A report on hemoglobinuric fever in the Canal Zone : a study of its etiology and treatment / by W.E. Deeks and W.M. James.

ISTHMIAN CANAL COMMISSION

A REPORT

ON

HEMOGLOBINURIC FEVER

IN THE

CANAL ZONE

A STUDY OF ITS
ETIOLOGY AND TREATMENT

BY

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LETTER OF TRANSMITTAL.

COL. W. C. GORGAS, Medical Corps, U. S. Army,
Chief Sanitary Officer, Isthmian Canal Commission,
Ancon, C. Z.

Sir:

We have the honor to submit herewith the report of our investigation into Hemoglobinuric Fever in the Canal Zone and its Etiology and Treatment; also a Synopsis of the Cases from which our data were derived, Appendix A; and a Discussion of the Various Hypotheses as to the Etiology of the Disease, based on our findings and the literature, Appendix B.

The conclusions reached by us are the result of deductions from our study, and were not determined by any preconceived opinions.

Very respectfully,

W. E. DEEKS,
W. M. JAMES.

ANCON HOSPITAL, *Canal Zone, April 2, 1911.*

INTRODUCTION.

In recent years there has been much discussion in regard to the etiology and treatment of hemoglobinuric fever, and most of the authorities agree that these are as yet unsolved problems in tropical medicine. The authors of this paper herewith submit evidence that bears on these problems, derived from an analysis of 230 cases of hemoglobinuric fever which occurred in Ancon Hospital. Many of these cases have been reported at other times by various physicians in the service of the Isthmian Canal Commission, particularly by Gorgas,[1] Brem,[2] and Connor,[3] and many of the conclusions reached by Connor in his careful study of the cases that occurred under his personal supervision, we have been able to confirm, as a result of our analysis of all of the cases that were treated in this hospital. However, we now present for the first time an extended study of the entire number of cases, and of collateral data as well.

That no misconception of the evidence presented may arise, we consider it well to state explicitly our view of the interpretation of the term "hemoglobinuric fever." It is well known that hemoglobin may appear in minute quantities in the urine, so that it can be detected by the guiacol-turpentine test, in several affections—notably scarlet fever, syphilis, estivo-autumnal malaria, septicemia due to the *streptococcus pyogenes*, and other diseases. In fact, any disease which produces a powerful hemolytic factor leads to a hemoglobinemia which may result in more or less hemoglobinuria.

Our conception of the disease cannot be expressed better than in the following excerpt from Marchiafava and Bignami.[4]

"The hemoglobinuric attack is a syndrome which is encountered not rarely, especially in hot climates, in the course of a malarial infection. The chief symptom of the attack is the emission of urine containing albumin and hemoglobin in greater or lesser quantity.

"All or nearly all authors place hemoglobinuria among the pernicious fevers. We maintain, however, that a special place should be reserved for hemoglobinuria among the clinical forms of the malarial infection. The pernicious fevers are grave estivo-autumnal malarial infections, the principal cause of which is to be found in the deterioration of the blood through the action of the very great number of parasites, the presence of which is easily demonstrable in the majority of

cases in which an examination of the blood is made; the relation between the intensity of the infection and the gravity of the symptom is usually quite evident. Hemoglobinuria, on the other hand, is a phenomenon which may be manifested during the course of an active infection as well as in one which has spent its course; it is intimately related to malaria, but there is no direct casual relation between this phenomenon and the malarial parasites, such as there is, for example, between the coma of a pernicious attack and the parasitic invasion of the capillary vessels of the brain. Nor do we believe that we can class together, as some have done, hemorrhagic malarial infections in general and hemoglobinuria. Indeed, cutaneous or mucous-membrane hemorrhage (nasal, intestinal, and the like) constitutes a symptom which may accompany grave malarial infections, while hemoglobinuria may develop in malarial subjects under the most varied conditions, as will appear in the course of our study. We may also add that, while the pathogenesis of the pernicious attacks has been in great measure cleared up by the recent parasitological investigations, the same cannot be said of hemoglobinuria, the pathogenesis of which is still not only obscure, but is also certainly more complex."

We have included in our analysis only those cases that in our opinion manifested the characteristic blackwater due to hemoglobinuria, with the presence of the granular detritus and the hemoglobin casts peculiar to the disease when a microscopical examination of the urine was made.

The onset of the blackwater is sudden and paroxysmal, and almost always is associated with a chill and more or less severe constitutional disturbances, such as fever, vomiting, abdominal distress, liver pains, and the appearance of jaundice more or less severe.

The resulting anemia depends upon the amount of blood destruction, and the prognosis upon the severity of the above-mentioned symptoms in conjunction with the kidney lesions. These latter vary from slight irritation to almost complete destruction of the epithelial tissues, thus leading to suppression. This condition, which almost always is fatal, will be referred to later.

A close relationship between malaria and hemoglobinuric fever has long been suspected, but whether that relationship is etiological or accidental has been a mooted point. The researches of Christophers and Bentley[5] into this problem have gone far toward establishing very strong presumptive evidence in favor of malaria as the necessary predisposing cause of hemoglobinuric fever. These writers, however, admit that every consideration must be given to the hypothesis of the specificity of some hitherto undiscovered organism.

At present, opinion as to the etiology of hemoglobinuric fever is divided between those who hold that malaria is directly or indirectly the prime factor, and those who assert that some organism related to the piroplasmata is responsible. Also, the relationship of hemoglobinuria to the administration of quinine has been, and still is, a point at issue. The data that we have collected will throw light on all these propositions.

A review of the literature of hemoglobinuric fever shows that many of the arguments advanced in favor of the different etiological hypotheses lack the confirmation of extended observation. A large number of cases has been recorded, but no single series of these has been observed over a prolonged period under control conditions.

The concurrence of malaria and hemoglobinuric fever among a certain class in a given locality has also been noted frequently, but there are few, if any, observations extending over a period of years that embrace all classes of people who reside in the same locality. The epidemiology of concurrent malaria and hemoglobinuric fever has been studied, but there has been no evidence adduced as to the relationship between hemoglobinuric fever and other concurrent diseases; and while it has been possible to compare the seasonal relationship between malaria and hemoglobinuria, there is no evidence bearing on a similar relationship between these two, and other diseases endemic in the same locality. In nearly all cases of hemoglobinuric fever there is a history of previous "fever," and such fever for the most part has been assumed to be malaria. In regions where malaria is epidemic, it is probable that such an assumption has been correct, but positive evidence of this correctness has been lacking.

The conditions on the Canal Zone are such as to furnish data of considerable reliability as a basis for an investigation into all these factors concerned in the etiology of hemoglobinuric fever. For over six years many individuals of three distinct races have been working in a country in which malaria is endemic at all seasons of the year, and each summer appears as an epidemic. But although this disease is responsible for a very large proportion of the sick rate, others occur in numbers sufficient to form a reliable basis for a comparison of all their etiological factors with those of malaria and hemoglobinuric fever. A large percentage of all diseases is under hospital supervision, and definite hospital records of previous admissions can often be substituted for personal histories and empirical experience. We do not claim that every diagnosis has been correctly made, and for reasons which presently will be apparent, the hospital records are not altogether complete; but abundant data in regard to the climatic, epidemiological,

and other etiological factors in the development of hemoglobinuric fever, malaria, and other diseases can be adduced, data which we believe to be substantially accurate, and certainly, as far as we have been able to ascertain, more complete than those hitherto reported from any one locality in a given period.

In undertaking this study of the factors concerned in the etiology of hemoglobinuric fever, we have been neither guided nor governed by any preconceived hypothesis. Our object has been solely to collect data, and to find if any definite conclusions could be induced from them.

That these data are reliable, a study of the following charts and tables will show. There is a substantial uniformity in the results that have been obtained. When it is considered that these results depend upon observations and diagnoses made by many physicians in the period from January, 1905, to September, 1910, the uniformity that is manifested at all times is in itself a proof of the correctness of the data.

We do not believe that any mistakes were made in the diagnosis of the 230 cases of hemoglobinuric fever in this series. While it is true that a microscopical examination of the urine was not made in every case, in the cases in which such a urinary examination was made, the characteristic findings in hemoglobinuria were always present. Moreover, every fatal case, so far as we have been able to ascertain, was correctly diagnosed before death, as the autopsy findings subsequently proved.

In order to make this study as complete as possible, we shall discuss the subject of our paper under the following heads, a consideration of which we believe to be necessary to a comprehension of the factors that enter into the problem of the etiology of hemoglobinuric fever in the Canal Zone:

I. The influence of the topography of the Canal Zone on the prevalence of malaria.

II. The racial distribution of the employees of the Canal Commission and their manner of living.

III. The prevalence of malaria in the Canal Zone.

IV. The distribution of malaria among the employees of the Commission.

V. The relationship between malaria and hemoglobinuric fever.

VI. Length of residence in a malarial country as a factor in the etiology of hemoglobinuric fever.

VII. An hypothesis as to the etiology of hemoglobinuric fever; the part played by quinine in the production of the disease; and the treatment of the malady.

I.

THE INFLUENCE ON THE TOPOGRAPHY OF THE CANAL ZONE ON THE PREVALENCE OF MALARIA.

The Canal Zone is a strip of land ten miles wide and forty-five miles long; the width being a distance of five miles on each side of the line of the Canal; the length, the line of the Canal from the Atlantic to the Pacific. The Chagres River joins the line of the Canal at a right angle about two thirds of the distance from the Atlantic to the Pacific, and follows this line to five miles from the Atlantic, where the river diverges, and empties into the ocean about six miles from the Atlantic end of the Canal. At the north end of the Canal is the city of Colon; at the south end, the city of Panama. Over the entire Canal Zone, and these two cities, the Government of the United States has the right of sanitary regulation.

The coast on the Atlantic side of the Canal Zone is made up of low alluvial flats, with many swamps and lagoons that extend inland for several miles. On the Pacific side the land is more elevated, but the high tides that prevail there make swamps whenever an inlet is afforded. In the interior are numerous hills and valleys, and through many of the latter tributaries of the Chagres make their way. In the valleys where there are no rivers, the heavy rainfall that prevails during most of the year produces pools and swamps, which are fed during the interval between rains by countless springs. Over all the country, when not removed by the hand of man, is a dense growth of jungle, whose heavy shade keeps the ground moist; and the tangled roots of the abundant vegetation favor the retention of the surface water in little ponds.

Before the Government of the United States took possession of this territory, the "Isthmus," as is commonly known, was a synonym for the habitat of all varieties of pernicious malaria, and yellow fever was a potent factor in the mortality rate. Hemoglobinuric fever was common and fatal among aliens and was known to the residents as "Chagres fever;" although sometimes this term was applied also to the cerebral form of pernicious malaria. It does not appear that other diseases were more common than elsewhere in the tropics. What is of importance is that the topography of the Canal Zone, and the prevailing climatological conditions in it, have made the country in the past an ideal breeding ground for the insect hosts of malaria and yellow fever; and for the future, solely by the most rigid enforcement of sanitary measures can these diseases be kept to a minimum.

With the advent of sanitation, in every sense that the word implies,

the former unhealthiness of the Canal Zone has been abated greatly. We say abated, for the conditions that cause unhealthiness are latent, and need no more than a relaxation of sanitary vigilance to bring about a return to former conditions. Places that favor the accumulation of filth and the propagation of mosquitoes have been eliminated from the cities of Panama and Colon; along the line of the Canal the jungle has been cleared; the pools and swamps in and about the Zone towns have been drained, and these towns are kept clean and dry; and an effective water supply and a sewerage system have been installed throughout the entire Canal Zone, and in the cities of Panama and Colon. The efficiency of such measures in promoting the health of the entire population, natives as well as aliens, is amply shown by a comparison of the present rates of mortality and sickness with those of the past, and also with those of more favorably located communities.

Notwithstanding the improved conditions of sanitation, malaria still manifests itself, and is decidedly the prevailing factor in the sick rate. This is due to conditions under which many of the laborers live; the constant need of new drainage, owing to the progress of the work; and the filling of the artificial lakes that are to become part of the waterway. It is our purpose to treat with the intimate relation which obtains between the prevalence of this malaria and that of hemoglobinuric fever; and to adduce the data which we have collected, to demonstrate whether the latter disease is dependent on malaria as a predisposing factor, or if it be of independent origin.

II.

THE RACIAL DISTRIBUTION OF THE EMPLOYEES OF THE CANAL COMMISSION AND THEIR MANNER OF LIVING.

Since the American occupation of the Canal Zone its inhabitants may be divided into two groups: the one composed of those who work for the Isthmian Canal Commission (referred to hereafter as the Commission); the other made up of natives of the country, with such immigrants as have been attracted by the increase in business. Upon the number and racial distribution of the persons included in the first group are based the data set forth subsequently. This group comprises three distinct races: the American, which is Anglo-Saxon in origin; the European, made up mostly of Spanish and Italian laborers, with a considerable preponderance of Spaniards; and the West Indian negro, coming in greater part from the islands of Jamaica and Barbados. The numerical ratio between these races, the time of residence in

this country of the individuals who comprise them, and the relative susceptibility of each race to disease must be kept constantly in mind, for these factors render complicated any attempt to compile reliable statistics that pertain to the total distribution of disease in this country. Two sets of figures are necessary, the one showing the total disease for all races, the other, totals for the separate races. And as far as possible, such figures have been obtained. The second group, that of natives and non-employees, is of importance only in so far as it acts as a means of conveyance of disease to the first; the prevalence of disease in it does not effect to any appreciable extent the figures used in the subsequent tables and charts.

These three races are natives of localities where, broadly speaking, malaria does not prevail to any great degree. The Italians are mostly from the north of Italy; the Spaniards from the north of Spain; and Jamaica is not badly infected with malaria, while Barbados is said to be free from endemic cases. Such immunity against malaria, as is present during the earlier part of a residence here, is therefore racial and not acquired. How much of such immunity exists will be shown later. It is sufficient at present to say that Americans and Europeans are alike susceptible to the disease, while the negro possesses a partial racial immunity.

The same general conditions of sanitation, such as drainage, water supply, sites from which grass and underbrush are removed, and inspection of quarters by the Department of Sanitation, obtain equally among the three races. But it is impossible to equalize the racial appreciation of such important individual sanitary measures as care of screening, predisposition to cleanliness, prophylactic use of quinine, and personal regard for health. These latter vary greatly among the races, and are directly responsible for the prevalence of malaria in proportion to racial susceptibility to the disease.

The American employees of the Commission are the skilled mechanics, clerks, foremen, responsible railroad employees, civil engineers, physicians, and nurses, and others who fill the many positions connected with the executive, constructive, and administrative functions of the Canal building. Since January, 1906, almost without exception, they have lived in houses provided by the Commission. These houses are equipped with screen doors, screened windows and verandahs, and are well kept by their inhabitants, any defects in the screening or the plumbing being reported promptly. Among these employees the use of quinine at the first onset of fever is universal, and prompt consultation with the nearest Commission physician is the rule. Each employee is granted six weeks' vacation, with pay, for twelve months' service, and

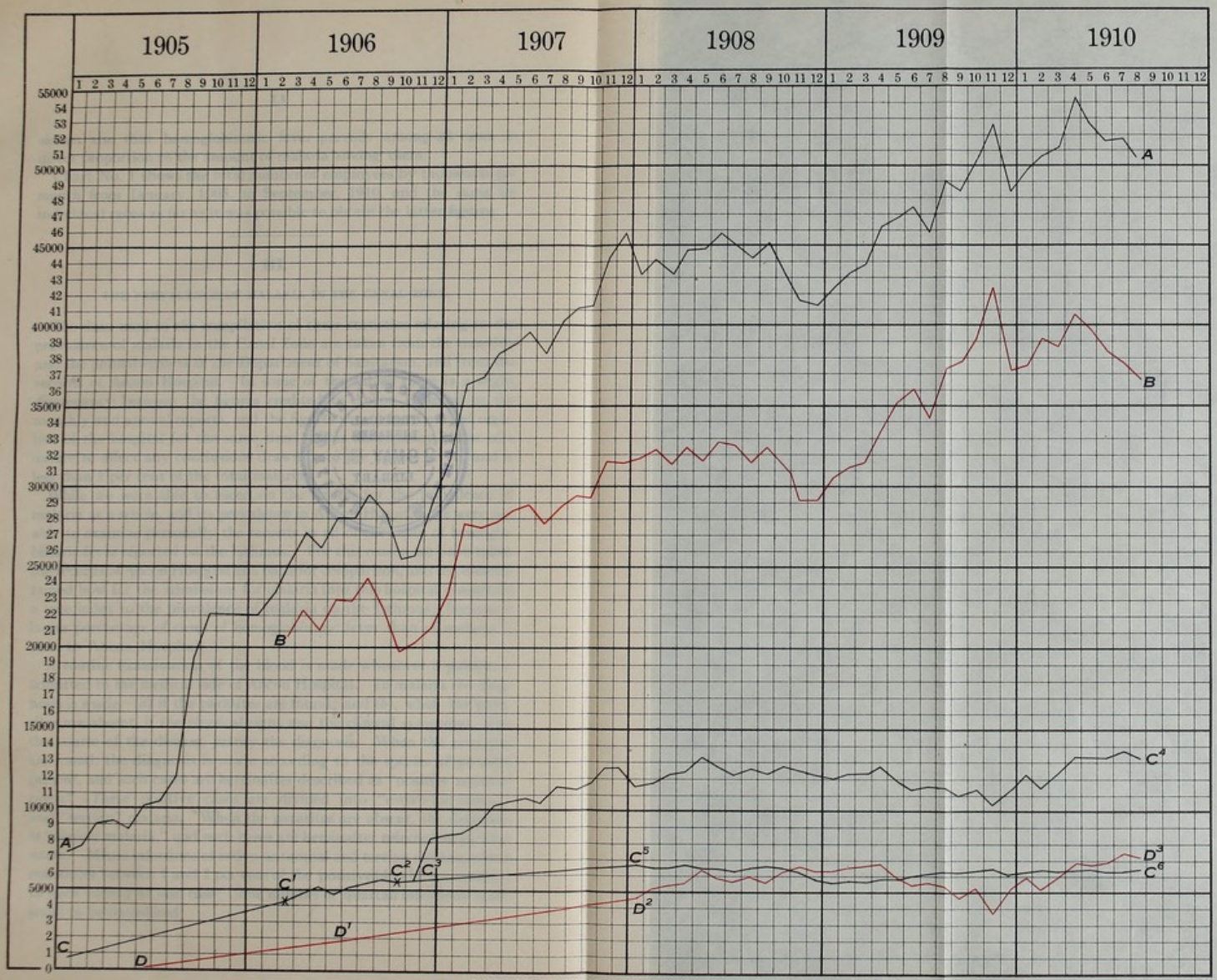
this vacation must be taken in the States or in a malaria-free country. If a bachelor is too ill to work he is sent to the Commission hospital at Ancon or Colon, and most married men, who, by reason of sickness, are unfit for duty, also avail themselves of the hospital service. A sanitarium for convalescent patients is maintained in the malaria-free island of Taboga, in the Gulf of Panama. The Americans do not frequent at night the native quarters in the Zone towns; do not expose themselves unnecessarily to malarial infection; and of their own initiative aid greatly in preserving their health and in keeping sanitary regulations. Classed with Americans, who are also called "gold" employees, are those white men of other nationalities who hold positions entitling them to similar quarters and treatment.

Those of the European laborers who so desire live in well kept and carefully screened barracks, and for families, screened quarters are provided. But no amount of advice seems to be effective in securing among them individual prophylaxis against disease. Every sanitary regulation needs to be rigidly enforced. They often prefer to sleep in hammocks or even on the ground under their quarters or in other places. They mingle freely at night with the natives, and cannot be kept indoors. As a race they are not addicted to strong liquor, but we are informed by Mr. LePrince, the Chief Sanitary Inspector, that an increase in malaria among them is always accompanied by an excessive consumption of rum, and very inferior rum, in the belief that the drink is an efficient medicine. They are indifferent to personal hygiene, and equally indifferent to their state of health until illness compels them to seek aid.

As elsewhere in the world, the enforcement of sanitation among the negroes is a gigantic task. A small percentage only of this race lives in the free quarters provided by the Commission. The rest either prefer cheap lodging houses, where they huddle together at night like so many sheep, or else they live in straw-thatched huts after the manner of the natives. The European laborer, though he mingles with the natives, does not live with them, but the negro lives and sleeps in their houses, exposing himself constantly to the endemic malarial infection there prevalent. As long as he has a roof over his head and a yam or two to eat he is content, and his ideal of personal hygiene is on a par with his conception of marital fidelity.

The conditions under which the three races live should be noted carefully, for they have a direct bearing on the distribution of malaria and hemoglobinuric fever. It will be shown that malaria is less frequent among the negroes, despite their many opportunities to acquire it, than among either of the other two races. And it will be

CHART No. 1

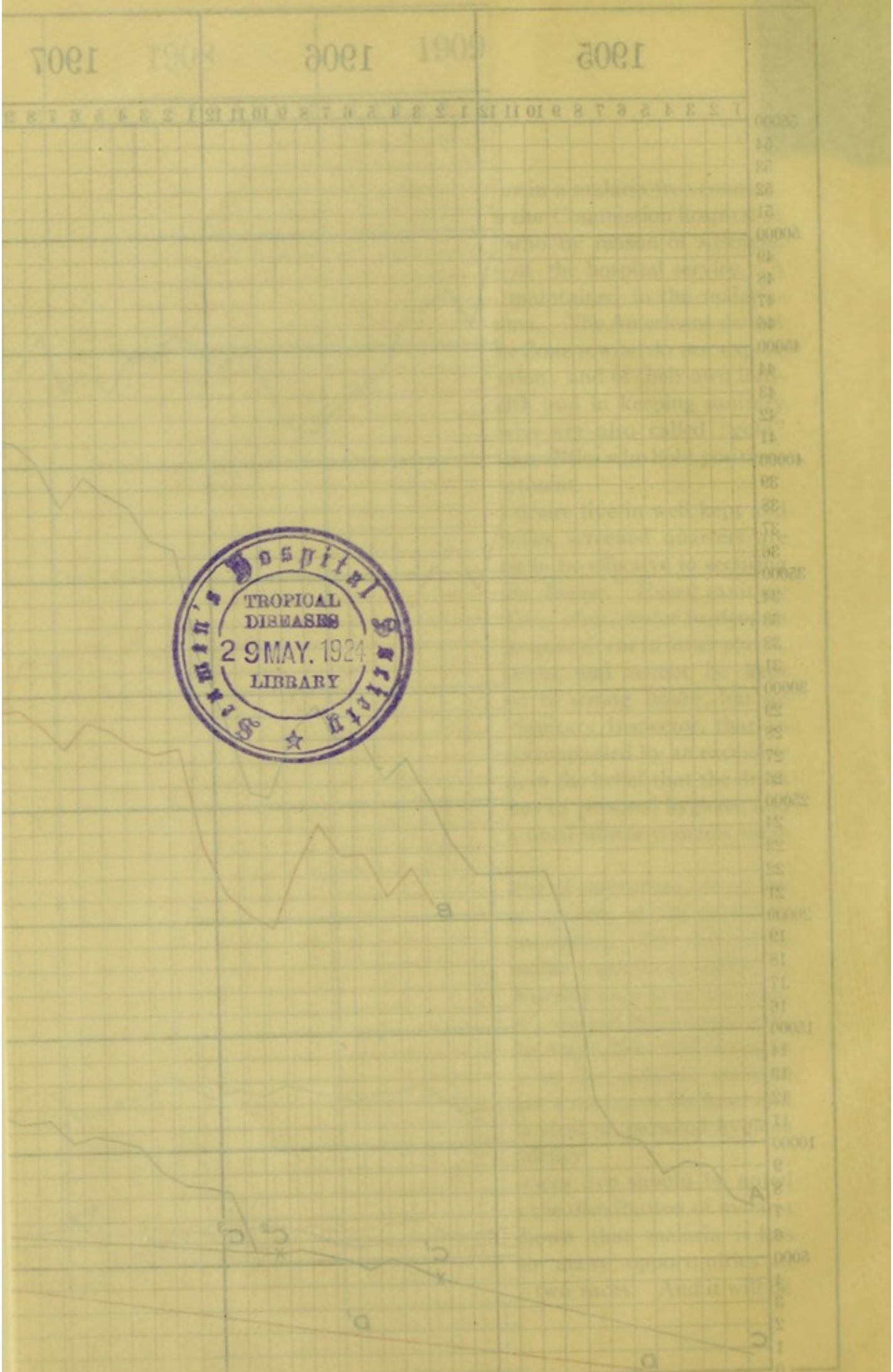


EMPLOYEES OF THE CANAL COMMISSION.

