The etiology of yellow fever : a preliminary note / by Walter Reed [and others].

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Publication/Creation

[Place of publication not identified] : [publisher not identified], 1900.

Persistent URL

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THE ETIOLOGY OF YELLOW FEVER

A preliminary Note

Walter Reed

The Philadelphia Medical Journal,
1900, Oct. 27.

vol. 6

Original Articles.

THE ETIOLOGY OF YELLOW FEVER.

A Preliminary Note.[1]

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AND

JAMES CARROLL, M.D., A. AGRAMONTE, M.D., JESSE W. LAZEAR, M.D.,[2] Acting Assistant Surgeons, U. S. A.

THE writers, constituting a board of medical officers, convened "for the purpose of pursuing scientific investigations with reference to the acute infectious diseases prevalent on the Island of Cuba," arrived at our station, Columbia Barracks, Quemados, Cuba, on June 25 of the present year, and proceeded under written instructions from the Surgeon-General of the Army, to "give special attention to questions relating to the etiology and prevention of yellow fever."

Two of its members (Agramonte and Lazear) were stationed on the Island of Cuba, the former in Havana, and the latter at Columbia Barracks, and were already pursuing investigations relating to the etiology of this disease.

Fortunately for the purposes of this board, an epidemic of yellow fever was prevailing in the adjacent town of Quemados, Cuba, at the time of our arrival, thus furnishing us an opportunity for clinical observations and for bacteriologic and pathologic work. The results already obtained, we believe, warrant the publication, at this time, of a Preliminary Note. A more detailed account of our observations will be submitted to Surgeon-General Sternberg in a future report.

The first part of this Preliminary Note will deal with the results of blood-cultures during life and of cultures taken from yellow-fever cadavers; reserving for the second part a consideration of the mosquito as instrumental in the propagation of yellow fever; with observations based on the biting of nonimmune human beings by mosquitos which had fed on patients sick with yellow fever, at various intervals prior to the biting.

In prosecuting the first part of our work, we isolated a variety of bacteria, but of this we do not purpose to speak at present. It will suffice for our purpose if we state the results as regards the finding of Bacillus icteroides, leaving the mention of other bacteria to our detailed report.

The cases studied during the Quemados epidemic had been diagnosed by a board of physicians, selected largely by reason of their familiarity with yellow fever. This board consisted of Drs. Nicolo Silverio, Manuel Herera, Eduardo Angles, and Acting Assistant Surgeon Roger P. Ames, and Jesse W. Lazear, U. S. Army.

Those studied in Havana were patients in Las Animas Hospital, and had been diagnosed as such by a board of distinguished practitioners of that city.

An examination of Table I will show the character of the attacks. The milder cases studied, few in number, were attended by jaundice and albumin in the urine.

I.

Bacillus Icteroides (Sanarelli) as the Cause of Yellow Fever.—The claim of Sanarelli for the specific character of B. icteroides as the causative agent in yellow fever, has excited such wide attention, since the publication of his observations, that it seemed to us of the first importance to give our undivided attention to the isolation of this microorganism from the blood of those sick with yellow fever, and from the blood and organs of yellow-fever cadavers.

A. *Cultures taken from the Blood during Life.*—The method followed was that ordinarily used in an attempt to isolate bacteria from the circulating blood; viz., from a vein at the bend of the elbow, a sufficient quantity of blood was taken with an hypodermic syringe, made sterile by boiling, and after careful cleansing of the skin with soap and water, followed by equal parts of absolute alcohol and ether, and 1:2000 bichlorid solution.

Exceptionally the blood withdrawn was plated on agar, but, as a rule, it was immediately transferred to sterile bouillon tubes (10 ccm.) in quantities of 0.5 ccm. to each of several tubes. These were then incubated at from 35° to 37° C. for a period of one week. They were examined daily and if growth was observed, plates in agar or gelatin, or both, were made and the colonies carefully studied by transferrence to ordinary laboratory media.

Eighteen cases have thus been carefully studied; of these 11 were designated as "severe" cases of yellow fever with 4 deaths; three as "well-marked" cases with no deaths, and 4 as "mild" cases with no deaths.

From these 18 cases, blood-cultures were made, as shown in the following table:

TABLE I.

BLOOD-CULTURES DURING LIFE.

DAY OF DISEASE.	CHARACTER OF ATTACK.	NO. OF CULTURES.	NO. OF BOUILLON TUBES INOCULATED.	BACILLUS ICTEROIDES.
1st	Severe.	3	4 (3 agar plates.)	Negative.
"	Well marked.	1	4	"
"	Mild.	1	3	"
2d	Severe.	6	18	"
"	Well-marked.	1	2	"
"	Mild.	1	3 (6 agar plates.)	"
3d	Severe.	7	18 (6 agar plates.)	"
"	Mild.	2	4	"
4th	Severe.	5	14	"
"	Well-marked.	2	6	"
"	Mild.	1	1	"
5th	Severe.	5	12 (3 agar plates.)	"
"	Well-marked.	1	3	"
"	Mild.	1	1	"
6th	Severe.	4	6	"
"	Well-marked.	1	2	"
7th	Severe.	1	2	"
"	Well-marked.	1	2	"
8th	Severe.	2	6	"
"	Well-marked.	1	2	"
9th	Severe.	1	2	"

Number of cultures 48
Number of bouillon tubes inoculated 115
Number of agar plates 18

It will be seen that of 48 separate cultures made from the blood on various days of the disease and representing 115 bouillon inoculations and 18 agar plates,

[1] Read at the Meeting of the American Public Health Association, held in Indianapolis, Ind., October 22-26, 1900.

