YELLOW FEVER

ETIOLOGY, SYMPTOMS AND DIAGNOSIS

BY

JOSEPH GOLDBERGER

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ETIOLOGY.

The claims, by various authors up to 1890, of having discovered the specific cause of yellow fever, were all effectually disposed of by the investigations of Sternberg. Since that time several investigators have reported finding the specific causative agent; but it is notable that no two of the micro-organisms for which this claim was made were identical, and since only one could be the specific organism, it is evident that the others could have no real claim to specificity.

Of the organisms referred to, that described by Sanarelli (1897) as the *Bacillus icteroides* attracted most attention and, indeed, was at first hailed as the long-looked-for germ.

A series [a] of epoch-making investigations and discoveries by a commission composed of Walter Reed, James Carroll, Aristides Agramonte, and Jesse W. Lazear, medical officers of the United States Army, which have been fully confirmed and in some respects amplified by independent workers—Cuban [b], Brazilian [c], American [d], French [e], German [f]—have resulted in establishing:

1. That yellow fever is transmitted, under natural conditions, only by the bite of a mosquito (*Stegomyia calopus*) that at least 12 days

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[a] Reed, Carroll, Agramonte, and Lazear, 1900; Reed, Carroll, and Agramonte, 1901a, and 1901b; Reed and Carroll, 1902.

[b] Guiteras, 1901.　[c] Barreto, de Barros, and Rodrigues, 1903.　[d] Ross, 1902; Parker, Beyer, and Pothier, 1903; Rosenau, Parker, Francis, and Beyer, 1904; Rosenau and Goldberger, 1906.　[e] Marchoux, Salimbeni, and Simond, 1903; Marchoux and Simond, 1906a, 1906b, 1906c.　[f] Otto and Neumann, 1905.

before has fed on the blood of a person sick with this disease during the first 3 days of his illness.

2. That yellow fever can be produced under artificial conditions by the subcutaneous injection of blood taken from the general circulation of a person sick with this disease during the first 3 days of his illness.

3. That yellow fever is not conveyed by fomites.

4. That the *Bacillus icteroides* Sanarelli stands in no causative relation to yellow fever.

As all preventive measures are based on the foregoing fundamental propositions, a somewhat more detailed consideration of each is desirable.

A.— *Yellow fever is transmitted, under natural conditions, only by the bite of a mosquito* (Stegomyia calopus) *that at least 12 days before has fed on the blood of a person sick with this disease during the first three days of his illness.*

The unusual prevalence of insects during some epidemics of yellow fever was noted more than a century ago. It was not until 1848, however, that any suggestion was made as to their etiological connection. In that year Josiah C. Nott of Mobile, Ala., reasoning from certain epidemic peculiarities of the disease, expressed it as " probable that yellow fever is caused by an insect or animalcule bred on the ground," and mentioned "mosquitoes, flying ants, many of the aphides" as illustrations of insects whose general habits were such as to fulfill the requirements as transmitters of the disease. At about this time there appears to have prevailed a fairly widespread belief in the existence of some relation between mosquitoes and yellow fever, for Dowler, writing in 1855, states that many persons regarded "any increase in the number of mosquitoes as a certain prelude or precursor to a yellow-fever epidemic."

The first to definitely assert that the mosquito is the medium of transmission and to specifically indicate the mosquito concerned was Carlos J. Finlay. In 1881, at a meeting of the Royal Academy of Medical and Physical Sciences of Habana, he stated that three conditions were necessary for the propagation of yellow fever, namely: "(1) The existence of a yellow fever patient into whose capillaries the mosquito is able to drive its sting and to impregnate it with the virulent particles, at an appropriate stage of the disease. (2) That the life of the mosquito be spared after its bite upon the patient until it has a chance of biting the person in whom the disease is to be reproduced. (3) The coincidence that some of the persons whom the same mosquito happens to bite thereafter shall be susceptible of contracting the disease." During the succeeding twenty years Finlay continued, tenaciously, to

maintain his theory which, in collaboration with Delgado, he attempted, though unsuccessfully, to prove.

To Reed, Carroll, Agramonte, and Lazear is due the credit for the masterly experiments which converted a discredited hypothesis into an established doctrine.

The transmission of the disease by the mosquito is not, as Finlay thought, a simple mechanical transfer from one individual to another, such as occurs at times in plague through the instrumentality of fleas or in surra through biting flies. In these diseases neither the flea nor the fly is necessary, but in yellow fever not only is the mosquito necessary, but it is essential that the mosquito be of a particular species or at least of a particular genus. Thus, attempts to transmit the disease by means of mosquitoes of other than the genus *Stegomyia*[a] have not been successful.

It has been found, furthermore, that in yellow fever, unlike either surra or sleeping sickness, a certain period must elapse after the infecting feed before the mosquito is capable of communicating the disease.[b] Experimentally this interval appears to be not less than 12[c] days, so that a susceptible individual may expose himself with impunity to repeated stings within the first 10 or (?) 11 days[d] after the mosquito has fed on a person sick with the disease. This is the period of "extrinsic incubation" of Carter, whose painstaking observations at Orwood and Taylor, Miss., in 1898, resulted in his tentatively fixing this interval as "usually in excess of 10 days" and served, in the light of the then recent discovery of the mosquito transmission of malaria, to direct the attention of the Army Commission to Finlay's mosquito as a possible "intermediary host" for this disease.

The duration of this period of "extrinsic incubation" is decidedly influenced by the temperature of the air. It is at its minimum at temperatures above 26° C (80° F), but becomes progressively longer as the temperature declines below this point.

The period of the disease at which the mosquito bites is another essential factor in the latter's power to transmit the disease. Thus all attempts to produce an attack by means of the bites of mosquitoes that had previously fed on cases after the third day of the

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[a] No experiments have as yet been recorded with any species of this genus other than *S. calopus.*

[b] In surra and sleeping sickness for example, no such interval exists. On the contrary, it is only during the two days immediately following the infecting feed that the tsetse flies concerned can transmit these diseases. After the third day their bite is perfectly harmless. In dengue this interval appears likewise to be absent.

[c] I say "appears to be," because the recorded experimental evidence is not sufficient to prove that it may not under favorable conditions be a (very) little shorter than 12 days.

[d] Nor do such bites during this period confer, as Finlay believed, an immunity from subsequent attack.

disease have failed,[a] whereas all successful attempts have been with such mosquitoes as had been allowed to feed on cases during the first three days.

There are some who, while granting that the mosquito is capable of transmitting the disease directly by biting, maintain that the disease may also be acquired by ingesting water in which the body of an infected mosquito has disintegrated. Again, there are others who, while admitting that the mosquito is the sole medium of transmission, hold, nevertheless, that there may be sources other than the one mentioned from which this insect may acquire its infection, and suggest black vomit or articles soiled by yellow-fever patients as pertinent illustrations. But neither the results of experiments especially designed to test these hypotheses nor the indirect evidence furnished by a large mass of observations give the slightest support to these assumptions. After the mosquito has become infective it probably remains so for life.

B.— *Yellow fever can be produced under artificial conditions by the subcutaneous injection of blood taken from the general circulation of a person sick with this disease during the first 3 days of his illness.*

The subcutaneous injection of a drop[b] (0.1 cc.) of yellow fever blood serum from a case in the first day of illness has produced an attack of yellow fever, whereas five times this amount from a case in the fourth day of the disease produced no symptoms.

C.— *Yellow fever is not conveyed by fomites.*

Before the demonstration by the Army Commission of the transmission of yellow fever through the mosquito it was very generally believed, notwithstanding a large mass of evidence to the contrary, that the disease was communicated by the exhalations of the sick, by contact with their excretions, or with articles that had been exposed to or been soiled by them.

In order to put this almost universal belief in fomites to a rigorous test, the Army Commission exposed each of a series of seven non-immunes to clothing and bedding which had been used by cases of yellow fever and which had become soiled with blood, urine, feces, and black vomit. The house in which the experiment was carried out was especially constructed for the purpose in an isolated place near Habana. In order to prevent access of mosquitos and to simu-

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[a] The recorded experimental evidence is not sufficient to show that this infective period may not at times extend into the fourth day. This is of considerable practical importance. A case of yellow fever should be protected from mosquitoes during four full days at least.

[b] Parker, Beyer, and Pothier (1903) induced an attack of yellow fever by the subcutaneous injection of 0.033 cc. of filtered serum from a case in the third day.

late the conditions thought most favorable to infection by fomites, the windows and doors were screened and so placed as to prevent free ventilation, special pains were taken to exclude sunlight, and provision was made for heating during the day so that an average temperature of 72.6° F. was maintained throughout the entire period. The men were exposed in squads for periods averaging 21 nights each. Each squad entered the house at night, removed the soiled articles from the boxes in which they were packed, shook them out, hung some about the room, and used some for making up the beds in which they slept. In the morning the various garments and articles of bedding were repacked and the men left the room to occupy a near-by tent during the day. The result of this experiment was entirely negative: the men remained in perfect health. Subsequently some of them submitted to mosquito inoculation and promptly sickened with the disease, showing conclusively that they were not immune.

It may be of interest to observe that the first experiments to determine the infective power of fomites were made over a century ago. In 1800 Cathrall reported having repeatedly applied black vomit to his tongue and lips and to the skin of various parts of the body without experiencing any ill effects. In company with a friend he had, besides, exposed himself to the fumes of heated black vomit, both in the open air and in a confined space, likewise without harm. In 1804 Ffirth, imitating Cathrall's example, went so far as to repeatedly swallow several ounces of fresh black vomit; he rubbed some into incisions in his arms and dropped some into his eye without experiencing any but momentary disagreeable effects.

In view of the foregoing, one can not but admire the acute reasoning of La Roche,[a] who, half a century ago, in discussing the evidence in support of transmission through the agency of clothes, bedding, merchandise, etc., concluded that "we may well infer" that in the record of such instances "some error has crept in—something has been omitted or overlooked—and that the production of the disease was really due to some other agency than the one contended for," a conclusion which will be concurred in by anyone who will take the pains to critically examine the recorded instances of alleged transmission by such means.

