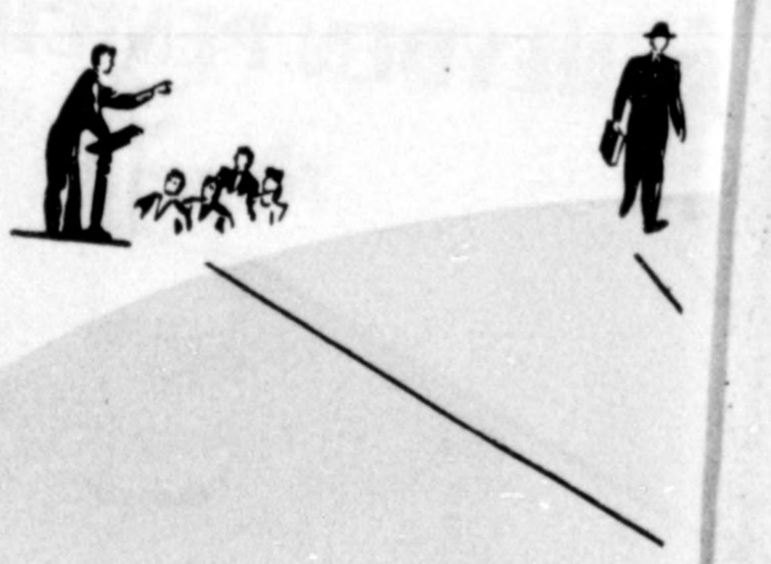

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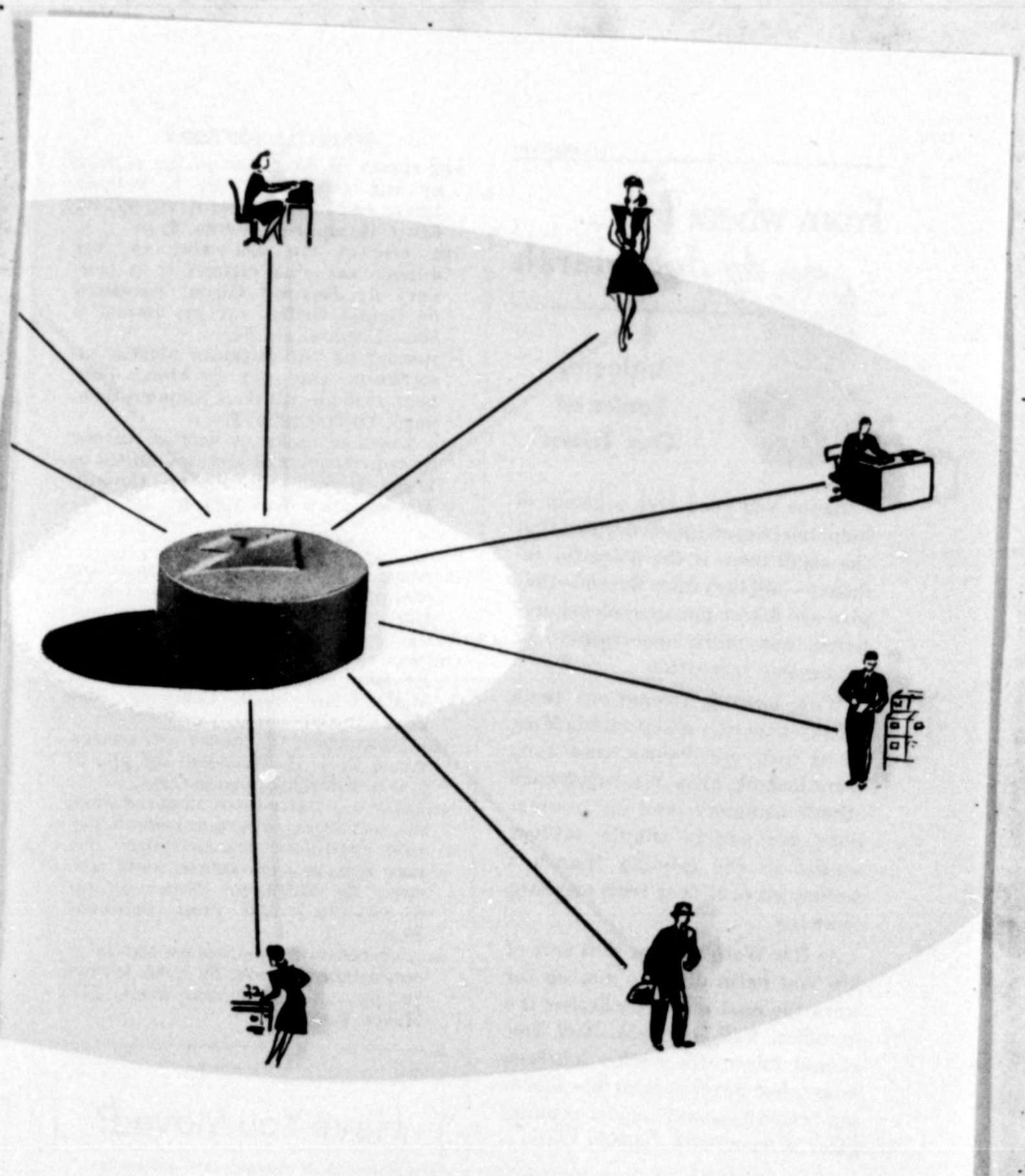

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Patients I Have Met

The editors will pay $2 for each story published. No contribution will be returned. Send your experiences to the Patients I Have Met Editor, MODERN MEDICINE, 84 South Tenth St., Minneapolis 2, Minn.

TROUBLE, TROUBLE!

While in Camp Van Dorn (Miss.) I was a medical officer for a colored battalion. One morning a colored soldier presented himself on a sick call.

"What's your trouble, soldier?" I asked.

"Well, sah. I'se got some awful dreams, I has. Every night I'se beaten up something awful, all black and

blue. And da' funny part is, I cawn't fight back. No sah. I cawn't fight back. Yah sah. This man boxes me earhs and all. Every night, yah sah. I'se shore got trubble."

After some deliberation on my part, I said: "Look, here. What you want to do to get over these dreams is to put on a pair of boxing gloves and fight back, fight hard."

"Well, sah. You'se all know who I'se to fight?" he asked.

"No. I don't know. Who is the man?"

"Joe Louis, sah, dat's who he is," the soldier told me.—J. J. B.

Night Call

The doctor had just got to sleep at 3 a.m. after returning home from a difficult o.b. The telephone rang. He stumbled downstairs, picked up the receiver, and shouted, "Hello." A voice at the other end said, "The baby is crying and I can't stop him. What shall I do?"

"Is he feverish?"

"No."

"Perhaps he is hungry, feed him," the doctor said and went back to bed.

No sooner had he got to sleep than the phone rang again. It was the excited mother. "The baby was hungry doctor, I thought you would want to know."

HE ASKED FOR IT

I had occasion, while opening a new office located over a general store, to bore some holes. I went downstairs to ask the storekeeper for a brace and bit. The old fellow was deaf, so I had to repeat my request as loudly as I could. The storekeeper smiled sympathetically, took me back to a rear window, and pointed to the woods.—H.S.W.

Fee Cutting

Specialist: Could you afford to pay for an operation if I decide that one is necessary?

Patient: Well, doc, tell me this. Will you decide that one is necessary if I can't afford to pay for it?

Rather Humerus

The man had been in an accident. When I arrived on the scene he pointed to his upper arm, saying, "My uterus is fractured."—S.E.B.

Through a Glass, Darkly

Throughout the operation the anesthetist watched the patient's right eye for pupillary reaction and corneal reflex only to discover afterward that the patient's right eye was of glass.

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THE PHYSICIAN'S VIEWPOINT

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DISPLACEMENT UPWARDS

Many cases of pruritus ani and irritation of the perineum are due to displacement from before backwards, and are met with in bachelors, homosexuals, cases of functional impotence, and unsatisfied women.

One rather dramatic case comes to my mind.

Mrs. C, aged 40, was a widow with a patch of eczema at the back of her head. She was the vivacious mother of two children, divorced from her ex-teacher, ex-parson husband, because of his penchant for penniless nursemaids and old women with wealth. After the divorce she lived impulsively on her energies as a shopkeeper with the financial help of her brother in Australia. By the time he died and his help ceased, she had learned to live on her charm. She also retained a conscience, but the two never functioned concurrently. During a more prolonged attack of impulse than usual she defied her conscience and managed to be admitted to the Roman Catholic Church. Then suddenly it dawned on her that she could never marry again. The Church satisfied her conscience; a married Canadian was satisfying her instinct, but neither would recognize the other. When I met her she had just managed to relieve herself of an early pregnancy. When asked how she squared that circle, she naively replied that she just put it at the back of her head. I could not help complimenting her on how successful she had been.—A. W. W.

Pregnant Reply

A young doctor decided to obtain some relaxation and went to a ball. Observing a beautiful maiden on the sidelines, he asked for a dance.

She looked at him coldly and replied, "I'm sorry, I won't dance with a child."

He replied sweetly, "I'm sorry, I didn't know you were in that condition."

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VOLUME FIVE | JANUARY, 1948 | NUMBER 1

PENICILLIN

INTERNAL MEDICINE

Endocarditis, Bacterial

Paul, O.; Bland, E. F., and White, P. D.: **Bacterial Endocarditis; Experiences with Penicillin Therapy at the Massachusetts General Hospital, 1944-1946,** *New England J.Med. 237:349 (Sept. 4) 1947.*

An analysis is presented of data from 44 patients with bacterial endocarditis treated with penicillin at the Massachusetts General Hospital in the 3-year period 1944-46.

Patients ranged in age from 3½ to 72 years. There was no relationship between age and successful treatment.

Rheumatic heart disease was present in 82% of patients; there was a high incidence of aortic-valve lesions.

Endocarditis followed upper respiratory infections in 19 patients (43%) and dental extractions in 5 (11%).

The alpha hemolytic streptococcus was the predominating organism, occurring in 82% of cases. In most of the 31 cases tested, the organisms were penicillin sensitive; in 5, 1 to 8 U./cc. was required for inhibition of growth. Increased resistance during treatment occurred in 2 cases.

The authors state that in vitro sensitivity was a reliable guide to penicillin dosage. In general, a blood level 5 times the in vitro inhibitory concentration is required. It is pointed out that other factors such as the method of administering penicillin, duration of treatment, the patient's immune response, and the anatomic features of the valvular lesion influence the course of the disease, as well as the sensitivity of the organism.

Penicillin was administered by various methods—intermittent intramuscular injection at intervals of 1 to 4 hours, continuous intramuscular or intravenous infusion, in oil and wax, intramuscularly, 3 times daily, and orally. The authors state that no conclusions can be made as to the efficacy of any method. The constant intramuscular method proved satisfactory provided that massive doses were not used and the volume of fluid was limited to 800 to 1,000 cc. daily. 5% glucose in distilled water was preferred to saline solution as the diluent.

The smallest curative dose was 2,685,000 units in 15 days, the average, 500,000 units daily for 3 weeks. Doses as high as 10,000,000 units daily were given. It is recommended that dosage based on the in vitro sensitivity of the organism be continued for 4 weeks, then therapy should be temporarily halted and progress evaluated.

Other medication given concomitantly included sulfonamides in 14 patients, benzoic acid in 9, typhoid vaccine in 1, and streptomycin in 1. Anticoagulants were not used.

Of the 44 patients, 29 (66%) were alive and well at the time of this report. In the 15 fatalities, the infection appeared to have been controlled in 9, bacteremia persisted in 6. Of those with apparently controlled infection, 1 died from a second attack of bacterial endocarditis, 8 from cardiovascular complications.

Schreck, P. M.: **The Treatment of Sub-Acute Bacterial Endocarditis,** *J. Oklahoma M.A. 40:369 (Sept.) 1947.*

A brief review on the treatment of subacute bacterial endocarditis with penicillin is presented.

Maintenance of a blood level 5 to 10 times that of the in vitro sensitivity of the infecting organism is stressed.

Continuous intravenous administration would appear to be the method of choice for this result; however, because of technical difficulties intermittent intramuscular administration is preferred

IMPORTANT NOTICE REGARDING PENICILLIN IN OIL AND WAX

According to a notice recently published by The Food and Drug Administration (Federal Register, Nov. 29, 1947), penicillin in oil and wax should not be administered subcutaneously. *Injection should be made intramuscularly only.* This applies to both the liquid and semifluid forms of penicillin in oil and wax.

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PENICILLIN

by many workers. The author states that doses at 2-hour intervals should be adequate. For organisms of low resistance (0.01 to 0.05 unit) daily dosages of 200,000 to 900,000 units have been suggested, and for resistant organisms, dosages as high as several million units daily.

Criteria of cure are listed as persistently negative blood cultures, a falling or normal sedimentation rate, and normal leukocyte count. An abnormal or rising white count suggests the need for further treatment.

Zimmerman, S. L.: **What's New in Cardiology,** *J. South. Carolina M.A. 43:265 (Sept.) 1947.*

As a part of a survey of the progress of cardiology during the past year, the author presents a brief summary of the literature on the use of penicillin in the treatment of subacute bacterial endocarditis and of the experience with this therapy at the Veterans Hospital (Columbia, S. C.).

He states that 69 to 70% of cases will respond to intensive and adequate penicillin therapy. Determination of the etiologic organism and its in vitro sensitivity is emphasized. Dosage is usually regulated to supply a pencillin blood level of 5 to 10 times that required for inhibition in vitro. Some cases may respond to a dosage of 500,000 units daily for 4 to 6 weeks while others may require dosages as high as 2 to 3 million units daily for longer periods.

The author states that at the Veterans Hospital intermittent intramuscular injection was used with satisfactory results. No anticoagulant therapy was used.

Relapses usually occur within 4 weeks after discontinuance of therapy. These require retreatment with larger doses of pencillin.

Grossman, M.; Feldman, D.; Katz, L. N.; and Brams, W.: **Treatment of Subacute Bacterial Endocarditis Due to Organisms Highly Resistant to Penicillin;** *Case Report, Am. Heart J. 34:592 (Oct.) 1947.*

That "intensive penicillin therapy may in certain cases of subacute bacterial endocarditis with resistant organisms convert treatment failures into treatment successes" is demonstrated by the case reported.

According to the authors the chief causes of failure of penicillin therapy in subacute bacterial endocarditis are inadequate dosage, too short a period of therapy, too great an interval between injections of penicillin, and an organism resistant to penicillin. Since resistance may be relative rather than absolute, it is recommended that a blood level 4 or more times the in vitro sensitivity be maintained continuously for at least a week.

The case reported was that of a 17 year old white boy who was admitted to the hospital for treatment of subacute bacterial endocarditis due to Str. viridans. Diagnosis had been made approximately a year earlier at another hospital. During the interval 4 courses of penicillin totalling 3,300,000 units, 3,600,000 units, 5,700,000 units and 2,400,000 units, respectively had been given. During each course blood cultures became sterile and remained so for periods of 2 weeks to a month after discharge. During the interval between the 2nd and 3rd courses of penicillin an "embolic infection of the kidney" occurred, for which sulfadiazine was administered.

Diagnoses following physical and laboratory examinations were "rheumatic heart disease with mitral stenosis and insufficiency and subacute bacterial endocarditis (Streptococcus viridans)." The organism was inhibited in vitro by 5 U. penicillin/cc.

Penicillin was given in a dosage of 3,000,000 units daily by continuous intravenous drip for 35 days, then 1,000,000 units for 1 day because of shortage of penicillin, then 6,000,000 units daily for 7 days.

Blood level with the 3 million unit dosage was 10 U./cc. However, on the 34th treatment day it dropped to 3.2 U./cc., believed due to improvement in kidney function. For this reason penicillin dosage was increased to 6,000,000 units daily and para-aminohippuric acid was added to the penicillin infusion for 5 days. During the administration of para-aminohippuric acid, blood levels were 20 to 40 U./cc.; after its discontinuance and with the same penicillin dosage the level dropped to 6.4 U./cc.

Blood cultures became sterile a few days after penicillin was started and remained so thereafter except for 1 positive culture during the 4th week of therapy, attributed to the breaking off of a friable vegetation. The sedimentation rate fell from 37 to 20 mm. in 1 hour.

On the last day of penicillin therapy, the patient suffered an attack of acute appendicitis. Operation was carried out without complications with penicillin (1,500,000 units daily) for 2 days postoperatively.

The patient was discharged in good condition on the 84th hospital day. A transient positive blood culture was obtained on the 6th day after discharge, believed to be due to carious teeth. 4 teeth were subsequently extracted under penicillin protection (6,000,000 units daily by intravenous drip) for 4 days prior to and for 54 hours following extractions.

During a 6-month period thereafter, the patient has remained clinically well, and afebrile, and blood cultures have been sterile.

In an addendum, the authors report the status of 17 patients treated with penicillin. 3 had died during or shortly after treatment. 2 died at 8 and 9 months, respectively, after treatment. Of the 12 living patients, 11 are fully active, 1 has progressively incapacitating congestive failure.

Orgain, E. S.: **Recent Advances in the Treatment of Cardiovascular Disease,** *North Carolina M.J. 8:641 (Oct.) 1947.*

A review of the literature on recent advances in the treatment of cardiovascular disease, including the use of penicillin in bacterial endocarditis and in cardiovascular syphilis, is presented.

The author states, "The greatest current achievement in the medical treatment of heart disease has been the practical application of penicillin to the therapy of bacterial endocarditis." A recovery rate of 67% has been reported in a total of 507 patients treated with penicillin. The recovery rate has not been significantly altered by supplementary anticoagulant therapy.

Results have been similar with the various methods of administration. The method of administration can therefore be selected with regard to the patient's comfort.

Daily dosage is of paramount importance and depends upon the in vitro penicillin sensitivity of the organism. Maintenance of blood levels at 4 to 10 times the in vitro sensitivity has been suggested. Concomitant administration of para-aminohippurate may aid in maintaining the desired level. A daily dosage of 500,000 units for sensitive organisms and not less than 1,000,000 units for resistant organisms is recommended. A treatment period of 4 to 6 weeks, depending on the patient's response, is suggested.

The author states that the therapeutic efficacy of penicillin in cardiovascular syphilis has not been fully evaluated. Caution is urged in the treatment of syphilis of the vascular system with penicillin because of the possibility of therapeutic shock.

Respiratory Conditions

Prigal, S. J.; Morganbesser, L. J., and McIntyre, F. P.: **Penicillin Aerosol in the Prevention and Treatment of Respiratory Infections in Allergic Patients,** *J. Allergy 18:325 (Sept.) 1947.*

That steam-generated aerosols of penicillin are useful in the treatment of infections asscciated with allergy is concluded from an analysis of results in 88 patients so treated.

In a previous publication, the authors have described the apparatus used (combined steam generator and aerosolizer), and blood levels obtained with the use of propylene glycol as the solvent and with various methods of administration (open inhalation, tent, small airtight chamber, breathing box). The breathing box proved most satisfactory. This is simply a small box into

which the penicillin-propylene glycol aerosol is blown and from which it is inhaled by means of an oronasal mask. The authors state that with the breathing box, penicillin aerosol therapy becomes a simple office procedure.

Penicillin dosage with the various methods was as follows: open inhalation—30- to 50,000 units 3 to 4 times daily; tent—100,000 units twice daily; chamber—200,000 units twice daily; breathing box—100,000 units once daily or 50,000 units twice daily. In severe cases in order to increase vital capacity and enhance penicillin absorption, inhalations of aminophyllin and/or ammonium chloride were given prior to penicillin inhalation. In some cases of mixed infection with organisms resistant to penicillin, sulfonamide inhalations were given after penicillin inhalation.

Results of treatment are discussed under the following classification:

Asthma and associated infection—61 patients. Patients are classified into 4 groups, according to the severity of the asthma. 40 patients were treated with the breathing box. All 9 patients with mild asthma (Group I) responded to treatment immediately, with cessation of cough and elimination of purulent nasal or bronchial secretions. Immediate improvement occurred also in 17 (80.9%) of 21 patients with moderate asthma (Group II) and 4 (40%) of 10 patients with severe asthma relieved by epinephrine or aminophyllin (Group III). Improvement was frequently temporary.

The tent method was used in the treatment of 6 patients with relatively severe asthma, with favorable response in 4. Because of the heat and humidity this method proved intolerable to some patients.

The chamber method was used in 3 patients. An adult treated with 180,000 units of penicillin in 3 hours remained free of asthma for 3 months. 2 asthmatic children were treated at home using the bathroom as the aerosolizing chamber; results were satisfactory in 1, while the other was relieved only temporarily.

The open inhalation method was used in 12 hospitalized cases of status asthmaticus (Group IV). Preliminary aminophyllin aerosol was administered in 3 with good response, although there was recurrence within a month. Preliminary therapy with aminophyllin and ammonium chloride aerosol and post-treatment with sodium sulfadiazine aerosol was effective in 8 of 9 patients so treated; however, there was recurrence in 4 within a month.

Upper respiratory infection associated with nasal allergy—28 patients treated with 100,000 units daily for 5 days, administered by means of the breathing box. Response was satisfactory in 11 (84.6%) of 13 cases of chronic infection and 11 (78.8%) of 14 cases of acute infection.

Prophylactic penicillin aerosol—Results in 12 patients subject to disabling illness following respiratory infection, who were treated with 100,000 units of penicillin 3 times daily, administered by means of the breathing box, suggest that such treatment during the early virus phase of a cold will prevent later bacterial infection.

The authors state that there were few reactions to aerosol penicillin—mild erythema in 2 patients and localized dermatitis around the nose and mouth in 2.

Causes of failure to respond to penicillin aerosol therapy are listed as incorrect diagnosis, penicillin resistant organisms, intolerance of steam, and irreversible lung pathology.

Snorf, L. D.; Shepanek, L.; Foltz, E. E., and Harding, H.: **Pneumonia Due to Proteus Mirabilis Treated with Penicillin and Streptomycin,** *J.A.M.A. 135:222 (Sept. 27) 1947.*

A patient with pneumonia due to Proteus mirabilis recovered following treatment with penicillin in massive doses and streptomycin, although the organism was highly resistant in vitro to both drugs. The authors state that it is probable that neither penicillin nor streptomycin exerted a direct effect on the primary infection, but were beneficial in controlling secondary infection.

According to the authors no other case of pneumonia due to a proteus has been reported in the literature, and only 3 other cases of pulmonary involvement have been reported, all of which were fatal.

The patient was a 63 year old woman who was admitted to the hospital with chills, vomiting, nausea and diarrhea of a week's duration. She gave a history of backache for the previous 3 years. Temperature was 99.4 F. Cultures on admission showed P. mirabilis in the feces and urine.

The lungs were clear on admission, but on the 11th day, consolidation in the right lung was noted and was confirmed roentgenologically, and temperature rose to 103.6 F. Penicillin was started in doses of 160,000 units daily, continued for 11 days.

Blood cultures taken on the 18th and 20th days were positive for P. mirabilis. During the following week the area of consolidation in the lung spread and the temperature spiked to 104 F.

At this time it was felt that since blood, urine and feces cultures showed P. mirabilis that this organism might also be responsible for the pneumonia. Penicillin dosage was increased to 1,300,000 units daily, continued for 5 days. After 4 days of intensive penicillin therapy, blood and sputum cultures were positive for the organism, although the patient improved clinically. Thereafter, blood, urine and feces cultures remained negative, and improvement continued.

Because a new area of consolidation developed during penicillin therapy, streptomycin was substituted, being given in a dosage of 2 Gm. daily for 5 days.

After 60 days of hospitalization, the patient was dismissed, asymptomatic, and with the chest normal roentgenologically and with blood, urine, feces and sputum cultures negative.

The organism in this case required for in vitro inhibition, 200 units of penicillin/cc. and 0.5 unit of streptomycin/cc.

Barach, A. L.: **Physiologic and Antibiotic Therapy of Bronchial Asthma,** *Connecticut M. J. 11:819 (Oct.) 1947.*

Physiologic and antibiotic therapy in intractable asthma is discussed, including a review of the pathologic physiology of obstructive dyspnea and the presentation of a program for bronchial relaxation.

The author states that progressive increase in the negative intrapleural pressure which occurs with obstruction to inspiration is the critical factor which results in secondary pathology.

Physiologic therapy in intractable asthma consists of measures to decrease the intrapleural negative pressure in inspiration—oxygen or helium-oxygen inhalations, positive pressure breathing, and bronchodilator or bronchovasoconstrictor drugs administered either systemically or by inhalation.

Antibiotic therapy is advised for patients with intrinsic asthma if the sputum has a purulent quality. The author recommends that penicillin be given systemically unless a highly resistant organism is found on sputum culture, in which event aerosol therapy is recommended.

Suggested dosage for intramuscular administration is 25,000 units 3-hourly, 50,000 units 4-hourly, 100,000 units 5-hourly, 200,000 units 6-hourly, or 400,000 units at 8- or 12-hour intervals.

For inhalation, 5 inhalations daily of 50,000 units in 1 cc. saline each are suggested. The author states that the use of tablets of crystalline penicillin, each containing 50,000 units, which can be placed directly into the nebulizer has simplified the technic of aerosolization. Aerosol therapy offers the advantage of maintaining effective blood levels and at the same time producing a high local concentration.

The various methods of administering penicillin aerosol are discussed, including nebulizers with power supplied by a hand bulb, by oxygen, or by an automobile foot pump, and inhalation by means of a mouthpiece, a mask, or a closed head tent. For penicillin therapy of sinus infections, an apparatus which produces negative pressure is described.

Sulfonamides and streptomycin may also be administered by nebulization.

Some cases of severe asthma may be benefited by fever therapy or by bronchoscopy and ether.

Baumann, F.; Crump, J.; Arthurs, A. C.; Seager, L. D., and Miller, R. E.: **Penicillin Therapy in Bacterial Asthma,** *J. Am. M. Women's A. 2:442 (Oct.) 1947.*

That oral penicillin "may become a valuable adjunct in the treatment of so-called bacterial asthma" is concluded from results in the study reported.

60 children and 15 adults were treated with oral penicillin (tablets buffered with basic aluminum aminoacetate). Prior to treatment all patients had edema of the mucous membranes typical of allergic rhinitis. X-ray findings suggested sino- or tracheobronchitis. Only patients showing penicillin sensitive organisms in cultures from the respiratory tract were included.

The penicillin dosage was changed during the latter part of the study. That now used is 50,000 units per dose for children and 100,000 units per dose for adults, every 4 hours day and night for 5 days.

The authors state that many of the patients had frequent respiratory infections during the winter, but few had associated asthma.

Cultures from the nose prior to treatment showed the predominating organisms to be Staph. aureus and albus, pneumococci, H. influenzae, nonhemolytic streptococci and Str. viridans. After treatment, cultures in adults showed the disappearance of pneumococci and streptococci; staphylococci persisted, but were mostly of the coagulase negative type. There was no correlation between the bacteriologic picture and control of the asthma.

Davis, D.: **Inhalation of Penicillin Aerosol and Penicillin-Streptomycin Aerosol in Office Practice,** *Arch. Otolaryng. 46:307 (Sept.) 1947.*

That inhalation of penicillin aerosol is a practical office procedure for the treatment of many conditions of the upper and lower respiratory tract is the author's conclusion from his experience over a period of 2 years. Illustrative case reports are given.

The technic used was that of Barach and associates and Vermilye. At first a mouthpiece fitted to the nebulizer was used, later a face mask was substituted. A nasal tip which allows suction and pressure was used for sinus treatments.

At first treatments were given hourly, using 5,000 to 50,000 units of penicillin for each inhalation, for 4 to 6 treatments daily. Later a single daily treatment with 100,000 units of penicillin in 1 cc. saline solution was used, and more recently, 100,000 units of penicillin alone or combined with 100,000 units of streptomycin in propylene glycol.

The author states that some patients were not benefited. However, good results were reported in many patients with acute and chronic bronchitis, pharyngitis and sinusitis which had failed to respond to pencillin administered intramuscularly.

In patients with laryngitis and tracheitis, relief from hoarseness, cough and inability to raise phlegm was usually obtained in 1 to 10 treatments.

Penicillin aerosol proved of benefit only in the infectious type of asthma.

Acute sinobronchitis was relieved after 1 to 5 treatments of 100,000 units of penicillin each. Chronic cases required longer treatment; the chief benefits in these cases were clearing of the head and thinning or elimination of secretions.

Aerosol therapy was not effective in nasal allergy due to pollens or dust, but was of benefit in some cases complicated by infection.

Acute colds of the head or chest were sometimes aborted by 1 or 2 inhalations. The ordinary sore throat or acute pharyngitis was usually completely relieved after 3 or 4 treatments.

The author emphasizes that ambulatory treatment with penicillin aerosol is frequently inadequate. Patients with acute follicular tonsillitis were treated with a single inhalation of penicillin, then were sent to bed and treated with sulfadiazine by mouth or intramuscular injection of penicillin-beeswax-peanut oil. A patient who failed to respond to 4 daily inhalations of 100,000 units of penicillin each was later found to have virus pneumonia. The author recommends that patients with fever persisting after the first inhalation be sent to an internist for a thorough check-up.

Delario, A. J., and Phelps, J. E.: **Cold Autohemagglutination and Hemolytic Anemia Occurring in Primary Bronchopneumonia of the "Virus" Type,** *Mississippi Valley M. J. 69:137 (Oct.) 1947.*

A case of atypical or so-called virus pneumonia in which autohemagglutination and hemolytic anemia occurred and which responded only to "huge" doses of penicillin is reported.

The authors state that autohemagglutination and hemolysis occur occasionally in patients with pneumonia of unknown etiology or of the virus type, not in cases of pneumococcus pneumonia. An increase in the pulse rate appears to be the first indication of impending hemolysis. When this occurs large doses of penicillin should be given immediately before hemolysis occurs.

In the case reported, x-ray findings on admission to the hospital suggested atypical or virus pneumonia. Sputum analysis showed only streptococci. Blood count showed Hb. 86, W.B.C. 9,100. Urinalysis revealed no blood corpuscles, crystals or casts. Neither sulfadiazine nor penicillin in doses of 40,000 units 3-hourly had any effect on the temperature or cough.

On the 2nd hospital day the pulse rate increased from 90 to 130. On the 3rd hospital day laboratory studies showed Hb. 62, W.B.C. 28,200, and occasional blood and epithelial cells and granular casts in the urine. Penicillin dosage was increased to one-half million units intravenously and 40,000 units intramuscularly every 2 hours.

On the 5th day the urine showed occult blood and hemolysis was demonstrated by the prothrombin time, platelet count, coagulation and bleeding time and fragility test. At this time it was reported that blood from suitable donors was agglutinated by the patient's serum. Cold agglutinations were positive in dilutions to 1:5,000. It was then felt that this was a virus infection and penicillin was discontinued on the 7th day.

Temperature declined to 99.5 to 100.5 and pulse rate to 80 to 90. 8 blood transfusions were given. The hemoglobin increased to 92, W.B.C. decreased to 14,200, the urine showed no blood cells or casts. Cold agglutination remained at 1:5,000.

On the 10th day, the pulse rate increased to 120 without an increase in temperature. On the 14th day temperature increased to 103 and evidences of hemolysis were again present. Sputum culture showed hemolytic streptococci, hemolytic Staph. aureus and Hemophilus influenzae. Chest x-ray revealed an increase of the virus type of pneumonia.

Penicillin therapy was reinstated — one-half million units intravenously and 40,000 units intramuscularly every 2 hours. Supportive therapy included daily blood transfusions and oxygen. After 6 days the temperature dropped to 99.5 and within 2 days (24th day) was normal. Penicillin was continued for 9 days after temperature had become normal. The cold agglutination test 3 days after temperature became normal was 1:64 and 11 days after was 1:32.

Chest x-ray revealed an increased area of density suggestive of beginning empyema at the time temperature became normal, but this area decreased in size during penicillin therapy. The authors state the belief that the large doses of penicillin prevented the development of empyema.

From observations in this case the authors suggest that all patients with "virus" pneumonia showing autohemagglutination and hemolysis be given "huge doses of penicillin."

Fishman, A. E., and Gelehrter, J.: **Penicillin Inhalation Therapy in Respiratory Infections; a New Efficient Ambulatory Method,** *M. Rec. 160:595 (Oct.) 1947.*

Treatment of respiratory infections by means of inhalation of a penicillin mist produced by a hand compressed nebulizer is described. The solution for inhalation is prepared by dissolving a tablet containing 50,000 units of crys-

talline penicillin G in 1 cc. of tap water. Illustrative case reports are given.

According to the authors, this method requires no elaborate equipment and permits ambulatory treatment. It is emphasized that it is not suitable for weak or debilitated patients, in acute generalized infections, or when there are mechanical obstructions in the respiratory tract. In such cases, penicillin administered by injection is preferable.

Penicillin is administered by inhalation primarily as topical therapy, although it has been demonstrated that adequate blood levels may sometimes be attained by this method.

In preliminary studies, x-rays taken after inhalation of a mist of a 10% solution of potassium iodide, which produces particles ranging in size from 2.5 to 5 microns, demonstrated that particles of this size penetrate into the bronchopulmonary tract. From this it is concluded that the mist produced by nebulization of the penicillin tablet in water, with particles ranging in size from 2 to 3 microns, penetrates to the same depth.

50 patients with bronchiectasis, bronchial asthma with secondary bacterial infection, asthmatic bronchitis due to bacterial allergy, sinobronchitis, or chronic or acute sinusitis were treated by penicillin mist inhalations every 3 to 4 waking hours. 76% (38 patients) experienced "marked relief," 16% "moderate to good relief" and 8% "fair or no relief."

Discontinuance of treatment was necessitated in 3 patients because of burning and swelling of the tissues of the oral cavity, or nasal irritation. It is suggested that local reactions may be minimized by rinsing the mouth with water after each inhalation.

The authors emphasize that penicillin inhalations are useful only for controlling infection due to penicillin sensitive organisms. Cure of allergies cannot be expected. However, after infection has been controlled, the allergic condition responds to treatment more satisfactorily.

Reich, N. E.; Ciaiolo, L. F., and Reinhart, J. B.: **Primary Atypical Pneumonia: The Diagnosis and Treatment of 440 Consecutive Cases Without a Fatality,** *Am. Practitioner 2:85 (Oct.) 1947.*

An analysis is presented of 440 consecutive cases of primary atypical pneumonia with no fatalities which occurred in the armed forces during the period June 1943 to June 1946. Illustrative case reports are given.

The authors state that in the armed forces, it seemed that primary atypical pneumonia occurred more frequently than all other forms of pneumonia combined. A prodromal stage of 15 hours to 14 days, average 4 days, occurred in almost all cases. Symptoms were similar to those of an upper respiratory infection. The most important diagnostic aid proved to be serial roentgenographic studies.

98 cases were treated symptomatically. 342 patients received specific therapy, 262 sulfonamides, 62 penicillin, and 18 both combined. The authors state that penicillin appeared to be slightly more effective than the sulfonamides as indicated by a shortening of the convalescent period by 5 days.

It is concluded that specific therapy is necessary only in cases showing evidence of progressive or massive pulmonary involvement, suggesting secondary bacterial invasion, or signs of severe toxemia, dyspnea and cyanosis. It is emphasized that penicillin or sulfonamides be given in adequate dosage. Combined therapy is considered unnecessary except in severely ill patients. Whole blood transfusions from convalescent patients are thought to be of value in dangerously ill patients.

Stevenson, I. P.: **Bronchial Lavage for Bronchiectasis; a Preliminary Report of a Simplified Technique,** *Am. Rev. Tuberc. 56:279 (Oct.) 1947.*

A simplified technic of bronchial lavage followed by direct instillation of penicillin solution into the lungs is recommended for the treatment of bronchiectasis. 3 illustrative case reports are given.

The procedure consists briefly of anesthetizing the posterior pharynx and larynx with a weak solution of pontocaine administered by spray; lavage with Bledsoe-Fischer solution (20 to 30 cc.) which is allowed to run into the larynx through a tracheal cannula (the fluid can be directed to affected bronchi by posturing); 20,000 units of penicillin in 20 to 30 cc. Bledsoe-Fischer solution administered in the same manner.

The author states that the solution should be retained as long as is possible comfortably, but that the cough reflex should not be repressed. The 20,000 unit concentration is considered adequate; stronger solutions may foam and may be irritating to the bronchi.

The author states that treatments should be given by the physician at first, but that later the patient can administer them himself. Treatments can also be spaced at longer intervals and the amount of fluid for each treatment can be reduced.

The procedure is not recommended for patients who have had recent acute respiratory infections or pulmonary hemorrhages. The author states that "it provides the best possible preparation for lobectomy and is far superior to penicillin inhalations alone." It may also be applicable to cases of pulmonary abscess and chronic purulent bronchitis.

Veach, O. L.: **Aerosol Treatment with Penicillin and Streptomycin,** *Rocky Mountain M. J. 44:816 (Oct.) 1947.*

That penicillin aerosol alone or combined with streptomycin aerosol is of definite value in respiratory infections is the author's conclusion from a brief review of the literature and his own experience.

He states that since January 1947 he has treated 77 cases with 498 treatments, the number of treatments per patient ranging from 3 to 40 or 50.

Patients with bronchitis, tracheobronchitis, and laryngitis following influenza or pneumonia were completely relieved; those with acute sinusitis were markedly benefited, while those with chronic infections experienced little or no improvement. In cases of bronchiectasis there was reduction of sputum and eventual cure in most instances. Cure is not to be expected in cases due to tuberculosis or those showing large saccular formation in the lung.

Several cases of nontuberculous chronic bronchitis and bronchiectasis were treated with combined penicillin-streptomycin aerosol, with sputum reduced to one-fourth the original amount after 1 week.

Dosage recommended is 25,000 to 50,000 units of penicillin and 1 to 2 Gm. of streptomycin, alone or combined, 1 to 5 times per 24 hours. In cases of asthma with bronchospasm, inhalation of 0.5 cc. of 25% neosynephrin solution prior to or together with the penicillin is suggested. Aminophyllin may also be added to the solution for nebulization. In cases of acute sinusitis with congestion of the nasal mucosa, 5 to 10 drops of tuamine or other decongestant may be added.

Miscellaneous Infections

Friedmann, I., and Por, F.: **Acute Interstitial Polymyositis Treated with Penicillin,** *Brit. M. J. 2:494 (Sept. 27) 1947.*

Penicillin therapy altered the course of the disease "from a moribund state to complete recovery" in a case of acute interstitial polymyositis reported from Czechoslovakia.

The authors point out that this disease is comparatively rare and usually terminates fatally.

In the case reported, the patient was a 42 year old woman who was admitted to the hospital on the 5th day of illness, weak and perspiring, and with the limbs swollen and painful, and the muscles (including abdominal recti) enlarged and lumpy. That evening temperature was 102 F.

Treatment with novurit, vitamin B, neosalvarsan and theobromine-caffeine was ineffective.

A diagnosis of trichiniasis was entertained when the patient recalled having eaten pork before becoming ill. A bi-

opsy specimen was taken from the right sternocleidomastoid. Histologic examination revealed the normal muscle tissue largely replaced by a cellular inflammatory filtrate consisting mainly of leukocytes and many eosinophils, and muscle fibers were widely separated. No trichinae were found. Diagnosis was acute interstitial eosinophilic polymyositis.

The patient's condition at this time, the 21st day of illness, was considered hopeless, but penicillin was started—15,000 units intramuscularly every 3 hours to a total of 1,500,000 units.

On the 6th day of treatment temperature became normal and the patient's general condition showed improvement. She was discharged on the 30th hospital day.

A biopsy taken before discharge showed that the inflammatory filtrate was almost gone and muscle fibers appeared normal.