A-A, Total of employees.
B-B, Number of negro employees.
C-C⁴, Number of white employees.

C-C¹, Number of American employees.
C¹-C², Number of white employees.
C³-C⁴, Number of white employees.

C²-C³-C⁵, Number of American employees.
D¹, Date when European laborers were first employed.
D-D³, Number of European employees.



shown also that hemoglobinuric fever prevails among all races in direct proportion to the amount of malaria among them.

Chart No. 1 shows the total number of employees by thousands per month from January, 1905, to September, 1910, and the same for individual races as far as it was possible to obtain the latter figures.

III.

THE PREVALENCE OF MALARIA IN THE CANAL ZONE.

The data used in the compilation of these statistics relating to the prevalence of malaria in the Canal Zone are taken from the monthly and the annual reports of the Department of Sanitation, and from the records of Ancon Hospital. In some of the tables there is a slight discrepancy between the figures credited to Ancon Hospital in the monthly and annual reports, and the figures shown by the ward registers of the hospital for the same time. This discrepancy is not of a nature to affect any conclusions drawn from the figures given, and is less than 1 per cent of the total malaria.

While we were able to ascertain the figures for the prevalence of malaria as a whole, and its prevalence in Ancon Hospital, we were not able to examine personally the records in all of the cases of hemoglobinuric fever reported on the Isthmus. For this reason we have taken the records of Ancon Hospital as a basis for comparison, and have ascertained how far the admissions for malaria into this hospital constitute a true index to the prevalence of malaria on the Isthmus; because a larger percentage of cases of hemoglobinuric fever than of malaria is sent to Ancon Hospital.

A routine examination of the blood is made whenever a patient is admitted to the medical side of Ancon Hospital. In malaria the diagnosis is made: (*a*) if the parasites are found; and (*b*), when the parasites are absent, if the physical signs and the clinical symptoms, with the course of the disease, justify the diagnosis. When the parasites are found, the diagnosis is made according to the species of parasite present, and such cases are hereinafter described as "positive malarial cases." These positive cases are divided into "estivo-autumnal," and "tertian" malaria. When the parasites are absent, the diagnosis is "clinical malaria," and such cases are hereinafter referred to by that name. Mixed infections of estivo-autumnal and tertian malaria, which constitute between 1 and 2 per cent of the positive bloods, are credited to each variety as one case. The number of quartan infections is too small to be considered.

TABLE I.—*Showing the total number of cases of malaria discharged per year from Ancon Hospital; the number of these cases per year that were positive infections; the percentage of each variety of malaria in both the total and positive cases; and the estimated percentage of the varieties of malaria in the total amount of the disease.*

Column 1.	Column 2.		Column 3.				Column 4.		Column 5.	
	Number of cases of malaria per year discharged from Ancon Hospital.		Percentage of the varieties of malaria according to the figures given in Column 2, *A*.				Percentage of the varieties of malaria in the positive bloods in Column 2, *B*.		Percentage of the varieties of malaria estimated for the total number of cases per year.	
Year.	*A*. Total number of cases discharged.	*B*. Number of these cases positive.	Estivo-autumnal.	Tertian.	Positive.	Clinical.	Estivo-autumnal.	Tertian.	Estivo-autumnal.	Tertian.
1905	4,523	2,850	51	12	63	37	81	19	85	15
1906	7,561	3,679	38	12	50	50	78	22	83	17
1907	6,505	3,590	36	20	56	44	64	36	68	32
1908	8,192	4,809	42	17	59	41	70	30	74	26
1909	8,837	5,168	42	16	58	42	70	30	75	25
1910—January to September	5,310	3,314	51	11	62	38	82	18	86	14
Total number of cases and average per cent, 1905–10	40,928	23,410	43	15	58	42	74	26	78	22

Table I shows the number of cases of malaria per annum discharged from Ancon Hospital from January, 1905, to September, 1910. The records of the hospital show discharges per month, not admissions; but since the average stay of a malaria patient is seven days, the table is approximately correct if it is also used to denote admissions. In column 2 (*a*) of this table are the figures showing the total number of cases per annum, discharged with a diagnosis of malaria; in (*b*), the number of these cases that were positive. In column 3, the percentage of each variety of malaria is given. In column 4 are the percentages of estivo-autumnal and of tertian malaria in the positive cases. In column 5 are estimated percentages of these two varieties as applied to the total number of cases.

The average percentage of estivo-autumnal malaria as shown in the positive cases, is 74. We believe that this is too low, if taken as the percentage of this variety in all cases of malaria. The true percentage of estivo-autumnal infection is at least 80. An explanation of the figures in this table will show why we regard the latter figure as preferable.

The average proportion of positive to clinical malaria is 58:42. Forty-two per cent of clinical cases may seem too high, and possibly suggests that many cases diagnosed as clinical malaria might have been due to other causes. We do not deny that occasionally such a mistake might have been made, but we do not believe that the error was common. There are several very good reasons why the percentage of clinical malaria is not lower. Among the Americans admitted to the hospital the percentage of clinical malaria is always very high, as will be shown later, for the reason that but few of these patients are admitted until they have tried to cure themselves with quinine at home. Prior to admission, a very considerable proportion of Europeans and negroes had been from one to four days in the sick camps, and while there had received liberal doses of quinine. In many of the cases but one blood examination was made; for at times, in some of the medical wards, as many as forty patients a day were admitted, and unless a patient was seriously ill, there was not time to make a more extended blood examination. If all of these facts are considered, a rate of 58 per cent of positive bloods is a very good average.

One of the objections urged against a diagnosis of clinical malaria is that in some of the cases so diagnosed no fever is present after admission. Daily we see patients in whose blood either estivo-autumnal or tertian parasites are found, and who have no rise in temperature after admission. If, in such patients, fever subsequent to admission is absent, certainly a similar absence of fever, in patients whose bloods

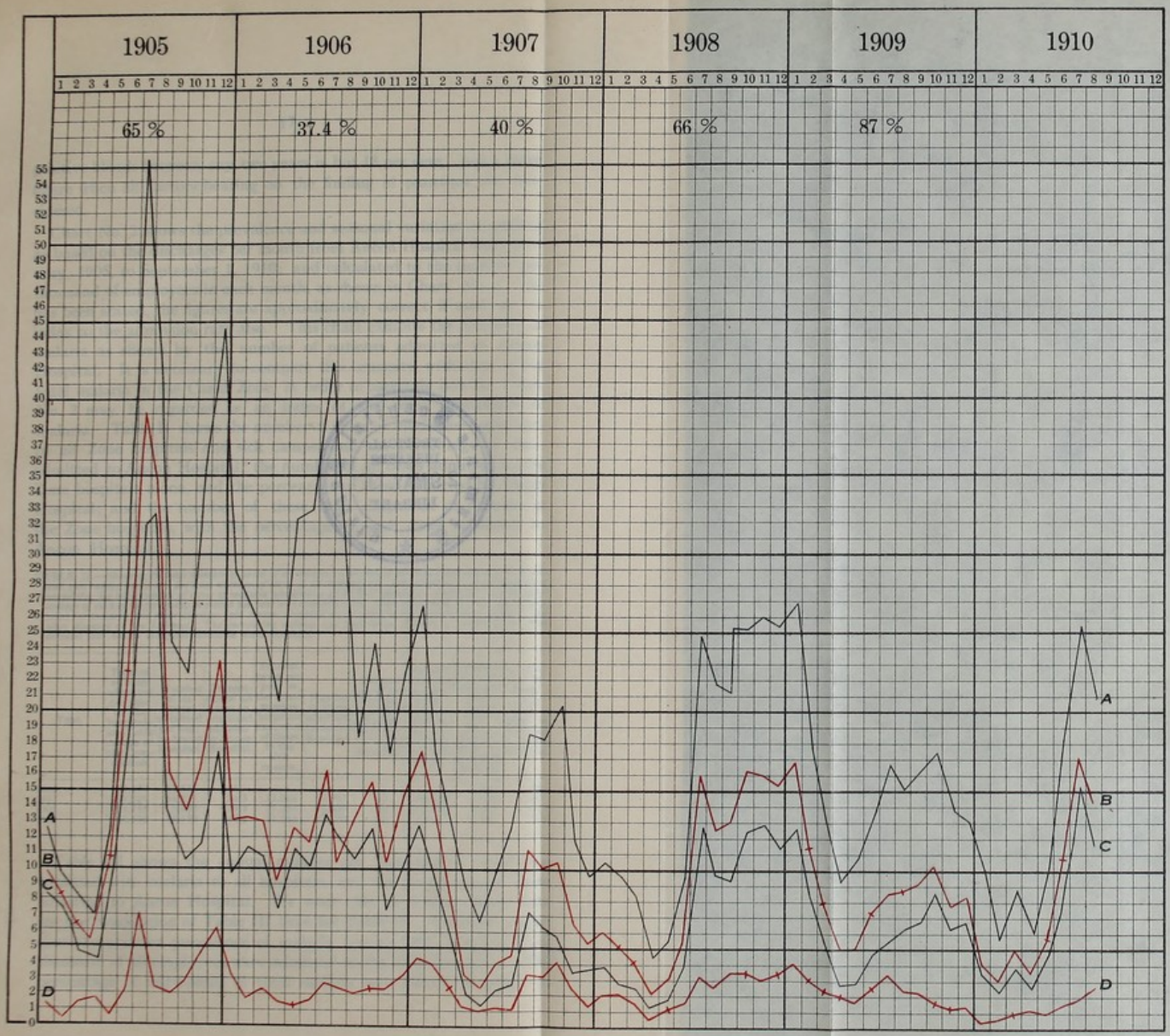
are negative but in whom other signs and symptoms point to a malarial infection, is no bar to a diagnosis of malaria.

It is in these clinical cases that a relatively larger percentage of estivo-autumnal malaria obtains than in the positive. In estivo-autumnal malaria there is frequently a time in the cycle of the parasites when none of them are present in the peripheral blood.* Often there is fever when no parasites can be found. The young estivo-autumnal parasite does not stain as readily as does the tertian, is smaller, and so is more easily overlooked. In tertain malaria the parasite is always present in the peripheral blood when there is fever, the gametes are more abundant, and are easily found. Also, tertian malaria is more amenable to quinine, and tends more frequently to spontaneous cure, so that there are relatively fewer admissions due to it than to estivo-autumnal malaria in the clinical cases. For these reasons, in estimating the percentage of the two varieties of malaria, we have added 10 per cent to the estivo-autumnal percentage in the positive cases, and have calculated the percentage of estivo-autumnal malaria in the clinical cases in the augmented proportion. This gives the estimated proportion, averaged for five and one-half years, of estivo-autumnal to tertian malaria as 78:22; Table I, column 5. This percentage of 78 we regard as a minimum, and, as we have stated previously, the true proportion of the two varieties is about 80:20.

That the figures given in Table I are approximately accurate is demonstrated by the comparatively small variation among them. The data on which these figures are based extend over a period of nearly six years. The diagnoses and blood examinations were made by many different physicians. Since 1906 we have depended on Wright's and Hastings' stains for blood work; at times the quality of these stains has not been good, and often the slides were examined by men who had not acquired a very definite knowledge of the parasites. In the year 1907, in which the variation in the percentages in Table I from the arithmetical average was greatest, the percentage of malarial cases admitted to Ancon Hospital, compared with that of the total malaria in the Canal Zone, was smallest. This means that such malarial patients as were admitted for that year had been treated with quinine before admission; a circumstance that always increases the positive tertian percentage and lowers the positive estivo-autumnal, because as a rule only those tertian cases who are quite ill come to the hospital. Including this year (1907) the greatest variation in the

*This statement refers to our routine examination, not to the "thick film" method.

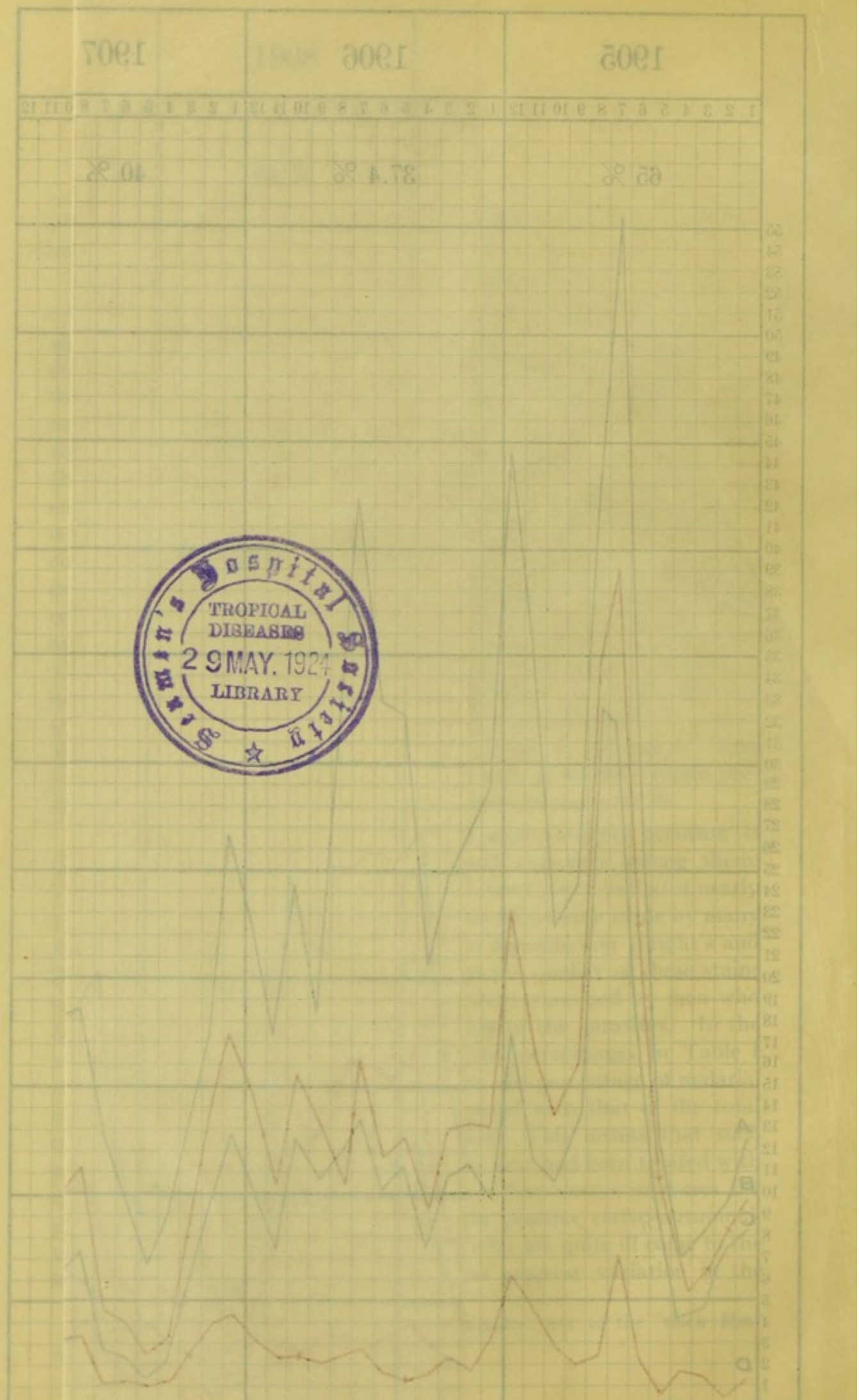
CHART No. 2



PREVALENCE OF MALARIA IN ANCON HOSPITAL.

A-A, Total malaria.
B-B, Positive cases.
The percentage figures refer to the proportion of the total malaria admitted to Ancon Hospital.

C-C, Estivo-autumnal malaria.
D-D, Tertian malaria.



positive bloods between any two years is but 18 per cent; not a large figure when all factors bearing on the finding of parasites are considered.

Chart No. 2 shows the prevalence and seasonal variation of malaria as based on the discharges per month from Ancon Hospital from January, 1905, to September 1, 1910; and calculated to the number per thousand of employees in each month, as shown in Chart No. 1. As has been stated, the figures are approximately correct if used as an index to the admission rate also. This chart exhibits the intensity of malaria as shown by the number of patients admitted to Ancon Hospital. It is necessary to compare this intensity with that of the total malaria in the Canal Zone, in order to ascertain how far Chart No. 2 may be regarded as an index of the total prevalence of malaria. Table II shows the number of cases of all diseases admitted to all Zone hospitals and sick camps, and the percentage of these admitted to Ancon Hospital; the number of all cases admitted to the Zone hospitals alone, and the percentage of these admitted to Ancon Hospital; and the number of these cases diagnosed as malaria in the Zone hospitals, with the percentage of such cases admitted to Ancon Hospital.

TABLE II.—*Showing the total number of cases of all diseases admitted to all of the Commission hospitals and sick camps per year; the total number of cases of all diseases per year admitted to the Commission hospitals; the total number of cases of malaria admitted to all of the Commission hospitals; and the percentage of each of the foregoing admitted per year to Ancon Hospital. This table shows how far the admissions for malaria and other diseases into Ancon Hospital is an index to the prevalence of malaria and other diseases on the Isthmus. The increasing number and percentage of cases of malaria and other diseases into Ancon Hospital should be noted carefully.*

Year.	Total of all cases admitted per year to the hospitals and sick camps of the Commission.	Number of all cases admitted per year to Ancon Hospital.	Percentage of all cases as admitted per year to Ancon Hospital.	Total of cases per year in the Commission hospitals exclusive of those in the sick camps.	Number of these admitted to Ancon Hospital.	Percentage of all hospital cases admitted per year to Ancon Hospital.	Number of cases per year diagnosed as malaria in the Commission hospitals.	Number of these cases per year that were diagnosed as malaria in Ancon Hospital.	Percentage of these cases diagnosed as malaria in Ancon Hospital.
1906.....	30,490	12,535	41	.....	.....	.....	.....	7,561	34.7
1907.....	58,521	14,237	24.3	32,063	14,237	44	16,429	6,505	40
1908.....	53,755	15,880	29.3	27,251	15,880	58.3	12,290	8,192	66.6
1909.....	46,593	18,750	40.2	27,184	18,750	68	10,071	8,837	87.6

Table III shows the annual number per thousand of employees admitted with malaria to all hospitals, and the percentage of these admitted to Ancon Hospital. We were able to procure more data for the compilation of Table III than for Table II. Table III shows that the greatest prevalence of malaria was in 1906, when 821 per thousand of all employees were admitted to the Zone hospitals. The percentage of admissions of total malaria into Ancon Hospital, as

shown in Table III, should be kept carefully in mind in examining Chart No. 2.

TABLE III.—*Showing the annual average of the total number of employees of the Commission per year; the number of admissions due to malaria per thousand of this annual average to all Commission hospitals; the various annual percentages of the maximum rate per thousand of admissions, which maximum occurred in 1906; the number of admissions due to malaria per thousand of the annual average to Ancon Hospital, and the percentage of these admissions of the total malarial admissions.*

Year	Average number of employees per year.	Number of admissions per thousand per year, due to malaria, into all hospitals.	Per cent per year of the 1906 maximum of admissions per thousand in all hospitals.	Number of admissions per thousand per year, due to malaria, into Ancon Hospital	Per cent of the total number of cases of malaria, per thousand employees per year, admitted to Ancon Hospital.
1905	13,331	514	61	339	65
1906	26,500	821	100	285	34.7
1907	39,343	424	52	165	40
1908	43,890	282	34	186	66
1909	47,167	215	26	187	87

We have not added to the figures and curves in Chart No. 2 the difference between the number of cases of malaria admitted to Ancon Hospital and the total number of cases of malaria, in order to show graphically the variation of the malaria rate for the Canal Zone; because a larger percentage of malarial cases is admitted to Ancon Hospital when the malaria rate is high than when it is low: for example, in 1907, 40 per cent of the malarial cases in the Zone hospitals was admitted to Ancon; but it is probable that a lower percentage than 40 was admitted in March, April, and May, and a higher in July, August, September, and October.

Chart No. 2, and Tables II and III, show that since 1906 malaria has steadily declined in prevalence. A well marked seasonal variation is plainly evident. This variation is somewhat exaggerated by the increased percentage of admissions when the malarial rate for the Zone is high, and the decreased percentage when the rate is low. The seasonal variations correspond exactly to the duration of the wet and of the dry seasons, the curve being high in the former and low in the latter.

This seasonal variation is due in a very great degree to the fluctuations in the amount of estivo-autumnal malaria. The difference between the curve of the total malaria and that of positive cases, in Chart No. 2, represents the amount of clinical malaria. At least 80 per cent of this clinical malaria is estivo-autumnal, and if this 80 per cent were added to the curve representing the prevalence of estivo-autumnal malaria shown by the positive blood examinations, the seasonal variation in this kind of malaria would be much more evident than the chart indicates. Even if the positive cases only are