D.—*Experiments to show that the* Bacillus icteroides *Sanarelli stands in no causative relation to yellow fever.*
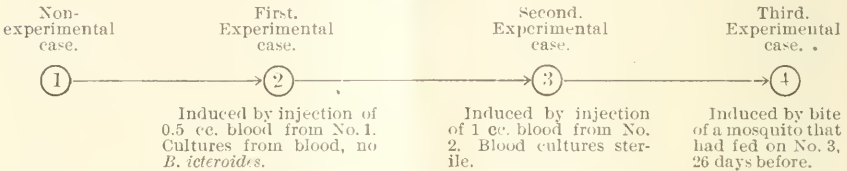
The fact that the Army Commission was able to produce three cases of yellow fever by the subcutaneous injection of blood which was shown to be sterile by the culture method is sufficient to eliminate

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[a] Vol. 2, p. 522.

B. icteroides from consideration. That the attacks of fever so produced were not simply such as might be caused by the injection of a soluble toxine circulating in the blood is shown by the following chain of experiments:

The first link in the chain was a fatal nonexperimental case of yellow fever which furnished the Army Commission[a] with blood that culturally showed the absence of *B. icteroides*, but 0.5 cc. of which injected subcutaneously into a nonimmune (W. F.)[a] induced an attack of fever having all the characters of yellow fever. From the latter case blood was drawn and 1 cc. injected into a second nonimmune (J. H. A.)[a]; culturally this blood was sterile, but nevertheless it caused an attack in all respects similar to yellow fever. Eight hours after the onset of this man's illness some mosquitoes were allowed to bite him, one of which, 26 days later, was applied to a nonimmune (Vergara)[b], who developed an attack of yellow fever 3 days, 10 hours later (see diagram).

Diagram.

Non-experimental case.	First. Experimental case.	Second. Experimental case.	Third. Experimental case. .
①	②	③	④
	Induced by injection of 0.5 cc. blood from No. 1. Cultures from blood, no *B. icteroides*.	Induced by injection of 1 cc. blood from No. 2. Blood cultures sterile.	Induced by bite of a mosquito that had fed on No. 3, 26 days before.

The only possible explanation of this chain of events is that there was present in the blood used for the subcutaneous injections an organism that can not be cultivated on ordinary media—*B. icteroides* grows readily on all ordinary media—and that the mosquito that bit the second of the experimental cases became infected with this organism and 26 days later transmitted this infection to a nonimmune. It is inconceivable that a toxine alone could infect a mosquito in such a way as to enable the latter, 26 days later, to reproduce the disease by biting a nonimmune. It may be observed in this connection that a person who has suffered from an attack of the disease, acquired naturally or experimentally through the bite of a mosquito, is immune to injections of virulent yellow fever blood serum and, vice versa, an attack of the disease induced by the injection of yellow fever blood protects against subsequent inoculation by means of infected mosquitoes.

The parasite.—While the organism of yellow fever has not yet been discovered, we are, nevertheless, in possession of some facts which enable us to form some idea of its character. The disease has been found to occur in nature only in man and the mosquito, so that it is

[a] Reed, Carroll, and Agramonte, 1901b, p. 16.

[b] Guiteras, 1901, p. 812.

inferred that the parasite is one of those that requires for the complete evolution of its life cycle a mammalian and an arthropod host. We have familiar analogies in *Piroplasma bigeminum* of Texas fever and the *Plasmodium* of malaria. Because of these analogies it is inferred that biologically it may be grouped with them as a protozoon. On the basis of these and other analogies, both Schaudinn (1904) and Novy & Knapp (1906) have suggested that it may be a *Spirochæta*. Stimson's recent discovery of a spirochæte-like organism in the tubules of a yellow fever kidney is, therefore, exceedingly interesting and suggestive.

The cycle in man is represented clinically by a stage of incubation and by a stage of fever. Some attempts to infect mosquitoes by allowing them to bite subjects during the stage of incubation, in one instance as late as 6 hours before the onset of the stage of fever, have been unsuccessful; whereas a mosquito that bit a case of the disease 8 hours after the onset became infected and conveyed the disease to a nonimmune 26 days later. This would indicate that the parasite does not appear in the circulating blood until the onset of the disease. We already know that it remains in the blood only during the first three days of the disease or, at least, it is only during those three days that it exists in a form capable of continuing its life cycle in the mosquito or in a fresh nonimmune.

In the circulation it exists in a form so minute as to be capable of passing through the finest grained porcelain filters, such as the Chamberland B and the Chamberland F.

Its resistance to deleterious influences is feeble when withdrawn from the circulation. When kept in a test tube exposed to the air in the dark, at a temperature of 24° C. (75° F.) to 30° C. (80° F.), it loses its virulence in 48 hours. Under the same conditions, but protected from the air by keeping under oil, it retains its vitality somewhat longer—up to between 5 and 8 days. Heating for 5 minutes at 55° C. (132° F.) apparently suffices to kill it. The effect of low temperatures has not been studied.

The cycle in the mosquito requires at least 12 (?) days[a] for its completion. As to the changes which it undergoes during this period we are in complete ignorance.

The French commission has recorded one experiment which would indicate that the parasite may, under certain circumstances, be transmitted to the progeny of an infected mosquito through the egg. An attempt by Rosenau and Goldberger to confirm this resulted negatively. The same commission attempted, but without success, to transmit the parasite from one mosquito to another by feeding larvæ with cadavers of infected adults; they appear, however, to have succeeded in trans-

[a] See page 5, footnote c.

mitting the parasite to a mosquito by feeding it with sirup in which the body of an infected insect had been crushed.

Judging from the variations in the virulence of different epidemics it is fair to infer that there is a corresponding variation in the virulence of the parasite. The variation in severity of individual cases appears, however, to be largely influenced by the susceptibility or resistance of the subject, for the bite of the same mosquito or mosquitoes will be followed in one instance by a severe and in another by a mild attack. Nor does there appear to be any appreciable difference in severity between attacks induced by the bite of a single as compared with those induced by the bites of several insects.

Susceptibility.—Attempts to induce the disease in the ordinary laboratory animals have been unsuccessful. Marchoux and Simond (1906a) caused a mild febrile attack in one orang-outang and in one chimpanzee by bites of infected mosquitoes. Thomas (1907) induced a mild febrile attack with albuminuria in a chimpanzee following an inoculation by infected mosquitoes.

All persons are naturally susceptible, but there is a difference in the degree of this susceptibility in different races. Thus the mortality in the negro is less than in the Caucasian. Age has a distinct influence on susceptibility, as is shown by the mildness of attack and relatively low mortality in children. Nativity and long-continued residence in an endemic focus were supposed at one time to "acclimatize" and thus protect against the disease, but it is now believed that this protection was obtained not by the occult influence of climate but by having had during childhood or at some other age a mild and unrecognized attack of the disease.

THE YELLOW FEVER MOSQUITO.

This insect has been known by a variety of names of which *Culex mosquito, Culex tæniatus,* and *Culex fasciatus* were in most common use up to 1901. In that year Theobald, having observed that some sixteen species of *Culex,* while agreeing amongst themselves, differed from the others of this genus in certain peculiarities of scale arrangement, separated these into a group to which he applied the name *Stegomyia.* In this group was included the yellow-fever mosquito whose name thereupon became *Stegomyia fasciata.* Blanchard (1905), however, has pointed out that the specific designation *fasciata* is not applicable to this insect, as it had first been applied to another, so that *calopus,* suggested by Meigen in 1818, has the right of priority. Therefore, under the rules of zoological nomenclature, the correct name is *Stegomyia calopus* (Meigen, 1818) Blanchard, 1905.