Thomson, J.; Bruce, L. M., and Green, M. G.: **H. Influenzae Meningitis in Relation to Treatment; a Clinical Study of Four Cases,** *Brit. M. J. 2:414 (Sept. 13) 1947.*

4 cases of H. influenzae meningitis treated with combined penicillin-sulfonamide therapy are reported. 3 of the patients recovered, the 4th died of bronchopneumonia complicating measles after the cerebrospinal fluid showed improvement.

Early and adequate treatment of H. influenzae meningitis is stressed.

Penicillin sensitivity tests and cerebrospinal fluid concentrations were determined in all but 1 case; however, no correlation was found between these results and the clinical response. Determination of the sensitivity of the organism to several sulfonamides is advised, and administration of 2 sulfonamides simultaneously, in full dosage, is recommended.

Intrathecal administration of 50,000 units of penicillin once daily until temperature has been normal for 7 days is recommended. Administration once daily is advised to minimize trauma from injection. Lumbar and cisternal puncture was used alternately to reduce trauma. In resistant cases where the fontanel is still patent, ventricular puncture is suggested. In 1 case in which cerebrospinal fluid block occurred, air and heparin were injected intrathecally. Preceding the injection by chloral hydrate orally or intramuscularly proved of benefit in reducing reactions.

Intramuscular penicillin concurrently with intrathecal administration and sulfonamides was used in these cases and is recommended—initially in aqueous solution at 4-hour intervals, replaced with an oil-wax suspension as recovery occurs.

Wilen, C. J. W., and Poole, P. P.: **Digestive Diseases Observed in a General Hospital in the Mediterranean Theater,** *Gastroenterology 9:253 (Sept.) 1947.*

The gastrointestinal conditions observed in a general hospital in the Mediterranean Theater are discussed.

From results in 6 patients, the authors conclude that penicillin is not an effective amebacide.

No improvement in the appearance of the ulcers was noted in 3 patients with typical amebic ulceration of the lower bowel who were treated with 1 million units of penicillin in 5 days. Active trophozoites were present in the ulcers during a period of 9 days. Diarrhea was lessened, attributed to bed rest.

3 patients with wounds, who had been treated with more than a million units of penicillin, experienced an exacerbation of chronic amebic dysentery within 2 weeks after the administration of penicillin.

Goerner, J. R.; Massell, B. F., and Jones, T. D.: **Use of Penicillin in the Treatment of Carriers of Beta-Hemolytic Streptococci among Patients with Rheumatic Fever,** *New England J. Med. 237:576 (Oct. 16) 1947.*

An investigation was made of the effectiveness of penicillin in controlling the beta-hemolytic streptococcic carrier state.

Since 2 instances of transmission of hemolytic streptococci from a chronic carrier to patients with rheumatic fever occurred at the House of the Good Samaritan in 1945, routine throat cultures were done in all patients. Those showing positive cultures were treated with penicillin. All persons with acute streptococcic infections were also treated as soon as diagnosis was made.

Penicillin dosage was the same for both groups—10,000 units intramuscularly every 2 hours to a total of 1,200,000 units in 10 days.

In 17 of 20 cases, beta-hemolytic streptococci were eliminated from throat cultures during posttreatment periods ranging from 20 to 146 days. In 15 of the 17 successfully treated cases, organisms belonged to group A. In 2 cases, throat cultures again became positive, but with different organisms.

In chronic carriers treated with penicillin, the antistreptolysin O titer was unaltered. In 2 cases of acute streptococcic infection treated promptly with penicillin, there was no rise in antistreptolysin titer, whereas in an untreated case the titer rose coincidentally with the development of symptoms of rheumatic fever.

Tonsillectomy was performed with penicillin prophylaxis in 5 of the treated cases at intervals of 25 to 185 days after treatment. Cultures of the throat, tonsillar fossae and sectioned tonsils showed no hemolytic streptococci.

At the Wellesley Convalescent Home, 6 patients with positive throat cultures were treated with penicillin in beeswax-peanut oil—a single injection of 150,000 units daily for 10 days. Throat cultures remained negative in 5 cases during the observation period (about 1 month).

Rubenstein, A. D.; Drew, D. W., and Law, A. G.: **Psittacosis; Report of an Outbreak,** *Am.J.M.Sc. 214:389 (Oct.) 1947.*

2 cases of psittacosis which occurred in Massachusetts during April and May are reported. Both patients had been in contact with sick parakeets. In addition, there were two contacts without clinical evidence of disease and 1 contact with an illness suggesting psittacosis.

In the 2 cases reported, diagnosis was based on the history, physical and x-ray findings, and the complement fixation test. Both patients recovered. Case 1 was treated with penicillin, begun on the 3rd hospital day—300,000 units in beeswax and peanut oil daily for 7 days. Temperature dropped to normal by lysis within 4 days. The patient was discharged on the 12th day. Case 2 was treated symptomatically only. The patient was discharged on the 11th hospital day.

PEDIATRICS

Sorsby, A.: **Penicillin Therapy in Ophthalmia Neonatorum,** *Brit. M. J. 2:322 (Aug. 30) 1947.*

That penicillin administered by intensive local application or massive systemic injections is a satisfactory treatment for ophthalmia neonatorum is concluded from an analysis of results in a series of 224 cases.

30 cases were treated with drops of aqueous solution, 2,500 U./ml. administered at 5-minute intervals, with clinical cure in 73% obtained in 15 minutes to 115 hours, average 24 hours, and with a total treatment period of 60 hours.

71 cases were treated with drops of the same concentration at 1-minute intervals for ½ hour followed by applications at longer intervals. Primary cure was obtained in 73% with a total treatment time of 6 to 96 hours, average 33 hours.

33 cases were treated with drops of an aqueous solution of crystalline penicillin in a concentration of 10,000 U./ml. instilled at 1-minute intervals. Cure was effected in 76% in 20 to 72 hours, average 48 hours.

In an attempt to diminish the frequency of penicillin instillations, penicillin incorporated in vehicles other than water was applied locally in 51 cases (lamellae in 14 cases, ointment in 5, oily suspension in 13, and methyl cellulose solution in 12). Results were unsatisfactory. The methyl cellulose solution proved irritating; however, it is stated that this vehicle might be de-

veloped to modify the 1-minute treatment with aqueous drops. 39 cases were treated with systemic penicillin—4 intramuscular injections of 200,000 units in 0.5 ml. water at 3-hour intervals—followed by penicillin drops (10,000 U./ml. in 1% methyl cellulose solution) at 2-hour intervals. Primary cure was obtained in 84.6% in 6 to 120 hours, average 46 hours.

An analysis of results in relation to the causal organism revealed that of the 30 cases treated with drops of commercial penicillin, 2,500 U./ml., 3 of the 4 failures showed inclusion bodies, while the 2 cases showing diphtheroids relapsed. Of the 25 failures with drops at 1-minute intervals, 11 showed inclusion bodies and 6 diphtheroids. An increase in the concentration of penicillin decreased the failure rate with inclusion bodies, but not with diphtheroids. With systemic penicillin, there was an unsatisfactory response in 1 of 5 cases with diphtheroids and 3 of 17 with inclusion bodies.

Lehrfeld, L.: **Prophylaxis Against Ophthalmia Neonatorum,** *Correspondence, J.A.M.A. 135:306 (Oct. 4) 1947.*

In a letter to the editor, the author points out that prevention of ophthalmia neonatorum should be directed to the treatment of the infected expectant mother with penicillin rather than local treatment of the eyes of the infant.

The author states that the efficacy of silver nitrate instillations lies only in the mechanical flushing of the eyes.

The author says that although complete sterilization of the birth canal probably cannot be accomplished, partial sterilization can be achieved by the use of penicillin vaginal suppositories or by a parenteral dose of 300,000 units in oil 24 hours before delivery. According to the author, the gonococcus is the only etiologic organism of ophthalmia neonatorum which causes damage. Should an occasional case of gonorrheal ophthalmia develop in the newborn, it can be cured within a few days without resultant damage to the eye.

Gottfried, S. P.; Steinman, J. F., and Kramer, B.: **Chemical Studies in Children with the Nephrotic Syndrome,** *Am. J. Dis. Child. 74:283 (Sept.) 1947.*

That "penicillin therapy has played a major part in reducing the fatality rate in this disease by decreasing the number of infectious complications which were chiefly responsible for deaths in the past" is concluded from an analysis of the data from 10 cases of the nephrotic syndrome in children studied over a period of 2 years.

Nephrosis is defined as "a disorder in which albuminuria, hypoproteinemia and edema are the dominant clinical features, but without evidence of progressive renal insufficiency."

Patients ranged in age from 16 months to 5 years. Data concerning the chemical composition of the blood, the clinical course, and the response to therapy are reported.

Penicillin was administered in all cases to control upper respiratory infection, to treat complicating pneumonia, cellulitis, urinary infections and unexplained fever, and prophylactically before and after paracentesis.

The authors state that there was no instance of pneumococcic peritonitis or bacteremia in the series and that all cultures of the blood and ascitic fluid were sterile. Staph. aureus and nonhemolytic streptococci predominated in nose and throat cultures, while pneumococci were rare.

Beach, M. W., and Ravenel, B. O.: **A Discussion of the Common Meningitides and Their Treatment,** *South. M. J. 40:813 (Oct.) 1947.*

The diagnosis and treatment of the more common types of pyogenic meningitis occurring in children are discussed. These are listed as tuberculous, meningococcic, pneumococcic and influenzal meningitis. Data from the charts of 201 patients with pneumococcic, meningococcic and influenzal meningitis admitted to the Roper Hospital from 1935 through August 1946 are tabulated and discussed.

The authors stress that intelligent treatment of meningitis requires determination of the causative organism by lumbar puncture and examination of the cerebrospinal fluid.

In all cases of meningitis, if spinal tap produces hazy or cloudy fluid, 20- to 25,000 units of penicillin diluted with cerebrospinal fluid is injected into the subdural space, and intensive intravenous sulfadiazine therapy is instituted (2 gr./lb. body weight). Supportive therapy is emphasized.

If tuberculous meningitis is diagnosed, only symptomatic treatment is available at present, but it is suggested that streptomycin may be helpful.

In meningococcic meningitis, sulfonamides are effective. Sulfadiazine is preferred. Combined sulfonamide—penicillin may be used. Penicillin dosage recommended is 20- to 30,000 units intramuscularly every 3 hours and 20- to 25,000 units intrathecally daily.

In pneumococcic meningitis combined penicillin-sulfonamide therapy is the treatment of choice. Type specific serum may be helpful in some cases.

In influenzal meningitis combined sulfonamide-rabbit serum therapy is the treatment of choice. Streptomycin promises to be of benefit.

Congress of French-Speaking Pediatricians, *Foreign Letters, J.A.M.A. 135:303 (Oct. 4) 1947.*

At a meeting of French-speaking pediatricians held in Lyon, Drs. Martin, Sureau and Milet reported that sulfonamide treatment of meningococci meningitis in children resulted in 92% of recoveries. Combined penicillin-sulfonamide therapy was used in recurrent cases and in nurslings. These observations were confirmed by R. Clement's observations in 50 cases of acute meningitis, half treated with sulfonamides alone and half with sulfonamides and penicillin. Early intraventricular injection of penicillin was recommended by Dr. Clement and Drs. Lelong, Joseph, Rosier and Alison.

That pneumococcic meningitis still has a 50% mortality in spite of penicillin-sulfonamide therapy was concluded from observations by Drs. Marquezy and Boeswilwald in 19 cases. Early treatment is emphasized, with intraventricular injection of 20,000 units of penicillin twice daily, in nurslings.

DERMATOLOGY

Gutch, C. F.: **Local Penicillin Therapy for Tropical Ulcer,** *U.S. Nav. M. Bull. 47:801 (Sept.-Oct.) 1947.*

Topical application of dry penicillin crystals proved effective in the treatment of tropical ulcer (phagedenic ulcer) in Chinese coolies in Szechwan Province.

The chief etiologic factors in tropical ulcer appear to be filth, trauma, malnutrition and fusospirillosis. Smears from the ulcers in this series revealed Vincent-like organisms and various cocci and bacillary organisms.

All ulcers were first cleansed with soap and water, followed by irrigation with hydrogen peroxide and normal saline, and removal of necrotic tissue. In some cases a dry pressure dressing was applied. Others were treated with local application of sulfanilamide powder. The latter treatment resulted in beginning epithelization in some instances in 7 to 10 days.

35 ulcers were treated with topical application of penicillin crystals (100,000 to 200,000 units) sprinkled on the wound, which was then covered with vaseline-impregnated gauze. The ulcers appeared clean and peripheral induration was diminished in 24 to 72 hours in all but 3 cases. In these the same effects were observed in 5 to 6 days. Small ulcers healed rapidly.

A case report is presented of a large ulcer of more than a month's duration, which showed beginning epithelization after 9 days' treatment, and showed complete epithelization within 3 weeks after pinch grafts were placed on the granulations.

Barnard, R. D.: **Marrow Aplasia and Estrapenia in Pemphigus Vulgaris; Case Report with Autopsy Findings and Notes on Relationship of Erythroid Marrow Function to Atopic-Exudative Skin Lesions,** *Urol. & Cutan. Rev. 51:586 (Oct.) 1947.*

In order to clarify the pathodynamics of pemphigus, a report is presented of

a case in which autopsy findings revealed marrow aplasia and estrapenia.

It is suggested that the manifestations of pemphigus may be due to erythroid marrow depression, failure of cholinesterase synthesis and cholinergic intoxication, and that fatal pemphigus may be classified as an atopic-exudative shock state.

Suggested therapy includes blood transfusion, penicillin, arsenic, and a trial of the antihistaminics benadryl and pyribenzamine, which are reputed to have an anticholinergic action.

The beneficial effects of penicillin are attributed to checking potential infection, sterilization of contactual flora, or reducing the nonspecific bacterial antigens that contribute to the cholinergic state.

The author states that penicillin should preferably be administered by mouth to avoid injections, and that therapy should be instituted cautiously as penicillin itself may elicit atopic reactions in atopic reactors.

Miller, J. L.; Rodriquez, J. J., and Domonkos, A. N.: **Evaluation of Penicillin in Topical Therapy,** *New York State J. Med. 47:2316 (Nov. 1) 1947.*

An evaluation of topical penicillin therapy was made in 250 patients treated locally with ointments containing penicillin (500, 1,000 or 2,000 U./Gm.) alone or combined with 10% sulfadiazine or sulfathiazole, furacin, a sulfur suspension, or bacitracin. Results in 173 patients followed sufficiently long are analyzed.

Cultures were made in all cases and the sensitivity of the organism to penicillin was tested. The necessity for removing crusts in superficial pyodermas by means of hot compresses of boric acid is emphasized.

Results with penicillin ointment were as follows:

Impetigo—91 cases followed adequately; cure in all but 2 patients who became sensitized to penicillin. Median time for cure was 6 days with ointments containing 500 or 1,000 U./Gm., and 5 days with ointments containing 2,000 U./Gm. or 1,000 units plus 10% sulfadiazine or sulfathiazole. Staphylococci were found in pure culture in 74% of cases.

Ecthyma—14 cases (7 treated with penicillin plus sulfonamide). Median time for cure, 6 days. Staphylococci in pure culture in 74%. All cases with mixed cultures were resistant to penicillin.

Folliculitis and sycosis vulgaris—Differential diagnosis based on duration of infection. 4 of 5 failures were in cases of more than 8 months' duration, the 5th in a patient who became sensitized to penicillin. Staph. aureus hemolyticus predominated.

Dermatoses with secondary infection—10 patients. Penicillin ointment of "outstanding value in clearing the secondary infection, but of no value against the primary dermatosis." Treatment failure occurred in 20%. Sensitization to penicillin occurred in 10% of patients, all with seborrheic dermatitis.

The authors conclude that penicillin ointment is of value in impetigo, ecthyma, and folliculitis, but not in true sycosis vulgaris. A concentration of 500 U./Gm. is considered adequate and less likely to cause sensitization than higher concentrations. The combination of sulfonamides with penicillin did not increase the efficacy of the latter and is not recommended because of the danger of sensitization.

46 patients were treated with furacin. Median time of cure in 16 cases of impetigo was 8 days, in secondary infections in hypostatic ulcers of the extremities, 7 days. 5% of patients developed sensitization.

Sulfur in suspension, used in a small series of patients, appeared of value in seborrheic dermatitis.

Bacitracin ointment, used in a few cases, appeared effective in superficial pyogenic infections.

VENEREAL DISEASE

Long, F.: **Some Evaluations of the Present Treatment of Syphilis and Gonorrhea,** *Nebraska M. J. 32:410 (Oct.) 1947.*

A brief evaluation of penicillin treatment of gonorrhea and syphilis is presented.

The author states that penicillin is the only known drug that is effective against both syphilis and gonorrhea. In gonorrhea 85 to 94% cures with one course of treatment have been reported. Since treatment of gonorrhea with penicillin may delay symptoms of a simultaneous syphilitic infection, tests for syphilis several months after treatment are advised.

In the treatment of syphilis, penicillin is superior to arseno-bismuth therapy because it is nontoxic and treatment is completed within a short time. Although optimum time-dose relationships have not as yet been definitely determined, present evidence suggests that a low blood level over a considerable period of time is desirable.

Penicillin has proved effective in primary and secondary syphilis, syphilis of pregnancy, and in certain forms of neurosyphilis. In congenital syphilis results have been proportional to the age at which treatment was given. In early syphilis, penicillin alone appears to be as effective as when combined with arseno-bismuth therapy.

The author points out that the serologic response following penicillin therapy is similar to that following arseno-bismuth therapy.

Gonorrhea

Lawler, A. L.: **Penicillin in the Treatment of Gonococcus Infection Urethra; Report of Three Hundred Cases,** *U.S. Nav. M. Bull. 47:796 (Sept.-Oct.) 1947.*

299 of 300 cases of gonococcus infection urethra which occurred on a United States cruiser during a 14-month period were successfully treated with penicillin.

The first 25 admissions followed contact exposure in the United States. All were successfully treated with 200,000 units given in doses of 20,000 units 3-hourly, followed by sulfadiazine (1 Gm. 4-hourly) for 5 days.

86 admissions followed contact exposure in Britain and the Mediterranean area. Most patients were not cured with the 200,000-unit dosage. All but 2 were successfully retreated with 400,000 units of penicillin, followed by 5 days' sulfonamide therapy. The 2 failures were successfully retreated with 400,000 units penicillin, sulfonamide therapy, and 3 anterior urethral instillations of penicillin.

178 admissions followed contact exposure in the China area. As a dosage of 200,000 units of penicillin was found inadequate, a routine dosage of 400,000 units followed by 5 days' sulfonamide therapy was adopted. There were 9 readmissions (4 had been inadequately treated with 200,000 units of penicillin). All but 1 were successfully retreated with additional penicillin and anterior urethral instillations.

The case report of the only treatment failure is presented. Pain and stiffness in the joints and an erythematous skin manifestation occurred during treatment. The gonococcic urethritis was not eliminated by a total dosage of 1,400,000 units of penicillin.

From the results in this series, the author recommends for the treatment of gonococcus infection urethra 4 intramuscular injections of penicillin of 100,000 units each at 4-hour intervals, followed by 5 days' sulfadiazine therapy.

Parkhurst, G. E.; Harb, F. W., and Cannefax, G. R.: **"Penicillin-Resistant Gonorrhea" *vs.* "Nonspecific Urethritis,"** *J. Ven. Dis. Inform. 28:211 (Oct.) 1947.*

That so-called "penicillin resistant gonorrhea" is in reality "nonspecific urethritis" is concluded from observations made at the Hot Springs Medical Center in the treatment of 2,821 cases of culturally diagnosed and bacteriologically cured gonorrhea and 226 cases of "nonspecific" urethritis.

The use of the spread method of diagnosis is believed responsible for many mistaken diagnoses. An established culture method should be used and the organisms should be subjected to penicillin tolerance tests before a diagnosis of penicillin resistant gonorrhea is made.

The authors state, "We have never observed strains of gonococci refractory to intensive penicillin therapy."

Bacteriologic cure is not always obtained with routine therapy—a single injection of 300,000 units penicillin in 1 ml. peanut oil containing 4.8% beeswax. 2 or 3 injections at 24-hour intervals may be required.

Since January 1947, patients with purulent discharge persisting after the initial injection of penicillin have been retreated with 2 additional injections. If the discharge persists, 3 irrigations daily with penicillin solution (1,000 U./ml.) are given for 2 days, and if the discharge still persists irrigations with streptomycin solution (1:1,000) are used. Except for a few cases of Reiter's disease and upper urogenital tract infections, there were no failures with this regimen. The cases of Reiter's disease responded to typhoid fever therapy.

Syphilis

Wammock, V. S.: **The Practical Application of Penicillin in the Treatment of Syphilis,** *J. Am. M. Women's A. 2:425 (Oct.) 1947.*

A comprehensive review of the penicillin treatment of syphilis is presented.

That penicillin is "an effective, nontoxic therapeutic agent in the treatment of early and late syphilis" is the author's conclusion from a review of the literature. She cautions that the principles of syphilis therapy apply to penicillin as well as to arsenicals and heavy metals. It is emphasized that for effective antisyphilitic therapy, the penicillin used should contain a large portion of the G fraction.

The preferred method of administering penicillin for syphilotherapy, at present, is hospitalization and intramuscular injection of the drug at intervals of 2 to 3 hours. Various methods of delaying absorption of penicillin to permit ambulatory treatment have been advocated. The intramuscular administration of penicillin in oil and beeswax appears to be the most promising.

Toxic reactions to penicillin therapy are usually minor. The most common are pain at the site of intramuscular injection, urticaria, and Jarisch-Herxheimer reactions. Injections appear to be less painful with purified crystalline G than with commercial penicillin preparations. The Herxheimer reaction is of little significance in early syphilis, but may be severe in pregnant women, and in infantile congenital syphilis and neurosyphilis. It may be avoided by the use of small initial doses of penicillin.

Recommended dosages for treatment of the various types of syphilis, in the light of present knowledge are as follows:

Early syphilis—Not less than 2,400,000 units (unless combined with arsenical or fever) given in divided doses at intervals of not more than 3 hours. The advisability of adding either arsenical or fever is controversial. Clinical and serologic follow-up for 3 years, with spinal fluid examination between the 6th and 12th months after treatment is recommended.

Syphilis in pregnancy—2,400,000 units in aqueous solution in divided doses at intervals of 2 to 3 hours for 7½ days. Retreatment with penicillin before delivery is suggested if clinical or serologic relapse occurs or if the serologic titer does not decline within 3 to 4 months after treatment. Monthly serologic tests of the infant to the age of 6 months is advised.

Congenital syphilis—100,000 U./Kg. given in 120 injections over a period of 15 days. Results in late congenital syphilis have been disappointing.

Latent syphilis—Same dosage as for early syphilis followed by 20 to 30 weeks of bismuth. Serologic reversal in cases serofast after arsenical and heavy metal therapy unlikely.

Late syphilis—Cutaneous, osseous and visceral lesions respond well. In cardiovascular syphilis therapeutic shock may prove hazardous.

Neurosyphilis—Results excellent in types involving primarily the meninges (asymptomatic neurosyphilis, acute syphilitic meningitis, late diffuse meningovascular neurosyphilis). Recommended dosage is 4 to 10 million units given in divided doses at 2-hour intervals for 10 to 20 days. Combined malaria therapy is suggested for paresis, taboparesis, tabes dorsalis and primary optic atrophy.

Early Syphilis

Bundesen, H. N.; Loewe, L.; Craig, R. M.; Schwemlein, G. X.; Barton, R. L., and Bauer, T. J.: **Therapy of Early Syphilis with Massive Doses of Penicillin,** *Arch. Dermat. & Syph. 56:339 (Sept.) 1947.*

That intravenous administration of massive doses of penicillin (10 million units) during a 24-hour period is unsuitable for the treatment of early syphilis is concluded from the results of the study reported.

129 patients with darkfield positive primary or secondary syphilis received 10 million units by intravenous drip during a period of 24 hours. Heparin in Pitkin menstruum was injected subcutaneously in an attempt to prevent thrombophlebitis. 119 patients had received no previous antisyphilitic therapy. 10 had proved refractory to arsenobismuth therapy. Patients were observed for periods of 7 to 11 months after treatment.

36 patients were lost to observation; all were seronegative when last examined.

61 patients were treatment failures. 51 of these relapsed in 4 months or less.

32 patients were clinically negative at 7 months after treatment. 8 were seropositive and 24 seronegative.

Kalz, F., and Dean, B.: **An Evaluation of Various Forms of Therapy in Early Syphilis,** *Canad. M.A.J. 57:221 (Sept.) 1947.*

An analysis was made at the Royal Victoria Hospital, Montreal, of the efficacy and safety of various types of therapy in early syphilis. Results are tabulated.

401 cases were treated between 1937 and 1946 with some form of arsenical. Serologic results are reported in 241 patients followed until reactions became negative, and treatment reactions in 243 patients.

Reactions occurred in about 30% of patients treated with mapharsen, but these were usually minor if the drug was not given more than 3 times weekly. Reactions with neoarsphenamine were more severe. The 5-day massive arsenotherapy method is considered obsolete because of the danger of encephalopathy.

The average time for complete seronegativity was 22 weeks with arsenoxide twice weekly, 23 weeks with massive arsenotherapy, and 29 to 43 weeks with the other arsenicals. No treatment failures occurred with arsenoxide twice weekly. There were 75% failures with massive arsenotherapy and 68 to 85% with other treatment schemes.

48 patients were treated with penicillin in total dosages of 1,200,000 to 10,000,000 units. In most cases therapy was combined with 300 mg. arsenoxide and 0.6 mg. bismuth subsalicylate.

The average time for seronegativity in 26 patients was 29 weeks. In 23 patients observed for 12 to 22 months, there were 4 failures (approx. 17%).

Aiken, R. B.: **Two Reports on Out-Patient Attendance for Treatment of Syphilis, Using Penicillin in Oil-Beeswax; II. Attendance Record of Patients Treated by Private Physicians,** *J. Ven. Dis. Inform. 28:224 (Oct.) 1947.*

A study was made by the Vermont Department of Public Health to determine whether patients with early syphilis being treated with penicillin in beeswax-peanut oil by private physicians would complete treatment.

The treatment schedule called for a total dosage of 4,800,000 units—a single injection of 600,000 units daily for 8 successive days.

101 patients were treated by 45 physicians. 70 patients (81.4%) completed treatment as outlined. 15 patients (17.4%) completed treatment in 9 to 11 days. Only 1 patient (1.2%) failed to complete treatment.

Glaser, R. J., and Scott, V.: **Destructive Osseous Lesions in Early Syphilis; Response Following Penicillin Therapy,** *Am. J. Med. 3:496 (Oct.) 1947.*

A case report is presented of destructive osseous lesions of the skull in

early syphilis which healed completely within a 7 month period following penicillin therapy.

The authors point out that destructive lesions of the bones are rare in early syphilis. Complete healing following prolonged treatment with arsenicals and bismuth has been demonstrated. Only 1 case treated with penicillin has been reported.

The patient in the case reported was a 23 year old white woman who was complaining of headaches of 6 weeks' duration. About 3½ months before admission the patient had bumped her head in the left occipitoparietal region. Headaches had begun about 6 weeks later. There was a history of penicillin therapy for a gonorrheal infection about 2½ months before admission. About 6 weeks before admission 3 skin lesions appeared. The patient stated that the serologic test for syphilis had been negative 4½ months prior to admission.

Physical examination revealed a hard tender mass over the left occipitoparietal region. Darkfield examination of serum from a lesion on the arm showed T. pallidum. Blood Kahn titer was 120. X-ray of the skull showed areas of bone destruction in the parietal and frontal bones.

Penicillin was administered intramuscularly in doses of 50,000 units every 2 hours to a total of 4.8 million units in 7.5 days.

Bone pain and tenderness were improved within 48 hours and disappeared in 5 days.

The blood Kahn titer was unchanged immediately after treatment, but had fallen to 40 at 29 days posttreatment and was 0 at 474 days after treatment. The cerebrospinal fluid was normal 9 months following treatment.

Serial roentgenograms of the skull showed no change 24 days after treatment. Improvement was noted by the 89th day, and in 208 days there was no evidence of the destructive lesions.

Hayman, C. R.: **Two Reports on Out-Patient Attendance for Treatment of Syphilis, Using Penicillin in Oil-Beeswax; I. A Study of Clinic Attendance,** *J.Ven. Dis. Inform. 28:221 (Oct.) 1947.*

In order to determine whether treatment of syphilis with penicillin-oil-beeswax on an out-patient basis was practical from the attendance viewpoint, a study was made in 107 patients treated at the Kent County clinics.

Penicillin was given in a single daily dose of 300,000 or 600,000 units for periods of 6, 7, 8, or 10 days (excluding Sunday).

87% of the patients completed the treatment schedule, 10% completed 90% of the schedule, and 3% completed 80% of the schedule. 49 former clinic patients who had been highly delinquent when receiving metal chemotherapy gave as good an attendance record with penicillin therapy as previously untreated patients.

Only 2 reactions occurred in the entire series—moderate soreness at the site of injection.

Koch, R. A.: **Ambulatory Intensive Treatment of Syphilis with Calcium Penicillin in Oil and Wax; Second Report,** *Urol. & Cutan. Rev. 51:569 (Oct.) 1947.*

A second report is presented on the treatment of patients with early syphilis at the San Francisco City Health Department Clinic with calcium penicillin in beeswax-peanut oil administered on an ambulatory basis.

All but 11 patients were treated with a uniform schedule of penicillin alone —2 injections of 150,000 units of penicillin in 0.5 ml. beeswax-peanut oil, morning and evening, omitting Saturday afternoons, Sundays and holidays, for 10 days (3,000,000 units). 11 patients received a single daily injection of 300,000 units for 10 injections.

279 patients were treated since August 1945, 238 of which completed treatment.

Reactions occurred in 18 patients (6.5%). These were chiefly a mild Herxheimer reaction. Severe reactions (generalized urticaria, edema of extremities and angioneurotic edema) requiring termination of treatment occurred in only 3 patients (1.1%). No severe reactions occurred after June 1946, attributed to the satisfactory use of benadryl for controlling urticarial reactions.

68 of 140 cases of primary syphilis and 26 of 98 cases of secondary syphilis attained seronegativity and were followed for periods of 3 to more than 18 months. 68 showed satisfactory clinical and serologic progress during the follow-up period. 37 cases were darkfield positive, seronegative primary syphilis. All but 8 remained seronegative during and after penicillin therapy. 6 became seropositive during treatment and 2 after completion of treatment; all subsequently became seronegative.

Lesions usually became darkfield negative within 24 hours. The author states that lesions appeared more resistant than with arsenical therapy.

The failure rate in 181 cases followed for 1 to 18 months was 10.5%. Failure rate previously reported was 4%.

A schedule for the ambulatory treatment of early syphilis which combines penicillin in oil and wax with arsenicals and bismuth, and which has been recommended to private physicians is as follows: Penicillin therapy for 10 days as outlined in this report; 5 injections of arsenical, beginning on the 1st penicillin treatment day, then every other day; 3 injections of bismuth given on the 2nd, 6th, and 10th treatment days.

Late Syphilis

Tucker, H. A., and Farmer, T. W.: **Penicillin in Cardiovascular Syphilis, Early Reactions to Administration,** *Arch. Int. Med. 80:322 (Sept.) 1947.*

Observations in 22 patients with syphilitic aortic insufficiency and 8 with thoracic aortic aneurysm treated at Johns Hopkins Hospital with penicillin in aqueous solution administered intramuscularly suggest that there is no need for small initial doses of penicillin or initial treatment with bismuth in these patients.

Instances of therapeutic shock in patients with cardiovascular syphilis during or after penicillin therapy have been reported. The authors state that none of these reactions are "certainly identified" as due to penicillin.

Results in the present series are discussed as follows:

Aortic insufficiency—22 patients. 6 patients received initial doses of 500 to 3,000 units, gradually increased to 30,000 to 100,000 units every 3 hours; 16 patients received doses of 25,000 to 100,000 units 3-hourly from the onset of treatment. Total dosages ranged from 2,000,000 to 15,000,000 units.

No differences were noted in electrocardiograms (10 patients), differential leukocyte counts and sedimentation rates before and after treatment.

4 patients had febrile reactions within the first 16 hours of treatment; all had received large initial doses. 2 patients had anginal attacks at rest during and after treatment; 1 had received large, the other small initial doses. Since these patients had had similar attacks for more than a year prior to treatment, the authors state that these reactions cannot be attributed to penicillin.

Aortic aneurysm—8 patients. 4 received initial doses of 500 to 2,000 units, 4 injections of 50,000 units and 1 of 100,000 units at 3-hour intervals from the beginning of treatment. Total dosages ranged from 2,000,000 to 10,000,000 units. A mild febrile reaction occurred in 1 patient at the beginning of treatment; initial dose was 500 units. Electrocardiograms made in 10 patients after treatment showed no change from the pretreatment status.

In discussion the authors point out that all febrile reactions occurred in patients with symptomatic late neurosyphilis. The incidence of febrile reactions, approximately 25%, was the same as the overall incidence reported for patients with neurosyphilis treated with penicillin. It is concluded that the febrile reactions are related to the neurosyphilitic rather than the cardiovascular process.

There were no significant differences in febrile reactions or cardiac symptoms in patients treated with small or large initial doses, nor were there significant differences in results with com-

mercial preparations of sodium penicillin and crystalline penicillin G.

Miller, W. S.: **Acquired Syphilitic Osteomyelitis; Report of Case Treated with Penicillin and Review of Literature,** *M. Ann. District of Columbia 16:543 (Oct.) 1947.*

The literature on acquired skeletal syphilis is reviewed and a case report is presented.

Acquired syphilitic involvement of the bone is a late manifestation of the disease. It occurs in about 0.5 to 0.7% of cases of acquired syphilis. Diagnosis may be difficult as the condition may be asymptomatic or may simulate other bone lesions, as tuberculosis, osteogenic sarcoma, pyogenic osteomyelitis, etc. The author states that in doubtful cases, diagnosis may be established by biopsy.

In the case reported excellent results were obtained with penicillin therapy. The patient was a 50 year old white man who had served in the Navy in World War I and World War II. He denied any venereal disease. He was admitted to the hospital on May 24, 1945 for treatment of severe, right sciatic neuritis. He gave a history of severe and continuous pain in the right hip and knee for 2 months. His condition had been progressively downhill and he was now bedridden. His weight had been 160 lbs. when he entered military service and was now 119 lbs.

Wassermann and Kahn blood tests were 4+; tuberculin test was 2+. Roentgenograms of the bones were suggestive of syphilitic osteomyelitis. Findings of a histologic examination of a specimen from the right ileum suggested either syphilitic or tuberculous involvement.

Because of the patient's downhill course, a routine course of penicillin therapy for syphilis was given—40,000 units intramuscularly every 3 hours to a total of 2,400,000 units in 7½ days.

During 8 weeks after penicillin therapy there was general improvement in the patient's condition, evidenced by disappearance of pain, improved motion in the involved joints, and a gain of 18 lbs. in weight.

At this time because of the extensive involvement and the fear of relapse, a course of mapharsen was given—14 weekly injections.

Serial x-rays showed significant improvement in the bone lesions.

Examination of the patient's military service record revealed a "chancroidal" infection in 1919.

Neurosyphilis

Dattmer, B.; Kaufman, S. S., and Thomas, E. W.: **Penicillin in Treatment of Neurosyphilis,** *Arch. Neurol. & Psychiat. 58:426 (Oct.) 1947.*

That "penicillin has proved to be a surprisingly effective therapeutic weapon in cases of neurosyphilis" is concluded from observations in 151 patients treated exclusively with penicillin and followed for periods of 6 to 28 months after treatment. The authors state that results in all types of neurosyphilis compared favorably with those with malaria therapy, and express the belief that penicillin will ultimately replace fever therapy.

Spinal fluid findings are considered the most reliable guide to the activity of a syphilitic infection of the spinal fluid and of the efficacy of treatment.

Only patients with syphilis of more than 2 years' duration and with active spinal fluids were selected for treatment. An "active spinal fluid" is defined as one with a positive complement fixation reaction and containing more than 4 cells/cu. mm.

All patients were treated exclusively with penicillin in aqueous solution administered intramuscularly at 3-hour intervals for total dosages of 2,000,000 to 9,000,000 units. More recently a schedule of 40,000 units every 3 hours for 150 injections totalling 6,000,000 units has been used for all types of neurosyphilis.

Spinal fluid examinations were made immediately before treatment and at intervals of 3 months for 12 to 18 months after treatment, thereafter every 6 months. Results are tabulated.

A satisfactory spinal fluid response is considered one showing a normal cell count, decreased complement fixation titer and total protein values, and improvement in the colloidal gold curves.

Following the initial course of treatment a satisfactory spinal fluid response was obtained in 131 (67%) patients, including 17 of 23 asymptomatic cases, 28 of 35 cases of the meningovascular type of neurosyphilis, 37 of 41 cases of tabes dorsalis, 30 of 33 cases of dementia paralytica and all 19 cases of the tabetic form of dementia paralytica.

17 of the 20 treatment failures were retreated with the following results: 4 have shown a satisfactory response; a debilitated patient with tabes dorsalis died; 12 patients are considered as "indefinite status" because of insufficient follow-up or indeterminate spinal fluid findings. It is pointed out that many of the treatment failures had received insufficient dosage.

6 patients with normal cell counts were retreated to determine whether additional penicillin would result in further clinical improvement. Results were not convincing.

Dementia Paralytica Treated with Penicillin, *Foreign Letters, J.A.M.A. 135:373 (Oct. 11) 1947.*

Drs. R. Orlando and M. Arndt have reported to the Society of Neurology and Psychiatry of the Argentine Medical Association results of penicillin therapy in 57 patients with dementia paralytica treated between August 1945 and August 1946.

Penicillin dosage was 2 million units administered in doses of 20,000 units intramuscularly every 3 hours.

Results of treatment were as follows: considerable improvement in 10 cases, some improvement in 11, transitory improvement in 8, no modifications in 15; 3 patients were worse; 4 died without modifications.

Good results occurred chiefly in initial cases or during the acute period.

Improvement in the cerebrospinal fluid was observed in 21 patients.

Results with penicillin therapy seemed inferior to those with malaria therapy. It is suggested that penicillin therapy be followed by malaria therapy. A series of patients is now being treated with a larger penicillin dosage (4 million units).

Grover, R. W.; Cope, E. P., and Bozalis, G. S.: **Practical Considerations in the Diagnosis and Treatment of Neurosyphilis,** *J. Arkansas M. Soc. 44:120 (Oct.) 1947.*

The diagnosis and treatment of neurosyphilis are discussed. An illustrative case report is presented.

In the diagnosis of neurosyphilis the authors emphasize the importance of a spinal fluid examination in every patient with a history of any venereal disease, as blood serologic tests are not reliable for predicting the development of symptomatic neurosyphilis.

Penicillin and malaria are the basis of present therapy for neurosyphilis at the Veterans Administration Hospital, North Little Rock, Arkansas, penicillin alone for early neurosyphilis, penicillin and malaria combined for the later stages.

Penicillin dosage for all phases of neurosyphilis is 9 million units given in doses of 50,000 units intramuscularly every 3 hours for 22½ days. In cases of suspected cardiovascular involvement, small initial doses are used.

Careful selection of patients for malaria therapy and close supervision during paroxysms are emphasized. Tertian malaria is used initially in white patients, quartan malaria in Negroes. The authors state that 8 to 10 paroxysms together with penicillin are usually adequate. When penicillin is given during malaria therapy, doses of 5,000 units 3-hourly are used for the first 2 days.