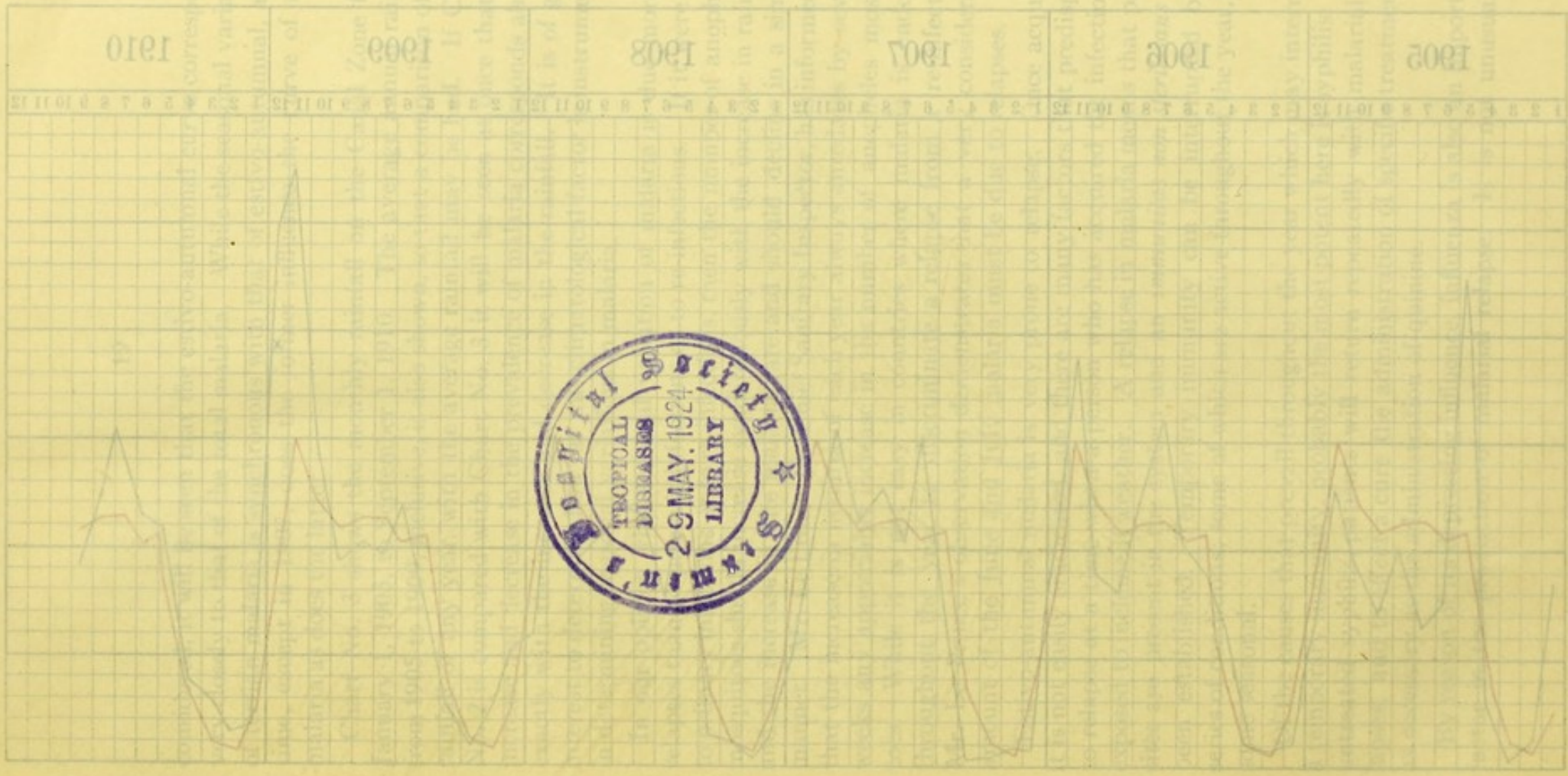
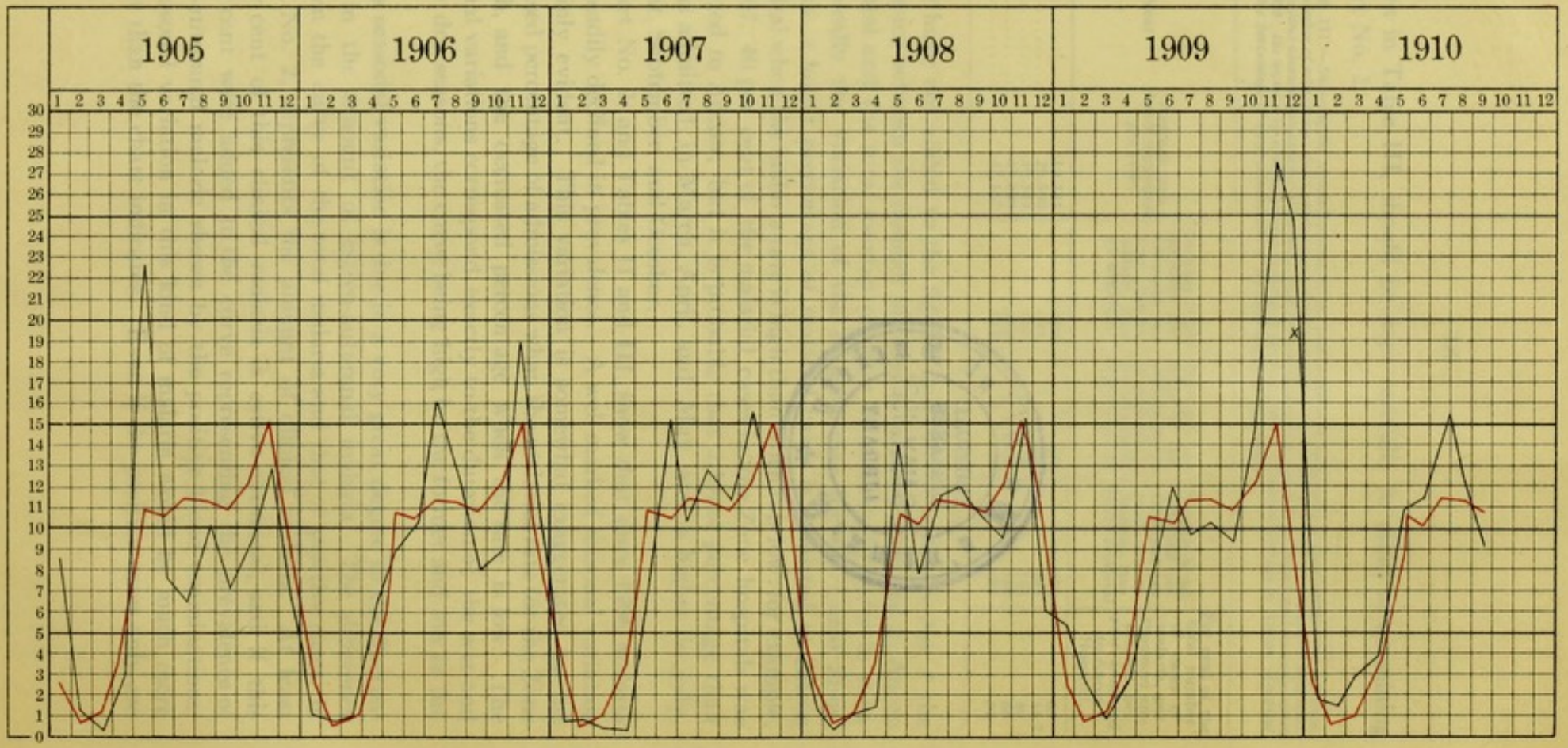


CHART No. 3



RAINFALL ON THE CANAL ZONE IN INCHES.

Black. Monthly rainfall.

Red. Annual average rainfall.

considered, it will be seen that the estivo-autumnal curve corresponds very closely to that of the total malaria. While the seasonal variation of tertian malaria is synchronous with that of estivo-autumnal, at no time, except in 1907, does the former influence the curve of total malaria as does the latter.

Chart No. 3 shows the monthly rainfall on the Canal Zone from January 1, 1905, to September 1, 1910. The average annual rainfall from 1905 to 1909, inclusive, is also shown, so that a comparison of the rainfall of any year, with the average rainfall may be had. If Chart No. 2 is compared with Chart No. 3 it will be seen at once that the increase and decrease in the prevalence of malaria corresponds almost exactly with the increase and decrease in the rainfall. It is of great interest to determine how far this climatological factor is instrumental in determining seasonal variations in malaria.

In our opinion this seasonal variation of malaria is due more to relapses than to primary infections or to re-infections. If it were due to primary infections or to re-infections, then the number of anopheles mosquitoes should increase synchronously with the increase in rainfall and the increase in the malaria rate and should decline in a similar manner. Mr. Le Prince, the Chief Sanitary Inspector, has informed us that the increase in malaria of each year always antedates by several weeks any appreciable increase in the number of anopheles mosquitoes. While it is not easy in countries where malaria is endemic throughout the year to discriminate a relapse from a re-infection, Mr. Le Prince's observation demonstrates that a very considerable amount of the June and July malaria must be due to relapses.

Estivo-autumnal malaria is very prone to relapse. Once acquired it is not easily eradicated, and there are many factors that predispose to relapse at a time when a person who has acquired the infection is exposed to inclement weather. A relapse in malaria means that parasites are present in the system and an *immunitas non sterilisans* has been established. Temporary immunity can be interrupted by a series of conditions; some of which are active throughout the year, and some seasonal.

Of the causes that prevail throughout the year which may interrupt a temporary immunity, probably the most potent here is syphilis. In untreated syphilis, patients will return repeatedly with malarial relapses, and to effect a cure the administration of specific treatment is as necessary as the administration of quinine.

By reason of its depressing influence, influenza is also an important factor in the production of malarial relapse. It is not unusual to

observe a patient when under treatment for influenza develop a chill and for parasites to be found when a careful search at the time of admission failed to reveal them.

Injury, an operation, the administration of an anesthetic, childbirth, any severe shock, all of which depress the patient, may interrupt the temporary immunity established in latent malaria, and an acute exacerbation of the latter may ensue.

Muscular fatigue has long been known to be an important means of precipitating a malarial chill. The explanation has been given that an accumulation of sarcolactic acid is formed in the tissues by excessive exercise, and that this accumulation interferes with the action of the protective alexins and opsonins which act best in a slightly akaline medium. The interference with the same protective agents by the excessive use of alcohol may be considered as a factor in producing relapses.

Among the seasonal factors that cause relapses, climatic change is most important. It is a very common experience to find an acute exacerbation when a person who has temporary immunity journeys from the tropics to a northern country, and vice versa. Probably the same cause that operates in this instance is in the Canal Zone the most frequent in producing relapses after exposure to wet and to cold.

These factors, exposure to wet and to cold, are considered by the Italian writers to be of the greatest importance. In the beginning of our rainy season, and throughout it, the laborers are frequently thoroughly wetted, and being far from their quarters, have no opportunity to change their clothing, and many of them would not change it if they had the opportunity. Hence there is a chilling of the body, and a temporary lowering of resistance, which brings about a malarial exacerbation. Whether such a relapse is due to a direct lowering of the phagocytic power of the leucocytes in their passage through the superficial capillaries, by lowering the temperature of the leucocytes, as has been suggested by some writers; or whether it is due to centripetal influences which affect the nerve centers that preside over nutrition and cell metabolism, thus inhibiting the elaboration of protective agencies in the body, and cellular food supply, it is difficult to state.

Any of the above named causes for relapse will be made more efficient by the climatological factors that prevail at the beginning of the wet season; and any cause will be less effective in the mild weather that prevails in the dry season.

It is because estivo-autumnal malaria is more prone to relapse than is tertian, and because it persists more tenaciously when once acquired, that the amount of the former is so much greater. After the rainy

season has advanced sufficiently to furnish suitable breeding places, the increased number of anopheles will account for a part of the increase in the malarial rate. But even this increased number of mosquitoes does not explain why estivo-autumnal malaria should increase actually and relatively more than tertian, unless the former is more susceptible to propagation. The same conditions which favor the spread of the one variety, favor also that of the other; is, then, estivo-autumnal malaria more readily disseminated?

Dr. S. T. Darling[6] has noted that the gametes of estivo-autumnal parasites remain for a longer time in the peripheral circulation than do those of tertian, in both cinchonized and untreated persons. He has also found that actually more zygotes develop in anopheles fed on blood which contains crescents, than in those fed on blood containing tertian gametes, when the number of gametes in the blood in each instance is taken into consideration. Darling has also shown that *Anopheles albimanus* is the principal carrier of malaria in the Canal Zone. He fed eighty-eight anopheles on blood that contained crescents. Of these, seventeen were *A. malefactor*, none of which were infected. Of the remaining seventy-one, zygotes were found in 50 per cent, nearly all in *A. albimanus*. Twelve anopheles were fed on blood that contained tertian gametes, and 50 per cent of these were infected, all *A. albimanus*. Of forty-two *A. albimanus* fed on blood that contained crescents, twenty-nine, or 70 per cent, were infected. Several of these were dissected between twenty-four and fifty-eight hours after infection, and it may be that the ookinets or the young zygotes were not found. Of seven *A. albimanus* fed on blood containing tertain gametes, six, or 85.6 per cent, were infected. From this, it is evident that *A. albimanus*, the principal carrier of malaria, is susceptible to infection equally with either tertian or with estivo-autumnal gametes.

Now, while it is true that crescents remain for a longer time in the peripheral blood than do the gametes of tertian malaria, the latter are relatively more abundant. It is but seldom that gametes are not present in the blood of patients admitted with tertian malaria, while crescents are not found in most estivo-autumnal infections on admission. We have observed that in infections with tertian malaria which either have incubated or relapsed while the patients were in the wards, gametes were present, thus proving that these have been developed by the time that the clinical symptoms had manifested themselves. In similar instances, in estivo-autumnal infections, and also in estivo-autumnal infections that were permitted to run without quinine, the crescents did not appear until several days after the onset of the fever.

It is evident from the foregoing observations that reasons other than those pertaining to the number of gametes in the peripheral blood of infected individuals, and other than the susceptibility of anopheles mosquitoes to infection from such blood, must be adduced to explain the increased prevalence of estivo-autumnal malaria in the rainy season. As Chart No. 2 shows, the annual increase occurs too suddenly to be accounted for entirely by an augmentation in the number of anopheles, although this augmentation undoubtedly contributes to the increase, and certainly is a considerable factor in maintaining it through the wet season. But the decrease is as sudden and marked as is the increase, and it is unreasonable to suppose that the very great number of anopheles accumulated during the wet season, perishes as rapidly as the malaria rate falls when the rains cease.

Undoubtedly the climatological changes, as shown in Chart No. 3, are very important influences in the marked seasonal variation in the malaria rate, and this variation is to a considerable degree independent of the agencies concerned in the transmission of malaria. These climatological factors are effective in that they influence the causes which determine relapses, and so produce the preponderance of estivo-atumnal malaria in the wet season. The importance of the preponderance of estivo-autumnal malaria in the determination of hemoglobinuric fever will be dicussed subsequently.

SUMMARY.

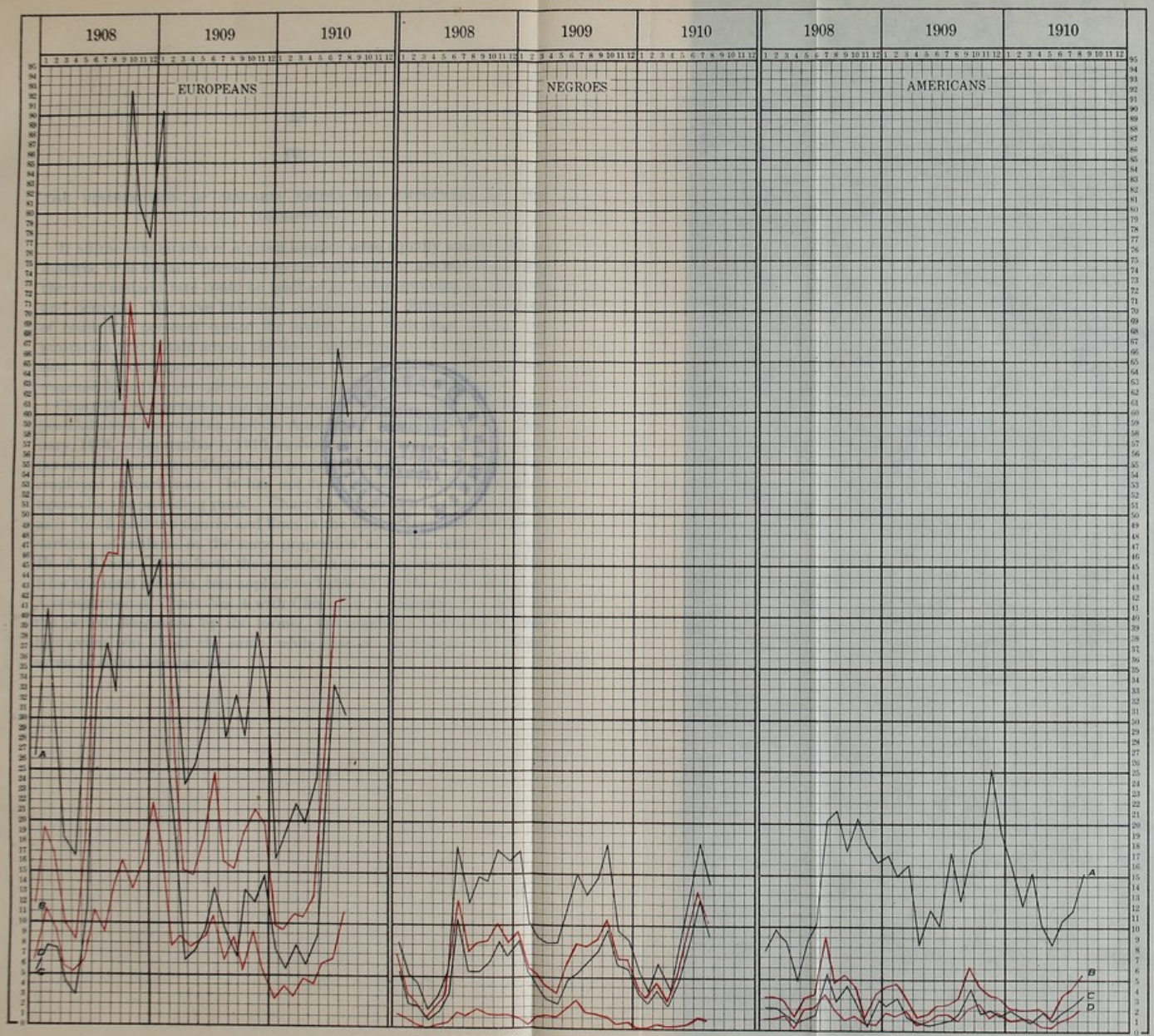
Malaria prevailed extensively in the Canal Zone in 1905 and 1906, and since then has been steadily diminishing in frequency.

There is a well marked seasonal variation in the malaria curve, and this variation is largely dependent on climatological influences.

Relapses are more frequent in estivo-autumnal malaria than in tertian, and the relapses contribute to a considerable extent to the seasonal variation in malaria.

Climatological influences determine to a great degree the number of relapses, and more malaria is due to relapses than to primary infections or to re-infections.

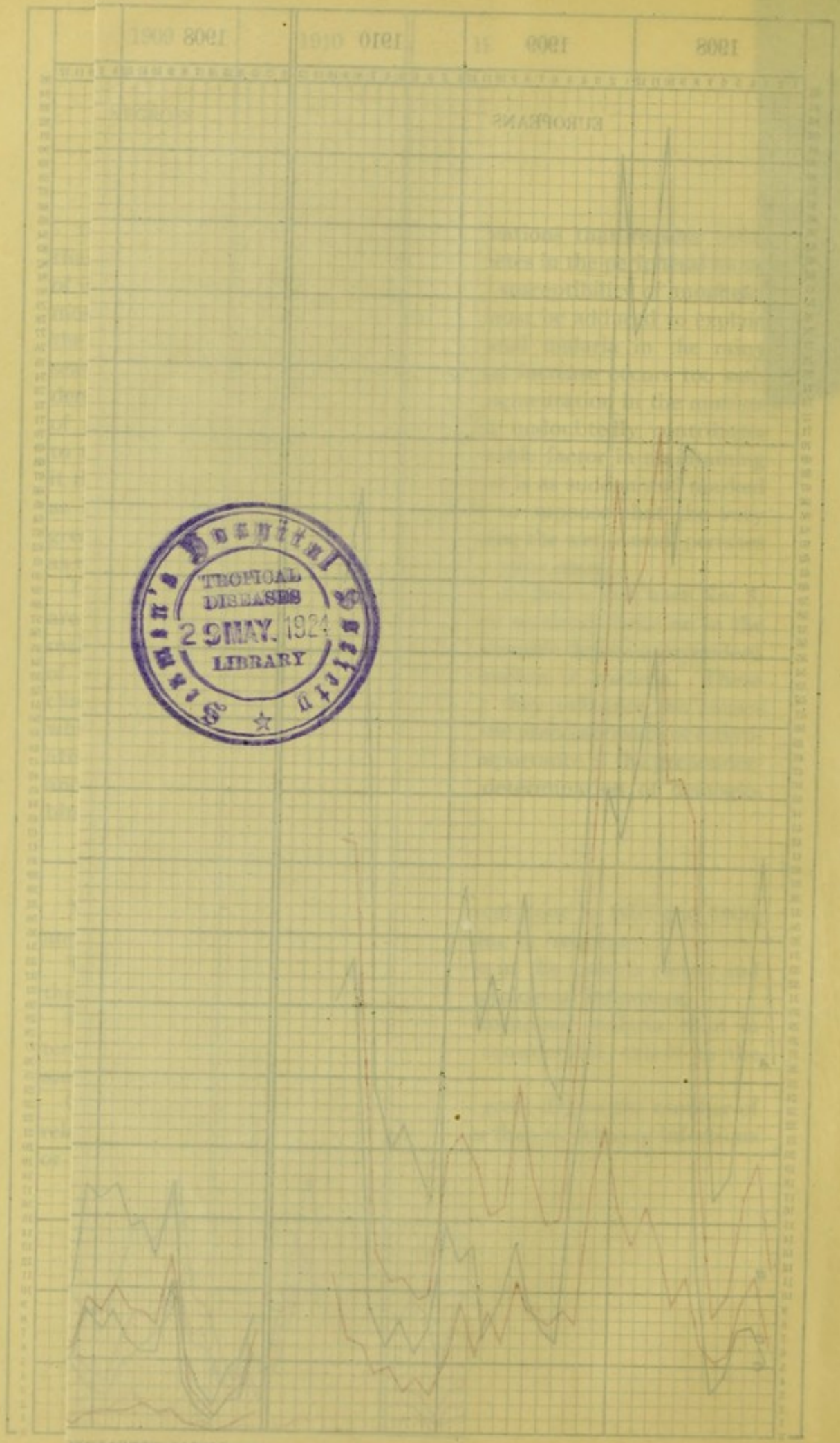
CHART No. 4



RACIAL PEEVALENCE OF MALARIA IN ANCON HOSPITAL.

A-A, Total malaria.
B-B, Positive cases.
C-C, Estivo-autumnal malaria.
D-D, Tertian malaria.

The figures refer to the monthly rate per thousand in each race.



IV.

THE DISTRIBUTION OF MALARIA AMONG THE EMPLOYEES OF THE COMMISSION.

If all the inhabitants of a given locality were equally susceptible to malaria, or if malaria prevailed to the same extent among all classes, the total malaria rate could be used as an index applying to all races and persons. We have indicated previously the different conditions of residence, personal regard for health, and individual respect for sanitation that obtain among the three races employed by the Commission. It is of importance to ascertain how far these conditions are responsible for the prevalence of malaria among these three races.

Chart No. 4 represents the prevalence of malaria among the European laborers, the negroes, and the Americans, for the period from January, 1908, to September 1, 1910, as shown by the number of discharges per month from Ancon Hospital in proportion to the number of persons employed of each race. It has not been possible to obtain similar figures for the preceding years. Chart No. 4 is drawn to the same scale as is No. 2, and the figures and lines in the former represent the same varieties of malaria in the same proportion as in the latter. Table IV, A, B, and C, sets forth the same data as are represented in Table I for the total malaria, but applied in Table IV to the separate races. A comparison of Chart No. 4 with Chart No. 1 demonstrates that in the period designated by the former, the number of Americans and Europeans was about the same, while that of the negroes was from seven to eight times greater.

TABLE IV.—*Showing the same data as given in Table I, applied to the three races employed by the Commission from January 1, 1908, to September 1, 1910.*

AMERICAN EMPLOYEES—A.

Column 1.	Column 2.		Column 3.				Column 4.		Column 5.	
	Number of cases of malaria per year discharged from Ancon Hospital.		Percentage of the varieties of malaria according to the figures given in Column 2, *A*				Percentage of the varieties of malaria in the positive bloods in Column 2, *B*.		Percentage of the varieties of malaria estimated for the total number of cases per year.	
Year.	*A*. Total number of cases discharged.	*B*. Number of these cases positive	Estivo-autumnal.	Tertian.	Positive.	Clinical.	Estivo-autumnal	Tertian.	Estivo-autumnal.	Tertian.
1908	1,004	262	16	10	26	74	60	40	67	33
1909	1,163	267	11.5	11.5	23	77	50	50	59	41
1910—January to September	571	169	17.1	12.4	29.5	70.5	58	42	65	35
Total number of cases and average per cent, 1908–10	2,738	698	14.8	11.3	26.1	73.8	56	44	63.6	36.3

EUROPEAN EMPLOYEES—B.

1908	3,786	2,598	49	20	69	31	71	29	74	26
1909	2,658	1,770	40	27	67	33	60	40	63	37
1910—January to September	1,885	1,128	44.5	15.5	60	40	74	26	78	22
Total number of cases and average per cent, 1908–10	8,329	5,496	44.5	20.8	65.3	34.6	68.3	31.6	71.6	28.3

NEGRO EMPLOYEES—C.

1908	3,747	2,309	49	13	62	38	79	21	89	11
1909	5,159	3,160	49	12	61	39	80	20	84	16
1910—January to September	2,776	2,025	64	8	72	28	89	11	91	9
Total number of caess and average per cent 1908–10	11,682	7,494	54	11	65	35	82.3	17.6	88	12

Although it was not possible to obtain data showing the relative amount of malaria prior to 1908, we are able to give some figures that enabled us to approximate closely this amount. Col. W. C. Gorgas, M. D., U. S. A., Chief Sanitary Officer, and Head of the Department of Sanitation, whose well known work in tropical sanitation has qualified him as an authority on the prevalence of tropical diseases, has told us that in his opinion the death rate per thousand from malaria is a very reliable index of the prevalence of the disease. We were able to ascertain this death rate for the period 1906–1909, and it is given in Table V. A comparison of the death rate in 1908–1909 with the prevalence of malaria in that time, as shown in Chart No. 4, shows that Col. Gorgas' hypothesis is substantially accurate.

TABLE—V.—*Showing the annual average of each race of employees, the number of deaths from malaria in each race, and the death rate in each race, per thousand per year, due to malaria.*

Year.	Americans.			Europeans.			Negroes.		
	Annual average of employees.	Number of deaths per year from malaria.	Death rate per thousand per year from malaria.	Annual average of employees.	Number of deaths per year from malaria.	Death rate per thousand per year from malaria.	Annual average of employees.	Number of deaths per year from malaria.	Death rate per thousand per year from malaria.
1906.....	5,464	7	1.33	2,000	?	?	26,500	211	7.8
1907.....	6,706	3	.44	4,000	30	7.5	28,634	146	5.11
1908.....	6,572	4	.60	5,811	25	4.25	31,507	25	.77
1909.....	6,056	0	0	5,606	14	2.38	35,505	25	.70

In 1905, as shown in Table III, the admission rate to all hospitals from malaria was 514 per thousand, of which 65 per cent was admitted to Ancon Hospital. Owing to the exposure to which they were subjected, malaria must have prevailed very extensively among the Americans at that time.