Adult.—The *Stegomyia calopus* (figs. 1 and 2) is readily recognized. It is a handsome insect—a study in black and white. The distinction
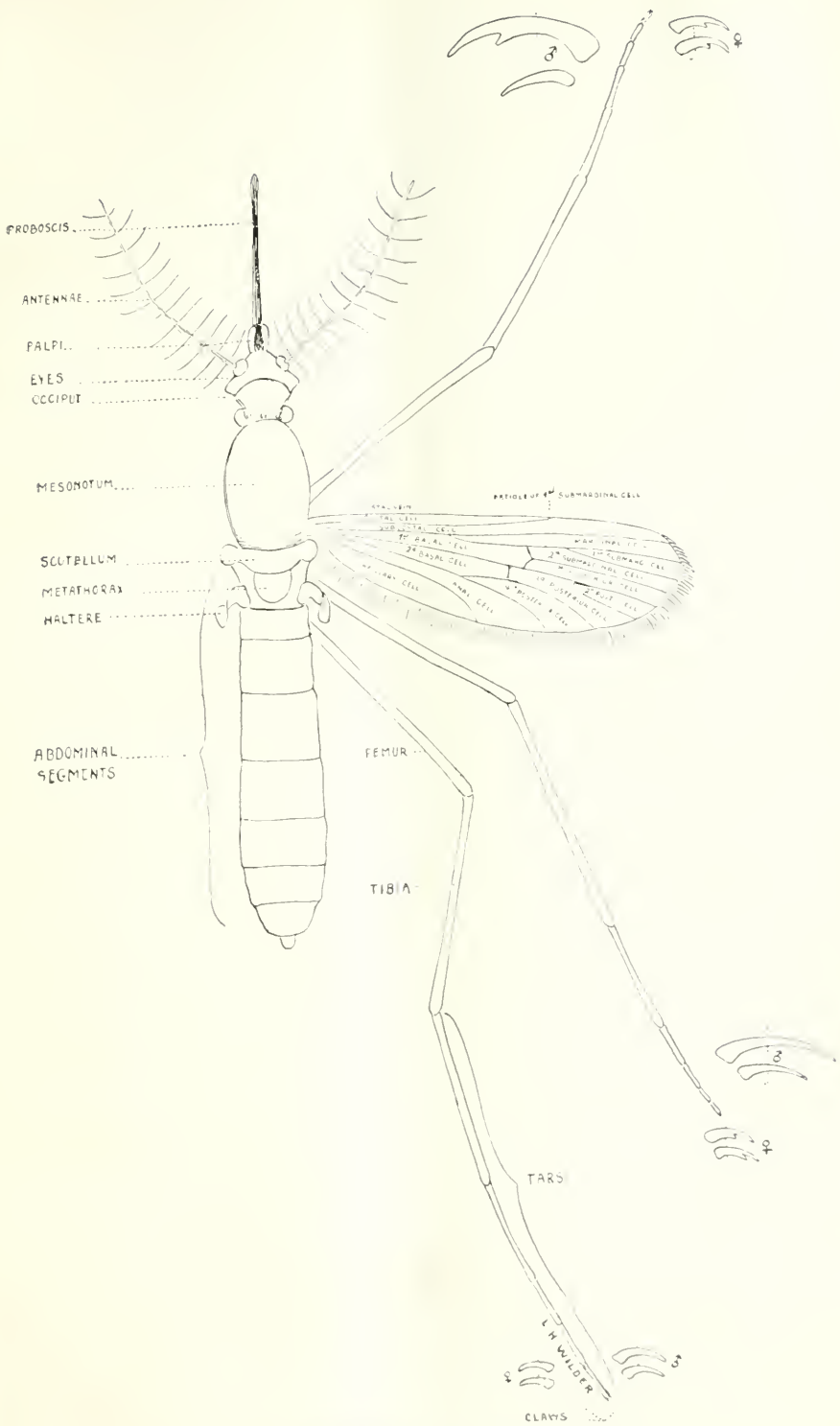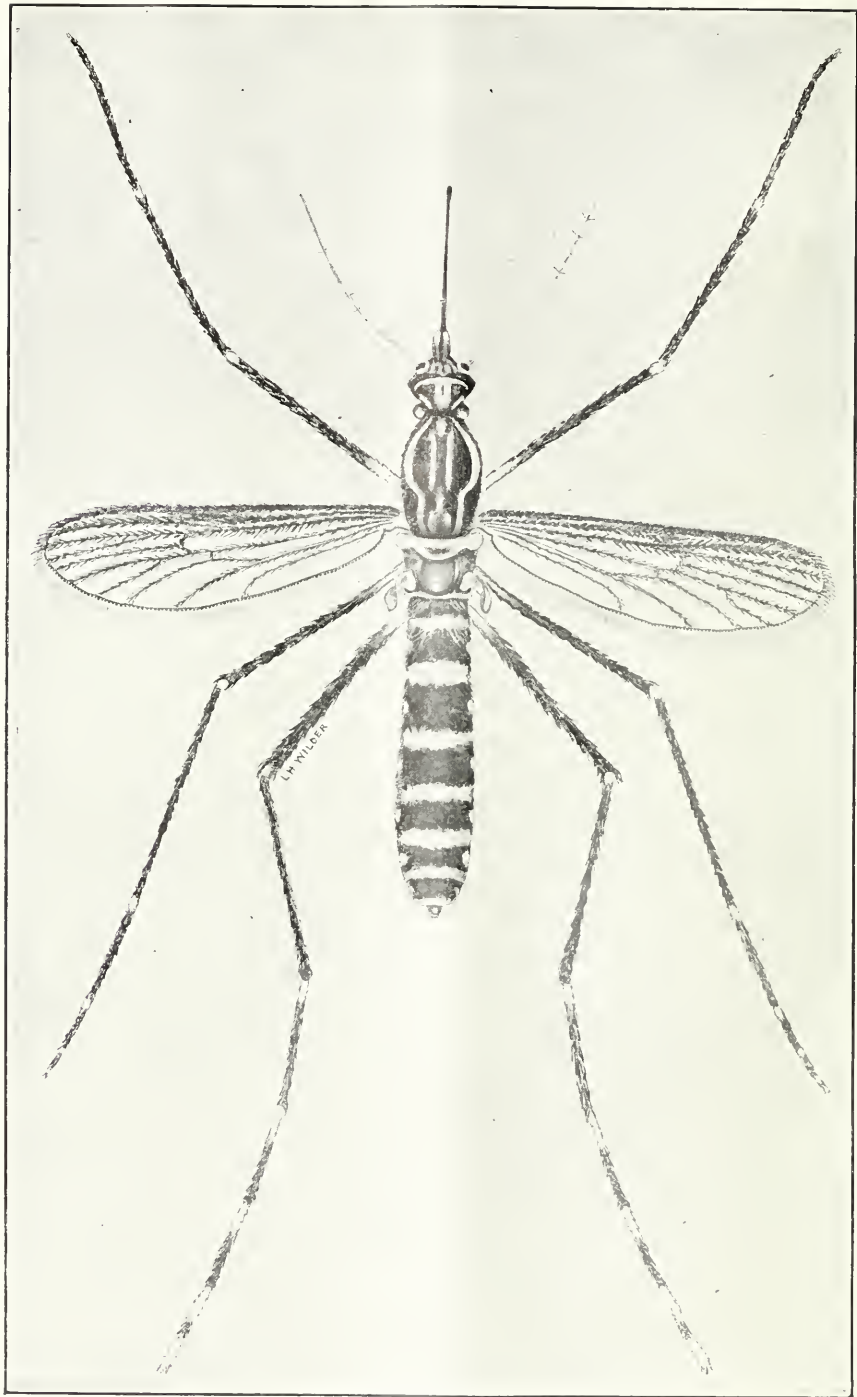
FIG. 1.—External anatomy of Stegomyia calopus.

Fig. 2.—Stegomyia calopus (female).

between the male and the female is readily discernible in the characters of the antennæ; in the former (fig. 3) these organs are prominent and feathery— decidedly hirsute. Another prominent point of difference exists in the length of the palpi: in the male they are long—almost as long as the proboscis, but in the female they are short—less than one-third the length of the proboscis.

The palpi in both sexes are black, but are ornamented with white scales which, in the male, are arranged as four narrow bands, while in the female they are collected into a white tuft at the tip.

The proboscis is black and is devoid of ornamentation, differing in this respect from both *Culex tæniorhynchus* and *Culex sollicitans*, each of which has the proboscis marked by a pale band in the middle. These two insects bear a superficial resemblance to *S. calopus*, for which they are not infrequently mistaken by the uninformed.

The head is clothed by the broad flat scales characteristic of the genus. These scales are black, except for a line of white down the middle extending to the neck and a narrow white border to the eyes.

The thorax is dark brown, almost black, ornamented with silvery white patches and lines of which the following are peculiar to and distinctive of this species, and enable one to recognize it at a glance: A well marked, easily recognizable, pure white curved line on either side of the back (mesonotum) be-

Fig. 3.—Appendages of head of Stegomyia calopus (male).

tween which, but less obvious to the naked eye, are two delicate median parallel lines; a prominent transverse white line of scales on the scutellum.

The abdomen is clothed with black and white scales, the latter collected in bands at the bases of the abdominal segments, and in distinct patches at the sides.

The legs are black scaled, except for white bands which are arranged as follows: A basal band on the first joint of the fore, on the first and second of the mid, and on all of the hind tarsi except the last, which is, as a rule, all white. Each leg is provided with a pair of claws which are equal in size in the female-but unequal in the male. They differ in other respects in the two sexes; in the female those of the fore and of the mid legs are provided with one tooth, those of the hind legs are simple; in the male all the claws are simple except the larger one of the forefoot.
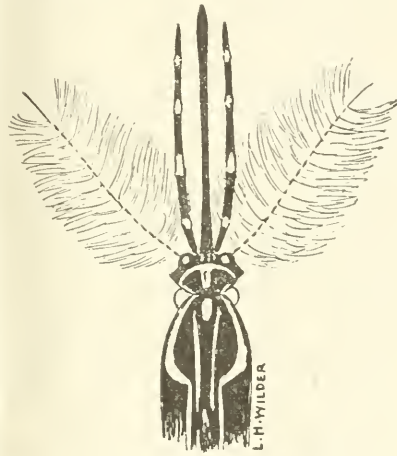
The veins of the wings are clothed with dark brown scales. The first submarginal cell is longer than the second posterior cell and the base of the former is nearer the root of the wing.

Biting.—The male insect does not bite; it lives almost exclusively on vegetable and fruit juices. In the females, however, a feed of blood is a necessary condition precedent to egg laying. At summer temperatures this insect will digest a full meal of blood in about 48 hours. If disturbed in the act of feeding it will fly away, but will return and attempt to finish its interrupted meal. In this way one infected mosquito in its efforts to obtain one full meal may bite several individuals, and so may, almost simultaneously, produce more than one case of yellow fever.

It has long been observed that communication with an infected town is distinctly safer during the day than after dark. In an effort to explain this phenomenon the French yellow fever commission first suggested, then made some experiments which appear to show that under natural conditions the yellow fever mosquito, after the first week, ceases to bite during the day and bites only at night—that is, between 5 p. m. and 7 a. m. These results are not, however, altogether in harmony with the observations of others, and there are cases recorded showing that yellow fever may be contracted by visiting an infected house during the day.[a] We must conclude, therefore, that the *Stegomyia calopus*, young or old, may bite at any time during the 24 hours, though probably it is most vicious about dusk and about dawn. The female is impregnated almost immediately after her birth, and then proceeds to seek a blood feed; 3 or 4 days after this she is ready to lay her eggs.

Breeding places.—The *Stegomyia calopus* appears to be strictly a house mosquito—a domestic though not domesticated animal. Her breeding places, therefore, may be expected, and actually have been found to be any collections of water in and about habitations, such as cisterns, wells, water barrels, tubs or jars with or without water plants, sagging roof gutters, more or less broken and discarded crockery, bottles and tins, fountains (not containing fish), cemetery vases, baptismal and other fonts in churches, chicken or horse troughs, grindstone troughs, and tubs or barrels containing water which has been softened and made more or less alkaline by the use of ashes. The larvæ have been found in tin cans containing fecal matter, in cesspools, and in some natural collections of water formed by leaves of certain tropical plants, such as the palm and century plant. Ordinarily, she does not seek street puddles or gutters, favorite breeding places for *Culex tæniorhynchus* and *Culex pipiens* (=*pungens*), though her larvæ have been found in these situations.

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[a] Carter, 1901b, p. 936.