Lescher, F. G., and Richards, H. R. M.: **The Modern Treatment of Neurosyphilis,** *Brit. M. J. 2:565 (Oct. 11) 1947.*

A comparison has been made of 3 methods of treating neurosyphilis based on results in 50 patients treated over a period of 8 years. Results are tabulated.

Adequate follow-up was available for 49 patients treated as follows:

Malaria followed by tryparsamide and bismuth—20 patients followed for 5 to 8 years.

Penicillin (125,000 units in oil twice

daily to a total of 4 million units)—10 patients.

Penicillin with malaria (penicillin-wax-oil preparation just before and during the acute stage of malarial infection, 250,000 units twice daily to a total of 4 million units—19 patients.

Best clinical results were in the following declining order: penicillin-malaria; penicillin alone; malaria-chemotherapy.

Spinal fluids became inactive and negative more quickly with penicillin-malaria than with the other methods. A greater number of spinal fluids became inactive and negative following penicillin-malaria or penicillin alone, but more fluids became negative and remained negative after malaria-chemotherapy.

From the results in this study, the following treatment of active neurosyphilis is recommended: immediate treatment with penicillin-malaria (unless there are contraindications to the latter) with treatment repeated in 12 months if the spinal fluid is still positive, or in 2 years if the spinal fluid remains inactive.

Worster-Drought, C.: **Penicillin in Neurosyphilis,** *Brit. M. J. 2:4527 (Oct. 11) 1947.*

The treatment of neurosyphilis with penicillin is reviewed. The author cautions that at least 5 years must elapse before the value of penicillin in neurosyphilis can be fully determined. He concludes, however, that "penicillin has a definite and established place in the treatment of neurosyphilis."

A minimum total dosage of 3,000,000 units is suggested for all forms of neurosyphilis, with doses of 4,000,000 to 5,000,000 units in parenchymatous neurosyphilis.

Intravenous administration, continuous or intermittent, is not recommended because of difficulties in administration and the danger of thrombophlebitis. Intrathecal administration of penicillin is considered unnecessary.

The preferred method of administration is by intermittent intramuscular injection—60 injections of 40,000 units each every 3 hours. If it should prove unnecessary to maintain continuously high blood levels of penicillin throughout the treatment period, single daily injections of 300,000 to 500,000 units for periods of 8 to 14 days may be substituted, or the oil-wax preparations may be used.

In order to avoid Herxheimer reactions, it is suggested that in all forms of neurosyphilis penicillin therapy be preceded by a series of bismuth injections.

Therapy recommended for the various forms of neurosyphilis is as follows:

Meningovascular neurosyphilis — Penicillin followed by arsenical-bismuth therapy.

General paresis—4 initial injections of bismuth, followed by a course of 4 or 5 million units of penicillin, then a full course of fever therapy, followed by the usual courses of arsenic and bismuth.

Tabes dorsalis—An initial course of intramuscular penicillin (4 to 5 million units) followed by arsenical-bismuth therapy for 1 to 2 years. Lightning pains may persist. The author states that in several cases freedom from pains for periods of 6 months followed treatment with systemic and intrathecal penicillin.

Primary optic atrophy—Penicillin (4 million units) followed by malarial therapy, then arsenical-bismuth therapy until serologic reactions become negative.

Late asymptomatic neurosyphilis — Therapy the same as for general paresis.

Erb's syphilitic spinal paralysis—Total dosages of 2 to 10 million units of penicillin have proved ineffective.

Syphilis in Pregnancy

Aron, H. C. S.; Barton, R. L., and Bauer, T. J.: **Prenatal Syphilis; Its Prevention by Use of Penicillin in Treatment of Pregnant Women with Early Infectious Syphilis,** *Arch. Dermat. & Syph. 56:349 (Sept.) 1947.*

Results in 36 pregnant women with proved early infectious syphilis treated with penicillin at the Chicago Intensive Treatment Center are reported. These results are compared with those in a comparable group of 28 women previously treated with intensive arsenotherapy and those in 2 groups of 31 and 26 women treated with penicillin designated the "Baltimore group" and the "Philadelphia group," respectively.

The 36 women designated the "Chicago group" were selected to fulfill the criteria of early infectious syphilis proved by darkfield examination and of delivery at not more than 7½ months after diagnosis and beginning of treatment.

In the 36 infants there were 2 deaths, 1 due to an accident not attributable to syphilis, the other a stillborn infant, an incidence of 2.8% failure. None of the 34 living infants showed physical, serologic or roentgenologic evidence of syphilis. In the group of 28 infants from mothers treated with arsenotherapy there were 3 instances of congenital syphilis, a failure rate of 10.7%. Goodwin and Moore reported a failure rate of 15% in cases from the literature treated with intensive arsenotherapy.

In the 34 living infants in the Chicago group there were 3 possibly premature infants, an incidence of 8.8%. Since the average incidence of prematurity has been reported to be between 7.5 and 10.2%, the authors state the belief that penicillin therapy does not predispose to abortion, miscarriage or prematurity.

The authors state that the results in the Chicago, Baltimore and Philadelphia groups treated with penicillin were in agreement. Combined, there were 96 infants with 1 death and 1 stillbirth, a failure rate of 2.1%.

In the Chicago group there were 2 mothers who had mucocutaneous relapse after penicillin therapy; however, the infants remained free of syphilis.

It is concluded that "of the various drugs which are used in the intensive forms of treatment and which are designed to prevent prenatal syphilis, penicillin is unexcelled."

In a footnote, the authors state that at the date of publication of this report, 81 infants had been delivered of mothers with early infectious syphilis treated with penicillin, with no additional instances of congenital syphilis, thus reducing the failure rate from 2.8 to 1.24%.

Experimental Syphilis

Kolmer, J. A.: **Penicillin in the Treatment of Experimental Syphilis of Rabbits; III. The Therapeutic Activity of Penicillin by Oral Administration,** *Arch. Dermat. & Syph. 56:344 (Sept.) 1947.*

From results obtained with oral penicillin in the treatment of experimental rabbit syphilis, it is concluded that the treatment of human syphilis with oral penicillin appears to be contraindicated. It is suggested that oral penicillin combined with oxophenarsine hydrochloride or bismuth and potassium tartrate might be useful in selected cases.

In the studies reported, rabbits were experimentally infected by intratesticular injection with the Nichols-Hough strain of T. pallidum. These were divided into groups of 3 animals each which were respectively treated with penicillin doses of 500, 1,000, 5,000, 10,000, 15,000, and 20,000 U./Kg. Penicillin was given as an aqueous solution by stomach tube. Each dose was mixed with 0.2 Gm. sodium citrate. The total dosage was given in 30 doses (9 A.M., 1 P.M. and 3 P.M. daily for 10 days). Efficacy of therapy was evaluated by lymph node transfers.

With all dosages there were temporarily negative results on darkfield examination, but results of lymph node transfers were all positive excepting 1 of the animals receiving doses of 15,000 U./Kg. and 2 of those receiving 20,000 U./Kg.

From these results it is concluded that the minimal curative dose of orally administered penicillin in experimental rabbit syphilis is between 15,000 and 20,000 U./Kg. 3 times daily for 30 doses, or total dosages of 450,000 and 600,000 units. The total minimal curative dose of intramuscular penicillin has been reported to be 16,000 units.

Based on the above data, the total minimal curative dose of oral penicillin for human adults has been calculated

to be between 30,000,000 and 40,000,000 units.

Beerman, H.: **The Action of Penicillin on Treponema Pallidum,** *Am.J.M.Sc. 214:442 (Oct.) 1947.*

A discussion of the action of penicillin on T. pallidum, based on a review of the literature, is presented under the following heads: "The activity of penicillin against T. pallidum in vitro, including commercial penicillins F, G, X and K; the effect of penicillin in experimental rabbit syphilis, including the effectiveness of commercial penicillin, penicillins F, G, X and K and impurities of commercial penicillin; resistance to penicillin; and the mode of action of penicillin on T. pallidum."

62 references are listed.

Granuloma Inguinale

Berkowitz, J.: **Granuloma Inguinale with Perianal Involvement; Report of a Case,** *New England J. Med. 237:665 (Oct. 30) 1947.*

A case of granuloma inguinale with perianal involvement is reported, in which there was no improvement after 41 days of hospitalization with treatment consisting of wet dressings and 6,300,000 units of penicillin. Cure was subsequently effected by a course of intragluteal injections of fuadin.

Granuloma inguinale occurs chiefly in Negroes and in warm climates. Perianal involvement is rare. The case reported is considered of interest as the patient was a white man living in Massachusetts.

SURGERY

Lam, C. R.: **Antibiotics in the Surgery of Trauma,** *Am.J.Surg. 74:302 (Sept.) 1947.*

A brief summary of the usefulness of the antibiotics (penicillin, streptomycin, tyrothricin, and bacitracin) in traumatic surgery is presented, based on reports from the literature and the experience at the Henry Ford Hospital.

The author states that the antibiotics have not obviated the need for orthodox surgery in the prophylaxis and treatment of infected wounds, but are valuable adjuncts. Ideally, their use should be accompanied by bacteriologic diagnosis.

The most widely used antibiotics are penicillin and streptomycin. The discussion of their usefulness has been presented under the following headings: Injuries of soft parts; compound fractures; burns.

The author states that at the Henry Ford Hospital, treatment of lacerations in the emergency room consists of the usual surgical procedures without antibiotics. Patients with complicated wounds receive penicillin intramuscularly in doses of 12,500 units 3-hourly for 5 days. In cases of contaminated serous cavities penicillin is administered systemically and is instilled locally (100,000 units).

Penicillin may be administered by intermittent intramuscular injection, a daily injection of a beeswax-oil preparation, or orally. In the author's opinion intermittent intramuscular injection is the most reliable.

In cases with gram negative organisms resistant to penicillin but sensitive to streptomycin, the latter drug may be administered intramuscularly in doses of 1 to 4 Gm. daily.

Penicillin has not been effective in tetanus although the tetanus bacillus is inhibited in vitro, but it is a valuable adjunct in the treatment of gas gangrene.

All patients with compound fractures at the Henry Ford Hospital receive prophylactic intramuscular penicillin for at least 2 weeks—50,000 units 3-hourly for the 1st week, half this dosage for the 2nd.

Penicillin is useful during the acute phase of a burn if symptoms of infection are present; it is especially valuable during skin grafting. 2 illustrative cases of the latter are given. Case 1 received 5 million units intramuscularly and 1.5 million units locally. Attempts at grafting were unsuccessful until penicillin therapy was instituted. Case 2 received 12,500,000 units intramuscularly. The author states that streptomycin should be useful in burns with pyocyaneous infection.

Tyrothricin is effective against gram positive cocci, but is suitable for topical application only. Bacitracin has been reported effective in a series of surgical infections due to cocci resistant to penicillin.

Golden, B. I.: **Single Massive Doses of Penicillin in Surgical Infections,** *West Virginia M.J. 43:344 (Oct.) 1947.*

Massive doses of local penicillin, either instilled into body cavities or infiltrated directly into the tissues are recommended for the prevention or treatment of surgical infections. 8 illustrative cases are reported briefly.

The author states that as local anesthesia mixed with penicillin has not reduced pain in infiltration procedures sufficiently to be of value, general anesthesia has been used routinely.

The following dosages are recommended:

Traumatic or infected wounds—After completion of debridement and plastic surgery, infiltration with 500,000 units of penicillin, using the same technic and amount of solution as for local anesthesia.

Carbuncles—Infiltration of all indurated and adjacent tissues with 500,000 units of penicillin in 30 to 100 cc. of water; incision only if pointing is present.

Abdominal surgery—Instillation of penicillin solution into the abdominal cavity through a catheter just before finishing closure—500,000 units in 20 cc. water for mixed infection due to a perforated appendix, for gangrenous gallbladder, and for infected fallopian tubes; 1,000,000 units in 20 cc. water for intestinal perforation of several hours' duration, for cesarean section after intrauterine manipulation, and for colon resection.

Amputations—Infiltration just before skin closure.

Thoracic injuries—In a case of massive through and through thoracic cage injury, penicillin-soaked packs were used to isolate the lung. 24 hours later, the anterior wound was closed and the posterior wound partially closed. Penicillin irrigation (500,000 units in 250 cc. water) was carried out continuously through a catheter.

Only 1 instance of reaction to the large doses of penicillin was observed (temporary dulling of the mental activity).

Schaefer, A. A.: **Antibiotics in Surgery,** *Wisconsin M.J. 46:1020 (Oct.) 1947.*

The usefulness of penicillin, streptomycin and tyrothricin in surgery is reviewed.

Penicillin has made possible successful treatment of postoperative pneumonias and infections, pelvic infections due to the gonococcus, furuncles, carbuncles and cellulitis, and acute osteomyelitis. The author cautions that penicillin treatment of osteomyelitis should be followed closely by x-ray and that if the process is progressive open operation should be done.

Penicillin alone may not be effective in thick-walled abscesses or in some cases of empyema. Surgical drainage should be provided.

The treatment of appendicitis without surgery is condemned. Conservative treatment, using both penicillin and sulfonamides, is recommended when generalized or localized peritonitis is present. Combined therapy is also recommended in operations on the colon.

Unlike penicillin, streptomycin is effective against both gram positive and gram negative organisms. Streptomycin has proved effective in tularemia and in infections due to the Friedlander bacillus. It is suggested that it may be a useful adjunct to surgery in sterilizing the intestinal tract preoperatively, and in biliary tract diseases.

Penicillin dosage which the author has found satisfactory is 20,000 to 50,000 units intramuscularly every 3 hours, 100,000 to 300,000 units intravenously in 24 hours, or 100,000 to 300,000 in beeswax-oil in a single intramuscular dose. Suggested streptomycin dosage is 100,000 units intramuscularly every 3 hours. Organisms rapidly become streptomycin fast. Because of toxic effects, it is rec-

ommended that streptomycin should not be used for more than a month.

Tyrothricin can be used only locally. Aqueous suspensions (0.5 to 1.0 mg./cc.) may be used in body cavities. Compresses or irrigations may be used to treat infected ulcers and wounds.

McKittrick, L. S.: **Surgical Problems in Patients with Diabetes Mellitus,** *Chicago M.Soc.Bull. 50:235 (Sept. 27) 1947.*

A brief review on surgical problems in patients with diabetes is presented, in which the author states that the use of penicillin has completely changed the concept of the management of carbuncles and has completely altered the approach to certain problems of the lower extremities in diabetic patients.

The author states that, formerly, large carbuncles were a threat to the life of the patient. Treatment required wide excision and prolonged hospitalization. Now, with penicillin given intramuscularly in doses of 60,000 units 3-hourly, the lesion usually disappears in 3 to 5 days, or becomes reduced to a small fluctuant area requiring a small incision. The author states that while carbuncles may be treated on an outpatient basis by penicillin in peanut oil or injected locally, hospitalization with intramuscular penicillin is the preferred procedure.

Problems of the lower extremities usually fall into 3 groups: 1. Lesions which are primarily infections of a foot with adequate circulation. 2. Lesions which are primarily due to defective arterial supply. 3. Neuropathic ulcerations.

The use of penicillin to control infection makes possible procedures which were formerly too dangerous. Penicillin is administered in doses of 300,000 to 500,000 units daily (60,000 units 3-hourly) for at least 24 hours before operation and for 5 to 7 days after operation. Operation above the area of gangrene and gross infection usually gives good results even when circulation is impaired. The author states that 92 transmetatarsal amputations were done with no deaths and with satisfactory functional and anatomical results. It is stated that in cases where one or more digits are involved, transmetatarsal amputation offers excellent insurance against later complications.

Wyke, B. D.: **The Treatment of Severe Intracranial Infection by Repeated Intraventricular Injection of Penicillin; Theoretical and Practical Considerations,** *Surg., Gynec.& Obst. 85:340 (Sept.) 1947.*

The literature on the passage of penicillin through the blood-brain barrier and on the direct introduction of penicillin into the cerebrospinal fluid is reviewed. The indications for intraventricular administration of penicillin, and the operative procedures and postoperative management of these cases are discussed.

Although there have been some dissenting opinions, the majority of reports in the literature indicate that therapeutically adequate concentrations of penicillin cannot be maintained within the cranial cavity by systemic administration in reasonable dosage. The author therefore concludes that all intracranial infections due to susceptible organisms, except comparatively benign cases, should be treated by repeated injection of penicillin into the cerebrospinal fluid circulation.

Reports on toxic reactions following intraspinal or intraventricular administration of penicillin have been controversial. Lumbar radiculitis and arachnoiditis and pleocytosis have been reported following massive intraspinal doses. The author suggests that these reactions were probably due to impurities in the product rather than to penicillin per se. Convulsive reactions have been noted following direct application of penicillin to the brain. This type of reaction appears to be related to the antibiotic activity of penicillin. However, the convulsive threshhold appears to differ in various species and in different areas of the brain. The author states that the direct introduction into the lateral ventricle of the brain of penicillin in a concentration of 10,000 U./cc. is "an entirely safe proceeding." He states that he has repeatedly injected 5 cc. of this concentration (50,000 units) in patients ranging in age from 2 months to 53 years without any reaction.

Repeated introduction of penicillin into the lateral ventricles of the brain is indicated in the following types of intracranial infection: (1) purulent, with penicillin sensitive organism, in which cerebrospinal fluid pressure and cell counts are high; (2) highly virulent or partially penicillin sensitive organisms, especially in children; (3) penicillin sensitive organism which fails to show early and progressive improvement with medical management; (4) penicillin sensitive organism, cerebrospinal fluid block suspected; (5) intracranial abscess formation suspected; (6) streptococci in the cerebrospinal fluid; (7) intracranial operations in the presence of potentially infected foci; (8) cerebrospinal rhinorrhoea following head injury; (9) penicillin sensitive organism, papilledema; (10) any comatose case.

The initial operative procedure is the same as for ventriculography. If subdural empyema is present it may be drained and penicillin instilled through tubes left in situ. In the presence of epidural or subdural infection, needles are passed into the lateral ventricles from the opposite side and the cerebrospinal fluid is aspirated. If ventriculography is performed, the wound is sutured and fresh brain needles are inserted through the wounds. 5 cc. of penicillin solution (10,000 U./cc.) is instilled following aspiration. The author states that instillations should be repeated daily until the cerebrospinal fluid pressure is normal and the returned fluid is clear, sterile, and of normal cell count. Usually not more than 6 to 9 intraventricular injections are required.

Christensen, H. W.: **Burns in Naval Personnel at Okinawa,** *Wisconsin M.J. 46:1022 (Oct.) 1947.*

The treatment of 317 burn patients aboard a hospital ship during a 99-day period at Okinawa is discussed. There were 11 deaths, most of which occurred during the first 12 hours of treatment.

The vaseline gauze pressure dressing method was used routinely. Supportive therapy was emphasized and included morphine, blood plasma, penicillin, sulfonamides, tetanus prophylaxis, oxygen and adrenal cortex extract.

Sulfanilamide powder was dusted lightly over the burned areas, however, systemic administration of sulfonamides was not used routinely.

Penicillin was given intramuscularly (25,000 units 3-hourly) in all cases of severe burns. The author states, "We feel it had a great deal to do with the prevention of infection and the treatment of infection already present."

Donnelly, J. H.; Phillips, F. J.; Bartlett, J. P., and Adams, W. E.: **An Evaluation of Methods of Penicillin Therapy in Thoracic Surgery,** *Ann.Surg. 126:579 (Oct.) 1947.*

An evaluation of the various methods of administering penicillin in thoracic surgery was made by determining penicillin levels in the blood and pleural fluids in humans and in dogs having lobectomy or pneumonectomy.

Results with the various technics were as follows:

Intramuscular injections—Serum levels in humans following intramuscular injection of 20,000 units were highest in 15 to 30 minutes after injection and reached a minimum in 2 hours. Average maximum level was 0.14 U./cc. The authors state that doses larger than 20,000 units or injections at intervals of less than 3 hours would prevent levels from falling to zero between injections.

In dogs, intramuscular injection of a proportional dose resulted in maximum serum levels (0.34-0.43 U./cc.) at ½ hour, with levels of 0.14 to 0.23 at 1½ hours.

Pleural fluid levels varied considerably, depending on duration of therapy, method of obtaining fluid, and the presence of penicillinase-forming organisms. Pleural fluid levels reached a maximum about 1½ hours after injection. Therapeutic levels were maintained for 2 hours or longer. With a dosage of 40,000 units levels were more than double those with 20,000 units.

Intratracheal instillations—With instillation of 50,000 units maximum serum levels (average 0.08) were attained after ½ hour; minimum therapeutic levels were present at 2 hours, only traces at 3 and 4 hours. Larger doses (90,000, 100,000, and 200,000 units) resulted in correspondingly higher serum levels.

Aerosol administration—With inhalation of 30,000 units in 1.5 cc. saline during 1 to 1½ hours, maximum serum levels (average 0.03) were attained immediately after completion of inhalation, with only traces of penicillin present ½ to 1½ hours later.

Intrapleural administration — With intrapleural instillation of 200,000 units of penicillin, serum levels varied widely; therapeutic levels were present within the first ½ hour and persisted for 9 to 12 hours.

Therapeutic levels in the pleural fluid were maintained for at least 60 hours and in some instances for 84 and 114 hours.

In dogs, blood serum and pleural fluid levels were not comparable to those in humans. At 24 hours there was no penicillin detectable in either the blood or pleural fluid.

The authors conclude that intramuscular administration is the most efficient method of maintaining adequate serum levels. A dosage of 40,000 units 3-hourly would also maintain effective pleural fluid levels.

Intrapleural injection, intratracheal administration, or aerosol administration may be of value when a high local concentration of penicillin is desirable.

Karron, I. G.: **Mediastinal Emphysema Following Thoracoscopy; a Case Report,** *Am.Rev. Tuberc. 56:308 (Oct.) 1947.*

A case of mediastinal emphysema following thoracoscopy is reported.

The patient was a 30 year old soldier with tuberculosis in whom a pneumothorax was unsatisfactory because of adhesions.

On the day following thoracoscopy, there was wide-spread subcutaneous emphysema and mediastinal emphysema accompanied by large collections of fluid. The fluid was believed to be blood or serous fluid caused by irritation of the mediastinum by air.

To prevent infection of the blood pockets, penicillin was administered intramuscularly — 25,000 units every 3 hours.

The fluid was aspirated on several occasions and penicillin was instilled intrapleurally in doses of 50,000 units at first, later in lesser amounts. Total amount of penicillin instilled was 140,000 units. Aspirated fluid was at first bloody, later a thin dark-brown fluid containing less than 1 Gm. hemoglobin per 100 cc. The chest fluid was negative on smear and culture for pyogens and tubercle bacilli.

Pneumothorax was reinduced and was successfully maintained.

Gage, M.; Lyons, C., and DeCamp, P. T.: **Essential Therapeutic Adjuvants in the Surgical Arrest of Wolff-Israel Actinomycosis,** *Ann.Surg. 126:568 (Oct.) 1947.*

That "penicillin is the antibacterial agent of choice during the period of hospitalization and initial surgical management" of patients with Wolff-Israel actinomycosis is concluded from observations in 5 bacteriologically proved cases.

A dosage of 25,000 to 50,000 units every 2 or 3 hours proved effective and resulted in few toxic reactions.

The use of sulfonamides was reserved for patients with inoperable disease or during established convalescence. The use of sulfonamides is contraindicated during the period of surgical management because of the high incidence of urinary tract complications, and in depleted persons because of their depressant effect on hematopoiesis, the intestinal synthesis of essential metabolites and the appetite.

Since depletion of blood proteins is a significant feature of the malnutrition observed in patients with Wolff-Israel actinomycosis, the authors recommend a high dietary intake of protein and transfusions of whole blood.

Hamilton, J. E., and Cattanach, L. M.: **Comparative Study of Chemotherapies in the Surgery of Pilonidal Sinus,** *Am. J.Surg. 74:449 (Oct.) 1947.*

In order to investigate the significance of chemotherapy in the healing of the postexcisional pilonidal wound, an analysis was made of 110 cases in which the wound was primarily closed and in which sulfonamides and penicillin, alone or combined, were administered.

Results were as follows:

No chemotherapy — 24 cases; 15 cases (62.5%) of per priam healing, 9 failures.

Sulfonamides only (orally, locally, or both combined)—18 cases; 14 cases (77.7%) of per priam healing, 4 failures.

Local penicillin and oral sulfadiazine (infiltration of penicillin solution, 250 to 500 U./cc.)—32 cases; 30 cases (93.8%) of per priam healing, 2 failures.

Parenteral penicillin, medium doses (20,000 to 25,000 units 3-hourly)—22 cases; 12 cases (54.5%) of per priam healing, 10 failures.

Parenteral penicillin, large doses (40,000 to 80,000 units 3-hourly) — 14 cases; 11 cases (78.6%) of per priam healing, 3 failures.

In some of the cases treated with parenteral penicillin, penicillin was also injected locally at operation.

From the results in these cases, the authors recommend the administration of oral sulfadiazine pre- and postoperatively and local injection of penicillin at operation, with massive doses of penicillin parenterally if there is evidence of wound cellulitis after closure.

Reichman, H. R.: **Pilonidal Fistula Complicated by Actinomycosis; Complete Healing Following Surgical Treatment, Sulfonamides, and Penicillin,** *Rocky Mountain M.J. 44:820 (Oct.) 1947.*

A case of pilonidal fistula complicated by actinomycosis which was successfully treated by surgical excision, sulfathiazole and penicillin is reported.

The patient was a 36 year old white male with a history of an intermittently draining pilonidal sinus for about 15 years. Examination revealed an area of induration extending over the buttocks. There were multiple external openings, but no primary opening of a fistula was revealed by anorectal examination.

At operation several tracts were identified and were widely excised by block dissection. Sulfanilamide powder was sprinkled into the wound. Sulfathiazole had been given preoperatively and was continued after operation. Penicillin was given postoperatively in doses of 20,000 units 4-hourly for 8 days.

Pathologic examination of the excised tissue revealed the typical structure of a pilonidal cyst with small rounded abscesses containing typical actinomycosis colonies.

The patient was employed in a dairy, but had had no contact with cows.

During a period of 15 months after operation, there was no recurrence and the patient remained asymptomatic.

Abdominal

Coppleson, V. M.: **Penicillin in Abdominal Surgery, with Special Reference to Its Intraperitoneal Use,** *M.J. Australia 2:292 (Sept. 6) 1947.*

That "penicillin should be used as a routine measure in all major abdominal operations, that its application should be intraperitoneal and that it should be applied in large doses" is concluded from the author's experience in a large series of patients treated over a period of 3 years. 12 illustrative case reports are presented.

Cases treated included acute abdominal emergencies, intestinal obstructions, and gastric and bowel resections. In the cases reported, penicillin was given by intramuscular injection pre- and postoperatively, and at operation 100,000 or 200,000 units of dry penicillin was placed in the peritoneal cavity.

The author states that in all cases in which penicillin was used intraperitoneally, "the postoperative course has been milder and the abdominal discomfort, distension, vomiting and other complications have been lessened."

The use of penicillin intraperitoneally was based on the evidence that penicillin does not penetrate well into serous cavities following intravenous or

intramuscular injection, and that penicillin is excreted slowly from the peritoneum, thus maintaining a high local concentration.

The following suggestions for the use of penicillin in abdominal surgery are given:

Acute intestinal obstruction or generalized peritonitis – Intramuscular penicillin in doses of not less than 100,000 units every 1 or 2 hours; 200,000 units in the peritoneal cavity at operation.

Other acute abdominal emergencies—Intramuscular penicillin, 100,000 units immediately before operation, 20,000 to 100,000 units at intervals of 1 to 3 hours postoperatively; 200,000 units intraperitoneally at operation.

Delayed treatment of appendicitis, cholecystitis, and for pneumococcal peritonitis and gonococcal salpingitis – 50,000 to 100,000 units every few hours.

Obstructive jaundice—Intramuscular penicillin, 20,000 units 3-hourly pre- and postoperatively; 100,000 units intraperitoneally at operation.

Resection of the large bowel—Sulfonamides orally for several days before and after operation; intramuscular penicillin, 100,000 units immediately before operation, 20,000 to 50,000 units 3-hourly after operation; 200,000 units intraperitoneally at operation.

Other major abdominal operations—Intramuscular penicillin, 60,000 to 100,000 units before operation, and continued postoperatively for about a week; 200,000 units in the abdomen at operation.

Minor abdominal operations—60,000 units intramuscularly before operation; 100,000 units in the peritoneal cavity at operation.

If infected areas are present in the region of the operative field, it is suggested that penicillin be given by injection for several days prior to operation, and also should be applied locally. When drainage tubes are used, instillation of penicillin solution (500 U./ml.) is advised.

Bower, J. O., and Freed, C. F.: **Report of the Third Statewide Survey of Acute Appendicitis Mortality (1946),** *Pennsylvania M.J. 51:58 (Oct.) 1947.*

A report is presented of the third statewide survey of acute appendicitis mortality in Pennsylvania. The mortality for 1937 was 3.39%, for 1942, 1.1%, and for 1946, 0.69%.

In 1946 there were 187 deaths, of which 75 were catastrophes, 31 unavoidable and 44 avoidable. Of the 112 deaths not due to catastrophes, 102 were due to spreading peritonitis, while 10 patients were not operated on.

Errors in management and technic chiefly responsible for death are listed as follows: routine removal of a perforated appendix; failure to evaluate the sulfonamides, penicillin and streptomycin; failure to drain or improper selection of type and site of drain; routine type of incision (right rectus).

The authors state that although it has been shown conclusively that "sulfonamides should not be installed in the peritoneal cavity under any circumstances or conditions," yet sulfonamides were so installed in 64 of the patients who died.

Penicillin was administered to 108 patients with spreading peritonitis who died. Dosage was inadequate—average of 32,500 units.

Only 8 patients received streptomycin. The authors recommend that streptomycin combined with penicillin be given routinely to patients operated on for spreading peritonitis.

Conroy, C. F.: **The Present Status in the Treatment of the Perforated Appendix,** *Wisconsin M.J. 46:1017 (Oct.) 1947.*

In order to evaluate chemotherapy and antibiotics in the treatment of peritonitis following a ruptured appendix, an analysis was made of cases of perforated appendix treated at the Milwaukee County Hospital during the years 1935-45.

According to the author, the chief means of reducing the mortality from perforation appears to be education of the public.

The author condemns the conservative treatment of appendicitis. Cases with walled-off abscesses are not surgical emergencies. These may be drained after the patient is in good condition, then about 3 months later when the inflammation has subsided the appendix may be removed.

Postoperative care is stressed. The author recommends morphine to keep the patient comfortable and hot stupes over the abdomen.

Since the introduction of sulfonamides, sulfanilamide (5 Gm.) was applied intraperitoneally in some cases. In 38 cases so treated the mortality was 10.5%, in 42 cases with no treatment, 7.38%. The author concludes that the use of sulfanilamide is of questionable value.

Penicillin was used in 12 cases. There were 2 deaths. The author states that in patients treated with penicillin, the temperature was lower and the amount of drainage less than in control patients.

Ravdin, I. S.: **Acute Appendicitis,** *J. Iowa M.Soc. 37:436 (Oct.) 1947.*

According to the author, although the mortality in acute appendicitis has been considerably reduced, it is still too high. Death is usually due to complications, such as gangrene, perforation, spreading infection, and intestinal obstruction. The chief factors contributing to death from complications are delay in operation and catharsis.

The author emphasizes that acute appendicitis is a surgical lesion. He states that mortality can be reduced by careful preoperative and postoperative therapy, selection of the proper time for operation, and the judicious use of anesthesia. In his opinion the muscle-splitting incision is the incision of choice. He states that the sulfonamides, penicillin and streptomycin are the most effective bacteriostatic agents available in spreading peritoneal infections.

The following regimen is now being used at the Hospital of the University of Pennsylvania in patients with peritonitis—5 Gm. crystalline sulfanilamide in the peritoneum at operation; combined penicillin-streptomycin therapy immediately after operation (500,000 to 800,000 units penicillin and 2 to 4 Gm. streptomycin per 24 hours, both being given in divided doses).

Corbett, R. A.: **Regional Ileitis Treated with Streptomycin,** *Rocky Mountain M.J. 44:821 (Oct.) 1947.*

A case of extensive ileitis which responded to conservative treatment with combined penicillin-streptomycin therapy followed by sulfathaladine is reported.

The patient was a 32 year old woman with a history of occasional mild indigestion and several severe attacks of appendicitis. Presenting complaints were general abdominal pain and nausea for the preceding 12 hours.

Examination revealed a "fairly soft" abdomen with generalized tenderness that gave "a different feel than that of an acute appendicitis." However, because of the history, surgery was advised.

At operation, the appendix was found to be acutely inflamed, the cecum appeared normal, but the entire ileum was edematous and reddened with patchy ecchymotic areas with a thickened mesentery. Because of the extent of the involvement, surgical removal was impossible. The appendix, likewise, was not removed. Sulfathiazole powder was sprinkled about the inflamed area and the abdomen was closed.

Postoperative therapy included: continuous nasal suction; intravenous glucose; penicillin (500,000 immediately, followed by 20,000 units 4-hourly); streptomycin (2 Gm. followed by 1 Gm. every 6 hours); prostigmen every 4 hours; sedation as needed. This regimen was continued until food was tolerated by mouth, when penicillin and streptomycin dosages were reduced and sulfathaladine was given by mouth.

The patient was discharged, asymptomatic, on the 14th day with instructions to continue sulfathaladine for a month.

Treiger, P.: **Acute Gastroduodenal Perforations; Plan for Postoperative Treatment,** *Am.J.Surg. 74:459 (Oct.) 1947.*

A comparative study was made of the morbidity and mortality in 73 cases of perforated peptic ulcer which were treated during the years 1930 to 1944 "according to the teaching of the times,"

and in 17 cases treated during the years 1944 to 1946 with a standardized postoperative regimen which included the administration of penicillin.

Penicillin dosage was based on the number of hours elapsing between perforation and surgery. In cases in which the lapse was 6 hours or less, an initial dose of 60,000 units was given, followed by 30,000 units intramuscularly every 3 hours until temperature is normal. In cases with a lapse of 7 hours or more, a total of 4,400,000 units was given in 8 days.

The regimen for the first 4 postoperative days (24 hours) is listed. In addition to penicillin, therapy included: morphine sulfate every 6 hours for 3 days; Wangensteen suction; intravenous protein hydrolysate the 1st and 3rd days; intravenous glucose the 1st day; vitamins B and C the 1st day; prostigmine followed by a soapsuds enema the 3rd day; patient out of bed twice (10-minute periods) the 2nd day and completely ambulatory the 4th; regular ulcer diet the 4th day.

In the 73 patients with varied postoperative therapy, wound abscess occurred in 4, evisceration in 12; a total of 52% had complications. Average hospital stay was 19.5 days. Mortality was 32.9%.

In the 17 patients treated according to the standardized regimen, there were only 2 (11.6%) complications, wound infection and evisceration, respectively. Average hospital stay was 10.8 days. There were no deaths.

Perforated Peptic Ulcer — Postoperative Pneumonia, *Surg. Staff Meet. Beth David Hosp., Am.Practitioner 2:138 (Oct.) 1947.*

The case is reported of a patient with a perforated peptic ulcer who developed a left lobar pneumonia on the second postoperative day despite the administration of oxygen inhalation and penicillin intravenously in doses of 30.000 to 50,000 units every 3 hours.

It is suggested that the pneumonia may have been due to obstruction of the bronchus by a plug of mucus, resulting in atelectasis with subsequent pneumonitis. When the obstruction is removed, penicillin becomes effective and the pneumonic process subsides.

An analogy to penicillin treatment of an abscess is suggested, wherein the effectiveness of penicillin is not usually evident until there is drainage.

Bone

Gilchrist, K. J.: **Suppurative Arthritis of Hip-Joint Treated with Penicillin: Report of Four Cases,** *Brit.M.J. 2:450 (Sept. 20) 1947.*

Good final results were obtained with combined local and systemic penicillin therapy in 4 cases of acute suppurative staphylococcal arthritis of the hip-joint reported from Suva, Fiji.

Patients ranged in age from 6 to 16 years. All cases were presumably secondary to septic skin lesions. In all cases aspirated pus yielded Staph. aureus.

Treatment in all instances consisted of intra-articular instillation of penicillin after aspiration (9,000 to 30,000 units) on alternate days for 2 to 4 injections; systemic penicillin (20,000 to 30,000 units 3-hourly) for 7 days, and extension on Thomas' splint for 10 days to 4 weeks. In 2 cases a hip spica plaster was applied after removal of the splint.

In all cases full movements of the joint were attained. The author notes that return of full movement was attained earliest in cases without plaster, suggesting its use to be unnecessary.

From results in these cases, the following regimen of treatment is suggested: immediate exploratory aspiration of pus with replacement by an equal volume of penicillin solution (3,000 units/ml.) on alternate days until there is "local freedom from pain and examination of pus shows absence or degenerate forms only of staphylococci"; intramuscular penicillin (30,000 U./ml.) 3-hourly for a week; immediate immobilization with extension, maintained until patient is asymptomatic and afebrile; bed-rest for 4 weeks, after which active movements of the joint are to be encouraged.

Grace, E. J., and Bryson, V.: **Chronic Osteomyelitis in War Wounded: A Report of Two Veterans Discharged with Intractable Osteomyelitis and Successfully Treated with Local Penicillin-Detergent Therapy,** *New York State J.Med. 47:2204 (Oct. 15) 1947.*

From the experience in the 2 cases reported and in 37 civilian patients with chronic osteomyelitis, the authors conclude that "the mutilating treatment of osteomyelitis by radical surgery and cauterization is outmoded and should be replaced by conservative procedures employing antibiotics, as in the method described."

The method described employs a solution of penicillin in Aerosol O.T. 0.1% (1,000,000 units in 50 cc.). This solution is instilled into the medullary canal by means of a T-tube or a rubber catheter; 2 to 3 cc. is injected every 3 hours for 10 days. An opening for the tube is made by excising the sinus tract down to the diseased bone, then curetting or drilling a hole.

Case 1 was a 29 year old ex-serviceman who had been operated on in military hospitals on 2 occasions, and who had a chronic draining sinus from an osteomyelitis of the os calcis. Culture revealed Staph. aureus, "slightly pigmented and moderately hemolytic." With treatment as described the discharge stopped and the sinus remained closed.

Case 2 was a 27 year old man who was discharged from the service with a draining chronic osteomyelitis of the head and upper shaft of the tibia, subsequent to a shrapnel wound. Treatment as described was carried out for 10 days. 3 weeks later the wound was closed.

The authors state that with the use of a detergent with penicillin there is a synergistic action on the efficiency of the latter.

Killeffer, J. J., and Robertson, R. C.: **Non-Operative Treatment of Acute Hematogenous Osteomyelitis: Preliminary Report,** *J.Tennessee M.A. 40:319 (Oct.) 1947.*

That "acute hematogenous osteomyelitis is best treated with penicillin and that surgical intervention is rarely indicated" is concluded from results in a series of 14 cases. 3 case reports are presented in detail.

In all cases diagnosis was based on the history and physical and laboratory examinations and was later confirmed by x-ray findings. Duration of symptoms ranged from 1 to 35 days, average 7.9 days.

Penicillin was administered intramuscularly in all cases in doses of 10,000 to 25,000 units 3-hourly. Total dosage ranged from 960,000 to 6,040,000 units. In 6 cases, sulfadiazine was given in addition for 2 to 6 days. The authors state that no increased benefit was observed in these cases.

Temperature became normal in 2 to 11 days, average 4.1 days, after beginning penicillin. Treatment was continued for 2 weeks to 2 months after temperature became normal.

There were no deaths in the series. Surgery was required only once—incision of an abscess which had formed prior to admission. In 3 cases there was radiographic evidence of sequestra which appeared to be revascularized. In 3 cases there was pathologic fracture resulting from inadequate fixation.