[2] Died of yellow fever at Camp Columbia, Cuba, September 25, 1900.

we failed to find Bacillus icteroides in any of our tubes or plates.

The results of cultures taken in 18[3] cases of unmistakable yellow fever, on various days of the disease, and in some cases on every day from the onset to death or recovery, would seem to exclude the presence of Bacillus icteroides in the blood of these cases during life.

It will, therefore, be seen that while Wasdin and Geddings, taking cultures from the ear-lobe (Report on the Cause of Yellow Fever, 1899), record that "in the blood of yellow fever cases extracted during life Bacillus icteroides has been found in 13 of the 14 cases, with 1 negative," (92.85%), we, by withdrawing the blood from the veins of 19 patients, have to record 100% of failures.

We have already stated that we will reserve for a later report a description of the bacteria isolated from the blood in these cases. We now remark that but few organisms were obtained and that, as a rule, our blood-cultures gave no growth whatever.

B. *Cultures from Yellow Fever Cadavers.*—We tried to obtain autopsies very soon after death, and sometimes succeeded in doing so. Tubes containing about 10 ccm. of flesh-peptone bouillon were generally used for the first inoculation direct from the blood and organs. As soon as the laboratory was reached, agar plates were made from these inoculated bouillon tubes, the former as well as the latter being then incubated at from 35° to 37° C. In nearly every case gelatin plates were also made from the recently inoculated bouillon tubes and kept at a temperature of 19° to 20° C.

If colonies were found in the agar or gelatin plates, on the following days, the corresponding bouillon tubes were also plated on agar and gelatin. The bacteria thus found in our plates were carefully isolated and studied upon the usual nutritive media, so as to enable us to identify them, if possible. We will here content ourselves with giving the results as regards the presence of B. icteroides only.

Table II.

No. of Case.	Day of Disease.	Time of Autopsy.	Source of Culture.	B. Icteroides.
1	Seventh.	2 hours after death.	Blood, liver, spleen, kidney.	Negative.
2	Sixth.	13 hours after death.	Blood, liver, spleen, kidney.	"
3	Fourth.	8 hours after death.	Blood, liver, spleen, kidney.	"
4	Eighth.	2 hours after death.	Abdominal, cavity, blood, liver, spleen, kidney, bile, duodenum.	"
5	Fourth.	4 hours after death.	Blood, liver, spleen, kidney, bile, duodenum.	"
6	Sixth.	6½ hours after death.	Abdominal cavity, blood, pericardial fluid, lung, spleen, kidney, liver, bile, duodenum.	"
7	Sixth.	50 minutes after death.	Blood, lung, liver, spleen, kidney, bile, jejunum.	"
8	Sixth.	½ hour after death.	Blood, lung, liver, spleen, kidney, urine, small intestine.	"
9	Fourth.	2 hours after death.	Liver, spleen, small intestine.	"
10	Fifth.	7 hours after death.	Liver, kidney, spleen, small intestine.	"
11	Third.	½ hour after death.	Liver, kidney, spleen.	"

Our failure to isolate B. icteroides in these 11 autopsies of yellow-fever patients was a result which we had not anticipated. One of us (Agramonte), who, at Santiago, Cuba, during the epidemic of 1898, succeeded in finding B. icteroides in 33% of his autopsies, has been much surprised at the absence of this bacillus in cultures from cadavers sectioned in or near Havana, during the present year. In 2 of the 11 cases we had reason to believe that from the appearance of colonies seen in gelatin plates, we would be able to isolate B. icteroides. These colonies, however, when transferred to other media and carefully studied, did not prove to be this bacillus. We wonder whether other observers have occasionally relied upon the appearance of colonies in gelatin plates, without further study. We only mention this as a possible explanation of the large percentage of positive results recorded by some observers.

Portier, of New Orleans, La., only succeeded, however, in isolating B. icteroides in 3 out of 51 autopsies (*Journal of American Medical Association*, April 16, 1898), and, if we remember correctly, Veazie, of New Orleans, has recently reported that during the epidemic of 1899 in New Orleans a pure culture of B. icteroides was not isolated in any case of yellow fever.

Lutz (*Revista d'Igiene e Sanita Publica*, xi, No. 13, July, 1900, pp. 474–475) says as the result of his extensive observations on yellow fever that Bacillus icteroides cannot be found by present laboratory methods in more than half of the cases of yellow fever, and that when present, the colonies are few in number. It is possible that our future autopsies may give more favorable results as regards B. icteroides.

II.

The Mosquito as the Host of the Parasite of Yellow Fever.—Having failed to isolate B. icteroides, either from the blood during life, or from the blood and organs of cadavers, two courses of procedure in our further investigations appeared to be deserving of attention, viz., first, a careful study of the intestinal flora in yellow fever in comparison with the bacteria that we might isolate from the intestinal canal of healthy individuals, in this vicinity, or of those sick with other diseases; or, secondly, to give our attention to the theory of the propagation of yellow fever by means of the mosquito—a theory first advanced and ingeniously discussed by Dr. Carlos J. Finlay, of Havana, in 1881 (*Anales de la Real Academia*, vol. xviii, 1881, pp. 147–169).

