day | | Male | Female | Male | Female | Male | Female | | | | |
| *Group I:* | | | | | | | | | | | | | | | | | | |
| Tamils .... | | 106 | 158 | 113 | 110 | | 107 | 118.8 | 23 | 36 | 15 | 15 | 38 | 51 | 89 | 70.6 | 7,454 | 1:0.4 |
| Tamils .... | | 41 | 31 | 30 | 27 | | 17 | 29.2 | 9 | 4 | 39 | 40 | 48 | 44 | 92 | 9.1 | 2,124 | 1:1.5 |
| Tamils .... | | 224 | 181 | 145 | 155 | 153 | 129 | 164.5 | 8 | 6 | 217 | 224 | 225 | 230 | 455 | 2.6 | 2,289 | 1:1.4 |
| Tamils .... | | 7 | 14 | 7 | 8 | | | 9 | 1 | 2 | 3 | 7 | 4 | 9 | 13 | 22.2 | 3,200 | 1:1.0 |
| Tamils .... | | 34 | 22 | 16 | 27 | 19 | 20 | 23 | 1 | 0 | 90 | 111 | 91 | 111 | 202 | 0.0 | 663 | 1:4.8 |
| Tamils .... | | 28 | 17 | 23 | 15 | 13 | 16 | 18.7 | 5 | 2 | 9 | 14 | 14 | 17 | 31 | 11.8 | 3,520 | 1:0.9 |
| Tamils .... | 18 | 14 | 18 | 13 | 23 | | 23 | 18.2 | 3 | 8 | 36 | 54 | 41 | 62 | 103 | 12.9 | 939 | 1:3.4 |
| Tamils .... | | | 8 | 3 | 11 | 7 | | 7.3 | 1 | 1 | 7 | 20 | 8 | 21 | 29 | 4.8 | 1,112 | 1:2.9 |
| Totals..... | 18 | 454 | 449 | 350 | 376 | 192 | 312 | | 51 | 59 | 418 | 485 | 459 | 545 | 1014 | | 21,301 | |
| Average... | | | | | | | | 51.2 | 6.4 | 7.4 | 52.3 | 60.6 | 58.6 | 68.1 | 126.4 | 10.8 | 2,406 | 1:1.3 |
| *Group II:* | | | | | | | | | | | | | | | | | | |
| Tamil ..... | 5 | 20 | 8 | 9 | 7 | | | 9.8 | 0 | 1 | 1 | 13 | 1 | 14 | 15 | 7.1 | 2,240 | 1:1.4 |
| Tamil ..... | 21 | 42 | 25 | 39 | 28 | | | 31.0 | 1 | 8 | 119 | 93 | 120 | 101 | 221 | 7.9 | 982 | 1:3.3 |
| Chinese ... | | 18 | 34 | 45 | 29 | | | 31.5 | 2 | 3 | 25 | 38 | 27 | 41 | 68 | 7.3 | 2,459 | 1:1.3 |
| Tamil ..... | 12 | 26 | 13 | 19 | 18 | | | 17.6 | 0 | 0 | 39 | 33 | 39 | 33 | 72 | 0.0 | 1,707 | 1:1.9 |
| Tamil ..... | 1 | 2 | | | | | | 1.0 | 1 | 1 | 11 | 4 | 12 | 5 | 17 | 20.0 | 640 | 1:5.0 |
| Chinese ... | | 10 | 3 | 5 | 13 | | | 7.8 | 2 | 4 | 4 | 1 | 6 | 5 | 11 | 80.0 | 4,992 | 1:0.6 |
| Tamil ..... | 68 | 92 | 69 | 67 | 75 | | | 74.2 | 6 | 12 | 138 | 90 | 144 | 102 | 246 | 11.7 | 2,326 | 1:1.4 |
| Chinese ... | 2 | 18 | 17 | 20 | 7 | | | 12.8 | 3 | 4 | 21 | 39 | 24 | 43 | 68 | 9.3 | 953 | 1:3.4 |
| Chinese ... | 1 | 0 | 1 | 1 | 1 | | | 0.8 | 0 | 0 | 6 | 6 | 6 | 6 | 12 | 0.0 | 427 | 1:7.5 |
| Totals..... | 110 | 228 | 170 | 205 | 178 | | | | 15 | 33 | 364 | 317 | 379 | 350 | 730 | | 16,728 | |
| Average... | | | | | | | | 21.7 | 1.7 | 3.7 | 40.4 | 35.2 | 42.1 | 38.9 | 81.1 | 9.4 | 1,785 | 1:1.8 |

These people are ill, removed, moved-in after the census, or were missed by the microscopist.

Besides this number calculated for treatment districts, there is an additional large number in certain other districts where transport is difficult or expensive, and where the per capita cost of treatment would be relatively great.

In campaign work, it may be expedient to omit from the preliminary program these remote and economically unfit places. But they continue to act as potential nests of infection and should not be dismissed from consideration in the comprehensive plan of campaign which aims at the eradication of hookworm disease.

Besides the missed cases and other untreated cases, considerable time is consumed in the diagnosis of the infection by the microscope. Meanwhile re-infection is going on to some extent at the same time; for the infected and untreated coolie will continue to pollute the soil. In order to avoid this re-infection, which necessarily occurs when the campaign slowly drags along through a community, it would seem to be strategic to treat everybody in the community in the shortest possible space of time; and in this way rapidly reduce both the worm and larval indices.

The hygienist can no longer expect to remove every last hookworm from everybody. That is a counsel of perfection impossible of achievement. By present administrative methods dealing with human factors in advanced communities, diptheria, scarlatina, typhoid nor tuberculosis has been eliminated to any degree such as is aimed at by the hookworm directors. We can apparently do no more than reduce the gross amount of infection to a minimum. The people living where the worm index is low, and where the larval index is also low, do not suffer from severe hookworm infection or disease, as Smillie (5) has recently emphasized. We know that they do suffer slight losses but the infections are so light that the losses can be made up with ease. The worm-counts which we have made in the Orient indicate that the groups which are lightly infected are so because there is low soil infestation. These people cannot acquire a high index because it is not in the soil to give it to them; and it is not in the soil because the people cannot furnish sufficient ova to raise the larval index in the soil.

Our worm counts show that there are places which have high worm indices and other places with low indices. We do not find one Batavia kampong with a low index and another with a very high one. Something is there which makes for uniformly low indices although there is very little difference between between the kampong gardens of Batavia and those of large villages in the interior and the people are all bare-footed and bathe in the polluted river.

We know that all the indices of Batavia, Endil, Tjimatjan, Gebong, are low: 35, 51, 6, 46; while those of agricultural villages like Kebasekan, 168; and Kalimaro 189 are high. We believe that this is due entirely to the greater amount of soil infestation (high larval index) in the latter places. If this high larval index is derived chiefly or exclusively from the people themselves and does not come from outside then it should be possible to place the villages with high indices in the category with those having low indices by intensive mass treatment of the entire population.

The amount of infection derived from bathing in polluted and infested water is unknown at present. Research is needed in this field; but wherever the people do not bathe in the polluted water, it should be possible to reduce the worm index and larval index in the way mentioned.

It is somewhat analogous to sowing seed in the ground. We get back from the soil what we put into it. Hookworm larvae do not, of course, multiply in the soil. No more larvae can develop from the ova than are expelled with the feces of infected persons on the soil. If few ova are seeded into the soil from people with low indices, only a few larvae are produced. If large numbers of ova are expelled on to the soil from persons with high worm indices, then the soil may become heavily infested with larvae, and the worm index remain high.

Light infections occur when people have low indices. Severe infections and high indices probably do not occur where the larval index is low.

We found in the Orient that infection is not usually acquired suddenly and explosively but depends on slow acquisitions from week to week or month to month. Fijians, exposed to soil infection from East Indian coolie sources, only very slowly acquire a small quota of *Ancylostoma duodenale* in addition to the number of *Necator americanus* which is natural to them and to the soil. The same was noted when the numbers of *A. duodenale* acquired by Tamil coolies from Chinese in the Federated Malay States were ascertained. Japanese in Brazil slowly acquire a Brazilian formula of worms resembling that of the Brazilians with whom they work. This slow acquisition of worms takes place in the places where the amount of soil infestation must be very great if we may judge by the worm indices of the autocthonous people in question.

In localities where the soil infestation and larval indices are low, as in mountain villages, in towns and villages, on coral reefs, and in arid countries, the rate of acquisition must be low for the net gain of worms per annum is very small indeed as shown by the low indices of children and adults.

It is this very small net gain of worms per year that should be the desideratum of the health officer; for, in this way, none of the people ever can become heavily infected or seriously diseased because there are not enough larvae in the soil to yield heavy infections.

Recent work of Cort and his colleagues in Trinidad seems to show that the hookworm larvae do not live as long in the soil as we have been in the habit of thinking they did.

If the larval period in the tropics is short, there would appear to be a decided advantage in treating a community group *en masse* so as to reduce at *once* the number of female worms and thereby the number of ova that would infest the soil. This will suddenly reduce the worm index and soil infestation, and the larval index will quickly follow the worm index in its fall. If an entire community could be treated within a few days, the community's environment would suddenly be purified of most of its larval infestation, and the community would be placed in the class of those places which have low worm indices and low larval indices. A community once placed in this advantageous situation, there is every reason for believing that it could stay in it just as other communities are remaining with the low larval indices at the present time. For, once a village has a low index, it cannot acquire a larger one without an influx of heavily infected persons from without.

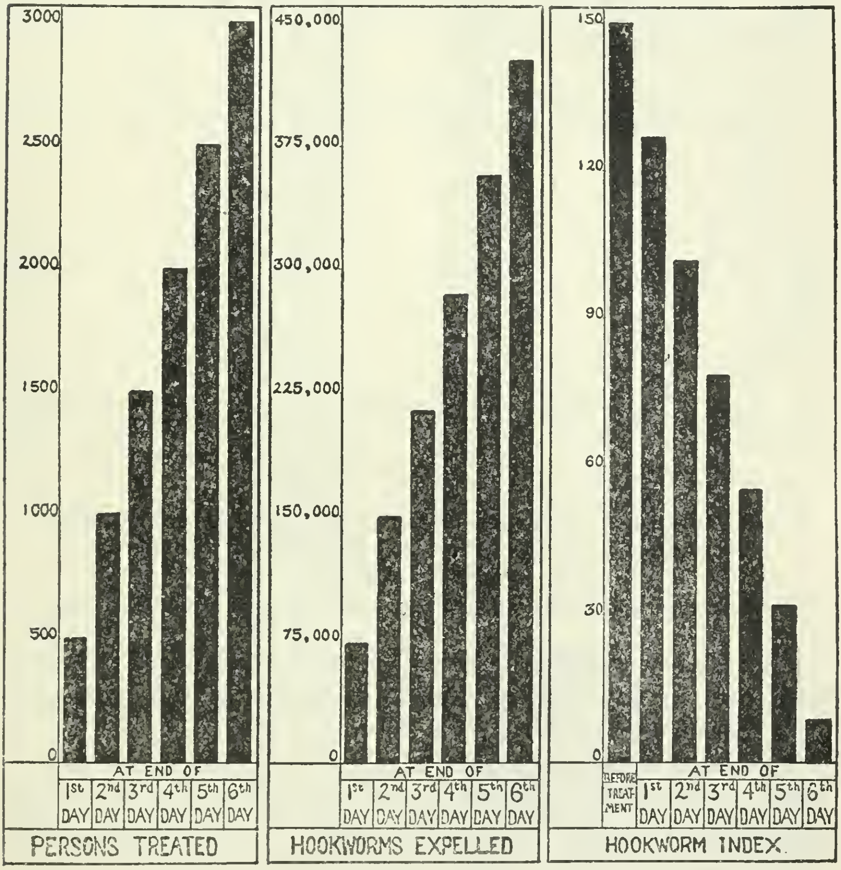


Fig. 1. Effect of Mass Treatment in Reducing Worm Index* of a Hypothetical Community

Population 3000; average worm content of inhabitants, 150. Five hundred persons reached and treated daily, and 95 per cent of their hookworms removed. Community burden of worms 450,000 before mass treatment; 22,500 one week later.

$$^{*}\frac{\text{Total number of hookworms}}{\text{Total number of persons}}$$

Graphs (figs. 1, 2, 3), shown are designed to illustrate what will probably occur in the soil and in the human hosts in a community if they subject themselves to mass treatment for hookworm.

A hypothetical village, plantation or other community of 3000 souls, is divided into six treatment groups and 500 persons are treated daily for six days. The worm index of the population is 150. The graphs show the degree of soil infestation and its reduction from day to day.

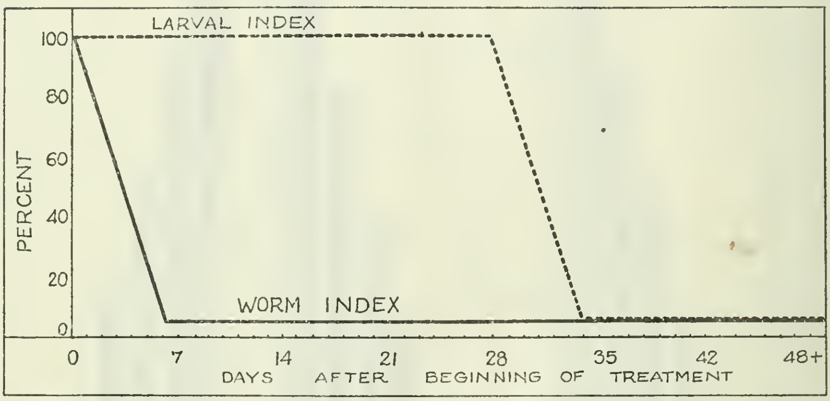


Fig. 2. Influence on Worm and Larval Index, of Mass Treatment, Extinction of Larvae in Soil, and Slow Rate of Acquisition of New Infection

The new worm and larval index of approximately 16 is relatively harmless

The initial worm burden borne by the people and its reduction from day to day, finally, the worm index of the population after treatment are shown.

The result is not the complete reduction of the index to zero; but a reduction to a minimum that can be borne by the people without any material reduction in their working efficiency, and a reduction to *an index which in other communities does not result in any severe infections at all.*

In Brazil (6), we found that in a heavily infected community with an index of 200 worms, two routine treatments with chenopodium would remove most of the worms, leaving an average of six worms per person, while 60 per cent of the population would be free from worms.

Taking the rural Brazilians as a class, they were found to have an index of 136 worms. When they had been treated once, from 83 to 93 per cent of the worms were removed, depending

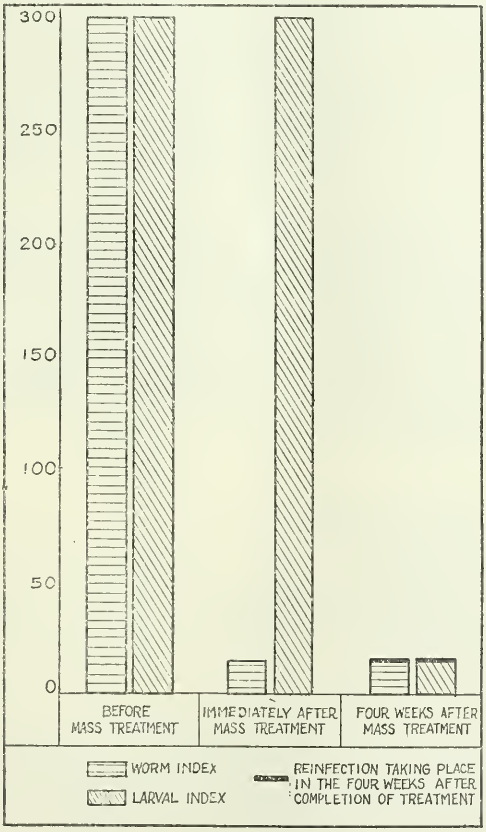


Fig. 3. Effect of Mass Hookworm Treatment upon Worm and Larval Indices of Hypothetical Community

These indices have remained at the same level for an indefinite number of days (or years) before mass treatment. Mass treatment lowers the worm index immediately, as indicated; the larval index follows the worm index at the end of four weeks, the intervening period representing the average length of life of larvae in the soil.

on care and attention to details of treatment. This left an average of 8 to 23 worms behind. A second treatment removing respectively the same percentages would leave an average of 2.8 to 7.4 worms per person.

Two and three treatments will be necessary in heavily infected communities to reduce the indices to a safe minimum. This will require from six or less to twenty-six days to complete. The great bulk of the worms will be expelled during the first six days, probably 90 to 98 per cent of the total. It will simplify matters, therefore, if we assume in our graphs that the removal of worms requires six days and that the percentage of worms removed is 95.

A population with an index of 150 will be bearing a total burden of 450,000 hookworms. Each group of 500 persons will have about 75,000 worms of which 95 per cent are removed by treatment. Each day's treatment removes 95 per cent of 75,000 worms, or 71,250 worms. Six days' treatment removes 6 × 71,250 = 427,500, leaving a remainder of 22,500 worms or 7.5 worms per person.

The daily reduction in number of worms:

| | |
|---|---|
| Before beginning treatment | 450,000 |
| After first treatment | 378,750 |
| After second treatment | 307,500 |
| After third treatment | 236,250 |
| After fourth treatment | 165,000 |
| After fifth treatment | 93,750 |
| After sixth treatment | 22,500 |

The larvae live for varying periods in the soil, the time depending on factors as yet not well ascertained. But from the data, we may assume tentatively a period of four weeks. It makes little difference for it may vary from a few days to two or three months in colder climates. Certainly the figures indicate an average period of approximately four weeks. Assuming that the larvae live four weeks, then four weeks after the treatment is begun, the larval index will begin to fall and its fall will be as rapid as the fall in the number of worms harbored. If the worm index is reduced 95 per cent, the larval index must fall *pari passu* and to an extent of 95 per cent and in the same time, namely, six days. So that after a period of thirty-four days from the date of the first treatment, the larval index will have been reduced to 95 per cent of its original number. As this index corresponds to a worm index of 7.5, we believe that no heavier infections than 7.5 can result from such an index unless more larvae are introduced from without the community by ova expelled from the person of a worm carrier.

As the worms harbored in a community are derived from larvae in the soil, it can be seen that if only a portion of the community are cleansed, the remainder will continue to keep the larval index up to a point at which light infections or low indices cannot be maintained, and the treated persons will be infected with facility. Of course, in a manner, every case treated, to that extent, removes so many female worms and thus reduces the larval index proportionately and is of advantage to the community. But if the index of a people is 150 and one-fourth of them are not treated, the remainder cannot remain cleansed long because of the continued soil infestation of the infected.

### *Can mass treatment be carried out?*

It has been shown how it should be possible to reduce the worm index and larval index by treating all the members of an infected community group at one time, so that only very light infections will presumably occur.

Doubtless it will be asked if this is a practicable measure. Where is such treatment carried out, and among what people?

Mass treatment is given against cholera in Batavia, Java to large numbers of natives who are ordered to appear at the office of the Wegmeister or official in charge of the kampong. 3000 to 5000 or more people are called up in hundreds, and given preventive inoculations of anti-cholera vaccine. Smallpox vaccine is administered in much the same way. The vaccinator divides the kampong or district into six parts. Batches of the people are called up to the office of the "kapala dessa," and vaccinated on successive days. On subsequent occasions, he examines the same persons to note the effect of the vaccination. It is true that the Javanese are very docile and amenable to administrative discipline. So are the Tamils and most of the people of Southern India. But other people can be called up in mass as easily as Javanese or Tamils. In the survey of Java and elsewhere it was necessary that we obtain representative samples of the population and samples of the ill persons as well, in order that the worm indices be ascertained. We have now worked with Malays ("the mildest men that ever scuttled a ship or cut a throat"), Tamils, Malabaris, Javanese, Chinese, Chinese women, Fijians, including chiefs, North Indians, both indentured and freemen, Brazilians, Italians, Spanish, Portuguese and South American Indians. Indentured laborers and Javanese villagers were easy to obtain for the planter or "kapala dessa" ordered, and the people obeyed. But where the people were free, it was always possible to get coöperation by some means or other. Different methods were used in various situations.

The attitude always assumed was that we had to get the information. No excuse of any kind would be accepted once it was ascertained that the person in question possessed information which we needed. Chinese women, who are very difficult indeed to manage, were treated and this was true of a small group of women who would not permit abdominal palpations for the splenic index.

All can be reached if the right avenues of approach are utilized.

Sometimes a non-coöperative or busy group of people would be encountered; and in Java, where most of the people live from day to day on what they earn that particular day, it was necessary to pay the coolies wages for the two days lost from work. But this wage of 20 to 30 cents is much less per capita than the cost less overhead charges in all of the places where campaigns are now being carried on.

It would be cheap at the price to treat entire populations at 20 cents per capita.

It may not be possible to carry out mass treatment in those communities where the people are scattered over a considerable area; and here it may be said that it is in such situations that heavy infections do not occur, as a rule. But there are many villages, plantations, estates and tea gardens, where the people and coolies are amenable and coöperative; and here it should be possible to treat large numbers expeditiously en masse.

On large estates it should be practicable to have annually a "day of purification" when all the coolies or the entire population of the location—the entire community—would be required to take a course of treatment.

Among native tribes that have meetings and gatherings at certain times of the year, it should be possible to make them take a treatment every year.

Can a campaign be undertaken in a country based on the method of mass treatment?

This would be possible. Wherever it is possible to assemble the people, as it is in many places in the Orient, it could be carried out.

The educational and disciplinary portions of the program are not to be entirely overlooked and should receive attention; but in the regions where high indices prevail, it is of greater immediate moment that the worm burdens be reduced without delay.

It will take a very long time to induce, cajole and require backward and custom-bound native people into the habit of using latrines. Meanwhile something can be done to ameliorate their condition, a condition which is often pitiable indeed, among those who live in the communities where the higher indices prevail.

Mass treatment has been carried out recently in Brazil, Borneo, Ceylon and Siam.

In Brazil mass treatments are given where the preliminary microscopic examination shows an incidence of 85 per cent. No microscopic examinations subsequent to treatment are ever made.

The laboring population in Ceylon tea estates are Tamils who are infested to the extent of 99 per cent (adults). There when specimens of a sample of the coolies show over 80 per cent infection the entire labor force is subjected to treatment without any other preliminary examination than a clinical one to ascertain their fitness for treatment.

In Siam preliminary examinations have shown that the people are highly infected, and treatment is administered to all who are willing and in physical condition to take it. The following excellent reasons are advanced by the director for giving mass treatment:

Difficulty of identifying and locating individuals.

Reduction of soil pollution (infestation).

Psychological—utilizing "follow the crowd" instinct.

Bringing many more people under treatment.

In Sumatra it was the practice to examine all coolies upon their arrival on the estate. They were sent to the estate hospital and their stools were examined by native microscopists and if found positive for hookworm, they were admitted to hospital for cure. On certain estates the coolies were inspected by examination of conjunctiva or by hemoglobinometer; and if their condition demanded it, they were subjected to hookworm treatment.

It has been urged that hookworm disease cannot be effectively controlled by treatment alone, because of the failure to control the disease in Porto Rico and Colombia; but in these countries, mass treatment on a community-group area basis was not carried out. In Porto Rico the method of attack was the "Dispensary;" and in Colombia it was "spasmodic" in character. Large numbers of people were treated but many infected persons were left untreated and these seeded the soil and maintained a sufficiently high larval index from which the treated persons became re-infected.

### *Hookworm control by medication*

Parasites which have more than one host may be attacked in one or the other of the locations according to the ease with which the parasite may be destroyed or controlled. The malaria organism is attacked in the mosquito host and in man. Ticks which transmit disease, or are merely noxious by their presence on cattle, may be destroyed when they drop off on to the soil, by keeping cattle away from them, by rotation of pastures and so depriving the ticks of nourishment. The ticks may be directly attacked by destructive agents applied to them while they are on the cattle. In this case, the dip is used; the cattle being passed through the dips at regularly stated periods, and the female ticks killed before they have become ripe for oviposition. In time the ticks become greatly reduced in number.

In South Africa, it has been possible to control tick infestation and the deadly Texas fever, and the deadlier East Coast fever, by periodical compulsory dipping of cattle. Not only have the ticks and the two deadly fevers disappeared almost altogether but other diseases of cattle have disappeared as well because the diseases could only maintain themselves on animals whose resistance was lowered by the fevers in question.

There are places where it has been thought inadvisable to attack the hookworm problem because of the difficulty of solving, at the same time, the more difficult one of soil sanitation. China, for example, requires the use of excreta in agriculture; and it does not seem feasible at the present time to carry on a campaign against hookworms in that country until some method of treatment of feces to destroy the hookworm embryo has been devised, or until we have learned how feces can be rendered harmless so far as hookworm and other helminths are concerned. While it is easier by far to treat cattle in the dip, than to treat entire populations by means of vermicides, yet the treatment of masses of people with vermicides is not essentially different from treating masses with quinine. As a matter of fact, there is better expectation of success in reducing hookworm infection by vermicides than there is of reducing malaria by quinine. Wherever it may be possible to treat entire populations as a unit and to rid them of their worms in a few days, there we may be sure the soil will quickly become free of hookworm larvae and the infection reduced to a harmless minimum. Such a reduction would doubtless reduce other diseases which are dependent on hookworm disease for a foothold.

Under these circumstances the control of hookworm infection might well be accomplished by medication alone.

It would indeed be interesting to observe soil sanitation accomplished by the administration of a vermicide.

## SUMMARY

The hookworm index or average number of hookworms harbored by a sample of the population is not only an indicator of the degree of infection in a group of persons, but is an index of the degree of soil infestation and of exposure to it in the district or environment habitually used by the group.

This index is a more accurate expression of the amount of hookworm infection in a community than a statement of the percentage of the people positive for hookworm ova; for the Uncinariasis Commission to the Orient found that of two groups of people who had 90 to 100 per cent of their number infected with hookworm, one group had an average of only 35 hookworms per man while the other had 273 worms per man.

The anemia and severity of the symptoms in general correspond with the number of hookworms harbored. This may not be apparent in the individual case because individual resistance may cloak the malignant influence of the worms which are none the less causing losses of blood and drains on the individuals powers.

Groups of persons and types of communities possess certain characteristic grades of infection. Agriculturists usually have a high worm index, while town-dwellers have a low index.

Intimate barefooted contact with infested soil is the factor of greatest importance in raising the hookworm index.

Diagnosis by vermicide is more accurate than diagnosis by microscopic examination for ova.