OBSTETRICS AND GYNECOLOGY

Meiling, R. L.: **Appendicitis Complicating Pregnancy, Labor, and the Puerperium,** *Surg., Gynec. & Obst. 84:512 (Oct.) 1947.*

A historical review of the problem of appendicitis complicating pregnancy or the puerperium is presented and 4 additional cases are reported.

The difficulties of diagnosing acute appendicitis during pregnancy are pointed out, yet early diagnosis is imperative for successful treatment.

Principles of therapy include: Caesarean section followed by appendectomy; intraperitoneal implantation of sulfanilamide or sulfathiazole crystals; massive doses of penicillin postoperatively;

gastrointestinal decompression; blood and plasma transfusions; intravenous nutrition.

The author points out that in the case reported which had a fatal termination, diagnosis was delayed. Right upper quadrant tenderness occurred during the 6th month of pregnancy. Symptoms subsided and the patient was delivered at term. Abdominal distention, generalized abdominal pain and temperature elevation developed on the 1st postpartum day. Penicillin was given, but according to the author, in inadequate dosage—100,000 units followed by 3 doses of 30,000 units each, then again on the 5th day, 50,000 units 3-hourly. The patient died on the 5th day.

In the 3 cases treated successfully, caesarean section and appendectomy were done in 1 case, while in the other 2, appendectomy was done on the 1st and 9th postpartum days, respectively, shortly after the development of symptoms. In 2 cases sulfathiazole crystals were placed in the peritoneal cavity; in the 3rd case sulfadiazine was given intravenously. Penicillin was given in doses of 100,000 units 4-hourly, 30,000 units 3-hourly, and 20,000 units 3-hourly.

Reich, W. J.; Wilkey, J. L., and Nechtow, M. J.: **A Supplementary Report on the Combined Gyneco-Urological Management of Vesicovaginal Fistula,** *Urol. & Cutan. Rev. 51:566 (Oct.) 1947.*

The management of vesicovaginal fistulas is discussed and brief illustrative case reports are given.

For small fistulas occurring subsequent to obstetrics or surgery, closure by simple fulguration with a Bugbee electrode, accompanied by adequate vitamin and chemotherapy, was found satisfactory.

For larger fistulas the procedure used was cystoscopy about 1 or 2 weeks prior to surgical repair, which was done about 3 to 4 months after formation of the fistula.

Cultures of the urine of these patients revealed B. pyocyaneus and Staph. aureus as the most frequently occurring organisms.

Penicillin in doses of 40,000 units every 3 hours was administered for 5 or 6 days, and 5 Gm. of sodium sulfadiazine in 500 cc. of distilled water was given intravenously on the day of surgery. Streptomycin was given only if indicated.

UROLOGY

Bell, J. G. Y.: **Penicillin as an Aid in Prostatectomy,** *Lancet 2:347 (Sept. 6) 1947.*

That penicillin administered prophylactically to prevent infection is of value to prostatic surgery is demonstrated by the observations reported.

Penicillin was administered to permit catheter drainage and cystoscopy and thus avoid preliminary cystostomy with its high mortality and prolonged hospitalization.

In preliminary studies, a dosage of 20,000 units of penicillin intramuscularly every 6 hours gave effective concentrations of penicillin in the urine. This was attributed to the fact that most men with enlarged prostates have poor renal function.

The following procedure was used in a series of 217 cases: In patients with acute retention, catheterization was carried out with a 5-eyed Tieman catheter. Penicillin was given in doses of 20,000 units 4-hourly for 2 days, then 6-hourly for as long as the catheter remained in place. The author states that more recently a dosage of 200,000 units 8-hourly has proved equally effective and less disturbing to the patient. If fever developed, penicillin was given at 3-hour intervals and a sulfonamide was given concomitantly. Cystoscopy was done about the 3rd day.

In the period between November 1939 and November 1945, 508 cases of prostatic obstruction (simple enlargement and carcinoma) were treated without penicillin with a mortality of 14.1%; 433 were cases of simple enlargement with a mortality of 11.3%. 219 cases were treated with penicillin between November 1945 and June 1947 with an overall mortality of 3.7%; in 192 cases of simple obstruction the mortality was 3.1%.

Before the use of penicillin, 36.9% of all patients had cystostomy, with a resultant mortality of 15%. With the use of penicillin, only 10.9% of patients had cystostomy, with no deaths.

In conclusion the author recommends that penicillin be administered for any period of indwelling catheter in prostatic surgery.

Stabler, A. A., and Campbell, S. J.: **Cortical Abscess of Kidney: Penicillin Therapy,** *Urol. & Cutan. Rev. 51:511 (Sept.) 1947.*

"Penicillin therapy was used successfully without resorting to surgery" in the case of cortical abscess of the lower pole of the right kidney which is reported.

The authors state that treatment of acute, severe focal infection of the renal cortex has usually been heminephrectomy or nephrectomy.

In the case reported the patient was a 22 year old aviation cadet who was admitted to the hospital complaining of "sore throat, fever, general malaise, general weakness, pain in the back, and pain in the right lower quadrant of the abdomen." Symptoms had begun about 2 weeks after the appearance of furuncles on the back and leg.

Diagnosis considered were atypical pneumonia or acute appendicitis; however, x-rays of the chest and caecum were normal. KUB x-rays showed "a well-defined left psoas shadow."

On the day following admission, sulfadiazine was started, but was discontinued on the 3rd day of administration because of the appearance of nausea and vomiting and crystalluria.

Penicillin (40,000 units intramuscularly every 3 hours) was started on the 2nd day of sulfadiazine therapy. On the day after sulfadiazine was discontinued (5th hospital day) there was no nausea, pain subsided and temperature decreased. On the 8th hospital day intravenous urogram showed normal dye concentration and a clearer delineation of the lower pole of the right kidney than previous films.

The patient remained asymptomatic and physical and laboratory findings were normal during 2 months' follow-up.

Berry, J. V., and Berry, N. E.: **Acute Exudative Cystitis of Undetermined Etiology,** *J.Urol. 58:260 (Oct.) 1947.*

The diagnosis, pathology and treatment of acute exudative cystitis of undetermined etiology are discussed, based on the experience in 24 cases, all soldiers. 3 cases are reported in detail.

According to the authors, this syndrome has been variously called acute exudative cystitis, acute interstitial cystitis, acute hemorrhagic cystitis, amicrobic pyuria and Reiter's disease. Findings common to all are nonspecific urethritis, intense cystitis, sterile urine and dilatation of the upper urinary tract. In Reiter's disease, conjunctivitis and arthritis appear in addition.

The authors state that this condition must be differentiated from gonorrhea, tuberculosis and malignancy. Reversal of the process in a short time with specific treatment (neoarsphenamines or mapharsen) appears to be diagnostic of the disease.

In this series of cases, mandelic acid, sulfonamides and penicillin seemed of little value, although in 1 of the cases reported, penicillin proved beneficial.

In 2 of the 3 cases reported, penicillin in total dosages of 600,000 and 900,000 units effected no improvement. In the remaining case, the patient had improved and temperature became normal after a course of Novarsenobenzol. Following this a course of 200,000 units of penicillin resulted in progressive improvement, with disappearance of joint pain and with the bladder becoming normal.

OTORHINOLARYNGOLOGY

Kahn, K. M.: **Role of Penicillin in the Management of Acute and Chronic Frontal Sinusitis,** *Arch. Otolaryng. 46:293 (Sept.) 1947.*

An analysis is presented of 7 cases of suppurative frontal sinusitis treated

with penicillin, from which it is concluded that penicillin therapy can be effective without surgery in acute frontal sinusitis if instituted before suppuration occurs, but that if suppuration is present penicillin is only a valuable adjunct to well planned surgery. Therapeutic procedures in the cases reported are tabulated. Cure was effected in all cases.

Case 1 was an acute nonsuppurative right frontal sinusitis. Cure was effected without surgery by the administration of 25,000 units of penicillin 3-hourly for 10 days.

The other cases were all acute or chronic suppurative sinusitis. Organisms isolated were hemolytic or nonhemolytic streptococci and hemolytic Staph. aureus. No penicillin resistant organisms were encountered.

In all these cases radical surgery was required to effect cure. Penicillin was administered preoperatively (all but 1 case) in doses of 25,000 units 3-hourly for periods of 2 to 7 days, and was continued postoperatively for 4 to 11 days. In 3 cases, penicillin was instilled locally (10,000 or 20,000 units 3-hourly) for 4 days postoperatively. In 1 case, acute suppurative frontosphenoethmoiditis, penicillin was administered intramuscularly (50,000 units 3-hourly for 21 days postoperatively), locally, and intrathecally (15,000 units daily for 8 days).

The author states that the use of penicillin protection permitted radical surgery without postoperative complications. The local instillation of penicillin postoperatively permitted primary closure, thus shortening the period of healing.

Waltner, J. G.: **Otogenic Abscess of the Contralateral Frontal Lobe; with Report of a Case,** *Arch. Otolaryng. 46:375 (Sept.) 1947.*

A case of acute purulent otitis media complicated by abscess of the contralateral frontal lobe is reported, in which complete recovery was effected by sulfadiazine and penicillin therapy, mastoidectomy, and drainage of the abscess after waiting long enough for encapsulation. The author states that this is the third recorded case of otogenic abscess of the contralateral frontal lobe in which the patient recovered completely.

The patient was a 54 year old white woman in whom otitis media developed subsequent to an upper respiratory infection. On the 12th day of otitis media, right hemiplegia occurred and meningeal symptoms were present. The patient became incontinent on the 13th day of the disease and on the following day aphasia developed.

Sulfadiazine therapy was started on the 12th day. Intramuscular penicillin (20,000 units 3-hourly) was started on the 13th day. Penicillin (30,000 units) was injected intrathecally on the 14th, 15th, 16th, 17th and 25th days.

Between the 16th and 21st days the patient's condition improved, with decrease in neck rigidity, improvement in speech, cessation of incontinence, and a decline of temperature to 99 F. The hemiplegia remained unchanged.

During the following 4 days, the temperature increased gradually to 101 F., but the neurologic picture showed no change.

Since it was felt that the otitis media was the focus of infection, a simple mastoidectomy was performed on the 30th day. Penicillin was administered postoperatively.

Air studies revealed an intracranial lesion on the left side. On the 55th day a left frontoparietal osteoplastic craniotomy was performed and the abscess was drained through a cortical incision. Sulfadiazine powder was placed in the cavity and penicillin solution (30,000 units) was instilled daily. 2 days postoperatively the hemiplegia began to disappear. At 15 months after discharge from the hospital, the patient was entirely free of complications.

Fenton, R. A.: **Tissue Changes Occurring in Sinus Membranes after Treatment with Penicillin,** *Soc. Trans., Am. Laryng. A., Arch. Otolaryng. 46:568 (Oct.) 1947.*

6 cats were experimentally infected with virulent sinusitis by instilling a culture of Str. pyogenes into the frontal sinuses. After treatment with penicillin solution (2,000 U./cc.) tissues were removed for study. Surface bacteria were more rapidly destroyed and fewer bacteria were present in the goblet cells and deeper tissues in the treated animals. Acute inflammation persisted longer in the treated animals.

In discussion, Dr. A. W. Proetz states the opinion that penicillin is practically useless in cases of chronic sinusitis, but probably has considerable value in cases of acute sinusitis. He states that his observations have shown that as the concentration of penicillin is increased beyond 250 U./cc., the duration of the ciliary beat is reduced.

Klinefelter, H. F., Jr., and Humphries, W. C.: **Cervical Actinomycosis with Embedded Foreign Body and Without Sinus Formation,** *Ann.Int. Med. 27:638 (Oct.) 1947.*

A patient with cervical actinomycosis subsequent to injury of the mucous membrane of the oropharynx with a straw was successfully treated with penicillin, sulfadiazine, potassium iodide and surgical incision 4 months after onset.

A 30 year old soldier pierced the mucous membrane of his mouth with a straw when he dived into a pile of hay while on maneuvers. He felt that a small piece of straw remained imbedded under the tongue, but none was found on examination.

Painless swelling of the left side of the neck became evident about 10 days after injury. The swelling increased gradually and about 3 months after injury the patient was hospitalized. Swelling continued to increase during 7 weeks' observation. Treatment with penicillin (30,000 units 3-hourly) for 3 days resulted in some decrease in the swelling. The patient was transferred to the Oliver General Hospital.

Examination revealed a hard mass in the left submandibular area. Results of physical, laboratory, and x-ray examinations were otherwise negative except for an elevated sedimentation rate.

Sulfadiazine (4 Gm. daily), penicillin (40,000 units 3-hourly), and potassium iodide (0.5 Gm. t.i.d.) were administered for 22 days. During this period there were no constitutional symptoms and the swelling of the neck decreased. However, numerous hard lymph nodes were palpable and it was thought that operation was indicated.

When the mass was removed, a piece of straw was found embedded in the tonsillar area. Pathologic examination of the mass revealed numerous actinomyces granules.

Penicillin (40,000 units 3-hourly) was continued for 6 days postoperatively, after which sulfadiazine and potassium iodide were administered for about 10 weeks.

The patient recovered uneventfully and was completely well 5 months after operation.

Anneberg, A. R.: **Dental Problems in Ear, Nose and Throat,** *J.Iowa M.Soc. 37:494 (Nov.) 1947.*

Closer cooperation between the dentist and the otolaryngologist is urged, and the following conditions of dental origin are discussed: maxillary sinusitis, antra-oral fistula, cellulitis, and infections of the parapharyngeal and sublingual spaces.

The maxillary sinus may become infected from diseased roots of teeth, retained unerupted teeth, or extraction accidents. The infecting organisms are usually the staphylococcus, streptococcus, pneumococcus or Vincent's organisms. A history of a faulty or aching tooth is important for diagnosis. The pus has a characteristically foul odor.

Treatment recommended includes extraction of the tooth, and irrigation of the sinus daily or every other day with normal saline, followed by instillation of 0.25% paredrine containing 800 units calcium penicillin/cc. If thick tenacious mucus forms, installation of a suspension of sulfathiazole crystals in paredrine is suggested. Surgery is recommended only for chronic cases, those with a persistent oral fistula or those containing a foreign body.

Cellulitis of the jaw or cheek may be secondary to caries, apical abscess, or extraction. Treatment during the first 48 to 72 hours with intramuscular peni-

cillin (25,000 units 3-hourly), arsenicals, sulfadiazine, and x-ray therapy is recommended.

The parapharyngeal space may be infected by tissue contiguity or by way of the lymphatics or blood vessels. Treatment suggested is the same as for cellulitis, except that the penicillin dosage is 50,000 units 3-hourly. External drainage is indicated if response to treatment is inadequate.

Treatment for infections of the sublingual space is the same as for cellulitis, with external drainage if indicated and irrigation with penicillin through a drain.

OPHTHALMOLOGY

Hoskins, L. C.: **Penicillin Therapy of Experimental Infections of the Lens and Vitreous with Clostridium Welchii,** *Arch. Ophth. 38:301 (Sept.) 1947.*

Intralenticular and intravitreal injection of penicillin proved effective in controlling experimental Cl. welchii infections of the lens and vitreous of rabbits' eyes if treatment was started within 3 hours after inoculation. Results were not as satisfactory when treatment was begun 6 hours after inoculation.

Direct injection of penicillin was chosen as this method had proved effective in staphylococcic infections of the lens and vitreous.

In preliminary experiments it was determined that the strain of Cl. welchii used was inhibited in vitro by penicillin in a concentration of 0.1 U./cc. Direct injection of 0.05 cc. penicillin solution containing 5,000 U./cc. produced concentrations of 0.14 and 0.12 U./Gm. respectively, at 48 hours after injection in the lenses of the eyes of 1 rabbit, only traces in the eyes of the other 2 rabbits at 24 and 96 hours. Dosage selected for treatment was 0.1 cc. of the 5,000 U./cc. solution.

Infection was produced by inoculation with 0.05 cc. of a 10^{-4} dilution of a culture of Cl. welchii. 1 eye of each animal was treated, while 1 was untreated and served as a control.

The lenses of the eyes of 16 rabbits were inoculated. Of 8 eyes treated 3 hours after inoculation, only 2 showed uncontrolled infection in the lens and vitreous; of 8 eyes treated 6 hours after inoculation, 3 showed uncontrolled infection. In eyes treated at 3 hours, the only damage to the globes was traumatic cataracts, while in the eyes treated at 6 hours, there was formation of strands of vitreous with retinal detachment.

The vitreous of the eyes of 16 rabbits were likewise inoculated. 13 of the control eyes were lost because of infection. Of the 8 eyes treated 3 hours after inoculation, 4 showed atrophy of the retina, at the site of injection, 1 showed detachment of the retina, and 2 showed cortical changes in the lens, while 6 showed strands of vitreous with retinal detachment.

Shuttleworth, F. N., and Benstead, J. G.: **Primary Meningococcal Ophthalmia,** *Brit.M.J. 2:568 (Oct. 11) 1947.*

2 cases of primary meningococcal ophthalmia are reported, both of which were successfully treated with no residual damage to the eye—one eventually with local sulfacetimide, the other with local penicillin.

The patients were 7 and 6½ years of age, respectively. In both cases a meningococcus was cultured from the pus from the eye. In neither case was a focus of infection demonstrable.

In case 1, the eye remained injected after hot applications and 1% atropine ointment twice daily for 7 days, but cleared following instillation of 30% sulfacetimide drops twice daily for 6 days.

In case 2, clearing followed treatment for 6 days with "hot-spoon" baths 3 times daily and instillation of penicillin drops (2,000 U./ml.) every 3 hours.

Klauder, J. V.: **Treatment of Interstitial Keratitis with Particular Reference to the Results of Penicillin Therapy,** *Am.J.Syph., Gonor. & Ven.Dis. 31:575 (Nov.) 1947.*

An analysis is presented of results of penicillin therapy in 59 cases of interstitial keratitis in whom visual acuity with refraction was determined at intervals for 1 to 3 years after treatment. Results are compared with those in a series of 54 patients with active interstitial keratitis treated with fever-chemotherapy, with treatment other than penicillin as reported by other investigators, and in 2 series of patients who were untreated. Data are tabulated. Illustrative case reports are given.

In 41 of the penicillin treated cases, commercial sodium penicillin was given intramuscularly at 4-, later 3-hour, intervals to a total dosage of 2,400,000 units in 8 days. 18 patients received total doses of 0.5 million to 4 million units in 8 to 15 days. Some patients received local penicillin in addition. The author states that 15 patients were later treated with 2,400,000 units of crystalline penicillin G with results similar to those with commercial penicillin.

Cases for the fever-chemotherapy group were selected on the following criteria: more than 50 injections of a bismuth compound, plus 8 to 12 febrile paroxysms.

The following observations were made in the penicillin treated group: That penicillin therapy did not prevent an initial attack of interstitial keratitis (suggesting that interstitial keratitis is not exclusively a syphilitic process), nor does it prevent involvement of the second eye or recurrence in the treated eye.

The author states that important criteria in evaluating results of treatment of interstitial keratitis are final visual acuity with refraction, and determination at least a year after subsidence of inflammatory symptoms in order to permit maximum absorption of corneal opacities.

The final visual acuity with the various types of therapy was as follows:

Penicillin—97 eyes; 84.5% 6/6 to 6/21, 11.3% 6/30 to 6/60, 4.2% less than 6/60.

Fever and chemotherapy—95 eyes; 84.2% 6/6 to 6/21, 8.4% 6/30 to 6/60, 7.4% less than 6/60.

Arsenic and bismuth or mercury (3 series)—110, 178, and 133 eyes, respectively; 58.0, 84.2 and 59.8% 6/6 to 6/21; 35.0, 11.8, and 21.9% 6/30 to 6/60; 7.0, 3.9, and 18.3% less than 6/60.

Mercury only—112 eyes; 55.8% 6/6 to 6/21, 24.4% 6/30 to 6/60, and 19.8% less than 6/60.

Untreated (2 series)—185 and 179 eyes, respectively; 51.1 and 55.7% 6/6 to 6/21; 37.0 and 25.6% 6/30 to 6/60, and 12.0 and 18.4% less than 6/60.

In conclusion the author states that the addition of penicillin to the therapy of interstitial keratitis does not give results superior to those with other forms of treatment, and that neither penicillin nor any other form of therapy eliminated residual industrial blindness (visual acuity of 6/60 or less). He states the belief, however, that penicillin can displace metal chemotherapy, and should be combined with nonspecific treatment in the form of fever therapy. Routine treatment now employed at Wills Hospital consists of 2,400,000 units of penicillin in 8 days and 8 to 12 febrile paroxysms given concomitantly.

GENERAL

Penicillin, Foreign Letters, *J.A.M.A. 135:528 (Oct. 25) 1947.*

At a meeting on penicillin held in London, Sir Alexander Fleming, discoverer of penicillin, opened the discussion with a general review of the history and usefulness of the drug. He deprecated indiscriminate use of penicillin and urged that it be given only when the infecting organism is sensitive to it.

Professor R. V. Christie reported results in 269 cases of infective endocarditis treated with penicillin. The most successful dosage was 500,000 units daily. Relapse usually occurred within 20 days after treatment, but sometimes occurred after a year. Analysis of end results demonstrated that infection could be controlled in 95% of cases, but that 39% of patients would die later. The degree of heart failure and the state of nutrition appeared to be the most significant prognostic points.

What's New in Medicine, *Panel Discussion, Chicago M.Soc.Bull. 50:268 (Oct. 11) 1947.*

In a panel discussion on new developments in medicine, Dr. Paul Holinger

discussed pulmonary lesions. He states that penicillin aerosol is of "tremendous benefit" in the treatment of bronchiectasis. Combined penicillin-streptomycin aerosol is suggested—200,000 units of penicillin and 500,000 units of streptomycin for 2 days' treatment. He warns that chemotherapy may delay the diagnosis of bronchogenic carcinoma.

Dr. W. W. Spink discussed chemotherapy in general. He states that tyrothricin, streptomycin and penicillin are the only antibiotics available for the treatment of infectious disease. Of the probably 8 penicillin fractions, penicillin G is the only crystalline penicillin available for clinical use in pure form. The author states that there is no advantage in using amorphous penicillin as satisfactory clinical results are obtained with crystalline penicillin G if enough is used. The author prefers the administration of crystalline penicillin G in aqueous solution, intramuscularly, at intervals of 2 to 8 hours, depending on the severity and type of the infection. Intramuscular administration of penicillin in beeswax-peanut oil may be used in some types of infections, particularly syphilis and gonorrhea. For oral administration 5 times the intramuscular dose is recommended.

Dr. John A. Bigler in discussing new developments in pediatrics states that penicillin, streptomycin and the sulfonamides have had a tremendous effect upon pediatric practice. Penicillin may be used alone or combined with sulfonamides in serious infections. Dr. Bigler states that he has found intramuscular penicillin more effective than oral penicillin in young infants. Streptomycin has been useful in the treatment of influenzal meningitis.

ADMINISTRATION—DOSAGE FORMS

Monash, S.: **The Use of Bismuth, Silver and Mercury Salts of Penicillin for the Prolongation of Penicillin Blood Levels: Preliminary Report,** *J.Invest. Dermat. 9:157 (Sept.) 1947.*

Studies made in 13 rabbits demonstrated that when an insoluble metallic penicillin salt is injected intramuscularly, the penicillin is reactivated in vivo and results in prolongation of blood levels for at least as long as 20 hours.

Blood levels produced with a 20,000 unit/Kg. dose of the various salts were as follows: sodium penicillate in peanut oil—no detectable level after 5 hours; silver penicillate—0.08 U./cc. at 17 hours, 0.03 at 20 hours; mercury penicillate—0.08 at 17 hours; bismuth penicillate—0.04 at 20 hours.

It is suggested that the use of these salts would be advantageous in the treatment of syphilis, since two spirocheticidal substances would be combined in one injection.

Monash, S.: **Use of Insoluble Penicillin Salts for the Prolongation of Penicillin Blood Levels,** *Science 106:370 (Oct. 17) 1947.*

Penicillin produces insoluble salts with many metals and with numerous organic substances, such as the triphenylmethane dyes, the acridine dyes, and Nile green, quinine, and other substances.

Based on the theory that if these inactive insoluble salts were reactivated in vivo, their use might prove a practicable means of prolonging penicillin blood levels, studies were made in rabbits.

A single intramuscular injection of 20,000 units penicillin/Kg. suspended in peanut oil produced no detectable blood level after 5 hours. A similar injection of silver penicillate produced a level of 0.08 U./cc. at 17 hours and 0.03 U./cc. at 20 hours; mercury penicillate 0.08 U./cc. at 17 hours; ferric penicillate 0.16 at 17 hours and 0.02 at 20 hours; brilliant green penicillate 0.16 U./cc. at 18 hours, and gentian violet penicillate 0.04 U./cc. at 18 hours.

Goldman, L., and Feldman, M. D.: **A. Contact Testing of the Vagina with Vaginal Suppositories Containing Penicillin; B. The Therapeutic Use in Dermatology of Vaginal and Rectal Suppositories Containing Penicillin; Preliminary Report,** *J.Invest. Dermat. 9:155 (Sept.) 1947.*

30 patients, ambulatory and hospital, 19 dermatological and 11 nondermatological, were treated with rectal and vaginal suppositories over a period of 1 week. Each suppository contained 100,000 units of penicillin in a base of cocoa butter with bismuth subcarbonate and beeswax added. The authors state that good clinical response was obtained in most patients. No reactions were observed in the series.

Serum levels were determined in 3 patients. In 1 patient after a rectal suppository, levels were 0.015 unit at ½ and 1 hour, 0.03 at 3 hours, and 0.25 at 5 hours. In 1 patient after a vaginal suppository, levels were 0 at ½ and 1 hour, 0.06 at 2 hours and 20.0 at 7 hours. No detectable levels were observed in the 3rd patient.

Patch tests of the vaginal mucosa were made in 5 patients by inserting suppositories fitted in a slat of a rubber vaginal nozzle. No local reaction was seen.

Royston, G. R.: **Penicillin by Intra-Oral Drip,** *Brit.M.J. 2:454 (Sept. 20) 1947.*

Administration of penicillin by continuous oral drip is suggested for the treatment of faucial infections caused by Vincent's organisms, other severe throat infections, as severe faucial diphtheria, and surgical conditions of the throat.

The method described employs a standard drip-transfusion set, with the needle replaced by a piece of soft thin rubber tubing. A piece of dental wire in the lumen permits the tubing to be bent into the shape of a J. The short curved end is placed in the mouth in the buccogingival sulcus. The tube is then taped to the face above the mouth, at the bridge of the nose, and on the forehead. A solution containing 50,000 units of calcium penicillin in 1 pint of normal or half-normal saline was delivered in 24 hours.

The author states that the drip was well tolerated. It was not removed during eating or sleeping. The only reaction observed was the development of a brown fur on the tongue in about one-fourth of the patients, associated in some instances with a metallic taste or headache.

In 18 cases of Vincent's infection of the tonsils and fauces, subjective improvement was noted within 6 hours after beginning the drip. 2 patients with glandular fever of the anginous type and 6 with acute tonsillitis were relieved of discomfort within a few hours. 7 diphtheria carriers of 3 weeks' duration became swab-negative after 72 hours; however, 3 days after treatment, all became swab-positive.

Intra-Articular Administration of Penicillin, *J.A.M.A. 135:530 (Oct. 25) 1947.*

Dr. Guido Costa Bertani has reported to the Society of Internal Medicine, Buenos Aires, rapid and successful results with intra-articular injection of penicillin in 6 cases of acute articular processes.

Penicillin dosage per injection was 5,000 to 20,000 units (10,000 U./cc.).

Brindle, H.; Fairbrother, R. W., and Jackson, F. B.: **Penicillin in 1% Beeswax-Arachis Oil,** *Lancet 2:505 (Oct. 4) 1947.*

Intramuscular injection of 300,000 units of crystalline penicillin in 1% beeswax-peanut oil contained in 1 ml. resulted in effective blood levels for 15 hours after injection and gave satisfactory results in 28 proved cases of acute gonorrhea.

In a study carried out at the Department of Pharmacy and Pharmacology, Manchester University, on the maximal prolongation of the effect of drugs by using suspensions in oil media, it was found that 0.5 to 1 ml. was the optimum bulk, and that there was no significant difference in results obtained with a plain oil vehicle and one containing 4-5% beeswax.

In preliminary studies with penicillin, a vehicle containing 1% beeswax in peanut oil proved to be fluid at room temperature, finely ground penicillin was readily diffusible by gentle shaking, and the mixture was easily administered through a moderately fine needle (No. 2 serum needle). A suspension of penicillin in plain oil settled

after a few days and was easily rediffused. A suspension of 2% beeswax was considered too viscous.

Blood levels were assayed by the broth dilution method after a single intramuscular injection of 300,000 units of penicillin in 1% beeswax-peanut oil and in aqueous solution. With the 1% beeswax-peanut oil vehicle, maximum levels of 0.5 to 2 U./ml. were obtained 3 hours after injection, levels of 0.03 were present 15 hours after injection, while no penicillin was detectable 24 hours after injection. With the aqueous solution, maximum levels of 2 U./ml. were obtained 2 hours after injection, levels of 0.125 were present at 8 hours, while no penicillin was detectable at 10 hours.

28 proved cases of acute gonorrhea were treated with intramuscular injection of 300,000 units penicillin in 1% beeswax-peanut oil with satisfactory results and without local reaction or pain.

Dowling, H. F.; Romansky, M. J.; Welch, H.; Robinson, J. A.; Chandler, V. L.; Zeller, W. W., and Hirsh, H. L.: **"Liquid" Versus "Solid" Penicillin Oil and Wax; The Effect of Particle Size and Type of Penicillin,** *J.A.M.A. 135:567 (Nov. 1) 1947.*

In order to determine the comparative efficacy of fluid ("liquid") and viscid ("solid") preparations of penicillin in oil and wax, blood levels were determined in 252 patients in the wards of the Gallinger Municipal Hospital following a single intramuscular injection of various penicillin preparations from 11 manufacturers. Data are charted and tabulated.

Preparations studied consisted of crystalline penicillin (sodium and potassium) and amorphous calcium penicillin in oil and wax. Dosage for each injection was 300,000 units of penicillin in 4.8% beeswax in oil contained in 1 cc.

Since it was noted that the size of the particles of penicillin influenced the blood levels, preparations were classified as "large particle" (containing "50% or more of the total relative weight of particles measuring greater than 50 microns") and "small particle" (containing less than 50% of particles of this size).

Blood levels were determined by both the Rammelkamp technic which uses the streptococcus as the test organism, and the "subtilis" method. The latter proved slightly more sensitive.

Results, based on the number of subjects showing demonstrable blood levels at various intervals after injection, demonstrated that preparations containing crystalline penicillin were superior to those containing amorphous penicillin when particle size and viscosity were the same. Best results with solid preparations were obtained with those containing crystalline penicillin of large or small particle size or amorphous penicillin of large particle size. Best results with liquid preparations were obtained with those containing particles of large particle size. Those with particles of small size gave inferior results.

Since liquid preparations are more easily administered, and since preparations containing crystalline penicillin remain stable at room temperature for longer periods than amorphous preparations, the authors state, on the basis of the above results, "the liquid preparations of crystalline penicillin of large particle size are recommended as the most satisfactory form of penicillin in oil and wax."

Trussell, P. C.; Sinclair, A. B., and Buchanan, S. C.: **Duration of Effective Blood Levels Following Administration of Penicillin in Peanut Oil and Beeswax,** *Canad.M.A.J. 57:387 (Oct.) 1947.*

Studies were made in patients at the Montreal General Hospital of blood levels following a single intramuscular injection of 300,000 units of penicillin in 1.5 ml. peanut oil and 2% beeswax, and following a similar intramuscular injection supplemented with oral penicillin in doses of 100,000 units each given 12, 15, 18 and 21 hours after injection. Results are tabulated.

The 2% beeswax vehicle was selected in an attempt to avoid reactions reported with the 4.8% mixture.

Blood levels were determined by a serial dilution method using blood serum and by a cup-plate method using defibrinated plasma. The latter method was considered preferable because of ease and rapidity of performance and accuracy of results.

Following a single intramuscular injection of 300,000 units penicillin in 2% beeswax-peanut oil, 80% of 19 subjects at 24 hours after injection had assayable blood levels. The average blood level at this time was 0.058 U./ml., twice the usual therapeutic concentration (0.03 U./ml.).

When combined penicillin-beeswax-peanut oil and oral penicillin therapy was used, the intramuscular injection was given at 8 P.M. and the oral doses were begun at 8 A.M. and continued at 3-hour intervals until 5 P.M. Assayable blood levels were present in all 11 subjects at 24 hours after injection. The average blood level at this time was 0.14 U./ml., or 4 times the therapeutic concentration.

Loewe, L.; Eiber, H. B., and Alture-Werber, E.: **Enhancement of Penicillin Blood Levels Following Oral Administration of Caronamide,** *Science 106:494 (Nov. 21) 1947.*

Oral caronamide, in doses of 3 Gm. every 4 hours for periods of 2 to 19 days, in 9 patients with subacute bacterial endocarditis who were receiving conjoint intravenous penicillin-heparin therapy, enhanced penicillin blood levels 2 to 7 times those attained without caronamide.

The daily dosage of penicillin (1,000,000 to 20,000,000 units) apparently did not influence the degree of augmentation. In most instances, caronamide in doses of 2 Gm. 4-hourly resulted in no augmentation of blood levels.

As demonstrated in 1 case, multiples of enhancement of the blood level can be achieved by doubling the penicillin dose, while maintaining the caronamide dose at 3 Gm.

The only reaction observed was transitory nausea in 2 subjects. A reducing substance was found in the urine of all patients, but disappeared after caronamide was discontinued.

PHARMACOLOGY

Eagle, H., and Newman, E.: **The Renal Clearance of Penicillin F, G, K, and X,** *J.Clin.Invest. 26:903 (Sept.) 1947.*

The renal clearance of the 4 penicillin species F, G, K, and X was determined in rabbits and in man over a wide range of plasma concentration and with varying rates of urine flow.

In human subjects continuously infused with penicillin F, G, K or X, the renal clearance of penicillin G, X and F approximated the total renal plasma flow and was 4 or 5 times the glomerular filtration rate determined with inulin or thiosulfate.

The renal clearance of penicillin K was ¼ to ½ that of the other species. The authors suggest that the lower renal clearance of penicillin K with rapid disappearance from the blood and low urinary recovery may be due to the fact that it is bound and inactivated by the plasma and tissues to a greater extent than the other species.

With all the penicillin species the renal clearance was independent of the penicillin blood level or the rate of urine flow.

Renal clearance of penicillins G, K, and X was determined in humans following a single intravenous or intramuscular injection in aqueous solution. Again the renal clearance of penicillins G and X approximated the total renal plasma flow and was 4 to 6 times the glomerular filtrate rate, while that of K was about ¼ as great.

The renal clearance of penicillin G as the potassium salt in beeswax-peanut oil, following injection in 2 subjects, averaged 687 and 471 ml./min. as compared with calculated renal plasma flows of 796 and 632, and were 4.2 and 3.3 times the glomerular filtration rate.

In rabbits also the renal clearance approximated the renal plasma flow. In 2 rabbits in which the tubular excretory mechanism was completely saturated,

the initial renal clearances corresponded to the glomerular filtration rate. As the serum concentrations fell to less than the tubular saturation level, the renal clearance became normal.

From the results in these experiments, the authors suggest that the renal clearance of penicillin could be used as a test of kidney function.

They conclude that attempts to retard excretion of penicillin by restriction of water and salt intake or by administering pitressin, are physiologically unsound, and that blocking the tubular mechanism with diodrast, para-aminohippuric acid and benzoic acid may be as expensive and as laborious as increasing the penicillin dosage.

The most effective method of delaying excretion of penicillin, at present, is by delaying absorption at the site of injection, as with penicillin-beeswax-peanut oil.

It is suggested that penicillin derivatives may be produced with lower renal clearances than the natural penicillins, and with correspondingly increased therapeutic activity.

Eisenberg, W. V., and Keenan, G. L.: **Microscopic-Crystallographic Properties of Crystalline Sodium Penicillin G,** *J.Am.Pharm.A. (Scient. Ed.) 36:294 (Oct.) 1947.*

An optical-crystallographic study was made of 5 preparations of the sodium salt of crystalline penicillin G.

3 crystalline habits were revealed: elongated, fibrous rods (needle-like crystals); plates; compact radial aggregates (spherulites). All examples could be converted to the same habit by recrystallization—6-sided plates which sometimes develop in hemimorphic formations. No change in the optical-crystallographic properties was produced by heating at 100° for 2 hours.

The authors state that the optical crystallographic properties may be used to identify crystalline penicillin sodium.

Antibacterial Action

Nutini, L. G., and Lynch, E. M., Sr.: **Response of Penicillin-Resistant Strains of Staphylococcus Aureus to Extracts of Beef Brain,** *J.Pharm. & Exper. Therap. 90:313 (Aug.) 1947.*

In previous studies it was demonstrated that an 80% alcohol-precipitated extract of beef brain tissue converts the S-form of Staph. aureus to the white R-form which is avirulent, and that this extract is superior to penicillin, in the dosages used, in Staph. aureus infections in mice.

In the present study an investigation was made of the comparative therapeutic and prophylactic activity of penicillin and brain extract in mice subcutaneously infected with penicillin resistant strains of Staph. aureus, and on the development of resistance of these organisms to brain extract.

Dosages used were 1,000 units of penicillin or 50 mg. brain extract daily until the animal died or the lesion healed completely.

In the prophylactic series (treatment 2 to 3 hours prior to infection) the mortality in 144 animals treated with penicillin was the same as in the control group—80%, more than half dying by the 5th day. Of the 144 animals treated with brain extract, 1 died of an injury, none of the infection.

In the therapeutic series, mortality for the control group was 84%, in the penicillin treated group 95%. In the brain extract group, 2 of 144 animals died; lesions in the survivors healed in an average of 8 days.

Turbidity studies on organisms grown continually in the presence of brain extract demonstrated that the organisms remained sensitive to brain extract during periods of 74 and 37 days, while similar studies with penicillin demonstrated that penicillin resistance was maintained. That the organisms grown in cultures containing brain extract were avirulent was demonstrated by in vivo experiments in mice.

Cumberland, M. C., and Turner, T. B.: **Comparative Effectiveness of Penicillins G, F, K, and X in Experimental Relapsing Fever,** *Am.J.Syph., Gonor. & Ven.Dis. 31:485 (Sept.) 1947.*

A study was made of the relative therapeutic efficacy of penicillins G, F, K, and X in experimental relapsing fever infections in mice, and to determine whether the results obtained could be correlated with those obtained in experimental syphilis in rabbits.

Mice were inoculated with plasma from rats that had been inoculated with Borrelia novyi. Graded doses of penicillin were injected intraperitoneally 24 hours after inoculation. Spirochete counts of the blood were made 24 hours after treatment. For evaluating comparative efficacy, the effective dose (ED) of penicillin was considered that amount necessary to lower the spirochete count to 2 or less.

The ED_{50} for penicillins G, F, K, and X was 8.3, 15, 37, and 24 mg./Kg., respectively. The relative efficacy of penicillins G, F, K, and X was on a gravimetric basis 100, 56, 22, and 35 respectively, and on a unitage basis 100, 57, 17, and 66 respectively. Thus, penicillin G proved to be the most effective of the penicillins.

It is concluded that the mouse test is satisfactory for a qualitative evaluation of the penicillin fractions in experimental syphilis, but not for quantitative, since it is not as sensitive as the rabbit test.