We were influenced to take up the second line of investigation by reason of the well-known facts connected with the epidemiology of this disease, and, of course, by the brilliant work of Ross and the Italian observers, in connection with the theory of the propagation of malaria by the mosquito.

[3] Cultures from the blood during life had been taken by Dr. Lazear in 3 other cases of yellow fever, but, owing to the death of our colleague, the necessary data as to the day of the disease on which cultures had been taken cannot be ascertained. These cultures were negative as regards the finding of Sanarelli's bacillus.

We were also very much impressed by the valuable observations made at Orwood and Taylor, Miss., during the year 1898, by Surgeon Henry R. Carter, U. S. Marine-Hospital Service (*A note on the interval between infecting and secondary cases of yellow fever, etc.*, Reprint from *New Orleans Medical Journal*, May, 1890). We do not believe that sufficient importance has been accorded these painstaking and valuable data. We observe that the members of the yellow fever commission of the Liverpool School of Tropical Medicine, Drs. Durham and Meyers, to whom we had the pleasure of submitting Carter's observations, have been equally impressed by their importance (*British Medical Journal*, September 8, 1900, pp. 656–7).

to us to the presence of an intermediate host, such as the mosquito, which having taken the parasite into its stomach, soon after the entrance of the patient into the noninfected house, was able after a certain interval to reconvey the infecting agent to other individuals, thereby converting a noninfected house into an "infected" house. This interval would appear to be from 9 to 16 days (allowing for the period of incubation), which agrees fairly closely with the time required for the passage of the malarial parasite from the stomach of the mosquito to its salivary glands.

In view of the foregoing observations we concluded to test the theory of Finlay on human beings. According to this author's observation of numerous inocu-

TABLE III.

INOCULATION OF NONIMMUNE INDIVIDUALS THROUGH THE BITE OF MOSQUITOS (CULEX FASCIATUS).

NO. OF CASE.	AGE.	NATIVITY.	DATE OF INOCULATION.	CHARACTER OF ATTACK AND NUMBER OF PATIENTS BITTEN.	DAY OF DISEASE.	TIME BETWEEN INFECTION OF MOSQUITO AND INOCULATION.	NO. OF MOSQUITOS.	RESULT.	REMARKS.
1	..	United States.	August 11.	Mild, 1.	Seventh.	5 days.	One.	Negative.	
2	..	United States.	" 11.	Very mild, 1.	Fifth.	5 "	One.	"	
3	24	United States.	" 12.	" " 1.	Fifth.	6 "	One.	"	
4	20	United States.	" 12.	" " 1.	Fifth.	6 "	One.	"	
5	24	United States.	" 14.	" " 1.	Fifth.	8 "	One.	"	
6	34	United States.	" 16.	" " 1.	Fifth.	10 "	One.	"	
7	22	United States.	" 18.	Severe, 1.	Second.	3 "	One.	"	
8	20	United States.	" 19.	Very mild, 1.	Fifth.	13 "	Two.	"	
				Severe, 1.	First.	3 "			
9	28	United States.	August 23.	Fatal, 1.	Second.	6 "	One.	Negative.	
				Mild, 1.	First.	4 "			
				Severe, 1.	Second.	2 "			
10	46	England.	August 27.	Severe, 1.	Second.	12 "	One.	Positive.	Severe attack of yellow fever.
				Mild, 1.	First.	6 "			
				Severe, 1.	Second.	4 "			
				Mild, 1.	Second.	2 "			
11	24	United States.	August 31.	Fatal, 1.	Second.	12 "	One.	Positive.	Well-marked attack of yellow fever.
				Mild, 2.	Second.	4 and 10 "			
				Severe, 2.	Second and ninth.	2 and 8 "			
				Severe, 3.	First, second and second.	2, 8 and 16 "	One.		
				Mild, 2.	First and second.	6 and 10 "			
				Fatal, 1.	Second.	12 "	One.		
				Severe, 1.	First.	2 "			
				Mild, 3.	First, second and second.	4, 6 and 10 "			
				Severe, 3.	All on first.	2, 4 and 8 "	One.		
				Mild, 1.	Second.	6 "			

The circumstances under which Carter worked were favorable for recording with considerable accuracy the interval between the time of arrival of infecting cases in isolated farmhouses and the occurrence of secondary cases in these houses. According to Carter, "the period from the first (infecting) case to the first group of cases infected, at these houses, is generally from two to three weeks."

The houses having now become infected, susceptible individuals thereafter visiting the houses for a few hours, fall sick with the disease in the usual period of incubation, 1 to 7 days.

Other observations made by us since our arrival confirmed Carter's conclusions, thus pointing as it seemed

lations in 90 individuals, the applications of one or two contaminated mosquitos is not dangerous, but followed in about 18%, by an attack of what he considers to be very benign yellow fever at most.

We here desire to express our sincere thanks to Dr. Finlay, who accorded us a most courteous interview and has gladly placed at our disposal his several publications relating to yellow fever, during the past 19 years; and also for ova of the variety of mosquito with which he had made his several inoculations. An important observation to be here recorded is that, according to Finlay's statement, 30 days prior to our visit, these ova had been deposited by a female just at the edge of the water in a small basin, whose contents had

been allowed to slightly evaporate; so that these ova were at the time of our visit entirely above contact with the water. Notwithstanding this long interval after deposition, they were promptly converted into the larval stage, after a short period, by raising the level of the water in the basin.