Egg.—The female lays her eggs (fig. 4) on the surface of the water or on the sides of the container at or just above the water line. The eggs do not adhere one to the other to form the compact boat-shaped masses characteristic of *Culex* (fig. 5), but lie on their sides more or less isolated, though frequently grouped into clumps. At the moment of laying the eggs are of a cream color but rapidly become jet black; they are somewhat cigar shaped with one end slightly broader and more bluntly rounded than the other. They measure on an average about 0.55 mm. in length and 0.16 mm. in width at the broadest part. Under the microscope the apparently cylindrical egg is seen to be slightly flattened on one side. The eggs are most commonly laid during the night or early morning,

Fig. 4.—Eggs of Stegomyia calopus (after Stephens & Christopher, 1904).

but they may be laid at any time during the 24 hours. The total number of eggs laid varies, the average being about 65 to 70; the maximum recorded is 144.[a]

The act of ovipositing appears to greatly exhaust the mosquito, so that it may fall on the surface of the water and die immediately after even the first egg laying. There are numerous exceptions, however, and the act may be repeated several times and the mosquito survive for some time after.
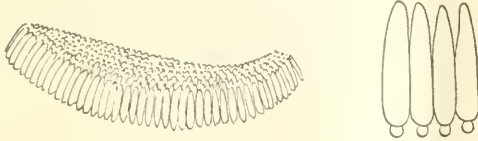

Fig. 5.—Eggraft and eggs of Culex (after Stephens & Christopher, 1904).

If laid on the surface of the water the egg floats, being supported by the surface film. Disturbance of the water surface may cause the egg to become wet and sink to the bottom, but this does not prevent its hatching out into the larva. The egg shows marked powers of resistance to unfavorable influences. Thus it may be kept dry for from two or three to six and one-half months[b] and still retain its vitality and hatch out when put back into the water. Reed and Carroll[c] have shown that freezing does not destroy its vitality. The egg probably plays the leading rôle in the hibernation of this mosquito.

Under the most favorable conditions as to temperature (30° C. (86° F.) and over) eggs hatch out in about 36 hours after they are laid, but with a lowering of the temperature this period becomes progressively longer until 20° C. (68° F.) is reached, below which they will not hatch at all.

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[a] Marchoux and Simond, 1906b.   [b] Francis, 1907.   [c] Reed and Carroll, 1901.

Larva.—The egg hatches into the larva ("wiggle-tail") (fig. 6), which can be distinguished readily from the larva of *Culex pipiens* (fig. 7), its most common messmate, by the color and proportions of the breathing siphon (air tube). In the *S. calopus* the respiratory siphon is black and somewhat barrel-shaped, with its greatest transverse diameter equal to about one-half of the length; whereas in *Culex pipiens* the air tube is brown, longer, more slender, and with the greatest transverse diameter less than one-third of the length of the tube. The larva, though it lives in the water, is strictly an air breather and must come to the
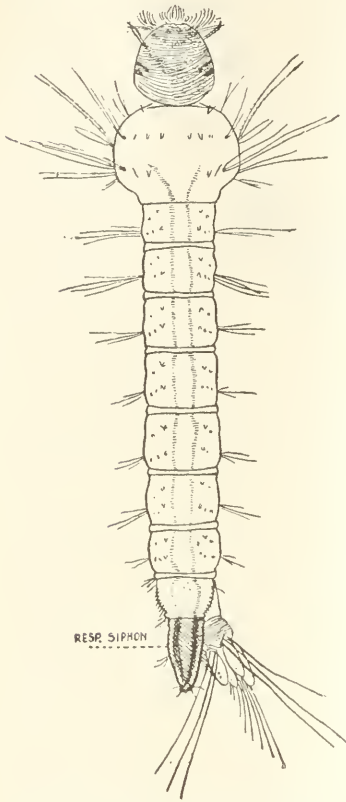

Fig. 6.—Larva of Stegomyia calopus (after Howard, 1901).

surface for air. It thrusts its breathing tube up into the surface film and remains suspended head down, at an angle somewhat less than 45°, for a variable time. A film of oil on the surface of the water is sufficient to obstruct the air tube, and thus cause the death of the larva by suffocation. The larva is very timid, so that a very slight jar or a sudden shadow will cause it to move rapidly to the bottom of the container where, indeed, it may very commonly be observed to feed.

Fig. 7.—Larva of Culex pungens (after Howard, 1901).

The duration of the larval stage is influenced by food supply and temperature. With an abundant supply of food and under favorable

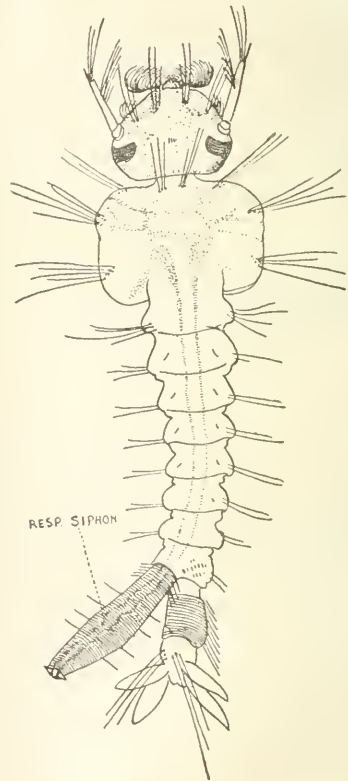conditions of temperature this stage lasts not less than 6 or 7 days; under conditions where the supply of food is scanty or the temperature reduced the duration of this stage may become very much prolonged (weeks) or development may altogether cease. In the latter case the larva may die without completing its metamorphosis or, with the return of favorable conditions, it resumes its development. Freezing for short periods does not appear to injure it.

Pupa.—After several moults the larva changes into the pupa (fig. 8). The pupa is not provided with a mouth and does not feed. It spends its time at the surface of the water for, like the larva, it is an air breather, and is provided with two trumpet-shaped breathing tubes which spring, not from the tail as in the larva, but from the dorsum of the thorax. It moves only when disturbed, and then rather rapidly and jerkily downwards into the depths. The pupal stage lasts at least 36 hours, during which time important changes take place in its internal organization preparatory to the emergence of the perfect insect or imago. The pupal, like the larval stage, is normally passed in the water. Berry has shown, however, that the pupa may be spilled on the ground without its metamorphosis being interfered with. Under the most favorable conditions it takes at least 9 days from the time the egg is laid to the appearance of the imago.

FIG. 8.—Pupa of Stegomyia calopus (after Howard, 1901).

Longevity.—The length of life of the adult female under natural conditions probably varies greatly. Experimentally, Guiteras (1904a) succeeded in keeping a presumably infected one alive for 154 days at the fall and winter temperatures of Habana. At summer temperatures, deprived of water, it does not usually survive longer than $3\frac{1}{2}$ to 4 days, and only very exceptionally 5 days. This fact has a bearing on the possibility of transporting the mosquito in bandboxes or trunks.

Its activity, which is greatest at about 30° C. (86° F.), distinctly diminishes as the temperature declines and approaches 20° C. (68° F.). Below the latter point and as the temperature of 15° C. (59° F.) is approximated the insect seeks obscure corners for protection, becomes very sluggish, and can only exceptionally be induced to bite. In a refrigerator at 8° to 10° C. (46.5° to 50° F.) Guiteras (1904a) was able to keep some mosquitoes alive without food or water for 87 days. How much longer they mave have lived it is impossible to say, because the experiment was terminated at the end of this time by some ants that gained access to and destroyed the mosquitoes. A freezing temperature kills the mosquito rather quickly.
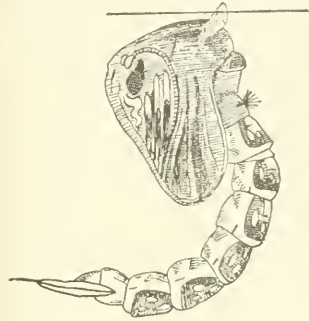
In the influence of variations in temperature on the rate of multiplication, on the activity and on the duration of life of the mosquito we have a satisfactory explanation of the peculiarities of seasonal prevalence of the disease in endemic foci, of the decline of epidemics with the advent of cool weather, and of their abrupt cessation on the occurrence of a severe frost. The occurrence of cases even after a killing frost is explained by the fact, already mentioned. that the *S. calopus* is peculiarly a house mosquito, and it is for this reason occasionally able to escape the full rigors of the climate.

Aërial conveyance.—On this subject I can do no better than quote Carter (1904), who has given it a great deal of attention.

Although direct observations on this problem are few, yet there are certain indirect ones bearing, however, entirely on the aërial conveyance of the *Stegomyia* infected with yellow fever. It is notorious that yellow fever is usually conveyed but a short ways aërially ''across the street'' or more often '' to the house in the rear,'' which is about as far as it was expected to be thus conveyed. This represents a distance of about 75 yards. The two longest distances recorded in recent times of aërial conveyance, one of 225 meters (Melier) and one of 76 fathoms—456 feet (the writer)—are entirely exceptional. So much for the distance which the ''infected'' *Stegomyia* is conveyed—or, rather, usually conveyed—aërially.

On the other hand, it is known that vessels moored in certain districts of the Habana harbor did not develop yellow fever aboard except in those who had been ashore or unless they lay close to other vessels which were infected. This experiment has been made on so large a scale, with so many vessels, and for so many years that we must accept as a fact that an infected *Stegomyia* was not conveyed aërially from the Habana shore to those vessels, or, allowing for errors, was very rarely so conveyed. The distance which had been found safe was something over 200 fathoms—1,200 feet. The prevailing wind was generally slightly on shore, but was not constantly blowing. Whether there is any difference in the distance to which infected or noninfected mosquitoes are conveyed is, of course, entirely a matter of surmise. There is no apparent reason why there should be. Yet the infected *Stegomyiæ* have almost certainly become so in a house, and with their very domestic habits must be found out of doors, where they would be subject to conveyance by the wind in much smaller numbers than the uninfected insects, and consequently a lesser *number* of them would be conveyed aërially. Observation is needed on this subject—the distance (across water) that *Stegomyiæ* are aërially conveyed.

Conveyance by railroads and vessels.—The yellow fever mosquito may be conveyed from one place to another in the railway car. I captured one in a day coach en route between Donalsonville and Bainbridge, Ga., in August, 1905. My experience in traveling by rail, both in Mexico and in the southern part of the United States, leads me to believe that the number thus conveyed is very small, so that the chance of conveying one that is infected is probably very slight.