It is important to know more about the personal hygiene of people and sites of pollution, for what has been called racial immunity may be nothing more than the result of different degrees of exposure to infested soil following different occupations, etc.

The relative immunity of the negro in the South and the apparent higher susceptibility of the white man may be due to the scattering of infection by the necessities of his vocation in the former, and the concentration of infestation in highly polluted nests by the whites.

There is some correspondence between the number of ova discharged in feces and the number of female hookworms harbored when large numbers of cases are considered.

Recent work by Baermann and Cort and Augustin lead us to believe that embryos of hookworms do not live for a long time in the soil, but in the tropics, at any rate, survive but a few weeks.

In hookworm control, it would seem to be strategic to treat by vermicide all the people in a community within as short a period of time as possible so that soil pollution and soil infestation will not continue but be abruptly terminated, and so that there will be no re-infection of those already treated. Mass treatment of entire communities is recommended wherever it is practicable. It is believed that when an entire community is purified of most of its worms by mass treatment within a few days, very few hookworm embryos will be passed to infest the soil, and the latter instead of remaining highly infested, as before treatment, rapidly becomes lightly infested and only light and relatively very harmless infections can result.

In places like China where agriculture is only economically possible through the use of dejecta as fertilizer and where hookworm campaigns are not thought to be feasible, it would seem to be possible to rid the soil of hookworm larvae by mass treatment of communities.

RESUMEN

El índice uncinárico, o sea el promedio de guzanos de uncinaria que aloja un individuo, no sólo indica el grado de infección en el grupo que aquel represente, sino que también es un índice del grado de contaminación del terreno y de la propensidad a la infección por parte de la comunidad representada.

Con este índice se expresa de una manera más exacta la infección de uncinaria existente en una comunidad, que dando simplemente el porciento de individuos cuyas evacuaciones son positivas. La Comisión de Uncinariasis que envió al Oriente la Junta de Sanidad Internacional nos dió a saber que entre dos grupos de aldeanos examinados que procedían de localidades infectadas desde un 90 a 100 por ciento de su totalidad,—al ex-

aminarse separadamente, en un grupo se encontró que habían 35 guzanos por promedio de cada persona examinada, mientras que en el otro el promedio alcanzaba la cifra de 273 guzanos por persona. Tales detalles de importancia no es posible obtener cuando sólo se juzga el por ciento de personas afectadas.

La anemia y la severidad de síntomas corresponden, generalmente, con el número de guzanos alojados. En casos aislados la verdad de este hecho no es aparente pues como se sabe la resistencia y defensas naturales del individuo son capaces de disimular la influencia maligna de los guazanos no obstante haya constante pérdida de sangre y debilidad de las fuerzas vitales del infectado. Las comunidades, sin embargo, pueden someterse a una clasificación, por sí solas o por grupos, de acuerdo son sus índices numéricos. Las regiones agricultoras tienen índices más altos que las urbanas.

El contacto entre el pie descalzo y el terreno contaminado es el factor de mayor importancia en esta infección.

La diagnosis por medio de vermicidas es más exacta que aquella que se hace mediante el exámen microscópico de huevos.

La higiene personal y los focos de contaminación rurales requieren cuidadosa investigación pues poco en realidad se sabe sobre ambas cosas. Lo que se conoce bajo el nombre de inmunidad racial puede que no sea mas que el resultado de diferentes grados de contacto con el terreno infestado. La inmunidad relativa de los negros en las comarcas del Sur y la alta susceptibilidad entre los blancos de la misma región puede que sean debidas a la costumbre de los primeros en regar y esparcir el excremento sobre el terreno en vez de colocarlo, como lo hacen los blancos, en sitios ya designados y escogidos por su previa contaminación.

Existe cierta correspondencia entre el número de huevos de uncinaria expulsados y el número de uncinarias hembras que aloje el intestino. Sin embargo el contaje de guzanos en general nos dará el numero de hembras con mas exactitud.

Las investigaciones de Baerman, Cort y Augustin nos hace creer que los embriones de la uncinaria sólo viven algunas semanas sobre el terreno de los trópicos. En campañas de exterminio de uncinaria es buena estrategia el tratar por medio de vermicidas a todos los individuos de una comunidad por un corto periodo de tiempo—de manera que ambas, infestación y contaminación del terreno, terminen abruptamente. Se evitará de esta manera la re-infección de los ya sometidos a tratamiento.

El tratamiento en masa de comunidades enteras se recomienda siempre que sea práctico el hacerlo asi. Cuando una comunidad se purifica de guzanos, de esta manera y en breve espacio de tiempo, los casos nuevos de infección que ocurran serán leves y de poca importancia.

En paises, como China, en donde la agricultura se hace económicamente posible mediante el uso del excremento humano como fertilizante, y en donde una campaña de limpieza de uncinaria no se ha creído conveniente poner en práctica, es posible el librar el terreno de las larvas de uncinaria mediante un tratamiento en masa, intenso, por medio de vermicidas.

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# A GRAPHIC ANALYSIS OF CERTAIN FACTORS IN HOOKWORM CONTROL[1]

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## INTRODUCTION

During the last few years the feeling has been developing that control measures in hookworm disease have been built up on an insufficient scientific foundation. The need of further investigations on the etiology of hookworm disease has been particularly evident in the numbers of questions which have confronted field workers, to which it has been impossible to give satisfactory answers, and in the difficulty which has been experienced by them in measuring accurately the results of control work or in comparing the efficacy of different control measures.

Recently there has been an awakened interest in the problems related to the various phases of hookworm control as shown by a number of important contributions, and certain new methods of attack have been devised which give promise of still further advances. The present paper is not an attempt to present new facts or new methods of hookworm control, but to point out by an analysis of our present knowledge, especially in the light of the more recent advances, certain factors and relations which have been too much neglected and to indicate lines along which further investigations are needed.

## FACTORS INVOLVED IN THE ETIOLOGY OF HOOKWORM DISEASE

Figure 1 gives a graphic representation of the factors involved in the spread of hookworm disease. To make understandable the following analysis of these factors it will be necessary first to discuss each one of them briefly.

[1] Read at the 18th annual meeting of the American Society of Tropical Medicine, May 2 and 3, 1922, at Washington, D. C.

*Human infestation*

An accurate measurement of human infestation is important in hookworm work to determine what methods of control should be applied in a particular project, to evaluate the different control measures and to discover the actual results which have been obtained. The measure of human infestation which has been usually applied in hookworm campaigns, has been a microscopical

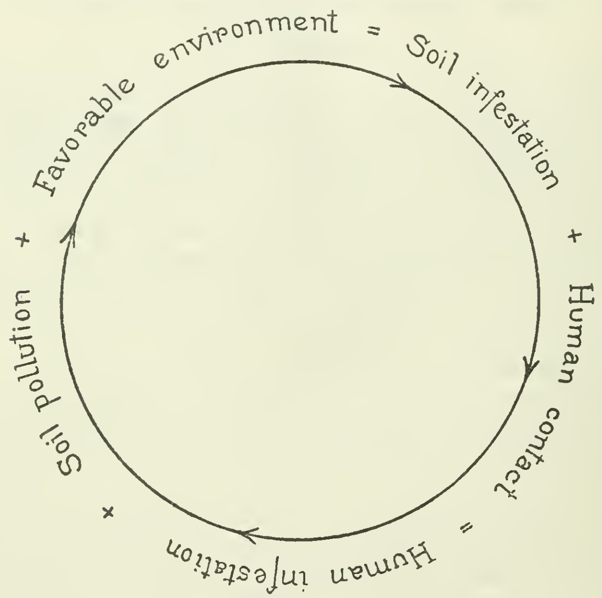



Fig. 1. A Representation of the Factors Involved in the Spread of Hookworm Disease

examination of the feces to detect the presence or absence of infestation. This method is inaccurate since it gives no data on the degree of mass infestation, i.e., the numbers of worms present. For example, an individual harboring only 10 worms, if marked positive, would have the same value in an analysis by this method as an individual harboring 300 worms. The use of fecal examinations to estimate human infestation in evaluating the results of control work has, in my opinion, led to serious errors. For example in a number of resurveys after hookworm compaigns recorded in the Annual Report of the International Health Board for 1918 (1) some show an incidence of infestation after the control work almost as great as before, although in these places it was evident, as noted in the report, that real progress had been made in the reduction of mass infestation. It is possible that the reduction in mass infestation in a population might be over 90 per cent and the results of the control work, therefore highly satisfactory with only a slight, if any, reduction in the number of positive cases as shown in a resurvey by the method of fecal examination. An hypothetical case will illustrate this point. Let us hypothecate that in a given area 70 per cent of the population were originally infested with hookworms with an average of 300 worms per individual. If we calculate on the basis of 100 individuals, the seventy positive cases would have originally carried 21,000 worms. It is easily conceivable that a control campaign might produce a reduction of 90 per cent in the number of worms in this group, and the 2100 worms which remained might be so distributed that a resurvey by fecal examinations would show no reduction in the number of positive cases. A reasonably accurate method of fecal examinations would probably mark as positive any one harboring over 20 worms and 2100 worms distributed among 70 individuals would give an average of 30 worms per individual. It is even possible that if in the resurvey there was used a more accurate method of fecal examinations than in the original survey, there would be shown an increased incidence of hookworms after the control work. A recent investigation by Smillie (2) has strikingly supported this view. He found in an area in Brazil where hookworm control work had been carried on for four years, that a resurvey by fecal examination still showed an incidence of 69 per cent infestation as compared with an original infestation rate of 71.2 per cent. A survey of the health of this population showed that hookworm disease had disappeared from this region, and a series of 86 worm counts gave an average of only 14 worms per individual. A comparison with four controls with an average worm count of 324 each, and with the worm count in similar groups where no control work had been done, indicated that the original worm count in this area must have been about 300 per individual. Here then was a reduction of mass infestation of about 95 per cent in an area where there had been only a reduction of 2.2 per cent in the number of individuals found positive by fecal examination.

The method of worm counts divised by Darling and his co-workers (3), if used properly will give an extremely accurate measure of the reduction of mass infestation by control measures. It is also of value in determining the relative value of different control measures. This method has not as yet been utilized to any extent by other workers. This is probably due to the disagreeable and trying character of the work involved and the difficulty in certain regions of sufficiently controlling the population for its successful application. However, the inportant investigations of Darling and his co-workers have shown that the worm count method can be applied under a variety of conditions. I believe that its further utilization will make possible important advances in our knowledge of the control of hookworm disease.

Baermann (4) and others have utilized the determination of haemaglobin in measuring the results of hookworm control work in the reduction of human infestation. Darling, Barber and Hacker (3) have shown that the haemaglobin index can, with certain limitations, be correlated with the degree of mass infestations with hookworms, where hookworm disease is uncomplicated with malaria. It is evident, therefore, that this method especially when correlated with the general health of the population would have value in the determination of the degree of mass infestation with hookworms.

Another method which has been utilized to some extent in estimating mass hookworm infestation is the determination of the output of eggs with the feces. Cort and Payne (5) used a rough application of this method to show the reduction in human infestation after treatment and sanitation in an area they were studying. Smillie (6) has shown that when a sufficient number of individuals are considered a positive correlation is present between the output of eggs and the mass infestation, but that there are wide individual variations in this relationship. It is possible that further investigations will make it possible to evaluate the sources of error in this method and that it will be made available for the estimation of human infestation under conditions where it is not feasible to make worm counts.

### *Soil pollution*

It is often of value in hookworm control work to determine the degree and distribution of soil pollution. This can be done by observing the habits of the people, by inspecting latrines and by surveying areas to discover the distribution of the soil pollution. An illustration of this kind of a study is given by the work of Cort and Payne (5) in Trinidad in which surveys of soil pollution were made to determine the effect of sanitary work.

### *Soil infestation*

Until the invention by Baermann (7) (8) of an apparatus by which infective hookworm larvae can be isolated from considerable quantities of soil, it was practically impossible to gain any accurate information in regard to soil infestation. This apparatus has been used by Baermann (4) and Cort and Payne (5) (9) to determine the sources of human infestation, the relation between soil pollution and soil infestation and to discover the effect of control measures in reducing soil infestation. It has, also, been possible by the use of this apparatus to study the length of life of the infective hookworm larvae in the soil. Augustine (10) and Cort and Payne (5) (9) have shown that under tropical conditions the length of life of the infective hookworm larvae in the soil is much shorter than was previously supposed. This discovery is of significance in this connection since the length of life of the larvae in the soil has an important bearing on any analysis of the factors in the etiology of hookworm disease.

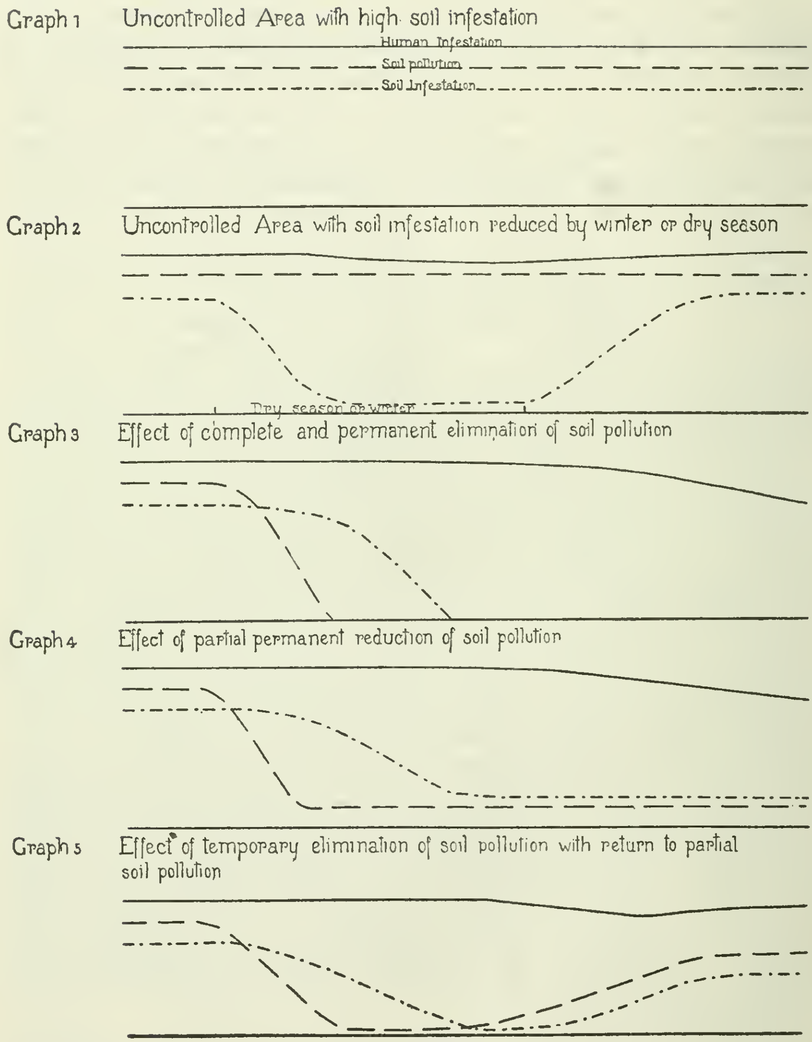
In connection with soil infestation there is another factor, which must be considered. It is evident from a number of considerations that in regions with cold or dry seasons there will be a great drop in soil infestation during those seasons. In the first place hookworm disease does not become endemic to any extent in regions with a very cold winter or in very dry regions. Further, in places in the hookworm belt which have a definite winter season, it has long been known that the spread of hookworm disease, as indicated by the prevalence of ground itch, comes in the summer time especially during rainy spells. Also in tropical regions with a long dry season, ground itch is unknown except in the rainy season. Add to these facts, what we know of the effect of low temperatures and desiccation on the development of hookworm larvae, and it seems evident that cold and dry seasons must have a very great influence in reducing soil infestation.

*A graphic analysis of the relation of human infestation, soil pollution and soil infestation in hookworm control*

In the graphic representation of the interrelation of human infestation, soil pollution and soil infestation, the first factor will be represented by an unbroken line, the second by a broken line and the third by a line made up of a series of dots and dashes. Graph 1 represents the balance obtained between these three factors in an uncontrolled area, when soil infestation is undisturbed by unfavorable environmental conditions and graph 2 their relationship under conditions in which soil infestation is greatly reduced for part of the year by a cold or dry season. In control work the relation of these three factors is disturbed by treatment campaigns to reduce infestation and by sanitary work to reduce soil pollution. In the series of graphs which follow I will attempt to show the changes produced in these three factors by control measures introduced under a variety of conditions. In the consideration of the effect of control measures in this analysis, they will be considered under practical rather than ideal conditions. For example, under actual conditions in a control campaign it is practically never possible to entirely eliminate human infestation by treatment or soil infestation by sanitation. Further it may be taken for granted that there will be almost without exception some resumption of soil pollution after the completion of a control campaign. Graphs 3 to 9 show the effect of control measures introduced under conditions of high soil infestation in which the original condition is represented by graph 1 and graph 10 represents changes in an original condition such as graph 2.

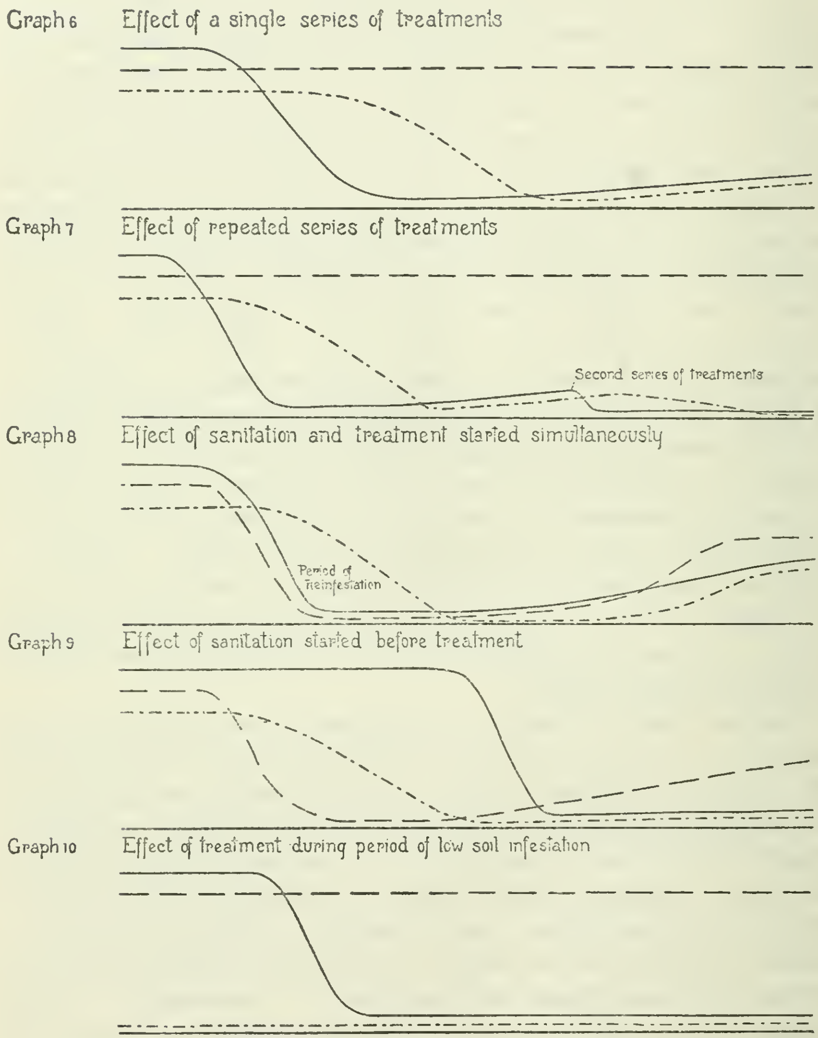
Graphs 3, 4 and 5 illustrate what probably happens when sanitary measures alone are utilized in hookworm control. In the case of graph 3 a theoretical rather than a practical condition is depicted, for as far as I know, with the possible exception of some of the control work in mines, it has never been possible to completely and permanently eradicate soil pollution in any hookworm infested area. If such a condition as that indicated in graph 3 was brought about, it would soon eliminate soil infestation as the infective hookworm larvae died out of the soil and would gradually eliminate human infestation as the adult hookworms died of old age. Graph 4 shows the effect of a permanent reduction of soil pollution which would soon reduce soil infestation and more gradually bring down human infestation to a new low level. Such a result as that indicated by this curve might actually be attained in any hookworm infested regions in which the standards of sanitation were raised, and probably shows what is actually now occurring in certain parts of the Southern United States where active hookworm campaigns are no longer being carried on, but where a considerable effort is being made to improve the habits of the people in regard to the disposal of human excrement. Graph 5 illustrates what probably usually happens where sanitary campaigns alone are carried on, in attempting to reduce hookworm infestation among people addicted to soil pollution. During the actual campaign there is usually a distinct reduction in soil pollution, which would be followed by a decided drop in soil infestation, and a slight reduction in human infestation. After the conclusion of such a campaign there would usually be at least a partial resumption of the habits of soil pollution, resulting in an increase in both soil infestation and human infestation.

Graphs 6 and 7 show the effect of treatment alone. Graph 6 shows the probable results of one series of successful treatments. By such a procedure the curve of human infestation is greatly reduced, the amount of reduction depending on the efficiency and completeness of the treatments, leaving a much reduced mass


Graph 1
Uncontrolled Area with high soil infestation
Human Infestation
Soil pollution
Soil Infestation
Graph 2
Uncontrolled Area with soil infestation reduced by winter or dry season
Dry season or winter
Graph 3
Effect of complete and permanent elimination of soil pollution
Graph 4
Effect of partial permanent reduction of soil pollution
Graph 5
Effect of temporary elimination of soil pollution with return to partial soil pollution

infestation, in the population. The amount of soil infestation would be reduced more slowly, depending on the length of life of the infective hookworm larvae in the soil. This would produce a period of reinfestation which would increase somewhat the human infestation and at the same time the soil infestation since soil pollution had not been reduced. This increased soil infestation would slowly increase the human infestation and the amount of both soil infestation and human infestation would gradually rise until a condition of balance was again reached. The value of treatment alone under such conditions as this would depend on how long it would be before human infestation returned to a point where it would again menace the health of the people. I know of no accurate information on this point. Graph 7 illustrates a method by which treatment alone could be made more effective. If under the conditions of graph 6, treatment was repeated after a period greater than the length of life of the infective hookworm larvae in the soil, the worms which had gained entrance during the period of reinfestation would for the most part be killed by the anthelminthic and human infestation again reduced. It is possible that three series of treatment given at intervals greater than the length of life of the infective hookworm larvae in the soil would give results of lasting value. Here again experimental evidence is badly needed.

Graphs 8 and 9 illustrate the effects of both sanitation and treatment. It is postulated in these graphs that, as is practically the universal experience, there will be a partial resumption of soil pollution after the completion of the sanitary campaign. Graph 8 shows that a combination of successful treatment and sanitation will greatly reduce human infestation and soil pollution. But since the reduction of soil infestation will lag behind for a period, depending on the length of life of the infective hookworm larvae in the soil, there will be a period of reinfestation. This will slightly increase the human infestation and if any appreciable degree of soil pollution is resumed after the conclusion of the control campaign, will also increase the soil infestation. Both human infestation and soil infestation will then slowly increase until a balance is reached, the amount of increase in human


Graph 6
Effect of a single series of treatments
Graph 7
Effect of repeated series of treatments
Second series of treatments
Graph 8
Effect of sanitation and treatment started simultaneously
Period of reinfestation
Graph 9
Effect of sanitation started before treatment
Graph 10
Effect of treatment during period of low soil infestation

infestation depending on the degree of resumption of soil pollution. If it were necessary in any campaign to start the treatment and sanitary work at the same time, the bad effect of the period of reinfestation could be pretty largely eliminated as was indicated in graph 7 by a second series of treatments separated from the first series by a period greater than the length of life of the infective hookworm larvae in the soil.

Graph 9 shows what seems to be the most effective method of eliminating reinfestation. From this curve it is seen that if an area in which a hookworm control campaign is to be carried on is presanitated and the treatment phase of the work is delayed for a sufficient length of time to allow the effects of the reduction of soil pollution to be reflected in the reduction of soil infestation, the period of reinfestation will be eliminated and the work will be of more permanent value than under the conditions of graph 8. The above analysis emphasizes the value of the method of presanitation usually adopted in the hookworm control campaigns of the International Health Board of the Rockefeller Foundation. The discovery that the infective hookworm larvae live only for a short time in the soil under tropical conditions, makes the carrying out of control work according to the conditions suggested by graph 9 a very easy procedure.

It remains only to consider whether it might not be possible to utilize a period of naturally reduced soil infestation to make control work more effective. Graph 10 shows the probable effect of treatment alone, started at a time when soil infestation was at its minimum due to a reduction by a cold or dry season. In such a campaign there would be no appreciable degree of reinfestation after treatment. Its effectiveness would then be dependent on the thoroughness of the treatment work and its results, according to my analysis, would be more permanent than those of a treatment campaign carried out under conditions of high soil infestation (cf. graphs 10 and 6).

## CONCLUSION

The analysis just given combined with recent important advances in our knowledge emphasizes the importance of giving more consideration to certain phases of hookworm control. In the first place the value of mass treatment as a control measure is emphasized. It seems to me that graph 7 shows pretty clearly that repeated mass treatment will effectively control hookworm disease even in a region where it is impossible to reduce soil pollution. The method of mass treatment in hookworm control has been advocated by Darling and his co-workers and has been put in operation by the men in charge of the International Health Board campaigns in Brazil.

Further a comparison of graphs 8 and 9 emphasizes the importance of carrying sanitary work to the point where soil infestation is reduced to a minimum before the treatment phase of the campaign is started in order to eliminate the period of reinfestation. In a tropical country such as Trinidad where the life of the infective hookworm larvae in the soil is limited to six or seven weeks, such a procedure is easily carried out. Just how far in practical control work the reduction of soil infestation by climatic conditions can be utilized (see graph 10) is problematical since most hookworm campaigns are of necessity organized on a year round basis. But it sems important in regions where there is a winter or a dry season that this factor should be taken more into consideration.