The few Europeans on the Isthmus also suffered severely, and heavy infections were common among the negroes, as an examination of the ward registers proved. The July epidemic of that year affected Americans in great numbers. Beyond the fact that malaria was universally prevalent in all three races in 1905, as shown by the admission rate and the ward registers, we were unable to get more exact data.

In 1906, the Americans were better protected than in the preceding year, and their death rate from malaria was 1.33 per thousand, as compared with 7.8 per thousand among the negroes. In this year the immigration of European laborers began, and this class must have become heavily infected with malaria.

In 1907 there was a death rate among Americans of only one-third of that of 1906, showing a marked decrease in the prevalence of malaria

in this race. The high death rate among Europeans demonstrates that malaria must have been very severe among them, and similarly malaria was severe also among the negroes.

In 1908 and 1909, the admission rate per thousand from malaria to all Zone hospitals fell to less than one-third of the same rate in 1906. The marked falling off in the death rate among negroes and Americans in these years agrees with the decrease in the admission rate. Compare Tables III and V. The death rate among the European laborers in this time also diminished, but was always much higher than in the other two races. Chart No. 4, when compared with Table V, demonstrates the preponderance of malaria among the Europeans.

The racial prevalence of malaria, as is evident from the foregoing observations, has varied greatly since 1905. In 1905 and 1906 there was a very considerable amount of malaria among the Americans, and since that time this amount has greatly diminished. In 1905–1907 the negroes were heavily infected but since January, 1908, have suffered but little. Malaria has prevailed extensively among the Europeans at all times, but has lessened in the last two years.

Chart No. 4 shows distinctly this preponderance of malaria among the Europeans and demonstrates most clearly the value of individual prophylaxis against the disease. The relative immunity of the negro is apparent. Notwithstanding the unfavorable conditions under which this race lives, and although in number it far exceeds the other two, in it in recent years the malaria rate is lowest. Especial attention should be given to the comparison of the prevalence of malaria in the Europeans and Americans. Both of these races are equally susceptible to the disease, but the higher regard for sanitary measures in the one keeps its malaria rate far below that of the other.

The seasonal variation of malarial due to relapse is well shown in Chart No. 4. It is manifested most clearly among the Europeans and is not so evident among the Americans. It will be observed that the curves of the prevalence of malaria among the Americans are much more irregular than those of the other two races. This supports the hypothesis which we have advanced; that the seasonal variation is due largely to relapses. Since among the Americans malaria not only is more easily eradicated, but is also under better control, there are fewer relapses and more primary fevers, which latter occur more irregularly than do the former.

Among the Europeans and the negroes, the advent of the wet season is productive of causes that predispose to relapses, and the beginning of the dry season removes the principal of these causes—namely, wetting and chilling. The sudden and marked rise in the malaria rate among

the Europeans, and, to a lesser degree among the negroes, needs other explanation than that of primary fevers or re-infections.

It was stated in the consideration of Chart No. 2, that the seasonal increase in malaria is mostly due to an augmentation in the estivo-autumnal variety. In the curves of malaria among the Europeans and negroes in Chart No. 4, this increased estivo-autumnal rate is well shown. If the statement is accepted, that by far the greatest part of clinical malaria is due to estivo-autumnal infection, most of the seasonal increase among the Americans is due also to the latter.

A study of Table IV reveals several important factors in the distribution of malaria among the races. That the disease is milder among Americans than among Europeans and negroes is seen by a comparison of the percentage in the positive bloods in Table IV. It is a truth that in any race admitted to the hospitals, relative and acquired immunity being excepted, the greater the percentage of positive bloods, the greater is the severity of malaria. For not many patients of any race are admitted unless they were unable to cure the disease by outside treatment, or until a neglected fever had acquired severe proportions. Among the Americans, as we have pointed out, the use of quinine at the onset of the fever is almost universal; and an attack of malaria promptly treated at the time when the prodromal symptoms or the primary paroxysm are manifested, is not likely to be severe. Also, many Americans treated outside of the hospital for malaria and cured, were later admitted that they might be sent to Taboga, as a rule of the Commission requires that all such persons shall first be admitted to Ancon or to Colon Hospital. For these reasons, it is not surprising to find so small a percentage of positive bloods among the Americans.

The percentage of positive bloods among the Europeans and negroes is about the same. But owing to the relative immunity of the latter against malaria the disease is severer among the former. This is an important fact and will be discussed in detail in consideration of the relationship of malaria to hemoglobinuric fever. In the dry season patients of these two races are treated in the dispensaries and sick camps and only those who are unable to work are sent to Ancon or Colon Hospital. After the wet season has set in the sick camps will not accommodate all who are ill and many patients are sent in directly and without treatment. Individual use of quinine is not common among these two races, and often the sick will not apply for aid until after several paroxysms of fever. In the bloods of such patients parasites are readily found, and malaria among them, being untreated, is severe, especially among the Europeans.

It will be noticed that the proportion of estivo-autumnal to tertian malaria is lowest among the Americans, highest among the negroes, and about a mean between the two among the Europeans. Very probably the proportion of primary infections with each species in all three races is about the same, but such infections are less likely to relapse among the Americans, owing to a more prolonged exhibition of quinine. And the percentage of tertain malaria, as compared with that of estivo-autumnal, is higher in primary infections than in relapses. Charts No. 2 and 4 show that the amount of tertain malaria in the dry season, when primary infections or re-infections are more common than are relapses, is always relatively higher when compared with the amount of estivo-autumnal than in the rainy months. The negro not only has a considerable relative immunity, but in him tertain malaria tends more readily to a spontaneous cure. Nor does he suffer much from the febrile paroxysm of this variety. We have seen frequently such paroxysms in members of this race who did not appear to suffer much discomfort. So that relatively few negroes with tertain malaria apply for treatment; and very often such as do apply are not ill enough to be sent to the hospitals.

SUMMARY.

Malaria prevails among the employees of the Commission in direct proportion to exposure to infection and susceptibility to disease.

In 1905 and 1906 all three races were exposed to malarial infection, and suffered in proportion.

Since January, 1907, and probably from the middle of 1906 Americans have been less and less exposed to malarial infection, with a consequent diminution in the malaria rate among them.

At all times the European laborers have been exposed to malarial infection, and, since this race is very susceptible, have suffered heavily.

The negro is exposed the most of the three races. It has a relative immunity against malaria, which in times of severe prevalence of the disease, as in 1905–1907, inclusive, keeps this race from decimation; and when the disease is not extensive, enables it to exhibit a comparatively low malarial rate.

The seasonal variation, due to relapses, is more marked in the malaria of the Europeans and negroes than in that of the Americans.

The tertian variety is not an important factor in the racial distribution of malaria among the Europeans and negroes.

V.

THE RELATIONSHIP BETWEEN MALARIAL AND HEMOGLOBINURIC FEVER.

The reader is referred to writings of Christophers and Bentley, Stephens,[7] Manson,[8] Deaderick,[8a] Marchiafava and Bignami, Craig,[9] Daniels,[10] and others for a discussion of the geographical distribution of hemoglobinuric fever, and the relationship between this distribution and that of malaria.* It is evident from their researches that hemoglobinuric fever is epidemic only in the countries where malaria also is endemic. It is true that occasional cases of hemoglobinuric fever present themselves at times in localities free from malaria, also it is argued that there are regions where severe malaria abounds, from which the other disease is absent; but in the former instance a history of previous residence in a malarial district can invariably be obtained, while even if the latter proposition be true, it does not invalidate the premise that hemoglobinuric fever is nowhere endemic except in malarial countries. Every year evidence is accummulating to prove that the disease prevails in regions which were previously thought to be free from its presence; and at this time the problem of its absence from malarial countries is, at least, subject to further research before a definite affirmative statement can be made.

In any country where malaria is endemic throughout the year, and at certain seasons epidemic, sooner or later the disease will be acquired by nearly all persons exposed to it, except those who are immune. It is obvious, then, that in hemoglobinuric fever or in any other disease, which is also endemic in such countries, a history of prior or coincident malaria will often be obtained.

To what extent such a history affects the etiology of hemoglobinuric fever, and to what extent it affects that of other diseases, are problems that must be determined before any opinion can be given upon the influence of malaria as a causative factor in the eventuation of hemoglobinuric fever. If it be demonstrated that prior or coincident malaria is associated with hemoglobinuric fever in a constant and definite manner, and that such association is lacking between malaria and other diseases, then it must be admitted that malarial infection is a necessary element in the production of hemoglobinuric fever.

We shall dicuss the possibilities of this association under the following heads:

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*A complete account of the geographical distribution of hemogolobinuric fever, and of the relationship between this disease and malaria in countries other than the Canal Zone, will be found in Appendix B, at the end of this paper.

1. A comparison of the epidemiology of malaria with that of hemoglobinuric fever.

2. A comparison of the epidemiology of malaria with that of the principal infectious diseases prevailing in the Canal Zone.

3. Malaria as a predisposing cause of hemoglobinuric fever.

4. Malaria as an exciting cause of hemoglobinuric fever.

5. The species of malarial parasite which is concerned in the production of hemoglobinuric fever.

A COMPARISON OF THE EPIDEMIOLOGY OF MALARIA WITH THAT OF HEMOGLOBINURIC FEVER.

From July, 1904, to September, 1910, there were approximately 83,000 admissions to Ancon Hospital. Forty thousand nine hundred and twenty-eight, or slightly less than 50 per cent of these were diagnosed as malaria, the rest were admitted for other medical diseases, or to the surgical side of the hospital. In the same period the number of patients admitted with hemoglobinuric fever or its after effects or who developed it after admission, was 232. This number is a minimum, for some cases diagnosed as hemoglobinuric fever were not accepted by us on account of insufficient data on the charts. We have used the charts and histories of 230 of these cases to obtain our data, and for convenience of reference have divided the cases as follows:

Class 1. Those with a history of hemoglobinuric fever prior to admission, but in whom no hemoglobinuria was manifested subsequently.

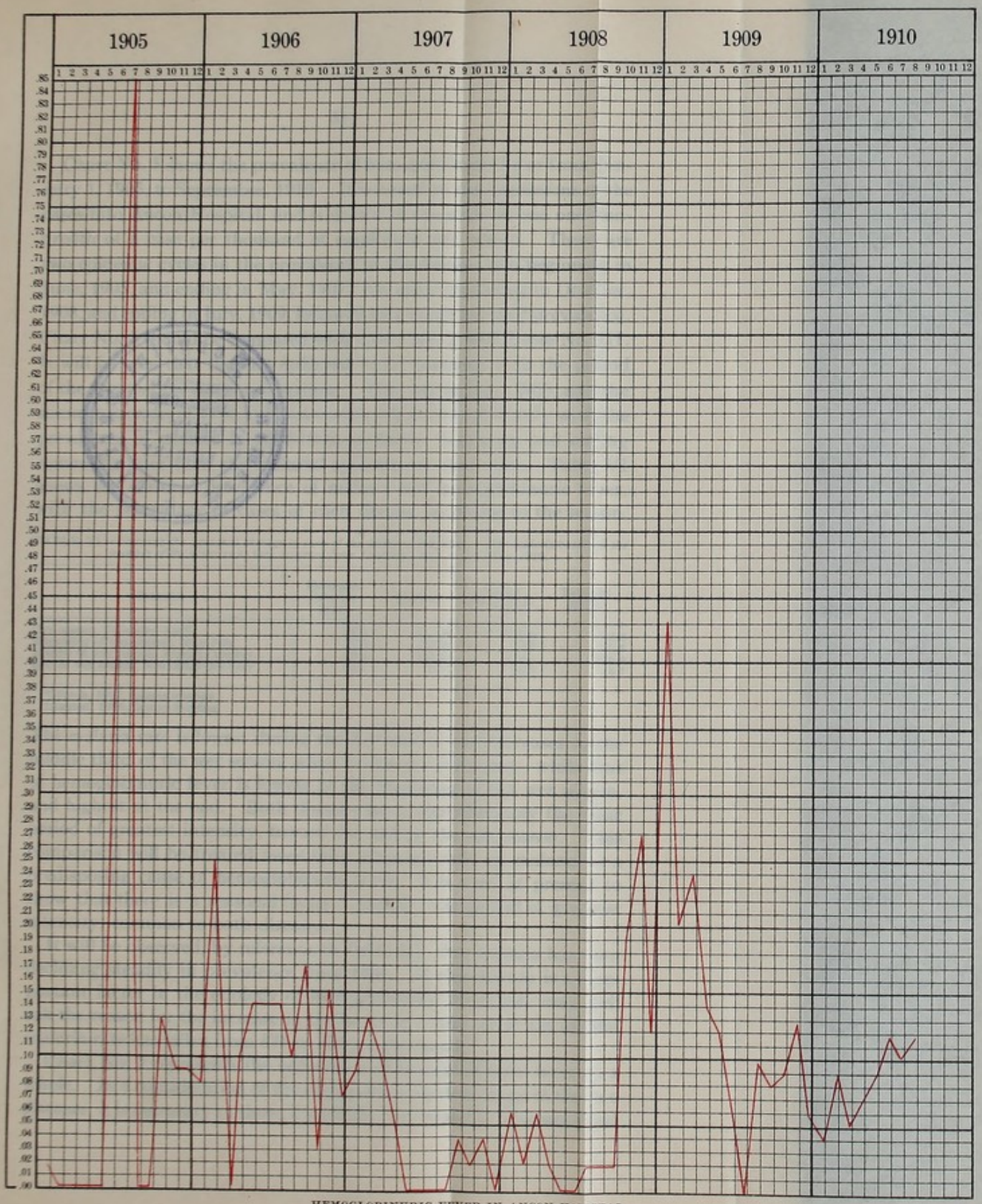
Class II. Those with hemoglobinuria at the time of admission.

Class III. Those in whom hemoglobinuria developed after admission.

In Class I there were 15 cases; in Class II, 113 cases, and in Class III, 102 cases.

Of great importance for epidemiological comparison are the cases in Class III. Ninety-eight of these were admitted with either positive or clinical malaria. The other four were admitted to the surgical side. In three of these latter a well defined malarial paroxysm preceded the onset of the hemoglobinuria, while in the fourth, in which there was a history of much previous malaria, the hemoglobinuria followed the experimental use of quinine. Since in this class, in which observations of the entire course of the disease could be made most favorably, hemoglobinuric fever developed in connection with malaria only, and no other malady, it is most probable that malarial infection is largely concerned with the etiology of hemoglobinuric fever. If so, then this connection should be shown in the comparative epidemiology of the two diseases.

CHART No. 5



HEMOGLOBINURIC FEVER IN ANCON HOSPITAL.

In one one-hundreths of a case per thousand of the total number of employees.

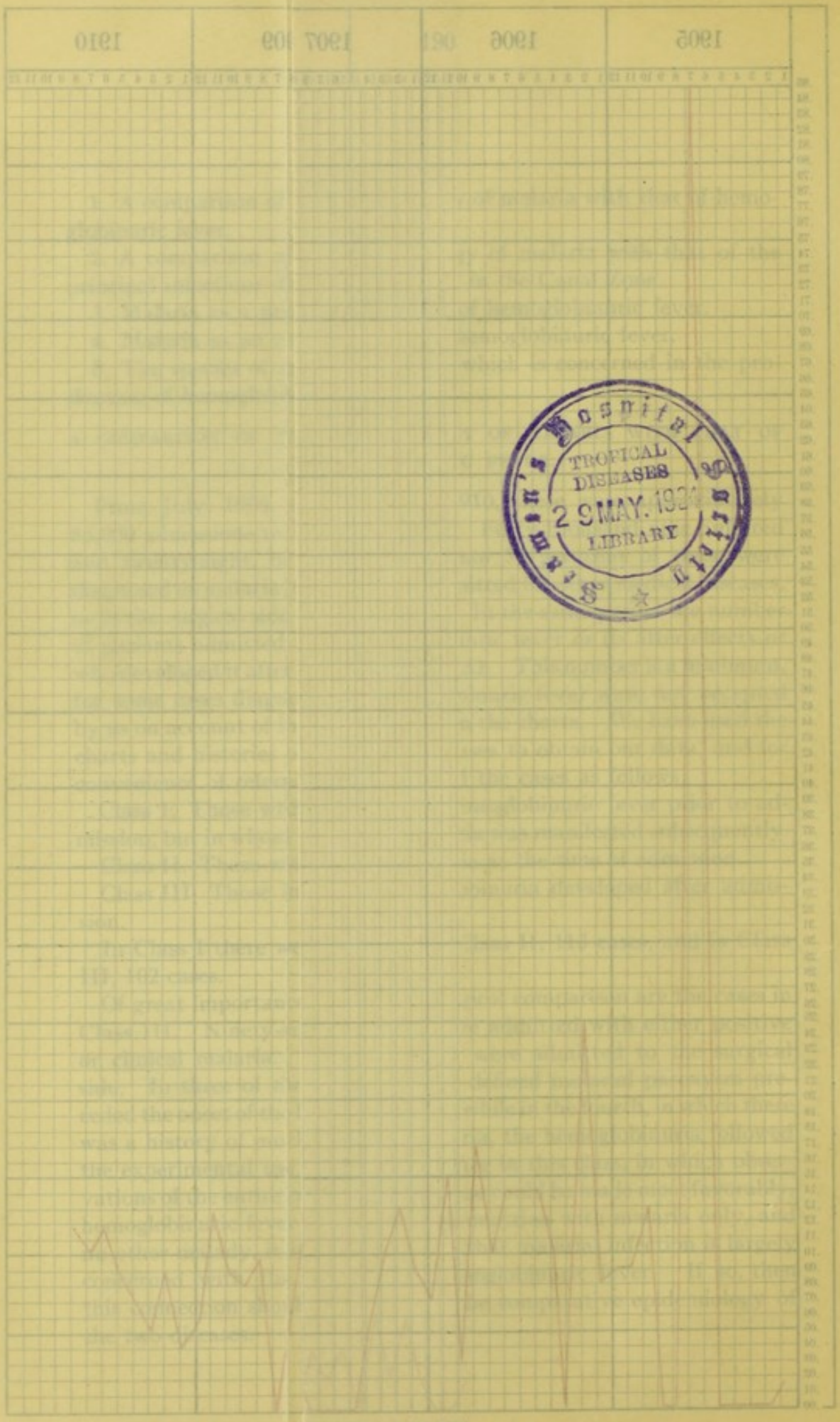


Chart No. 5 shows the prevalence of hemoglobinuric fever from January 1, 1905, to September, 1910. It is based on the admissions of the cases into Ancon Hospital, and is drawn to the scale of one one-hundredth of a case per thousand of employees per month. There are two epidemic cycles in the prevalence of the disease, one beginning in June, 1905, and ending in May, 1907; the other beginning in October, 1908, and ending in July, 1909, followed by a much lessened prevalence. Chart No. 5 should be compared with Chart No. 2, and Table No. III. It will be seen that the first epidemic cycle coincided with the period of the greatest prevalence of malaria. This was in July, 1905, and the summer months of 1906. The second cycle coincided closely with the prevalence of malaria in 1908-1909, inclusive, beginning and ending somewhat later than the malarial epidemic at that time. Table VI shows the seasonal prevalence of malaria and hemoglobinuric fever, with the percentage of cases of each disease according to the season.

TABLE VI.—*Showing the seasonal average of each of the diseases indicated. This table is based on the number of the diseases as they occurred from January, 1905, to January, 1910.*

Seasons.	Hemoglobinuric fever.	Malaria.	Lobar pneumonia.	Typhoid fever.
Dry season, February-April	26.3	*17.18	*20.9	*22.8
Beginning of wet season, May-July	17.5	23.76	32.0	35.5
Middle of wet season, August-October	20.7	†30.17	†23.1	†26.9
End of wet season, November-January	34.7	28.7	26.9	16.7

*March, 1907, figures missing.
†August, 1906, figures missing.

The malaria rate is lowest during the dry season, and increases to the middle third of the wet season, when it remairs stationary, while that of hemoglobinuric fever is lowest at the beginning of the wet season, and highest at the end. Both diseases have approximately the same period of greatest intensity, toward the end of the wet season. This comparison will be treated more fully when we take up malaria as a predisposing cause of hemoglobinuric fever; it is used at present to show that there is a seasonal factor—namely, the period of greatest intensity, common to both diseases.

It will be observed, by reference to Table III, that malaria has been declining steadily in prevalence since 1906. If this disease is an important factor in the etiology of hemoglobinuric fever, one may well ask the reason for the increase in the latter at a time when the annual malaria rate has fallen from 821 to 282 per thousand.

Chart No. 5 represents the occurrence of hemoglobinuric fever as a whole. In a consideration of the comparative epidemiology of the two diseases, it is necessary to show, if possible, that malaria was associated

with the second cycle in the same manner as with the first, if malaria has an epidemiological connection with hemoglobinuric fever.

The intensity of malarial infection in the period 1905-09, inclusive, has been given in a previous section of this paper. It will be remembered that Americans were exposed most in 1905 and 1906, the period of greatest exposure to infection being the wet season of 1905, and the first part of 1906. The negro was also heavily exposed in 1905 and 1906, and somewhat less in 1907, after which time comparatively little malaria has prevailed among that race. But at all times the Europeans have suffered severely from malaria.

Table VII shows the annual rate per thousand of cases of hemoglobinuric fever among the three races. It is based on the admissions into Ancon Hospital, and the annual average per thousand of each race. This latter could be obtained with reasonable accuracy for the negroes and Americans for all years. We estimated the annual average of European laborers for 1905 at 1,000, for 1906, at 2,000. These figures are probably somewhat high. In 1907, 47.3 per cent of all cases diagnosed as hemoglobinuric fever was admitted to Ancon Hospital; in 1908, 44.5 per cent, and in 1909, 81.6 per cent.