Distribution by vessels may not infrequently be observed. They have been found on steam vessels, but much more commonly and in greater numbers on sailing vessels, because the latter are more likely to present easily accessible breeding places. It can hardly be doubted that the outbreaks of yellow fever in such northern cities as Baltimore, Philadelphia, New York, Boston, and Quebec were due to the

importation on sailing vessels of infected mosquitoes. These in proportion as they found conditions favorable, multiplied more or less rapidly and abundantly and produced epidemics which were more or less closely confined to, or in the neighborhood of, the shipping.

Geographic distribution.— The *Stegomyia calopus* has been found to be one of the most widely distributed of mosquitoes. It is primarily a tropical insect, but has extended north and south along lines of travel, establishing itself permanently wherever the conditions of temperature and moisture are favorable. Speaking broadly, it belts the globe between 38° north and 38° south latitude.

Within the United States the points at which it has been found, with few exceptions, "fall within the limits of what are known as the tropical and lower austral zones. These life zones include practically all of the southern United States which border on the Atlantic Ocean and the Gulf of Mexico, with the exception of those portions of Virginia, North and South Carolina, Georgia, and Alabama which constitute practically the foothills of the Appalachian chain; in other words, western Virginia and North Carolina, the extreme northwestern corner of South Carolina, the northern part of Georgia, and the extreme northeastern corner of Alabama. Further than this, the lower austral zone includes the western half of Tennessee, the western corner of Kentucky, the extreme southern tip of Illinois, the southeastern corner of Missouri, and all of Arkansas except the northern portion. It also includes the southern portion of Indian Territory, southern Arizona, and some of northern Arizona, and southern strips in Utah, Nevada, and California.

"In the greater part of the territory thus indicated, and *where the climate is not too dry, Stegomyia fasciata* will, with little doubt, upon close search, be found.

"All the rest of the lower austral territory just indicated, and *where the climate is not too dry*, will constitute a region where the yellow-fever mosquito, if once introduced, will undoubtedly flourish. Even in the dryer portions of western Texas, southern New Mexico, southern Arizona, southern California, and southern Nevada, where the climate is exceptionally dry, there is a possibility that this species, if once introduced, will breed in the water supply of ranches, except, possibly, where the water is impregnated with alkali."[a]

INCUBATION.

In 29[b] cases of experimental yellow fever, recorded in the literature, produced by mosquitoes *in nonimmunes that had not been subjected to*

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[a] Howard, 1903.

[b] This does not include one case apparently induced by mosquitoes that had acquired their infection by feeding on sirup in which the bodies of infected mosquitoes had been crushed. In this case the incubation period would appear to have been not less than 9 nor more than 12 days.

previous inoculations with blood serum, the period of incubation varied
from not less than 2 days 1 hour to 6 days 2 hours. In 25 of these
cases the incubation period did not exceed 5 days, leaving four cases,
or 13.8 per cent of the total, in which this period was in excess of 5
days. There is some reason for believing that this period may, excep-
tionally perhaps, be prolonged to 8^a or 10^b days.

The limits of variation of this period in the experimental cases pro-
duced by blood injection were from 1 day 15 hours to 12 days 18
hours in subjects that had not been subjected to other than the one
blood inoculation.

The length of the period of incubation appears to bear no direct
relation to the number of mosquitoes used for the inoculation; nor
does it appear to bear any direct relation to the age of the insect or
insects or to the character (mild or severe) of the case from which
they obtained their infection or which they induce.

SYMPTOMS.

Yellow fever is a disease that manifests itself in all grades of severity,
from an attack suggesting a "slight attack of grippe" or "indiges-
tion" of such mildness as hardly to interfere with one's daily routine,
and not calling for medical attention, to an attack of such malignancy
that the physician finds himself powerless to stay its course to a fatal
termination. Besides this great difference in the virulence of indi-
vidual attacks, there is considerable variation in their duration and in
the relative prominence of certain symptoms. These differences have
been used by different writers in various ways as a basis for dividing
the disease into different clinical types. As these divisions are of no
practical use they will not be considered.

Onset.—In most cases the transition from a state of well being is
abrupt and may be marked by the occurrence of a chill or chilliness,
or by the appearance of a severe frontal headache, or pain in the lum-
bar region of such severity as to suggest an attack of smallpox or,
occasionally, in children by the occurrence of convulsions. In these
cases close questioning will not infrequently elicit a history of
indisposition for perhaps 12 to 24 hours before the occurrence of the
symptom or symptoms that definitely mark the onset of the disease.
In a smaller proportion of cases the patient takes to his bed in conse-
quence of a rapidly increasing lassitude with or without headache.

The disease may be ushered in at any time during the 24 hours, so
that one not infrequently obtains a history of the patient's having
been awakened at night by the occurrence of a chill, or awakening in
the morning with fever, headache, and nausea.

[a] Carter, 1901a, p. 366.
[b] Marchoux, Salimbeni and Simond, 1903, p. 674, footnote.

Pains.—Pain in some form is one of the earliest and one of the most constant symptoms. It is usually marked, but at times, in children, and occasionally in mild cases in adults, it may be slight, and in the former sometimes altogether absent. Frequently marking the onset or, if not, appearing soon after, are headache, pain in the back and limbs. After two or three days, with the decline in the fever, the severity of these usually diminishes. The headache is usually frontal, but it is sometimes temporal or occipital; there is usually associated with it more or less aching of the eyes. The pain in the back is sometimes described as if it had been produced by blows with a rod, on which account the French in the West Indies have called it the *coup de barre;* in some instances it is not unlike the lumbar pain of smallpox. The aching in the limbs has its seat in the muscles, and affects more particularly the muscles of the thighs and calves of the legs.

Facies.—With the onset of the disease the face usually becomes flushed and somewhat swollen. The flushing may be slight or occasionally altogether absent, or it may be so marked as to suggest the initial rash of dengue, especially if it extends, as it sometimes does, down the neck to the upper part of the chest. The amount of swelling varies; it may be inappreciable or it may be sufficient to smooth out somewhat the lines of expression. Coincident with the flushing of the face the eyes become congested and red and sensitive to light. In mild cases the injection of the conjunctiva may be shown only as an abnormally prominent capillary mesh; in the severe cases the conjunctiva may appear as if inflamed, and in rare instances it may become raised around the cornea from infiltration of serum and blood. The flushing of the face and the injection of the eyes usually diminish as the temperature begins to decline.

In certain grave cases, coincident with the appearance of black vomit, the face becomes pale, the lips cyanosed, the eyes sunken, and the redness of the conjunctivæ becomes replaced by a more or less distinct tinge of yellow.

Skin.—At first the skin is warm to the touch and usually, but by no means always, dry; sometimes, indeed, it is covered with perspiration which may persist throughout the disease. Later, in some cases, with the occurrence of black vomit, the skin becomes cool and clammy. Jaundice occurs in all but some mild cases; it usually appears first about the third day as a slight tinging of the ocular conjunctiva. At almost the same time, or very soon after, it may be noticed that the skin also has acquired a pale yellow tint. Its early detection may be facilitated by pinching up a fold of skin and causing a momentary local anæmia.

As the case progresses the icteric tint, which at first is faint, gradually becomes more pronounced. The depth of color attained varies

from a pale lemon to an orange or a saffron hue. In some cases the jaundice may appear somewhat earlier than the third day; in others somewhat later, or not until convalescence. In some fatal cases it may not present itself until after death. After convalescence is established the icterus more or less rapidly fades away.

Various accidental eruptions, such as sudamina, herpes, and echymotic patches are occasionally observed.

Odor.—An odor variously described has been noted by many writers. Some have considered the odor so peculiar as to be almost pathognomonic. While I have myself never detected any odor that I could differentiate from that which may occasionally be noted in other diseases, and while I can conceive that as the result of pathological changes volatile odorous matters may be given off by the skin (or lungs) that are peculiar to the disease, I am, nevertheless, constrained to believe that some, at least, of the observers who have noted these "characteristic" odors have deceived themselves, especially when I read that the odor was detected "twelve days before the development of the fever."

Temperature.—With the onset of the disease the temperature rises and usually continues its ascent for from 24 to 48 hours. During this initial rise the fever frequently reaches the highest point which it attains during the disease. This does not commonly exceed 40.2° C. (104.5° F.). A temperature above 41° C. (105.5° F.) is but rarely recorded. Its subsequent course varies considerably, but on scrutiny it will, speaking broadly, conform to either of two general types: In one the fever having reached its acme the temperature declines progressively and more or less rapidly, with or without evening exacerbations until it reaches normal (charts 1, 2, 3, and 4). In the other the temperature continues with more or less marked oscillations for 3, 4, or 5 days at or near the point to which it first rose, and then, more or less rapidly, declines to the normal (charts 10 and 11). The cases which conform to the latter type are usually the more grave and more likely to be fatal; but some of the most rapidly fatal cases (chart 2)—the so-called *foudroyante* cases of the French—belong in the former category.

The initial rise is occasionally interrupted by a decided, though short, remission or by a complete intermission which may last 6 to 10 hours. I have seen an intermission lasting at least 6 hours occur 14 hours after the onset (chart 6). Both the remission and the intermission may be, and more commonly are, delayed until the completion of the initial rise and are then, particularly the remission, somewhat more prolonged (charts 5, 7, 8, and 9). The remission may be repeated (without the occurrence of black vomit) so that the temperature curve assumes a distinctly remitting character (charts 8 and 9). A fall in temperature frequently marks the onset of black vomit. It is for this

Chart 1.

Chart 2.