Foley, E. J., and Lee, S. W.: **A Method for Showing Antibacterial Activity of Minute Quantities of Gramicidin or Penicillin,** *J.Lab.&Clin.Med. 32:1136 (Sept.) 1947.*

A method is described by which the antibacterial activity of millimicrogram quantities of penicillin or gramicidin can be measured.

The method is based on that of Jones and Simms who showed that inhibition of colony size and hemolytic zones produced by Group A streptococci on blood agar plates was a measure of bacteriostasis. Dilutions of penicillin were made in water, tyrothricin or gramicidin in 50% propylene glycol-water. The hemolytic zone produced by the test organism was 2.0 mm. in diameter. The inhibitory activity of the drug tested could be measured by comparing the size of the colonies and hemolytic zones produced with and without the drug.

With this method, amounts of penicillin and gramicidin as small as 0.8 millimicrogram/ml. blood agar showed detectable inhibition. Penicillin appeared more active than gramicidin on a weight basis. Since tyrocidine in a concentration of 1 microgram/ml. blood agar failed to inhibit the test streptococcus, the amount of gramicidin present in tyrothricin samples can be calculated.

Weld, J. T.: **A Streak Plate Method for Determining Growth Curves,** *J. Lab. & Clin.Med. 32:1139 (Sept.) 1947.*

A simple streak plate method for determining growth curves of Staph. aureus under the influence of antibacterial agents is described.

The method was briefly as follows: A 3½ hour culture of Staph. aureus was prepared the day before the test and the bacterial count estimated on a test plate. Agar plates were prepared and stored for 3 or 4 days to dry. On the day of the test the culture was diluted to contain 100,000 to 600,000 cells/cc. 1 cc. amounts of solutions of the antibacterial substances were placed in tubes. 0.5 cc. of the test culture was added to each tube. The test fluids were placed in a bath. At intervals of 1 or 2 hours 2 loopfuls (0.002 cc. each) were withdrawn and spread evenly on a horizontal section of an agar plate. If a large bacterial count was expected an entire plate was used for a single test.

The author states that using this method 6 antibacterial agents, each in 8 dilutions, can be tested at 1-hour or 2-hour intervals by one worker.

Results are summarized as follows:

Phenol—rapidly bactericidal, killing organisms in a concentration only slightly higher than the noninhibitory concentration.

Streptothricin, streptomycin, clavacin, penicillin, and protoanemonin—kill organisms in 8 hours or less in concentrations not more than 40 times the noninhibiting doses.

Manganese protoporphyrin, alcohol-sulfur and carbowax-sulfur—bacteriostatic only; inhibit growth in low concentrations, but fail to kill organisms in the highest concentrations tested.

SERIAL DILUTION ASSAY METHOD
EMPLOYING BACILLUS SUBTILIS FOR DETERMINATION OF PENICILLIN CONCENTRATIONS IN BLOOD AND BODY EXUDATES

Because of the many requests received from physicians for information regarding methods of penicillin assays, the assay method used in the laboratories of C.S.C. Pharmaceuticals is described herewith. Familiarity with this procedure will give the physician a better understanding of the significance of blood levels, and incidentally, will demonstrate that the method is not a chemical one, but rather is based on the biologic properties of the test organism. The serial dilution method developed by the Food and Drug Administration, slightly modified, is the procedure employed. It has been found to be satisfactory for relatively large-scale blood assay work and its results are uniformly dependable.

Assay Medium: Medium II of Schmidt and Moyer, which is commercially available in the dehydrated form called "Yeast Beef Broth," is prepared by dissolving 17.5 Gm. of the powder in 1000 ml. of distilled water. The pH is normally about 7.0. The medium is sterilized in the autoclave at 15 lb/in² for about 20 minutes.

Organism: *Bacillus subtilis,* N.R.R.L. No. 558. The culture is grown submerged by shaking in the above medium, 100 ml. in a 300 ml. Erlenmeyer flask, at 37°C. for 24 hr. This suspension is employed as described below.

Equipment: This consists of a Brewer Automatic Pipetting Machine Model 40, 12 x 100 mm. test tubes, small wire racks capable of holding 4 series of 10 tubes each, and rustproof metal covers to fit the wire racks for the purpose of covering the tubes so that plugging will be unnecessary to maintain sterility.

Procedure: About 2 to 3 ml. of blood is obtained under aseptic conditions. This is collected in a sterile 12 x 100 mm. tube which contains about 5 to 10 mg. of sodium citrate. The blood should be well shaken at intervals during sampling to prevent clotting. The blood samples are centrifuged at 2000 to 3000 R.P.M. to separate the clear plasma from the solid material.

One ml. of the clear plasma is drawn into a sterile 1-ml. pipette which is marked at 0.5 ml. One-half ml. of this plasma is added to both the first and second tubes of the series. By means of the pipetting machine, 0.5 ml. of the sterile assay medium is added to each tube in the series *except the first.* A serial dilution is made starting with the second tube by transferring 0.5 ml. from the second tube to the third. A 0.5 ml. sample is then transferred to the fourth tube and so on through the tenth tube.

After all of the serial dilutions of the blood samples are completed, one to two standard series are prepared using a 1 International Unit per ml. penicillin standard. These dilutions are made in the same manner as the serial dilutions for the blood plasma.

Upon completion of all of the serial dilutions, the yeast beef broth assay medium is inoculated with 1 to 2 ml. of the *B. subtilis* suspension described previously, mixed with 100 ml. of broth. This is added to all tubes to the extent of 1 ml. per tube by means of the automatic pipetting machine. Care should be taken to see that sterile broth (from the previous deliveries of 0.5 ml. per tube) is flushed out of the equipment so that each tube will be properly inoculated.

The racks of tubes with covers in place are incubated for 18 hours at 37°C. The series are then observed for extent of inhibition of growth. The break is generally very sharp between the tubes supporting growth and those in which growth is inhibited. Since the assay is based on a reading of growth of organism versus complete inhibition, the nutritional effect of the blood plasma is minimized. If small amounts of erythrocytes or leucocytes happen to be present in the blood plasma sample, no great damage is done since the test organism, *B. subtilis,* is nonhemolytic in contrast to some other test organisms. After incubation the cells generally settle to the bottom of the tube without hemolysis. If the tubes are not agitated or handled roughly, there is usually no difficulty in determining the presence or absence of bacterial growth in the supernatant liquid.

EXAMPLES OF SERIAL DILUTION ASSAY DATA

In the following example the 1 I.U./ml. standard shows inhibition through tube 7:

Tube No.	1	2	3	4	5	6	7	8	9	10
	Bacterial Growth									
Standard, 1 I.U./ml.	0	0	0	0	0	0	0	+	+	+
Unknown	0	0	0	0	+	+	+	+	+	+
I.U./ml. indicated	0.015	0.031	0.062	0.125	0.25	0.5	1	2	4	8

Where tube 7 is the last inhibited tube in the standard series, final series inhibition at tube 7 indicates 1 I.U./ml., final series inhibition at tube 6 indicates 0.5 I.U./ml. and so on. The unknown shown in the sample data would indicate 0.125 I.U./ml. in the unknown solution.

The assay is generally capable of determining as little as 0.015 I.U./ml. in blood plasma or 0.005 I.U./ml. in the assay culture medium.

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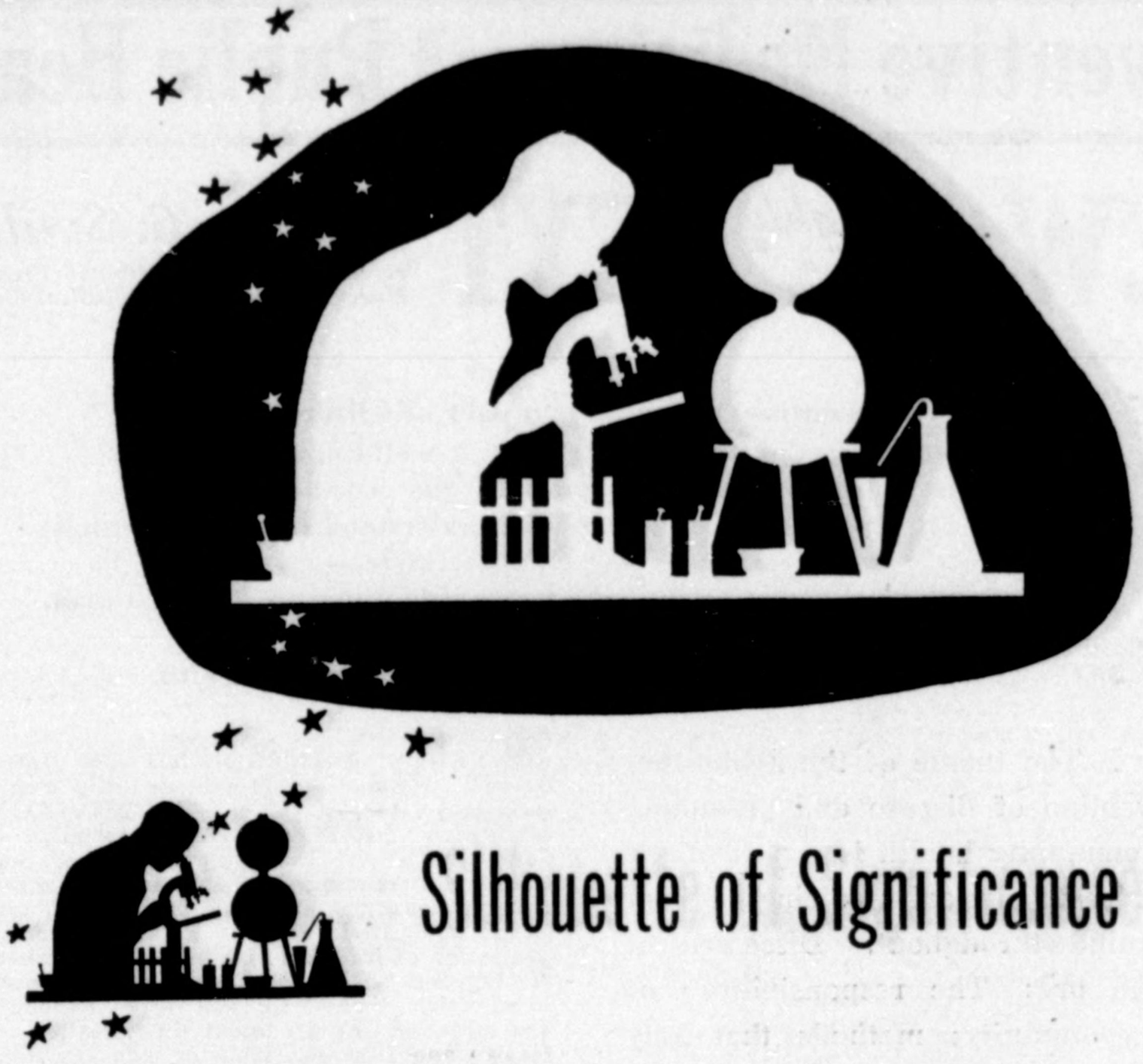

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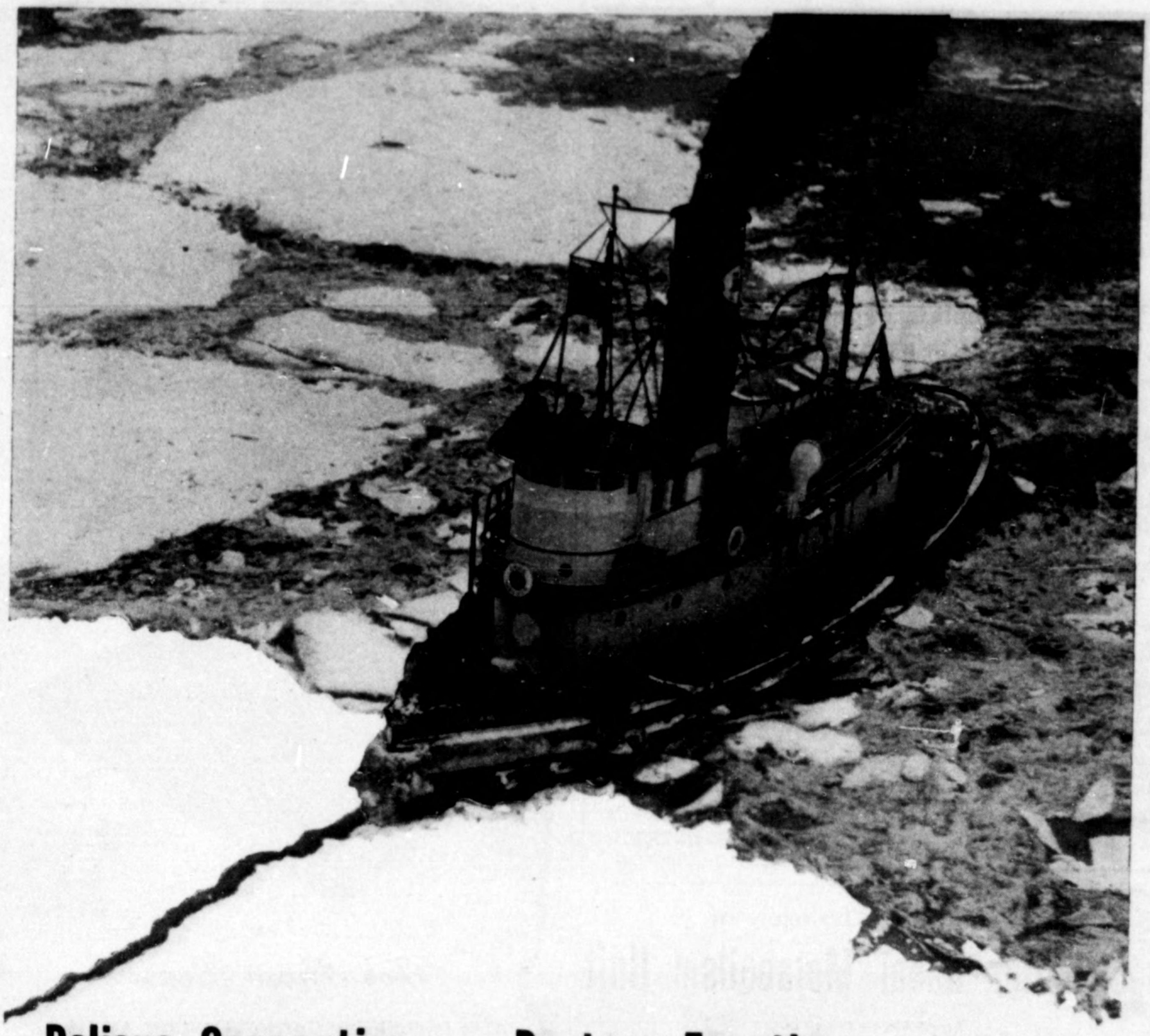

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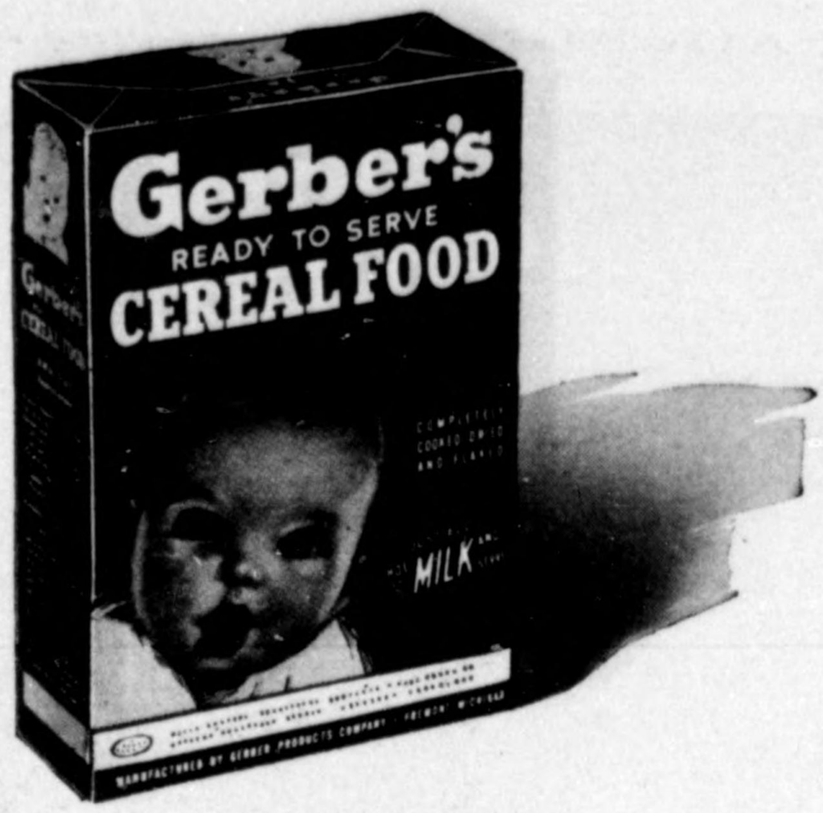

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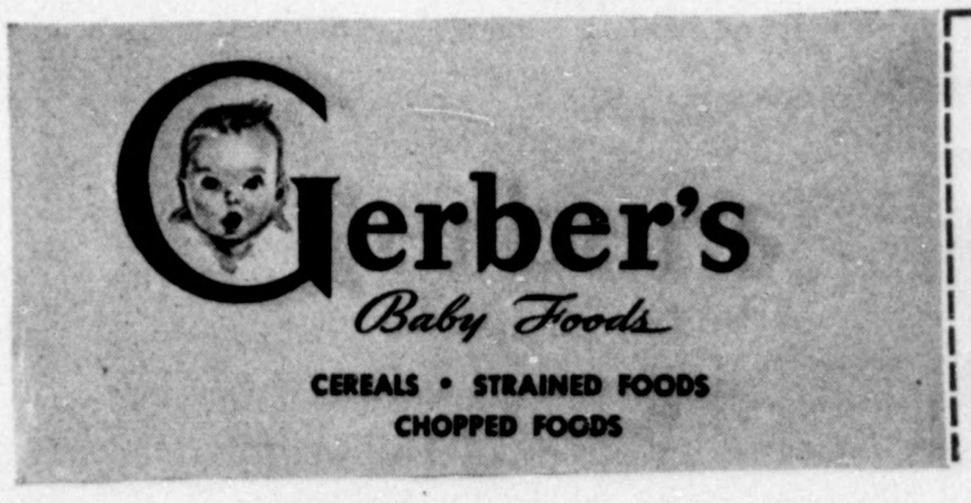

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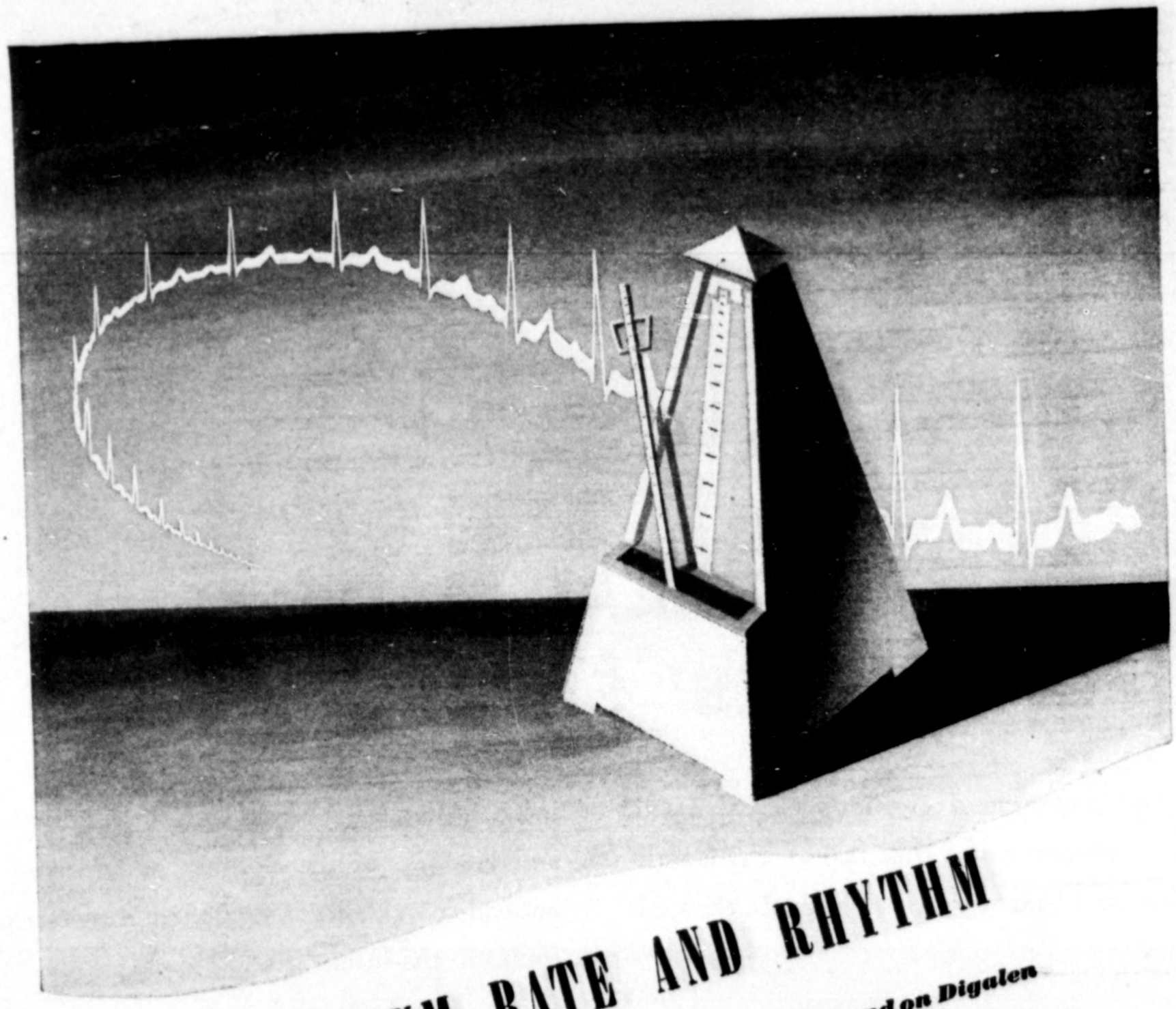

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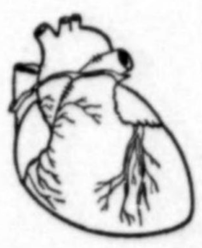

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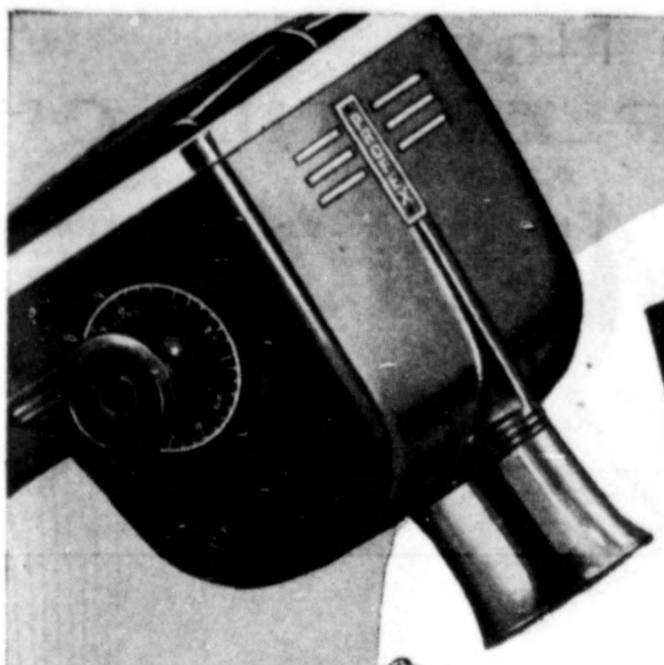

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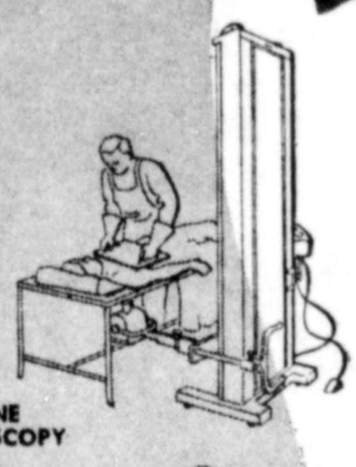

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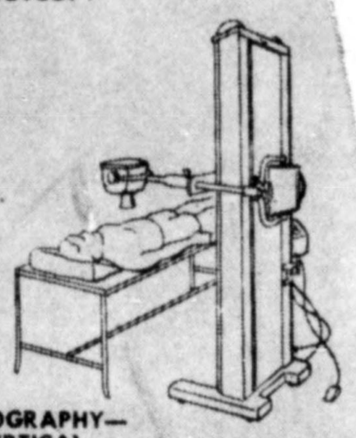

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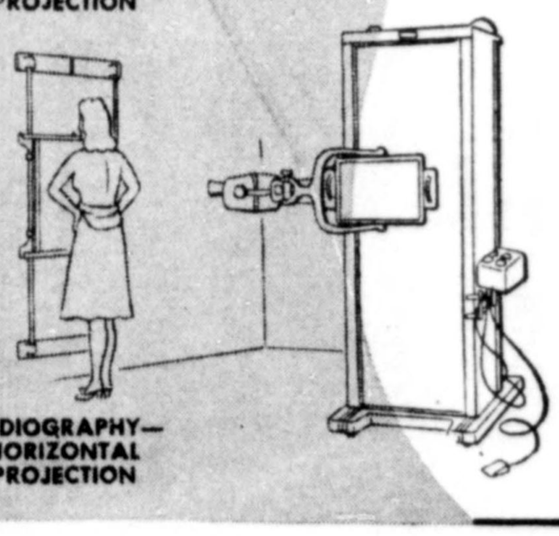

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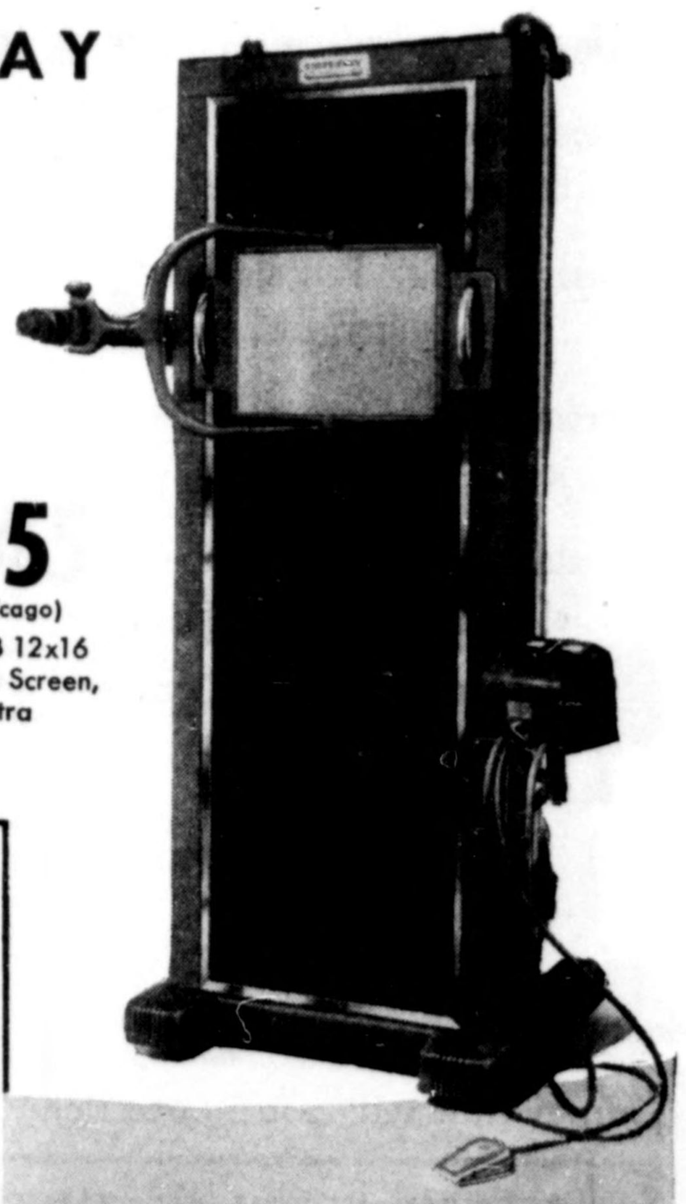

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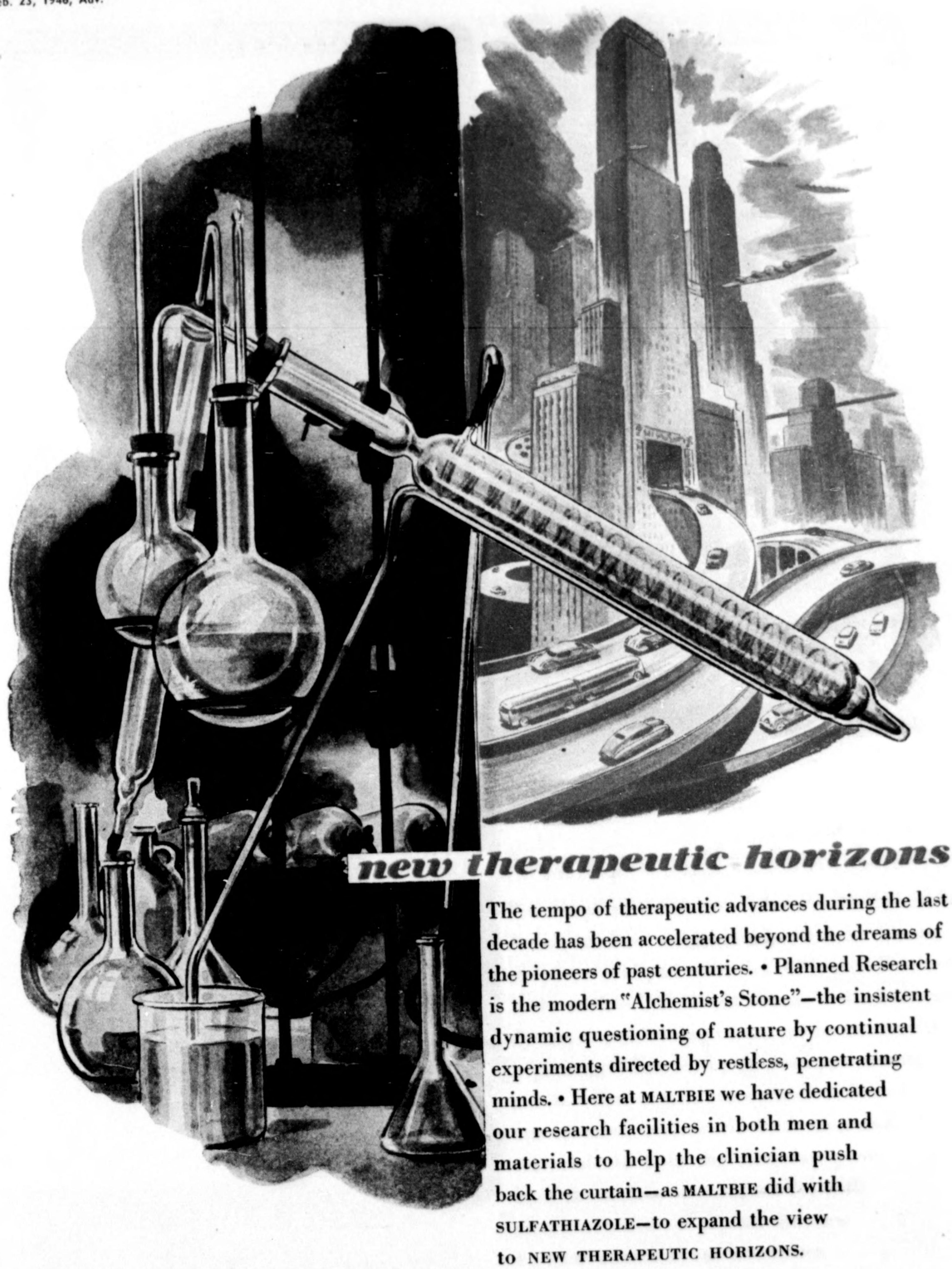

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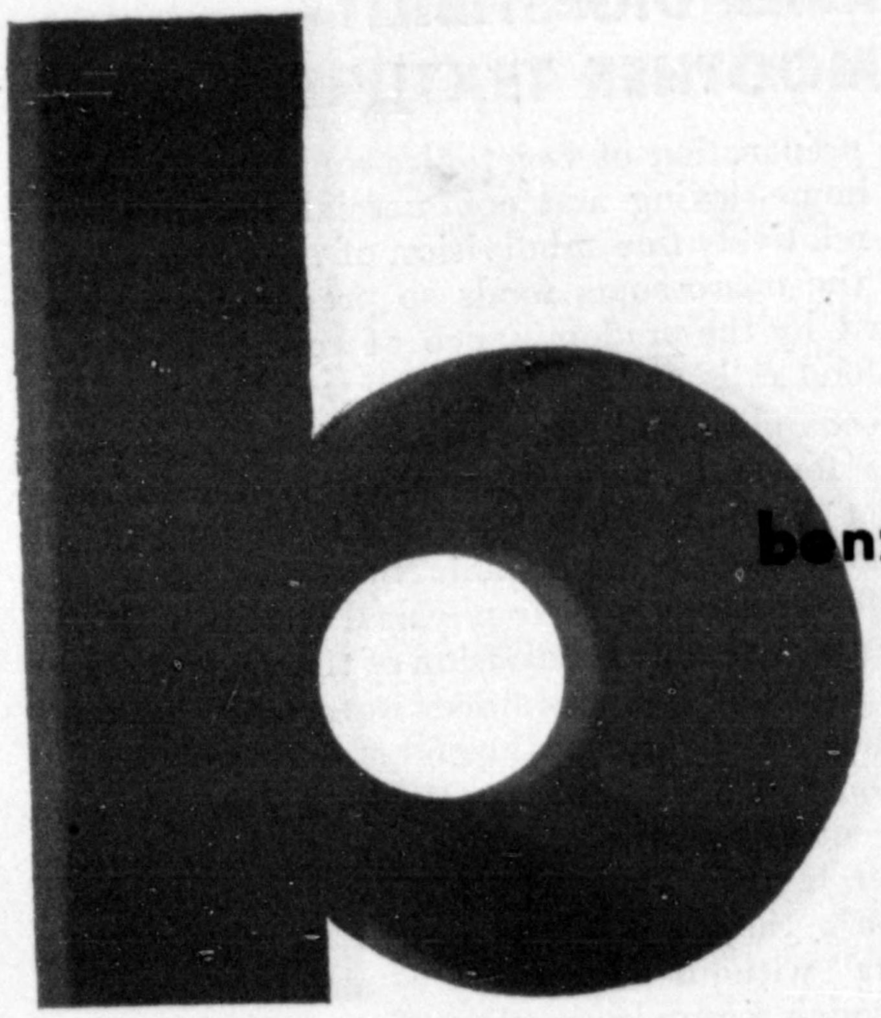

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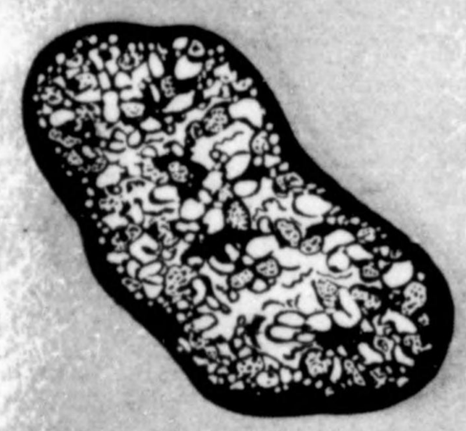

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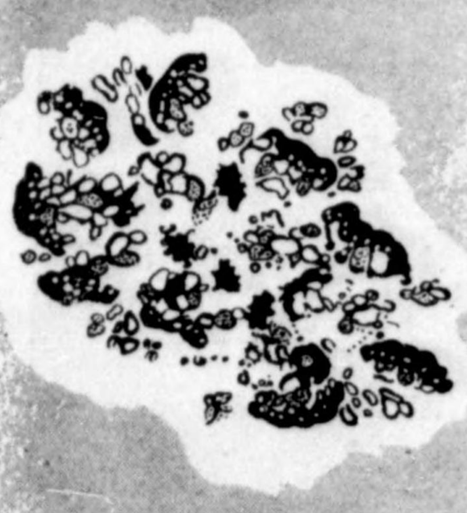

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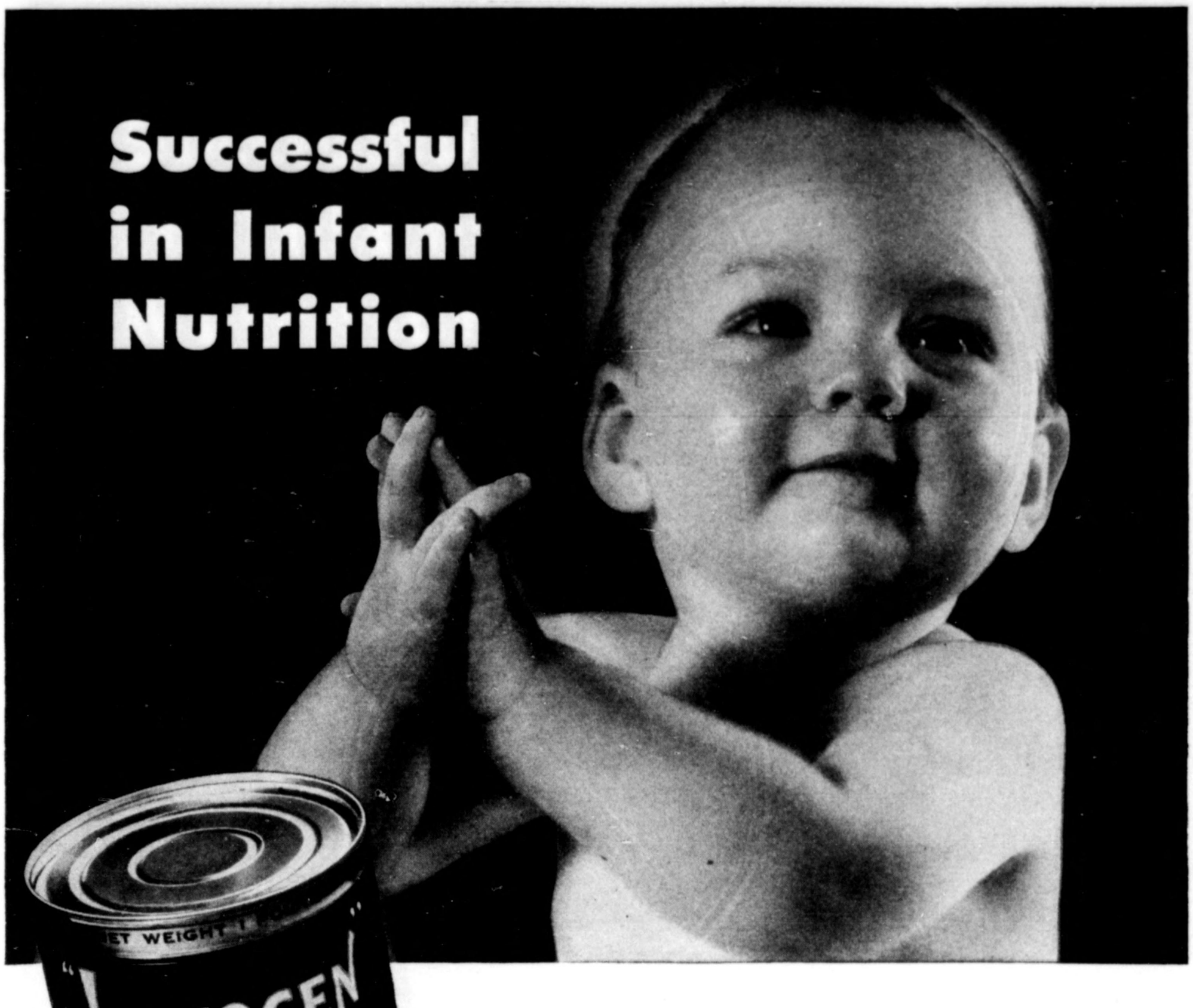