With the mosquitos thus obtained we have been able to conduct our experiments. Specimens of this mosquito forwarded to Mr. L. A. Howard, Entomologist, Department of Agriculture, Washington, D. C., were kindly identified as *Culex fasciatus*, Fabr.

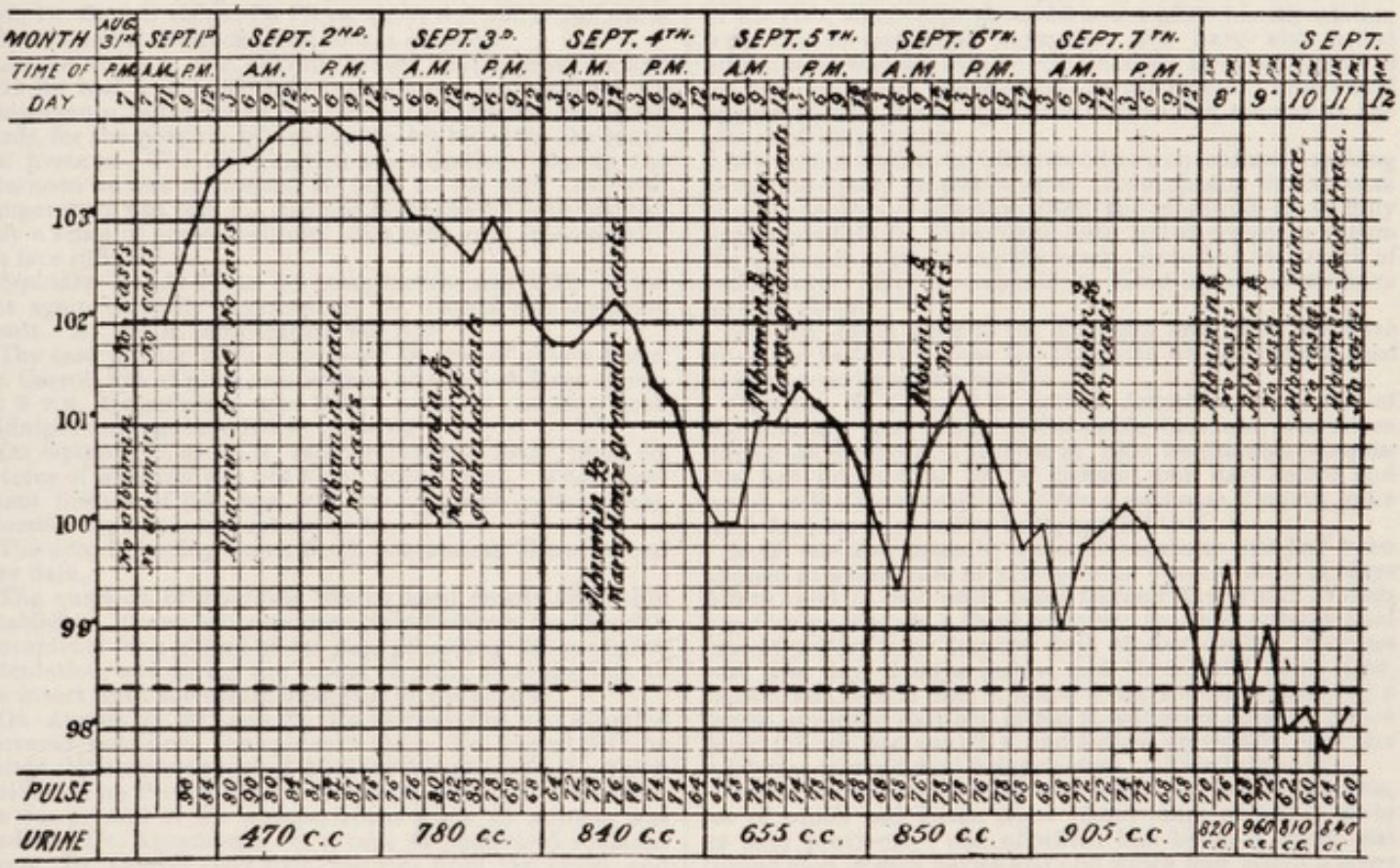
In this preliminary note we have not space to refer, at length, to the various interesting and valuable contributions made by Finlay to the mosquito theory for the propagation of yellow fever. In addition to the paper already quoted, his most valuable contributions

by the author of this theory, we believe that he has not, as yet, succeeded in reproducing a well-marked attack of yellow fever, within the usual period of incubation of the disease, attended by albumin and jaundice, and in which all other sources of infection could be excluded.

The experiments made by us on 11 nonimmune individuals are embraced in the preceding table (III), which should be carefully studied. The mosquito used in all cases was *Culex fasciatus* Fabr.

It will be seen that we record 9 negative and 2 positive results. It is, we think, important to observe that of the 9 failures to infect, the time elapsing between the biting of the mosquito and the inoculation of the healthy subject varied in 7 cases from 2 to 8 days (Nos. 1, 2, 3, 5, 7, and 9) and in the remaining 2 from 10 to 13 days (Nos. 6 and 9).