TABLE VII.—*Based on the number of admissions due to hemoglobinuric fever into Ancon Hospital, and the number of cases of that disease which developed in the hospital from January, 1905, to September, 1910, and showing the incidence of the disease per thousand in each race according to the annual average of each race, as shown in Table V.*

Race. (Number of cases of hemoglobinuric fever per thousand per year.)	1905.	1906.	1907.	1908.	1909.
In Americans	3.30	1.9	.70	.39	.48
In Europeans	5.00	5.5	1.25	5.88	11.36
In negroes	.33	.59	.28	0	.25

Table VII shows plainly that in the first epidemic cycle the occurrence of hemoglobinuric fever among the Americans and Europeans was very nearly in proportion to that of malaria. This proportion is materially less in the negro than in the other two races, and the reasons for this relative immunity against hemoglobinuric fever as well as malaria will be discussed later. Table VIII gives in detail the number of cases of hemoglobinuric fever in Ancon Hospital from July, 1904, to September, 1910, showing the nationality and length of residence in months of each case. It will be observed that in the first epidemic cycle there was a distribution of hemoglobinuric fever among all three races. In the second epidemic cycle this distribution is almost entirely among European laborers. In fact, in 1908, 91.8 per cent of the cases admitted to Ancon Hospital were in that race, and in 1909, 80.5 per cent. The great preponderance of malaria among the

TABLE VIII.—*Showing the number of cases of hemoglobinuric fever in Ancon Hospital, as they occurred per month, per year, among the races. U. S., denotes Americans; E., Europeans; and B, negroes. The figures preceding the letters show in months the time of residence in the Canal Zone. The table embraces the period from the opening of the hospital in May, 1904, to September, 1910. (?) Denotes residence not given.*

Month.	1904.	1905.	1906.	1907.	1908.	1909.	1910.
January		*1 E	13 U. S., 16 E.	16 B, 7 B, 5 E	(?) E, 12 E, 12 E	24 B, 6 E, 18 E, 17 E, 24 E, 54 U S, 18 E, 19 E, 14 E, 24 E, 9 E, 20 E, 16 E, 19 E, 24 E, 23 E, 26 E, 26 E, 20 E.	24 E, 40 B.
February			12 E, 6 U S, *2 U S, 8 E, 36 E, 22 yrs E.	4 U S, 72 E, 12 E, 12 E.	15 E	54 U S, 24 E, 23 E, 19 E, 25 E, 26 E, 15 E, 5 E, 16 E, 27 E.	48 B, †Life E, 30 E, 16 E, 4 E.
March				14 U S, 16 U S, 14 U S, 24 B.	25 E, 8 E, 24 E	21 E, 22 E, 40 E, 18 E, 20 E, 28 E, 27 E, 14 E, 7 E, 24 E.	48 E, 18 E, 6 E.
April			*19 U S, *8 U S, 2 B	4 B, 6 B	16 E	30 B, 33 E, 7 E, 24 E, 23 E, 24 E, 10 E.	*9 E, 10 B, 38 E, 22 E.
May			3 B, 3 U S, *6 U S, 20 yrs. U S.			28 E, 21 E, 30 E, 10 E, 32 E, 27 E, 18 E.	60 B, 26 E, 8 E, (?) B, 23 E.
June		5 E, 5 B	12 B, 14 E, (?) B, 10 B.			29 E, 11 E, 36 E	36 E, 6 B, 10 B, 40 E, 48 E, 36 E.
July	2 U S	*1 U S, 6 U S, 18 E, 4 U S, 2 U S, 3 B, 1 U S, 6 B, *2 B.	12 B, 5 B, (?) B, 3 E		20 E		36 E, 12 B, (?) E, *6 B, *8 E.
August			7 B, 24 B, 9 B		15 E	4 B, 60 E, 24 E, 25 E, 16 E.	41 B, 29 E, 30 B, (‡) E, 60 B, (‡) E.
September	Life E		12 B, 4 E, 28 U S, 7 E, 8 E.	4 B, 3 B	(?) U S	24 B, 27 B, 48 U S, 28 E.	
October	(?) B	15 U S, *5 U S, 4 E.	3 U S	20 E	(?) U S, 19 E, 20 E, 23 E, 18 E, 4 E, 3 E, 15 E, 9 E.	18 B, 36 E, 36 B, (?) E, 36 E.	
November		48 U S, 15 E	8 B, 4 B, 7 B, 15 B.	18 B, 3 U S	13 U S, 18 E, 21 E, 24 E, 23 E, 2 E, 18 E, 17 E, 15 E, 17 E, 15 E, 5 E.	36 E, 48 E, 12 E, 26 E, 32 E, 15 E, 27 E.	
December	11 B	2 U S, 7 U S	14 U S, 1 E		24 E, 5 E, 24 E, 26 E, 24 E.	30 B, 48 B, 28 E	
Total	4	19	38	18	37	80	34

*Cases marked thus denote a history of prior residence in another malarial country.
†This was in a native of European parentage.
‡Two cases in August, 1910, not otherwise recorded.

European laborers during the time of the second epidemic cycle is shown in Chart No. 4. Since in 1905-07, inclusive, hemoglobinuric fever occurred among all races at a time when all members of these races were exposed to malaria, and since in 1908-09, inclusive, malaria prevailed extensively only among the Europeans; it follows that in the second epidemic cycle malaria was associated with hemoglobinuric fever in the same manner as in the first—that is, the latter prevailed in proportion to the prevalence of malaria. This is also shown by the fact that at all times the large amount of malaria among the Europeans has been associated with a preponderance of hemoglobinuric fever in that race; compare Table V and Chart No. 4 with Table VII. It should be remembered that in 1907 the very large increase of European laborers tended to lessen decidedly the rate per thousand of hemoglobinuric fever in that year.

The same epidemiological factors in malaria and hemoglobinuric fever in the first epidemic cycle were: a seasonal prevalence that reached its greatest intensity at the same time as that of malaria; the occurrence of hemoglobinuric fever as a whole in definite proportion to that of malaria as a whole; and the incidence of the one disease in proportion to the incidence of the other among the different races. In the second epidemic cycle these factors are the same. The seasonal prevalence of hemoglobinuric fever in 1908-09 bears the same relation to the seasonal prevalence of malaria in that time, as was shown in 1905-07. The Europeans, at the time of the second cycle, were the race most subject to malaria, and hemoglobinuric fever prevailed mostly in that race. And at this time Americans and negroes were but little affected with malaria and but little with hemoglobinuric fever.

It is evident from the foregoing statements that there are similar factors in the epidemiology of the two diseases and that these factors are constant. Each disease has the same period of maximum intensity. Hemoglobinuria as a whole prevails directly in proportion to the occurrence of malaria as a whole when this occurrence is analyzed. Although in the time of the second epidemic cycle the total malaria rate was diminishing, the rate among the European laborers was very high, and it was in this class that nearly all of the hemoglobinuric fever occurred.

A COMPARISION OF THE EPIDEMIOLOGY OF MALARIA WITH THAT OF THE PRINCIPAL INFECTIOUS DISEASES OF THE CANAL ZONE

It has been stated that in any country in which malaria is both endemic and epidemic, a history of prior or coincident malaria in other diseases will very often be obtained. It has been shown in the

preceding section that there is a definite epidemiological relationship between malaria and hemoglobinuric fever. It may well be asserted that since these two diseases prevail for the most part in unhealthy seasons, when chilling and wetting of the body predispose to their occurrence, a similar seasonal prevalence will be found in other endemic infectious diseases; moreover, a like relationship to malaria may also be found in them.

We have demonstrated in those cases in which hemoglobinuric fever developed after admission to the hospital that a positive or clinical malaria preceded the onset of the hemoglobinuria. The principal endemic infectious diseases, other than malaria are: typhoid fever, lobar pneumonia, amoebic dysentery, and pulmonary tuberculosis. From 1905 to 1909, both inclusive, 1,043 cases of typhoid fever, 1,283 of lobar pneumonia, 360 of amoebic dystentery, and 487 of pulmonary tuberculosis were admitted to Ancon Hospital. In addition there were many thousand cases of other affections, medical and surgical, admitted during the same period. With the exception of the four cases previously noted that occurred on the surgical side, not one case of hemoglobinuric fever developed among the 42,000 admissions due to causes other than malaria. It is plain, then, that other diseases do not predispose to hemoglobinuric fever as does malaria.

These other diseases may be complicated with prior or coincident malaria, but not to the extent that hemoglobinuric fever is so complicated.* Taking only those cases of hemoglobinuric fever in which positive malarial infections were found; in Class II, patients admitted with hemoglobinuric fever, 23 per cent of the blood examinations were positive, and in Class III, patients in whom hemoglobinuria developed after admission, 61 per cent. In no other disease are such high percentages of positive bloods obtained. It has not been possible for us to examine all the charts of cases of the four diseases mentioned, nor to ascertain the proportion of the surgical cases complicated with malaria; but the data that we could obtain makes it probable that not over 10 per cent of all other medical and surgical cases were admitted with coincident malaria or developed the disease while in the hospital. So that other diseases prevalent in the Canal Zone are not by any means complicated with active malaria to the extent that hemoglobinuric fever is so complicated.

The comparative epidemiology of malaria and hemoglobinuric fever demonstrated: that each disease has the same seasonal period of

*This subject is treated more fully in Appendix B.

maximum intensity; that hemoglobinuric fever as a whole prevails in proportion to the occurrence of malaria as a whole; that hemoglobinuric fever obtains among a race in proportion to the susceptibility of that race to malarial infection, and the amount of such infection; and it may be noted here that hemoglobinuric fever is in proportion also to the amount of previous malarial infection. It is now of importance to ascertain if a similar comparison of malaria with other diseases will show the same results.

Chart No. 6 demonstrates the prevalence of typhoid fever, lobar pneumonia, amoebic dysentery and pulmonary tuberculosis, as shown by the discharges and deaths from and in Ancon Hospital from January, 1905, to September 1, 1910. It is drawn to a scale of one-tenth of a case per thousand of employees for each month. In the curve representing typhoid fever, the discharges and deaths have been antedated one month, in order to approximate more closely the time of onset. In lobar pneumonia, which has a high death rate, but in cases of which the average duration in the hospital is three weeks, the curve represents discharges and deaths per month. Amoebic dysentery and pulmonary tuberculosis are of uncertain duration, not only prior to admission, but subsequently as well. In both of these diseases it is hopeless to try to represent the time of onset, and the best that can be done is to show their prevalence as represented by discharges and deaths per month.

As a considerably greater propotion of the total number of cases of these diseases than of malaria is admitted, the curves of typhoid fever and lobar pneumonia represent very accurately the seasonal prevalence of the two.

A comparison of Chart No. 6 with Chart No. 2 shows at once that while there appears to be some resemblance between the seasonal prevalence of malaria and that of lobar pneumonia, the regularity of the seasonal prevalence in the former is lacking in the latter. Lobar pneumonia shows its greatest increase in 1906, at a time of the year somewhat later than the greatest prevalence of malaria. After 1907 the occurrence of the former is lessened and irregular, while that of the latter, although diminished, maintains its seasonal regularity. In Table VI is given the percentage of cases of lobar pneumonia according to seasonal prevalence. This is lowest in the dry season, reaches its maximum at the beginning of the wet season, and then declines. So that the period of maximum intensity in lobar pneumonia is earlier than in malaria. Moreover, the periods of increase in the prevalence of lobar pneumonia last but a few months at the most, and recur at irregular intervals, while those of malaria are very definite in duration

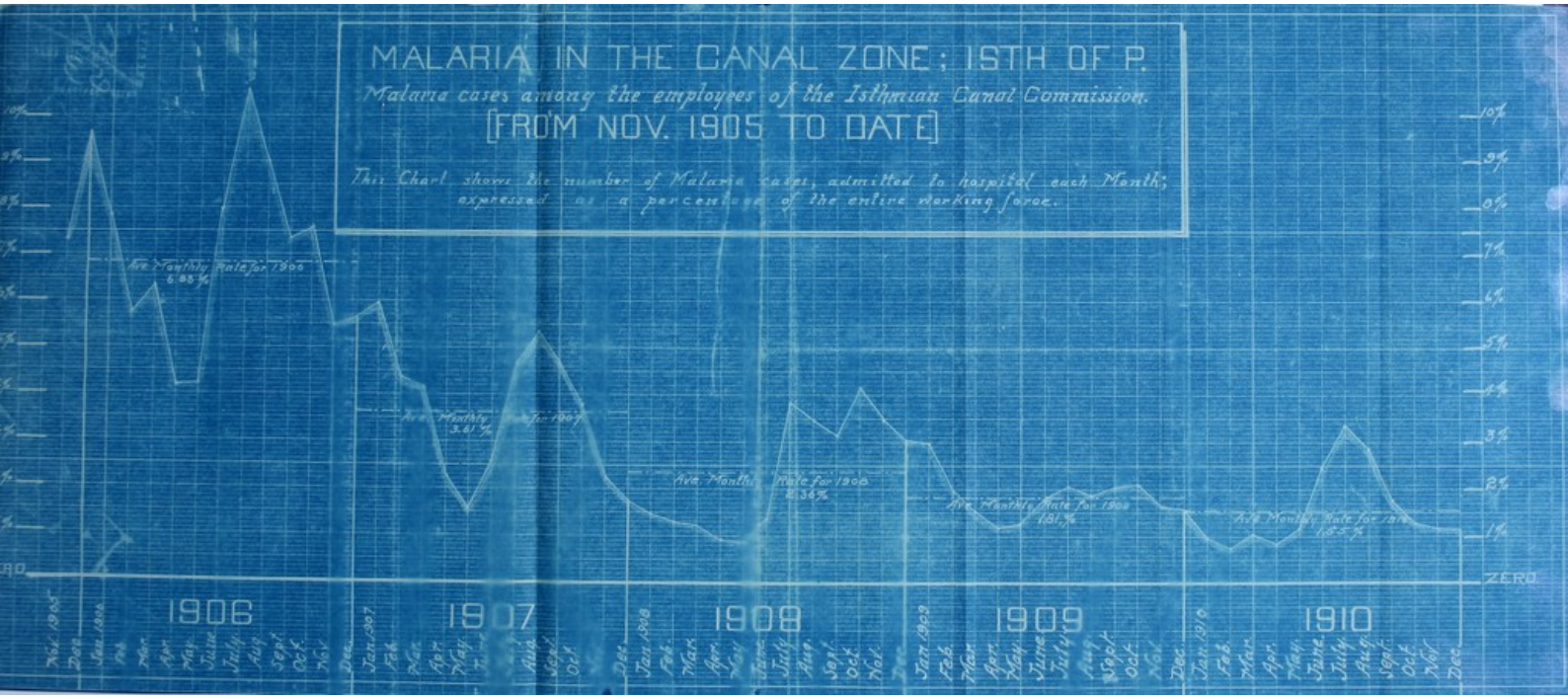
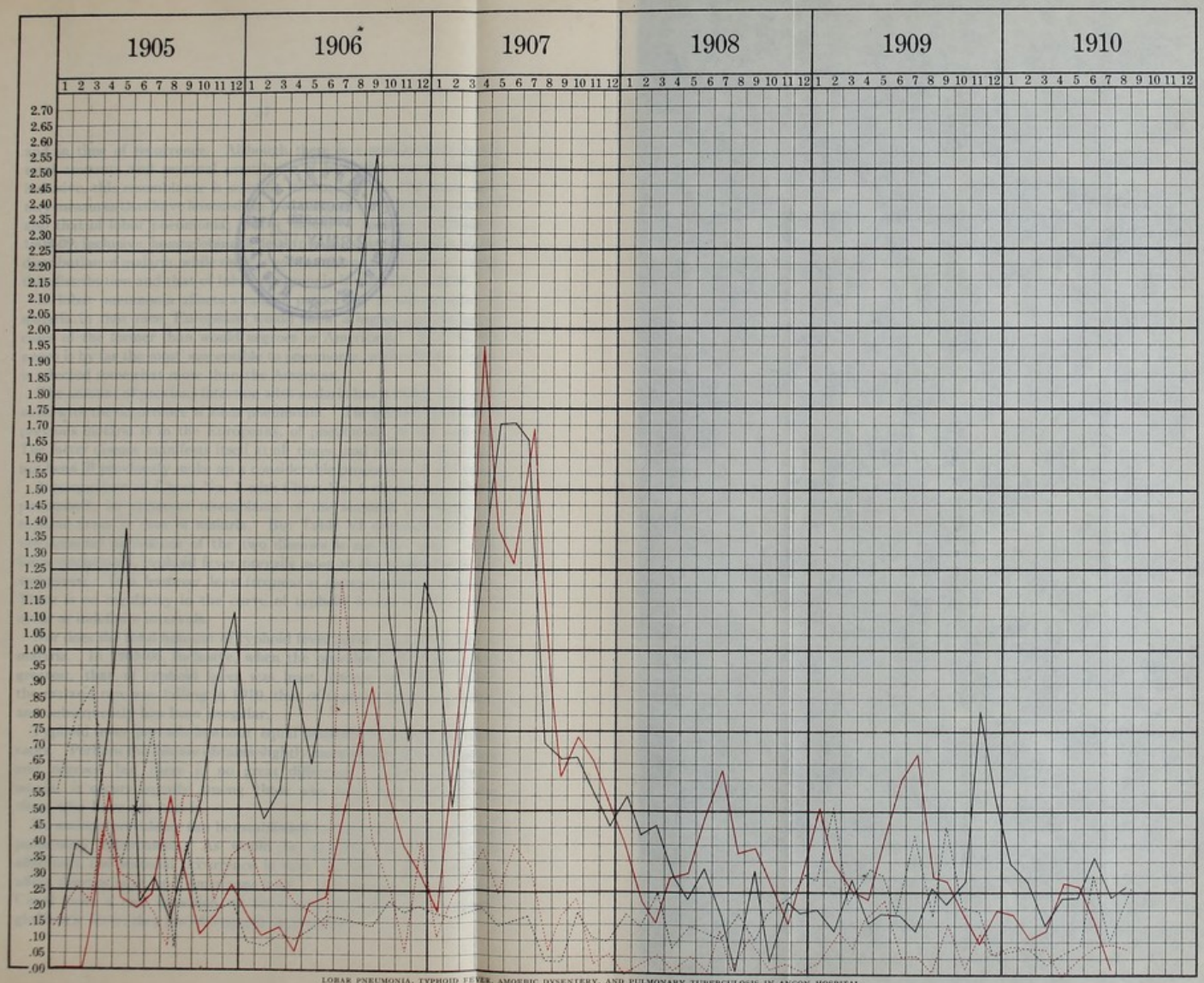

MALARIA IN THE CANAL ZONE; 15TH OF P.
Malaria cases among the employees of the Isthmian Canal Commission.
[FROM NOV. 1905 TO DATE]
This Chart shows the number of Malaria cases, admitted to hospital each Month; expressed as a percentage of the entire working force.
Ave. Monthly Rate for 1906 6.88%
Ave. Monthly 3.61%
Ave. Monthly Rate for 1908 2.56%
Ave. Monthly Rate for 1909 1.81%
Ave. Monthly Rate for 1910 1.85%
10%
9%
8%
7%
6%
5%
4%
3%
2%
1%
ZERO
1906
1907
1908
1909
1910

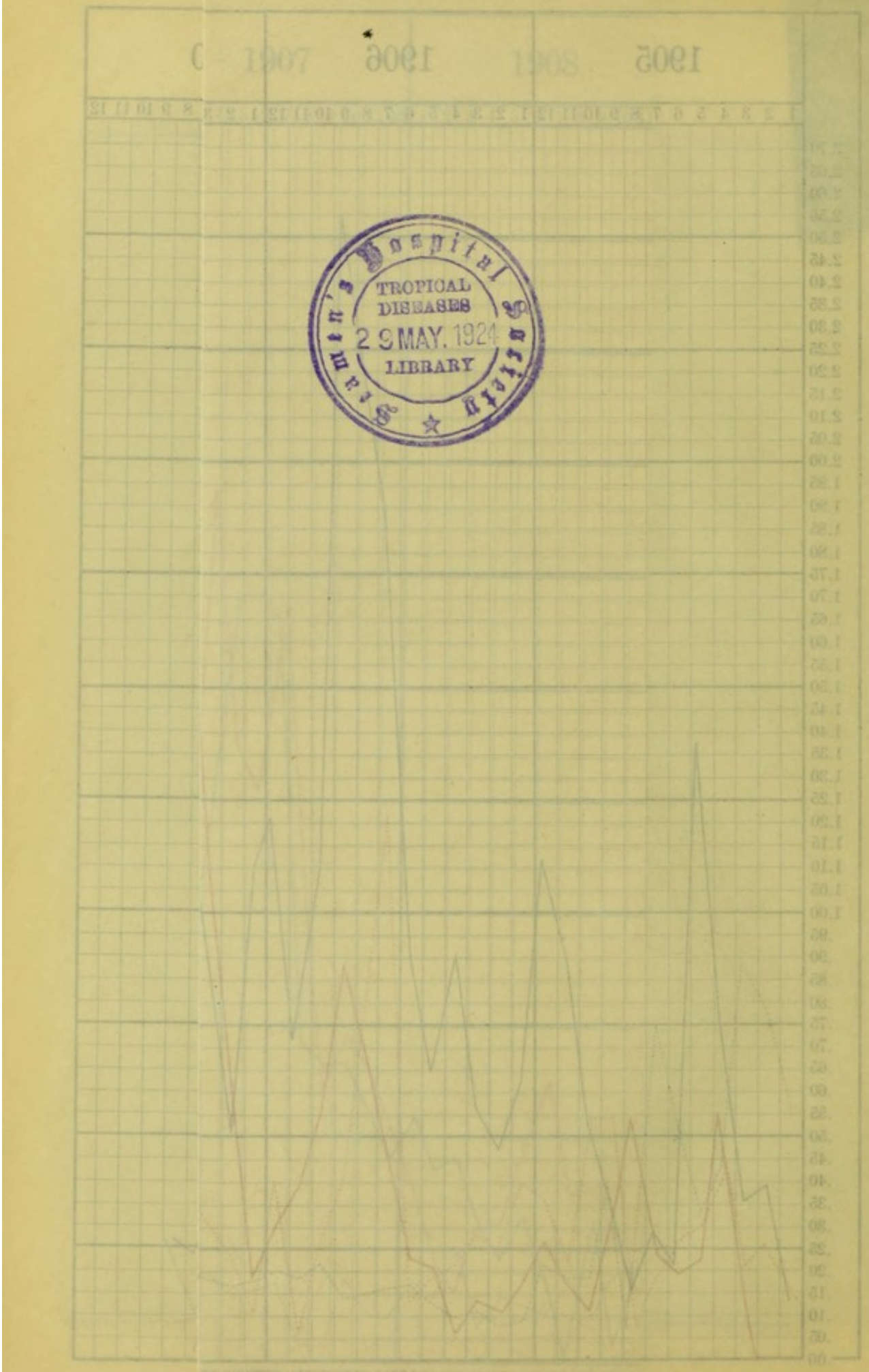
CHART No. 6



LOBAR PNEUMONIA, TYPHOID FEVER, AMOEBIC DYSENTERY, AND PULMONARY TUBERCULOSIS IN ANCON HOSPITAL,
IN TENTHS OF A CASE PER THOUSAND OF THE TOTAL NUMBER OF EMPLOYEES.

Black. Lobar pneumonia
Red. Typhoid fever.

Dotted Black. Pulmonary tuberculosis.
Dotted Red. Amoebic dysentery.



and in time of recurrence. Although there is a resemblance in the total amounts and seasonal prevalence of both diseases in 1905-07, inclusive, this resemblance is wanting subsequently. The same sanitary measures that have lessened the frequency of malaria have lessened also that of lobar pneumonia; but it should be remembered that in 1908-09, inclusive, hemoglobinuric fever prevailed in proportion to the distribution of malaria, while there is no resemblance whatever between this distribution and that of lobar pneumonia in the same period.

If lobar pneumonia affects a race in proportion to the amount of malaria in that race, Europeans would show a higher percentage of cases of the former than would negroes or Americans. As it is, the negro is by far the most susceptible to pneumonia, while the European is affected somewhat more than the American.

The amount of previous infection with malaria has nothing whatever to do with the occurrence of lobar pneumonia. The greatest amount of previous malaria is in the Europeans, of pneumonia, in the negroes. The latter disease manifests itself at all times, and patients who have not been ill previously make up a considerable proportion of the cases.

A comparison of Chart No. 2 with Chart No. 6 shows, as in lobar pneumonia, an apparent resemblance of the seasonal prevalence of typhoid fever to that of malaria. But Table VI demonstrates that the seasonal prevalence of the two diseases is not the same. Like lobar pneumonia, typhoid fever prevails most at the beginning of the wet season. It is, however, least frequent at the end of the wet season. There is no regularity in the curve of typhoid fever, and its apices occur at indefinite intervals.

Nor does the total amouut of typhoid fever agree at all with that of malaria. In 1905-06, inclusive, when the prevalence of malaria was greatest, that of typhoid fever was least, except in 1910. When the malaria rate was falling in 1910, that of typhoid fever was rising, and subsequently has been irregular.

Typhoid fever prevails in about equal proportions among all three races. Perhaps the disease obtains slightly more among the Europeans and negroes, but there is no great difference. Like lobar pneumonia, it occurs equally among those who have had malaria and those who have not had it.

No seasonal prevalence can be established for amoebic dysentery and pulmonary tuberculosis. As would be expected in such chronic affections, the seasonal occurrence is very irregular. Both diseases affect negroes most and Americans least. Among the natives of the Canal Zone, a race in which we have seen but one case of hemoglobinuric fever, they are of frequent occurrence.

The etiology of all four diseases is well understood. But if it were not, and one should endeavor to trace a positive connection between malaria and any one of them, such as has been traced between malaria and hemoglobinuric fever, the attempt would not result in any definite findings. For while there are times when these diseases occur in proportion to the prevalence of malaria, the contrary is as often true. Active malaria is seldom present in their clinical course.* A history of previous malaria is frequently present, but as often can be excluded. There is not in any distribution of these diseases, total or racial, the orderly sequence of cause and effect that is shown in the comparison of the epidemiology of malaria with that of hemoglobinuric fever; in which comparison the total, racial, and seasonal prevalence of the latter was found to correspond with that of the former.

For these reasons we maintain that there is no definite relationship between the epidemiology of malaria and that of other diseases prevalent in the Canal Zone.

MALARIA AS A PREDISPOSING CAUSE OF HEMOGLOBINURIC FEVER.