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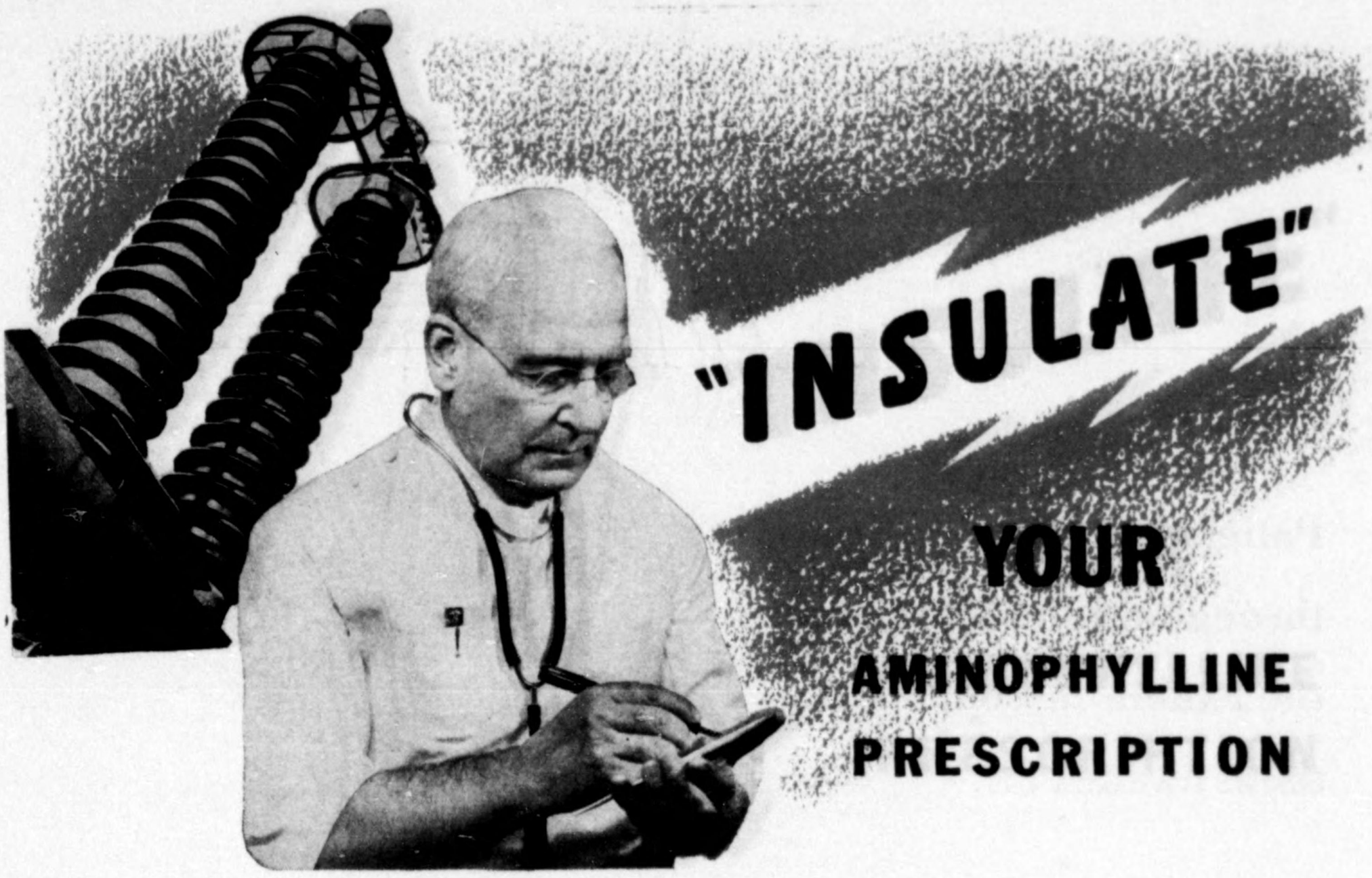

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[1]*Goodman, L. and Gilman, A.: Pharmacological Basis of Therapeutics, 1941, p. 281.*

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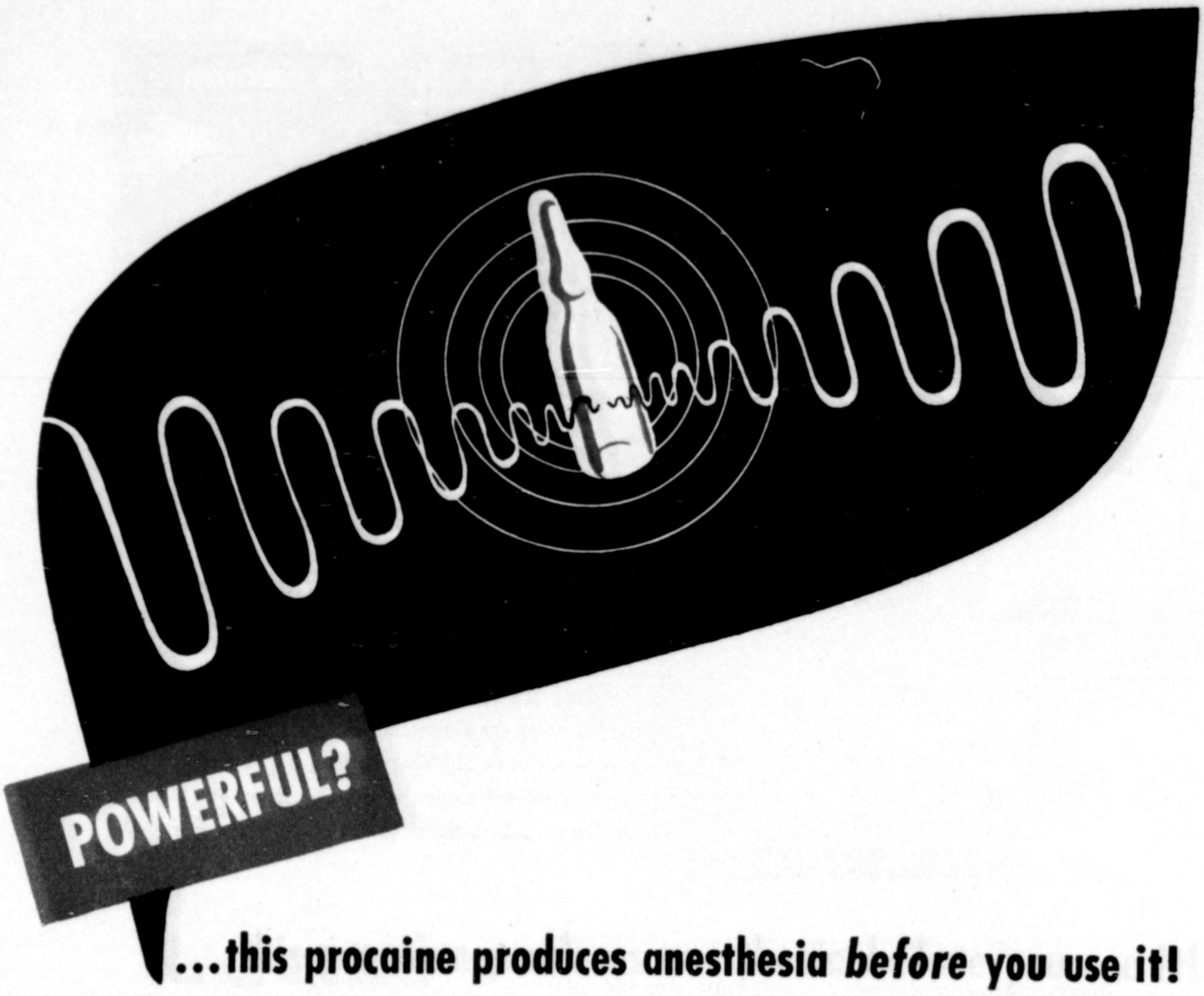

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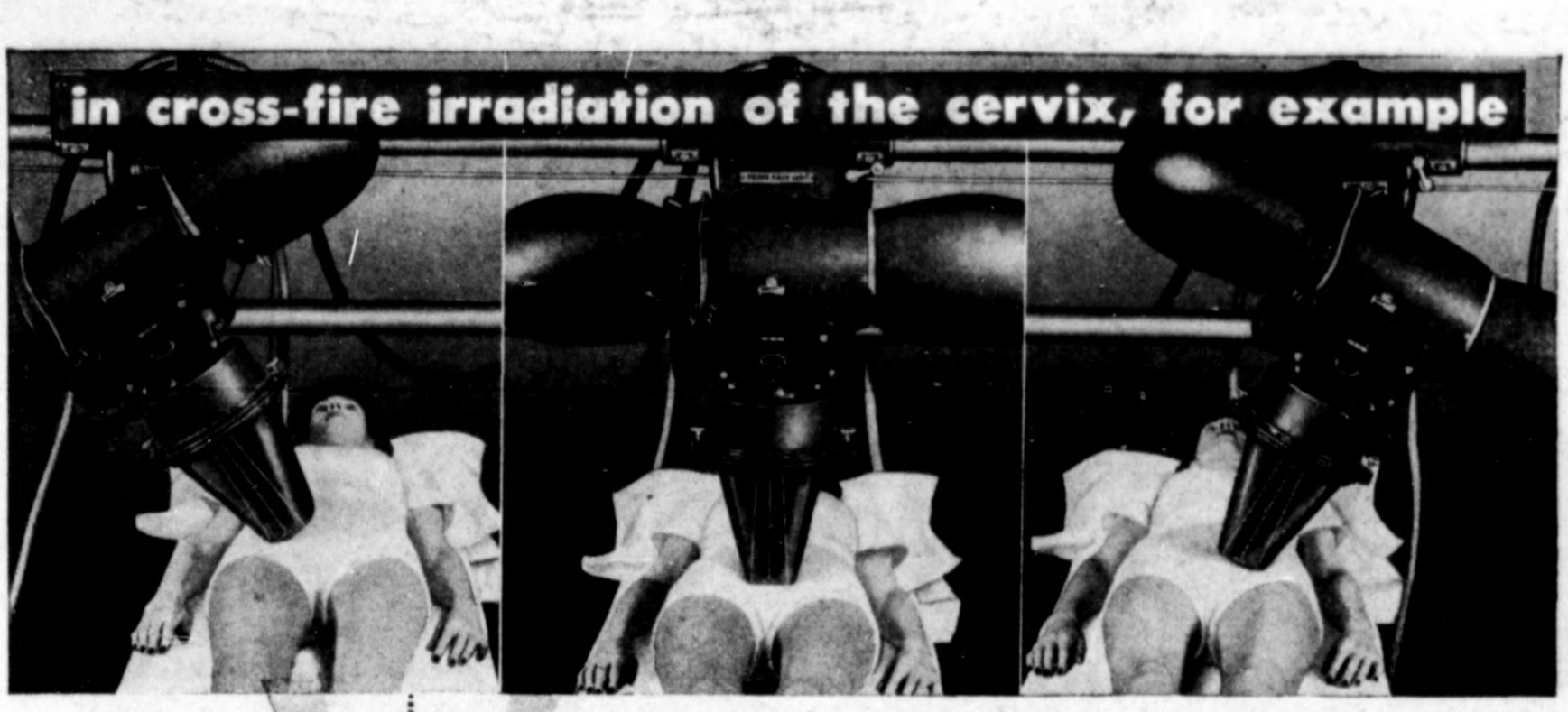

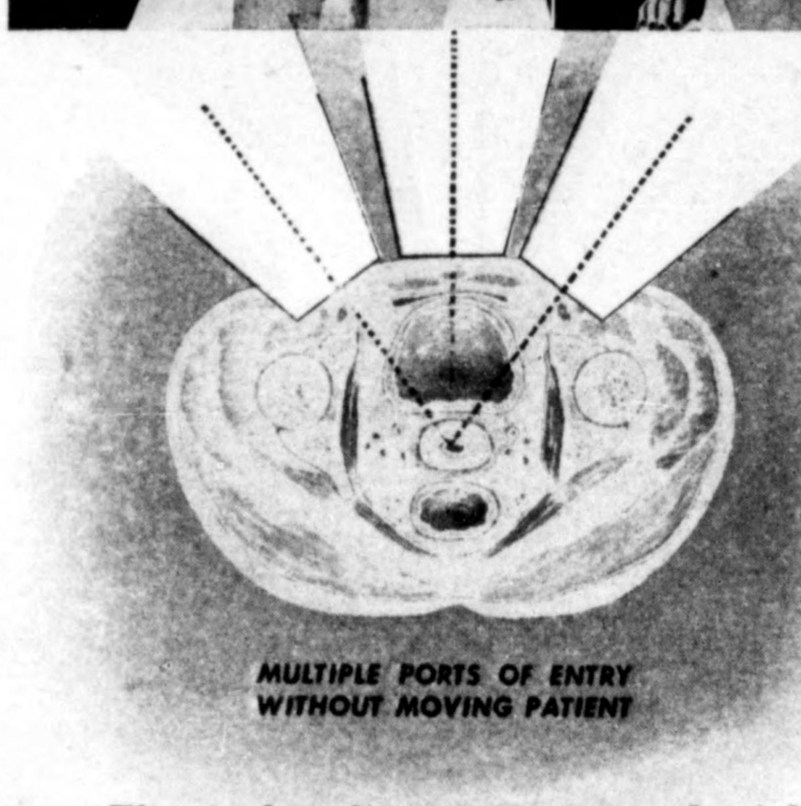

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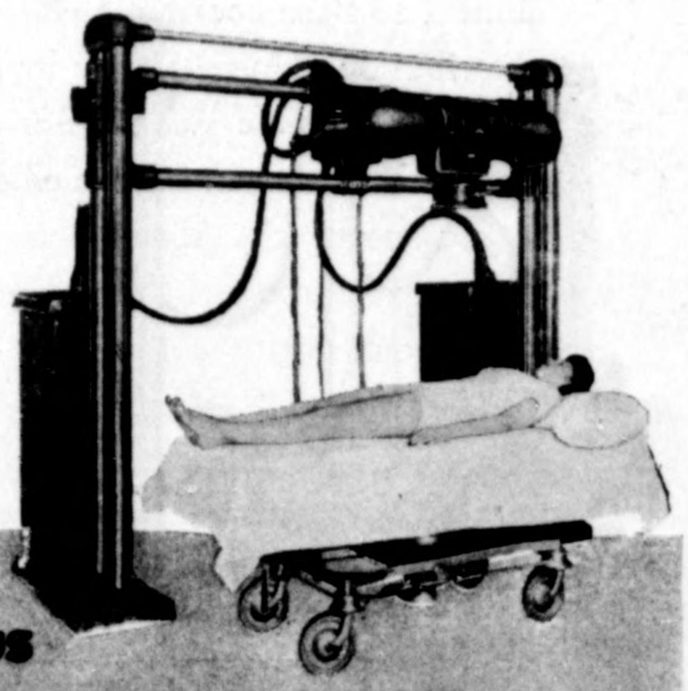

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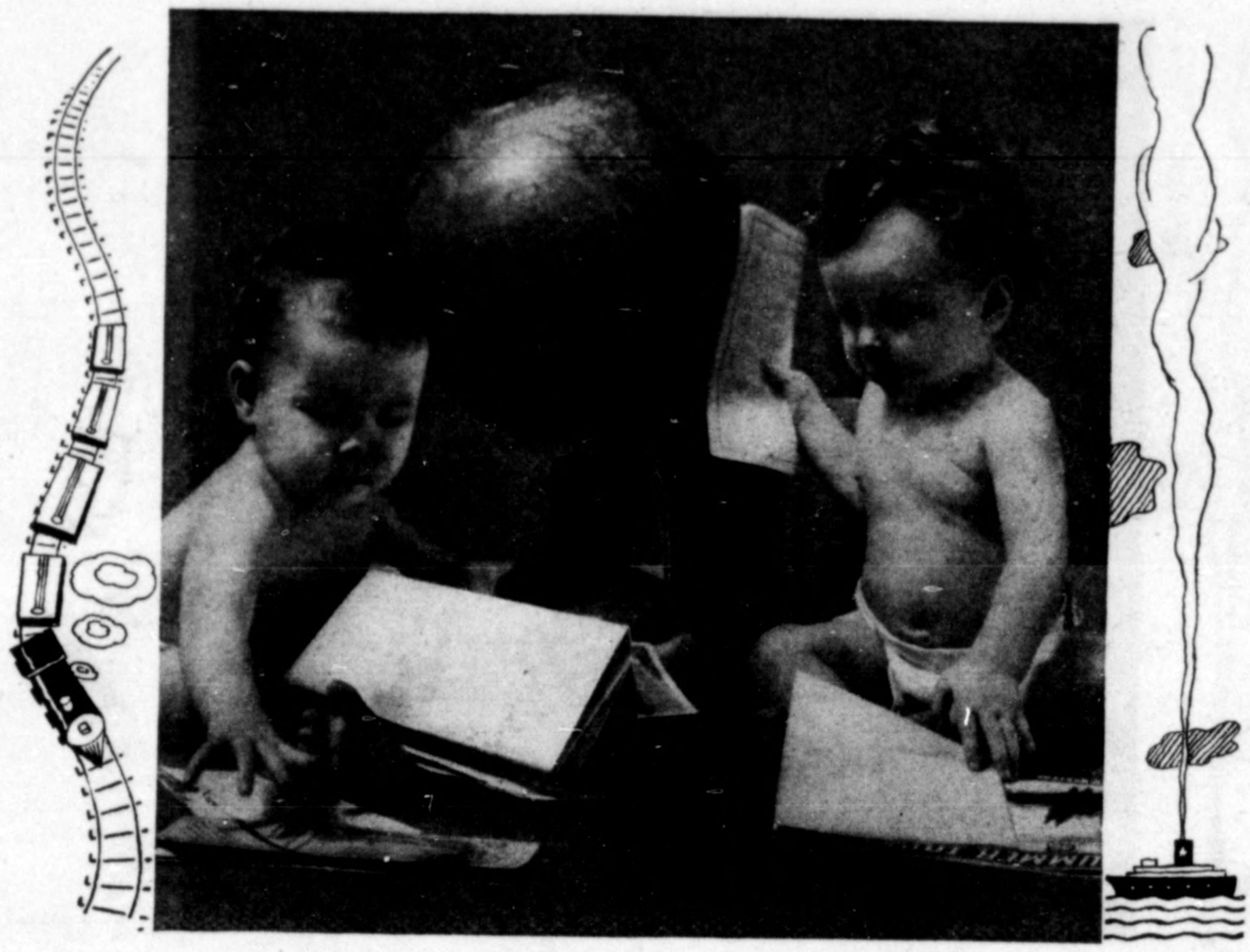

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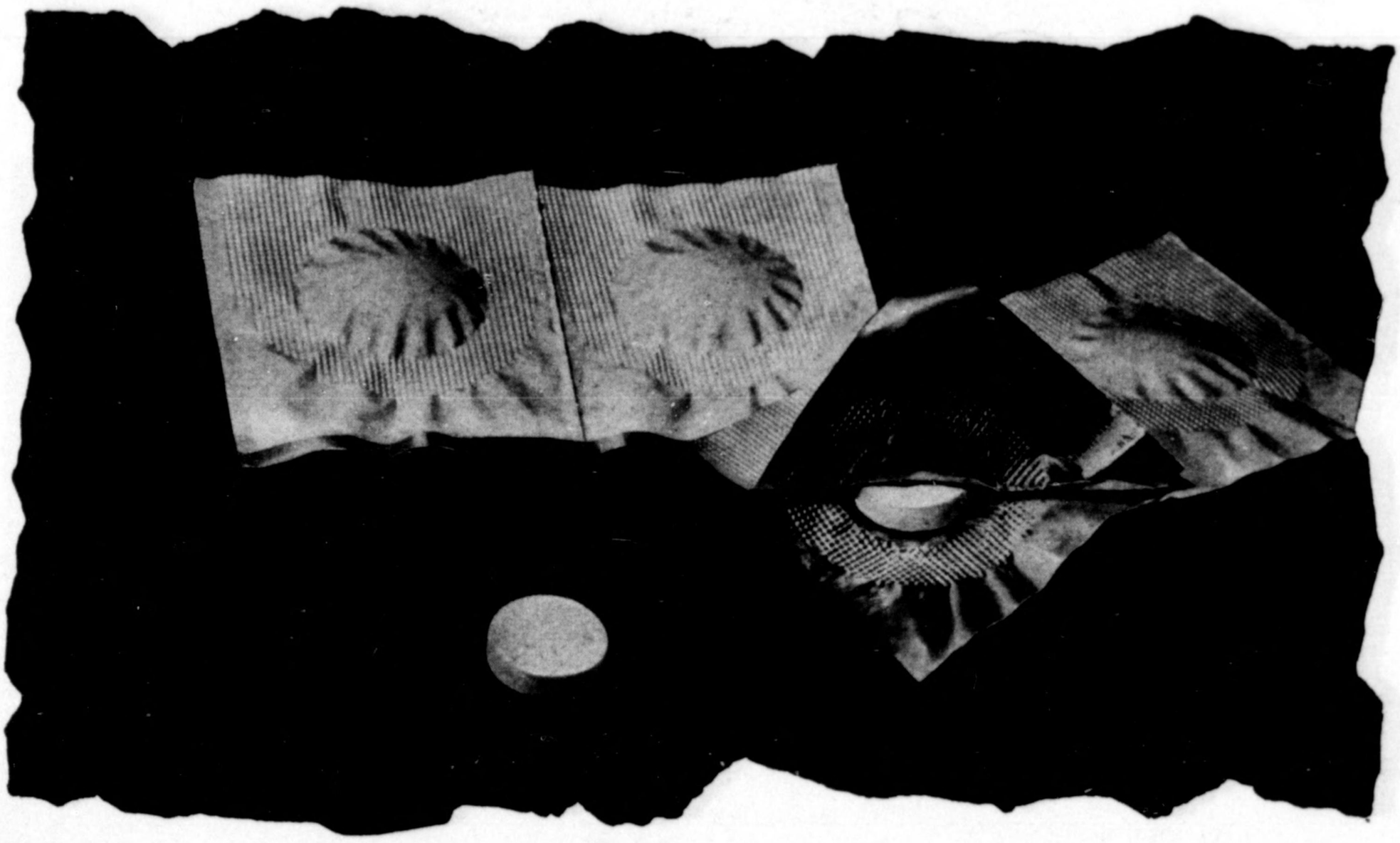

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THE SURGICAL TREATMENT OF ESSENTIAL HYPERTENSION

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Ann Arbor, Mich.
and
EMIL M. ISBERG, M.D.
Miami Beach, Fla.

Since the first bilateral supradiaphragmatic splanchnicectomy and lower dorsal sympathetic ganglionectomy was performed by one of us (M. M. P.) in November 1933, more than 1,500 patients have received this surgical treatment for essential hypertension at the University Hospital as of September 1945. Surgical treatment has long been accepted here as an integral part of the therapeutic armamentarium for hypertensive disease. Its acceptance has been tempered with the realization that its limitations are definite, that its failures are not uncommon. Rarely does surgical treatment result in a cure of hypertensive disease, but it has given remarkable benefit and prolonged the life of many hypertensive patients.

Reports of the results of surgical treatment in hypertensive disease are numerous. For the most part they are concerned with small groups followed postoperatively for a relatively short time. The largest series of cases previously reported is that of Peet, Woods and Braden,[1] with results in 350 cases followed for nine months to seven years. The most recent evaluation of a significant series is Smithwick's[2] 156 patients followed one to five years.

Those familiar with the life course of hypertensive disease readily realize that much time must be allowed to elapse before passing judgment concerning the influence of a therapeutic incident on the life history of a chronic, constitutional disease. It is with this thought in mind that we present the results in 437 cases of essential hypertension treated surgically five to twelve years ago.

CLASSIFICATION OF HYPERTENSIVE PATIENTS

Essential hypertension is a disease complex with great individual variations. In evaluating the effect of surgical treatment on this variable constitutional disease it is advisable to classify patients according to definite categories in order to determine the influence of the operation on the individual category. In this way the knowledge gained may enable intelligent selection of candidates for surgical treatment. In this way one may learn what to expect from the operation for each clinical type of essential hypertension.

A classification based merely on the height of the blood pressure level or on the width of the pulse pressure fails to take into consideration the constitutional effects of the disease. The degree of elevation of blood pressure is not a sound prognostic criterion. In their study on a large group of persons with transient hypertension, Levy, White, Stroud and Hillman[3] found no significant differences apparent between the various systolic and diastolic levels in relation to the death rates with cardiovascular-renal disease. The relative height of a temporary rise in blood pressure did not appear to foretell the severity or extent of the lesions which eventually were the cause of death.

The classification of Keith, Wagener and Barker,[4] based primarily on the severity of the hypertensive changes in the ocular fundus, is sound, but it is not entirely applicable in evaluating surgical treatment, for both the patient with far advanced heart disease and the one with no cardiac involvement whatever may have angiospastic changes in the ocular fundi; 2 such cases should not be in the same category when one evaluates the effect of the operation on a category.

We have therefore classified the 437 cases in this series according to their general clinical profile, with the constitutional course of the disease forming the primary basis for classification:

Group 1. Early, mild hypertension. These patients were entirely asymptomatic, had normal or grade 1 fundi, and showed no evidence of cardiac, cerebral or renal involvement.

Group 2. Symptoms predominate. All patients in this group complained of symptoms and had abnormal fundi but displayed no evidences of cardiac, cerebral or renal impairment.

Group 3. Organic heart disease is predominant. In each case the diagnosis of heart disease was confirmed by either or both a definitely abnormal electrocardiogram and a teleoroentgenogram showing cardiac enlargement.

Group 4. Cerebrovascular disease is predominant. Each patient in this group had one or more previous cerebral accidents.

Group 5. Impaired renal function is predominant. Each patient showed diminished concentrating ability and urea clearance values.

Group 6. Malignant hypertension. These patients had severe neuroretinitis with definite papilledema of 1 diopter or more and displayed a rapidly progressive, downhill course.

From the Departments of Surgery and Internal Medicine, University of Michigan Medical School and University Hospital.

1. Peet, M. M.; Woods, W. W., and Braden, S.: The Surgical Treatment of Hypertension: Results in 350 Consecutive Cases, J. A. M. A. **115:** 1875 (Nov. 30) 1940.

2. Smithwick, R. H.: Surgical Treatment of Hypertension: Effect of Radical (Lumbodorsal) Splanchnicectomy on the Hypertensive State of 156 Patients Followed One to Five Years, Arch. Surg. **49:** 180 (Sept.) 1944.

3. Levy, R. L.; White, P. D.; Stroud, W. D., and Hillman, C. C.: Transient Hypertension: The Relative Prognostic Importance of Various Systolic and Diastolic Levels, J. A. M. A. **128:** 1059 (Aug. 11) 1945.

4. Keith, N. M.; Wagener, H. P., and Barker, N. W.: Some Different Types of Essential Hypertension: Their Course and Prognosis, Am. J. M. Sc. **197:** 332 (March) 1939.

METHOD OF STUDY

Each patient received an extensive preoperative workup. Detailed histories were taken and physical examinations performed in the departments both of medicine and of neurosurgery. Funduscopic examination through dilated pupils was done in the ophthalmology department. A teleoroentgenogram and electrocardiogram were obtained on each patient. Kidney function studies included the determinations of urea clearance, maximum concentrating ability and blood nonprotein nitrogen and urinalysis. Excretory pyelograms were done in a majority of the series; since 1939 this has been part of the routine preoperative procedure. The aim of the preoperative examinations is to rule out all specific causes of hypertension and to determine the constitutional extent of the hypertensive state in each case. Frequent blood pressure determinations were recorded in both arms with the patient sitting, standing and recumbent, and the readings were averaged.

Follow-up data were obtained largely through subsequent, periodic visits and reexamination as described. Of the 251 patients now living from the first 437 operated on and on whom we could obtain adequate postoperative data, 146 recently returned to the University Hospital for evaluation. Information on the remaining 105 living patients was obtained from both the patient and his home physician by letter. Information concerning the deceased patients was obtained from the referring physician and near relatives.

The technic of bilateral supradiaphragmatic splanchnicectomy and lower dorsal sympathetic ganglionectomy has been described in detail.[5]

5. Peet, M. M.: The Surgical Treatment of Hypertension, California Acad. Med. **5**: 58, 1935-1936.

TABLE 1.—*Sex Distribution*

	Number	Per Cent
Males	210	48
Females	227	52
Total cases	437	

TABLE 2.—*Age Distribution at Time of Operation*

Age	Number	Per Cent
10 to 19	6	1.4
20 to 29	33	7.6
30 to 39	120	27
40 to 49	208	48
50 to 59	69	15.8
63	1	0.2
Total cases	437	

TABLE 3.—*Distribution of Preoperative Blood Pressure Levels*

Pressure in Mm. Hg	Number	Per Cent
270 plus / 155 plus	52	12
240 to 269 / 140 to 154	119	27
210 to 239 / 125 to 139	151	34
180 to 209 / 110 to 124	99	23.5
160 to 179 / 95 to 109	16	3.5
Total cases	437	

PREOPERATIVE DATA

From November 1933 to December 1940, 578 hypertensive patients were operated on by various members of the neurosurgery staff. The same technic was employed in all cases and a large majority of the operations were done by the same surgeon (M. M. P.). No adequate follow-up data could be obtained for 120 of these patients, leaving a series of 437 studied.

Fifty-two per cent of the 437 patients were females (table 1).

Ninety-two per cent of the series were 30 years or more of age, with 48 per cent in the fifth decade. The youngest patient was 10 years of age and the oldest was 63 (table 2).

The blood pressure levels in these patients were very high. Twelve per cent had blood pressures of 270/155 or greater. Seventy-three per cent had blood pressures above 210/125 (table 3).

One hundred and twelve patients, or 26 per cent of the series, had malignant hypertension (table 4); this diagnosis was made only when severe neuroretinitis with 1 diopter or more of papilledema was present together with a rapid, downhill course. Thirty-five per cent of the patients, not including any with malignant hypertension, had organic heart disease, confirmed either by a teleoroentgenogram showing definite cardiac enlargement or an abnormal electrocardiogram or both. Fifty-three patients, or 12 per cent, had previous cerebral accidents. Forty-one patients, or 9 per cent, had impaired kidney function by urea clearance and maximum concentration tests. The figures for the last two groups do not include those patients who had previous cerebral accidents or impaired kidney function with malignant hypertension, for all cases of malignant hypertension are in a separate group.

TABLE 4.—*Preoperative Classification*

Group	Number	Per Cent
1. Asymptomatic and early	5	1
2. Symptomatic, with no complicating disease	72	17
3. Organic heart disease	154	35
4. Cerebrovascular disease	53	12
5. Impaired renal function	41	9
6. Malignant hypertension	112	26
Total cases	437	

It is apparent that the hypertensive state in 82 per cent of the patients in this series had already progressed to serious organic illness prior to operation.

POSTOPERATIVE RESULTS

Adequate postoperative information was obtained on 437 of the 578 consecutive patients operated on from November 1933 to December 1940. Two hundred and fifty-one patients, or 57.5 per cent, are living five to eleven years after operation. The operative mortality was 3.6 per cent (table 5).

Of the 186 patients who died subsequent to the operation, 91 had malignant hypertension (table 6). Thus 81 per cent of the preoperative group with malignant hypertension have not survived five to eleven years. Approximately one third of each of the preoperative groups with organic heart disease, cerebrovascular disease and impaired renal function are dead. All of the 5 patients with early, mild, asymptomatic hypertension are still living, and 95 per cent of the 72 patients in group 2 of our classification are alive five to eleven years after operation.

Our findings substantiate the long-known fact that hypertensive disease is of much more serious import in

the male than in the female (table 7). One hundred and seventeen males died; these constitute 62 per cent of the total deaths and 56 per cent of the total number of males in the series. Only 30 per cent of the total number of females subsequently died.

The age of the patient at the time of operation has no influence on survival. The distribution of deaths according to preoperative age is exactly comparable to the preoperative age distribution for the entire series (table 8). As has been pointed out before, it is the preoperative extent of constitutional involvement by hypertensive disease that influences length of postoperative survival.

EFFECT OF SURGICAL TREATMENT ON BLOOD PRESSURE LEVELS

The 251 patients living five to eleven years after operation have obtained and maintained significant blood pressure reductions (table 9). In 20.3 per cent blood pressure has been reduced to normal. The upper limits of normal blood pressure have been arbitrarily placed at 140/90 for ages up to 40 and at 150/95 for ages over 40. There has been definite reduction, but not to normal levels, of more than 80 mm. systolic and 25 mm. diastolic, in another 26 per cent of the living patients. Significant reduction, of more than 40 mm. systolic and 15 mm. diastolic, occurred in 35 per cent. Of the living patients 18.7 per cent showed either no significant change or increase in blood pressure.

This high percentage of good results among the living patients grantedly is enhanced by the fact that the poor results have been eliminated by death. Yet when all the deaths in the series are included, the effect of the operation on blood pressure levels still remains significantly effective. Of the entire series 46.7 per cent show significant reduction in blood pressure five or more years after operation. The latter computation suggests that all patients who died subsequent to surviving five postoperative years manifested no beneficial effect on blood pressure levels after the fourth postoperative year. Actually this was not so. Thirty-two patients survived five years and subsequently died during their sixth to tenth postoperative years; several of these maintained significant reduction in blood pressure during the intervening years between operation and terminal illness. Nevertheless, in our statistical analyses these 32 cases are not segregated from the overall group of 186 deaths even though they were "five year survivals."

Of the 5 patients in group 1, with mild and asymptomatic hypertension, 4 have maintained normal blood pressure and 1 has maintained a definite reduction for five years and more (table 10). Of all patients in group 2 who had symptoms and fundus changes but no cardiac, cerebral or renal impairment, 77.2 per cent maintained normal, definitely reduced and significantly reduced blood pressure levels for five years and more. Similar blood pressure reductions were shown by 48 per cent of those with organic heart disease, 52.8 per cent with cerebrovascular disease and 58.4 per cent with renal impairment. Of the patients with preoperative malignant hypertension 16 per cent maintained significant blood pressure reductions for five years and more.

It is thus seen that the patient whose hypertensive state has not yet progressed to evident involvement of the heart, cerebral arteries or kidneys stands an excellent chance for prolonged blood pressure reduction from surgical treatment. Nevertheless a remarkable percentage of patients with organic heart disease, cerebrovascular disease and renal impairment have maintained significant blood pressure reductions for long periods of time.

It may justifiably be assumed that, if a patient had significantly reduced blood pressure at an examination in the seventh or eleventh postoperative year, the reduction had been maintained over the entire postoperative

TABLE 5.—*Postoperative Data*

	Number	Per Cent
Total cases with adequate postoperative information	437	
Total living 5 to 11 years after operation	251	57.5
Total deaths subsequent to operation	186	42.5
Operative mortality in 578 consecutive operations from November 1933 to December 1940	21	3.6

TABLE 6.—*Subsequent Deaths According to Preoperative Classification*

Group	Number	Per Cent of Total Deaths	Per Cent of Preoperative Group
1	0	0	0
2	4	2	5
3	59	32	38
4	19	10	33
5	13	7	32
6	91	49	81
Total	126		

TABLE 7.—*Subsequent Deaths According to Sex*

	Number	Per Cent of Total Deaths	Per Cent of Total of Same Sex
Males	117	62	56
Females	69	38	30
Total deaths	186		

TABLE 8.—*Comparison of Preoperative Age Distribution and Distribution of Deaths According to Preoperative Age*

Peroperative Age	Preoperative Distribution		Distribution of Deaths	
	Number	Per Cent	Number	Per Cent
10 - 19	6	1.4	3	1.6
20 - 29	33	7.6	11	6
30 - 39	120	27	52	28
40 - 49	208	48	88	47
50 - 59	69	15.8	32	17.4
63	1	0.2	..	....
Total cases	437		186	

TABLE 9.—*Effect of Surgical Treatment on Blood Pressures in 251 Patients Living Five to Eleven Years After Operation*

	Number of Cases According to Preoperative Classification						Per Cent of Living Patients		Per Cent of Total Series, Living and Dead	
	1	1	3	4	5	6				
Reduced to normal (140/90 for ages up to 40) (150/95 for ages over 40)	4	21	9	9	6	2	20.3		11.7	
Definite reduction (more than 80 mm. systolic and 25 mm. diastolic)	1	17	28	6	6	7	26	81.3	15	46.7
Significant reduction (more than 40 mm. systolic and 15 mm. diastolic)	..	17	37	13	12	9	35		20	
No change	..	10	14	4	2	2	12.7			
Increased	..	3	7	2	2	1	6			
Total cases	5	68	95	34	28	21				

It may justifiably be assumed that, if a patient had significantly reduced blood pressure at an examination in the seventh or eleventh postoperative year, the reduction had been maintained over the entire postoperative

period. Many of the patients in this series have returned to the University Hospital for periodic checkup examinations and for the previous surveys of this series; those who now have significant blood pressure reductions have repeatedly demonstrated this on previous examinations.

TABLE 10.—*Analysis of the Effect of Surgical Treatment on Blood Pressure Levels Five to Eleven Years After Operation in 437 Patients, Including 186 Deaths*

Blood Pressure	Preoperative Classification 1	2	3	4	5	6
Reduced to normal	80%	30%	6%	17%	14.6%	1.8%
Definite reduction	20%	23.6%	18%	11.3%	14.6%	6.2%
Significant reduction	....	23.6%	24%	24.5%	29.2%	8%
Unchanged, increased, or subsequent death	....	22.8%	52%	47.2%	41.6%	84%

TABLE 11.—*Effect of Surgical Treatment on Symptomatology During Interval Between Operation and Terminal Illness of 186 Deceased Patients*

Postoperative result	Number	Per Cent
Definite improvement	41	22
Moderate improvement	48	26
No relief	54	29
No data	43	23
Total cases	186	

EFFECT OF SURGICAL TREATMENT ON HYPERTENSIVE SYMPTOMS

The beneficial effect of surgical treatment on hypertensive symptoms is an established and accepted result. This therapeutic measure must always be considered in the management of hypertensive patients with severe, incapacitating headaches, dizziness, fatigability, epistaxis, urinary frequency and nocturia, nausea and vomiting, or blurring of vision. For these symptoms bilateral supradiaphragmatic splanchnicectomy offers a definite opportunity for relief.

TABLE 12.—*Effect of Surgical Treatment on Symptomatology in 251 Patients Living Five to Eleven Years After Operation*

Preoperative Status	Total	Postoperative Result: Complete Relief	Definite Improvement	Moderate Improvement	Unchanged	Worse
No significant symptoms						
Number	8	..	..	..	8	
Per cent	..	..	..	..	(100%)	
Moderate symptoms						
Number	67	14	30	14	5	4
Per cent	..	(21%)	(44.5%)	(21%)	(7.5%)	(6%)
Severe, incapacitating symptoms						
Number	176	47	81	36	7	5
Per cent	..	(27%)	(46%)	(20%)	(4%)	(3%)
Total cases	251					

Of 176 patients who had severe, incapacitating symptoms before operation, 27 per cent were maintaining complete relief five to eleven years later, another 46 per cent felt definitely improved and only 7 per cent were unchanged or worse (table 12). Of 67 patients who had moderate hypertensive symptoms preoperatively 21 per cent now were enjoying complete relief, another 65.5 per cent were definitely or moderately improved and 13.5 per cent were unchanged or worse.