Chart I. Yellow fever following, within the usual period of incubation, the bite of an infected mosquito (Culex fasciatus).



to this important theory are to be found in the articles designated as follows:

Estadistica de las Inoculaciones con mosquitos contaminados, etc., Reprint, Havana, 1891; *Fiebre Amarilla, Estudio Clinico Patologico y Etiologico*, Reprint, Havana, 1895; and *Yellow Fever Immunity—Modes of Propogation—Mosquito Theory*, 8th Congress of International Hygiene and Demography, Budapest, 1894.

His present views on this subject may be stated in his own language:

"First, reproduction of the disease, in a mild form, within 5 to 25 days after having applied contaminated mosquitos to susceptible subjects. Second, partial or complete immunity against yellow fever obtained even when no pathogenous manifestation had followed these inoculations." (*Medical Record*, Vol. 55, No. 21, May 27, 1899.)

Without reviewing the cases regarded as mild forms

Five individuals out of the nine who failed to show any result (Nos. 2, 3, 4, 5 and 6) were inoculated by mosquitos that had bitten very mild cases of yellow fever on the fifth day of the disease, and one individual by a mosquito that had bitten a mild case of yellow fever on the seventh day of the disease. (This latter patient was discharged from the hospital three days later.) To this fact may possibly be attributed the negative results. Of the remaining three negative cases (Nos. 7, 8 and 9) and which had been inoculated by mosquitos that had bitten severe cases of the disease, the interval between the bite and the inoculation varied from 2 to 6 days.

In the two cases (Nos. 6 and 8) where the interval was respectively 10 and 13 days, the inoculations had been made with mosquitos that had bitten very mild cases of yellow fever on the fifth day of the attack. No.

8 was also bitten by a mosquito which had been infected by a severe case of yellow fever 3 days before.

We refrain from commenting further at this time upon the 9 negative cases, preferring to record the results obtained rather than to indulge in speculation.

Of the 2 cases which we have recorded as positive in Table III, we now propose to speak at greater length.

CASE 10.—Dr. James Carroll, Acting Assistant Surgeon U. S. Army, a member of this board, was bitten at 2 P.M. August 27, 1900, by *Culex fasciatus*. This particular mosquito has bitten a *severe* case of yellow fever on the *second* day of the disease *12 days* before; a *mild* case of yellow fever, on the *first* day of the attack, *6 days* preceding; a *severe* case of yellow fever, on the *second* day of the attack *4 days* before and a *mild* case of yellow fever, on the *second* day of the attack *2 days* before inoculation.

Dr. Carroll remained well until the afternoon of the 29th, when he states that he felt tired and for this reason, when on a visit to Las Animas Hospital the same afternoon (29th) some time between 4 and 6 P.M., after visiting a few patients, he left the wards and waited outside on the porch, while his companions remained in the wards.

August 30. During the afternoon, although not feeling well, Dr. Carroll visited La Playa, about one and a half miles from Columbia Barracks, and took a sea-bath.

August 31. A.M. Dr. Carroll realized that he was sick and that he had fever, although he refrained from taking his temperature, but did visit the laboratory, distant about 140 yards, for the purpose of examining his blood for the malarial parasite. The examination was negative. During the afternoon he was compelled to take to his bed. At 7 P.M. temperature was 102° F. He had no headache or backache; only a sense of great lassitude. His eyes were injected and his face suffused.

September 1. At 7 A.M. his temperature was 102°. Blood was again carefully examined by Dr. Lazear with negative result. At 11 A.M. temperature was 102°.

The case having been diagnosed as one of yellow-fever, Dr. Carroll was at noon removed to the yellow fever wards. At 9 P.M. temperature was 102.8°, pulse 90; at 12 o'clock midnight temperature 103.4°, pulse 84.

On *September 2*, at 8 A.M., temperature was 103.6°, pulse 80. A trace of albumin was not found in the urine. The subsequent history of the case was one of severe yellow fever. *Jaundice* appeared on September 3.

The accompanying chart, No. 1, contains all of the necessary data.

The question of diagnosis having been clearly and easily established, it now becomes important to follow Dr. Carroll's movements for a period of ten days preceding the mosquito inoculation, and during the period elapsing from the bite of the insect until the commencement of the attack.

On August 21, 22, and 23, Dr. Carroll was at Columbia Barracks, outside of the epidemic zone. On August 24th he visited the autopsy-room of Military Hospital, No. 1, which is situated on Principe hill overlooking the city of Havana. He was present in the autopsy-room while an autopsy was made by Dr. Agramonte on a case of pernicious malarial fever. Dr. Carroll only took cultures from the blood and organs as the section proceeded. He was there about half an hour, and then returned to Columbia Barracks. Subsequent microscopic study of sections of the liver and spleen showed that the case autopsied on the 29th was really a case of pernicious malarial fever.

It should be stated that although cases of yellow fever are not admitted to Military Hospital No. 1., an English sea-captain had been admitted to its wards a few days before, whose case developed into one of yellow fever with fatal results, and autopsy had been held upon the body by Dr. Agramonte in this death room on the day preceeding Dr. Carroll's visit to it. According to Dr. Carroll, the room was by no means in a cleanly condition. As Dr. Carroll's visit to this room was made on August 24, and as he began to complain on August 29, about the average period of incubation of yellow fever, there is a possible chance for infection in this way. We must call attention, however, to the fact that Dr. Agramonte, whenever he performs an autopsy in this room, is always attended by a young soldier of the Hospital Corps, U. S. Army, who is detailed for that purpose, and whose duty it is to assist and afterwards to tend to the cleaning of the autopsy table. This soldier, a nonimmune American, was present when Dr. Carroll was there, and remained afterward to attend to his duties. He has not contracted yellow fever by his duties in this room from day to day. Our own experience would seem to accord with others, viz., that attendance upon autopsies and the handling of portions of organs of yellow-fever cases removed to the laboratory is unattended with danger. Certainly the three nonimmune members of this board, up to the time of these mosquito inoculations had, during the past three months, come in close contact with the dead bodies and organs of yellow-fever cases, freely handling and examining these organs, including the small intestine, even kept at thermostat temperature for 24 hours, without contracting the disease. We have, of course, never neglected to cleanse our hands with disinfectants.