## SUMMARIT

Las siguientes ecuaciones expresan de una manera sencilla los factores que favorecen la diseminación de la uncinaria:

1. Infestación humana contaminación del terreno ambiente favorable—infestación del terreno.

2. Infestación del terreno contacto humano.—infestación humana.

Cuando sólo se emplea la ciencia sanitaria como medida de dominio, los resultados seran perdurables si se consigue eradicar completa y permanentemente la contaminación del terreno o por lo menos reducir la grandemente. Bajo tales condiciones la contaminación del terreno desaparecerá después de un período relativamente corto que depende del vigor vital de las larvas de la uncinaria. No obstante, la infestación humana se reducirá

lentamente según vayan muriendo de vejez los guzanos adultos. Por lo tanto, si se resumiera la contaminación del terreno antes de la completa desaparición de los guzanos adultos, habrá un renuevo de infestación del suele con un aumento consiguiente de infestación humana.

El tratamiento humano, por sí solo, reducirá la contaminación del terreno, pero sinembargo, existirá un período de re-infestación mientras las larvas esten muriéndose. Esta re-infestación aumentará gradualmente la infestación del piso, y de paso la humana, pues la contaminación del piso no ha sido reducida. Dos métodos se sugieren por sí mismos para hacer el tratamiento más efectivo. Uno sería el reducir la re-infestación mediante tratamientos repetidos despúes de períodos de tiempo mayores que la duración de la vida de las larvas en el suelo. El otro sería el llevar a cabo los tratamientos durante la estación fría o seca cuando está en su mínimo la infestación del terreno.

El método corriente de poner en ejecución une campaña de exterminio en contra de la uncinaria, es el combinar las medidas sanitarias con el tratamiento. Si ambas cosas se empiezan al mismo tiempo habrá un período de re-infestación antes de que las larvas mueran sobre el terreno. Esta re-infestación puede eliminarse por medio de una segunda serie de tratamientos que esté distanciada de la primera por un período mayor que la duración de vida de las larvas en el terreno. El mejor método a seguir, es el proceder con el trabajo sanitario hasta que la contaminación del terreno sea reducida todo lo más posible y entonces acometer con las diversas fases de tratamiento. Este método, con tal de que las medidas sanitarias tengan éxito, eliminarán el período de re-infestación y hará que el esfuerzo sea más duradero.

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# THE INFLUENCE OF MALARIA ON THE CIRCULATION[1]

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It is rather difficult to estimate the functional loss and the structural lesion that the human organism has received from an attack of any acute or chronic disease. The pathologist can describe the morbid anatomy in the dead patient, but the clinician has far more difficulty in estimating the clinical damage to the convalescent living patient. Diagnosis is the time consuming element in medicine: after diagnosis, treatment is easy and takes little time; but more difficult than either is this problem of the clinical damage to the individual. In malaria, for example, is the patient's functional power less, either in single organs or in the system as a whole? Will his structural pathology shorten his life? Is he a malaria carrier, and therefore, a clinical liability to the community? Are there parasites lurking in the trabeculae of the spleen and the sarcoplasm of the cardiac muscle ready to reproduce and cause the disease when the normal resistance is lowered below an unknown level? Particularly is the influence of a tropical disease on the various systems or organ important, because tropical diseases more than others affect populations living in definite stretches of latitude, more or less exposed by a common climate, and the infected patients may often be the unconscious agents in the further dissemination of the disease. We say glibly that malaria causes anemia, splenomegaly and cachexia, and is often fatal. It was thought that a summary of the influence of this disease on the circulation might illustrate this ever present problem of clinical damage and at the same time concentrate attention on the circulation as the chief field of activity of the parasite, and of clinical damage to the patient.

[1] Read at the eighteenth annual meeting of the American Society of Tropical Medicine, May 2 and 3, 1922, Washington, D. C.

The malarial parasite exerts a selective destruction on the blood. In its reproducing time it mainly lives on and destroys the red corpuscle. One migrating parasite may destroy several erythrocytes. This destruction may continue between paroxysms. In pernicious malaria of the cerebral type, in certain capillaries, every erythrocyte may contain a parasite. This is the local vascular limit of infection. Probably the clinical limit of safety to the patient is not above 5000 parasites per cubic centimeter. Parasites may select the less resistant erythrocytes, which are apt to be the younger ones. The peripheral erythrocytes may be sparsely infected, and yet those of the visceral capillaries may be numerously infected. Normoblasts occur indicating the strain on the bone marrow. The hemoglobin is decreased in the surviving erythrocytes, presumably due to the influence of the malarial toxin or parenteral protein. With decreasing hemoglobin, the erythrocytes assume the variable shapes and sizes characteristic of anemia with variable pallor of the centers. Destruction of the erythrocytes by the reproducing parasites and hemolysis by a toxin are natural precursors of an anemia proportionate to the amount of destruction. The clinical paroxysm is the time of blood destruction in the greatest degree. I have found no opinion that the fragility of the erythrocytes is affected either by the paroxysm or afterwards.

The destructive influence of the parasite is exerted on the white cell as well as on the erythrocyte. The leucopenia following the paroxysm is probably to be regarded as leucocytic anemia, affecting chiefly the polymorphonuclears from the bone marrow and less the lymphocytes and mononuclears from the lymph and vascular tissues. The large mononuclears are therefore, less affected and are actually relatively and absolutely increased, but such increase is not diagnostic of itself of malaria. Myelocytes may occur, in pernicious types as high as 5 to 8 per cent, indicating like the normoblast, the labor of the bone marrow. Between paroxysms there is commonly a leucopenia, less commonly a normal count, and rarely a leucocytosis. During the paroxysm leucocytosis is common with the subsequent leucopenia.

The leucocyte curve often follows the temperature curve in the simple tertians and quartans. The leucocytosis is probably due to the reaction following the sudden liberation of the malarial toxin and the toxin from the parenteral protein of the destroyed corpuscles. Clinically and chronologically, this corresponds to the cold, fever and sweat of the paroxysm. As a rule, the greater the splenomegaly, the less the leucocytes, for here in the spleen is the massing of the parasites and the graveyard of the leucocytes. The leucocytes may be proportionately reduced far more than the erythrocytes, and may return to normal during convalescence far more slowly. As the parasite does not live on the leucocyte, this probably indicates the benumbing effect of the malarial poison on the bone marrow and the consuming power of the large endothelial cells on the phagocytes. Phagocytosis is carried on chiefly by the mononuclears and transitionals, less by the neutrophile polymorphonuclears and hardly at all by the eosinophiles. The neutrophiles however, carry pigment. The neutrophile blood picture with the Arneth count shows a decided shift to the left which may persist during the treatment and even after fever. There is some reason why the polymorphonuclears shy at phagocytosis. For some reason the mononuclears are more able to attack the parasite and their increase may be both a defensive reaction and an effort at immunity.

The pigments of malaria are of blood origin. Whatever finer differences of opinion may exist in regard to their chemistry and qualities, such pigment is circulatory in distribution and is found in no other disease. MacCallum well says that this visceral pigmentation, whose finer particles are held by innumerable leucocytes, endothelial cells and wandering macrophages, is the most characteristic feature of the necropsy of a malarial body. Intravascular black pigment is pathognomonic of malaria (Manson). It is a by-product of malarial reproduction in the destruction of the erythrocyte and must certainly be related to hematin, with which it seems to agree in solubility, spectroscopic qualities and iron content. The segmenting parasites drop this pigment into the blood stream, and the distribution follows to its leucocytic and endothelial homes. Pigment clumps in the peripheral blood may indicate profound infection and destruction of erythrocytes in the viscera even though peripheral parasites are scarce. The yellow pigment or hemosiderin occurs in the parenchymatous tissues as well as in the capillaries and is not pathognomonic of malaria, but like the black pigment, is of blood origin. It comes from erythrocytes dissolved in the plasma, a true hemolytic process as in pernicious anemia. It may be stored, in the liver, spleen, bone marrow, etc., and may be used to stock new reds from the bone marrow. The increase of urobilin and bilrubin follows easily and naturally. The icteric tint in several malarial anemia and cachexia so well known to the clinician, analogous to the hemolytic anemias, is quite natural, as is the association in the mind of the laity with the so called "biliousness" and "bilious fever."

The specific gravity of the blood tends to fall on account of the destruction of the corpuscles. A true decrease in the total blood volume occurs in advanced cases. Therefore, with repeated attacks and increasing anemia the tendency of the blood pressure is toward hypotension. This hypotension may be a decided clinical factor in the weakness of the cachectic. Of course, the anemia is the chief cause of the hypotension. During the acute paroxysm, the pressure rises during the cold stage. The fever is rising synchronously, and here for a time is one of those rare occasions in medicine when the shock of the toxin has more influence on the peripheral constriction and the rise in the pressure than the heat of the fever has on the peripheral dilatation and the pressure fall. The rise in the cold stage varies from 20 to 30 mm. above normal. During the hot stage and most pronounced at the height of the fever, the pressure falls from 20 to 30 mm. below normal. In early paroxysms when the corpuscular destruction and hemoglobin fall is slight, the pressure returns to normal in twenty-four hours. As the infection and anemia increase to the cachectic degree, the pressure falls and usually remains low. In one paroxysm of a benign tertian, the oscillation in pressure may vary 60 mm.

Malaria produces anemia. True it is a secondary anemia with the cause well known, but an anemia of whatever name whether primary or secondary and of known or unknown cause or causes, makes the patient suffer the damages of an anemia proportionate to the decrease in the hemoglobin and corpuscular variation in quality and quantity. Too often in malaria other parasites aid the anemia producing powers of the malaria parasite. John B. Elliott in New Orleans showed me a patient in the Charity Hospital with malaria, amebiasis, hook-worm disease, Ascaris and Tenia infection at the same time.

The anemia of malaria is probably the chief cause of the inertia, pallor, weakness and cachexia that result from the disease. The malarial parasite poisons and destroys the blood. The anemia is probably five fold in origin. (1) The partial and complete destruction of the red corpuscle by the parasite. (2) The influence of the toxin produced by the parasite on the erythrocyte. (3) The probably lessened power of the bone marrow to produce erythrocytes in adequate numbers during the paroxysms and in the severe infections between paroxysms. (4) The exhaustion of the blood forming organs from long forced manufacture without rest incident to the severe chronic infections. (5) The decreased food intake during paroxysms and the decreased digestive powers of the patient.

All gradations, severities, sudden fall and rise, relation and lack of relation to prognosis occur in this secondary anemia. Active proliferation of the parasite may take place in the blood stream in enormous numbers with the concomitant erythrocytic destruction. The hemoglobin may be as high as 85 per cent. with a fatal outcome and as low as 20 per cent with recovery. Not only are erythrocytes destroyed, but there is a decrease in the hemoglobin content of the surviving corpuscles, and therefore, the fall in the hemoglobin may be proportionately greater than the fall in the erythrocytes. Malaria produces the most rapid fall in hemoglobin and erythrocytes of any acute infection, and therefore, the quickest and most acute anemia. The clinical chemistry entailed by a single paroxysm is of no small moment to the organism. The corpuscles may drop from 500,000 to 100,000 per paroxysm in the pernicious type, or to just a few thousand per paroxysm. Usually, the decrease in erythrocytes and hemoglobin is proportionate to the number of parasites in the blood. The total number of parasites may rise in twenty four hours from 5400 to 95,400 and as high as 295,000 per cubic centimeter have been found in the peripheral blood. As high as 1,348,300 per cubic centimeter have been found at necropsy in spleen blood and 190,000 in brain blood. The erythrocytes drop in the severe infections usually to 3,000,000 or below and as a rule decrease with the severity and chronicity of the infection.

Malarial cachexia is a secondary anemia of dangerous degree consequent to the malarial infection. It is characterized by advanced anemia, sallow, earthy and icteric tint and skin, enlarged spleen and sometimes liver, hypotension, weakness, rapid pulse on exertion, perhaps edema, with or without fever. It is a disease of the blood due to malaria. It may with difficulty be distinguished from a primary splenomegaly, particularly if no parasites are found. Both are pictures of a severe secondary anemia with leucopenia and splenomegaly, and both are circulatory diseases. The history may be more valuable than the blood count in the differential diagnosis. It is evident that a patient with such cachexia recovers slowly and in children growth hesitates and even a state of infantilism may result.

The ideal conditions for malarial anemia are present in the two-fold factors of peripheral blood destruction and alteration in the structure and function of the bone marrow. With corpuscular destruction, the bone marrow must increase its labor and manufacture. Normoblasts and myelocytes in the peripheral blood are evidences of this demand of the tissues for increased blood production. With anemia from a suspected malaria and with myelocytes in the blood, the search for the parasite should continue. Clinically severe malarial anemia may with difficulty be distinguished from aplastic or pernicious anemia. Here the very structure of the bone marrow varies with pigmentation added. Erythrocytes loaded with parasites, fat replacement with vascular tissue in the long bones, pigmentation and congestion in the spongy bones. With hyperplasia absent in the marrow, an aplastic state has arrived. In mild infections, the marrow responds to the demand for more erythrocytes.

The pathology of the blood vessel in malaria is the source of many clinical symptoms, particularly in the pernicious forms. The malarial toxin seems to have a selective, destructive and degenerative action on the endothelial lining of the vessel, more so perhaps than on any other tissue except the erythrocyte. The endothelial cells may contain pigment, parasites, engulfed phagocytes, fat droplets, degenerated nucleus, and be swollen and free in the vessel. With pigment, parasites, and capillaries strutted to blocking, a local stasis of the circulation, "the toxic effects on the endothelial wall may be so great as to give rise to multiple hemorrhages." The comatose, meningeal and diarrheic cases may be traced to this capillary strutting and blocking. With hemorrhages added, the case clinically is worse. On vessel rupture blood, parasites, pigment and debris are found in the hemorrhagic area. In the brain these punctate spurts cause necrosis, variable paralysis and mental symptoms; in the intestines, often blood and mucous in the stools with diarrhea and choleraic attacks; in the kidney, nephritis and hematuria which Dock has so well described; in the pancreas, acute hemorrhagic pancreatitis, and rarely sugar is found in the urine in malaria; in the spleen, with great enlargement, which with various cellular proliferations, may lead to rupture, either spontaneously or from trauma; in the adrenals, thrombosis and hemorrhage in the parenchyma; in the thyroid, blocking, thrombosis and perhaps hemorrhage occurs to account for the symptoms of thyreotoxicosis that may develop suddenly in malaria. Submucosal hemorrhages occur in the nose, stomach, intestines and pulmonary tissues. These last may give rise to pneumonic symptoms and diapedesis of the erythrocytes into the alveoli is not uncommon. The eye symptoms of retinitis, amaurosis, and scotoma are probably capillary and arterial in origin. All such hemorrhages tend to increase the number of symptoms, the anemia, and weakness. The hemoglobinuria is an intravascular hemolysis caused by a great destruction and degeneration of the erythrocytes, really an acute hemolytic anemia. It is estimated that one-sixtieth of the hemoglobin must be set free from the cells to produce an attack. A powerful provoking toxin and a state of lowered resistance must unite to produce such a hemic and chemical dilemma.

The heart muscle is probably more often affected than was formerly considered. On the other hand, mortal malaria may at necropsy reveal in the heart muscle comparatively little change. The myocardium is jealous of its nutrition, and in all the grades of malaria anemia from the slightest to the most severe, functional evidence of myocardial insufficiency proceeds proportionate to the degree of the anemia. In any severe type, fatty changes may occur around the nucleus of the muscle fibre. In what is named the "cardiac" or "septicemic" type, death may apparently be due to cardiac failure alone. Rapid pulse, tic tac, equal and distant heart sounds, a falling pressure and circulatory embarrassment are the clinical signs, progressing rapidly to failure in the fatal cases. Dilatation and hypertrophy may keep pace with the symptoms. Recent reports confirm pathological changes in the heart proportionate to the clinical signs of heart failure. In forty five cases of fatal malaria examined by Dudgeon and Clarke, twenty three showed evidence of fatty degeneration of the muscle. Parasites loaded the distended capillaries in severe cases and thrombosis occurred in two cases. In other cases reported by Gaskell and Millar, acute degeneration of the muscle was extreme, but striation and the nuclei were preserved to a marked degree. This is evidence of a profound toxic influence acting acutely on the heart muscle. In the severe but more chronic types, the fatty change was slight, but striation was largely lost,—a granular change. Nuclear degeneration was wide spread. Enormous numbers of parasites were found in the lymph spaces and sarcoplasm. The heart may be dilated and very soft, falling slopingly over the hand that holds it. In one case, 140,000 parasites, per cubic centimeter were found in the blood from the left ventricle.

The clinical examination of the heart is very variable. In the shaking chill the heart sounds are somewhat obscured by the contracted muscles of the pectoral region that really roar in the stethescope in their clonic activity. In the cold stage the pulse is rapid and apt to be small and rather contracted. As the fever rises and the sweating begins, the heart becomes faster, its sounds clearer and booming, and the pulse large, full and soft. I have often been struck with the similarity between the full pulse of the fever stage and the full pulse in a severe acute follicular tonsillitis. With anemia and cachexia, the pulse is rapid on exertion, soft and of low tension, and hemic murmurs occur of variable location and degree. The bellows murmur at the apex may be found. Dilatation and increase in the transverse diameter of the heart occurs in the cardiac types. These are often so rapidly fatal that it amounts to an attack of acute heart failure. An ordinary benign malarial infection without notable anemia probably does no harm to the heart. It is difficult to prove that any malaria produces a systemic arteriosclerosis.

The liver tends to hyperemia but the most marked change is the pigmentation deposited from the blood in the distended sinuses. The endothelial cells of the sinuses incorporate the hematin, and perhaps are able to dissolve it to a degree. The busy endothelial cells are consequently swollen and with the dilated vessels compress to some degree the liver cells, a mechanical pressure atrophy of vascular origin. Dots of repair and cirrhosis occur. In advanced cases of pernicious infection, the liver increases in weight, and at death may be slaty, soft and friable. The hepatic damage is circulatory in origin. With hyperemia, increase in hematin and hemosiderin, increase in blood nitrogen from destruction of erythrocytes, leucocytes and parasites, with pressure atrophy, areas of necrosis and fibrosis, rare icterus, (bile is hemolytic)—the general clinician is probably correct in the plea that malaria is a blood infection that injures the liver, often permanently, both in structure and function.

## CONCLUSIONS

1. The seriousness of a disease is proportionate to the structural and functional injury to the individual. This may be expressed as clinical damage. It is rather difficult to estimate in malaria.

2. Malaria is a parasitic disease of the blood, and its clinical damage occurs through the circulation.

3. There is erythrocytic, leucocytic, and endothelial cell destruction varying from an unimportant to a fatal degree.

4. Malaria produces a variable secondary anemia, usually quickly developed and quickly cured.

5. Hemorrhages occur from toxic damage to the vessel wall. The mechanical strutting of the vessel may be a factor in the rupture. The toxin may be from the parasite or the destroyed protoplasm or both.

6. The heart may be untouched or a myocardial death may result.

7. The liver injury is vascular in origin.

8. The pigment is from the blood.

9. The blood pressures may oscillate 60 mm. during a paroxysm, but they tend to hypotension from the anemia and weakness.

10. The heart sounds and the pulse vary during the paroxysms.

## CONCLUSIONES

1. La seriedad de una enfermedad es proporcional al grado de daño estructural o funcional que haya recibido un individuo. Este puede expresarse clínicamente. Es muy dificil apreciarlo o avaluarlo en la malaria.

2. La malaria es una enfermedad parasítica de la sangre y el daño clínico ocurre por medio de la circulación

3. Hay destrucción de eritrocítos, leucocítos y de células endoteliales que varían en grado desde lo insignificante hasta lo fatal.

4. La malaria produce una anemia secundaria variable generalmente de desarrollo rápido y que se cura rápidamente.

5. Ocurren hemorragias por averías tóxicas de la pared vascular. El entesamiento mecánico del vaso puede que sea el factor que ocasiona la ruptura. La toxina puede que origine del parásito, del protoplasma destruído, o de ambos.

6. El corazón puede que no sea afectado. Muerte por miocarditis puede ocurrir.

7. El daño al hígado es de origen vascular.

8. El pigmento es hematógeno.

9. La presion sanguínea puede que oscile en los 60 mm. durante un par oxismo, pero tiende a la hipotensi6n debido a la anemia y debilidad.

10. Los ruidos cardiacos y el pulso varían durante el paroxismo.

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# THE ACTION OF LIGHT IN THE PRODUCTION OF RELAPSE IN MALARIA.[1]

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For many years it has been recognized clinically that various conditions would cause a relapse in a person who has recovered from an acute attack of malaria; and one of these conditions is exposure to the sun. As it came to be recognized that the malaria parasite commonly passes the winter in the blood of man, it was realized that many of the cases of malaria occurring early in the spring are relapses in persons who have carried the parasite from the previous summer; and sunlight is considered to be one of the important causes of such relapse.

Lenz (1) was in charge of 13,000 healthy Russian prisoners, some of whom developed malaria as spring came on. He observed 80 cases of malaria among these prisoners: in the first year, nearly all of his cases were relapses; while in the second year, there were new infections as well as relapses. The curve of relapses, as well as the curve of new cases, followed the temperature curve.

Neergaard (2) had charge of a large number of cases of malaria, and found that relapse was less frequent as spring came on. But Lenz points out that Neergaard's cases were all chronic malaria, who had been under treatment for many months, and were sent to the higher altitude for treatment because they had resisted treatment. The cases were sent to the higher altitude in December, 1916, and no wonder relapses were less frequent as spring came on.

Schaedel (3) observed 375 relapses in Mainz; and he confirms Lenz's observations. The relapse curve corresponded with the

[1] Read at the Washington, D. C., meeting of the American Society of Tropical Medicine, May 1, 1922.

curve of the average yearly temperature. With a high temperature, dry atmosphere, and few clouds, the more intense the sunlight the greater the number of relapses. But the maximum of the relapse curve was reached in June, one month before the maximum of the temperature curve.

Both Lenz and Schaedel think that the sunlight is the cause of the relapse; and, accepting Schaudinn's explanation of the mechanism of relapse, they consider that the increased intensity of the sunlight acts as a greater stimulus to the gametocytes and causes them to start the asexual cycle.

### RELAPSE IN TREATMENT AND DIAGNOSIS

Accepting Schaudinn's explanation of relapse, the idea of many German workers has been that latent malaria should be treated by producing relapse by stimulating the macrogametocytes to reproduce the asexual cycle, and then treat with quinine. When all of the macrogametocytes have been disposed of in this way, the case would be recovered. However, Nocht pointed out that gametocytes would be formed during the relapse, and that no satisfactory results could be expected from such a method of treatment.

There is also the idea of causing the parasites to come out from the internal organs to the peripheral circulation, where they can be reached by quinine. Reinhard (4) undertook to cure malaria by exposing the patient to ultra-violet rays, with the idea of causing the parasites to come into the peripheral circulation as a result of the lowered blood pressure resulting from exposure to these rays. In his work, schizonts appeared in the blood in four to five days: 63 per cent of 38 cases became positive—in one-half of them within seven days, and in five-sixths of them within twelve days. In his cases not exposed to the rays, spontaneous relapse took place in about three and one-half weeks.

While some workers have used the provocative methods with the idea of driving the parasites into the peripheral circulation, where they can be destroyed by quinine, others have used the methods for diagnostic purposes.

On this basis, a number of methods of provoking relapse have been suggested. Sassen (5) discusses the provocative measures in malaria, in four classes:

1. Foreign proteins—horse serum being the best.
2. Substances acting on the circulation—as adrenalin, by squeezing the parasites out into the peripheral circulation.
3. Various drugs—as quinine in small doses.
4. Physical agents—as ultra-violet rays, hot and cold douches, hot packs, and massage of the spleen.

He considers that horse serum, adrenalin, and ultra-violet rays are the best provocative measures.

The question of the mechanism of relapse is not under discussion here, and I have already (6) given my opinion, based partly on my study of bird malaria, as favoring the explanation given by Ross and Bignami and opposed to the explanation given by Schaudinn. In the work then reported, I showed that the malaria parasites were always present in the peripheral blood of infected birds as long as I was able to observe them (the longest I have seen an infected bird live was twenty-nine months after infection, and I have never seen a bird recover; but other workers have reported a few cases of recovered birds). The parasites became too scarce to find on any ordinary examination, after a few months; but injection of blood from a wing vein of the infected bird always produced infection in a clean bird; and this seems to be the best way to determine recovery. This means that the parasites are always present in the peripheral blood in a form that will produce infection when injected into a clean bird; this means that the asexual forms are there. Thayer (7) and others have shown that the injection of human blood containing only gametocytes into another person does not cause infection; and in various parasites of lower animals (as Haemoproteus), when there are only gametocytes in the peripheral blood, it is impossible to transmit the infection by the injection of blood. The short life of the red blood cell means that any parasite in the cell cannot have been there long, and it cannot remain there long; so the asexual cycle must be going on when gametocytes are found in the blood.

All of my work since that time has only confirmed that opinion.

### RELAPSE OF REDISTRIBUTION

But, before proceeding to a consideration of light and relapse, it is necessary to note the point that there is difference of opinion as to whether some of the provocative methods produce a relapse or only a redistribution of the parasites, by driving them from their position in the internal organs into the peripheral circulation; also the fact that adrenalin is one of the most satisfactory substances for use as a provocative—relapse or redistribution.

Thus, Reinhard had the idea of driving the parasites out from the internal organs into the peripheral circulation—a redistribution—and there is nothing in his article to indicate that he did not think that was what he actually did. But Lenz says that it was relapses and not a driving of the parasites out into the peripheral blood. The article does not give data on which one might base an opinion.

Schittenhelm and Schlect (8) found that after the injection of 1 mgm. of adrenalin, they got a typical attack of malaria; at times, on the day of injection; more often, on the next day; and parasites were found in the blood. Their fever charts are those of typical febrile attacks. At times the fever did not set in until four days after the injection, and the blood was occasionally not positive until as late as seven days after injection.

So, from the work of Schittenhelm and Schlect, it is evident that the adrenalin caused relapse, and not a simple squeezing-out of the parasites.

On the other hand, Dazzi (9) says that with adrenalin injection there is not a typical attack of malaria, but the parasites are uniformly present in the blood. They appear about twenty minutes after the injection, reach their maximum number in about an hour, and are gone in twenty-four hours.

So, from the work of Dazzi, it appears that there is no relapse, but that it is a temporary squeezing-out of the parasites into the peripheral circulation.

This question will have to be discussed at another time; but we must bear in mind this point—of relapse or redistribution of parasties; and also the point that adrenalin does bring about one condition or the other—or both.