If malaria be a predisposing cause of hemoglobinuric fever, a history of prior infection with the former should be found in all or nearly all cases of the latter; and hemoglobinuric fever should prevail, as a whole, in proportion to the total amount of previous malarial infection, and should obtain in any particular race of people according to the extent of previous malarial infection in that race.

From the histories of the 230 cases of hemoglobinuric fever we have compiled the following data relative to previous malarial infection. As an examination of the hospital records subsequently demonstrated, these histories were fairly accurate. They may be analyzed in two ways; previous admissions, without statements by the patients as to the nature of the former diagnosis, and previous admissions which the patients stated were due to malaria.

In 215 of these cases the hospital records were searched in order to ascertain the diagnoses of the previous admissions. This was a very difficult task, as most of the patients were European and negro laborers, whose names were frequently misspelled, and for this reason their previous admissions could not be found in our card index. Moreover, not all previous hospital admissions recorded on the charts were to Ancon Hospital. Yet we were able to identify positively the previous admissions of seventy-five patients. Table IX gives the result of our findings. Seventy-one of the seventy-five patients, or 94.6 per cent,

*Except in amoebic dysentery. See Appendix B.

showed one or more previous admissions due to malaria. Of these, forty-seven, or 66.4 per cent, were positive. Forty-one of these positive infections were estivo-autumnal, five were tertian, and one was a quartan. So that 87.2 per cent, of the positive bloods, and, if the same ratio be applied to the diagnosis of clinical malaria, 87.2 per cent of this previous malaria was due to estivo-autumnal infection. It should be noted that the percentage of positive bloods in these prior admissions was above the average.

TABLE IX.—*This table shows the number of cases of hemoglobinuric fever in which we were able to verify the previous admissions by means of the hospital records. Seventy-five cases were found to have been previously in the hospital, and the findings in these previous admissions are given in the table. This table shows only whether the previous admissions were positive or negative for malaria, and does not include previous admissions due to hemoglobinuric fever. Prior multiple admissions for malaria are counted only once, and the numbers of the multiple admissions are given elsewhere. The object of the table is to show, as far as possible, the per cent and kind of malaria in the previous admissions.*

Number of cases in which prior admissions were verified	75
Number of these diagnosed as malaria in the prior admissions	71
Percentage of verified prior admissions diagnosed as malaria	94.6
Number of verified prior admissions in which the blood was positive	47
Percentage of these positive	66.4
Number of estivo-autumnal infections in the verified prior admissions	41
Percentage of estivo-autumnal infections in the positive bloods	87.2
Number of tertian infections in the verified prior admissions	5
Percentage of tertian infections in the positive bloods	12.1
Number of quartan infections in the verified prior admissions	1
Percentage of quartan infections in the positive bloods	1.4
Number of clinical malarial infections in the verified prior admissions	24
Percentage of these clinical infections	33.6

Since the cases whose prior admissions were thus ascertained comprised one-third of the number examined, and were not purposely selected, but occurred at more or less regular intervals in the series, there is no reason to doubt that the previous admissions which we could not confirm would show the same per cent, 94.6, of malarial diagnoses. In no disease other than hemoglobinuric fever is there so large a percentage of prior admissions due to malaria. Not even in malaria itself, with its numerous re-infections and relapses, is this percentage so high. It is plain then, that a very large number, at least 90 per cent, of previous admissions of patients prior to the hemoglobinuric attack was due to malaria.

Table X gives an analysis of the statements on the charts in regard to previous admissions or previous attacks of malaria.* In this table a "prior attack of malaria" means that the attack occurred sometime prior to admission. In those cases in which no history of a previous admission or of a prior attack of malaria could be obtained, there is evidence to show, as we shall explain, that an attack of malaria preceded the onset of the hemoglobinuria, either outside or while the patient was in the hospital. And such an attack we shall consider as a predisposing cause, for we do not claim that every case of hemoglobinuric fever develops only after repeated infections with malaria.

*Not all of these statements are accurate, but in the aggregate they are substantially so.

*TABLE X.—*Showing the findings as to previous hospital admissions or prior attacks of fever, as taken from the histories of the patients who had hemoglobinuric fever.*

Class.	Number of cases.	Percentage of cases in each class.	Remarks.
Denied previous malaria...	6	2.60	Of these, three, or 50 per cent, were admitted with positive infections. Two had hemoglobinuria before admission, and one had clinical malaria.
No record of previous admissions or prior febrile attacks.	24	10.43	Of these, fourteen, or 58.3 per cent, were admitted with positive infections. The others had hemoglobinuria before admission, or clinical malaria on admission.
Charts were marked "No previous admissions" or "No prior febrile attacks."	17	7.39	This may mean that there were no admissions to Ancon or other hospitals, but does not exclude admissions to dispensaries or sick camps, and there may have been fever without treatment or hospital admissions.
One previous hospital admission or one prior attack of fever.	65	28.26	Forty-six cases gave histories of one previous hospital admission. Nineteen cases gave histories of one prior attack of fever.
Two previous hospital admissions or two prior attacks of fever.	34	14.78	Twenty-two cases gave histories of two previous hospital admissions. Twelve cases gave histories of two prior attacks of fever.
Three previous hospital admissions or three prior attacks of fever.	23	10.00	Nine cases gave histories of three previous hospital admissions. Fourteen cases gave histories of three prior attacks of fever.
Four previous hospital admissions or four prior attacks of fever.	18	7.82	Eight cases gave histories of four previous hospital admissions. Ten cases gave histories of four prior attacks of fever.
Over four previous hospital admissions or over four prior attacks of fever.	43	18.43	Twenty-two cases gave histories of over four previous hospital admissions. Twenty-one cases gave histories of over four prior attacks of fever

*This table was made before the case reports were verified as to previous admissions. The few discrepencies between the table and the case reports are due to errors in the history.

Six patients denied a history of previous malaria. Parasites were found on admission in the bloods of three of these; two others were admitted with hemoglobinuria, a condition, that as we shall show, makes the finding of parasites very difficult, and the sixth patient was admitted with a well-marked clinical malaria, in him the hemoglobinuria did not develop until later. Now, we have demonstrated that in every instance in which hemoglobinuric fever developed while the patient was under observation in the hospital, the onset of the disease was preceded shortly before by an attack of positive or clinical malaria. There were 102 such cases, and it is no more than reasonable to suppose that a similar malarial attack preceded the hemoglobinuria in those patients who were admitted with the latter disease. So that in none of the six cases in which a history of previous malaria was denied can the existence of a malarial attack prior to the hemoglobinuria be excluded, and in four of these there was positive evidence of such an attack.

In those cases in which there were no records on the charts as to previous admissions or prior malaria, the blood was positive in fourteen, or 58 per cent. All others were admitted with either a clinical malaria which preceded the hemoglobinuria, or with the latter already developed.

The same is true of the seventeen cases that had no history of previous hospital admissions; either positive or clinical malaria preceded the hemoglobinuria, or the latter was present on admission.

The remainder of the cases in Table X are those in which one or more prior hospital admissions or prior malarial attacks were designated in the histories. The same reasons as given above apply to that small proportion of these cases in which the previous admissions might not have been due to malaria, in order to show in these a malarial attack that preceded the onset of hemoglobinuria. A summary of the table shows that the cases may be divided into two groups; in one of which there was no history or record of previous admissions or prior febrile attacks; in the other, a history or record of one or more of each of these. In both groups an attack of malaria that closely preceded the hemoglobinuria can be shown for many of the cases and safely inferred for the remainder. The large number of cases in which there were multiple previous admissions or prior febrile attacks is worthy of consideration. In every instance in which three or more of the previous admissions could be verified, two of these were always due to malaria, and very often all of them. In our summary of the 230 cases of hemoglobinuric fever in Appendix A at the end of this paper, these prior admissions, when found, are included in the case reports. There is, then, in practically every one of these cases a definite history of a malarial attack at some time prior to the onset of the hemoglobinuria. In no case is there reason to exclude such a history. So great an amount of previous malarial infection is not to be found in the histories of cases of other diseses, not even in malaria itself, as has been noted, and is ample proof that malaria is in some way a predisposing cause of hemoglobinuric fever.

We shall now consider the premise, that if the malaria is such a predisposing cause, hemoglobinuric fever should prevail in any particular race in proportion to the amount of previous malarial infection in that race. When considered as applying to a race as a whole, previous malarial infection occurs in two ways. In time of severe prevalence of malaria, such as in 1905 and 1906, a race may acquire a greater amount of infection than in a period of several years when the malarial rate is low. Consequently previous malarial infection is in proportion to the prior prevalence of malaria; and a great amount may be acquired in a short while, or an extended length of time may be necessary to obtain it.

The universal and severe prevalence of malaria in 1905 and 1906 has already been described, and the fact noted that hemoglobinuric fever obtained not only as a whole in proportion to this prevalence, but also in proportion to the racial distribution of malaria, among the Americans and Europeans. It has also been shown that since 1907 the proportion of hemoglobinuric fever has increased among the Euro-

peans and decreased among the Americans. In Table XII is given the length of residence prior to the onset of hemoglobinuric fever in our series of cases. It will be seen that in 1905 and 1906 the time necessary for the development of the disease was much shorter, as a rule, than subsequently. Since 1907 the few cases in Americans have occurred in those who have been a year or more on the Canal Zone. It is estimated at this time (September, 1910) that not over 15 per cent of the Americans now employed have been on the Isthmus over four years. In the last three years but little malaria, comparatively speaking, has prevailed in this race; and, as the table shows, but little hemoglobinuric fever also.

It will be noted that in 1908 nearly all of the cases of hemoglobinuric fever in the Europeans occurred in those who had been between one and two years in this country. And in 1909 and 1910 most of the cases occurred in those who had been here between one and three years. That is, the disease has prevailed chiefly in those who arrived in the latter part of 1906 and in 1907. In these years, as has been explained, there was a continual immigration of those laborers. Malaria has been very prevalent among them since 1907, but not as severe as in 1905 and 1906. So that it has taken a longer time to acquire the necessary amount of previous infection.

In analyzing the cases which occurred in 1905 and 1906, it was found, with two exceptions, that every case gave a history of previous malaria. In the two cases excepted, there was a positive malarial infection in one, and the other was admitted with hemoglobinuria. So that in times of great prevalence of malaria repeated attacks of that disease occur at short intervals, and most of the cases of hemoglobinuric fever that occurred in this period were in persons who had been less than a year in the Canal Zone.

The prevalence of malaria among the negroes in 1905-06 was disproportionate to the occurrence of hemoglobinuric fever. Table V shows that in 1906 and 1907 the death rate from malaria in this race was very high, and that in 1908 and 1909 it fell to a very low point. Table VII demonstrates that at no time has the rate per thousand for hemoglobinuric fever been so high in proportion to the malaria rate as in the white races, and that for some reason hemoglobinuric fever does not follow malaria in the negro to any great extent.

Now, while it is true that the negro is relatively immune to malaria, he is very prone to pernicious attacks of the disease. Not many of the Americans or of the European laborers will allow a malarial attack to continue without treatment for any length of time. But in the negro a malarial paroxysm or two is often followed by a so-called spontaneous

cure, due very likely to the calling forth of certain factors that render him immune. When this relative immunity is once overcome, the disease, if untreated, proves rapidly fatal. For this reason, in times of great malarial prevalence, the death rate among the negroes, when compared with that of other races, is relatively higher than the amount of infection. Relapses are much less likely to occur in this race than in the European, as is plainly shown by the small rate per thousand for malaria of the negro in 1908-10 (See Chart No. 4). And the evidence hitherto adduced is conclusive as to the importance of relapses in malaria as a predisposing cause of hemoglobinuric fever. It is plain, then, that notwithstanding the disproportion between the rates per thousand of hemoglobinuric fever and malaria, in 1905-06, the relative immunity of the negro against the latter disease has a parallel in his relative immunity against the former.

That hemoglobinuric fever prevails in proportion to the amount of previous malarial infection is evident from a consideration of the previous arguments. In the section devoted to the comparative epidemiology of the two diseases, of the two cycles of hemoglobinuric fever, the first was shown to follow the general prevalence of malaria at a time when all races were exposed to this disease; and the second, to come after prior malarial infection in the only race that was heavily infected.

One other proof of the necessity of prior malarial infection may be adduced. The seasonal occurrence of hemoglobinuric fever, shown in Table VI, follows that of malaria. It is not until malaria has been prevailing for a few months that the other disease reaches its seasonal maximum. This is what should be expected of a disease dependent upon prior infection with another for its etiology. The dependent disease ought to increase in frequency after the manifestation of the prior disease; and that this is true, a comparison of the seasonal prevalence of the two diseases shows.

SUMMARY.

Prior to the onset of hemoglobinuric fever in cases that developed while under observation in the hospital, in every instance there was a manifestation of positive or of clinical malaria. In a large proportion of all cases of hemoglobinuric fever there was a history of previous hospital admissions, and of these that could be verified, 94.6 per cent were due to malaria. Most of the patients gave histories of repeated malarial attacks.

In proportion to the prevalence of prior malaria among the races employed by the Commission, and particularly in proportion to their

susceptibility to malaria and relapses, hemoglobinuric fever developed subsequently.

The amount of previous malaria, whether recent or remote, determines the prevalence of hemoglobinuric fever.

From these conclusions, it is very evident that malaria is a predisposing factor of great importance in hemoglobinuric fever.

MALARIA AS AN EXCITING CAUSE OF HEMOGLOBINURIC FEVER.

The constant association of an active malarial infection with hemoglobinuric fever has been noted by many writers on tropical diseases. Stephens[7] has collected 23 cases in which the blood was examined on the day before the onset of hemoglobinuria. Of these, twenty-two, or 95.6 per cent, showed a positive infection. On the day of the attack the blood examination showed in sixty-three instances parasites in thirty-nine, or 61.9 per cent. On the day after the blood was positive in eleven of sixty-four examinations, or 17.1 per cent. These findings make it plain that parasites are found for the most part immediately prior to the onset of the disease and subsequently lessen in frequency.

Although the percentage of positive bloods in our series of cases is not as high as in the foregoing, the results obtained from an analysis of our blood findings are approximately the same. In our cases the blood examinations were mostly made as a matter of routine and no especial attention was paid to the finding of parasites.

We have divided our cases into three Classes for convenience of reference. Class I—those in which there was hemoglobinuria prior to admission, but not subsequently; Class II—in which hemoglobinuria was present on admission; and Class III—in which it developed after admission. Since in most cases the blood was examined only at the time of admission, while the hemoglobinuria occurred at varying intervals prior to admission and subsequently, we are unable to give exact data as to the presence of parasites immediately before, during, or after the onset of the disease.

In the fifteen cases in Class I the bloods were all negative on admission. In two patients in this class malaria developed subsequently, fifteen days after admission in one and twenty days after in the other.

Table XI, *a* and *b*, gives in detail the blood findings in Classes II and III. In Class II there were one hundred and thirteen cases. The blood examinations were positive in twenty-seven, or 23.8 per cent of these. A careful study of the histories in these cases has convinced us that too much reliance should not be placed on the stated length of time prior to admission that the hemolglobinuria occurred; for, "passing blackwater" one, two, or three days may mean either

including or excluding the day of admission. Moreover, many of these patients were very ill at the time of admission, and histories as to the duration of the disease might have been inaccurate.

TABLE XI, *A* and *B*.—*Shows, A, the results of the blood examinations on admission in cases of hemoglobinuric fever that developed before admission to the hospital, in which hemoglobinuria was present on admission; and B, the results of blood examinations on admission when the hemoglobinuria developed after admission.*

A.

[Result of blood examinations on admission.]

Admitted to Ancon Hospital with hemoglobinuria that began—	No. of cases in which estivo-autumnal parasites were found.	No. of cases in which tertian parasites were found.	No. of cases in which the blood was negative	Total number of cases.	Total number of cases in which the blood was positive.	Percentage of positive bloods.
The day of admittance before entrance into the hospital	5	1	16	22	6	27.2
One day prior to admission	4	3	35	42	7	16.6
Two days prior to admission	4	.....	10	14	4	28.5
Three days prior to admission	1	.....	3	4	1	25.0
Four days prior to admission	.....	.....	2	2	0	.0
(?) days prior to admission	7	2	20	29	9	31.0
Totals, and average percentage	21	6	86	113	27	23.0

B

[Hemoglobinuria developed.]

*The day of admission after entrance into the hospital	6	.....	8	14	6	42.8
One day after admission	9	5	14	28	14	50.0
Two days after admission	14	2	6	22	16	72.7
Three days after admission	9	3	5	17	12	70.5
Four days after admission	4	2	2	8	6	75.0
Over four days after admission	4	2	7	13	6	46.1
Totals, and average percentage	46	14	42	†102	60	†61.0

*It is not possible to say, in all cases, if the blood was examined before or after the onset of hemoglobinuria.

†Four bloods not examined prior to the onset of the hemoglobinuria.

It is in Class III, to which we have referred several times, that the most satisfactory information of the frequency with which malaria is associated with hemoglobinuric fever may be ascertained. Table XI, *b*, gives the percentage of positive bloods at the time of admission, and shows also the length of time that elapsed before the occurrence of hemoglobinuria. The one hundred and two cases in this group were carefully observed and the data given are quite accurate. In all, 61 per cent of the blood examinations were found positive, and in those cases in which negative bloods were found, clinical malaria was manifested.

The reasons for the apparently low percentage of positive bloods in the total malaria have been explained. These same reasons apply to the percentage of positive bloods in Class III. The average for all blood examinations in malaria was 58 per cent positive; in

Class III, this average was 61 per cent. There is no reason to doubt the accuracy of the diagnoses of clinical malaria in this class, and it is safe to say that a close association with a malarial infection is shown in all cases in it. Certainly those patients whose bloods were negative had every other sign and symptom of malaria prior to the onset of hemoglobinuria, as an examination of the case reports will make plain.

Although it is possible from the data given in this section, and the preceding ones, to infer that an active malaria occurs very often immediately prior to the onset of hemoglobinuria, and a short while before, is always in evidence, it is not easy to estimate the precise importance of such malaria as an exciting cause of the disease. There is evidence to show that in a very few individuals but one attack of malaria preceded the hemoglobinuria. And at other times hemoglobinuria did not develop until the patient had taken enough quinine to be cured of malaria. Such instances, although infrequent, make it improbable that the malarial attack alone is always the exciting cause, for in most part such an attack prior to the hemoglobinuria had been preceded by other malarial manifestations at varying intervals. Our opinion, from the evidence, is that active malaria, prior to the onset of hemoglobinuria, is one of the final determinative factors in the eventuation of this disease; and in a few instances one malarial attack may act as both an exciting and predisposing cause. It is certain, however, that such active malaria is intimately connected with the development of hemoglobinuric fever, and our data as a rule confirm the opinion of Stephens, "Not only is blackwater dependent on a malarial infection at some previous time, but the relationship is a very close one, depending on the actual presence of parasites (or, in our experience, either parasites or clinical malaria) immediately prior to the attack. To deny the significance of these parasites (or of the clinical malaria), as has been done, seems equivalent to denying the significance of parasites (or of clinical malaria) in an equivalent number of malarial cases, and to be contrary to common sense.[7]" The parentheses are ours.

THE SPECIES OF MALARIA PARASITE THAT IS CONCERNED IN THE PRODUCTION OF HEMOGLOBINURIC FEVER.

In the two hundred and thirty cases of hemoglobinuric fever, estivo-autumnal parasites were associated sixty-eight times with the disease, and tertian parasites twenty-one times. The percentage of estivo-autumnal parasites in the positive bloods was 76.4, that of the tertian parasites, 23.6. These percentages approximate very closely those for the positive bloods in the total malaria. (See Table I.)

It would appear from this that each species of the parasite is associated with hemoglobinuric fever in about the same proportion as in the total malaria. However, it should be remembered that previous malarial attacks occurred in a large number of patients who had hemoglobinuria. The percentages of the species of malaria concerned in the production of these previous attacks, were, as shown in Table IX, estivo-autumnal, 87.2; tertian, 12.6. (One patient who developed hemoglobinuria had at the time of onset a tertian infection, and had been twice before, in the two months preceding his hemoglobinuria, in the hospital with quartan malaria.) These figures show that estivo-autumnal parasites, as an antecedent factor, predispose in considerably greater proportion to hemoglobinuric fever than do the other species.

When the species of parasite responsible for prior infections is ascertained in individual instances even stronger evidence of the importance of estivo-autumnal infection may be induced. As far as it was possible to obtain it, a comparison of the species of parasite found on admission with the species present in prior admissions was made. We have summarized the results of this comparison as follows:

1. In twenty-one instances in which the blood examination at the time of admission for hemoglobinuric fever showed estivo-autumnal parasites, the blood findings for previous admissions were: estivo-autumnal parasites, 15; tertian, 2; negative, 4. Percentage of estivo-autumnal parasites in the positive bloods, 88.2; of tertian parasites, 11.8. In three instances there were two prior estivo-autumnal infections.

2. In ten instances in which tertian parasites were found, the blood findings in the previous admissions were: estivo-autumnal parasites, 6; tertian parasites, 1; negative, 2; quartan, 1. Excluding the quartan infection, the percentage of estivo-autumnal parasites in the positive bloods was 85.7; of tertian, 14.3. There was one former mixed infection.

3. In forty-two instances in which the blood was negative on admission, the findings for previous admissions were: estivo-autumnal parasites, 21; tertian, 2; negative, all clinical malaria, 17; mixed infection with tertian and estivo-autumnal malaria, 2. Excluding the mixed infections, the percentage of estivo-autumnal parasites in the positive bloods was 87; of the tertian, 13. In six of these there were two previous infections with estivo-autumnal parasites, and in three, three such previous infections.

We were able also to ascertain the blood findings in several admissions subsequent to the hemoglobinuric attacks. Estivo-autumnal malaria at the time of the hemoglobinuria was followed four times by

the same variety, but not by tertian malaria. Similar coincident tertian infections were followed three times by estivo-autumnal malaria, but not by tertian itself. Admissions for hemoglobinuric fever in which the blood was negative were followed four times by estivo-autumnal malaria, but not by tertian. One quartan infection followed a previous hemoglobinuric attack associated with estivo-autumnal parasites.

Although we were able to make the preceding comparisons in but one-third of our cases of hemoglobinuric fever, there is no reason to doubt that the parasites would have been found in the same percentages had it been possible to get records of the blood findings in all previous and subsequent admissions. If this is true then the estivo-autumnal parasite is by far the more important of the two in the production of hemoglobinuric fever.

There is a very strong probability that many of the patients who had tertain infections at the time of the hemoglobinuria may have had also coincident estivo-autumnal infections. In a series of experiments to determine the temperature curves in estivo-autumnal and in tertian malaria, we withheld quinine. Fifteen of these experiments were with what we thought at first to be unmixed tertain infections. Before the experiments were concluded, in eleven of these tertain infections we found either estivo-autumnal schizonts or crescents at some time in the course of the fever. In several, estivo-autumnal infections entirely replaced the tertian, but we did not observe the converse. It should be noted that tertain infection occurred twice only prior to hemoglobinuria associated with estivo-autumnal parasites; and once only prior to similar association with tertian parasites.*

It is not possible to exclude absolutely tertian or quartan malaria in the etiology of hemoglobinuric fever, either as exciting or predisposing causes. Case No. 204, a Spanish boy, 9 years of age, died four days after the onset of a most pernicious hemoglobinuric attack. Up to the hour of death, this patient's blood showed the heaviest tertian infection we have ever witnessed; and, although a careful search was made during life, and in autopsy smears, no estivo-autumnal parasites were found. This boy had been nine months on the Isthmus and had lived three years previously in Cuba. In Case No. 71, a German, a well marked triple quartan infection developed on May 3, 1905, after the patient had been six weeks on the Isthmus. There was a relapse of this infection on May 25. On July 15, of the same year, he was

*Since this was written, in working with the "thick film," we frequently find crescents associated with tertian infection

admitted to Ancon Hospital with tertian parasites in his blood.* On July 16, hemoglobinuria developed. Although it is not possible in either of the above cases to exclude an estivo-autumnal infection, they present evidence that any species of malaria may be present at the time of hemoglobinuria and may be taken to have etiological significance.