Dr. Carroll, upon his visit to the before-mentioned dead-room, only used the platinum loop for taking cultures, and did not come in contact with the autopsy table.

The only other opportunity for infection in his case would appear to have been during his visit to Las Animas Hospital, situated in the suburbs of Havana, as yellow-fever patients are admitted in large numbers. We have already pointed out that Dr. Carroll was complaining of lassitude at the hour of his visit, which was about 50 hours after his inoculation with the contaminated mosquito. We have also called attention to the fact that he remained, for the greater part of his visit, outside of the hospital, on the piazza. This would appear to cast doubt upon his visit to Las Animas as the source of his infection.

We do not wish to be understood as unnecessarily seeking to lay too much emphasis upon the exclusion in this case of other sources of infection than the mosquito, as we fully appreciate that Dr. Carroll had been on two occasions within the epidemic zone during the week preceding his attack of yellow fever. His movements on these occasions we have already given.

We will again refer to Dr. Carroll's case, after we have given the history of Case No. 11, which we have designated as our second positive result.

CASE 11.—X. Y., aged 24, white, American, a resident of the military reservation of Columbia barracks, was bitten during the forenoon of August 31, 1900, by the *same mosquito* that had bitten Case 10 (Dr. Carroll) four days before, and which in the meantime had bitten a *mild* case of yellow fever (first day) *two* days before being applied to X. Y.

X. Y. was also bitten by a second mosquito that had been applied to a fatal case of yellow fever (second day) 12 days before; and to two mild cases (second day) 4 and 10 days previously; also, by a third mosquito that had bitten a fatal case of yellow fever (second day) 12 days before; a severe case first day) 2 days before, and three mild cases (first, second, and second day) 4, 6, and 10 days before; finally by a fourth mosquito that had bitten three severe cases of yellow fever (all on first day) 2, 4, and 8 days previously, and one mild case (second day) 6 days before. (*Vide* Table III)

It will be seen that X. Y. was bitten by *four* mosquitos, *two* of which had bitten *severe* (*fatal*) cases of yellow fever *12 days* previously; one of which had bitten a *severe* case (*second day*) *16 days* before and one which had bitten a *severe* case *8 days* before.

X. Y. began to experience a sense of dizziness and disinclination to work. This was just five days from the time of the mosquito inoculation; 24 hours later he was still dizzy and light-headed in attempting to move about. During the afternoon (sixth day after inoculation), he had chilly sensations, followed by fever and restlessness during the night.

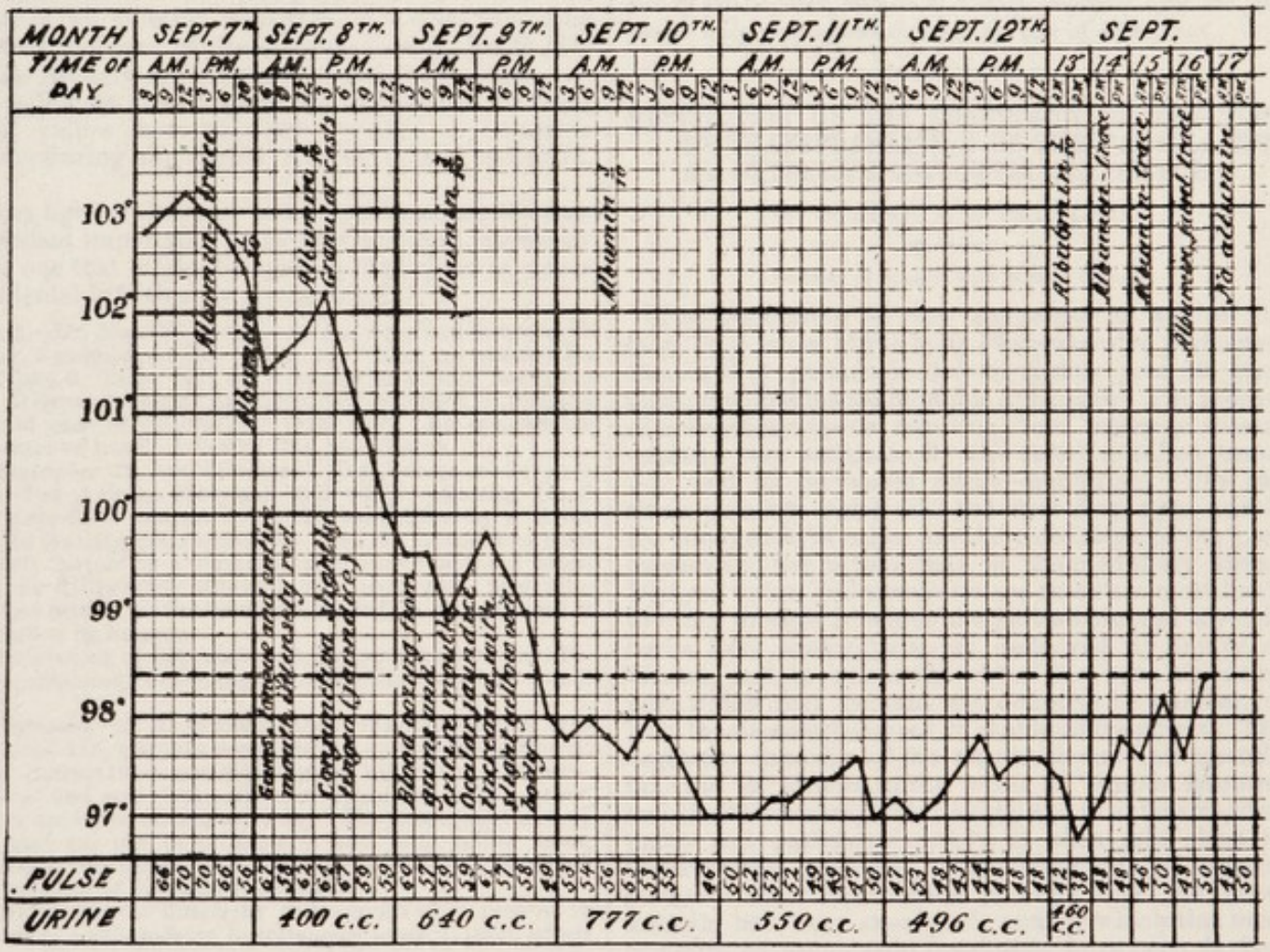
On the following day (seventh day after inoculation) 8 A.M., temperature was 102.8° F., his eyes were slightly injected, and his face suffused. The patient was removed to the yellow fever wards; at 9 A.M., temperature was 103° F., pulse 66. A trace of *albumin* was found in the urine during the afternoon (third day of the attack). This increased during the following days. The conjunctivæ were slightly *jaundiced* on the fourth day of the disease, which was more distinct and could be plainly seen on the anterior aspect of the chest on the fifth and following days. *Bleeding* from the gums was noticed on the third and subsequent days after admission. Repeated examinations of the blood failed to show any malarial parasites.