## THE PRESENT WORK

Since there is clinical evidence that relapse in malaria is associated with exposure to sunlight (undoubtedly there are other factors in the spring relapse), and also that exposure to ultra-violet rays is one of the best methods of producing relapse in malaria, it seemed advisable to study the action of light in producing relapse in malaria in an experimental animal. As I already had a strain of *Plasmodium relictum* that has been carried along in canaries since 1913, I have undertaken to study the action of light in malaria in these birds. The ordinary domestic—or captive—canary is susceptible to infection with *Plasmodium relictum*, but is never found infected in nature, so it is a satisfactory animal for the work.

As it would be difficult to study the reaction from the clinical side, I chose parasitic relapse as the standard for the study, and I chose Ross' (10) method of counting parasites by examining an ordinary moist smear of blood with an oil immersion lens, and counting the number of parasites found in a certain time, taking fifteen minutes as the standard. On account of the occasional finding of a parasite in the blood of an infected bird at any time after the apparent disappearance of the parasites from the blood, I always insist on finding two or more parasites in the standard time, before the presence of the parasites is considered significant in reference to relapse.

The blood of the bird is examined before exposure to the light and is then examined daily after the exposure. In view of the fact that adrenalin will cause relapse or redistribution of the parasites, a control bird is always run through: a bird treated exactly as the birds being exposed to the light, except that it is not exposed to the light. Also, since individual birds will differ in the amount of fright, and so perhaps in the part adrenalin would play in the reaction (11, 12), each bird is used as a control—and its blood repeatedly examined—before it is exposed to the light.

The substance of the feathers is opaque to ultra-violet rays; but it is possible to get relapse in birds exposed to the ultra-violet rays, without removing the feathers, probably as a result of the rays passing through the spaces in the feathers, or by their action on the skin where the feathers are few or lacking, as under the wings. However, in order to avoid the disturbing factor of the feathers, the feathers are removed from the breast of the bird, and the lamp is so placed that the light is directed at the breast.

An air-cooled quartz mercury vapor lamp has been used in most of the exposures, but a water-cooled lamp has also been used; the meter reading being constantly checked and recorded. A distance of 24 inches is used. A thermometer is placed on the table at the side of the bird being exposed.

In the reports of the use of the ultra-violet rays as a provocative, there is no statement as to whether any filter was used, and it is probable that the quartz mercury vapor lamp was used without filter. While this lamp is rich in ultra-violet rays (about 30 per cent of the total radiation [13]), it also emits a large amount of visible rays (over 50 per cent of the total radiation), but is weak in the ultra-red or heat rays (less than 20 per cent of the total radiation). (In the sun's rays, the ultra-violet is 1 to 2 per cent, the visible is 40 to 50 per cent, and the infra-red is 50 to 60 per cent of the total radiation. Of course, the intensity also plays a part; and the extent of the spectrum into the ultra-violet and the ultra-red is different in the sun's rays and the quartz mercury vapor lamp.)

Since the rays from this lamp are by no means limited to the ultra-violet, the plan of the work was first to determine a dose of unfiltered light that will cause a relapse in a large part of the birds, and then to determine what part of the spectrum of the lamp causes the relapse, by cutting down on the spectrum with filters and prisms. Finally, it is planned to work back this dosage of rays of a particular wave length to sunlight and determine what exposure to sunlight would furnish the same dosage of this particular wave length. Of course, the work is only started, and I can only report what has been done to date—and cannot draw any conclusions. There has been difficulty in obtaining the desired filters and prisms; but that difficulty has now been overcome, and the filters and prisms will soon be available.

Without going into detail as to the various birds, the results to date indicate that:

1. An exposure of two hours to the infiltered light of a quartz mercury vapor lamp, at a distance of 24 inches, with the meter reading at 75, with the feathers left on the bird, will cause a relapse in a bird.

2. An exposure of fifteen minutes to unfiltered light, as in 1, with the feathers off the bird, will cause a relapse in a bird.

3. An exposure of ten minutes to unfiltered light, as in 1, with the feathers off the bird, will not cause a relapse in a bird.

4. An exposure of fifteen minutes to light filtered through ordinary window glass, otherwise as in 1, with the feathers off the bird, will not cause relapse in a bird.

There is no rise in the temperature of the air, as indicated by a thermometer placed on the table beside the bird under the light.

In the controls, one bird with parasites still found in the blood, placed in the position and under the conditions which are necessary during the exposure—but not exposed to the light—showed a marked increase in the number of parasites in the blood. In none of the apparently recovered birds, when handled as controls, was there any evidence of a relapse, or any appearance—even temporarily—of parasites in the peripheral blood.

The work is being continued, and filters and prisms will be used. In the meantime, no conclusions are drawn.

### MANNER OF ACTION OF ULTRA-VIOLET RAYS

What is the action of ultra-violet rays on the body, with particular reference to how sunlight acts to produce relapse in malaria?

It is generallly agreed that the ultra-violet rays have little power of penetraton—not over 0.5 to 0.8 mm of skin. Rollier (14) showed that the spectrum as far over as the violet is unable to bring about pigmentation of the skin; and Hausser and Vahle (15) showed that the wave lengths of 302 to 297$\mu\mu$ have the strongest action in producing erythema and pigmentation of the skin. The ultra-violet rays appear to be absorbed in the blood.

Levy (16) and Gassul (17) have reported work done to determine the action of ultra-violet rays on the internal organs. They used the quartz mercury vapor lamp, without filter. In mice, the *spleen* showed marked enlargement, hyperemia and hemorrhages, and changes in and around the follicles. In the *liver* there was hyperemia, with hemorrhages, and necrosis of liver cells. The *lungs* were hyperemic, with pouring of red cells into the alveoli, so the lungs looked as though there were hemorrhagic infarcts. The *kidneys* were less regularly hyperemic, the hyperemia showing mainly in the glomeruli. There was no constant change in the bone marrow; and the other organs showed no change.

The changes were in general the same in rats—according to Gassul's work; while Levy found in one rat that the spleen change was different from that in mice: there was no enlargement or hyperemia, and microscopically the change was in the pulp—thickening of the stroma, with marked loss of cells, and the deposit of clumps of brownish pigment.

Gassul found that a red (neon) lamp had no action.

So there is evidence of a marked action of ultra-violet rays on the internal organs—especially on the spleen, next on the liver, then on the lungs, and finally on the kidneys; and this gives us some suggestion as to the lines which our work may follow. The fields of chemical action, light sensitization, and fluorescence, are all open: a later report will deal with the action of light in conjunction with quinine and its derivatives, following the lines of the work of Reitler (18) and others.

De Groer (19) finds that exposure to the sun and to the quartz mercury vapor lamp causes at first a leucopenia and then a leucocytosis. He also studied the action of light in the Schick test, and in the tuberculin test. He discusses the general reaction accompanying extensive sunburn; and concludes that the action of light is the same as the action of parenteral protein—it acts as a poison.

### THE ACTION OF X-RAYS IN MALARIA

Finally I wish only to mention that exposure to X-Rays has been reported to give cures in chronic intractable malaria—and not relapse. Wolff (20) treated five cases of intractable malaria with X-Rays; the cases recovering and remaining well for ten to seventeen months, the periods of observation.

The nearest to recovery I have had in any of the canaries—as determined by inoculation of clean birds, and difficulty to relapse with the quartz mercury vapor lamp—was a bird that was given one Holzknecht unit (one-fourth of a skin dose) of X-Rays. The X-Rays did not relapse the bird.

But this is another line of work that is being carried on, and it will have to be considered at another time.

## RESÚMEN

Existiendo pruebas clínicas de que el relapso en la malaria tiene cierta relación con la acción de la luz solar y la de los rayos ultra-violetas, aunque en realidad existen otros factores causativos, el autor ha creído conveniente estudiar experimentalmente en animales las causas del efecto de la luz en la producción de recidivas maláricas. Con tal objeto eligió para sus experimentos un número de canarios y como agente infectivo una raza del *Plasmodium relictum* la que había sido mantenida en pájaros de esa misma especie desde el 1913. El canario doméstico corriente, o sea el cautivo, aunque nunca se ha encontrado infectado con malaria cuando vive en su ambiente natural, es sin embargo, muy susceptible a la infección con el *Plasmodium relictum* y por lo tanto se considera muy a propósito para esta investigación.

Despúes de entrar en una serie de interesantes y detalladas consideraciones, basadas en las observaciones de varios investigadores inclusive sus propios experimentos en pájaros, ya publicados, acerca de todas aquellas medidas de que se hacen uso para provocar la malaria con fines terapéuticos, evoca el estado de incertidumbre presente tocante a si los tales métodos provocaticos son causa de un relapso puro o simplemente de una redistribución de los parásitos desde los órganos internos a la circulación periférica—como sucede por e jemplo cuando se administra adrenalina.

En los experimentos aquí publicados el autor nos demuestra el efecto de la aplicación de los rayos ultra violetas como provocativo de recaídas de malaria. Brevemente son como sigue:

1. Una exposición de dos horas a la luz de una lámpara de cuarzo de vapores de mercurio, a distancia de 24 pulgadas—y

a través de las plumas del canario, con el contador señalando 75, causa relapso en el pájaro de experimento.

2. Una exposición de 15 minutos la misma luz, sin filtrar, y bajo idénticas condiciones que en el párrafo primero, pero habiéndose antes quitado las plumas al canario, es causa también de relapso.

3. Una exposición de 10 minutos a la misma luz, y bajo idénticas condiciones que las arriba descritas en el párrafo, primero pero sin plumas, no causa relapso.

4. Una exposición de la misma luz durante 15 minutos, condiciones idénticas que en el parrafo 1, excepto que se filtró a través de cristal de ventana corriente y se desplumó previamente el pájaro, no causa recaída.

El autor termina comentando la acción de los rayos ultravioletas y la evidencia de su efecto sobre los órganos internos e indica varias fases de experimentación que aun no se han tocado.

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48[7]

# FINAL REPORT ON THE CONTROL OF YELLOW FEVER, IN MERIDA, YUCATAN, MEXICO


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In a preliminary report on yellow fever in the Yucatan peninsula the suggestion was offered that this disease may have played a major part in the destruction of the early Maya civilization. Dr. H. J. Spinden, eminent archeologist and authority on Maya ruins, has given considerable thought to the suggestion and in his article, "Yellow Fever, First and Last," has developed an interesting story from the picture writings and the transcribed and translated records of the early Mexican peoples. His studies leave little doubt of the devastation caused by yellow fever in Maya communities and confirm the belief that this disease existed in Yucatan prior to the coming of the Spaniards.

The last recorded case of yellow fever in the state of Yucatan is shown in statistics of the National Health Department as of December 20, 1920, and occurred at Tizimin, a small interior town about 100 miles from Merida. This case was not seen by a physician; diagnosis was made on evidence furnished by relatives of the deceased. The last case of the disease to originate in the city of Merida is recorded as of December 28, 1919.

It is probable that during the early months of 1920, mild cases of yellow fever existed in Merida or were introduced from outside the State, for there had been, between January and July of that year, considerable movement of troops into this area from regions known to be infected and where in some instances the infection had assumed the proportions of an epidemic. However, if cases were present or imported during this period they were of a very benign character for they completely escaped the vigilance of the local physicians, even in Merida where there are many medical men who know yellow fever, who have seen the disease in all its phases and who have carefully studied the infection in the various epidemics that have occurred here in former years.

From my studies of this disease in the gulf coast region of Mexico and more especially in Yucatan, I am convinced that the principal and largest and most constant endemic center of yellow fever in Mexico and possibly on the North American continent was in Yucatan, and that at the time of the Spanish invasion of the Peninsula the region of endemicity unquestionably covered a wide area. The focus of infection which we of a later day found in Merida was very limited in extent, but doubtless there was more than one endemic center in the area occupied by the first Maya civilization, since the population of this region, as evidenced by the size and distribution of the ruins, was clearly large—by some archeologist it is estimated as having reached into the millions—and there was great concentration of population around the water holes. A recent census for Yucatan gives a population of approximately 362,000.

Due to wars, to flight from oppressors, to disease, and to prophesies of an impending epidemic of yellow fever or, as it was then known, "the blood vomit disease," the cities of the Mayas were depopulated and thus through failure of the human host was brought about the elimination of the earlier endemic centers of yellow fever. Before this had been actually accomplished a new focus had been started in Merida, a city founded in 1542 by the Spaniards on the site of a ruined Indian village and destined to become in a relatively short time the principal city of the colony and the center of governmental and commercial activities.

The Mayas developed the cistern or "chultuns" as the receptacle for storing fresh water. They also used earthern jars and gourds, which were filled at need from the cisterns. The jars and gourds are small receptacles kept inside the home and as a rule filled daily, whereas the cistern is a container frequently large enough to conserve water sufficient for over a year. The chultuns, aided in part by the containers used inside the home, were the prime factors in maintaining a high *Aedes calopus* index in the Maya communities. The water-holes or "zenotes" probably contained fish, as they do today, and therefore could not have been then, nor are they now, breeding places of the *Aedes calopus*. The builders of the city of Merida continued to use the chultuns for conserving their domestic water supply. The Merida cistern of today—known as an *aljibe*—is quite like the one used by the ancient Maya. It consists of an excavation lined with cement and is located so as to be convenient of access to the occupants of the home. It is filled during the rainy months from the house roof and sometimes from the cement-covered *patio*.

From observations made in many countries I am convinced that, in localities where the *Aedes calopus* has acquired domesticity, the cistern is the breeding place "de luxe" of this mosquito—presenting as it does the best chances for the development of her young. It is by far the safest breeding haunt in Merida and throughout this zone. It holds an abundance of water, for there are not more than five days in a normal year when it is dry; plenty of air is provided by means of ventilating areas: there is ample space in which the mosquito may hide during the rainy months when water is entering the cistern; there is a bountiful supply of food gathered by the rain as it passes over the roof or *patio* on its way to the cistern; and lastly, the sun is excluded from the surface by the cistern roof, which is complete except for the small opening through which a pail is lowered for water. The same conditions obtain in cisterns from which the water is drawn by means of a pump, since small openings are always left in the roofs of these for ventilation purposes.

After more than a year's study and observation in Yucatan I do not find any sound reason for the belief that yellow fever has been endemic in recent years among the haciendas in the interior of the state. Unquestionably in the early days of the colony infection did exist endemically in these centers, but following the depopulation of the Maya communities and the introduction of indentured labor, these interior foci disappeared or were transferred, as it were, to Merida. For many years Yucatan has been a country of a single product, henequen, and until 1915 indentured labor was generally used. Laborers were not allowed to leave their haciendas until the expiration of the period of indenture, a system which resulted in the building up of a resident force which had no contact with laborers of other haciendas. If yellow fever were introduced among such a population it would be as an epidemic, with very little prospect of becoming endemic. The records of Yucatan clearly show that the terms of the indenture were rigorously carried out, and under these conditions it would be exceedingly difficult to establish endemicity of yellow fever.

The preliminary survey strongly indicated that Merida was the seed-bed of infection for all Yucatan. When cases did develop in the nearby haciendas the source of infection could generally be clearly traced to the city of Merida. In view of these findings a program was developed to reduce the *Aedes calopus* population in Merida by anti-larvae measures to the critical number or "safety index;" the rest of the state was deliberately neglected.

The interpretation of the preliminary survey has, I feel, been justified by the results of the campaign. It is reasonable to assume that had there been infection lurking in the interior of the state it would have declared itself in the course of fourteen months, particularly as the physicians everywhere in the Peninsula kept vigilant watch for suspicious cases.

The Stegomyia index in Merida at the beginning of the campaign—February 10, 1921—was nearly 50 per cent; by October 28 it had been reduced to 8.5 per cent. Since that time the entire campaign has been under the immediate supervision of Dr. Gil Rojas A., who has succeeded in further lowering the index to 1.75 per cent, a rate representing almost complete extinction of the *Aedes calopus*.

The plan of campaign as outlined in the preliminary report has been conducted solely on the principle of reducing the adult Stegomyia mosquito through the destruction of its larvae in receptacles used for storing fresh water in or near human habitations. There remains approximately the same number of containers in actual use today as at the beginning of the campaign. It has not been practicable to reduce the number to any degree nor has it been economically possible for the city to extend its present inadequate water system.

The anti-larvae measures in practice are: (a) Stocking containers with fish, (b) covering tanks, (c) oiling, (d) removal of larvae from containers.

The water receptacles used in the homes have been classified as follows: (a) Cisterns or aljibes, (b)tanks, (c) barrels, (d) wells, (e) lejia tins, (f) other receptacles.

There are nearly fifty thousand receptacles that come every ten days under the inspection of the campaign service.

The plan of administration is briefly as follows:

*a.* The city is divided into eleven districts with one inspector and an assistant in charge of each district. The duty of the inspector is to visit each home in his area and personally to examine all containers in use for conserving fresh water, all flower vases, and ant-guards around flower beds, under table supports, etc. The inspector carries with him a copy of Service Instructions which outline for him the method of treating each class of receptacles.

*b.* The inspector notes on a specially prepared form all data which the central office requires for its reports.

*c.* The cycle of inspection is ten days, including Sundays and a half holiday on Saturday. The inspections start in every district on the same day and at the same hour, and the districts are so arranged as to size that the work should be concluded on the same day throughout the city. It sometimes happens that an inspector is delayed, in which event the central office sends into that area an auxiliary squad. The Service insists that the inspections in all districts shall start simultaneously because, in addition to making for good discipline, the procedure is agreeable to the public. The people soon come to know that once every ten days the inspector will visit their premises, and they are accordingly ready to receive him, thus avoiding the long delays which are frequent when a definite cycle has not been established.

*d.* Each inspector is visited in his district by the Inspector-General who enters his signature and the time of his visit in the proper column of the inspector's daily report. The Inspector-

General adjusts minor differences that may arise between the inspector and the public.

*e.* At the end of each inspection cycle a general conference is held in which all members of the service take part. At the conference, problems are discussed and suggestions for the bettering of the service are received and acted upon. It is a pleasure to record here that many of the suggestions submitted by the inspectors and their assistants have proved of real worth and are in practice today.

## ANTI-LARVAE MEASURES

Anti-larvae measures will be discussed in the order of their importance and in conjunction with the class of container to which the measure is best applicable.

### *Fishes*

The *mojarra,* a perch, is in Merida the fish *par excellence* or destroying the mosquito larvae in fresh water containers of all classes with the exception of galvanized iron tanks and lejia tins. It is a hardy bottom-feeding fish and a voracious consumer of mosquito larvae. It thrives as well in a relatively small container as in a large one.

In the early weeks of the campaign objections were raised against the use of fishes in the cisterns, on the ground that their excretions would pollute the water. This fear has not materialized, but as a precaution against the possibility, the Service directs that the inspectors place only one fish, preferably a male, in each container. It is not definitely known how long the mojarra will live in a container, but we have knowledge of instances where fish of this variety, placed over one year ago, are still alive and active. When the young fishes in our hatcheries have attained the length of two inches they are considered to be the right size for distribution.

In the Merida campaign the top-feeding fishes have been discarded in favor of the *mojarra.* Top-feeders require frequent replacement and do not react promptly—in some instances not at all—from the fatigue sustained in transportation in the inspectors' pails. With the *mojarras*, replacements are relatively few, being heaviest at the time the cisterns are being cleaned to receive the new rains. Once this process has been concluded the replacements for the entire city can be easily attended to by one man. Again, top-feeders are sensitive to temperature changes such as occur here with frequency during the northern season. When the temperature reaches 69 degrees F. the mortality among these fishes is tremendous. This sensitiveness is not noticeable in the case of the *mojarra*.

### *Covering tanks*

There are fishes that will thrive in tanks, but to make certain that those placed in such containers remain alive and consume larvae, the inspector must, on each visit to the home, carefully search the tank for both fish and larvae. The majority of tanks are placed on an elevated frame work or are nailed to the wall partition well up toward the ceiling; the standard galvanized iron tank, which is placed at ground level, is 6 or more feet in height. To examine these receptacles, therefore, the inspector must use a ladder, and such extra equipment calls for additional help, a need which is eliminated when the tanks are sealed. A properly covered tank requires no attention from the inspector unless the cover has been removed or tampered with. To aid him in determining whether this has occurred during the interval of his visits, the Service directs that all tanks o.k'd by it as mosquito-proof shall be sealed in such manner that the cover cannot be removed without breaking the seal; and this seal is so conspicuously placed that the inspector can tell at a glance from ground level if it has been tampered with.

The sealing of a tank is a measure that must be properly carried out if it is to achieve its purpose; that is to say, before the seal is placed the cover must be so adjusted that the tank is positively mosquito proof. A sealed tank is a notice to the district inspector that this receptacle must not be touched by him until he observes evidence of its having been meddled with; therefore, unless every precaution is taken to see that the tank is mosquito proof before being sealed a persistent breeding place will be created which may lead to disastrous results.

The sealing process is very simple. In Guayaquil the plan was to use two strips of paper, each five inches long and about two inches in width, upon which was printed a warning to the owners not to remove or tamper with the seal without the permission of the central office. In Merida the plan is slightly different. Here we use adhesive strips about five inches in length and half inch in width. We find that adhesive strips resists well the fierce sun of Yucatan as well as the rain. The ends of the strips are covered with putty and into this is pressed the seal of the National Health Department, thus making the act official. On the sealed tank is posted a notice that the seal should be removed only upon receiving written permission from the central office.

Up to the present time I have not noted Stegomyia breeding in either the house-roof or the windmill tank. This may be explained in the case of the windmill tank by its distance from the home proper, which is greater than the usually accepted flight distance of the Stegomyia mosquito. The explanation for the avoidance of the roof tanks by the *Aedes calopus* may lie in the fact that this mosquito is now so thoroughly domesticated that it will not venture into places unfrequented by human beings; and in Merida house roofs, while nearly flat, are never used for clothes drying nor for servants quarters, nor as family gathering places in the early hours of the evening as is the custom in some countries. For over a year the Service has left the roof and windmill tanks without treatment, though some have covers with openings large enough for the mosquito to enter and leave at will while others have no covers at all.

### *Oiling*

The anti-larvae campaign for the control of yellow fever does not contemplate the general use of oil in reducing the Stegomyia mosquito, but occasionally it is necessary to employ this measure in order to avoid friction. An instance in point is the case of the lejia tin. *Lejia* is a softened water made by mixing hard water and wood ashes; the resulting mixture, notwithstanding its strongly *alkaline reaction* is a favorite breeding place for mosquitoes, more especially the *Aedes calopus*. *Lejia* is in general use throughout the east coast region and almost universally used in Merida. To throw away *lejia* on washday would be a real hardship. The Service plan is therefore to cover the surface of the *lejia* with gas, oil, or kerosene whenever larvae are found therein.

## REMOVAL OF LARVAE FROM CONTAINERS

During a protracted dry season it frequently happens that water for domestic purposes must be purchased from the public venders, usually at an exorbitant price. To throw away this water when it is found to contain larvae would be unfair and would give rise to a serious friction. In such instances it is the practice of the inspector to strain the water through muslin and thus eliminate the larvae. If the container in which the water is stored is large enough to support fish life the inspector stocks the receptacle.

As sub-soil water in Merida carries a high content of calcium there is a general prejudice against its use as a drinking water and in some instances for the more usual domestic purposes. Rain water is used by preference and is generally conserved in small containers in the home. These containers frequently become breeding places of the *Aedes calopus*. During the dry months this water is saved to the people by straining out the larvae. This "straining-out-the-larvae measure" becomes less necessary as the campaign advances and the people become more proficient in protecting small containers against the mosquito.

## CONCLUSION

The city of Merida and all Yucatan have now been free of yellow fever for a period of over twelve months, and there is every reason to believe that the disease has been eradicated from the area. If Merida were the only focus of infection in Mexico it would be proper to recommend that the present campaign in that city be terminated, but in view of the recent announcement of a case of yellow fever among the haciendas to the south of the city of Vera Cruz the recommendation is made that the present intensive efforts in Merida be continued for at least six months after the appearance of the last confirmed case of this disease in the gulf coast region.

ACKNOWLEDGMENT

I hereby acknowledge thanks to Dr. Gil Rogas A., Delegado Sanatorio Federal and Director-in-Chief of the yellow fever campaign in Yucatan, for the many courtesies and facilities extended me while I was directing anti-larvae measures in Merida during 1921.

I desire also to record my appreciation for the loyalty and energy shown by the sanitary inspectors and their assistants and more especially to Sr. Manuel Cervantes Arana, Inspector-General, and to Sr. Alfonso Ruz, and M. Revisador. To all these men is due the greater share of the credit for the success obtained in the campaign.

Thanks are acknowledged to Mr. W. M. James and to Mr. Ricardo Gutierrez, both of whom so generously placed their '*pilas*' at the disposal of the Service for establishing hatcheries, thereby insuring to the public an abundant supply of *mojarras* for future use.

RESUMEN

La ciudad de Mérida y en realidad todo Yucatán, han sido librados de la fiebre amarilla desde hace doce meses y firmemente se cree que la enfermedad has sido eradicada de aquella región. Con tal motivo lo natural sería el recomendar la terminación de la campaña sanitaria que hasta ahora allí se viene librando Mérida, sin embargo, no es el único foco de infección en Méjico como lo demuestra el hecho de un caso comprobado últimamente en una de las haciendas del sur. Lo más logico es el continuar el trabajo sanitario con la intensidad de costumbre por un período de seis meses subsiguientes a la comprobación del último caso que aparezca en cualquiera parte de la región de la costa del Golfo.

# A PRELIMINARY SURVEY OF TROPICAL DISEASES IN MASSACHUSETTS[1]

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## PLAN OF WORK

The purpose in view was to obtain information regarding the occurrence and relative frequency of tropical diseases in Massachusetts and to learn something of the origin of the cases.

Data have been obtained from the records of the Massachusetts State Department of Health regarding such of the diseases in question as are reportable and this has been supplemented by examination of the records of the larger hospitals in and near Boston. Duplication of cases has been eliminated by comparing the names of the patients. The hospital data cover the period of five years from January 1, 1917, to December 31, 1921, inclusive, but the state data made use of cover only four years. This is because it is difficult to obtain from the state records the names of the patients prior to 1918 and possible duplication of cases can only be prevented by comparing the names of cases in the hospital records with those in the state records. Accordingly, the state cases were made use of for the four-year period from January 1, 1918, to December 31, 1921. State records for 1917, therefore, were omitted from the list.

From the hospitals information was obtained about many diseases which are not reportable and which are not included in the state records.

The list which follows is compiled from hospital records plus State records of the reportable diseases for the periods stated above.

[1] Read before the meeting of the American Society of Tropical Medicine at Washington, D. C., May 3, 1922.