Yellow fever, descending type; fatal in 2 days 20 hours.
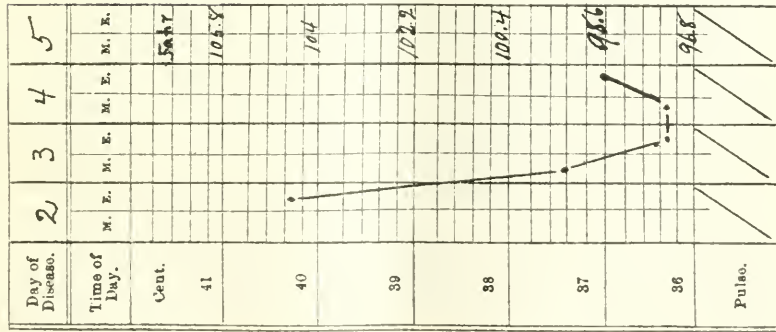
Yellow fever, descending type; very mild.
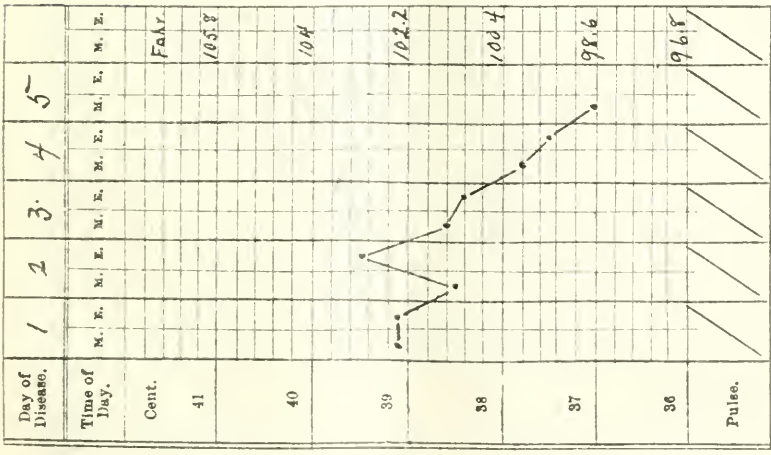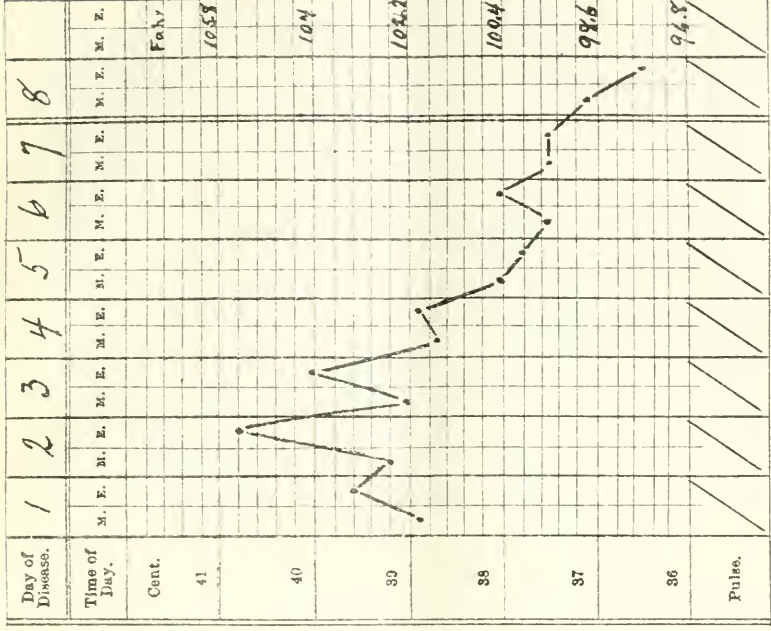
CHART 3.

CHART 4.

Yellow fever, descending type; mild; duration, 5 days; recovery.

Yellow fever, descending type; medium severity; duration, 8 days; recovery.

CHART 6.

Month.	21	22	23	24	25	26	27						
Day of Disease.	1	2	3	4	5	6	7					
Time of Day.	M. E.	M. E.	M. E.	M. E.	M. E.	M. E.	M. E.					
Cent.							Fahr.					
41							105.8					
40							104					
39							102.2					
38							100.4					
37							98.6					
36							96.8					
Pulse.												

Yellow fever, intermitting type; severe; intermission, 14 hours after onset. [Onset September 21 at 10 a. m. September 21 at 12 p. m. (14 hours after onset) temperature was 98.6° F. (37° C.); September 22 at 6 a. m. it was 98° F. (36.7° C.), and at 12 m. it was found at 101.4° F. (38.5° C.). Duration of intermission, at least 6 hours.]

CHART 5.

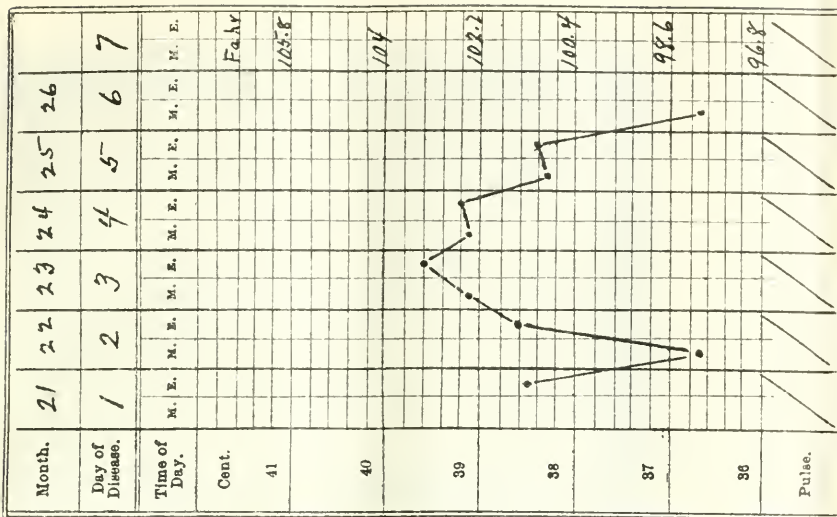| Month.	23	24	25	26	27	28	29	30				
Day of Disease.	2	3	4	5	6	7	8	9				
Time of Day.	M. E.	M. E.	M. E.	M. E.	M. E.	M. E.	M. E.	M. E.				
Cent.								Fahr.				
41								105.8				
40								104				
39								102.2				
38								100.4				
37								98.6				
36								96.8				
Pulse.												

Yellow fever, intermitting type; mild; intermission, 40 hours after onset. [Onset September 22 at 2 p. m. September 24 at 6 a. m. (40 hours after onset) temperature was normal and remained so till 4 p. m., when it began to rise. Duration of intermission, about 10 hours.]

Chart 7.

Yellow fever, intermitting type; intermission, 34 hours after onset. Experimental, by bite of *Stegomyia calopus*. (Reed, Carroll, and Agramonte. 1901.)

CHART 8.

Month.	28	29	30	31	1	2	3	4	5
Day of Disease.	1	2	3	4	5	6	7	8	9
Time of Day.	M. E.	M. E.	M. E.	M. E.	M. E.	M. E.	M. E.	M. E.	M. E.

Cent.	Fahr.
41	
40	106.8
	104
39	
38	102.2
	100.4
37	98.6
36	96.8

Yellow fever, remitting type; severe.

CHART 9.

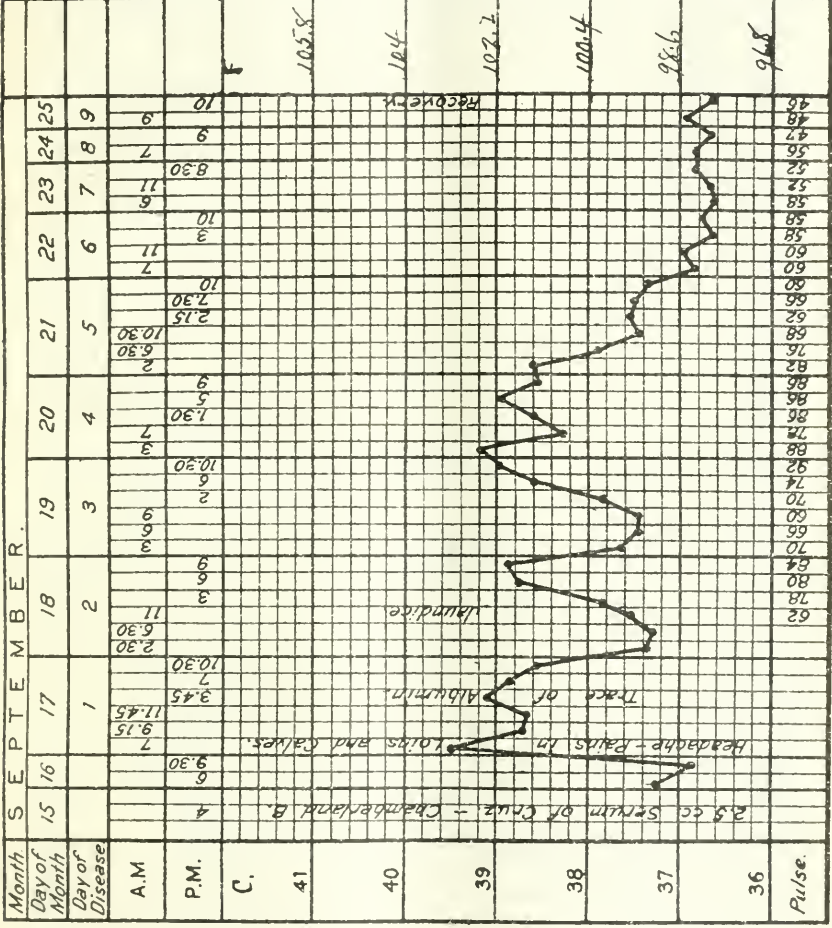Yellow fever, remitting type; mild, with remission 24 hours after onset. Experimental by intravenous injection of filtered blood serum. (Rosenau, Parker, Francis, and Beyer. 1904.)