The course of the fever, the appearance of albumin in the urine, with jaundice and hemorrhage from the gums, together with the slow pulse, all pointed distinctly to the diagnosis of yellow fever. His attending physician, Dr. Roger P. Ames, U. S. A, an expert in the diagnosis and treatment of this disease, did not hesitate to diagnose X. Y's attack as one of "well pronounced yellow fever." Dr. Ames was not cognizant of the method of inoculation in this case. (*Vide* Chart II).

from May, 1900, the average monthly population of this station, including civilian employes, has been 1,400, nearly all of whom are young nonimmunes.

There have occurred amongst this nonimmune population from May 1 to October 13, 1900, 16 cases of yellow fever, all of which have been easily and readily traced to a visit to within the boundaries of the epidemic zone, except cases 10 and 11 of Table III., and one other case of which we shall presently speak. These cases have been distributed as follows:

Chart II. Yellow fever following, within the usual period of incubation, the bite of an infected mosquito (Culex fasciatus,



The diagnosis, therefore, not being in doubt, we must follow this patient's movement's during the 10 days preceding the bite of the mosquitos and from this time until 5 days later, when the attack began. It so happens that we can follow X. Y.'s movements for a much longer period. Fifty-seven days prior to his inoculation, he spent a day and night in the City of Havana; 16 days before the inoculation, he rode on horseback with 6 other nonimmunes a distance of about 1½ miles towards the seashore and returned to his dwelling, without in the meantime dismounting from his horse. From this time until his complete convalescence was established, he had remained within the immediate vicinity of his home. So that it may be positively stated that X. Y. had not absented himself from the Military Reservation of Columbia Barracks during a period of 57 days prior to his inoculation (with the exception above stated) nor between the date of his inoculation and the establishment of convalescence.

Let us now inquire whether the military reservation of Columbia Barracks is outside of the epidemic zone of yellow fever. To this we answer that since the commencement of the present epidemic of yellow fever in Havana, dating

May 24	1	July 29th	1
June 10th	1	August 11th	1
" 17th	1	" 12th	1
" 19th	2	" 16th	1
" 21st	1	" 31st	1
" 29th	1	September 7	1
July 9th	1	" 19	1
" 26th	1	Total,	16 cases.

Ten of these cases have occurred amongst an average monthly military population of 1,295 men and six cases in an average civilian population of 105. Whenever these cases have occurred, as soon as the patient has been removed to hospital, most careful measures of disinfection have been immediately carried out by a trained sanitary squad, under the personal supervision of a medical officer. These measures have consisted of destruction by fire of matresses, the disinfection of bedding and clothing with 1 to 500 bichlorid solution, and the application of the same solution freely to the ceiling, walls, and floors, by means of a force pump.

We repeat that no case has ever been connected with a

preceding case, but that the source of infection has been readily shown to have occurred during the individual's visit to Havana, 6 miles distant, or to some other nearer Cuban settlement.