*List of diseases recorded during period investigated*

| *Name of disease* | *Number of cases* |
|---|---|
| Malaria (reportable) | 414 |
| Dysentery (reportable) | 228 |
| Small-pox (reportable) | 137 |
| Heat-stroke | 122 |
| Pellagra (reportable) | 75 |
| Uncinariasis (reportable) | 33 |
| Elephantiasis | 27 |
| Actinomycosis (reportable) | 12 |
| Leprosy (reportable) | 12 |
| Echinococcus cyst | 11 |
| Typhus fever (reportable) | 7 |
| *Bothriocephalus latus* | 5 |
| Beri-beri | 5 |
| Bilharziosis | 5 |
| Aleppo boil | 3 |
| Blastomycosis | 2 |
| Sprue | 1 |
| *Taenia nana* | 1 |
| Myiasis | 1 |
| Phagedena | 1 |
| Circomonas | 1 |
| *Trichomonas intestinalis* | 1 |
| *Strongyloides stercoralis* | 1 |
| Mycetoma | 1 |
| Total of cases | 1106 |

Diagram A shows graphically the relative numbers of the common reportable diseases.

## MALARIA

The most common disease listed is malaria. Although the laboratory of the State Department of Health and other health laboratories in the state are prepared at all times to examine smears of blood for malaria, comparatively few such specimens are sent them for exmination. As an unfortunate consequence the state records do not show in what proportion of cases the diagnosis was confirmed by finding parasites in the blood. The hospital records, too, are deficient in this respect in many instances and, in others, plasmodia were searched for but not found.

In a considerable number of instances in which parasites were found the kind of plasmodium seen is not recorded. It may be inferred, however, with approximate accuracy that in such instances it was the tertian parasite which was seen.

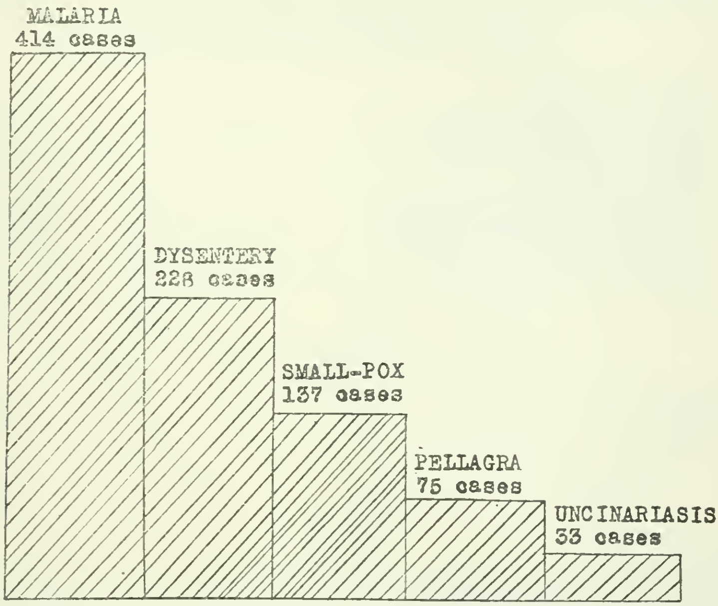



DIAGRAM A. Showing relative frequency in Massachusetts of common reportable diseases based on state and hospital data.

*Analysis of laboratory findings in hospital cases*

| | | |
|---|---|---|
| Tertian | 47 | 78 |
| Unqualified | 31 | |
| Subtertian | | 11 |
| Quartian | | 3 |
| Looked for but not found | | 30 |
| Doubtful | | 6 |
| No notes | | 42 |
| Total of hospital cases | | 170 |

The overwhelming majority of cases of malaria is attributable to the tertian parasite. There were a few cases of subtertian infection and the quartian plasmodium was found rarely.

The sources of malaria in Massachusetts can not be very accurately traced from the data in hand because neither the place of birth nor that of residence at the time of admission to a hospital give clear evidence of the source of infection.

DATA FROM HOSPITAL RECORDS

*Residence at time of admission to hospital*

| | | |
|---|---|---|
| In or near Boston | 57 | 68 |
| Other parts of Massachusetts | 11 | |
| Other parts of New England | | 2 |
| Southern states | | 2 |
| U. S. Naval Hospital, Chelsea | 67 | 93 |
| U. S. Marine Hospital, Chelsea | 18 | |
| U. S. Immigration Station, Boston | 8 | |
| Not stated | | 5 |
| | | 170 |

*Cases by sex*

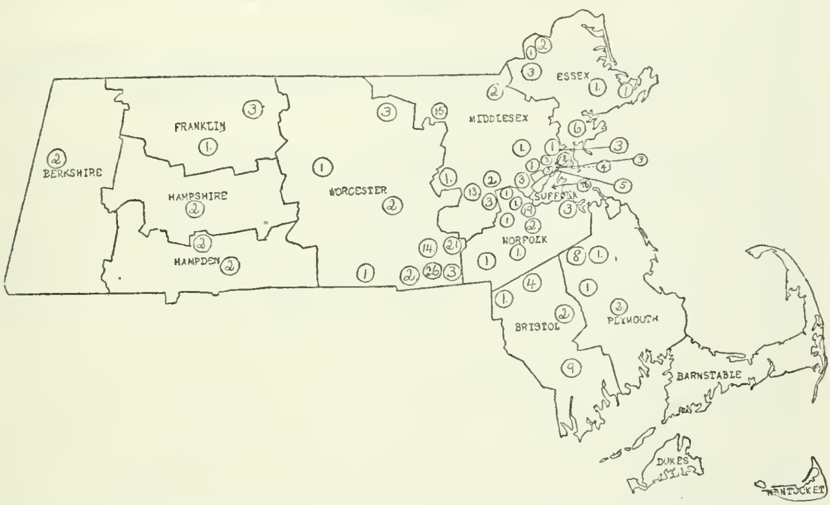
| | |
|---|---|
| Males | 155 |
| Females | 15 |
| | 170 |

*Birthplace*

| | | |
|---|---|---|
| Boston | 7 | 99 |
| Other parts of Massachusetts | 18 | |
| Other parts of New England | 18 | |
| Southern states | 23 | |
| Western states | 26 | |
| New York and Pennsylvania | 7 | |
| Italy | 16 | 56 |
| Russia | 9 | |
| Northern Europe | 12 | |
| Greece | 7 | |
| British Isles | 7 | |
| Canada | 5 | |
| Other places not in the United States | | 8 |
| Not stated | | 7 |
| | | 170 |

The residence of 57 patients or about one-third of the hospital cases of malaria was in Boston or vicinity. Of these cases 36 gave a history of travel in the tropics, in other places abroad, or in the southern states, leaving 21 cases which probably contracted the disease in or near Boston. The figure for cases from other parts of the state is too small to be significant if analyzed separately.

Briefly, it appears that more than one-third the malaria patients in the hospitals are residents of Massachusetts (68:170),




Map I. Showing location of cities and town from which cases of malaria were reported among residents of Massachusetts:

*Incidence by counties*

| | | | |
|---|---|---|---|
| Suffolk | 110 | Plymouth | 12 |
| Middlesex | 59 | Franklin | 4 |
| Worchester | 73 | Hampden | 4 |
| Norfolk | 29 | Berkshire | 2 |
| Bristol | 16 | Hampshire | 2 |
| Essex | 14 | | |

and that a large proportion of the residents have, presumably, contracted the disease elsewhere but that a certain number of cases of malaria develop in or near Boston.

The cases from the United States Naval Hospital, which treats navy personnel or war-risk patients only, plus those from the United States Marine Hospital, which handles patients from the merchant marine and from the United States Immigration Station, added together make more than one-half of the hospital cases (93:170). Most of these patients undoubtedly contracted the disease outside the state.

The data for birthplace show that decidedly more than half the patients were native-born (99:170) and that of the foreign-born the largest number of patients from a single country came from Italy.

The overwhelming majority of male as compared with female patients is probably due partly to travel and partly to immigration.

Map I is based on cases in residents of Massachusetts of which 244 were from state records and 81 were from hospital records.

The map clearly shows that malaria is common in and near Boston, that there is a less important focus in the south-eastern part of Worcester County, that appreciable numbers of cases are found through Middlesex and Norfolk, and that in other parts of the state malaria is infrequent.

The numerical predominance of cases of malaria in and near Boston is attributable to several factors: Firstly, to immigration; secondly, to the inclusion of cases from hospital records which have been examined only in Boston and vicinity; and thirdly, to the relative density of population in and near Boston. When all these factors are taken into account it seems surprising that the figure for Boston is not higher. The 21 cases which probably developed in Boston or vicinity in the course of five years in an area inhabited by nearly 1,000,000 people gives a rate of only 0.2 per 10,000.

Comparison of the names of patients from State and hospital records shows that not all the cases diagnosed in hospital appear on the State records. There are several reasons for this. Firstly, for 1917 only hospital cases were used for tabulation; and secondly, the Naval Hospital does not make returns for patients in the "Service."

That the trend of malaria incidence in Massachusetts is downward is shown by the table which follows:

*Malaria from state records by years*

| | cases |
|---|---|
| 1917 | 78 |
| 1918 | 81 |
| 1919 | 72 |
| 1920 | 60 |
| 1921 | 49 |

## DYSENTERY

Dysentery comes next to malaria in order of frequency. The total number of cases from state and hospital records is 228. In this group of cases laboratory confirmation of the diagnosis is lacking except in 23 cases in which amoebae were found. Although it can safely be assumed that a relatively small proportion of the reported cases of dysentery were due to amoebae and that the overwhelming majority were of bacterial origin, nevertheless amoebic dysentery is probably much commoner here than the figures indicate.

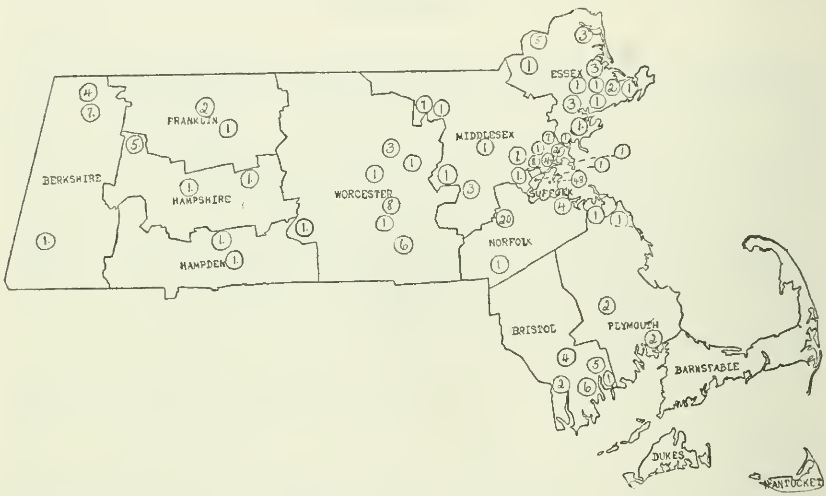
Map II is based on cases in residents of Massachusetts of which 160 were from state records and 44 were from hospital records.

The map indicates that dysentery is most frequently found in Suffolk County and vicinity and that it is scarce on Cape Cod and in the western part of the state.

Diagram B, which is based on state records by ages, shows that dysentery is infinitely more common in the first decade of life than at later periods. Diagram C, based on hospital records, shows the peak of the curve between the ages of twenty-one and thirty. The difference in the diagrams is due probably to several factors of which two are certainly important: firstly, the hospital data do not include figures from hospitals where young children are treated in large numbers, and secondly, the figures do include a considerable proportion of returned soldiers.

Tabulation of the dysentery cases by years shows a much larger number of cases in 1917 than subsequently. Sixty of these cases were reported from a large state hospital for the insane at Medfield. The same hospital had 13 cases in 1920. Boston in 1917 had 56 cases of dysentery, a number much larger than for succeeding years.

In 1917 Drs. Mary Elizabeth Morse and Geneva Tyron[2] made a careful study of an epidemic of dysentery at the Boston State Hospital. They found the causative organism to be a member of the "paratyphoid-enteritidis group, more closely allied, as shown by agglutination tests, with paratyphoid B, *Bac. suipestifer*, and *Bac. enteritidis* than with (paratyphoid) A, but not identical




Map II. Showing location of cities and towns from which cases of dysentery were reported among residents of Massachusetts:

*Incidence by counties*

| | | | |
|---|---|---|---|
| Suffolk | 48 | Berkshire | 12 |
| Middlesex | 38 | Hampshire | 7 |
| Norfolk | 26 | Plymouth | 6 |
| Essex | 23 | Franklin | 3 |
| Worcester | 21 | Hampden | 2 |
| Bristol | 18 | | |

with any of them." It seems probable that the large proportion of the 56 cases reported in 1917 from the city of Boston were at the Boston State Hospital but the data at hand for this year do not indicate the residence of the patients.

Further data about dysentery were published in the report of the State Department of Health of Massachusetts for 1917. According to this report (page 198) in that year there were "five

[2] Boston Medical and Surgical Journal, 1917, 177, clxxvii, 173, 216, 255.

outbreaks of dysentery, two in State institutions for the insane, two in educational institutions, and one, which was very mild in character, widespread throughout a large city. The outbreak of dysentery which occurred in the Medfield State Hospital in

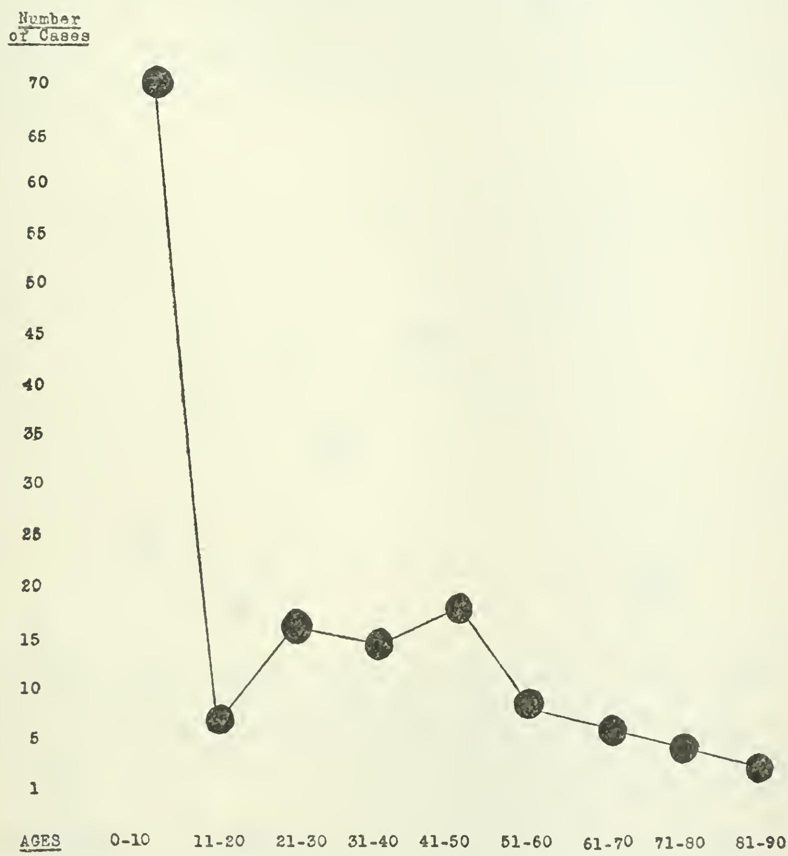



DIAGRAM B. Showing age-incidence of dysentery from records of the Massachusetts State Department of Health between the years 1918 and 1921 inclusive. Based on 145 cases.

September and October was of a peculiarly malignant character, there being 31 deaths in a total of 60 cases, a fatality rate of more than 50 per cent." Of the cases listed for Boston after 1917 one was reported from the Children's Hospital and the remainder from dwelling houses.

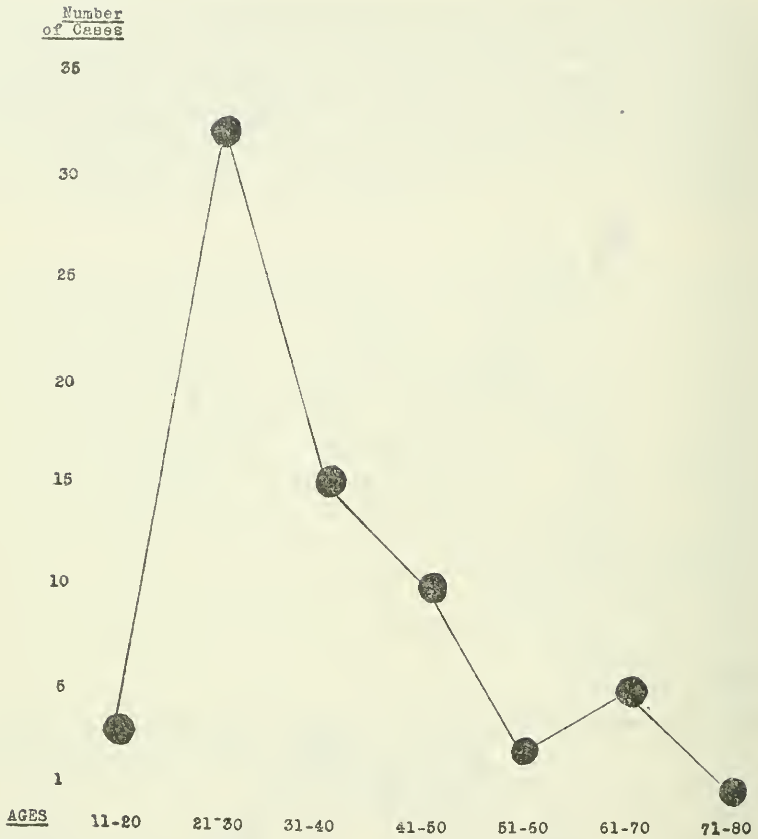


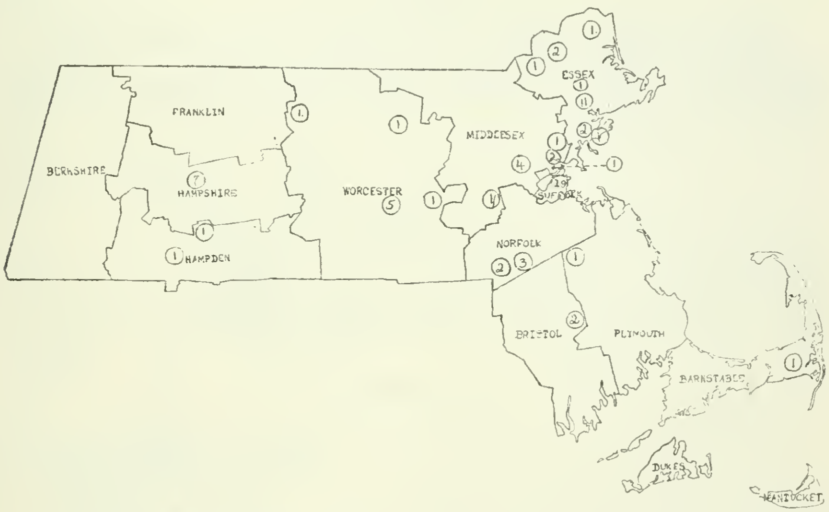

DIAGRAM C. Showing age-incidence of dysentery from records of seven hospitals in or near Boston between the years 1917 and 1921 inclusive. Based on 68 cases.

*Cases of dysentery reported to Massachusetts State Department of Health by years*

| YEAR | STATE | CITY OF BOSTON | STATE HOSPITAL AT MEDFIELD |
|---|---|---|---|
| 1917 | 160 | 56 | 60 |
| 1918 | 77 | 10 | 7 |
| 1919 | 23 | 6 | 0 |
| 1920 | 37 | 3 | 13 |
| 1921 | 25 | 5 | 0 |

## SMALL-POX

Small-pox is third in order of frequency showing a total of 137 cases for the period. The largest number of cases for a single county developed in Essex where there were several small outbreaks of the disease with a total of 45 cases. Suffolk County comes next with 38 sporadic cases. The other counties, except Middlesex, had very few cases or none at all, as a glance at map III will show.




Map III. Showing location of cities and towns from which cases of small-pox were reported among residents of Massachusetts:

*Incidence by counties*

| | | | |
|---|---|---|---|
| Essex | 45 | Worcester | 9 |
| Suffolk | 38 | Norfolk | 4 |
| Middesex | 22 | Dukes | 3 |
| Hampden | 13 | Bristol | 2 |

All but one of the cases of small-pox occurred in residents of Massachusetts. Map III is based on cases in residents of Massachusetts of which 126 were from State records and 10 were from hospital records.

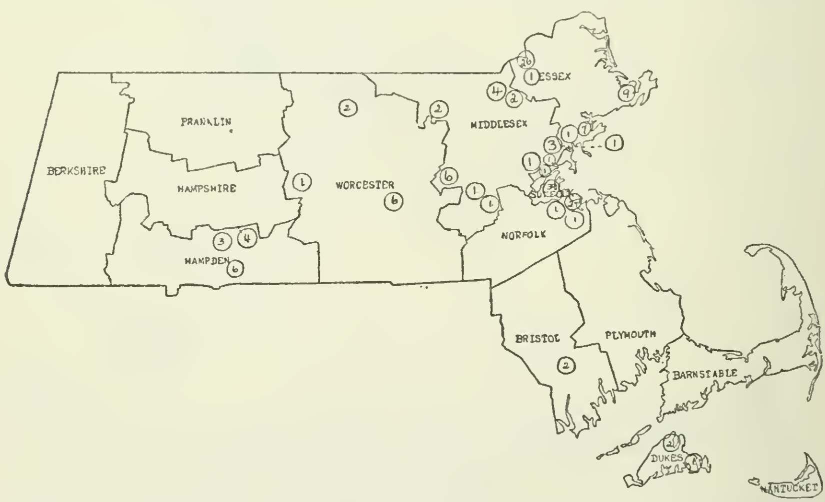
## HEAT-STROKE AND HEAT-EXHAUSTION

Heat-stroke and heat-exhaustion cases, numbering 122 from hospital records, come fourth on the list. This figure does not include State statistics because heat-stroke is not reportable: neither does the number include the many mild cases treated at the relief stations, branches of the City Hospital, from which patients return to their homes unless the condition is sufficiently serious to require a stay in hospital.

No attempt has been made as yet to differentiate the group into cases of true heat-stroke and of exhaustion due to heat.

## PELLAGRA

Pellagra, with a total of 75 cases, stands fifth in order of frequency. Map IV is based on cases in residents of Massa-




Map IV. Showing location of cities and towns from which cases of pellagra were reported among residents of Massachusetts:

*Incidence by counties*

| | | | |
|---|---|---|---|
| Essex | 19 | Norfolk | 5 |
| Suffolk | 19 | Hampden | 2 |
| Middlesex | 9 | Bristol | 2 |
| Worcester | 8 | Plymouth | 1 |
| Hampshire | 7 | Barnstable | 1 |

chusetts of which 50 were from state records and 23 were from hospital records. The map showing distribution of the disease gives 19 cases from Essex County, and 19 from Suffolk County.

Middlesex, Worcester, Hampshire and Norfolk Counties each had a small number of cases. In the other counties there were very few cases or none at all. Of these, 29 or about three-eighths were reported from State hospitals for the insane or from State schools for the feeble-minded. I do not as yet know whether these patients developed their pellagra in the asylums or were admitted for mental symptoms incidental to pellagra. The diet at the asylums is believed to be satisfactory. Very few cases of pellagra have been reported from almshouses in Massachusetts.

Comparison by sexes shows 23 male and 52 female patients.

Analysis of the hospital records of 23 cases shows that 17 patients were recorded as white. In the remaining cases the color was not stated so that it seems probable that these patients also were white.

Seven were born in Massachusetts and lived there as well. Three others were born in New England, and one in Michigan. Nine were foreign-born. The members of this group belonged to 5 different nationalities, no one of which contributed more than 3 cases.

*Birthplace*

| | |
|---|---|
| Massachusetts | 7 |
| New England | 3 |
| Michigan | 1 |
| Not stated | 3 |
| Canada | 2 |
| Ireland | 3 |
| Italy | 2 |
| Sweden | 1 |
| Russia | 1 |
| | 23 |

*Residence at time of admission to hospital*

| | |
|---|---|
| Boston | 13 |
| Other parts of Massachusetts | 8 |
| New Hampshire | 2 |
| | 23 |

Comparison of dates of admission to hospital by seasons shows a marked predominance in spring and summer.

*Incidence by seasons*

| | Admissions |
|---|---|
| Spring (March, April and May) | 8 |
| Summer (June, July and August) | 10 |
| Autumn (September, October and November) | 2 |
| Winter (December, January and February) | 3 |
| | 23 |

The incidence by ages is well shown on diagram D which is based on state records. Hospital records give a like result. By far the largest number of cases reported were between forty and fifty years of age.

The occupations of hospital patients were various and no marked preponderance of any employment is shown. It is noteworthy that only two patients had been engaged in farm work. Two others were laborers and one a teamster.

*Occupations*

| | |
|---|---|
| Home | 5 |
| Not stated | 3 |
| Farmer | 2 |
| Laborer | 2 |
| Factory | 2 |
| Teamster | 1 |
| Machinist | 1 |
| Plumber | 1 |
| Teacher | 1 |
| Sea captain | 1 |
| Shoe-laster | 1 |
| Laundryman | 1 |
| Mill hand | 1 |
| Store | 1 |

It may be said in conclusion that pellagra in Massachusetts shows no marked predilection for rural districts or farm laborers and that a not inconsiderable number of cases apparently develop in or near Boston.

According to the stage figures, pellagra is twice as frequent here in women as in men.

## ELEPHANTIASIS

Twenty-seven cases of elephantiasis were found in the hospital records. There are no state figures. In 7 cases a note states that examination of the blood for filaria was negative. In 1 case, at the Carney Hospital, however, "the cross-section of what appears to be a worm" was seen in a small vein or lymphatic.