The foregoing statistics do not include the 186 deceased patients in the series. Information obtained from referring physicians and near relatives shows that 22 per cent of the 186 dead obtained definite symptomatic relief during the interval between operation and terminal illness (table 11), 26 per cent obtained moderate relief and 29 per cent no relief. No data were obtained on the remaining 23 per cent.

It is apparent that patients who live a long time after the operation continue to obtain symptomatic benefit during all that time. Relief from the distressing symptom of hypertensive headache is most striking. To observe the previously incapacitated patient return to gainful occupation several months after the operation and still continue at full time work five to eleven years later is most gratifying.

EFFECT OF SURGICAL TREATMENT ON EYEGROUNDS

Of the 251 living patients in the series, only 146 received a recent funduscopic examination five to eleven years postoperatively (table 13). Eleven had normal fundi preoperatively, and all 11 retained this status over the long postoperative period. Thirty patients showed sclerotic changes only of the retinal arterioles, and 83.3 per cent of these remained unchanged while 10 per cent progressed to worse changes. Of the 88 patients who had angiospastic retinitis with or without sclerosis and

TABLE 13.—*Effect of Surgical Treatment on Eyegrounds of 146 Patients Living Five to Eleven Years After Operation*

Preoperative Status	Cases	Postoperative Result: Improved	Unchanged	Worse
1. Normal fundi	11	.....	11 (100%)	.....
2. Sclerosis only	30	2 (6.7%)	25 (83.3%)	3 (10%)
3. Angiospastic retinitis, with or without hemorrhages and exudates	88	72 (82%)	15 (17%)	1 (1%)
4. Papilledema	17	17 (100%)		
Total cases	146			

with or without hemorrhages and exudates preoperatively, 82 per cent were improved in that localized vasospasms had disappeared and no new hemorrhages or exudates had occurred; 17 per cent of these 88 patients remained unchanged and 1 was worse.

Twenty-one of 112 preoperative patients with malignant hypertension with severe neuroretinitis and 1 diopter or more of papilledema are still living five to eleven years after operation and 17 received recent funduscopic examination. In all these 17 patients the papilledema had disappeared.

This evaluation of the influence of splanchnicectomy on the ocular fundi in hypertension does not include the 186 deceased patients of the series. Thus from the foregoing statistics one must come to no further conclusion than that among the patients living five to eleven years after operation a remarkably high percentage of those who had had angiospastic retinitis, hemorrhages, exudates or papilledema have maintained funduscopic improvement over the long postoperative period. Greatest improvement occurred in those with preoperative angiospastic retinitis, for it is common for localized vasospasm to disappear postoperatively. On the other hand, sclerosis of the retinal arterioles is a permanent change; the effect of splanchnicectomy in these cases is to limit further progression for all but a small percentage.

EFFECT OF SURGICAL TREATMENT ON THE HEART IN HYPERTENSION

Of the living patients 141 had recent electrocardiograms taken (table 14). Of the 84 patients whose electrocardiograms were normal preoperatively 93 per cent maintained an unchanged, normal electrocardiogram five to eleven years after operation; in only 7 per cent did the electrocardiogram become abnormal. Of the 57 patients who had abnormal preoperative electrocardiograms 52.7 per cent showed significant improvement five to eleven years later, consisting of significant left axis deviation returning to normal or of previously inverted T waves in leads 1 or 2 returning to normal. Of the abnormal electrocardiograms 42 per cent showed no significant change, while 5.3 per cent progressed to worse changes.

Of 80 living patients with normal heart size preoperatively, 91.2 per cent maintained normal heart size by comparative teleoroentgenograms five to eleven years later; 7 patients, or 8.8 per cent, had significant increase in heart size (table 15). Forty-eight living patients had preoperative cardiac enlargement of 18 per cent or more above the predicted normal area. Twenty-five, or 52 per cent, of these patients with enlarged hearts showed significant reduction in heart size. Sixteen of these 25 had had slight cardiac enlargement of 18 to 30 per cent above predicted normal area, and in each instance the teleoroentgenogram five to eleven years after operation showed no cardiac enlargement; the remaining 9 patients had had moderate cardiac enlargement of 30 to 75 per cent above the predicted normal area preoperatively, and each showed significant reduction in size to only slight cardiac enlargement. Only 4.2 per cent of the living patients with preoperative cardiac enlargement now show further increase in heart size.

TABLE 14.—*Effect of Surgical Treatment on the Electrocardiogram in 141 Living Patients Five to Eleven Years After Operation*

Preoperative Status	Cases	Postoperative Status: Significantly Improved	No Significant Change	Worse
Normal electrocardiogram	84	.....	78 (93%)	6 (7%)
Abnormal electrocardiogram	57	30 (52.7%)	24 (42%)	3 (5.3%)
Total cases	141			

It is remarkable that, of the patients who had heart disease before operation and who are still alive, more than half maintain significant improvement in their electrocardiograms and significant decrease in heart size. But splanchnicectomy has not benefited such a great percentage of the entire group of 154 patients who had organic heart disease prior to operation. Thirty-eight per cent of this group were dead in 1945. In addition, many of the patients who had malignant hypertension subsequently died in congestive heart failure.

Splanchnicectomy has possibly prevented progression to organic heart disease in hypertensive patients who manifested no evidence of cardiac involvement preoperatively. Of 87 patients who did not have heart disease prior to operation, 79 still showed no evidence of heart disease five to eleven years later; only 9 per cent subsequently developed heart disease.

EFFECT OF SURGICAL TREATMENT ON CEREBROVASCULAR DISEASE

There are still living five to eleven years after operation 48 of a total of 73 patients who had had definite cerebral accidents prior to operation. Forty-three of the 48 have had no subsequent cerebral accidents during the long postoperative period. It thus appears that splanchnicectomy affords some protection against subsequent cerebral accidents in those hypertensive patients who have had this unfortunate complication.

TABLE 15.—*Effect of Surgical Treatment on Heart Size, Measured by Teleoroentgenogram, of 128 Living Patients Five to Eleven Years After Operation*

Preoperative Status	Cases	Postoperative Result: Significant Decrease in Heart Size	No Significant Change	Increase in Heart Size
Normal heart size	80	.....	73 (91.2%)	7 (8.8%)
Cardiac enlargement (18% or more above predicted normal area)	48	25 (52%)	21 (43.8%)	2 (4.2%)
Total cases	128			

Of the 437 patients in this series, 61 have died of cerebrovascular disease. Twenty-five of these deaths occurred in persons who had had preoperative cerebral accidents, and 13 of the 25 also were cases of malignant hypertension. Thirty-six deaths from cerebrovascular disease occurred of patients with no preoperative clinical evidence of such involvement, but 20 were cases of malignant hypertension.

EFFECT OF SURGICAL TREATMENT ON KIDNEY FUNCTION

An eighteen hour concentration test of kidney function[6] was performed recently on 117 of the living patients five to eleven years after operation. Sixty-two of these patients had normal kidney function before operation, and 51 of these have maintained normal concentrating ability for the long period of time since operation; 11 patients have manifested impaired concentrating power since operation (table 16).

Of 55 patients who had impaired kidney function prior to splanchnicectomy 20, or 36.4 per cent, have shown significant improvement in concentrating ability five to eleven years later; 52.6 per cent showed no change, and 11 per cent are worse.

TABLE 16.—*Effect of Surgical Treatment on Renal Concentrating Ability of 117 Patients Living Five to Eleven Years After Operation*

Preoperative Status	Cases	Postoperative Result: Significant Improvement	No Change	Worse
Normal function	62	.....	51 (82.3%)	11 (17.7%)
Impaired function	55	20 (36.4%)	29 (52.6%)	6 (11%)
Total cases	117			

It appears that a considerable percentage of patients with preoperative impaired kidney function have maintained significant improvement of kidney function during the long period of time since operation. Of the 186 deaths in the series, 21 were caused by uremia.

6. Isberg, E. M., and Newburgh, L. H.: An Eighteen Hour Concentration Test of Kidney Function, Am. J. M. Sc., to be published.

EFFECT OF SURGICAL TREATMENT ON THE LIFE HISTORY OF ESSENTIAL HYPERTENSION

The ultimate test of the value of surgical treatment is whether it significantly alters the inevitable, progressive, fatal course pursued by the great percentage of cases of essential hypertension. Now that a series of surgically treated hypertensive patients has been followed for a long time, fair comparisons can be made with the several series of medically treated cases in the literature.

In Janeway's [7] series of 458 patients, one half of the males had died within four years and one half of the females within five years of the time of development of symptoms; by the tenth year half of the remainder had died. Hamman [8] had a mortality of 30 per cent at the end of five years and 78 per cent at the end of ten years.

King, Carlile and Blackford [9] followed 481 patients for ten to sixteen years, and the mortality was 73 per cent. In half of the cases in their series the discovery of hypertension was purely an incidental finding.

Five years ago Woods and Peet [10] compared 76 patients (included in the present report) who were then alive five to seven years after operation with the series of Keith, Wagener and Barker.[4] The present, larger group of 437 patients followed for a longer time compares just as favorably as the smaller group did five years ago. One hundred and forty-six, or 62 per cent, of the 219 patients in the Keith-Wagener-Barker series had malignant hypertension, while 112, or 26 per cent, of our 437 patients had malignant hypertension; theirs is a more seriously ill group. Only 19 patients, or 8.6 per cent, of their series were alive five to nine years after the first examination. Of our 437 patients 57.5 per cent are living five to eleven years after operation. Our survival rate thus also compares very favorably with that of Janeway, of Hamman and of King, Carlile and Blackford. At the end of five postoperative years, 64.8 per cent of our patients were living.

TABLE 17.—*Causes of Death Up to Eleven Years After Operation of 186 Surgically Treated Patients with Essential Hypertension*

	Number	Per Cent
Congestive heart failure	66	35.4
Cerebrovascular accident	61	32.8
Uremia	21	11.3
Coronary occlusion with myocardial infaretion	16	8.6
Dissecting aneurysm of aorta	2	1.1
Causes other than hypertension	10	5.4
Cause unknown	10	5.4
Total cases	186	

It is in malignant hypertension that fair comparisons can be made between our present series and the Keith-Wagener-Barker series. Twenty-one patients, or 19 per cent, of our 112 with malignant hypertension treated surgically are alive five to eleven years after operation. Of the 146 patients with malignant hypertension in the Keith-Wagener-Barker control series 79 per cent were dead at the end of the first year, 88 per cent at the end of the second year, 94 per cent at the end of the third year, 98 per cent at the end of the fourth year and 99 per cent at the end of the fifth year. Only 1 patient with malignant hypertension in the control series survived five years.

Surprisingly, the cases of malignant hypertension in the surgically treated series of de Takáts, Heyer and Keeton [11] did not respond with any benefit. They, just as the Keith-Wagener-Barker control series, had a five year mortality of 99 per cent. They even list malignant hypertension as a contraindication to surgical treatment. Allen and Adson [12] also stated that malignant hypertension does not respond satisfactorily to surgical treatment. We have found that there is hope of prolonged survival for 19 per cent of the patients with malignant hypertension surgically treated. We firmly feel that no patient with malignant hypertension, otherwise suitable for operation, should be denied this 1 chance in 5 to prolonged life of more than five years, compared to the one chance in 146 offered by general medical management.

It appears from comparison of survival statistics that the life span of the hypertensive patient may be significantly lengthened by surgical treatment.

Fifty-one patients in this series have maintained blood pressure levels within normal limits for five to eleven years since operation; 28 show no evidence whatever of hypertensive disease at the present time. These 28 persons not only have maintained normal blood pressure levels, but also they are completely free from symptoms, their eyegrounds are either normal or show only sclerotic changes, and they manifest no evidence of cardiac, cerebral or renal involvement. These 28 persons could be termed "five year cures"; actually we have never made claims that essential hypertension could be cured by splanchnicectomy. The hypertensive predisposition always persists following surgical treatment, regardless of the fall of blood pressure to normal levels.

COMMENT

The foregoing information obtained from observing a large group of surgically treated hypertensive patients over a long period of time should enable more accurate identification of the patients who may obtain good results from operation. The postoperative data have been presented in a manner so that one may now know what to expect from splanchnicectomy in the individual case selected for operation.

Intelligent management of a case of essential hypertension requires a knowledge of the complete clinical profile of the patient. The workup of the patient must include in addition to the routine history and physical examination an ophthalmoscopic examination, electrocardiogram, teleoroentgenogram, excretory pyelogram and kidney function studies. The patient should be followed by checking on these various aspects of hypertensive disease from time to time. Then one may know whether or not the hypertensive state in a given case is progressive in nature. The patient whose hypertensive disease shows evidence of progression and activity is a candidate for surgical treatment.

It is well known that there is a group of persons who tolerate essential hypertension exceedingly well. They live out a normal life span without any symptoms or complicating accidents of hypertensive disease. Naturally, this group needs no active treatment.

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9. King, R. L.; Carlile, T., and Blackford, J. M.: Hypertension: Follow-Up Study of 481 Cases, Northwest Med. **41**: 298 (Sept.) 1942.
10. Woods, W. W., and Peet, M. M.: The Surgical Treatment of Hypertension: II. Comparison of Mortality Following Operation with That of the Wagener-Keith Medically Treated Control Series; a Study of Seventy-Six Cases from Five to Seven Years After Operation, J. A. M. A. **117**: 1508 (Nov. 1) 1941.
11. de Takáts, G.; Heyer, H. E., and Keeton, R. W.: The Surgical Approach to Hypertension, J. A. M. A. **118**: 501 (Feb. 14) 1942.
12. Allen, E. V., and Adson, A. W., cited by Wegener, H. P., and Keith, N. M.: Diffuse Arteriolar Disease with Hypertension and the Associated Retinal Lesions, Medicine **18**: 317 (Sept.) 1939.

When elevated blood pressure is discovered as an incidental finding, a complete hypertensive study of the patient is indicated. If the blood pressure is only moderately elevated and there are no symptoms, no fundus abnormality and no cardiac, cerebral or renal involvement, management of the patient by general medical measures and periodic examination is advisable. If evidence of progression is discovered—such as hypertensive symptoms, or angiospastic-retinal changes or cardiac, cerebral or renal involvement—the patient has become a candidate for surgical treatment. No form of medical therapy has yet been shown to be as efficacious as surgical treatment in arresting the pernicious, progressive character of hypertensive disease, promoting improvement and increasing life span.

It has been shown that hypertensive patients with symptoms and fundus changes, but no evidence of cardiac, cerebral or renal involvement—group 2 of our classification—may expect excellent results from surgical treatment. Ninety-five per cent of the patients in this category were living five to eleven years after operation; the five year survival rate was 98.6 per cent. for three of the four deaths in this group occurred subsequent to the fifth postoperative year. Three of the four deaths in this group were from causes other than hypertensive disease, and all 3 patients had maintained normal blood pressure levels until death occurred. One of the 3 deceased patients passed an army final-type physical examination and was commissioned; he maintained a normal blood pressure during two and one half years of rigorous infantry training, and he was killed by a German sniper while at his regimental command post on a Normandy beachhead. The second died of acute intestinal obstruction, and the third died of carcinoma of the testis with metastasis.

Thirty per cent of the patients in group 2 have maintained normal blood pressure levels, and another 47 per cent have maintained definite or significant reductions. Symptoms have been completely relieved or definitely improved and angiospastic-retinal changes have been improved in remarkably high percentages. Their normal electrocardiograms, heart size and kidney function have been adequately protected.

Approximately one third of all the patients who showed preoperative evidence of either organic heart disease, cerebrovascular disease or impaired kidney function did not survive five to eleven years. Evidence of involvement of any one of these vital organ systems is indicative of generalized vascular involvement. Hypertensive heart disease is not to be considered singularly; it is a part of a constitutional disease. Not all patients with hypertensive heart disease die in congestive failure; many die of a cerebrovascular accident and some in uremia. The patient who has had a cerebral accident may later die of a cardiac lesion.

Half of the patients in preoperative groups 3, 4 and 5 may expect significant blood pressure reductions maintained for at least five to eleven years. Their hypertensive symptoms—such as headache, dizziness, tinnitus, epistaxis, fatigability, weakness, nocturia, nervousness, irritability and blurring of vision—and retinal angiospasms are relieved in the same high percentages as in group 2. Of those who had abnormal electrocardiograms and cardiac enlargement before operation and are still living, more than half have maintained significant improvement of these objective aspects for five to eleven years.

Sixty per cent of patients who have suffered a cerebral accident may expect prolonged life with no subsequent cerebral accident after splanchnicectomy.

Nineteen per cent of the 112 patients with preoperative malignant hypertension are living five to eleven years later. Eighteen of these 21 living patients are maintaining significant reductions in blood pressure. Seventeen of these patients received funduscopic examinations, and papilledema had disappeared in all. In the survivors, symptomatic improvement has been remarkable. Splanchnicectomy offers hope for prolonged life to 1 out of every 5 patients with malignant hypertension.

Any patient who is under 60 years of age, who is not in congestive heart failure, whose blood nonprotein nitrogen level is below 45 mg. per hundred cubic centimeters and who has not sustained a major cerebral accident during the previous month may be considered as a reasonable operative risk.

The age of the patient at time of operation has no influence on postoperative survival. The extent of the hypertensive disease process is the important factor in survival.

SUMMARY

Four hundred and thirty-seven patients with essential hypertension have been followed since receiving the surgical treatment of bilateral supradiaphragmatic splanchnicectomy and lower dorsal ganglionectomy five to twelve years ago.

Two hundred and fifty-one patients, or 57.5 per cent of the series, are living five to eleven years after operation. At the end of five postoperative years 64.8 per cent of the entire series was alive. The hypertensive state in 82 per cent of the patients in this series had already progressed to serious organic disease prior to operation.

Fifty-six per cent of all the males have died, while the female mortality was only 30 per cent.

Ninety-five per cent of hypertensive patients who showed no preoperative evidence of cardiac, cerebrovascular or renal involvement are living five to eleven years after operation.

Approximately one third of all patients who manifested preoperative evidence of organic heart disease, cerebrovascular disease or impaired kidney function did not survive five to eleven years.

Nineteen per cent of 112 patients with preoperative malignant hypertension are living five to eleven years later.

Fifty-one patients have maintained normal blood pressure levels and 28 show no evidence whatever of hypertensive disease five to eleven years after operation.

Significant reductions in blood pressure, complete and definite symptomatic relief, improvement of eyegrounds and improvement of abnormal electrocardiograms, cardiac enlargement and kidney concentrating ability have been maintained for five to eleven postoperative years in a remarkable percentage of patients.

Sixty per cent of patients who had previous cerebral accidents suffered no recurrence during the long postoperative period.

Surgical treatment is a measure to be considered in the management of every case of essential hypertension, but to be utilized only when indicated. Evidence of progression and activity of hypertensive disease constitutes indication for surgical treatment.

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EFFECT OF FOLIC ACID ON PERSONS WITH MACROCYTIC ANEMIA IN RELAPSE

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That macrocytic anemia in relapse is promptly relieved by either the parenteral or the oral administration of synthetic folic acid was reported by Spies, Vilter, Koch and Caldwell [1] in November 1945. The following month Vilter, Spies and Koch [2] reported another series of cases in which these results were confirmed. At the same time Spies, López, Menéndez, Minnich and Koch [3] reported that the macrocytic anemia of tropical sprue found in Cuba responds in a similar manner.

The present report, which is a tentative evaluation of the status of folic acid as a therapeutic agent, is presented because of the large number of requests for information from physicians regarding the use of folic acid as a therapeutic agent. It has been disheartening to write to so many physicians that leukemia, aplastic anemia and some of the anemias of undetermined origin do not respond specifically to this substance.

The present communication is based on my observations of the effect of folic acid in anemia. These observations were made on patients in Birmingham, Ala., and in Havana, Cuba. All except 2 of the patients were studied in conjunction with one or more of the associates mentioned.

In selecting the cases, the following criteria were used: 1. The patient must have a macrocytic anemia with red blood cell counts of 2.5 million or less and a color index of over 1. 2. He must be untreated, or he must not have been treated recently enough to interfere in any way with our evaluation of the effect of folic acid. 3. He must not have any complicating disease which might be lethal during the course of the study. 4. The bone marrow must contain megaloblasts and have the typical erythroblastic arrest seen in macrocytic anemia. A fifth criterion used for the selection of any patient in Cuba, where we were studying sprue, was that he must have "fatty stools" and weight loss.

With these criteria in mind, we selected for special study a group of 45 patients. This group included 8 patients with so-called nutritional macrocytic anemia, 8 with pernicious anemia, 11 with sprue, 3 with anemia associated with pregnancy, 1 with anemia associated with carcinoma, 1 with anemia associated with chronic alcoholic addiction, cirrhosis of the liver and neuritis, 3 with anemia of undetermined origin, 3 with aplastic anemia, 3 with anemia associated with leukemia and 4 with iron deficiency anemia.

The diagnoses of the patients shown in the accompanying table were arrived at after intensive study by a number of physicians. The clinical separation of these various syndromes is somewhat arbitrary; but in view of the findings reported in this paper and in our previous publications on folic acid, the classification probably is not of as great importance as it has been considered in the past. As far as possible, the cases are classified arbitrarily in order to aid other investigators who may wish to study the effect of folic acid on similar patients.

Forty-one of the 45 patients had typical macrocytic hyperchromic anemia diagnosed on the basis of criteria used in the past in the Nutrition Clinic at Hillman Hospital.[4] The other 4 patients had iron deficiency anemia characterized by a low color index. A diagnosis of pernicious anemia was made only when there was no free hydrochloric acid, pepsinogen or rennin in the gastric juice after histamine stimulation. A diagnosis of sprue was made only in the presence of steatorrhea. If pregnancy was the only etiologic agent present, a diagnosis of macrocytic anemia of pregnancy was made. If the patient had a blood picture typical of macrocytic anemia and if there was free hydrochloric acid, pepsinogen and rennin in the gastric juice, a diagnosis of nutritional macrocytic anemia was made. In most instances there was complete agreement on the part of the physicians with regard to the clinical classification of these cases. The cases in which there was a difference of opinion were classified as indeterminate.

Pellagra, which was diagnosed only in the presence of characteristic tongue or dermal lesions, was present at the time folic acid therapy was initiated in 7 cases: 1 (case 3) of nutritional macrocytic anemia, 2 (cases 7 and 10) of pernicious anemia, 2 (cases 17 and 19) of sprue, 1 (case 21) classified as indeterminate and 1 (case 24) of macrocytic anemia of pregnancy. In 2 of the cases of pernicious anemia, neurologic alterations indicative of mild postolateral sclerosis were present. In the group of cases classified as nutritional macrocytic anemia, severe polyneuritis was present in 1 and mild peripheral neuritis in 2. In 2 of the cases of sprue there was also evidence of peripheral nerve involvement.

All except 4 of the patients were hospitalized for preliminary observations, base line determinations and treatment. Four of the patients who lived near the Nutrition Clinic in Birmingham were treated as ambulatory cases. They came to the clinic daily throughout the study. A detailed medical and dietary history was obtained and a careful physical examination was made in each case. During the control period and also during the period of most active regeneration, red and white cell counts, reticulocyte counts and hemoglobin determinations were made daily.[3] Thereafter these determinations were made at increased intervals. Bone marrow studies were also made in each case.

The diet of 35 of the 41 hospitalized patients was rigidly controlled during the whole period of study. Meat, meat products, fish and poultry were excluded, and only 1 quart of milk and one egg daily were allowed. Bread, cereals, sugar, fats and vegetables were permitted in any amount desired. In a previous study of anemia, 75 patients had been restricted to this diet, and not 1 of them had had a so-called spontaneous remission. We felt certain, therefore, that any hemopoietic response by the patients on folic acid therapy would be attributable to the folic acid rather than to the foods included in the diet. The other 6 hospitalized patients (the 3 with leukemia and the 3 with aplastic

The folic acid for the study was supplied by Lederle Laboratories, Inc.
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University of Cincinnati Studies in Nutrition at Hillman Hospital, Birmingham, Alabama, and at the Calixto García Hospital, Havana, Cuba, in cooperation with the Institute of Nutrition of Cuba, the Coordination Committee for Cuba and the University of Havana.

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anemia) were given the usual hospital diet ad libitum. The 4 ambulatory patients ate their meals at home. However, because of financial limitations these 4 persons were unable to vary their diets to any extent from day to day and, according to their dietary histories, the food they ate at home was similar to that eaten by patients with aplastic anemia, leukemia, cirrhosis of the liver and carcinoma. An adequate diet had been available to all the patients with macrocytic anemia of pregnancy, but vomiting and loss of appetite had caused them to reduce their food intake far below the desired level. In every case of nutritional macrocytic anemia,

Effect of Folic Acid on Peripheral Blood in Macrocytic Anemia

Case No.	Type of Macrocytic Anemia	Red Blood Cells, Million			Hemoglobin, Gm.			Reticulocytes, per Cent			Folic Acid Therapy	
		Initial	14th Day	Final Day	Initial	14th Day	Final Day	1st Day of Rise	Day of Peak	Per Cent at Peak	Daily Dosage, Mg.	Mode of Administration
1	Nutritional	2.16	2.69	4.08 (40)	8.8	9.3	11.7 (40)	4	8	14.8	20	Intramuscular
2	Nutritional	2.98	3.14	3.20 (20)	9.3	8.3	9.2 (20)	4	4	4.6	100	Oral
3	Nutritional	1.64	3.24	4.07 (19)	7.1	10.2	9.8 (19)	3	5	19.2	100	Oral
4	Nutritional	2.01	3.57	3.82 (30)	9.9	10.1	12.1 (30)	6	8	10.0	100	Oral
5	Nutritional	1.79	2.81	3.38 (30)	8.7	11.3	13.0 (30)	3	6	10.0	100	Oral
6	Nutritional	2.97	3.23	3.55 (27)	8.0	10.5	13.4 (27)	3	3	6.6	100	Oral
7	Pernicions	1.95	2.59	3.22 (55)	7.0	9.8	11.0 (55)	6	8	6.4	20	Intravenous
8	Pernicious	1.96	2.92	3.54 (49)	7.8	11.7	12.1 (49)	6	8	14.6	20	Intravenous
9	Pernicious	1.61*	1.58	1.58 (18)	6.2	8.0	8.0 (18)	7	10	11.0	20	Intravenous
10	Pernicious	2.01	2.69	4.22 (40)	8.3	10.7	13.9 (40)	4	6	14.8	100	Oral
11	Pernicious	2.59	3.14	3.72 (21)	8.6	10.6	10.1 (21)	4	7	14.4	100	Oral
12	Sprue	2.11	3.04	3.40 (23)	9.0	10.4	11.7 (23)	5	7	17.2	200	Oral
13	Sprue	2.16	2.66	3.13 (21)	9.5	9.7	9.8 (21)	5	7	17.2	200	Oral
14	Sprue	1.51	2.55	3.25 (20)	6.8	8.6	11.5 (20)	4	6	22.7	200	Oral
15	Sprue	2.17	2.85	2.85 (14)	8.1	10.0	10.0 (14)	6	8	12.5	200	Oral
16	Sprue	1.47	2.47	2.47 (14)	5.9	8.1	8.1 (14)	5	6	31.8	200	Oral
17	Sprue	1.87	2.60	2.60 (14)	8.1	10.0	10.0 (14)	3	6	19.5	200	Oral
18	Sprue	1.63	2.65	2.65 (15)	5.9	8.6	7.5 (15)	5	7	22.9	200	Oral
19	Sprue	1.48	2.72	2.72 (14)	5.9	10.9	10.9 (14)	5	12	18.7	200	Oral
20	Indeterminate	2.35	3.53	4.29 (48)	7.8	9.9	12.4 (48)	5	7	21.4	150	Oral
21	Indeterminate	2.32	3.31	3.38 (21)	8.0	11.2	11.7 (21)	4	7	19.6	100	Oral
22	Indeterminate	1.82	2.23	2.92 (22)	7.7	10.1	9.8 (22)	4	6	10.4	50	Intravenous
23	Pregnancy	1.63	2.30	4.25 (40)	7.3	9.1	12.2 (40)	4	6	29.0	50	Intravenous
24	Pregnancy	1.30	2.10	3.80 (30)	7.0	9.0	12.1 (30)	4	7	24.0	20	Intravenous
25	Pregnancy	1.80	2.70	3.90 (25)	9.0	10.1	11.6 (25)	4	6	23.1	20	Intramuscular
26	Associated with chronic alcoholic addiction, cirrhosis and neuritis	1.30	1.91	2.60 (30)	6.9	8.1	9.8 (30)	5	7	17.2	100	Oral
27	Carcinoma	1.10	1.92	3.19 (40)	6.5	7.1	7.8 (40)	4	7	17.2	100	Oral
28-45 inclusive, see text												

* In case 9 the initial red blood cell count is interpreted as being in error since it is out of line with the other determinations. At any rate the blood responded following treatment.

the patients on the controlled diet. As soon as the studies were completed, each patient was advised to eat a liberal, well balanced diet including lean meat, eggs and milk.

The diet of 2 patients with pernicious anemia and pellagra had been inadequate for many years. Of the other 3 patients with pernicious anemia the diet had been well balanced and, as a rule, adequate, although in some instances the total food intake had been reduced because of loss of appetite. This was true also of the in every case of sprue and in the 3 indeterminate cases the diet had been grossly inadequate for several years. Although some of the patients included in this study live in Alabama and others live in Cuba, an analysis of their diets showed that, while the types of foods differed somewhat in the two countries, the nutritional quality of the diets of the two groups was strikingly similar. In both groups the diets tended to be low in animal proteins, minerals and vitamins, high in concentrated carbohydrates and relatively high in fat.

All the patients complained of loss of strength, vigor and appetite, and in most instances there had been a considerable loss of body weight. The diarrhea of the patients with sprue was characterized by stools which ranged in frequency from five to twenty times daily. The stools were yellow or white, watery, foamy and foul in odor. When diarrhea was present in cases other than sprue, the stools were watery and brownish, and the odor was not particularly foul. All the patients with diarrhea stated that it was more severe after meals.

The folic acid was administered either parenterally or orally. In 2 cases it was administered intramuscularly and in 6 cases intravenously. In order to get the folic acid into solution for parenteral administration, we converted it into a soluble salt by adding a normal sodium bicarbonate solution. To insure sterility the solution was then passed through a Seitz filter. When the folic acid was given orally in amounts of 20 mg. or more a day, one half the total dose was given in the morning and the other half in the afternoon. For oral administration each dose was prepared by mixing the folic acid to a smooth paste with four or five drops of cold water and then adding 20 cc. of cold water while the mixture was stirred constantly. After the patient drank this material, a small amount of water was used to rinse the glass thoroughly, and the patient drank this also to insure his getting as much of the folic acid as possible.

The laboratory findings and the response to folic acid therapy can be seen in the table, in which the results in 27 cases are shown. Data on 18 patients are not included in the table: 3 with aplastic anemia, 4 with iron deficiency anemia and 3 with the anemia associated with leukemia, none of whom responded to folic acid therapy; 5 patients [5] in whom we were attempting to establish the minimal dosage of folic acid and who did respond satisfactorily though perhaps not maximally on the amount administered (study of these cases is being continued, but it is too early to present data on them), and 3 patients with sprue who, we noted during the preliminary period of observation, were having a hemopoietic response. These 3 patients denied having had antianemic therapy recently, but on further questioning we found that they had been treated although they did not realize that they had received treatment for anemia. This indicates the importance of making base-line determinations in every case. Because these 3 persons had received antianemic therapy recently, they were not given folic acid at this time.

The results presented in the table show that only 1 of the patients included (patient 2) failed to respond to folic acid in amounts above 10 mg. a day. Although this patient is classified as having nutritional macrocytic anemia, a satisfactory diagnosis has never been made despite the fact that she has been seen by many competent physicians. The patient is still under observation in an endeavor to obtain more exact hematologic information.

The white blood cell counts of patients with nutritional leukopenia are not shown in the table. The white blood cells also tended to increase following the administration of synthetic folic acid. Early observations on this study were reported recently by Berry, Spies and Doan [6] and by Vilter, Spies and Koch.[2]

Prompt improvement occurred in the general condition of 26 of the 27 patients reported in the table. On the third or fourth day following the initiation of folic acid therapy these 26 patients volunteered that they felt stronger. At the same time there was a definite improvement in their appetites: those under observation in the hospital began eating all the food on their trays and frequently asked for additional servings, and those who were being treated as ambulatory patients and who ate their meals at home voluntarily told us that they had a similar improvement in appetite. This subjective improvement coincided with or was followed by an increase in the reticulocytes in the peripheral blood and by subsequent rises in the red blood cells and in the hemoglobin content of the blood. The reticulocytes began to rise on the third, fourth, fifth or sixth day of folic acid therapy and reached a peak on the sixth, seventh or eighth day. This improvement occurred regardless of the mode of administration.

It is of considerable interest that the case of macrocytic anemia associated with chronic alcoholic addiction, cirrhosis of the liver and peripheral neuritis (case 26) and the case of macrocytic anemia associated with carcinoma of the stomach with metastasis to the lungs (case 27) each showed a significant hemopoietic response following folic acid therapy.

In the patients with aplastic anemia, leukemia and iron deficiency, no improvement could be detected either clinically or by means of laboratory determinations.

SUMMARY AND CONCLUSIONS

These findings and others that my associates and I have reported show that synthetic folic acid administered either parenterally or orally is effective in producing a significant hemopoietic response in persons with nutritional macrocytic anemia, or with the macrocytic anemias of pellagra, of pernicious anemia, of sprue or of pregnancy. This hemopoietic response is characterized by an increase in reticulocytes, red blood cells, white blood cells, platelets, normoblasts and hemoglobin. The megaloblasts in the bone marrow are decreased following therapy.

It is worthy of emphasis that none of the patients with aplastic anemia, iron deficiency anemia or the anemia associated with leukemia showed any improvement. We have found that folic acid corrects the leukopenia of certain nutritional conditions but does not correct the leukopenia of a number of infectious diseases or idiopathic states.

The subjective and the objective improvement which follows the administration of folic acid to persons with macrocytic anemia in relapse is similar to that which follows liver extract therapy. There is a tremendous upsurge of well-being, an increase in strength and vigor, a return of appetite and a desire to walk about. It is too early in our studies to know whether or not folic acid is as effective as liver extract in maintaining the blood levels or in protecting against combined system disease.

The exact minimal and optimal doses of folic acid have not been determined, but our studies indicate that there is some variation from patient to patient. Although we have found that the administration of as much as 400 mg. daily has not caused any untoward symptoms, a daily dosage of from 5 to 10 mg. parenterally or some 10 mg. by mouth will often produce a maximum hemopoietic response. In order to determine the optimal and the average doses, the study of many patients will be required. The response of 5 patients to a daily dosage of 10 mg. by mouth may be an indication that the average doses, when they are finally determined, will be lower than those we are suggesting at this time.

5. Unpublished observations by Tom D. Spies, Carl F. Vilter and Richard W. Vilter.

6. Berry, L. Joe; Spies, Tom D., and Doan, Charles A.: A Note on the Influence of "Folic Acid" on Leukocyte Equilibrium in Malnourished Patients, South. M. J. **38**: 590-592 (Sept.) 1945.

Unpublished observations of mine have shown that dried brewers' yeast powder, yeast concentrate or liver extract produces a response in persons with macrocytic anemia in relapse, a response which is out of proportion to the folic acid content of these substances. A number of patients have failed to respond fully to folic acid at the level of 3 or 4 mg. per day by mouth and have responded to liver extract or yeast administered in amounts which supply 1 mg. or less of folic acid daily. These findings suggest that the antianemic factor present in liver extract or yeast may be a combination of chemical substances or that it may be a much larger molecule than folic acid. From a practical point of view it must be stressed, however, that folic acid administered either orally or parenterally will give a satisfactory response in patients with macrocytic anemia.

I have studied 2 additional patients with macrocytic anemia who have developed such severe sensitivity to various forms of liver extract that they were unable to tolerate injections in sufficient amounts to maintain proper blood values. In both cases folic acid was substituted for the liver extract safely and satisfactorily.

It must be stressed that neither folic acid nor any other single chemical substance can be expected to take the place of all the nutrients essential for health. The patients in this study were given a restricted diet in order to test more effectively the antianemic properties of folic acid. A restricted diet is not recommended in the treatment of macrocytic anemia. On the contrary, we prescribe a diet high in protein, minerals and vitamins.

The laboratory observations obtained from frequent examinations of stools and bone marrows will form the basis of a separate report. Suffice it to say that the stools and the bone marrow both tend to approach normal following administration of a satisfactory amount of folic acid.

Despite the fact that there are no published reports confirming this work,[7] the findings are so striking that I have no hesitancy in making the statement that folic acid (synthetic Lactobacillus casei factor), a vitamin present in liver, yeast and other food materials, is a potent antianemic factor in certain types of macrocytic anemia in relapse. Folic acid performs a specific function in the maturation of the various cells of the bone marrow and has other obvious profound effects on our bodies.

7. Since this writing, personal communications from C. A. Doan and his associates at Columbus, Ohio, and from C. V. Moore and his associates at St. Louis have been received confirming the antianemic action of folic acid.

Intracranial Pressure.—Sudden intense increased intracranial pressure is brought about by deformation of the skull and acceleration of the head. The well known observation that the cranial cavity is spheroid in shape and that any change in its diameters would tend to decrease its volume capacity indicates one cause for increased intracranial pressure in closed wounds of the head. Another is the sudden setting of the head to motion or acceleration. Severe circumscribed depressed fractures may be associated with increased pressure due to the plunger effect of the depression. More extensive depressions may be associated with increased intracranial pressure, depending on their extent and the time period of their production. Cannon and Kocher felt that there was an increase in intracranial pressure at the time of the blow, and Scott demonstrated this change by the use of the Hamilton manometer. The increase in pressure is of such short duration that ordinary means of recording do not demonstrate it.—Gurdjian, E. S., and Webster, J. E.: Experimental and Clinical Studies on the Mechanism of Head Injury, in Trauma of the Central Nervous System, Baltimore, Williams & Wilkins Company, 1945.

SEVERE POSTOPERATIVE HYPOGLYCEMIA

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The clinical state associated with hypoglycemia is assuming an increasing importance in the differential diagnosis of atypical nervous system reactions. Since the first description of this condition by Harris[1] in 1924 there has developed a large body of literature pertaining in particular to etiologic mechanisms. Many organs of the body, including the liver, pancreas, adrenal, thyroid and pituitary, have seemed to play a role in various instances, but there have been certain other cases for which no acceptable explanation was apparent.

In the numerous reports of these cases of unexplained spontaneous hypoglycemia, little has been written concerning a decrease in blood sugar in previously asymptomatic individuals following a surgical procedure. Coma following an operation, while relatively rare, is a disturbing complication and the cases reported here illustrate another etiologic possibility which must be considered in the presence of this perplexing problem. In the past two years we have had 3 examples of such profound hypoglycemia following surgical procedures:

CASE 1.—Mrs. E. K., aged 76, white, a housewife, admitted to the fracture service of the Presbyterian Hospital for the second time on Sept. 16, 1943, complained of pain in the left hip of four months' duration. Her first admission had been in September 1941 for a fracture of the neck of the left femur. This had been successfully treated by fixation with a Smith-Petersen nail. She had been well since that time except for considerable fatigue, which was occasionally accompanied by substernal pressure and moderate dyspnea. Her general health had always been good and she had had no weight loss, headaches, vertigo or fever. She had never had ankle edema, orthopnea, cough or cyanosis. Her son stated that on several occasions she had complained of mild vertigo in the midafternoon or at bedtime. At the age of 22 she had a uterine fibroid removed and had had typhoid at 12. The family history was noncontributory. The patient was thin and nervous. The only positive findings on physical examination were slight narrowing of the arterioles of the fundi, a lower abdominal scar and a blood pressure of 160/88. Reflexes and neurologic signs were not abnormal.