CHART 10.
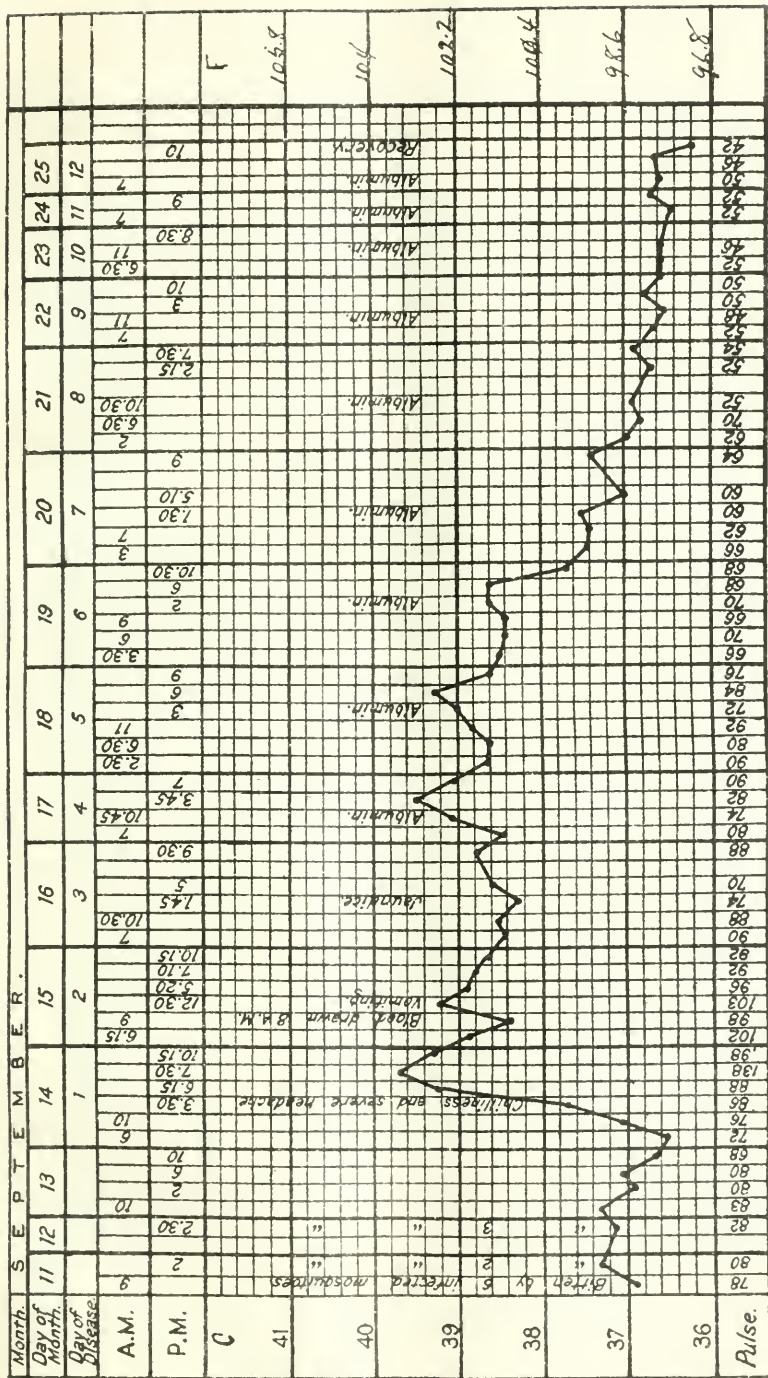
Yellow fever, continued type; moderate severity. Experimental by bites of *Stegomyia calopus*. (Rosenau, Parker, Francis, and Beyer. 1904.)

CHART 11.

Yellow fever, continued type; very severe. Experimental by bites of *Stegomyia calopus*. (Parker, Beyer, and Pothier. 1903.)

reason that there may be observed in many cases a progressive lowering of the temperature with the approach of a fatal termination, so that at the end the temperature may be little if any above normal. In some fatal cases, however, the temperature remains elevated to the end; or, if it has fallen, rises acutely before death and may continue its ascent for some minutes after. Agonic and post-mortem temperatures of 42.5° and 43° C. (108.5° and 109.5° F.) have been observed. During the first days of convalescence the temperature is usually somewhat below normal.

Pulse.—At the outset the pulse is usually full and bounding, and the number of its beats may register 120 or 125 per minute. As the fever progresses the tension and the rapidity of the pulse diminish. At intervals in the course of the disease the pulse may be distinctly dicrotic. At the close, in fatal cases, it becomes rapid and feeble; in those terminating favorably the pulse not infrequently falls to 50 and occasionally even less. It is often stated that slowness is a peculiar characteristic of the pulse in yellow fever, but this is not altogether correct. While, to be sure, the pulse in this disease is not a rapid one, its peculiar character consists in the sluggishness with which it responds to the stimulus of a rise in the temperature. This sluggishness at times amounts to an actual irresponsiveness which is so marked, early in many cases, that there is witnessed the phenomenon of a stationary or falling pulse rate with a rising temperature, or a falling pulse with a stationary temperature. This is not simply a lack of correlation such as is sometimes observed in typhoid, but an actual divergence between the two. Attention was first called to this phenomenon by Faget, of New Orleans, who considered it pathognomonic.

Unfortunately this sign is not always present and, when present, it is not always as well defined as could be wished. Its minor manifestations are occasionally observable in other febrile affections, such as pneumonia, malaria, dengue, and septicemia.

Respiration.—The number of the respiratory movements is usually not notably increased. The character of the respiration is, in many cases, altered somewhat. Many patients experience a feeling of thoracic oppression so that at variable intervals their breathing is punctuated by a sighing respiration. In the latter stages of some cases hiccough appears; it is always an ominous sign.

Blood.—The results of blood examination are characterized chiefly by their negative character. Morphologically the cellular elements show no alteration. In uncomplicated cases the number of the red corpuscles and the percentage of hemoglobin are not, as a rule, reduced, but, on the contrary, frequently show an increase above the normal. The number of the white corpuscles is somewhat diminished, and the proportion of the different forms is slightly altered. The chief alteration consists in an increase in the percentage of the polymorphonuclear

leucocytes and a diminution in the eosinophiles. Sometimes there is a slight increase in the large mononuclears. There is usually a noticeable increase in the number of the blood platelets. The coagulability of the blood does not undergo any material change.[a] With the onset of convalescence there is a fall in the number of the red corpuscles and in the percentage of hemoglobin.

Hemorrhages.—A tendency to hemorrhage is one of the marked characteristics of the disease. As a rule, this does not manifest itself before the third day. The most common and, in a very large proportion of the cases, the only manifestation of this tendency is bleeding from the gums. The gums become more or less swollen and the blood may ooze from them spontaneously or, more commonly, only after some traumatism, such as a slight pressure of the examining finger. Epistaxis is almost as frequent a symptom as bleeding from the gums; it may occur at the onset, but more commonly, like bleeding from the mouth, does not appear until the fourth or fifth day. In women, menorrhagia or metrorrhagia are common manifestations. During pregnancy death of the fetus and miscarriage are of common, though not invariable, occurrence.

Hemorrhage from the stomach, appearing as black vomit, occurs in the graver cases only. It varies considerably in amount; in the lighter grades it may be barely perceptible, as dark streaks or specks in the vomited matter, but in the severer forms it may be so profuse that the vomitus is uniformly dark red or black, like coffee grounds. Blood originating in a hemorrhage from the nose or mouth which has been swallowed may give to vomited matter precisely the same character as blood which has its origin in the stomach. Black vomit, therefore, does not necessarily mean gastric hemorrhage. Melæna may result from passing altered blood which had its origin in the stomach, or it may be due to hemorrhage from the intestine. The quantities of black vomit ejected and melæna discharged per rectum are at times surprisingly large.

Digestive tract.—In some of the severer forms the lips become dry and cracked and bleeding. In almost all cases the gums become more or less swollen, and at first covered with a white epithelial coating which rapidly wears off, leaving them red and spongy and disposed to bleed on slight pressure. The tongue at first is commonly moist, with a gray coating over the center and dorsum and with red tip and edges. As the disease progresses, in severe cases, the tongue becomes dry, red, fissured, and more or less streaked with blood. The appetite is lost from the first, but returns rapidly with convalescence. Thirst is frequently marked. Nausea and vomiting are commonly, but not invariably, present. In general, they appear with or soon after the onset, and, as a rule, become more or less accentuated with the prog-

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[a] Marks, 1906.

ress of the disease. There is nothing peculiar about the character of the vomited matter in any but some of the grave or the fatal cases. At first it may consist of food remnants or of such liquids as may have been swallowed; later it consists of a thin mucus, which soon becomes bile-stained. In some grave cases, about on the third day, sometimes on the second, but more commonly on the fourth or fifth, streaks of red or black may be detected in the vomited matter. These streaks are more or less altered blood and are the first signs of black vomit. In some cases it does not go beyond this, but in some very severe cases and in most of the fatal ones the vomited matter soon becomes more or less uniformly black in color. In some fatal cases black vomit does not manifest itself during life, but is found post-mortem. In the severer cases there is sometimes associated with the vomiting or retching more or less distressing hiccough. In the cases terminating favorably the gastric irritability gradually diminishes and disappears. The bowels are usually constipated. The movements are at first natural in color and remain so in all but some of the grave cases, in which they may become dark and tarry. Some tenderness, especially in the severer cases, can usually be elicited by pressure in the epigastric region as early as the second day. Abdominal pains of a colicky character are occasionally complained of; sometimes they are very severe and cause the patient intense suffering.

Urine.—In mild cases and in those of moderate severity the urine may show but slight alteration in character as regards quantity and density. In severer cases it becomes reduced in volume and somewhat in specific gravity. Complete suppression is not a rare occurrence in fatal cases. The suppression may, however, only be apparent and due to retention, as may be demonstrated by catheterization.

In all but the mildest cases albumin appears in the urine at some time in the course of the disease. It may appear within 24 hours after the onset, though usually not until the end of 48 hours; or it may delay its appearance until after the subsidence of the fever. At first it appears only in small amounts—a slight trace, perhaps— which in some cases is not increased, while in others it rapidly aug-ments in volume up to 80 to 90 per cent. In favorable cases the amount begins to diminish almost at once or very soon after the maximum has been recorded, and will be found to have disappeared in from three or four days to two or three weeks from the time it first appeared. In some cases, however, the albuminuria is very transitory and may not be detected unless every specimen of urine passed be examined. When jaundice is present, biliary pigment appears in the urine, as may frequently be noted when making the nitric-acid test for albumin. Albertini and Guiteras[a] report the absence of the diazo

[a] Guiteras, 1904b, p. 594.

reaction in this disease. Haylin, granular and epithelial casts, which may be bile-stained, are commonly encountered in the sediment.

Liver.—Except jaundice, which has already been discussed, there appear in uncomplicated cases no symptoms referable to this organ, the dimensions of which are, as a rule, not materially altered.

Spleen.—In uncomplicated cases the spleen does not undergo any material change in size.

Nervous system.—Sleeplessness, more or less marked, is a frequent symptom. Delirium is of common occurrence; in many cases it is only a slight mental wandering during the first or second night after the onset. In some of the grave cases this wandering gives place to a muttering or an active maniacal delirium; toward the end in some fatal cases unconsciousness, more or less profound, supervenes and the scene is closed with tonic convulsions involving particularly the muscles of the face and flexors of the arms. In all mild, in many grave, and in some fatal cases the mind is clear and alert throughout the course of the attack.