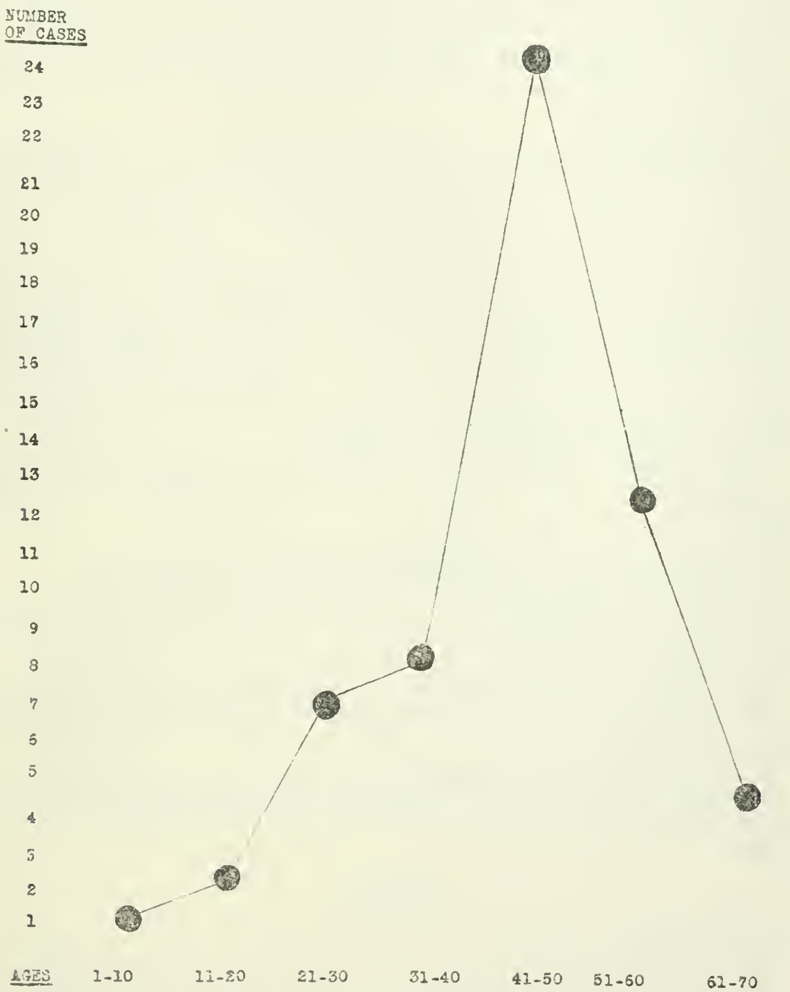



DIAGRAM D. Showing age-incidence of pellagra from records of the Massachusetts State Department of Health between the years 1918 and 1921 inclusive. Based on 58 cases.

The patient was a female telephone operator living in Quincy who had never been away from the north-eastern part of the country. For six years she had had swelling of the right leg which, when the patient was admitted to hospital, extended from ankle to hip. The Kondoleon operation was performed.

Had the supposed worm been identified as a filaria, this would have been the first case, so far as I have heard, to contract filariasis in this vicinity.

That filariasis may be contracted here seems to have been proved by finding a nocturnal microfilaria repeatedly in the blood of a woman on the service of Dr. C. T. Howard at the Boston Homeopathic Hospital. This observation was made very recently and as the case will be published later in detail, it is only necessary to say now that the patient was born in Boston and had lived there all her life. She stated repeatedly that she had never travelled south of Boston. This case is mentioned with the kind permission of Dr. Howard.

Elephantiasis, presumably non-filarial in origin, is not very uncommon in this vicinity. The Massachusetts General Hospital had 17 of the 27 cases.

Comparison of the sexes showed 16 females and 11 males.

Twenty-one patients were white, 1 was black and in 5 cases the race was not specified.

In nearly all of the cases (23:27) one or both legs were affected.

The extreme chronicity of the disease is shown in the table of duration which follows.

The prominence of house-work in the list of occupations is attributable to the larger proportion of women affected with the disease.

*Birthplace*

| | |
|---|---|
| New England | 17 |
| New York | 1 |
| Southern states | 2 |
| Russia | 1 |
| Canada | 3 |
| Other countries | 3 |
| | 27 |

*Residence at time of admission to hospital*

| | |
|---|---|
| Boston and vicinity | 15 |
| Other parts of Massachusetts | 9 |
| Maine | 2 |
| Ohio | 1 |
| | 27 |

*Sex*

| | |
|---|---|
| Males | 11 |
| Females | 16 |
| | 27 |

*Parts affected*

| | | |
|---|---|---|
| Left leg only | 11 | 23 |
| Right leg only | 7 | |
| Both legs | 5 | |
| Genitals | | 2 |
| Right arm | | 1 |
| Cheek and lip | | 1 |
| | | 27 |

*Duration of disease*

| | |
|---|---|
| Less than 1 year | 4 |
| 1–5 years | 10 |
| 5–10 years | 7 |
| 10–15 years | 1 |
| 15–20 years | 1 |
| 20–25 years | 2 |
| 25–30 years | 1 |
| Not stated | 1 |
| | 27 |

*Race*

| | |
|---|---|
| White | 21 |
| Black | 1 |
| Not stated | 5 |
| | 27 |

*Occupations*

| | |
|---|---|
| Housework | 10 |
| Factory | 6 |
| Janitor | 1 |
| Laborer | 1 |
| Nurse | 1 |
| Telephone operator | 1 |
| Cobbler | 1 |
| Police officer | 1 |
| Not stated or none | 5 |
| | 27 |

## UNCINARIASIS

Uncinariasis is the least frequently seen of the commoner tropical diseases in Massachusetts. The series numbers 31 hospital and 2 state cases making 33 cases in all.

Of these, 30 were males and 3 were females. Almost half of the patients were born in the southern states and nearly as many resided there as well. A smaller group of patients were born in the Philippine Islands and an equal number came from the Cape Verde Islands.

Two-thirds of the cases were traceable directly to the Navy, 2 cases to the Army, and 7 to the Immigration Station. These groups added together account for 29 of the 31 hospital cases. Of the seven immigration station cases, 5 came from the Cape Verde Islands.

Examination of the group of 20 naval cases shows that 12 were born in the southern states and resided there as well. A smaller number were natives of the Philippine Islands, and only one naval patient came from a northern state.

By way of summarizing, it may be said that the majority of cases of uncinariasis seen in Boston are found among the personnel of the Navy and that a smaller group of cases comes from the immigration station.

Analysis of the former group indicates the Southern States as the probable source of infection in a majority of these cases and the Philippine Islands as a less important source. Among the immigrant cases the Cape Verde Islands seem to be the principal source of the disease.

The tables for hospital cases follow.

*Laboratory reports*

| | |
|---|---|
| Ova found in | 14 |
| No ova found in | 7 |
| Doubtful | 3 |
| No notes | 7 |
| | 31 |

*Race*

| | | |
|---|---|---|
| White | 5 | 23 |
| Not stated (presumably white) | 18 | |
| Colored (including Cape Verde Islanders and Chinamen) | | 8 |
| | | 31 |

*Birthplace*

| | |
|---|---|
| Southern states | 14 |
| Massachusetts | 1 |
| New Hampshire | 1 |
| Nova Scotia | 1 |
| Portugal | 1 |
| Cape Verde Islands | 6 |
| Philippine Islands | 6 |
| Not stated | 1 |
| | 31 |

*Residence*

| | |
|---|---|
| Southern states | 12 |
| Massachusetts | 3 |
| New Hampshire | 1 |
| New Jersey | 1 |
| California | 1 |
| Philippine Islands | 5 |
| Portugal | 1 |
| Cape Verde Islands | 5 |
| Not stated | 2 |
| | 31 |

*Source of cases*

| | | |
|---|---|---|
| Navy | 20 | 29 |
| Army | 2 | |
| Immigration Station | 7 | |
| (?) | | 2 |
| | | 31 |

*Naval cases*

| | |
|---|---|
| Born and residing in Southern States | 12 |
| Born in southern states | 1 |
| Born and residing in Philippines | 3 |
| Born in Philippines | 2 |
| Born in Porto Rico | 1 |
| Born and residing in New Hampshire | 1 |
| | 20 |


SUMMARY

Data are presented which throw light on the frequency and source of such tropical diseases as are found commonly in Massachusetts. The incidence only is shown for tropical diseases less common or rare in Massachusetts.

When interpreting the figures a distinction must be drawn between reportable diseases regarding which both state and hospital data are available and the diseases which are not reportable. Information about diseases not reportable was obtained only from the larger hospitals in or near Boston.

Among the reportable diseases it seems very probable that amoebic dysentery and pellagra are decidedly more common than the figures indicate. The same doubtless is the case for the rarer diseases which are not reportable.

The figures for all the diseases listed above should be regarded as minimal.



It is a pleasure to express thanks particularly to the members of the Statistical Division of the Massachusetts State Department of Health and to the record-room personnel of the hospitals for cordial co-operation and assistance in obtaining the data desired.

Grateful acknowledgments are extended to the authorities of the hospitals listed below for permission to examine and to make use of their records.

Boston City Hospital
Carney Hospital
Massachusetts General Hospital
Massachusetts Homeopathic Hospital
Peter Bent Brigham Hospital
United States Marine Hospital
United States Naval Hospital

SUMMARIO

Este trabajo ha tenido por base datos obtenidos de dos orígenes; primeramente, de los archivos del Departamento de Salud Pública del Estado de Massachusetts, y segundo, de los archivos de los mayores hospitales de las cercanías de Boston. Ambos cubren un período de cinco años.

Los datos del Departamento de Salud Pública del Estado sólo incluyen enfermedades de las que hay que dar parte según lo requiere la ley tal como aparecen en la lista obtenida durante el período de investigación. La información acerca de las otras enfermedades se obtuvo de los archivos de hospital únicamente. En total de enfermedades en lista es de 1106. Los datos acerca de malaria, disentería, pelagra, y uncinariasis han sido analizados en detalle. Otros puntos de interés que demuestra el análisis, son los siguientes:

1. La incidencia de malaria en Massachusetts tiende a disminuir.

2. La pelagra en Massachusetts no se limita a los distritos rurales, ni a los agricultores, y es más cómun entre las mujeres que entre los hombres. Es indiscutiblemente endémica en Massachusetts y particularmente en Boston y su vecindad.

3. La major parte de los casos de uncinaria en dicho Estado proceden del exterior o de países extrangeros.

4. Es probable que la disentería amébica y la pelagra sean más comunes que lo que demuestran las cifras. Igualmente puede que suceda con las otras enfermedades.

# PORTO RICO AS A FIELD FOR THE STUDY AND INVESTIGATION OF TROPICAL HYGIENE[1]

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During the summer months of 1921 (June 1–September 15) Dr. F. M. Root and the writer made a survey of the island of Porto Rico with the object of determining what advantages this island offers as a field for the study and investigation of tropical hygiene.

## LIVING CONDITIONS

Porto Rico is a rectangular island about 100 miles long and 36 miles wide. It lies entirely within the tropics; has an average temperature of about 80°F.; an annual rainfall of about 60 inches and an atmosphere of high humidity. In the central mountainous part of the island coffee, tobacco, oranges and bananas are raised, and along the sea coast, sugar-cane, grape fruit, and pineapples. The population is now about 1,250,000 or about 350 persons per square mile, and consists of whites, mostly Spanish, blacks, and various mixtures of Spanish whites with blacks and Indians.

Porto Rico was taken over by the United States in 1899 and is now under the jurisdiction of the United States Bureau of Insular Affairs and the Secretary of War. In 1917 American citizenship was granted to all Porto Ricans.

The living conditions of most of the Porto Ricans are not such as to enable them to enjoy healthy normal lives. Overpopulation, ignorance and low wages are in large part responsible for this state of affairs. Coffee workers receive sometimes only about 30 cents per day and laborers in the cane fields average about 75 cents per day in the off season. The native huts are often

[1] Read by title before the Eighteenth Annual Meeting of the American Society of Tropical Medicine, May 2–3, 1922, Washington, D. C.

very inadequate and the supply of food is lacking in both quantity and quality. Meat in many families is served only about once per month; bananas constitute a large part of the bill of fare; and vitamine containing fresh vegetables and milk are not provided in sufficient quantities.

Very little consideration seems to be given to the water supply. Oil cans are frequently used as containers and water is dipped up from springs or streams that are more or less contaminated. In the larger communities water is distributed in pipes under pressure but this supply is, at least in some cases, very badly infested with both vegetable and animal organisms. In Santurce, a rather exclusive suburb of San Juan, the writer allowed water from the faucet to pass through a Berkefeld filter (size no. 5) for forty minutes and found in the residue the following organisms:

1. A newwork of algae, including Spirogyra, Oscillatoria, desmids, diatoms, and green colonial forms.
2. Bryozoa.
3. Annelids.
4. Nematodes of several sizes.
5. Rotifers of several species.
6. Flagellates of several species.
7. Amoebae.

Soft drinks are served from push carts and in large numbers of small cafés under sanitary conditions that cannot help but result in contamination.

In spite of the efforts made by the health authorities only a small proportion of the inhabitants of Porto Rico use latrines; the soil pollution is prevalent throughout the island. This has led, as will be shown later, to a very high incidence of intestinal protozoa and worms and probably accounts for the great number of cases of intestinal disturbances, especially prevalent among children.

## TROPICAL DISEASES

### *Malaria*

Malaria is one of the most important diseases in Porto Rico. Not only is the death rate high, but, as in other regions of the world, economic losses due to chronic malaria and non-lethal cases are extremely great. The deaths from malaria during the year 1919–1920 numbered 1576 which was 5.2 per cent of the general mortality.

Malaria is endemo-epidemic in Porto Rico, being especially prevalent in the neighborhoods of Barcelonata, Guanica, Aguirre, Salinas, Arecibo, and Patillas. There are no very accurate data regarding the incidence of malaria. Dr. Grant (1920) found by blood examination (a method that is probably less than 50 per cent effective) that 73 or 16.3 per cent of 449 persons were positive. From time to time the Insular Board of Health has attacked the malaria problem by cinchonization and mosquito reduction, and at present is coöperating with the International Health Board in a mosquito reduction campaign at Aguirre under the direction of Mr. H. W. Green. Almost all the laborers live in unscreened houses and the incidence of malaria in this region is close to 100 per cent. *Plasmodium vivax* and *P. falciparum* are the most common parasites present, *P. malariae* being rare.

Associated with malaria but still imperfectly known is blackwater fever. This disease occurs frequently in the malarious regions of the island.

### *Hookworm disease*

Soon after the American occupation of Porto Rico efforts were inaugurated to combat the ravages of the hookworm. In 1899 Dr. Bailey K. Ashford discovered the parasite and recognizing its importance, was able to convince the health authorities that a large part of the ill health and mortality on the island was due to hookworm disease. In 1904 an Anemia Commission was appointed and from that time up to 1920, $357,000 had been appropriated for the control of hookworm disease. In spite of the great amount of work that has been done surveys show that this parasite is still widely spread and present in large numbers. Dr. Grant in his recent survey found the incidence to be from 90 to 100 per cent in a number of localities and records an average of 80.8 per cent for the entire island. A hemoglobin index and worm count showed that the infection is severe. Examinations of large numbers of soldiers during 1918 disclosed an incidence of 94 per cent. During the year 1919–1920, 1004 deaths or 3.3 per cent of the total mortality was reported as due to hookworm disease. At present patients are treated at dispensaries in various localities on the island. Of special interest is the work being done at Utuado and Quebradillas. At Utuado the Insular Board of Health has a hospital where large numbers of patients are treated and at Quebradillas, with the help of the International Health Board and under the direction of Dr. R. B. Hill, an extensive control project is well under way.

### *Other parasitic worms*

No very definite data exist regarding the prevalence of intestinal worms in Porto Rico other than the hookworm. A large proportion of the persons examined for hookworm have been found to harbor one or more of the following species: Ascaris lumbricoides, Trichuris trichiura, Schistosoma mansoni, Strongyloides stercoralis, and Enterobius (Oxyuris) vermicularis. Ascaris is present in from 75 to 100 per cent of the population; Trichuris is about as widely spread; Schistosoma has an incidence of 15 per cent in certain localities (Utuado); and the other species are less prevalent. Some persons are parasitized at one time with all the species mentioned and double and triple infections with different species are quite common. Cestodes are occasionally encountered by physicians being frequent enough to make it worth while for certain doctors to advertise their ability to remove them.

Blood inhabiting worms are also common in Porto Rico. Cases are continually coming to the attention of physicians especially in San Juan and the Ponce region, some of them resulting in typical elephantiasis conditions.

### *Intestinal protozoa*

That intestinal protozoa are numerous and widespread among the inhabitants of the island was proved by the examination by the writer of stools from 83 natives, none of whom were suffering from intestinal disturbances. Ninety per cent of these were found to be infested by protozoa and related organisms, the list including *Entamoeba coli*, *E. histolytica*, *Endolimax nana*, *Iodamoeba bütschlii*, *Giardia intestinalis*, *Trichomonas hominis*, *Chilomastix mesnili*, *Blastocystis hominis* and *Spirocheta eugyratum*.

### *Yaws*

The disease known as framboesia or yaws, due to the presence of a spirochete, Treponema pertenue, is said to exist in various parts of Porto Rico being confused as a rule with syphilis. It is often called buba and was imported with negro slaves.

### *Leprosy*

The lepers of Porto Rico live on a small island near San Juan. Here are gathered together about 35 patients, some white and some colored, of various ages and in various stages of the disease. Recently treatment with chaulmoogra oil derivatives has been given to the sufferers with marked improvement as a result. An attempt is to be made to raise in Porto Rico the trees from which this therapeutic agent is obtained.

### *Bubonic plague*

During the spring and summer of 1921 bubonic plague again made its appearance on the island necessitating the concentrated efforts of the health authorities to eradicate the rats. The disease proved fatal in a number of cases.

### *Beriberi, pellagra and sprue*

Three so-called deficiency diseases occur in Porto Rico, namely, beriberi, pellagra, and sprue. Beriberi has recently been reported among the soldiers in the barracks at San Juan. Pellagra frequently occurs but is more prevalent on the neighboring island of St. Thomas.

Sprue is an endemic disease in Porto Rico of widespread and considerable importance. Drs. Ashford, Gutierrez, Michel and Martinez of the Institute of Tropical Medicine and Hygiene in

San Juan have devoted many years to its study and believe that they have not only determined its etiology, but have perfected complement deviation tests which are negative in persons not having sprue and positive for at least 80 per cent of those who have it. They have also seemed to hasten the cure of the diseases in many cases by using, in addition to a diet free from sugar of commerce and cereals, a vaccine prepared from killed cultures of *Monilia psilosis*.

These investigators have produced a rapidly fatal result by intraperitoneal inoculation of cultures of this yeast, and in addition have apparently reproduced many of the symptoms of sprue and subsequent death from the disease by feeding *Monilia psilosis* which had reached a high degree of virulence through passage.

### *Mycoses*

Very little is known about the fungi on the island that attack man but they exist in considerable numbers and are widely spread. They give rise to diseases known as mycoses, principally of the skin.

### *Dengue*

Dengue is a tropical fever, the unknown causative agent of which is transmitted by the mosquito, *Stegomyia fasciata*. It has appeared in the past in epidemic form in Porto Rico and may be encountered infrequently at any time.

### *Insects*

As in most tropical regions insects are abundant in Porto Rico. Among these are many that act as vectors of disease producing organisms, including Stegomyia, Anopheles and Culex mosquitoes, rat fleas, house flies, etc.

## MORBIDITY AND MORTALITY

The morbidity and mortality in Porto Rico are both very high. This is in large part due to the density of the population, to poor housing and food conditions, and to ignorance of hygienic principles. The average annual death rate for the decade 1909–1919 was 28,750 or 24.095 per thousand of inhabitants.

Especially marked is the high infant mortality, the percentage that infant mortality is of the general mortality averaged 44.71 during the decade 1910–1920. Due to lack of registration many births are never recorded and the records of causes of death are no doubt often erroneous. The data available, however, indicate that this enormous infant mortality is due largely to 4 causes: (1) congenital debility, (2) rickets, (3) infantile tetanus and (4) enteritis, under 5 years, and that the last named accounts for almost one-third of all deaths. This suggests the probability that improper food and intestinal parasites are responsible in large part for the high death rate among infants. Adequate studies, however, have never been made of the group of diseases included under the name enteritis.

The mortality during the year 1919–1920 from the various diseases usually included in treatises on tropical medicine is as follows:

| | |
|---|---|
| 1. Diarrhea and enteritis, under two years | 3487 |
| 2. Diarrhea and enteritis, two years and over | 1751 |
| 3. Malaria | 1576 |
| 4. Hookworm disease | 1004 |
| 5. Dysentery | 114 |
| 6. Leprosy | 6 |
| 7. Pellagra | 4 |
| 8. Effects of heat | 5 |

Deaths have occurred during 1921 from bubonic plague and beriberi, and other so-called tropical diseases may be more or less prevalent, such as sprue, mycoses, filariasis, schistosomiasis, ascariasis dengue, giardiasis, entamoebiasis, yaws, and blackwater fever. The suffering and economic losses due to the above mentioned diseases cannot easily be estimated but are extremely great.

## PUBLIC HEALTH ORGANIZATION

Porto Rico has well organized agencies for protecting the health of its inhabitants. The Board of Health consists of four physicians, a chemical expert, a sanitary engineer, and a secretary. The Commissioner of Health has charge of health protection and sanitation throughout the island. His office and laboratories are in San Juan. He has associated with him an assistant commissioner with clerical force, a sanitary engineer with assistants, several bacteriologists and assistants, a chief chemist and assistants, a chief of the division of statistics and transmissible diseases with a pathologist and assistants, and a field force consisting of medical inspectors and assistants. There are excellent health laws in Porto Rico but they are not adequately enforced. The Board of Health has charge of a number of charitable institutions including a tuberculosis sanitarium, an insane asylum, boys' and girls' charity schools and a blind asylum.

## DISCUSSION

It is very easy to become enthusiastic over the opportunities offered by Porto Rico as a field for the study of tropical hygiene. The arguments in its favor are many and important.

1. *Government.* Porto Rico is a part of the United States; no passports are required and work can be done with less difficulty than would be possible if the island were controlled by a foreign government.

2. *Accessibility.* Porto Rico is one of the nearest tropical regions in the eastern part of the United States. The distance from New York to Porto Rico is not great and requires only 4 or 5 days of travel. Three steamship companies operate passenger steamers between New York and San Juan. The cost of transportation is not prohibitive.

3. *Transportation on the Island.* Railroads connect the principal city, San Juan, with other sea coast cities. Excellent roads have been built through the mountains of the interior and motor busses are numerous. Any region of the island can therefore be reached from any other region within a few hours and in comfort.

4. *Tropical conditions.* The inhabitants of Porto Rico belong to tropical races and are living under typical tropical conditions; the huts of the natives are largely of thatch and no artificial heat is required. The temperature is tropical but not extreme;

humidity is high; and the annual rainfall is about 60 inches. The vegetation is tropical including coconut and royal palms, bamboo, mangoes, bananas, pineapples, oranges, grapefruit, etc. The food of the inhabitants is limited and inadequate for good health.

5. *Tropical diseases.* Only a very few of the important tropical diseases are absent from the island. These include Asiatic cholera, yellow fever, trypanosomiasis and leishmaniasis; the last two may occur but have not yet been reported. The other tropical diseases that can almost always be observed on the island are malaria, hookworm disease, entamoebiasis, giardiasis filariasis, schistosomiasis, ascariasis, blackwater fever, mycosis, yaws, dysentery, leprosy, bubonic plague, sprue, beri-beri, pellagra, and various forms of diarrhea and enteritis.

6. *Facilities for study.* Many of the diseases listed above are very inadequately known and are available for study in Porto Rico under very favorable conditions. The directors of the following institutions aided us in every way possible and will no doubt assist anyone who is qualified to do scientific work in tropical hygiene.

*a.* The Sanidad. The Commissioner of Health, Dr. A. Ruiz Soler, has under his control well equipped laboratories where such subjects as bacteriology, medical zoology, chemical hygiene, and immunology may be studied. He can furnish access to the leper colony, to patients in the quarantine hospital suffering from bubonic plague and other highly contagious diseases, to the tuberculosis sanitarium, to the hospital for the control of hookworm disease at Utuado, and to various dispensaries throughout the island.

*b.* The Institute of Tropical Medicine and Hygiene. This is primarily a research institution located in San Juan. It has good laboratory rooms, excellent equipment and a very good working library. The director, Dr. Gutierrez Igaravidez, and the members, Drs. Ashford and Martinez, are ready to do anything to help the cause of tropical medicine and hygiene either through the use of their laboratories for study and research or by means of clinics established in the agricultrual districts. In such a clinic at Utuado 10,140 persons were handled in 60 working days.

Thus wonderful opportunities are afforded for investigation and field work under most favorable conditions.

*c.* The University of Porto Rico. The Commissioner of Education and the Dean of the University are glad to establish relations with other institutions and with men interested in tropical diseases. The University laboratories are well equipped and are available for study and research.

*d.* International Health Board Projects. At present (1921) the International Health Board is carrying on two campaigns in Porto Rico. An effort to control malaria by mosquito reduction is being made at Aguirre under the direction of Mr. H. R. Green, and field work for the control of hookworm disease is in progress in the neighborhood of Quebradillas in charge of Dr. R. B. Hill. Through the kindness of these men opportunities are available for observing these types of field work in medical zoology under tropical conditions.

*e.* Sugar centrals. The authorities at the various large sugar centrals are usually glad to assist in any undertaking that aims to better the health of their employees and their families. Thus the Aguirre Central is aiding the malaria campaign mentioned above.

*f.* Hospitals. There are several hospitals on the island where tropical diseases may be observed and studied, notably the Presbyterian hospital at Santurce near San Juan, and St Luke's hospital in Ponce.

We are very fortunate to have such a convenient area as Porto Rico near at hand for the study of tropical hygiene but we are of course, chiefly interested in reducing the morbidity and mortality of the inhabitants. Nothing would benefit these people more than to teach them the general principles of hygiene and public health and to help them put into effect special measures for the prevention and control of the diseases to which their high death rate is due.

SUMMARIO

El Departamento de Sanidad de Puerto Rico está bien organizado pero es impotente para abarcar adecuadamente el problema

del dominio de las enfermedades existentes. Se dá buena acogida y se ofrece ayuda a los estudiantes e investigadores de la Medicina Tropical. El Instituto de Medicina Tropical e Higiene en San Juan, la Universidad de Puerto Rico en Río Piedras y los directores de la campaña en contra de la uncinaria y de la malaria (esta última bajo low auspicios de la Junta de Sanidad Internacional) ofrecen toda ayuda posible a los investigadores.