We now invite attention to the fact that from August 17 to October 13, a period of 57 days, *only 3 cases of* yellow fever have occurred amongst this population of 1,400 nonimmune Americans, and we consider it very important to note that *2 of these had been bitten within 5 days of the commencement of their attacks, by contaminated mosquitos.*

Taken in connection with Case 11, in which we have been unable to find any other source of infection than the bite of an infected mosquito, five days preceding the attack, the case of Dr. Carroll (Case 10, Table III) becomes strongly confirmatory of the same origin.

We will now briefly give the history of the third case of yellow fever that has occurred at Columbia Barracks during the period August 17 to October 13, 1900.

In the light of Cases 10 and 11, we consider this case of sufficient importance to be here included, especially as it is one that might be possibly designated as a case of accidental infection by a mosquito.

CASE 3.—Dr. Jesse W. Lazear, Acting Assistant-Surgeon, U. S. Army, a member of this board, was bitten on August 16, 1900 (Case 3, Table III) by a mosquito (Culex fasciatus) which 10 days previously had been contaminated by biting a very mild case of yellow-fever (fifth day). No appreciable disturbance of health followed this inoculation.

On *September 13 1900* (*forenoon*), Dr. Lazear, while on a visit to Las Animas Hospital, and while collecting blood from yellow-fever patients for study, was bitten by a Culex mosquito (variety undetermined). As Dr. Lazear had been previously bitten by a contaminated insect without after-effects, he deliberately allowed this particular mosquito, which had settled on the back of his hand, to remain until it had satisfied its hunger.

On the evening of September 18, 5 days after the bite, Dr. Lazear complained of feeling "out of sorts," and had a chill at 8 P.M.

On *September 19*, 12 o'clock noon, his temperature was 10 24°, pulse 112; his eyes were injected and his face suffused; at 3 P.M. temperature was 103.4°, pulse 104; 6 P.M., temperature 103.8° and pulse 106; albumin appeared in the urine. Jaundice appeared on the third day. The subsequent history of this case was one of progressive and fatal yellow fever, the death of our much-lamented colleague having occurred on the evening of September 25, 1900.

As Dr. Lazear was bitten by a mosquito while present in the wards of a yellow-fever hospital, one must, at least, admit the possibility of this insect's contamination by a previous bite of a yellow-fever patient. This case of accidental infection therefore cannot fail to be of interest taken in connection with Cases 10 and 11.

For ourselves, we have been profoundly impressed with the mode of infection and with the results that followed the bite of the mosquito in these three cases. Our results would appear to throw new light on Carter's observations in Mississippi, as to the period required between the introduction of the first (infecting) case and the occurrence of secondary cases of yellow fever.

Since we here, for the first time, record a case in which a typical attack of yellow fever has followed the bite of an infected mosquito, within the usual period of incubation of the disease, and in which other sources of infection can be excluded, we feel confident that the publication of these observations must excite renewed interest in the mosquito-theory of the propagation of yellow fever, as first proposed by Finlay.

From the first part of our study of yellow fever, we draw the following conclusions:

1. The blood taken during life from the general venous circulation, on various days of the disease, in 18 cases of yellow fever, successively studied, has given negative results as regards the presence of B. icteroides.

2. Cultures taken from the blood and organs of 11 yellow-fever cadavers have also proved negative as regards the presence of this bacillus.

3. *Bacillus icteroides* (*Sanarelli*) *stands in no causative relation to yellow fever, but, when present, should be considered as a secondary invader in this disease.*

From the second part of our study of yellow fever, we draw the following conclusion:

The mosquito serves as the intermediate host for the parasite of yellow fever, and it is highly probable that the disease is only propagated through the bite of this insect.

RESTITUTION OF THE CONTINUITY OF THE TIBIA BY TRANSPLANTATION OF THE PATELLA INTO AN EXTENSIVE OSTEOMYELITIC DEFECT.

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THE restoration of the continuity of any of the large long bones of the body after extensive permanent traumatic or pathologic defects always presents great and sometimes insurmountable difficulties. The absence of osteogenetic tissue resulting from injury or disease explains very satisfactorily the defective callus formation and its inevitable result—nonunion. The two tissue elements which take the most important part in the production of callus are the osteoblasts of the periosteum and the myeloblasts of the medullary tissue. Delayed union and nonunion are therefore most liable to occur in cases in which the periosteum and myeloid tissue have been extensively destroyed by injury or disease, and in persons in whom the bone-producing cells which they contain are defective in number, or lack the necessary degree of reproductive power. The vegetative capacity of the tissues is not infrequently taxed to its utmost in the repair of simple fractures and limited osteomyelitic defects, and in extensive traumatic and pathologic defects it often falls short in restoring the continuity of the bone. It is in such instances that implantation of bone from the lower animals has been attempted, and for which the most complicated autoplastic operations have been devised and practised. The former procedure has been studied experimentally on a very large scale, the result of which, as well as a large clinical material which has accumulated, combine to demonstrate its utter uselessness in effecting bone-repair in man. Such operations have invariably proved a failure. Experimental research has established the fact that in the lower animals the transplantation of bone from one species to another is uniformly followed by a similar negative result. The transplantation of small pieces of bone from one human being to another has been performed repeatedly with success, but such opportunities are seldom presented, so that the surgeon has usually to rely on autotransplantation in furnishing the material for the repair of large bone-defects. In limited defects of the long bones the space between the fragments can be filled in with chips of bone removed with chisel and hammer from the surface of the bone ends which are implanted into the gutter between the vivified fragments. I have performed this operation in a number of cases with signal success. In the technic of the operation it is