Laboratory examination revealed hemoglobin 14.5 Gm., red blood cells 4.7 million and white blood cells 8,250 with 48 per cent polymorphonuclears, 45 per cent lymphocytes, 4 per cent monocytes and 3 per cent eosinophils. The urine was normal. An electrocardiogram showed low voltage of T_1 and isoelectric T_4F which suggested some myocardial damage. X-ray examination of the heart showed no evidence of cardiac enlargement.

On the fifth hospital day the Smith-Petersen nail was removed from the left hip. The preoperative medication was morphine sulfate 0.006 Gm. and scopolamine 0.0003 Gm. Anesthesia was local with procaine hydrochloride and the total duration of the procedure was forty minutes. No epinephrine or nitrous oxide was used. The patient withstood the procedure well and was returned to her room in good condition. Five hours later she began to feel very weak and thirsty and perspired freely. The lungs were clear and the blood pressure was 160/78. The pulse was irregular. Within two hours she was stuporous and perspiring profoundly but could be aroused. Blood pressure was 140/40. There was no cyanosis, and the lungs were clear. The speech had become sluggish, and she complained of a sense of pressure in the chest. In view of the past history of substernal oppression a myocardial infarction was suspected, but the picture more closely resembled the hypoglycemic state and therefore the blood sugar was determined, 24 mg. per hundred cubic

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1. Harris, S.: Hyperinsulinism and Dysinsulinism, J. A. M. A. **83:** 729-733 (Sept. 6) 1924.

centimeters. Following an infusion of 5 per cent dextrose in saline solution the patient gradually improved, so that within six hours she was well oriented and talkative.

Next day the patient had four tonic-clonic convulsions, relieved immediately by intravenous 50 per cent glucose. Her blood sugar during these episodes was as low as 35 mg. per hundred cubic centimeters. Serum bicarbonate was 20.9 milliequivalents per liter and serum chlorides 107.3 milliequivalents per liter. An electrocardiogram taken this day showed changes which suggested an active process in the myocardium. Because of the persistent hypoglycemia the patient was started on a continuous intravenous drip of saline solution alternating with 10 per cent glucose. During the first postoperative day she received 75 Gm. of glucose. In order to increase this, on the following day a Miller-Abbott tube was introduced, and this, plus the intravenous route, allowed an intake of 1,050 Gm. of carbohydrate. Approximately the same regimen was continued. The fluid intake and output were more than adequate throughout.

During the ensuing days it was found that the patient required from 800 to 1,000 Gm. of glucose daily to remain out of hypoglycemia, but even on this regimen the blood sugar was as low as 39 mg. per hundred cubic centimeters. On the fourth postoperative day it was obvious that the patient was losing ground. Her fasting blood sugar was 40 mg. per hundred cubic centimeters; it was also 40 mg. per hundred cubic centimeters before lunch and rose only to 61 mg. per hundred cubic centimeters following the meal. Serum chlorides were 100 mEq./L., bicarbonate was 20.1 mEq./L., and the "calculated serum sodium" 130 mEq./L. The blood count showed only a mild anemia with no leukocytosis. An electrocardiogram taken that day showed further changes diagnostic of myocardial damage. X-ray examination of the chest showed peribronchial consolidation in the middle zone of the right lung. Her temperature had gone to 102.4 F. immediately after operation and to 103 F. on the second postoperative day, and now on the fourth day it rose suddenly to 103 F. A transfusion was given at this time and seemed to improve the general condition. She had considerable diarrhea, believed to be due to the tube feedings of glucose.

Because of the possibility of a pancreatic adenoma, an emergency exploratory operation was done on the fourth postoperative day. At operation there was a moderate amount of amber colored peritoneal fluid. The peritoneum was not inflamed, but the stomach was distended. The liver was smaller than normal, was dark green and showed numerous areas of fibrosis, especially in the region of the gallbladder. The whole organ was much firmer than usual. The gallbladder was normal. No abnormalities were seen or felt in the pancreas after careful examination. By the time the pancreas was exposed the heart beat had become imperceptible, and in spite of continued artificial respiration the patient died. Permission for autopsy was not granted.

Case 2.—V. U., a white man aged 27, a lawyer, was admitted to the urologic service of the Presbyterian Hospital on May 10, 1944 complaining of intermittent hematuria, left inguinal pain and urinary frequency of six months' duration. His past history and family history were noncontributory. There was no history of tuberculosis, acute rheumatic fever, diabetes or heart disease. Seven years previous to admission he had had an operation for intestinal obstruction, and subsequently an ectopic right kidney was removed following a severe attack of pain during the convalescent period. The appendix had been removed fifteen years previous to the present admission. Following the removal of the right kidney the patient had intermittent painless hematuria until six months before admission, when it became associated with left inguinal pain, frequency of urination and vomiting, which continued to the time of admission. There had been a 5 pound (2.3 Kg.) weight loss in two years. On physical examination the patient appeared well developed and in no acute distress. The temperature was 99.6 F., pulse rate 76, respiratory rate 20 and blood pressure 130/80. There were a McBurney incision and lower right rectus scars. The liver and left kidney were palpable but not tender. There was a well healed scar on the lateral aspect of the left thigh and upper part of the leg. Neurologic examination was negative.

Laboratory examination revealed hemoglobin 16.2 Gm., red blood cells 5.22 million, white blood cells 5,600 with 67 per cent polymorphonuclears, lymphocytes 30 per cent, monocytes 3 per cent. The urine showed a specific gravity of 1.011, alkaline reaction, albumin 2 plus, glucose negative and microscopically 15 to 20 red blood cells and 25 to 35 white blood cells per high power field. The Kline reaction was negative. The sedimentation rate was 3 mm. fall in one hour. Blood urea nitrogen was 9.8 mg. per hundred cubic centimeters. Retrograde pyelography demonstrated the presence of renal calculi in a nonrotated hydronephrotic left kidney and an absent right kidney.

In view of these findings a left pyelolithotomy was done on the fifth hospital day. The preoperative medication was morphine sulfate 0.012 Gm. and scopolamine 0.0004 Gm. The anesthesia was nitrous oxide, oxygen and ether by the closed method. The anesthesia was without incident and the duration of the operation thirty minutes. At operation two large stones composed of calcium and ammonium phosphates were removed from the left kidney pelvis. The blood pressure remained normal throughout the operation, and the condition of the patient was satisfactory at the end of the procedure.

Postoperatively the patient was given only 1,500 cc. of isotonic solution of sodium chloride. Ten hours later he was found to be moderately stuporous and within two hours comatose. The blood pressure was 120/55. Both diabetic coma and uremia were considered. Urinalysis showed a specific gravity of 1.013, albumin 4 plus, glucose negative and microscopically a few pus cells. Four hours later the patient was still comatose, had developed Cheyne-Stokes respiration, was perspiring profusely and had conjugate deviation of the eyes to the right with nystagmus to the right. The pupils were fixed to light. Reflexes were equal and active, and the Chvostek sign was negative. Intravenous calcium gluconate was given with no benefit. Blood sugar taken at the time was 38.5 mg. per hundred cubic centimeters, serum bicarbonate 20.5 mEq./L., urea nitrogen 18.2 mg. per hundred cubic centimeters. Fifty cc. of 50 per cent glucose solution was given intravenously, with gratifying improvement. The patient roused immediately and became oriented. The respirations became normal and the pupils again reacted to light. There were no localizing neurologic signs. A continuous intravenous drip of 10 per cent glucose was started, but the patient continued to have recurrent coma and restlessness. The patient was seen later that day by a neurologist, who believed the condition to be a result of hypoglycemia with possible permanent cerebral damage. A lumbar puncture was done. The fluid was crystal clear at a pressure of 196 mm. with normal manometric studies. It contained 4 cells per cubic millimeter, protein was 43 mg. per hundred cubic centimeters and the Wassermann reaction was negative. On the first postoperative day the temperature began to rise and did so steadily. It was considered that the patient possibly had an atypical pancreatic adenoma, and for this reason exploration was done. At the operation the duodenum was mobilized and after careful investigation no pathologic condition could be found in the pancreas. A biopsy of the liver was done at the time, which showed no abnormalities. The patient's blood sugar two hours after operation was 143 mg. per hundred cubic centimeters, but he remained in coma in spite of intravenous 50 per cent glucose solution. Blood sugars before and seventeen minutes after the administration of epinephrine showed no change at this time. There was a leukocytosis of 21,500, with polymorphonuclears 88 per cent. The serum bicarbonate was 21.9 mEq./L., chlorides 103.8 mEq./L. Two 10 mg. doses of desoxycorticosterone acetate were given with no beneficial results.

The patient continued in coma and on the seventh hospital day the temperature suddenly went to 107 F. and he died. Permission for autopsy was not granted.

Case 3.—E. L., a white man aged 55, a photographer, was admitted to the surgical service of the Presbyterian Hospital on Feb. 20, 1945 complaining of abdominal pain of three days' duration. Family and past history were noncontributory. For several months preceding admission he had felt considerable fatigue, particularly in the afternoon, but this was not related to the intake of food. There was occasional mild vertigo with

these episodes but no particular perspiration. The patient had been greatly overworking for several months preceding admission. He was well until three days before admission, at which time he developed nonradiating pain in the lower part of the right upper quadrant just to the right of the umbilicus. This pain came on at night and was intense enough to prevent sleep. Accompanying this was a moderate amount of "heartburn" and considerable anorexia but no nausea. Bowel movements were normal. This pain was very persistent and continued to the day of admission. The day before, following the taking of sodium bicarbonate in warm water, he vomited, with some relief. On physical examination he was alert and cooperative and appeared to be in mild distress. There was considerable tenderness in the right upper quadrant and to a lesser degree over the entire right side of the abdomen. There was also a left indirect inguinal hernia and some tenderness in the right subcostal region. Blood pressure was 140/80.

Laboratory examination revealed white blood cells 14,100 with polymorphonuclears 84 per cent, lymphocytes 9 per cent, monocytes 6 per cent and basophils 1 per cent. The urine showed a specific gravity of 1.027, acid reaction, albumin 1 plus, glucose negative and microscopically 5 to 6 red blood cells and a rare white cell per high power field. The Kline reaction was negative. A flat plate of the abdomen showed no urinary calculi.

The patient was observed for two days in the hospital and the abdomen became definitely more tender over the right upper quadrant, but during the second day this tenderness moved down into the right lower quadrant, especially laterally, and it was considered that the appendix was the most probable source of difficulty. Therefore, on the second hospital day an exploratory celiotomy was done under nitrous oxide, ether and oxygen anesthesia by the closed method. The preoperative medication was morphine sulfate 0.012 Gm. and scopolamine 0.0005 Gm. The duration of the anesthesia was one hour and twenty minutes. The procedure was done through a right lower quadrant intermuscular incision. No pathologic condition was found, but the appendix was removed and on section showed only distal occlusion. The patient had vomited once during the induction state of anesthesia but had been in good condition otherwise. After completion of the operation he suddenly became quite cyanotic. The pulse was 84 and of good quality and the blood pressure, which had been 120/70, went only to 130/70. He responded well to oxygen and was supported by this measure for three hours in the operating room. During this period he responded slightly and it was noticed that the right eye was divergent. The left side of the chest showed relative limitation of movement and therefore bronchoscopy was done while he was still in the operating room and a moderate amount of mucus was removed. Aspiration of gastric contents or a cerebrovascular accident was suggested as a possible complication. During the next twenty-four hours the patient responded to a moderate degree but was very drowsy and difficult to arouse. The following morning a blood sugar test was 42 mg. per hundred cubic centimeters and he was again comatose. He had been moderately alert during the preceding six hours. Blood pressure was 120/80, temperature 102 F., pulse rate 88, respiratory rate 12. All extremities were flaccid and there was a slightly positive Babinski sign on the right. The knee jerks were absent. The pupils were small but reacted to light, and there was a right external strabismus. The left side of the chest was still relatively limited in motion. Nonprotein nitrogen was 43 mg. per hundred cubic centimeters. The x-ray of the chest showed peribronchial pneumonia at the right lung base. For this sulfadiazine was given and a level of 7 to 15 mg. per hundred cubic centimeters maintained. Because of the hypoglycemia the patient was put on a regimen of 5 and 10 per cent glucose intravenously and in spite of this was alternately in and out of hypoglycemic shock. A lumbar puncture was done and yielded crystal clear fluid at an initial pressure of 200 mm. The protein was 31 mg. per hundred cubic centimeters and sugar 56 mg. per hundred cubic centimeters. Alcohol and cholesterin Wassermann antigens were negative. X-ray examination of the skull showed no abnormalities.

The patient was continued on intravenous glucose for the hypoglycemia, and oxygen for the persistent cyanosis and dyspnea. The presence of an expanding intracranial lesion was believed to be improbable. Further chemical studies were done in an effort to find a solution. Serum bicarbonate was 29.7 mEq./L., serum amylase 32 units, inorganic phosphorus 4 mg. per hundred cubic centimeters, alkaline phosphatase 5.3 Bodansky units, urea nitrogen 18 mg. per hundred cubic centimeters, serum bilirubin a very faint trace, cholesterol 150 mg. per hundred cubic centimeters, total serum protein 6.5 per cent, albumin 4 per cent, globulin 2.5 per cent, cephalin flocculation negative. There was no anemia or leukocytosis. The sedimentation rate was 66 mm. in one hour. Venous pressure was 76 mm. of saline solution.

During the postoperative course the patient had many blood sugar determinations. The lowest recorded was 21 mg. per hundred cubic centimeters. During the first three days the patient's state of consciousness was well correlated with the degree of hypoglycemia as controlled by glucose injection. At that time he was placed on a regimen of epinephrine in oil intramuscularly 1 mg. every four hours, and a high protein diet. He was given 100 cc. of amigen and 100 cc. of orange juice by stomach tube on alternate hours. On this intake of 1,000 to 1,200 Gm. of carbohydrate in each twenty-four hours his blood sugar was maintained around 80 mg. per hundred cubic centimeters.

On the fourth postoperative day with no change in regimen the blood sugar went to 314 mg. per hundred cubic centimeters and continued in that range, reaching a high of 482 mg. per hundred cubic centimeters. There was an accompanying glycosuria. The following day the amigen diet was discontinued and, as he was then completely conscious and cooperative, a regular diet started. No insulin was given. By the following morning the blood sugar was 64 mg. per hundred cubic centimeters and the patient was again stuporous. However, this state was transient and his blood sugar soon returned to normal limits and he became asymptomatic. It was thought inadvisable to do a glucose tolerance curve. A cholecystogram done just before discharge revealed a definite gallbladder calculus. He left the hospital on the twenty-second day asymptomatic and on a regular diet without supplemental feedings. A fasting blood sugar done two weeks after discharge was 98 mg. per hundred cubic centimeters, and six weeks later he is apparently normal.

COMMENT

Conn [2] has offered a very complete classification of the etiologic mechanisms productive of hypoglycemia, but none of these cases fit into his schema. There was no evidence of disorder in the adrenals, pituitary, thyroid or ovaries. The pancreas as the primary factor must be considered. In the first 2 cases exploration did not necessarily rule out the pancreatic origin of the low blood sugar. Such factors as extrapancreatic islet cell tumors and diffuse hyperplasia of the pancreas [3] should be mentioned. However, with the sudden onset and the previously negative history their existence seems improbable. Harris [4] has shown that a subacute pancreatitis can produce symptoms of hypoglycemia. With the persistent elevation of the sedimentation rate in the third case plus the history of abdominal pain with no surgical pathologic change to account for it, the possibility of such a lesion must be admitted. The atypical history, normal amylase, severity of the hypoglycemia and again the fact that it came on suddenly following a surgical procedure provide evidence to the contrary.

2. Conn, J. W.: The Spontaneous Hypoglycemias: Importance of Etiology in Determining Treatment, J. A. M. A. **115**: 1669-1675 (Nov. 16) 1940.

3. Valk, A. deT., and MacMillan, E. A.: True Hyperinsulinism Due to Diffuse Hyperplasia of Islet Tissue, North Carolina M. J. **2**: 648-652 (Dec.) 1941.

4. Harris, S.: Hyperinsulinism: Definite Disease Entity; Etiology, Pathology, Symptoms, Diagnosis, Prognosis and Treatment of Spontaneous Insulogenic Hypoglycemia (Hyperinsulinism), J. A. M. A. **101**: 1958-1965 (Dec. 16) 1933.

Serious liver damage is a recognized source of hypoglycemia. In case 1 there was evidence of fairly definite cirrhosis, but the liver was not involved in the other 2 cases. However, it is unusual [5] to find clinical or laboratory evidence of hypoglycemia in any but the most pronounced involvement of the liver parenchyma, and such was not the case in the patients in this series.

Patient 3 was known to have cholelithiasis. Coller and Jackson [6] believe that gallbladder disease and involvement of the biliary tract may cause changes in liver function of sufficient intensity to produce hypoglycemia. Conn [2] reported the occurrence of hypoglycemia in a patient with cholecystitis relieved by cholecystectomy. Although a similar situation cannot be definitely ruled out in our case, it again seems improbable in view of the sudden onset and the absence of evidence of acute gallbladder disease.

The possibility of a primary disturbance in the central nervous system must be mentioned. It is known experimentally [7] that stimulation of the right vagus will produce hypoglycemia, but only of a minor degree. Furthermore, Keller [8] found it necessary to sever free the ventral one third to one half of the thalamus in order to produce a hypoglycemic crisis in the dog. With this information in mind and considering the intensity of the hypoglycemia in these cases, it seems unjustified to assume that such a nervous system lesion is the cause of the hypoglycemic state in our patients.

Quirno and Linzoain [9] in 1943 reported a case of hypoglycemia in a woman following a cesarean section. The authors were of the opinion that possible causes were the known diminution in liver glycogen in pregnant women, plus the increased utilization during labor, and the added factor of an absolute lack of carbohydrate intake for forty-eight hours from the time of the operation to the onset of symptoms. The patient subsequently recovered.

Holman, Wood and Stockton [10] in 1943 reported a case of hypoglycemia of severe degree in which recovery occurred spontaneously following pancreatic exploration with negative findings. No explanation was offered for the phenomenon.

Failing to demonstrate in our patients any of the well recognized mechanisms productive of hypoglycemia, the next step is a search for some common denominator. The surgical procedures were in no way similar nor was the anesthesia; local anesthesia was used in only 1 case. The known common factors were morphine, scopolamine and the general shock of an operation. It is difficult to accept these routine therapies as a significant contribution to the production of hypoglycemia, although it is perhaps more than a coincidence that all three followed immediately on a surgical operation.

While in the present state of our knowledge it is idle to speculate as to the cause of the reactions, it is nevertheless worth while to point out that hypoglycemia should be considered when there are unusual responses during or following an operation. Differentiation from surgical shock might at times be a problem. According to Papper and his associates [11] the characteristic differentiating points are those of severe diaphoresis, an increased pulse pressure and a forceful pulse in hypoglycemic shock as opposed to a decreased pulse pressure and thready pulse in surgical shock. Hypoglycemic shock postoperatively is not a common occurrence, and its consequences if untreated are serious. Since it is easily diagnosed and amenable to therapy in its early stages, its recognition is of prime importance.

SUMMARY

1. Of 3 unusual cases of severe postoperative hypoglycemia 2 ended fatally. The third patient recovered and has remained normal to date.

2. In spite of a consideration of the possible etiologic mechanisms, no explanation of the phenomena seems apparent.

3. Although rare, the hypoglycemic state must be considered and a blood sugar level determined in any abnormal central nervous system response following a surgical procedure, even though it is a minor one.

5. March, H. E.: Hyperinsulinism: Report of Cases, Wisconsin M. J. **30:** 340-343 (May) 1931.

6. Coller, F. A., and Jackson, H. C.: Surgical Aspects of Hypoglycemia Associated with Damage to the Liver, J. A. M. A. **112:** 128-134 (Jan. 14) 1939.

7. Clark, G. A.: Influence of Vagus on Islets of Langerhans: Vagus Hypoglycemia, J. Physiol. **59:** 466-471 (March) 1925. Britton, S. W.: Studies on the Conditions of Activity in the Endocrine Gland: The Nervous Control of Insulin Secretion, Am. J. Physiol. **74:** 291-308 (Oct.) 1925.

8. Keller, A. D.: Hypoglycemia and Increased Insulin Sensitivity Following Hypothalamic Lesions, Proc. Soc. Exper. Biol. & Med. **42:** 837-838 (Dec.) 1939.

9. Quirno, N., and Linzoain, E. A.: Como hipoglucémico espontáneo; complicación post-operatoria de una cesárea, Rev. Asoc. méd. argent. **57:** 1127-1128 (Dec. 30) 1943.

10. Holman, E.; Wood, D. A., and Stockton, A. B.: Unusual Cases of Hyperinsulinism and Hypoglycemia, Arch. Surg. **47:** 165-177 (Aug.) 1943.

UNCOMMON CLINICAL MANIFESTATIONS OF VIVAX MALARIA

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The clinical diagnosis of vivax malaria in this country is often not difficult. The patient, in many instances, can suggest the correct diagnosis at the onset of an attack, and this can easily be confirmed by the demonstration of malarial parasites in one or more examinations of blood smears. There is a history of residence in an endemic area and, except for the first attack, there have been previous similar attacks. The symptoms of a "paroxysm" (acute attack) as a rule are quite characteristic, consisting of chilliness followed by a chill of varying severity and high fever of short duration followed by sweating, headache, backache, generalized aching and malaise, weakness, abdominal pain and tenderness and frequently nausea and vomiting. Vague muscular and joint pains, malaise, headache, backache and slight fever may precede the acute attack by several days.

Without treatment, paroxysms recur daily or every other day for a varying period. In a small number of patients spontaneous recovery takes place after one or more days, while in the majority of untreated patients the disease continues its activity for an extended period. With proper treatment there is prompt control of fever and other symptoms, and usually recovery from the acute attack is complete within a week. Complications or sequelae are rare, but one or more relapses follow in a majority of cases.

In studies comprising large numbers of patients with infections due to Plasmodium vivax several distinctly uncommon clinical manifestations have been encountered. Unless one is familiar with such modes of onset

11. Papper, E. M.; Stern, M.; Baeding, E., and Rovenstine, E. A.: Insulin Shock During Sodium Pentothal and Cyclopropane Anesthesia, Anesthesiology **3:** 660-662 (Nov.) 1942.

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the diagnosis of vivax malaria may not be suspected, correct treatment will be delayed, and in some instances other treatment potentially dangerous to the patient may be instituted. Our purpose in this paper is to present briefly a few of the less common clinical manifestations of malaria due to P. vivax.

A. "DELAYED PRIMARY" ATTACKS SIMULATING FEVERS OF UNKNOWN ORIGIN

Military or civilian personnel who have been on duty in endemic areas and have taken quinacrine regularly and in sufficient amounts for effective suppression will give no history of malaria while overseas. Sooner or later after they have returned to the United States they will discontinue taking suppressive medication. Those who have been infected with P. vivax will exhibit clinical signs and symptoms of active malaria within several weeks or months after stopping quinacrine. The onset of the disease in this group as well as in primary attacks when no antimalarial had been taken frequently does not conform to that usually associated with malaria by the general practitioner. The disease may begin insidiously with malaise and headache. The temperature, which is elevated slightly at the onset, rises gradually or abruptly within a few days to 103 or 104 F. and the pattern of the temperature may be completely irregular or of a septic remittent type. Severe shaking chills, which are so characteristic of relapses, may be absent during the first few days of the delayed primary attack despite high fever. Further, and often confusing to the physician, is the fact that one or two routine smears made early may be negative for malaria parasites. We have seen patients with delayed primary vivax malaria who had negative thick smears (less than 1 parasite in 72 squares, 0.1 cubic millimeter) when examined twice daily for two to five consecutive days despite high fever and daily chills before parasites could be demonstrated. When parasites do appear they may be present in relatively small numbers, in contrast to a relapse, in which the smears are usually positive on the first examination and the parasite count is relatively much higher.

We appreciate the quandary of the physician faced with a patient who has been sick for several days with rising fever, vague complaints and little in the way of physical findings. The white blood cell count is usually low, and if the spleen is palpable one may think of typhoid or some other bacterial blood stream infection. The temptation to prescribe sulfonamides or penicillin is great, especially if the first few blood smears are negative for parasites, and we have seen patients with this type of onset who received large amounts of penicillin without benefit.

We suggest that unexplained fever in the returned serviceman should not be treated until a definite diagnosis has been established unless laboratory facilities are not available. Thick smears should be examined twice daily by a trained technician and continued for at least a week. In the meantime, other diagnostic studies can be carried out without compromising the patient's chances of recovery by waiting or withholding therapy. If malaria parasites are demonstrated, the disease has been correctly documented and this is important as a baseline for future recurrences of a similar nature. It must also be remembered that in a few individuals the delayed primary attack may occur as long as a year after suppressive medication has been discontinued. Nevertheless it is helpful in the management of cases of fever of unknown origin as described to know whether the patient has been in endemic malaria areas, when he stopped suppressive medication and whether he has had similar episodes previously controlled with antimalarial medication.

B. SIMULATED PRIMARY ABDOMINAL CONDITIONS

1. *Acute Episodes.*—Attacks of vivax malaria are frequently accompanied by gastrointestinal symptoms and signs of varying severity. Nausea, vomiting and abdominal pain and tenderness are common, usually follow the paroxysm and are rarely of such intensity as to confuse the diagnosis of malaria.

In a small number of patients, however, the abdominal symptoms and signs may precede the paroxysm by a day or two and be of such severity as to suggest a primary acute abdominal condition, particularly acute appendicitis, intestinal obstruction or acute cholecystitis. Unless one is aware of this possibility, needless surgery may be performed.

At this hospital alone we have seen 3 patients who could easily have undergone laparotomy because of severe abdominal signs and symptoms which preceded an attack of malaria by one or two days. Two of these patients were referred to the hospital for surgery from nearby military establishments with the diagnosis of acute appendicitis. The history was identical in the 2 and consisted of abdominal pain followed by nausea and vomiting and localization of the pain in the lower abdomen. There was diffuse tenderness but no rigidity. In 1 the white blood cell count was normal and in the other it was low. Both patients had a slightly elevated temperature. Malaria parasites (P. vivax) were discovered in the thin smear in 1 case while the differential count was being done, and in the other they were found in the thick drop. One patient had a typical chill and other characteristic symptoms of vivax malaria on the same day of admission and the other had his attack the day after he was admitted. Signs and symptoms related to the abdomen disappeared with specific antimalarial treatment. In contrast to the usual findings in acute appendicitis the abdominal pain in malaria is more diffuse, tenderness is present in both lower quadrants, muscular rigidity is absent and rectal examination is not localizing.

A third patient was under observation for two days because of intractable nausea, vomiting, abdominal pain and suspected intestinal obstruction. There was slight fever, the abdomen was diffusely tender and the white blood cell count was 23,000 per cubic millimeter. On the second day the patient volunteered the fact that he had had two previous episodes of severe abdominal pain and vomiting which were followed in from one to three days by an attack of malaria. Thick smears were examined and found to contain a moderate number of parasites (P. vivax). Treatment with parenteral quinacrine was begun. Fluids were given intravenously and nothing by mouth. Later in the day the patient had a typical paroxysm with a rise in temperature to 104.2 F. Quinacrine therapy was continued by the intramuscular route for the remainder of the day. On the following day vomiting had ceased, the temperature and white blood cell counts were normal and specific medication was continued orally. This patient, who was a member of our detachment, had a similar attack of severe abdominal pain, vomiting, leukocytosis and slight fever approximately four months later. At this time the first observed episode was recalled, smears were examined and found positive, and specific treatment was begun with quinacrine intramuscularly. Recovery was prompt and complete.

Gallbladder disease is most apt to be confusing in those cases in which there is slight enlargement and tenderness of the liver with minimal icterus from previous paroxysms. On the other hand, we have seen a patient whose gallbladder perforated while his right upper quadrant pain, nausea and vomiting were attributed to his malaria.

Apropos of simulated acute abdominal conditions due to malaria, it should be remembered that they occur more frequently and with greater severity in acute falciparum infections. We have seen laparotomy performed for suspected intestinal obstruction, cholecystitis and extrahepatic biliary obstruction in 3 cases. At autopsy in each case the primary cause of death was acute falciparum malaria! In these cases the acute abdominal findings overshadowed the possibility of malaria, but careful histories and repeated careful blood examinations could in all probability have established the correct diagnosis.

In a small number of patients an attack of malaria may be preceded by several days or ushered in with a period of brisk watery diarrhea. If fever and vomiting occur before the chill, one may suspect acute gastroenteritis. The smears are almost always positive and within a short time the typical chill, high fever and other symptoms will suggest the correct diagnosis. In many of these cases the symptoms accompany each relapse and a good history is extremely helpful.

2. *Signs and Symptoms of a Chronic Nature.*—Occasionally protracted low grade malarial activity in some individuals with good immunity may be manifested by slight to moderate anemia, slight icterus and enlargement of the liver and/or spleen. Inadequate treatment of frequently occurring mild attacks may also produce the same findings. Either there is no fever or, if present, it is low grade. Parasites are almost always present in the circulating blood, but their density may be very low. In such a combination of findings one may suspect some intrinsic disease of the liver, gallbladder or biliary system or some hematologic disorder rather than malaria. We have seen several such cases with a red blood count as low as 2.2 million per cubic millimeter and in each instance careful study of blood smears proved the underlying condition to be vivax infection. Specific therapy with antimalarial drugs produces a reticulocyte response, recession of the liver, disappearance of signs and symptoms and recovery from the anemia without iron or other drugs.

One of us (H. M.) has seen a Chinese patient with enlargement of the liver and spleen and reduction in all the formed elements of the blood in whom the diagnosis of Banti's syndrome led to splenectomy. Several weeks after recovery from the operation the patient complained of chills and fever. Examination of blood smears disclosed numerous quartan parasites (Plasmodium malariae) and review of preoperative filed blood smears likewise disclosed very rare parasites. While this condition may not occur often if at all in vivax malaria it is worth noting what the effect of protracted low grade malaria infection may be regardless of the species of parasite.

If the possibility is borne in mind that gastrointestinal symptoms and signs of varying intensity or chronicity may be related to underlying infection with P. vivax in some cases the correct diagnosis may be established and needless surgery avoided. It is not suggested that all acute or chronic gastrointestinal conditions occurring in patients who have had malaria are related to that disease. In fact, we have seen a moderate number of patients with a history of prior malaria suffering currently from chills, fever, abdominal or other signs and symptoms who were treated without benefit with antimalarial drugs on the assumption that the findings were due to malaria. Smears were negative and the white blood cell count elevated, which is exceptional in malaria. The conditions subsequently shown to be incorrectly diagnosed as malaria were, in their order of frequency, acute follicular tonsillitis, cellulitis, thrombophlebitis, pyelitis, pneumonia and cholecystitis.

A careful history particularly of previous similar episodes related to proved attacks of malaria, physical and laboratory examinations including careful search for malaria parasites and evaluation of all the findings possibly in conjunction with a surgeon when indicated should lead to a rational plan of management of the individual case.

C. CENTRAL NERVOUS SYSTEM MANIFESTATIONS

Signs or symptoms referable to the central nervous system in malaria occur most frequently in severe infections with Plasmodium falciparum. It is for this reason that there is a tendency to label all central nervous system manifestations occurring in malaria as "cerebral malaria," with the alarming implications and necessity for vigorous treatment which severe falciparum infections carry. The changes in the brain in falciparum infections consist of occlusion of small vessels with parasitized red cells, parasites, pigment and débris, multiple small discrete or ring shaped hemorrhages and other pathologic alterations. No such changes in the brain in vivax infections have ever been described to our knowledge. Furthermore, falciparum infections, if adequately treated or suppressed with quinacrine, rarely relapse. However, if central nervous system systems and signs occur at the onset of an attack of malaria and there is any question about the history or species of parasite observed or if no history can be obtained, the safest procedure to follow is the institution of vigorous parenteral antimalarial therapy until it can be decided whether or not the infection is due to P. falciparum.

We have seen definite and severe symptoms and signs referable to the central nervous system at the onset of attacks of vivax malaria which are worthy of note. Severe headache is common but is not alarming, and symptomatic treatment suffices. Delirium is seen in some patients and is probably an expression of hyperpyrexia in individuals sensitive to high fever. Antipyretics, sponging, parenteral fluids and ice caps to the head usually are effective in controlling this symptom. Acute psychoses may occur during treatment and represent a rare manifestation of quinacrine toxicity unrelated to malaria itself. Severe stiffness of the neck preceding or accompanied by fever and a chill at the onset of an acute attack of vivax malaria may be suggestive of meningitis which must be excluded. The spinal fluid is normal, the white blood cell count tends to be low and the blood smears contain parasites (P. vivax).

Convulsions at the onset of an attack of vivax malaria may be alarming but fortunately occur rarely. We have seen only 3 examples of convulsions in proved cases of vivax malaria in the course of treating several thousand attacks. Brief reference will be made to these cases:

Case 1.—A man seen shortly after a generalized convulsion was perfectly oriented and stated that he had had convulsions during several previous severe attacks of malaria. These were

documented in his medical record, and his transfer diagnosis was "recurrent cerebral malaria." No record of the species of parasite for these previous attacks was available. On the day of the current convulsion the patient had a severe paroxysm. Numerous asexual forms of P. vivax were present in the blood smears. The temperature rose quickly to 104 F., but the patient was fairly comfortable. However, within another half hour the temperature had risen to 105.8 F., shortly after which he had the convulsion. Salt and glucose were administered intravenously immediately afterward as well as 1 Gm. of acetylsalicylic acid by mouth. The patient was sponged with cold water and the naked body cooled with two electric fans. The temperature fell quickly and no further difficulty was experienced. In an attempt to prevent a paroxysm the following day, 1 Gm. of quinacrine was given intramuscularly in divided doses on the first day. There was no subsequent fever and the patient received 1.8 Gm. of quinacrine by mouth during the next six days, after which he continued to receive 0.1 Gm. daily for five months. The spinal fluid, neurologic examination, x-rays of the skull and electroencephalogram were normal. On questioning the patient we learned that he had had convulsions during childhood with measles and during early boyhood with scarlet fever and not again until he had his first attack of malaria many years later. In our opinion, convulsions during an attack of vivax malaria in this patient represent a central nervous system reaction to hyperpyrexia.

CASE 2.—This man likewise was returned from overseas with a diagnosis of "cerebral malaria" because of a severe convulsion during an attack of malaria. The species of parasite had not been identified. While under observation in a malaria study group he complained of severe headache and "spasm" of the right hand. X-rays of the skull, neurologic examination and the spinal fluid at an overseas hospital were normal. The patient stated that he had sustained a severe head injury followed by a short period of unconsciousness and subsequently developed constant headache, which he attributed to the head injury. Shortly after arrival in this country and while in the hospital for study he had a severe epileptiform convulsion starting on the right side and quickly becoming generalized. The patient shrieked at the onset, bit his tongue and was incontinent of urine. The convulsion subsided and the patient remained drowsy for about ten minutes, after which he was confused for another twenty minutes. In the meantime, blood smears were examined and reported as containing numerous malaria parasites (P. vivax). The rectal temperature was 102.8 F. Antimalarial and anticonvulsant drugs (diphenylhydantoin [dilantin] sodium and phenobarbital) were administered simultaneously by mouth. On the second day the patient was afebrile and complained only of a severe headache. There was amnesia for the details of the recent convulsion and slight weakness of the right hand; otherwise complete neurologic examination was negative. The spinal fluid was normal in all respects. At the end of a week antimalarial drugs were discontinued. In the meantime it was learned from another patient that the boy who had the convulsion had been observed in the midst of several convulsions outside the hospital. When we confronted our patient with this information he admitted having had convulsions but said that he was reluctant to report them for fear of being branded epileptic or submitted to cranial surgery. Electroencephalograms showed a localized area of abnormal excitability, but air visualization of the ventricular system was normal. The neurologist and neurosurgeon did not believe that surgery was indicated and classified the disease as a post-traumatic convulsive disorder ("postconcussive encephalopathy with focal area of degeneration, left cerebrum, central area"), recommending that anticonvulsant drugs be continued indefinitely. Two months later the patient, while still on anticonvulsant drugs, experienced a severe attack of malaria with a hard chill and high fever without developing any signs or symptoms related to the brain other than severe headache. We believe there is good evidence in this case that the convulsions which occurred during acute attacks of vivax malaria were due to underlying disease of the brain and that the fever or some other factor in the malaria attack acted as a trigger to set off the seizure. The patient was then kept on quinacrine suppression and anticonvulsant drugs without subsequent malaria or convulsive seizures.

CASE 3.—A white man aged 24 was returned from the Southwest Pacific area with a transfer diagnosis of "psychosis, unclassified, severe, manifested by agitation, blocking of thought and auditory hallucinations." His malaria history overseas disclosed that he had four attacks of malaria while in New Guinea and that during the last two he had convulsions and subsequently developed behavior changes for which he was returned to the United States. The only features in the past history which are relevant are the facts that he had criminal tendencies, spending short periods of time in a state reformatory or under parole, that he was poorly adjusted socially and that infrequently he had vague "spells" which could possibly have been "petit mal." It also seems probable from a review of his overseas record that his first serious attack of malaria during which he was in coma and had convulsions was due to infection with P. falciparum. Examination in this country failed to show evidence of any psychosis. Neurologic examination was negative. The spinal fluid on several occasions showed slight elevation in protein. Two electroencephalograms were considered abnormal and were "suggestive of epilepsy or some related disorder." While under observation at another hospital in this country he had one episode related to a vivax relapse during which there were symptoms and signs referable to the nervous system. These consisted of sudden onset of stuporousness and signs of minimal bulbar palsy characterized by nasal regurgitation, drooling and continual clearing of the throat because of impaired pharyngeal reflex. A prior attack of supposed falciparum malaria treated early at the same hospital was not accompanied by signs or symptoms related to the nervous system.

While the patient was under observation at this hospital smears were examined repeatedly and no suppressive medication was given. On Aug. 27, 1945 the patient had a positive smear for P. vivax but had no fever or symptoms. The following day, while lying on his bed trying to have a nap, he had a generalized convulsion. He was seen at once and found unconscious, frothing at the mouth and breathing rapidly for a short time followed by a longer period of apnea. The head was retracted to the left; otherwise the neurologic examination was negative. The rectal temperature was 102.2 F. Following recovery from the convulsion, 0.8 Gm. of quinacrine was given intramuscularly in divided doses and glucose in saline solution by vein. The patient remained confused the greater part of the day, but on the following day he had completely recovered except for not remembering the details of the previous day's attack. A total of 2.8 Gm. of quinacrine was given to terminate the recent vivax relapse.

It is difficult to correlate the patient's central nervous system symptoms solely on the basis of vivax malaria. It seems to us that he may well have had changes in the brain in a general way related to convulsive disorders (epilepsy) prior to his first attack of malaria. Secondly, that the initial attack of severe falciparum malaria overseas either aggravated the underlying condition or in itself induced some permanent changes in the brain. Subsequently vivax relapses resulted in the central nervous system signs and symptoms described, which were due to underlying disease of the brain caused or aggravated by prior falciparum malaria with cerebral localization.

The immediate diagnosis in patients with central nervous system signs and symptoms related to an attack of malaria may be difficult. We believe that central nervous system findings in the presence of a late relapse of malaria are probably associated with vivax infection but that the nervous system manifestations are due to underlying disease of the brain such as may be found in epilepsy, following head injury or in rare cases following prior severe falciparum infections with cerebral localization. Regardless of the species of parasite