Las ventajas prácticas que ofrece Puerto Rico como campo de investigación en higiene tropical, son las siguientes:—

(1) Es parte de los Estados Unidos. (2) Está situado en los trópicos. (2) Está poblado por habitantes que ignoran los principios de la sanidad, que tienen malas viviendas y están mal alimentados y surtidos con agua contaminada. (4) Prevalecen varias de las enfermedades del trópico. (5) Abundan los mosquitos de la malaria. (6) La contaminación del terreno es cosa muy corriente. (7) Hay estaciones y laboratorios de campaña disponibles para el uso. (8) Los medios de transportación en la isla son fáciles y baratos. (9) Vapores confortables hacen la travesía entre New York y la isla en cuatro días.

# CULTIVATION OF TRICHOMONAS FROM THE HUMAN MOUTH, VAGINA, AND URINE[1]

KENNETH M. LYNCH

*Dallas, Texas*

In 1915 the writer reported artificial cultivation of Trichomonas from the vagina and mouth of the same person. In direct preparations as well as in culture from both places the flagellate appeared to be the same and it was called *Trichomonas vaginalis* Donné. The organism from both sources had four anterior flagella.

In 1917 Chira and Noguchi (1917) reported cultivating a Trichomonas from the human mouth which they, following Parisi's creation of the sub-genus Tetratrichomonas, called *Tetratrichomonas hominis*. In the same year but a bit later Goodey and Wellings (1917) published a report on a Trichomonas, also having four anterior flagella, from the human mouth which they name *Tetratrichomonas buccalis* n. sp.

Kofoid (1920) in a timely review of the nomenclature of intestinal flagellates of man reverses the tendency to limit the generic term Trichomonas to the flagellate possessing three anterior flagella and to accept Tetratrichomonas for the four flagellated organism. This he does for the reason that the genus is founded on *Trichomonas vaginalis* Donné, which although originally described with one flagellum, has been proven to possess four. Consequently in his opinion, and apparently correctly, Trichomonas must remain the name of the genus carrying four anterior flagella and Tetratrichomomas becomes a synonym. He creates the generic term Tritrichomonas to cover those carrying three anterior flagella and designates *Trichomonas augusta* as the type.

Since Trichomonas has become so firmly established as the

[1] Read at the Eighteenth Annual Meeting of the American Society of Tropical Medicine, May 2–3, Washington, D. C.

name of common flagellates of the human body it is fortunate that it is properly retained and the writer accepts Kofoid's conclusions.

According to him the question as to whether the organisms from different sources in the human body are the same or are different species is yet an unsettled one and until proven identical *Trichomonas vaginalis* Donné (1837) is the correct name for the parasite from the vagina, *Trichomonas hominis* Davaine (1854) for the intestinal form, and *Trichomonas buccalis* Goodey and Wellings (1917) for that of the mouth, although Steinberg (1862 proposed three names, *Trichomonas elongata, Trichomonas caudata and Trichomonas flagellata* for trichomonads of the mouth which he thought were distinct types.

As to the identity or differentiation of the trichomonads from the human intestine, vagina, and mouth it seems that now since artificial cultivation has become possible and even easy of accomplishment—Dobell's (1921) conclusions to the contrary notwithstanding—we may look to much more exact studies than may be possible with direct material.

## CULTIVATION

The first cultures of Trichomonas were obtained in beef broth. This includes Trichomonas from the vagina and mouth and also from the intestine (Lynch, 1915, 1915a). Ohira and Noguchi (1917) cultivated Trichomonas from the mouth, best in equal parts of ascitic fluid and Ringer's solution. Boyd (1918) cultivated *Trichomonas hominis* in a mixture of feces and physiologic salt solution. Pringault (1920) used Ohira and Noguchi's medium for *Trichomonas hominis* successfully as did Reufing (1921) working with *Trichomonas vaginalis*, according to Hogue. Hogue (1921) obtained a pure line culture of *Trichomonas hominis* from feces, the cell having four anterior flagella, using a medium made of Locke's solution and egg albumin and also an ovomucoid medium. The best growth obtained when blood serum was added to the media. Boeck (1921) cultivated *Chilomastix mesnili* in a medium composed of four parts of Locke's solution to one of human blood serum.

Regardless of these successes Dobell (1921) states that, "At the present time, however, it is not possible to cultivate this organism with certainty in any medium." "All attempts which we ourselves have made have been failures." All of which it is difficult for one to understand who has repeatedly and at will obtained swarms of Trichomonas, with a large per cent in active division, in several media.

Because of the difficulties obtaining in respect of the first medium used, as have also been encountered by subsequent experimenters, the writer has used a number of different media since that time with much better success. Liquid blood serum ascitic fluid, ovarian cyst fluid, and pleural fluid, diluted even to equal parts with physiologic solution will grow Trichomonas at 37°C. Excellent results have been obtained with Trichomonas from the mouth, vagina, intestine, and urine (Trichomonas of vaginal origin) in liquid human blood serum diluted with from four to ten parts of 0.5 to 0.9 per cent sodium chloride solution, Ringer's solution, and Locke's solution, as well as in ascitic fluid diluted with from one to four parts of the same salt solutions Ability to produce prolifically varies in different cases and probably the associated bacterial growth has much to do with this. All of these media are slightly alkaline and become more so. The best uniformly good medium which has been used is human blood serum diluted with ten volumes of 0.5 per cent sodium chloride solution. In this medium growth is usually steadily progressive for four or five days, during which time transplants are easily made, and then the parasites disappear in the course of a few days, some having remained for as long as twelve days. The organism grows best at the bottom of a fairly long column of medium and is best removed with a capillary pipette. In culture *Trichomonas vaginalis* has not shown as much free swimming as *Trichomonas hominis*. Usually it is found feeding in colonies among or attached to a mass of bacteria.

## MORPHOLOGY

*Trichomonas vaginalis*, especially in culture, varies considerably in size, young forms of about 5 by 10 microns, matured adult forms about 10 by 16 microns, and large forms preparing for division or dividing occurring up to about 15 by 25 microns. The shape is typically that called pear-shape but the body is very flexible, especially the anterior end, and they may be much elongated and distorted. In crawling around and feeding in a mass of bacteria the body may become elongated and attenuated and slide along with almost slug-like motion. Then too, the head end may be extended on a neck-like attenuation of the anterior part of the body and may be so moved about as to give the organism a goose or turtle-like appearance. When this occurs the nucleus remains in its usual relationship to the anterior extremity, the undulating membrane appears only on the elongated anterior part, and the posterior half seems entirely passive. The flagella are not to be counted with certainty on an active cell. Their motion may be best seen, and so may also be the undulating membrane, by dark field illumination. They are extended back over the dorsum—calling the feeding surface the ventral side—usually in a group, catching bacteria in loops of their extremities and bring these food particles into contact with the anterior quarter or third of the ventral surface or border where lies the undulating membrane working in unison with but faster than the flagella. Food particles (bacteria) are received on this surface or border and some are taken in and some passed on by the undulating membrane. This part of the ventral surface or border is specialized to receive food; it is flexible and frequently forms delicate pseudopod-like irregularities which may be projected distinctly in taking up bacteria. No specialized border or definite opening to this area has been seen but it is nevertheless a specialized mouth-piece. The undulating membrane arises with the flagella from the blepharoplast at the anterior pole, usually in a visible knob. It is delicate and is directed back about the region of the food receiving area for about one half or more of the length of the body, depending on the extent of elongation of the cell. There is commonly no posterior free flagellar end to be seen but occasionally in stained specimens the terminal extremity of the free border projects slightly from the surface. The posterior end comes to a short point unless the cell is anchored by it, as it commonly is, when it is drawn out into a longer attenuation. Not infrequently the axostyle projects from the surface of the posterior quarter. Sometimes the posterior end of the axostyle is within the tail-like extremity. Dividing forms seen in fresh preparation vary from enlarged shield-shaped cells with flagella at the anterior corners to cells of equal size, each with distinct complete anterior parts with the posterior still undivided.

In staining these organisms Heidenhain's iron-hematoxylin method and Wright's stain have been used with varying success. The iron-hematoxylin method when completely successful gives a splendid differentiation but in these cultures with considerable albumin in the spread to be coagulated it is very difficult to get good specimens. By great care, using thin films, and very particular timing, Wright's stain gives splendid differentiation and beautiful staining. The cytoplasm, which stains blue, is of an alveolated character, being more fluid in the active food receiving and digesting portions, which occupy broadly the ventral half of the body and most of the posterior half, while the head end, the dorsum, and the borders of the posterior part are more dense. Bacteria are present, of variegated colors, in varying numbers, in vacuoles. The nucleus is within the anterior half, with in a short distance of the blepharoplast, and stains pink. It is smaller and closer to the blepharoplast in the young undividing forms. It is then more perfectly ovoid and is composed of a large compact chromatin body within an unstained area. Whether this is the periphery of the nucleus with the membrane unstained or the expanded axostyle, in which the nucleus may lie, is uncertain. Preliminary to division the nucleus swells, becomes more elongated, and the chromatin separates into definite bodies loosely distributed, and the membrane becomes more distinct by reason of their attachment. The nucleus divides before the splitting of the cell commences, and more than two nuclei of the multiple dividing form, as described by Ohira and Noguchi, are encountered. This is comparatively rare and is probably a developmental irregularity. The nucleus is connected with the blepharoplast by a faintly pink-staining granular or linear connection which is best seen in macerated specimens where the stain can reach it. The axostyle takes origin from the blepharoplast, although as it is usually seen it is distinct only from the nucleus, where it often appears to be expanded. It may run backward in mid-line and project within the caudal process or it may project on the surface of the posterior quarter. Frequently it fails to stain except where it is projected from the surface but in some it stains pink throughout its course. The blepharoplast is a pink-stained body or group of bodies in the extreme anterior end, and from it come the flagella and the free margin and basal rod of the undulating membrane, all of which stain pink. The flagella are four in number when properly seen. They are commonly seen to be of uneven length, two being about the length of the body and two about three fourths of this. The free chromatinic margin of the undulating membrane is delicate. The body of the membrane is usually narrow and only a few of its folds may be seen. Sometimes there is the appearance of several loops of fine chromatinic lines at the feeding area and often delicate cytoplasmic projections, sometimes pseudopod-like, occur at this zone. The basal rod also commonly remains unstained but in a good preparation it is distinct over the ventral border, curving backward over the ventral surface for about one half or more of the length of the body. The uudulating membrane seems to be active mainly over the food receiving zone and rarely shows a free posterior extremity.

### MULTIPLICATION

Kofoid and Swezy (1915) after careful study and analysis conclude that true mitosis is the method of division of Trichomonas. The four-flagellated organism of this study apparently follows this rule. It has not been possible to prepare specimens for the great detail necessary to follow the complete process but frequent nuclear figures appear to make it unquestionable. Preliminary to division the nucleus, previously composed of a large compact mass surrounded by a clear zone, becomes larger and looser, the chromatin separates into particles which are distributed through it, the membrane is now more distinct, and the chromatin rearrangement produces some fairly good spindle formations. Before completion of nuclear division the cell assumes a broad flattened appearance of the forward end, shield shaped, with flagella at the corners, these being the two heads of the forming organisms. After nuclear division is complete the cell commences to split by a depression down the middle of the forward end, each half now having a full organization. By the time the splitting is half completed the organism may have the appearance of transverse division. As a matter of fact the latter part of the severance of the two is transverse.

### RELATION OF TRICHOMONAS VAGINALIS AND TRICHOMONAS BUCCALIS

From a careful study of the descriptions and published illustrations of Ohira and Noguchi's and Goodey and Welling's Trichomonas of the mouth and the organism of this study from the mouth and vagina it has not been possible to differentiate them. Although there is a fairly wide difference in size of organisms from the same source and in the same culture the average of the active mature non-dividing forms is about the same. The flagella, four in number, may appear to be of the same length or may be uneven. Cystostome, axostyle, and free margin and basal rod of the undulating membrane, when well observed are apparently alike, although these structures are subject to a large degree of misinterpretation in poorly prepared specimens. The nucleus in different preparations and at different stages may appear differently, but it is not difficult to reconcile seeming differences according to the method of prepartion. The form of the active organism during life, typically pear-shaped, is subject to variation, the anterior part being particularly flexible, elongated and twisted about at will. In the case from which the original cultivation was done, where Trichomonas occurred in the vagina and mouth of the same person, the impossibilty of differentiation was particularly impressive. There is no doubt in the mind of the writer that they were the same and that even if

*Trichomonas buccalis* becomes distinctly differentiated, *Trichomonas vaginalis* may occur in the mouth.

The writer is of the opinion at the present that *Trichomonas vaginalis* and *Trichomonas buccalis* have not been clearly differentiated and that they are probably one organism.

SUMMARIO

Se publican experimentos tendentes a conseguir el cultivo artifical de los protozoarios flagelados, *Trichomonas vaginalis y Trichomonas buccalis* (?). Se describen los organismos, métodos de estudio y se somete una discusión de su probable identidad.

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# CULTIVATION OF BLASTOCYSTIS AND DETERMINATION OF SPECIES[1]

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In the preliminary communication (Lynch, 1922) of this study it was proposed that there are at least three species of Blastocystis occurring in the intestine of man, the differentiation being based upon the methods of reproduction in culture.

The first of these was tentatively identified with *Blastocytsis enterocola* Alexieff (1911) because it was not certain whether the multiple fission which occurred in culture was the same process as Alexieff's "bourgeonnement multiple" which he described and illustrated as multiple secondary cyst formation within the primary or parent cyst. After further study of this form it is certain that the two processes are different and it is now proposed to differentiate this species from *Blastocystis enterocola* and to identify it with *Blastocystis hominis* Brumpt (1912) which was described as reproducing only by fission, although Brumpt studied direct preparations and not cultures. Blastocytis enterocola was studied by Alexieff mainly in lower animals but his observation of the species in man has been supported by the finding of his multiple secondary cyst formation by Wenyon, and although it has not been encountered in any of these cultures its occurrence in a recent stool examination confirm it as an inhabitant of the intestine of man.

The first type of this study, which it is now proposed to identify with *Blastocystis hominis* Brumpt, is illustrated in plate 1. The nucleus, placed within the thicker side of the rim of the cell, divides, possibly by mitosis, and the two become placed at oppo-

[1] Read before the American Association of Pathologists and Bacteriologists, Washington, May 3, 1922.

site sides. The cell then divides into two apparently exactly similar offspring. Each of the two nuclei may divide again and the four become placed at regular intervals in the rim, with four similar cells resulting from completion of the division (figs. 6 to 11). Multiple fission into six, or eight, or possibly more, may occur in like manner. Reproduction in culture may occur to such an extent as to give rise to a colony of cells within the mucilagenous envelope or matrix as seen in plate 3, figure 9. Before division into two has been completed the process may be initiated in each of the cells, thus giving the form seen in plate 1, figure 9, where two nuclei are present in each. With the stain (Wright's blood stain) used on the specimens illustrated, the rim of cytoplasm is blue and alveolated, the nucleus is red, and the central body is pink.

The second species, named in the preliminary communication Blastocystis gemmagina (Lynch, 1922) is illustrated in plates 2 and 3, all being drawings, plate 2 of unstained specimens and plate 3 of specimens stained by the iron-hematoxylon method. Fission in *Blastocystis gemmagina* appears to be no different to that occurring in *Blastocystis hominis*. It is, however, uncommon that more than binary division occurs and this takes place mainly within the first twenty-four to forty-eight hours in culture. Beginning at about the time that fission becomes less prominent, multiple peripheral budding takes place and commonly becomes profuse during the next twenty-four to forty-eight hours. In this process buds may be formed singly, in groups, or in large numbers over the whole of the surface of the organism. The nuclei divide as the cell grows larger—and it may reach one hundred microns or more—until an enormous number may be present, as in plate 3, figures 5–8. These nuclei are distributed singly or in groups over the periphery and where they are placed arise the buds. The buds are pinched off from the surface and are often attached to the mother organism by long tendrils before being freed.

The third proposed species of the preliminary communication, there named *Blastocystis sporogina*, is illustrated in plate 4. Binary division occurs in the young cultures just as in the two other forms. Before it ceases, however, there begins a complicated internal process with apparently the formation of spores. This process continues for about forty-eight hours and terminates with liberation at the spore-like bodies by disintegration of the primary cyst. The spores show first as small globules forming within and apparently from the central body. They grow in number and size and the original central body disappears. The process has been difficult to study and interpret and satisfactory staining has not been accomplished. Whether this form represents a valid species may therefore be subject to question.[2]

SUMMARIO

El autor hace referencia a su comunicación anterior (1922) preliminar acerca de las tres especies de Blastocystis que ocurren en el intestino humano y su diferenciación por su manera de reproducción en cultivo. En esta comunicación nos hace saber que la clasificación tentativa de la primera especie que se creyó fuera idéntica con el *Blastoystis enterocola*—Alexieff 1911—no es tal y que estudios subsiguientes de reproducción, cultivos, etc. demuestran que el parásito es idéntico con el *Blastocystis hominis*—Brumpt 1912—y que debe denominarse bajo ese nombre. Acerca de la segunda especie, *Blastocystis gemmagina*—Lynch 1922—nos informa que la fisión es binaria y también que al cesar la fisión, gemación periférica múltiple empieza y es profusa en la primeras 48 horas. De la tercera especie, *Blastocystis sporogina,* nos dice que la división binaria también ocurre en los cultivos jóvenes como en las otras formas. Antes de cesar dicha división dó comienzo un complicado proceso interno con la formación aparente de esporos que continúa por 48 horas y termina con la liberación de esos cuerpos. El cuerpo original desaparece. Concluye manifestando la dificultad de estudio de esta variedad, lo dificil de conseguir teñido y en general la duda de la validez de esta especie. Cuatro ilustraciones acompañan a la comunicación.

[2] In discussing this paper Prof. C. A. Kofoid raised the question as to whether this form is not really Blastocystis hominis parasitized by another organism such as the Sphaerita which occurs in Endolimax nana. It is obvious that this criticism is appropriate and this explanation of the form may be correct.

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All are free-hand drawings of specimens as they were seen in culture

PLATE 1

Blastocystis hominis, Stained with Wright's Blood Stain, Showing Stages of Division Into Two and Four Cells


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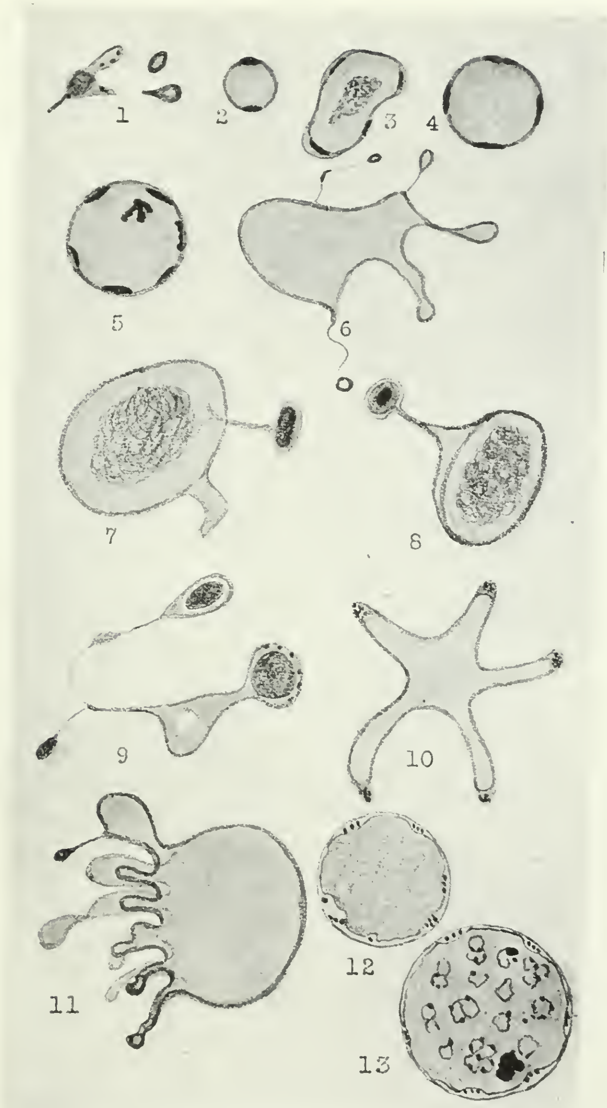
PLATE 2

Blastocystis gemmagina, Fresh Unstained, Showing the Process of Multiple Peripheral Budding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## PLATE 3

### Blastocystis gemmagina

Figures 1–8, stained by the iron-hematoxylon method, showing growth of the cells and nuclear distribution in the process of multiple peripheral budding. *Blastocystis hominis*, figure 9, stained with iron-hematoxylon, showing a colony of dividing cells.

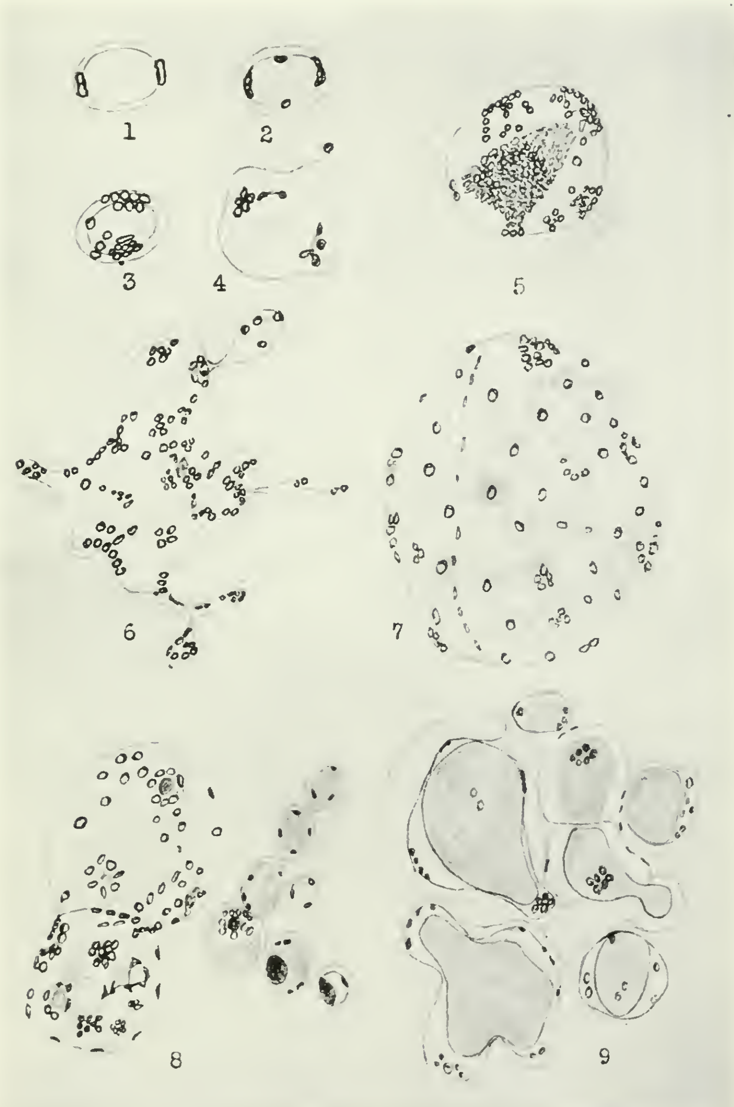
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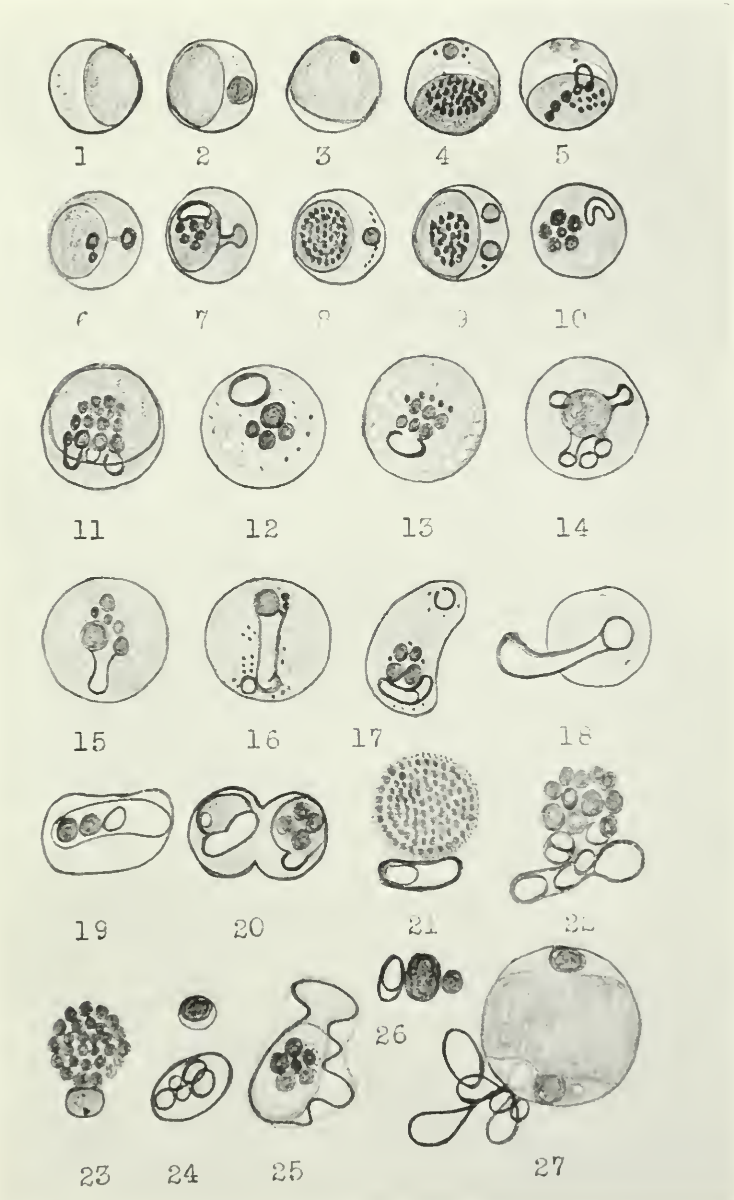
PLATE 4

BLASTOCYSTIS SPOROGINA? FRESH UNSTAINED

Showing specimens of the complicated process of formation and liberation of spores or *Blastocystis hominis* parasitized by a sporeforming organism.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# SPECIAL ENTOMOLOGICAL MOUNTS[1]

C. S. LUDLOW

*Army Medical Museum, Washington, D. C.*

In endeavoring to prepare mounts of mosquitos with especial reference to use with opaque projection or lantern slides, and especially for facilitating photography, and which would avoid the objectionable shadow caused by the usual mounts the following methods have been developed.