Duration.—The great majority (75 per cent) of all cases terminate before the ninth day. A fatal termination rarely occurs before the third day, but it has been recorded as late as the twenty-second.

Complications.—In the vast majority of cases yellow fever runs its course without any disturbing complications. Occasionally, however, a deep-seated muscular abscess or an inflammation of the parotids may occur.

The most common complication is malaria, which may manifest itself either during the febrile period or, and more commonly, during convalescence.

Yellow fever may occur as a complication in the course of some chronic diseases such as pulmonary tuberculosis, cirrhosis of the liver, dysentery, malarial cachexia and ankylostomiasis, or some acute infections such as typhoid fever and gonorrhea.

Convalescence.—With the termination of the fever the patient finds himself, even after a relatively mild attack, markedly depressed in strength. As a rule, however, recuperation is rapid. Occasionally convalescence is retarded by the occurrence of complications such as malaria, furunculosis, and peripheral neuritis.

Relapse and second attacks.—A return of the fever and other symptoms characterizing an attack of yellow fever after convalescence has been established is rare. Cases of relapse have, however, been observed after an interval of 2 or 3 days to 2 weeks or a month. It is a question whether so-called relapses occurring after an interval of 2 weeks or a month should not more properly be considered second attacks.

As a rule with but very rare exceptions one attack of the disease confers immunity on the individual for life. Nevertheless, there are

on record some fairly convincing instances of a second more or less grave attack a year or longer after the first.

DIAGNOSIS.

The increase in knowledge concerning the etiology of various communicable diseases and the improvement in methods devised for their recognition have been followed, among other things, by a broadening of our conceptions relating to the degrees of severity which they may assume. Thus when, for example, we speak of typhoid or cholera we think not only of the severe classical types, but we have in mind also those mild and irregular forms which are recognizable only because of the improved tests which are at our command.

We now know that, like cholera and typhoid, yellow fever also manifests itself in all grades of severity; but unfortunately, unlike the former, we have no test whereby in any particular case we can say definitely that this is or is not yellow fever. The recognition of this fact is of the very highest importance with respect to prevention, for it makes it imperative that in infectible regions every case of fever, however mild, should be considered as potentially yellow fever until this disease can positively be excluded.

On taking charge of a case of fever the practitioner, in the South, should therefore start with the assumption that he is dealing with a case of yellow fever, and in formulating his final, definite diagnosis, in which this disease is excluded, he must use the greatest care and caution. The clinician must fix it firmly in his mind that yellow fever is not excluded simply because he knows of no other previous case; obviously he may be dealing with the first case himself, or several cases may have occurred in such as, for one reason or another, had received no medical attention. Nor is yellow fever eliminated from consideration because he fails to detect *any* so-called " characteristic " sign or symptom.

Ordinarily the *combination* of an *acute fever* with *albuminuria, jaundice,* an *irresponsive* or *divergent pulse,* a *tendency to hemorrhage* from the mouth, and *gastric irritability,* with no material alteration in the size of the liver and spleen, should leave no doubt in the observer's mind as to the nature of the disease with which he is dealing.

The diseases with which yellow fever may be confused are malaria, hemoglobinuric fever, dengue, grippe, bubonic plague, typhoid fever, acute yellow atrophy of the liver, Weil's disease, and relapsing fever.

Malaria.—Yellow fever at times simulates certain irregular forms of malaria very closely, and in the absence of any known infection the grave error of mistaking it for malaria has, not rarely, been committed. On the other hand, during epidemic seasons the mistake is not infrequently made, both within and without the infected zone, of calling malaria yellow fever.

Careful examination of stained blood smears will show an absence of the plasmodia in the former group and their presence in the latter; but while the absence of the plasmodium from the blood excludes malaria in the first instance, its presence in cases of the second group does not eliminate yellow fever from consideration. In these cases, yellow fever should be excluded only after a careful study of the case. Careful observation for several days after the adminstration of a few doses of quinine, preferably subcutaneously [a] or intravenously, may be necessary. The abrupt decline in the fever coincident with the disappearance of the parasites from the circulation following the exhibition of the quinine in the manner indicated, with absence of albumen from the urine or its presence only as a trace, with no jaundice and no tendency to hemorrhage, may generally be interpreted as probably excluding yellow fever. The mere decline of the fever after the administration of quinine without a previous examination of the blood to determine the presence of the malarial parasite does not exclude yellow fever.

Hemoglobinuric fever.—This grave manifestation of malaria resembles yellow fever in its abrupt onset, bilious symptoms, jaundice, and albuminuria, but differs in being characterized by a rapid blood destruction and enlargement and tenderness of the liver and spleen. The blood destruction manifests itself by a reduction in the number of the red corpuscles, low hemoglobin percentage, and by the red or black color of the urine, due to the elimination of hemoglobin.

Dengue.—The differentiation between well-marked types of dengue and yellow fever is a matter presenting no serious difficulty after the first two or three days. The points of difference most to be relied on are the presence of an eruption and the absence of jaundice in dengue. Albuminuria, which is so prominent a sign even in relatively mild attacks of yellow fever, is slight and commonly altogether absent in even quite sharp attacks of dengue. In the latter disease the percentage of the polymorphonuclear leucocytes is reduced whereas in yellow fever it is more or less increased.

When, however, we come to deal with cases that are ill-defined, cases that present no eruption (or in which none has been detected), in which jaundice is doubtful or absent, and in which no albumin or only a dubious trace of it can be detected, we encounter a very real and serious difficulty in deciding as to which of the two diseases we have before us. While it is of the very greatest importance to recognize that we have no means of surely identifying individual cases of

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[a] The injection should be given into a muscle, not into the subcutaneous cellular tissue. With good aseptic technique the intravenous injection is preferable. Give 1 gram (15 grains) of the bimuriate dissolved in 1 cc. (15 minims) of distilled water and repeat three times at 12-hour intervals; the solution and syringe must, of course, be sterile.

this type, nevertheless a clue to their nature will, as a rule, be discovered if a careful study of a series of cases be made. In a group some individuals are very likely to be found that will show, if they are yellow fever, unmistakable jaundice and a degree of albuminuria quite out of proportion to the mildness of the attack, whereas, if they are dengue, some cases will be found that will exhibit the characteristic rash. In isolated instances, or until cases presenting distinctive symptoms are encountered, the observer will do well to suspend judgment and not assume, as is too frequently done, that mildness of attack and a failure to die are pathognomonic of dengue. He should remember, also, that the two diseases may occur side by side, thereby multiplying the difficulties of the problem and rendering caution imperative.

Grippe.—An attack of influenza is characterized, as a rule, by symptoms referable to a catarrhal condition of the upper air passages. Cases in which these symptoms are marked hardly come into consideration in the diagnosis of yellow fever. As with dengue it is the less well-defined cases of influenza that counterfeit and are simulated by mild and ill-defined cases of yellow fever; and much that has been said concerning the diagnosis from dengue is here also applicable.

Bubonic plague—In localities where yellow fever and plague prevail, and at quarantine stations in connection with vessels from such ports, the question of differentiating the two diseases may arise. Clinically there is only a very superficial resemblance between the two, but in all cases of doubt a careful bacteriological examination should be made of the sputum, blood, or aspirated juice from enlarged glands; the latter, by the way, are but very rarely met with in uncomplicated yellow fever, while in plague they are not only enlarged but inflamed and the surrounding tissue infiltrated.

Typhoid fever.—Early in the disease typhoid may be mistaken for yellow fever, but the resemblance is slight and observation of the patient for 3 or 4 days will be certain to resolve any doubts. At this stage the general appearance and the increasing apathy of the patient are distinctive. The temperature is a gradually ascending one or has reached the fastigium, and the pulse, though not fast, follows the daily oscillations of the fever and does not, as in yellow fever, tend to become slower from day to day. Jaundice is, at best, but a rare complication of typhoid and may be said almost never to occur early in the disease. The urine frequently gives the diazo reaction, and at this time is usually free of albumin, though occasionally traces of the latter constituent may be met with; nephritis is a late and not common complication of typhoid fever. The bacillus of Eberth may be isolated from the blood.

In an attack of yellow fever of three or four days duration and with a corresponding elevation of temperature the combination of symptoms distinctive of a well-defined attack of this disease would be clearly

manifested. In some of the severer forms of yellow fever the temperature is occasionally prolonged for two to three weeks, and some of the accompanying symptoms are, in some of these cases, suggestive of typhoid. Typhoid fever, in the second or third week, will give the Widal reaction and Eberth's bacillus may be isolated from the blood. These are, of course, absent in yellow fever.

Acute yellow atrophy of the liver.—This is a very rare disease. It occurs most commonly in women, and in these more particularly during pregnancy. The disease is ushered in like a case of catarrhal jaundice. A marked and rapid reduction in the size of the liver is distinctive.

In yellow fever the size of the liver is unaffected. In malignant jaundice albuminuria is of frequent occurrence, but it is not as marked nor as constant as in cases of yellow fever of the same degree of virulence. The duration of over 75 per cent of the recorded cases of malignant jaundice has been in excess of seven days; the duration of almost 75 per cent of the cases of yellow fever does not exceed seven days. An early fatal termination in such a case would decidedly favor a diagnosis of yellow fever, but a later termination should not, however, be regarded as excluding yellow fever.

Weil's disease.—This disorder is characterized by fever, intense jaundice, swelling and tenderness of the liver, diarrhea, notable enlargement of the spleen, and nephritis. In yellow fever neither liver nor spleen are enlarged, a tendency to constipation is the rule, and in cases of a corresponding grade of severity, the hemorrhagic symptoms are likely to be more marked and to appear earlier.

Relapsing fever.—The presence of the *Spirochæta* of Obermeier in the blood is distinctive.

Catarrhal jaundice.—This may in some instances have to be considered. In this condition the jaundice appears with little or no elevation of temperature, preceded by slight, if any, symptoms of indigestion and accompanied by clay-colored stools. In yellow fever the jaundice appears after at least two or three days of fever and will be accompanied by the other symptoms characterizing a well-defined attack; the stools are not clay colored.

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