A consideration of the data given above shows that about 87 per cent of the malarial attacks prior to the onset of hemoglobinuric fever was due to estivo-autumnal malaria. In the small percentage of previous malaria due to tertian infection, there is a strong probability that estivo-autumnal malaria might have been associated with the milder infection.† In this connection it is well to note the geographical distribution of hemoglobinuric fever. This disease prevails only in regions where estivo-autumnal malaria also prevails, and is not endemic in countries where tertian and quartan malaria only obtain. The more intense the prevalence of estivo-autumnal malaria, the greater the proportion of hemoglobinuric fever, is the rule in countries where the latter disease is endemic, and our data bear out this observation.

We do not deny the possibility of tertian infection, or of quartan, as a predisposing cause of hemoglobinuric fever, but the evidence in favor of these two varieties of malaria is neither so strong nor so convincing as to enable us to attribute to them much etiological importance.

VI.

LENGTH OF RESIDENCE IN MALARIAL COUNTRY AS A FACTOR IN THE ETIOLOGY OF HEMOGLOBINURIC FEVER.

Most authorities state that hemoglobinuric fever attacks in greatest numbers those who have resided one or two years in a country where the disease is endemic. Otherwise than as it offers an opportunity for the acquirement of a condition resulting from repeated malarial infections or relapses, it is not claimed that such length of residence is an etiological factor.

Table XII gives the time of residence in the Canal Zone for the 226 cases of hemoglobinuric fever in the period from January 1, 1905, to September 1, 1910. The time of residence for the cases in 1904 is shown in Table VIII. Such Europeans as were entitled to quarters similar to those of Americans are classed with the latter. There were very few of these. In the period 1905-07, inclusive, it will be seen

*There is some doubt as to the correctness of this diagnosis of tertian malaria. It would appear that the quartan relapsed.

†In recent investigations with the "thick film" method, we find crescents in 40 per cent of tertian infections.

that most of the cases occurred within the first twelve months of residence. For convenience, we shall refer to all cases in this time as "Group A." In 1908-10, inclusive, most of the cases developed after twelve months' residence; all cases in this period are referred to as "Group B."

It is obvious that in Group A, length of residence did not play as an important part in the production of hemoglobinuric fever as in Group B. If we assume that the same cause which produced the disease in the first group produced it also in the second, it will be of interest to determine why this cause should operate with comparative rapidity in one group and slowly in the other.

Table XII shows that in every year a certain proportion of the cases occurred in the first twelve months.

TABLE XII.—*Showing the cases of hemoglobinuric fever grouped according to the period of residence on the Isthmus.*

Time on Isthmus—figures represent months.	1905.				1906.				1907.				1908.				1909.				1910. Jan. to Sept.				Per cent of cases in each period.
	US	E	B	Total	US	E	B	Total	US	E	B	Total	US	E	B	Total	US	E	B	Total	US	E	B	Total	
1–3	4	2	2	8	3	2	2	7	1	....	1	2	....	2	....	2	....	....	....	....	....	....	....	....	8.4
4–6	3	2	2	7	2	1	3	6	1	1	3	5	....	3	....	3	....	2	1	3	....	3	1	4	12.3
7–9	1	....	....	1	1	3	3	7	....	....	1	1	....	1	....	1	....	3	....	3	....	3	....	3	7.0
10–12	....	....	....	....	....	1	4	5	....	2	....	2	....	3	....	3	....	4	....	4	....	....	3	3	7.5
13–24	1	1	....	2	3	2	2	7	3	1	3	7	1	22	....	23	....	32	3	35	....	5	....	5	34.9
25–36	....	....	....	....	1	1	....	2	....	....	....	....	....	2	....	2	....	23	5	28	....	6	1	7	17.2
37–48	1	....	....	1	....	....	....	....	....	....	....	....	....	....	....	....	1	2	....	3	....	4	3	7	4.8
Over 48	....	....	....	....	1	1	....	2	....	1	....	1	....	....	....	....	2	1	....	3	....	....	2	2	3.5
*Life	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	1	....	1	0.4
Unknown	....	....	....	....	....	....	2	2	....	....	....	....	2	1	....	3	....	1	....	1	....	1	1	2	3.5
Total	10	5	4	19	11	11	16	38	5	5	8	18	3	34	....	37	3	68	9	80	....	23	11	34	

*One "life" European in Table VIII is credited in this table with "over 48."

In Table XIII the percentage of cases that occurred in each year under and over twelve months of residence is given. No figures are given for 1910, as all the data for this year are not yet available. Table XIII shows that since 1905 the number of cases that developed under twelve months' residence has gradually decreased, while the number over that period has steadily increased. A reference to Chart No. 1 partially explains the reasons for this. In 1905 the employees of the Commission had not been on the Isthmus for a year. We are not dealing with a fixed population, but one of changing immigration from non-malarial countries to a malarial one. It is evident that in 1905 and 1906 such diseases as occurred, including hemoglobinuric fever, would necessarily appear in persons who for the most part had been less than a year in the Canal Zone. In 1908 and 1909 an average residence of from two to three years had been established for a considerable number of employees, but not all, as there is a constant immigration and emigration among all three races employed.

TABLE XIII.—*Showing the percentage of cases of hemoglobinuric fever per year that had been on the Isthmus under and over twelve months. Cases whose histories showed a residence of twelve months are grouped as under that time.*

	1905.	1906.	1907.	1908.	1909.
Percentage of cases under twelve months' residence .	84.2	65.8	55.5	24.3	12.5
Percentage of cases over twelve months residence . . .	15.8	34.2	44.5	75.7	87.5

It will be noted that since 1907 by far the greater number of cases have developed in European laborers. In 1908, 91.8 per cent, and in 1909, 80.5 per cent of the hemoglobinuric fever in Ancon Hospital was in this class. In the preceding years the disease was distributed far more equally among the three races. In 1908 and 1909 the average length of residence among Europeans was as great as that of most of the Americans and many of the negroes, owing to the shifting of the population in the last two. Why, then, of those who had been from one to two years on the Isthmus, should the Europeans be affected so disproportionately? And as, since 1907, there has been a constant arrival of Americans and negroes to take the places of those who were leaving, why should there not be the same occurrence of hemoglobinuric fever in the new arrivals as in 1905 and 1906?

An examination of the histories of the nineteen cases in 1905, and the thirty-eight in 1906, shows that in 1905, fourteen of the nineteen patients had had prior attacks of fever other than those associated with the hemoglobinuric fever; and in 1906, thirty-six of the thirty-eight had been similarly affected. In these two years, as has been shown, the malarial rate per thousand was very high among all races, and in 1905 was especially so among the Americans. Since January,

1907, this rate has decreased very noticeably among the Americans and negroes, but to a much less degree among the Europeans.

From these data it can be inferred that in 1905 and 1906 repeated re-infections and relapses were common among the Americans and negroes, even among those who had been but two or three months in the country. So that if repeated malarial infections be a primary cause of hemoglobinuric fever, this cause operated to a far greater extent and more rapidly in these two races in 1905 and 1906 than subsequently. And it follows, that to be effectual, the cause would need a longer time, owing to the greatly decreased malarial rate, in 1907-10, inclusive. That such is the truth is evident from the length of residence prior to the onset of hemoglobinuria, as shown in Table XII, for the Americans and negroes in 1908-10.

The effect of the continual exposure to malaria in a given race is beautifully demonstrated by the examination of the results of such exposure among the Europeans. In 1905 and 1906 those of this race who were resident in the Canal Zone were greatly exposed to malarial infection, and acquired hemoglobinuric fever in proportion, as shown in Table VII. In the latter part of 1906 and throughout 1907 about four thousand of these laborers arrived on the Isthmus. Although these new arrivals were exposed to malaria, this exposure was not so great as that of their predecessors, and owing to the great increase of more than four hundred per cent in their number, naturally the rate per thousand for hemoglobinuric fever fell off in 1907 in this race. But with the advent of the wet season of 1908, the malarial rate among them was increased to a large extent (Chart No. 4). This increase, as has been explained, was greatly due to relapses in those who had acquired the infection during the preceding year. And in 1909, some of those who had escaped hemoglobinuric fever in 1908, had accumulated enough previous malarial infection to develop hemoglobinuria, while at the same time later arrivals who were more susceptible were developing the disease. As a result of this continued exposure to malaria from 1907, in 1909 the hemoglobinuric fever rate per thousand reached a maximum (See Table VII, European rate per thousand in 1909), although in this year the malaria rate among the Europeans was lower than in 1908 (Chart No. 4).

Most authorities agree that after a residence of from three to four years in an endemic region the hemoglobinuric fever rate diminishes. At present (September, 1910) the average residence of an employee is between two and three years. Owing to the greatly diminished malarial rate among the Americans and negroes, we are unable to say what may be the precise effect on the frequency of hemoglobinuric

fever of such a residence in these two races. Among the Europeans, as is shown in Table VIII, there is a decided decrease in the first part of 1910 as compared with the same months in 1909. As in 1910 most of these laborers had been on the Isthmus between two and three years, it would appear that hemoglobinuric fever diminishes in frequency after that time.

Since 1905-06 very few of this race who were here in those years have since developed hemoglobinuria.

In determining, then, the effect of length of residence in the development of hemoglobinuric fever, two things must be considered: the effect of this residence in individuals who are less and less liable to malarial infection; and the effect in those who are continually exposed. It can be said, that of individuals continually exposed to malarial attacks, a certain proportion will develop hemoglobinuric fever with the first few months of residence and a greater proportion during the second and third years. But when the chances of subsequent infection with malaria or relapses due to it are lessened, hemoglobinuric fever will prevail in greater proportion in that period when malaria is most prevalent, and will decline in frequency with the decline in the malaria rate. In our opinion, length of residence is a factor in the production of hemoglobinuric fever in direct proportion to the amount of malarial infection acquired in that time.

VII.

AN HYPOTHESIS AS TO THE ETIOLOGY OF HEMOGLOBINURIC FEVER; THE PART PLAYED BY QUININE IN THE PRODUCTION OF THE DISEASE; AND THE TREATMENT OF THE MALADY.

Sir Patrick Manson, in the latest edition of his "Tropical Diseases," states that one of the most important problems in tropical medicine yet unsolved is that of the etiology of hemoglobinuric fever. This eminent authority is inclined to the belief that a specific organism is the cause of the disease, and that such malarial infections as occur prior to the onset of blackwater are accidental. Christophers, Stephens, and Bentley, whose recent researches into this problem are most thorough, believe that every consideration should be given to the possibility of such a specific organism; although these writers do not find any proof of its occurrence. They believe that prior infection with estivo-autumnal malaria is the necessary predisposing factor, and that this prior infection in some manner produces an hemolysin that is the causative factor in the manifestation of hemoglobinuria. It is

not our intention to consider in this place the arguments for and against the various hypotheses of the etiology of the disease, further than such arguments apply to the data that we have collected. Our inquiry is limited to the etiology of hemoglobinuric fever in the Canal Zone, and we shall not say at present how far the conclusions derived by us will apply to the hemoglobinuric fever of other countries.*

However, all suppositions as to the etiology of hemoglobinuric fever may be brought together under four hypotheses, as was done by Christophers and Bentley[5], and it is our purpose to apply to these hypotheses the results of our analysis of the data which we have collected. These four hypotheses are:

1. That hemoglobinuric fever is the manifestation of an active malarial infection.
2. That it is the result of quinine poisoning.
3. That it is due to a specific organism.
4. That it is the result of a condition brought about by previous malarial infection.

1. That hemoglobinuric fever is the manifestation of an active malarial infection.

In a previous section we discussed at length the influence of malaria as an exciting cause of hemoglobinuria. The evidence showed plainly that all attacks of the latter disease were preceded at some time by an active malarial infection. This evidence, however, did not exclude the fact that in some instances the blackwater set in at a time when the active infection had run its course. It is not reasonable to suppose that the onset of hemoglobinuria is due to active malaria after quinine has been administered from five to twenty-two days in doses of thirty grains a day, and all acute malarial symptoms have subsided. Such instances, though uncommon, are of unquestioned authenticity and have occurred not only in our series, but have been reported as well by other observers. We consider that the evidence previously adduced shows beyond question that active malarial infection is undoubtedly connected with hemoglobinuric fever in such a manner that the infection is often an exciting cause, but the instances cited demonstrate that some other factor undoubtedly must be present before the hemoglobinuria is determined. Exceptionally this factor may be provoked by one attack only of malaria, but this happens very seldom, so seldom as to make possible the belief that in such cases there must be an individual idiosyncrasy.

*See Appendix B.

In this country hemoglobinuric fever is a comparatively rare disease while acute malarial infection is very common. In Ancon Hospital, the former happens in about 0.5 per cent of the latter, and also makes but 0.25 per cent of the total disease. If acute malarial infection alone were the cause of hemoglobinuria, certainly the latter would occur more often than it does, especially when the intimate relation between the two affections is considered.

Although we admit the importance of acute malaria as an exciting factor, it is our opinion that before the eventuation of blackwater can be determined some other agent must be present also at the time of the acute malarial attack.

2. That hemoglobinuric fever is the result of quinine poisoning.

Neither in our clinical experience, which embraces a very large number of cases other than malaria in which the drug was given, nor in the experience of other observers under similar circumstances, has hemoglobinuria followed the administration of quinine to patients who did not have a history of previous malaria. We shall show that hemoglobinuria does occur at times when the administration of quinine, and whatever effect is thereby produced, can be excluded, and there are in the literature reports of many similar cases. In acute malaria, and in persons with a history of previous malaria, as we shall demonstrate presently, the administration of quinine sometimes determines hemoglobinuria; but much more often no such effect is produced, and this fact, together with those just cited, is sufficient proof that quinine alone is neither the exciting nor the predisposing cause of the disease.

3. That hemoglobinuric fever is due to a specific organism.

The analogy between the clinical symptoms of hemoglobinuria in animals, in which the disease is produced by piroplasmosis, and the clinical symptoms in man, is responsible for the belief that human hemoglobinuria is due to a similar specific organism which is yet undetermined. If such an analogy, which, as Stephens has said, "the weary investigator has only too often wished were true," if such an analogy held good for all aspects of the two kinds of hemoglobinuria, the hypothesis that a specific organism is responsible for the production of hemoglobinuric fever in man should obtain well deserved consideration. But this analogy goes no further than the resemblance in the clinical symptoms; and without more substantial proof, one might as well say that all continued fevers have the same etiology, as to assert that because hemoglobinuria in animals is due to a specific organism, it follows that a similar organism produces the disease in man.

Hemoglobinuria in animals depends entirely on infection with a definite organism, which is present in numbers proportional to the

severity of the disease. The insect host of the parasite is well known, and no previous illness is necessary before the disease is manifested. Immunity against the disease is not obtained unless the animal recovers from an attack or is artificially protected by inoculation methods, when an immunity is established. All non-immune animals suffer in proportion to the extent to which they are exposed to infection, and in cattle, as far as we have been able to ascertain, there is no natural immunity.

On the other hand hemoglobinuric fever in man exhibits entirely different characteristics. It prevails exactly in proportion to the extent of previous or present malarial infection, and where this is absent, hemoglobinuric fever is absent also. No organism except the malarial parasite is found constantly associated with the disease. A relative immunity exists against hemoglobinuric fever only in those races that are relatively immune to malaria. An attack of the disease does not confer immunity, in fact, the opposite belief is held by most writers, and in our cases we were able to find sixteen instances of recurrence excluding those cases that relapsed in the ward. This comparison is sufficient to show that aside from the clinical symptoms no further relationship can be traced between the diseases in man and in animals.

Our patients were admitted from all parts of the Canal Zone, but to no locality could be attributed a number of cases disproportional to that of the others. If the disease be due to a specific organism, it is evident that this organism does not exist in any very great numbers. It is true that there are diseases here that occur less frequently than does hemoglobinuria, which are due to infections with recognized parasites—for example, leprosy, quartan malaria, filarial disease, and very rarely a skin disease, oriental sore, due to the presence of *L. tropica* an organism resembling the Leishman-Donovan body, as reported by Darling.[1] But these are chronic diseases for the most part; their occurrence has no relation to that of any other malady, nor do they show a seasonal prevalence.

Hemoglobinuric fever is a very acute disease, and if it depends upon an undiscovered parasite, this parasite must have exceedingly remarkable powers of vitality in its extra-corporeal existence. That a malady so acute as hemoglobinuric fever is not in the least infectious is evidence against its exciting agent being a parasite. It is not difficult to understand how rare diseases such as leprosy and filariasis are continually endemic, for such maladies are infective over a long period of time, but there are intervals when almost no hemoglobinuria is present, and it is not easy to account for the survival of the supposed parasite at such times.

Some advocates of the specific organism urge that the regularity with which hemoglobinuria follows malaria is not an argument in favor of the latter as the cause of the former. Manson argues that because tuberculosis frequently follows typhoid fever, it would be unreasonable to say that the first disease is etiologically dependent on the second. But this authority overlooks the fact that tuberculosis for the most part develops without a previous typhoid infection, whereas hemoglobinuric fever never develops unless there has been at least one previous attack of malaria.

Craig states[9]: "This fact (Stephens' observations of the number of times the malarial parasite is found associated with hemoglobinuric fever) has been used in the endeavor to discount the proofs of the absence of the plasmodia in hemoglobinuric fever, but there are scores of cases upon record in which the blood was examined both before, during, and after the attack, and no plasmodia were ever found. If the fever is due to the presence of plasmodia, why is it that in case after case these organisms are not found though repeated and careful search is made for them, the spleen having been punctured in some cases with a negative result?"

Stephens does not claim that hemoglobinuric fever is due solely to the presence of parasites at the time of the blackwater. And though "scores of cases" are on record in which the blood was negative for malarial parasites, it should be remembered that such cases are not taken from records extending over a certain length of time in a given locality. Arguing from such premises, it would be as easy to show 100 per cent of positive malarial infections associated with hemoglobinuria, as to exclude the coincidence of the parasites altogether. The almost constant presence of malarial parasites, when sought for properly, in the disease is proof of a connection between hemoglobinuria and malaria, but this presence is not urged as the actual cause of the disease. The point is, that malarial infection produces in the body some condition that determines hemoglobinuric fever, and this condition, while frequently associated with malarial parasites, may exist without them.

By some who uphold the hypothesis that a specific organism is responsible for hemoglobinuric fever, it is urged that the same climatological and epidemiological factors that cause the seasonal change in the malarial rate, and that produce epidemics, may also cause similar seasonal changes and produce similar epidemics in hemoglobinuria. In other words, since filariasis and probably dengue are disseminated by means of the mosquito, the organism of hemoglobinuric fever may also be disseminated in the same manner. If so, then certainly the seasonal

resemblance between malaria and hemoglobinuric fever would be in great part accounted for, although the higher prevalence of the latter in the dry season would need additional explanation. But the analogy implied in the hypothesis is not confirmed by existing facts. Negroes expose themselves far more to mosquitoes and all other insects that act as endo-parasitical hosts than do the Europeans. Filariasis and quartan malaria, for instance, are conveyed by means of mosquitoes, and, although rarer diseases than hemoglobinuria, are found in greater proportion among the negroes than among the Europeans and Americans.

We do not know of any possible means of conveying any endo-parasitical infectious disease in the Canal Zone which would not obtain more among the negroes than among the other races, when the manner of living of the former is considered. In order to sustain the hypothesis, it is necessary to infer either that the agent which distributes the organism is more partial to Europeans than to Americans or negroes (and we are unable to understand how this can be true to the extent that the hypothesis would imply), or else, to presuppose that although the negro is more exposed to the suppositious infection, he is relatively immune to it in the same manner that he is to malaria. And if this last be true, the difference between the epidemiological and etiological factors that determine the life history of the hemoglobinuric parasite, and those that affect the life history of the malarial organism, is so small that the former would probably exist symbiotically with the latter.

Against the hypothesis of a specific organism we wish to urge the following facts. If hemoglobinuric fever be due to a specific organism, then at some time this disease should complicate a malady other than malaria, or should manifest itself during the process of some of the chronic affections so prevalent here. The records of Ancon Hospital show instances of malaria complicating practically every other disease that is admitted. Pneumonia is seen with and without typhoid fever; tuberculosis and even leprosy are sometimes associated with amoebic dysentery; all varieties of nephritis occur in acute and chronic ailments; but neither clinically nor at autopsy has hemoglobinuric fever complicated any infectious disease other than malaria. Of the many thousand patients who have been admitted to the surgical side of this hospital only four have exhibited hemoglobinuric fever, and in each of these, the onset of the disease was preceded by the symptoms of positive or clinical malaria. In not one case of hemoglobinuria can evidence of malaria, either remote or immediately prior, be excluded.

Perhaps there may be a specific organism that can account for the facts above stated, we do not deny the possibility of its existence, but until such an organism will have been found, we prefer to believe that previous malaria, as we have endeavored to show, is the predisposing cause of hemoglobinuric fever. In this connection we wish to state that hemoglobinuric fever is almost unknown among the adult natives of this country, and that acute malaria is also rare.

4. That hemoglobinuric fever is the result of a condition brought about by previous malarial infection.

The data above submitted apparently leave no alternative to the conclusion that the chief and necessary etiological factor in the production of hemoglobinuric fever is malaria. It would appear as a rule that not one but several attacks are necessary, either by recurrence or re-infection, or that a state of chronic malaria is produced, before the toxicity accumulating in the system is sufficient under some exciting cause to precipitate the hemolysis.

As above stated, though tertian and quartan organisms have been found in patients coincident with or prior to the hemoglobinuric attack, we are inclined to the belief that estivo-autumnal parasites are responsible. If so, this would account for the statement so often made that hemoglobinuric fever does not always occur where malaria flourishes, for tertian and quartan malaria may be endemic where no estivo-autumnal malaria exists.

That estivo-autumnal parasites are solely responsible as predisposing factors for hemoglobinuric fever we are at present unable to prove. The exciting factor, however, is another question, which permits discussion, and probably depends on more than one agent.

The malarial organisms in their parasitical development within the human host generate toxins. This is evident, not only from the constitutional disturbances present and the pathological findings, but also because such generation is a necessary result in all endo-parasitical processes. The important investigations on the toxins of bacterial invasions elucidate the analogous processes in malarial infections.

There appears to be a specific toxin not only for every infective agent, but also for other closely related substances which play a different role, physiologically and chemically. Immunity apparently depends on the production of bodies which result from the reaction of the specific toxin on the tissues, while the related substances, hemolysins and cytolysins, lead to blood and other cell destruction. If immunity be the result invariably of the action of a specific toxin on the tissues, and if it can be shown that malarial immunity exists, then we must infer that a specific malarial toxin exists. Celli[12] instances cases of acquired

immunity, and also states that there are individuals immune not only from natural but also from experimental malaria.

What is our experience here? As can be seen from the above charts, the negro and the negroid races have undoubtedly a certain degree of natural immunity. The amount of malaria in the newcomers is out of all proportion to that which occurs in the native population, a fact in itself sufficient to prove that acquired immunity exists. Whether or not a permanent immunity can be established is a problem, but in any case there undobtedly is a temporary *immunitas non sterilisans* in malarial patients. In these patients, though they seem apparently well, some form of the parasites persists in a quiescent state, and lights up when the resistance of the body is lowered from any cause.

If, then, analogous to bacterial infections, a specific toxin exists, what of the related substances, the hemolysins and cytolysins, with which we are more directly concerned?

In the course of an acute malarial attack it is not an unusual clinical observation to see a sub-conjunctival hemorrhage, either slight or involving the whole surface of the eyeball. This is particularly true in the cerebral forms. These hemorrhages are due to a loss of the capillary continuity by a cell solvent or cytolysin. They are not due to an alteration in the blood or to hemophilic tendency, for the clotting index is unchanged.

Cytolysis is also responsible for some forms of paralysis, aphasias, hemiplegias, etc., which are occasionally met with in severe malarial infections. We have observed patients in whom these forms occur at the same time as the sub-conjunctival hemorrhages and clear up simultaneously. In favorable cases the paralyses, due to capillary blocking by malaria-infected blood and endothelial cells, clear up in a few hours after the administration of quinine hypodermically. This is not the case where blood is effused into the tissues.

Furthermore, every severe malarial attack is associated with more or less kidney irritation. At times this amounts to a severe general diffuse nephritis of peculiar type, and may result in death, or after a tedious convalescence, leave the kidneys permanently damaged. Undoubtedly the kidney cell destruction is the result of cytolytic toxemia.

Post-mortem focal necroses in the parenchyma of other viscera point to the same agent of cell destruction.