1. Place in the center of a clean glass slide a drop of Canada balsam, and in it stand on end a slender clear glass bead about 1 centimeter long, so that it forms a small pillar. Place the preparation on a level surface until the balsam is sufficiently hardened to retain the bead in position.

The commercial bead often is not broken at right angles to its axis, so that at least one end is irregular, and if used as a base tends to let the bead fall to a horizontal. For this reason it is necessary to select the beads and use the square cut end as a base, watching the preparation and keeping the bead perpendicular, otherwise, the result will be quite unsatisfactory.

When the balsam is sufficiently hardened to retain the "pillar" in position a very small amount of balsam (acid free is probably better) on top will serve to fasten the mosquito in the desired position, and so soon as this has hardened the slide is ready to use.

The balsam has the same refractive index as the glass, therefore if the bead be filled, as it naturally tends to by capillary attraction, some of the difficulties caused by refraction will be eliminated, and if it be desired to lessen the visibility of the mount still further a capillary tube may be used instead of the bead.

[1] These mounts were prepared for, and on exhibit at the Army Medical Museum during the meetings of the American Society Tropical Medicine, May 2–3, 1922, Washington, D. C.

When these preparations were photographed it was found they were not well adapted to a black-ground and at the suggestion of Major Geo. R. Callender, M.C., U. S. Army, Curator, another method was worked out which in practical application resulted in the following.

2. Take a black "insect pin" no. 2, bend it at right angles about 0.5 cm. from the head, and attach the mosquito to the head of the pin, at the angle desired, by a minute drop of Canada balsam. The pin may be stuck in a piece of cork at any desired angle.

If a black back-ground be used the pin is barely visible, the effect being almost that of a free insect, which can be viewed from any angle by change of the position of the pin.

These mounts are both very frail, and the first will probably not stand transportation, the second being subject to the same injuries in travel that occur to the usual mount, but require the utmost care in handling, the insect being particularly exposed. It hardly needs to be said that the real value of the first method is where, because of color conditions a white back-ground is desired and the angles are within the limits of the adjustment of the position of the slide, while the second method lends itself best to a black back-gronnd and allows of many positions.

Fig. 1. The Glass Bead Balsam Mount on a Glass Slide

Fig. 2. Black Entomological Pin Which May Be Stuck in Cork at Any Angle Best Suited for Illumination

When light is parallel to the short arm mount is obscured

# THE USE OF NUTRIENT AGAR FOR REARING DIPTEROUS LARVAE

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A study of the biology of Tabanidae was begun during the past summer, at the suggestion and with the help of Dr. Robert Matheson, in which the writer made use of the ordinary nutrient agar to provide a suitable medium for the larvae.

The writer learned of the use of agar for this purpose from Dr. J. Chester Bradley's journal which he sent to the college while on his collecting trip to South America. Dr. Bradley wrote:

> Dr. Lutz has a remarkably interesting method of rearing the larvae of Tabanidae and other mud-dwelling species. He puts them into a glass dish and covers them with agar, which forms a transparent substitute for mud which pleases them very well. They lie perfectly still in this for days at a time and at intervals he feeds them by putting in a snail or two, or better still, when he has them some oligochaete worms. When the agar becomes broken and he wishes to study them under the binocular he flows over a fresh supply.

Raw beef, as well as worms, snails and maggots, has been used as food for horse-fly larvae. The writer thought that by using beef-extract agar he would be providing both food and a substitute for mud at the same time. Consequently this form of media was used.

This method of rearing Tabanid larvae was put in practice almost at the start of the summer's work and larvae placed in this media on June 20, 1921, and subsequent dates are, at the present time, December 15, as healthy, apparently, as when first collected. This media has several great advantages over the natural media, mud and muck, of Tabanid larvae, as can be readily understood. It is of uniform consistency and can be made of any desired firmness, and thru the use of petri dishes an optimum of moisture can be easily maintained. The bacteria and fungi which may contaminate the media are apparently, very largely aerobic, and as the larvae always remain below the surface of the medium they are subject to but little danger from the attacks of any harmful bacteria and fungi which may be present.

The chief advantage of this media is its transparency. One may easily observe every movement of the larva, and, what is of considerable importance, cast skins can be immediately detected and saved, something which cannot be said for the natural environment of horse-fly larvae. Transfers from one petri dish to another are easily made and, if the cultures are kept in a cool place, this only needs to be done every month or so.

The idea has occurred to the writer (unfortunately too late to be put into practice this season) that this medium would be ideal for rearing many other kinds of dipterous larvae, particularly those that habitually breed in meat: Sarcophaga, Phormia, Lucillia, Chrysomyia and many other Muscoid genera.

A species of *Phoridae* (*Aphiochaeta* sp.) contaminated several of the petri dishes. The females were probably attracted by the somewhat putrid odor of cultures one to two weeks old and laid their eggs at the edge of the dish. The first stage larvae, being of course minute, were able to crawl under the petri dish cover and gain entrance to the medium. The larvae remained on the surface during their entire larval period and also pupated there. The adults, a small dark brown species, were obtained about ten days later. No attempt was made to ascertain whether the species would breed for more than one generation in the same dish. This observation will perhaps be of interest to geneticists who may be on the lookout for experimental material.

Another point that still further recommends nutrient agar to the use of entomologists is the form in which it is now placed upon the market. The Digestive Ferments Company, Detroit, Michigan, now puts up a dehydrated form of their Bacto-Nutrient Agar. It is only necessary to add a certain amount of water to the proper amount of the dehydrated media and boil or autoclave it in order to get it ready for use. All of the bother of weighing the various substances, titrating and filtering is done away with by using this form of media.

To the writer this method of rearing dipterous larvae seems to possess much promise, particularly for certain of the Muscoids. Extensive rearings can still be carried on to advantage for such groups of Sarcophaga, Wohlfartia, Chrysomyia, etal and beef-extract agar would seem to be especially adapted for them. Rather frequently larvae of these forms are found infesting living tissues of animals and this media probably offers a ready substitute for their original environment.

RESUMEN

El autor ha usado con mucho éxito el agar en combinación con el extracto de carne de buey en el cultivo de las larvas de los dípteros—especialmente de las especie de los Tabánidos. El autor cree que este método es aplicable a la mayor parte de las especies conocidas. Entre las ventajas marcadas que se obtienen se menciona la anaerobiosis en el fondo de las placas de cultivo que excluye la mayor parte de las bacterias de contaminación y a transparencia que permite observación directa.

# AN EXPERIMENTAL INVESTIGATION OF THE SUPPOSED POISONOUS QUALITIES OF THE COLORADO POTATO BEETLE LEPTINOTARSA DECLEMLINEATA

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The Colorado potato beetle, *Leptinotarsa decemlineata,* was greatly feared at one time for its supposed poisonous qualities as well as its destructiveness to potatoes and other crops. Although the interest in this supposed toxicity was keen, little definite work was done, and the results which were obtained by the various workers were widely divergent. Little is heard on the subject now-a-days and the issue was left undecided. For this reason it seemed worth while to check up if possible the previous experiments and to endeavor to arrive at some definite conclusion regarding the alleged poisonous qualities of the beetle.

Since the potato beetle was compared most frequently with blister beetles in its toxicity, cantharides, or powdered blister beetles were used to control the experiments.

During the period of 1850 to 1876 while the potato beetle was migrating eastward from the Rocky Mountains where it feeds on one of the potato family, *Solanum rostratum,* the rate of progress was estimated at fifty to seventy miles a year. It is therefore easy to understand that an unknown pest, suddenly present in large numbers should be looked upon with suspicion.

The current newspapers as well as medical and entomological literature have been found to contain numerous reports regarding this insect, in which the concensus of opinion seems to be that it is poisonous to man, and possibly to chickens and wild fowl.

The attitude of many people concerning the potato beetle at that time may be expressed by the following quotation from an article by Dr. E. M. Hale, Professor of Medical Botany in the

Hahnemann Medical School of Chicago, (1869): "For what purpose this vile thing was created, except as one writer expresses it, that man might look upon it and the desolation it produces and still keep the Third Commandment unbroken, is yet to be discovered." Later Dr. Hale says: "A large amount of reliable testimony can be presented to prove that the Colorado potato bug is one of the most virulent poisons in the animal kingdom."

The author divides poisoning by Leptinotarsa into three groups: poisoning from inhaling fumes from insects killed in boiling water; by inhaling fumes from insects killed by dry heat; and by bruising them between the fingers or in the palms of the hands.

The poisoning was supposed to be not localized, but rather of a systemic nature, and in eleven cases reported by Dr. Hale (none from his own practice) the symptoms presented were described as follows; Swelling of the whole body and especially the hands and face, blood-shot protruding eyes, stupor, delirium, gastro-intestinal disturbances, vomiting, fever, and often great prostration. Death occurred in four of these cases. That these reports are authentic, however, is to be questioned since many of them come from newspaper items and the statements made are manifestly exaggerated. For example, one report concerns two women who had been destroying potato bugs in the field. "One ate her dinner without washing her hands after killing the vermin, and died in most terrible agony. The other received venom through sores in her hands and died immediately."

To quote a second case:

> A man had been engaged in picking and crushing bugs from potato vines; he had a slight abrasion on the wrist, soon the abraded surface began to be painful, swelling ensued and the whole arm became involved; a deep ulcer developed on the wrist, of the character of cancer, red and angry, with sticking, stinging sensations through the whole arm; it afterward assumed the form of a sloughing ulcer, the bones of the wrist being exposed. At the time this report was made the man still lived, but we have seen no further account of the case.

Dr. Hale has also included a report of an experiment carried out by Dr. C. Ruden of Joliet, Illinois which seems very definite.

In this experiment the substance used was "a saturated tincture" of which Dr. Ruden took gradually increasing amounts, beginning with 5 drops twice a day and increasing to 20 drops twice a day. During this time the symptoms were very well marked, and in general like those reported before; severe swelling of the entire body, face and eyes congested with blood, fever, gastro-intestinal pain, dysuria, intense weakness and stupor.

Dr. Ruden further reports that the symptoms observed in a case under his care had a great resemblance to those caused by the bite of a rattle snake, which suggests to him that the poison might be of somewhat the same nature. Many physicians compare poisoning from this insect with that from cantharides, but Dr. Ruden is of the opinion that the Colorado potato beetle causes results far more profound and disastrous.

Walsh and Riley, in the American Entomologist for 1868, published a note by J. G. Irwin on poisoning by potato beetles, in which it was stated that prairie chickens eat them readily but that they sicken and many die. An entire family became ill from eating prairie chickens which had eaten these beetles. Domestic chickens seem also to be posioned.

It should be noted that no accurate data are included in the report, and while the cause and effect relationship seems apparent enough, as in the previously considered cases of poisoning, it is possible that it may be entirely false, and serve only to obscure the true interpretation.

In looking through the reports of C. V. Riley, State Entomologist of Missouri, there are many references to the poisonous qualities of these beetles, in which the opinions vary from regarding them as violently poisonous to comparatively innocuous.

In 1875 Riley mentions the opinion of Prof. T. J. Burrill of the Illinois Industrial University, who stated that the potato beetle is not poisonous. His support for this view was that he had rubbed juice from the mashed insects into a flesh cut, and had accidentally squirted some into his eye and had not had any injurious effects from either. In this same report Riley mentions three cases of poisoning which he considers authentic, and which he explains by saying that though many people are immune from the poison, there is no doubt that, with blood in certain bad conditions, poisoning may result.

In the Eighth Annual Report (1876) there are included some interesting experiments carred out by Grote and Kayser, which were read before the American Association for the Advancement of Science. These workers collected the potato beetles from unsprayed fields and made an aqueous and an alcoholic solution from them. Feeding these two solutions in 0.5 cc. doses to frogs produced no effect. Inoculation into frogs caused paralysis and death in thirty minutes with the alcoholic tincture, and no result from the aqueous solution.

Grote and Kayser therefore concluded that the insects are not poisonous and that cases of poisoning result from the arsenic used in killing the insects or from carbon monoxide produced by incomplete combustion when large amounts of beetles are thrown into a fire.

In discussing these experiments Riley brings out the following points: first, that the reagents used to extract the poison may not be the proper ones, and may only serve to coagulate it instead of to extract it, second, that the effect of the poison may differ on warm and cold blooded animals.

Dr. Hering in volume III of the Journal of Materia Medica has discussed the problem from the standpoint of therapeutics. He names several antidotes for the poison of potato beetles, which he considers to be one of the most violent poisons in nature.

An analysis of *Leptinotarsa decemlineata* was made by a pharmacist, Dembinski (1877) in which he attempted to extract cantharidin with chloroform and with ether, but with negative results.

## EXPERIMENTAL WORK

### *Preparation of material*

The adult beetles and the larvae were collected from unsprayed potato fields so that there was no possibility that arsenic or any other insecticide could enter into the subsequent reactions. The insects were dried in an oven or a drying chamber until they were sufficiently brittle to be pulverized, and then ground to a powder. The powder was used as the experiment indicated, and in other experiments the fresh insects were used.

The experiments were of four types; feeding experiments, vesicating experiments, subcutaneous inoculation and inhalation experiments. In every case except the last group a check experiment was run, using identical preparations made from blister beetles of the genus Mylabris.

### *Feeding experiments*

#### A. Experiments with rats

1. Three young rats were fed 1 gram each of the powdered Leptinotarsa mixed with distilled water to facilitate feeding. They showed no ill effect during the week following the feeding.

2. The same three rats were fed 2 cc. each of an extract made by boiling 1 gram of insects in 15 cc. distilled water down to 6 cc. They showed not the slightest effect.

3. Two rats were starved for forty-eight hours and then fed 2 grams each of powdered beetles in small capsules. They were not affected unfavorably.

4. One rat from the same litter was fed 0.250 gram of Mylabris in water. It immediately became distressed and died with symptoms unobserved during the following night. Dissection showed a deeply inflamed body cavity and inflammation of the entire alimentary canal. Additional rats were not used because these results were typical of those previously obtained by the writer in feeding cantharides to these animals. Dissection of one rat from the previous experiment showed no inflammation or other pathological symptom.

#### B. Experiments with chickens

1. Six chickens three weeks old were each fed 1 gram of Leptinotarsa in a little water. They were observed carefully and showed no effect immediately following the feeding or for the four subsequent days.

2. Six chickens of the same age were kept in the same run as controls. The weather turned damp and cold at this time, and resulted in both the experimental and control chicks dying off rapidly, since they were not provided with a brooder to keep them warm. At the end of nine days after feeding, four of the Leptinotarsa chicks had died and five of the controls, so that it was deemed necessary to repeat the experiment.

3. Five chickens three weeks old were each given 1 gram of powdered beetles on three sucessive days. Observed during two weeks following, none showed the slightest reaction.

4. The five control chicks in this experiment also remained healthy during the two weeks.

5. Five chicks were each fed 0.5 gram of dried powdered larvae. Since they showed no effect, the feeding was repeated twice, making a total intake of 1.5 grams a piece, but their condition remained unchanged.

*Vesicating experiments*

The preparations used for these experiments were made using the reagents worked out by various pharmacists experimenting on cantharides. It has been found that the solvents of cantharidin are the essential oils, ether, alcohol, chloroform, acetic ether, acetic acid and water. Accordingly these reagents were used in an effort to extract cantharidin, as in previous work on *Calendra granaria* (Defiel, 1922a).

The solutions were applied as in Fabre's work on urticating insect larvae (translated 1916) by applying saturated lens paper or cotton, covering it first with a rubber bandage and then with gauze.

1. Dried and fresh Leptinotarsa were rubbed on the skin of the inner arm with no appreciable effect.

1a. One fresh blister beetle, *Meloe angusticollis* was rubbed on the arm. After drying, redness began to develop, and in three hours became intensified until a small blister formed.

2. One-half gram dried Leptinotarsa was added to 6 cc. distilled water and boiled down to 3 cc. The extract was filtered and applied on cotton. After eight hours there was no effect.

2a. The check preparation with Mylabris caused a blister in three hours.

3. A paste made of powdered Leptinotarsa in distilled water was bandaged on for nine hours, but caused no reaction.

7. one gram Leptinotarsa was macerated in acetic ether for one week. The resulting yellowish brown fluid had no effect on the skin after twelve hours.

7a. A similar preparation of Mylabris blistered the skin in four hours.

8. One gram Leptinotarsa was macerated in 95 per cent alcohol for one week. The clear yellow fluid had no effect on the skin after twenty-four hours of application.

8a. The control solution of Mylabris caused the formation of a blister at the end of five hours.

9. One gram Leptinotarsa was macerated in cedar oil for one week. The filtered solution did not affect the skin.

9a. A similar solution of Mylabris caused an exceedingly large blister to form in three and one-half hours.

10. One gram of powdered Leptinotarsa larvae was macerated in chloroform for six days. This solution was also inert when applied on the inner arm for eight hours.

11. One gram of powdered larvae was macerated in 95 per cent alcohol for one week. The solution had no effect on the skin after six hours of application.

*Inoculation experiments*

An extract was made by boiling 1 gram of powdered Leptinotarsa in 8 cc. of distilled water down to 4 cc. and then diluting to 8 cc. with salt solution of double isotonic strength. The resulting isotonic solution was sterilized and injected. A similar check solution of Mylabris was made up at the same time.

A. Experiments with rats

1. Five adult white rats were each injected subcutaneously with 2 cc. of the sterile solution. During the following ten days no reaction could be detected.

2. Five rats were inoculated at the same time with sterile salt solution as controls and these likewise showed no effect.

3. Four rats from the same litter were each inoculated with 2 cc. of sterile Mylabris solution. They did not regain their normal activity as the other rats did, but lay stretched out breathing convulsively. The convulsions gradually increased in severity, until death occurred in approximately two hours. Dissection of one from each group showed that the first two were normal, in contrast to the Mylabris injected rat, which showed a great deal of inflammation. The most notable feature was that the entire area surrounding the injection point was congested with a clear yellowish jelly similar to coagulated blood serum, and adhering closely to the body wall; it might be described as a subcutaneous blister, approximately three centimeters in diameter.

B. Experiments with chickens

1. Four young chickens were each inoculated subcutaneously with 2 cc. of Leptinotarsa solution, prepared as in the preceding experiment. The fluid was absorbed in less than an hour, but was without effect on the chickens.

2. The control chickens, inoculated with Mylabris solution and salt solution, were likewise unaffected.

C. Experiments with frogs

1. Two adult frogs were injected in the hind leg with 2 cc. of Leptinotarsa solution prepared as before. They remained normal and showed no reaction during the two subsequent weeks.

2. Two frogs were injected with 2 cc. of an extract of the beetles in 95 per cent alcohol (Grote and Kayser, 1876). They became paralyzed and inert, and in a few hours were excessively puffed up. One died in twelve hours and the other in thirty-six hours.

3. Two frogs were injected with 2 cc. of pure 95 per cent alcohol. They showed the same reaction as in the preceding experiment and both died in twelve to twenty-four hours.

*Inhalation experiments*

1. A young rat was put in a wire container closely covered with a damp towel. Steam from a retort in which 10 grams of fresh Leptinotarsa was boiling in distilled water was directed into the cage. The temperature was not allowed to exceed 35°C. Although the experiment lasted for forty-five minutes, and was carried out on four successive days there was no reaction observable.

2. The above experiment was checked by inhalation of pure steam, and here also the rat was unaffected.

3. One hundred grams of fresh beetles were spread out on a flat tray to dry in a hot box 4 by 4 by 4½ feet, at a temperature of 60°C. The box was kept tightly closed for several hours and became filled with acrid unpleasant fumes. The box was opened and the fumes breathed by the writer for twenty minutes. This was repeated on the following day. While the odor was intensely unpleasant, none of the symptoms were developed which were reported in the above mentioned papers.

4. Ten grams of beetles in distilled water were boiled in a retort, and the steam inhaled by the writer for two periods of thirty minutes each. Beyond an unpleasant taste in the mouth, there was no effect.

## SUMMARY

To summarize the results of the experiments, in no instance has the writer found experimental evidence which would support the beliefs that *Leptinotarsa decemlineata* might be used as a substitute for the Spanish blister beetle, or that the beetle contains any substance poisonous to inhale or ingest.

## SUMARIO

Nos dice la autora que la supuesta toxicidad del "escarabajo de patatas de Colorado," *Leptinotarsa decemlineata,* y asi mismo su destructibilidad hacia dichas legumbres, nunca ha sido definitivamente comprobada por medio de experimentos. Se ha usado como guía en los estudios anteriormente hechos, a la mosca cantárida pulverizada debido, según se ha creído, a la similaridad de propiedades venenosas. Hasta ahora ha existido la mayor divergencia de opinión acerca del carácter agresivo del mencionado insecto. Con tal propósito nos ofrece la autora una serie de experimentos que prueban, según ella, que no hay razón para creer la *Leptinotarsa decemlineata* tenga caracteres idénticos con la mosca de España (*Cantharis vesicatoria* y que por lo tanto nunca debe usarse una en substitución de la otra. También pone en evidencia el hecho de la falta de substancias venenosas en el escarabajo de Colorado que se manifiesten por inhalación o ingestión.

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# A NOTE ON THE EFFECT OF TARTAR EMETIC INTRAVENOUSLY ON THE NON-PROTEIN NITROGEN OF THE BLOOD

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The more or less specific effect of tartar emetic intravenously in conditions known as granuloma inguinale has brought to the attention of the profession of this country a drug about which little is generally known. Reports of cases of granuloma inguinale coming from various parts of the United States indicate that this infection may be encountered in any latitude. The combination of the tartrate with antimony to form tartar emetic gives us a compound in which either of its components may cause serious effects when given in toxic doses or to susceptible individuals. Experimental work conducted by Underhill, Pearce and Ringer, Salant, and others, has shown that the tartrates when injected into dogs and rabbits are capable of producing a definite nephritis with retention of the non-protein nitrogen elements in the blood. While such work has not been done with antimony, the similarity of the drug with arsenic suggests that it would produce the same effect as arsenic in the individual.

In order to determine whether tartar emetic given intravenously in the dosage usually employed in treatment had any deleterious effect upon the individual, the following experiments were undertaken:

Six cases of varied medical ailments were selected from the medical wards of the hospital, and complete blood analyses done—the Folin and Wu system being employed; and the chlorides being determined by McLean and Van Slyke's method.

These cases were all on the ordinary house diet, and were ambulant cases.

Tartar emetic, in a 2 per cent solution was given intravenously every other day—six doses being given—starting with 0.5 cc. and ending with 5 cc. This procedure was observed in every case except the case J.H., he being given 7 cc. for the final dose. The accompanying tables show the results of our examinations before and after the treatment with tartar emetic.

TABLE 1

*Before treatment*

| CASE | DIAGNOSIS | BLOOD PRESSURE | URINE | | BLOOD CHEMISTRY, MILLIGRAMS PER 100 CC. | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Albumen | Casts | Non-protein N | Urea N | Uric acid | Creatinine | Chlorides | Sugar |
| H. E. | Portal cirrhosis of liver | 142/80 | – | – | 31.6 | 15.0 | 2.8 | 1.8 | 550 | 144.0 |
| J. McC. | Paresis, chronic nephritis | 225/148 | – – | – | 75.0 | 37.5 | 3.8 | 2.0 | 560 | 153.8 |
| J. H. | Imbecile | 132/86 | – | – | 30.0 | 15.0 | 2.8 | 1.9 | 500 | 148.0 |
| J. F. | Paresis | 108/72 | – | – | 33.3 | 16.2 | 3.7 | 1.9 | 525 | 102.5 |
| J. L. | C. S., syphilis, hemiplegia | 140/80 | Trace | Hyaline, few | 33.6 | 15.3 | 3.8 | 1.8 | 550 | 122.6 |
| T. F. A. | Arterio-sclerosis, hemiplegia | 160/80 | – | – | 33.6 | 15.7 | 3.2 | 1.8 | 537 | 125.0 |

It is seen that tartar emetic intravenously even in small doses over a comparatively short period of time is capable of producing a decided increase in the non-protein nitrogen elements of the blood. In the rather free use of this drug which is likely to obtain in treating granulomatous conditions, the above results should be kept in mind.

## RESUMEN

La profesión esta familiarizada con el uso específico del tártaro emético en esas infecciones que se denominan bajo el nom-

TABLE 2

*After treatment*

| CASE | DIAGNOSIS | BLOOD PRESSURE | URINE | | BLOOD CHEMISTRY, MILLIGRAMS PER 100 CC. | | | | | | TARTAR EMETIC GIVEN | REMARKS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Albumen | Casts | Non-protein N | Urea N | Uric acid | Creatinine | Chlorides | Sugar | | |
| H. E. | Portal cirrhosis | 142/80 | – | – | 31 | 15.3 | 2.4 | 1.2 | 575 | 133.0 | Five doses, alternate days, 0.5, 1, 2, 3, 4, 5 cc. 2 per cent solution | Slight nausea after third dose—no change in blood chemistry |
| J. McC. | Paresis, chronic nephritis | 225/148 | ++ | – | 120 | 87.7 | 5.0 | 3.7 | 537 | 142.0 | Same as above | No nausea—marked increase in non protein N elements |
| J. H. | Imbecile | 132/86 | – | – | 31 | 15.0 | 3.0 | 2.0 | 550 | 142.0 | Same as above except last dose was 7 cc. | No nausea — no change in blood chemistry |
| J. F. | Paresis | 108/72 | – | – | 31 | 15.3 | 2.9 | 2.0 | 550 | 142.0 | Same as first case | No nausea — no change in blood chemistry |
| J. L. | C. S., syphilis, hemiplegia | 140/80 | Trace | Hyaline, few | 50 | 25.0 | 5.3 | 2.0 | 537 | 142.8 | Same as others | Vomited after second and third injection—increase in non protein elements |
| F. T. A. | Arterio-sclerosis, hemiplegia | 160/80 | – | – | 50 | 27.2 | 4.1 | 2.3 | 550 | 166.6 | Same as others | No nausea — increase in non protein elements |

bre de granuloma inguinal. Sin embargo, poco se sabe de los efectos tóxicos de la droga. El tártaro emético es muy peligroso administrado en ciertas cantidades máximas o en casos de susceptibilidad individual. Experimentos verificados por otros han demostrado que los tartratos inyectados en perros y conejos producen nefritis. Los experimentos que aqui damos a la luz prueban que la administración intravenosa aun en pequeñas dosis del tártaro emético es capaz de producir un aumento decidido de los elementos no-nitrogenados de la sangre. Este hecho debe tenerse presente cuando se use la droga en el tratamiento de condiciones granulomatosas.

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