Hemolysis is a phenomenon closely related to cytolysis, caused by a toxin selective for the erythrocytes. It plays a role in the pathological blood changes in all severe bacterial infections, particularly in some forms of septicemia. In bacterial infections the growth and the multiplication of the organisms is not paroxysmal, as in malaria, neither is the

production of their toxins, and the liver is able to take care of the red cell destruction as it occurs without the production of marked hemoglobinemia and subsequent hemoglobinuria. If Ponfick's[13] experiments be true, then one-sixth of the red cells must be destroyed simultaneously before hemoglobinuria results. In some of our observations, from red cell counts and hemoglobin estimations it would appear that less than that number is necessary, though it is not uncommon for 25 per cent or more to be destroyed in a single paroxysm.

We are therefore forced to the conclusion that, as cytolysis and hemolysis are regular concomitant phenomena of bacterial development in the human host, so also are they in those cases where malarial organisms are the parasites, the main difference being that in one type the pathological changes are more or less continuous, in the other, paroxysmal, thus corresponding to the respective life histories of the infective agents. In patients who develop hemoglobinuria there is a combination of red cell and toxin, or in Ehrlich's terminology, of the haptophore group of the toxin, which when sufficiently saturated becomes united with the toxophore element, leading to the destruction of the red blood cell.

Corresponding to the physiological and chemical nature of a toxin, an hemolysin has two groups, a combining group, and an injuring or destructive group. Before a cell can be destroyed there must be a union of the first group of the hemolysin with the cell before the other group can act to destroy it. The natural protective agents of the body prevent or attempt to prevent this destruction by their action on the injuring or toxophore group of the hemolysin by converting hemolysin into hemolysoid. Whatever, therefore, that would tend to prevent this action would precipitate the cell destruction.

Three groups of conditions suggest themselves as exciting factors to that end. First, renewed malarial paroxysms with the production of sufficient accumulated toxin to overwhelm the cell. Second, a lowering of body resistance by any of the causes mentioned in connection with malarial relapses. Third, the administration of quinine, which may act in either of the two ways: (*a*) by depressing the vital processes of the body (it is well known that in large doses quinine depresses the circulatory system, interferes with blood oxygenation, and leucocyte activity), and (*b*) by acting as the toxophore radical of the hemolysin. That quinine is sometimes a factor in the production of hemoglobinuric fever is beyond question.

Since Tomaselli,[14] in 1874, first reported "that there were persons who every time they took quinine, even in small doses, manifested a severe fever paroxysm with hemoglobinuria," there has been a conflict of authority as to the etiological importance of this drug in the pro-

duction of hemgolobinuric fever. It was observed that in some persons hemoglobinuria regularly followed the administration of quinine, and on the other hand that hemoglobinuric fever developed at times when the prior administration of quinine could be excluded. Between these two extremes every possible variation has been observed. Hemoglobinuria that followed one dose of quinine did not occur when the second dose was administered; in some instances paroxysms followed after successive administrations of the drug, and did not recur when it was given later; quinine was sometimes given throughout the attack and subsequently, with no further hemoglobinuria, and at other times the hemoglobinuria persisted; and finally, death followed in some instances whether or not quinine was administered.

In our cases all of the foregoing incidents were observed in such variety that we were unable to classify the results which followed the administration of quinine. We present in detail at the end of this paper the treatment of each case of hemoglobinuric fever that we have admitted to this series, and a careful study of all the cases so reported will convince the reader that no regularity of results following the administration of quinine can be predicated.* We do not mean to infer that quinine does not play an important part in the etiology of the disease, but simply to state that the part so played is very complex.

That there are persons in whom hemoglobinuria follows the administration of quinine we are able to affirm. Case No. 42 was that of a young Frenchman who had been on the Isthmus for six years. He had suffered from several attacks of malaria, and during each attack had taken quinine, with the result that he invariably manifested a paroxysm of hemoglobinuria. He was admitted to the service of Dr. A. B. Herrick, Chief of the Surgical Clinic in Ancon Hospital, on February 14, 1907, with a fracture of the external condyle of the right humerus. His temperature was irregular after his admission (see report, Case 42), and although no parasites were found in his blood on admission or immediatley prior to the onset of hemoglobinuria, Dr. Herrick felt that quinine should be exhibited. The patient told Dr. Herrick that blackwater always followed when he took quinine, and for that reason he, the patient, had suffered much from malaria, as he was afraid of the result of taking quinine. Dr. Herrick obtained his consent to administer a very small dose, and on February 21, at 11 a. m., one grain of quinine was exhibited. Prior to this the urine was examined and found to contain no albumin. At 1 p. m. the patient voided

*See Appendix A.

three and one-half ounces of very dark red urine that contained twenty per cent of albumin. The heat and acetic acid test was used.

At 2.30 p.m., two ounces of dark urine were voided; albumin, 33⅓ per cent.

At 4.30 p. m., seven ounces, dark red in color; albumin, 30 per cent.

At 7 p. m., seven ounces, light red; a trace only of albumin.

At 8.40 p. m., twelve ounces, light red.

At 4 a. m., sixteen ounces of urine, clear in color were passed. No albumin was found.

We are indebted to Dr. Herrick for permission to report this case.

The prompt occurrence of hemoglobinuria after the administration of quinine in several of the patients who were admitted to the hospital with positive or clinical malaria has led us to believe that such cases as the one just recorded are not uncommon. In some of the patients in whom hemoglobinuria was manifested until death, and to whom quinine was administered throughout their illness, perhaps such an idiosyncrasy obtained. Other cases, however, in which, under similar treatment the urine cleared before death, demonstrate that the result of the administration of the drug cannot be foretold with any certainty.

It can be affirmed that hemoglobinuria following the administration of quinine does not occur except in those who have had a previous attack of malaria. In the large number of patients admitted to this hospital, to whom quinine was given, and whose illnesses at the time that they were in the hospital were not malaria, no hemoglobinuria followed the administration of the drug. And in many cases of malaria, in which the exhibition of quinine was followed by hemoglobinuria, the length of the time that elapsed, and the varying amounts of the drug that were taken, before the hemoglobinuria developed, make it impossible to state how much the administration of the drug had to do with the eventuation of the disease. We shall give below the details of a few such cases.

Case No 205.—The patient was an Italian, who had been thirty-seven months on the Isthmus. He was admitted to Paraiso Hospital on April 5, 1910, with symptoms of malaria. On that day three ten-grain doses of quinine were given. On April 6, about 4 p. m., after his fifth dose of quinine, he had a severe chill, and fifteen minutes later hemoglobinuria developed. The next morning the patient was transferred to Ancon Hospital. His blood was examined on admission and was negative for malarial parasites. The urine was loaded with albumin, was dark red in color, and hemin crystals were found. No quinine was administered and on April 10 the urine was clear. On April 20 the afternoon temperature was 101; on the 21st there was no

fever; on the 22d there was a febrile paroxysm (see report, Case 205) and a double infection with tertian parasites was found in the blood. Twenty grains of quinine were given at once and doses of ten grains three times a day were ordered. On the morning of the 23d hemoglobinuria was present. The quinine was continued, and on the morning of the 25th, the urine was clear. On April 28 the drug was discontinued and renewed on May 2, without further hemoglobinuria.

Cases similar to this and others, that varied somewhat in the results following the administration of quinine, are Nos. 4, 12, 33, 67, 128, 142, 164, 172, 174, 186, 187, 189, 190, and 221. For details of these cases see their reports in Appendix A.

That hemoglobinuria will develop when no quinine has been administered immediately prior to the onset of the attack we can affirm also.

*Case No. 185 was admitted on November 21, with a history of hemoglobinuria for two days past. On admission the urine was dark red in color, and hemin crystals were demonstrated in it. Twenty grains of quinine were given on admission, and ten grains the following morning, when the drug was discontinued, after which the urine cleared. On the 30th, at 4 p. m., hemoglobinuria began, which cleared on the next day. On December 10, and again on the 12th, there were febrile paroxysms, these times without hemoglobinuria, and on the latter date the blood was found to contain estivo-autumnal parasites. Quinine was given in full doses, thirty grains per day, and no hemoglobinuria followed. This case is most interesting in that it exhibits a hemoglobinuria not due to quinine, that of November 20, followed by malarial paroxysms and the administration of quinine without further hemoglobinuria.

Case No. 200.—This patient manifested true paroxysmal hemoglobinuria that did not follow the use of quinine. He was admitted on February 11, with hemoglobinuria. Prior to admission he had taken some quinine, and he claimed that the hemoglobinuria had preceded the taking of the drug. No quinine was given on admission, and the urine cleared on the 14th. On the 17th the urine was clear and did not contain albumin. On the 18th there was a febrile attack, accompanied by hemoglobinuria, and hemin crystals and albumin were found. On the 19th the urine was clear. On the 20th there was another febrile attack, with hemoglobinuria. On the 21st the urine cleared and remained clear. On this date large doses of quinine were administered by hypodermic, as the patient was unable to take anything

*This case has been reported previously by Dr. R. C. Connor, Proc. Canal Zone Med. Soc., 1909, page 87.

by mouth, and the severity of his symptoms was out of proportion to the amount of hemoglobinuria. A careful search for parasites was made every day for ten days after admission, but none were found. The patient was critically ill for several days after the last appearance of the hemoglobinuria, and his symptoms resembled those of a severe malaria. Ultimately he made a good recovery and has remained well. He has taken quinine several times since without untoward results.

Case No. 226.—The patient was admitted with hemoglobinuria on July 26, 1910. On the 28th and 29th quinine was administered in moderate doses. The urine cleared on the 29th. On August 9 thymol treatment for uncinariasis was administered. On the 11th there was a febrile paroxysm, with hemoglobinuria. As this occurred forty-eight hours after the last dose of thymol had been administered, in the meantime the patient had remained without any untoward symptoms, and the thymol had been cleared from his intestinal tract by the purges that we give after such treatment, it is improbable that the hemoglobinuria developed as a result of poison by the drug. On the 17th quinine was given in doses of ten grains three times a day and continued with no further hemoglobinuria. His attack may have been caused by lowered resistance due to thymol treatment.

A consideration of these cases, and the case reports at the end of this paper, will make it very clear that, as we have stated, the part played by quinine in the eventuation of hemoglobinuria is very complex. Hemoglobinuria has developed from within an hour or two after the administration of the drug to as late as twenty-two days after the first dose, the quinine being given in doses of ten grains three times a day in the meanwhile. From this it is very plain that some factor other than the action of quinine must be present in order to produce the hemoglobinuria, and such an hypothesis would explain the variety of conditions under which hemoglobinuria appears and disappears following the administration of the drug.

In considering the production of hemoglobinuria, the question arises, if certain red cells are destoyed, why not all?

According to physiologists, the life history of a red blood cell is probably not more than four weeks, and naturally this means the complete regeneration of the erythrocytes every twenty-eight days. Having red cells, then, of different ages, exposed to a toxin with which they enter into chemical combination, it means that different degrees of toxicity are present, and the older cells, having absorbed more toxin, are more prone to destruction. So that in cases in which quinine has been given, we do not believe that quinine alone, but quinine plus

malarial toxicity is necessary to produce the phenomenon. One must exclude individual idiosyncrasy for drugs.

It is known further, that bacterial toxins, like enzymes, unite with the tissue units they act on, and if Marchoux's[15] observations that quinine elimination does not take place during the attack, but subsequently, be correct, we have positive proof that quinine can unite with some constituent of the body tissues under hemoglobinuric conditions, which conditions prevent its immediate elimination, and we have every reason to infer that this union is with the stroma of the erythrocytes.

It has been stated that chemically and physiologically cytolysins and hemolysins are closely related, and that malarial toxicity plus quinine poisoning is responsible frequently for hemoglobinuria; can evidence be produced to show that malarial toxemia plus quinine can produce cytolysis? Cytolitic phenomena, as previously mentioned, are not uncommon in the course of malarial infection, but quinine as an exciting factor was not discussed.

A case recently came under our observation which is unique, and bears directly on this point, paralleling exactly those cases of hemoglobinuria in which quinine is a factor.

A. H——, negro, Barbadian, age 22, was admitted to the hospital on August 15, 1910, after a residence of twenty-six months on the Isthmus. During 1908 he was admitted to this hospital in June and again in December with fever. Although the blood was found negative, the temperature curve and the manner in which his fever yielded to quinine on one of these admissions suggested malaria of the estivo-autumnal type. However this may be, quinine was given in doses of ten grains three times a day on one occasion for seven days, and on the other for eight days, and no note was made of any untoward effect. In 1909 he suffered from an attack of diarrhea, but there has never been a history of bleeding from any part of his body previous to his last admission. There is no history or stigma of syphilis, and physically the patient is a well-built negro. On the present admission he complained of headache, fever, chills, and nausea. He had the usual signs of malaria, and his blood was positive for estivo-autumnal parasites.

On the day of his admission twenty grains of quinine, with the usual calomel and salts, were given. On the next day he began to bleed from the mouth. On examination there could be seen two patches of capillary oozing, one on the cheek and one on the soft palate, each about the size of a ten cent piece, and also a series of smaller spots on the gums. All of these patches were covered by a fungating, dirty looking mass, which examination showed to be blood clots. These were readily removed, and the bases showed no ulceration, but a torn

looking membrane, through which the blood oozed. The clotting index of the blood was found to be normal on the 18th. Smears from the bases of three of these fungating masses showed gram-positive diplococci, and a few gram-positive micrococci and bacilli; no fungi were discovered. The blood culture was negative. He received thirty grains of quinine on the 16th and on the 17th; thirty grains hypodermically on the 18th, 19th, and 20th, when it was discontinued. On the 17th hematuria was present, red blood cells appearing in the urine. This hematuria persisted until the quinine was discontinued on the 21st; his pulse rate rose from 90 on admission to 120 on that date. On the 20th petechial hemorrhages appeared all over his body. These hemorrhages also ceased with the withdrawal of the quinine. By the 23d, the hemorrhagic symptoms had all disappeared, and on the 24th quinine was again administered in three ten-grain doses, with the reappearance of all the hemorrhagic symptoms. On the 25th quinine was again discontinued, with the disappearance of the hemorrhages. On the 29th quinine was again resumed, and on the following day the gums began again to bleed. The quinine was continued until September 3, with more or less constant oozing from the gums during the whole time. Quinine was then discontinued and the patient rapidly convalesced. On the 10th, 11th, and 12th, the patient received fifteen grains of quinine daily, without recurring . hemorrhagic symptoms, and was discharged on the 15th, having recovered entirely.*

This case demonstrates beautifully the development of a cytolysin affecting the capillaries, and determining hemorrhages, more or less general, in a patient with no hemophilic tendencies, inherited or acquired, during the past twenty months, excited by quinine, and apparently inactive without it.

That the patient had no inherited idiosyncrasy is evidenced by his former hospital histories, and we know that he had malaria on admission, and this is the probable source of his cytolysin. This case is of great value because of the light that it throws upon the etiology of quinine hemoglobinuria, which is an analogous phenomenon.

It would appear, then, beyond question that malarial toxin, or a toxin developed in the human organism as a direct result of malarial infection, plus quinine, does produce hemoglobinuria.

We have now to consider hemoglobinuria which develops without the exhibition of quinine when no more than slight traces of hemoglobin can be detected in the urine. It has been stated above that the estivo-

*This patient was admitted subsequently with estivo-autumnal malaria. Quinine was given in full doses without the reappearance of the cytolitic phenomena.

autumnal parasite is probably responsible for hemoglobinuric fever. In the intra-cellular development of the tertian and quartan parasites all of the hemoglobin of the erythrocyte is utilized as a pabulum. The estivo-autumnal parasite, however, does not use up all of the hemoglobin of the cell, probably not more than one-half or two-thirds of it. At every sporulation, therefore, free hemoglobin is liberated in the blood stream, producing thereby a certain degree of hemoglobinemia. This accounts for the transitory trace of hemoglobinuria detected in patients suffering from severe estivo-autumnal infections. This, however, is not hemoglobinuric fever as we understand it.

To sum up. All bacterial infections produce at least three substances in the human organism:

1. Specific toxins, which cause tissue reactions that result in immunity.

2. Cytolysins, which produce cell destruction.

3. Hemolysins, which are selective for the erythrocytes.

Malarial infections produce analogous substances, and this production is paroxysmal.

The selective force of the individual agents is expended according to personal idiosyncrasy, natural cell resistance, occupation, habit, etc.

Although usually the accumulative toxic effects of more than one malarial attack are necessary to produce hemoglobinuria, even the toxic effects of one attack may be sufficient, depending upon the personal equation.

When the natural protective agents of the body, the alexins and opsonions, are unable to take care of the hemolytic effects of the toxins, as in the sudden production of an overwhelming amount of these, or through a variety of agents which lower body resistance, or through the administration of quinine, then hemolysis with hemoglobinemia and hemoglobinuria results.

The coincident development of cylotic phenomena, and particularly their action on the kidneys, goes far in determining the prognosis.

Clinically, we may divide hemoglobinuric fever into three types.

1. The paroxysmal, when after a severe chill with attendant fever, there is an onset of blackwater, the duration of the whole attack being from a few to twenty-four hours.

2. The sub-continued, when the febrile attack or the blackwater, or both, persist from one to three days.

3. The continued, when the passage of blackwater persists for four or more days, with high fever; or the fever may be moderate or absent,

In all types at the onset of the attack there is some suppression of urine, followed as a rule by a hypersecretion. The degree of suppression determines frequently the gravity of the case. We have seen a comparatively mild paroxysmal attack, associated after the passage of the first urine with complete suppression and apparently but little blood destruction, go on to a fatal issue in from one to two weeks. Suppression occurs in all types and is a symptom of the greatest gravity. In our cases we have had but one recovery when suppression was complete.

Apparently the suppression is associated with more or less complete destruction of the epithelium of the straight and convoluted tubules.

Hypersecretion is always a favorable sign in prognosis if the passing of blackwater does not persist too long, or until the degree of anemia is so great as to bring about death from it. We have seen a red blood count of 800,000 with subsequent recovery, when the hemoglobin estimate was as low as 10 per cent, too low in any case to be read by a Dare's or a Sahli's hemoglobinometer. When recovery does take place in these cases convalescence is very tedious, and more or less permanent damage to the kidneys is frequent.

The condition of the blood is fairly characteristic of the disease. During the first few hours after the onset of the attack the appearance of the corpuscles, fresh or stained, is practically normal. Later, there is great difficulty in making good smears, owing to the apparently injured condition of many of the cells. A tendency to all forms of bizarre shapes and poikilicytosis is seen, but an examination of the fresh specimen will show that these appearances are due to accidents in the spreading of the smears, for in the fresh specimen the erythrocytes are normal in shape and size. In a day or two more, however, the blood takes on the appearance of an anemia more or less profound, and macrocytes, microcytes, and nucleated red blood cells are found.

There is no fixed characteristic febrile curve in hemoglobinuric fever. With the onset there may be only an acute febrile paroxysm and a subsequent normal temperature, or the fever may persist as long as the patient is passing blackwater. It is not uncommon to observe a post-hemoglobinuric fever that persists from several days to two or three weeks, very irregular, and often as high as 101 or 102. Occasionally this fever appears to have been favorably affected by quinine, and at other times it has persisted notwithstanding the very large amounts of the drug that often were given by mouth and hypodermically.

The jaundice in this disease is a very striking clinical symptom. It varies from a pale, lemon-yellow to the depth of color seen in an almost

complete biliary obstruction. This symptom, of course, depends not only on the amount of blood destruction, but also on the ability of the liver to handle the destroyed cells. The jaundice and the anemia together make a very characteristic clinical appearance.

We have very little to add to the symptomatology of hemoglobinuric fever in general. Many authors have done justice to this subject, but there are a few points whose importance has not been dwelt on sufficiently, from the diagnostic as well as the therapeutic standpoint.

Frequently these cases of hemoglobinuric fever develop prior to the admission of the patient to the hospital, and an unreliable history leaves the clinician in doubt as to the diagnosis. The blackwater may have disappeared and no urinary findings sufficiently characteristic are present. In such instances evidence of a confirmatory character can be obtained by a careful examination of the liver, spleen, and eye.

The liver of a patient suffering from malaria of any variety is enlarged unless either cirrhosis or atrophy is present. In hemoglobinuria this enlargement is more pronounced and the liver is distressingly tender on palpation during the acute attack. If the fever persists, as frequently it does after the blackwater has ceased, the liver symptoms are usually more marked than in malaria, and this will help to determine the diagnosis. In tertian and quartan infections the parasites will always be found if there is any degree of fever whether or not quinine has been administered, but in estivo-autumnal infections there is often fever when the parasites are absent from the peripheral blood. In post-hemoglobinuric fever, however, the liver is more swollen and tender than in the estivo-autumnal malaria.

In tertian or quartan infections the spleen is considerably enlarged and most always palpable. As a result of repeated infections with estivo-autumnal malaria, the spleen may attain a size sufficient to render it palpable, but a primary infection very seldom produces a palpable spleen. From a great many examinations we believe this statement to be clinically correct. In hemoglobinuric fever, however, the spleen is always enlarged and tender as long as the fever persists, and certainly this suggests accumulated toxicity.

These symptoms, manifested in the liver and spleen, are not in themselves sufficient to determine a diagnosis after the blackwater has disappeared, although they are of considerable collateral importance. But the clinical picture presented by the appearance of the eye, which feature has not been dwelt upon in the literature, as far as we have been able to learn, is very characteristic, and persists for a considerable period after the blackwater has ceased. The conjunctiva is of a uniform lemon-yellow tint, varying in depth of shade, but always lighter

near the cornea, according to the severity of the case and the depth of the jaundice. The subconjunctival blood vessels seem depleted and are exceedingly pale. In the malarial eye the blood vessels are always more or less injected and the icterus is less marked and less uniform.

The condition of the urine is interesting. It shades in color from a light sherry-red to almost black. A characteristic sediment is present, formed of granular detritus, consisting of minute hemoglobin bars, apparently secreted by the kidney epithelium independent of any kidney lesions. This detritus appears frequently in the form of kidney tubule casts more or less closely cemented together by some hyaline substance. They disintegrate readily, forming the granules of the detritus. Frequently granular, epithelial and hylaine casts are found, indicating an old or a fresh nephritis. With proper tests, nucleo-albumin, serum-albumin, and serum-globulin can be demonstrated in the urine, and with a spectroscope the bands characteristic of oxyhemoglobin or of reduced hemoglobin are visible, depending on the length of time that has elapsed since the specimen was passed.

In the severe forms of nephritis going on to suppression, the lethal outcome takes place within three weeks. We have not witnessed any cases that outlasted that period. In such cases the urinary findings are those of a severe acute nephritis.

The treatment of hemoglobinuria is of great importance, and the relatively low death rate (15.5 per cent) that we are able to show, speaks eloquently for the method followed here.

If malaria, recurring or due to re-infections, is the necessary etiological factor in the production of hemoglobinuria, with some superadded factor, such as an acute exacerbation of malaria, quinine administration, or lowering of the natural resistance by some depressing agent, then the treatment must be conducted along certain lines which vary with the existing conditions. Often we are in the predicament of treating a patient suffering from malaria for which we have but one known remedy, and that remedy likely to provoke a hemoglobinuria which may result fatally.

In August, 1908, one of us (W. E. D.) instituted in this hospital a more or less systematic treatment of hemoglobinuric fever, which has given favorable results. This may be described, (*a*) as measures adopted during the acute attack, and (*b*) those adopted after the subsidence of the acute symptoms.

During the acute attack, vomiting, epigastric distress, intolerable thirst, and hiccough are the predominating symptoms. The patient calls for water, which, when taken, is immediately rejected. These

distressing symptoms are very often immediately relieved by the administration of normal saline solution per rectum or by hypodermoclysis. As a rule, the former is sufficient, eight to sixteen ounces every two or three hours are readily absorbed, and it is astonishing and gratifying to note how quickly this simple measure relieves the patient. Hot moist applications over the stomach and loins are also grateful. The only medication given in the early stages is calomel, followed in a few hours by magnesium sulphate.

If parasites are present, then quinine is indicated, and its effects are carefully watched. If the stomach is sensitive, then the drug must be given by the rectum, or hypodermically, the latter is better, in doses of ten to fifteen grains every four to six hours. It must be borne in mind that hypodermic injections of quinine are very prone in these patients to provoke tissue necrosis, as in every other condition of lowered tissue resistance. Massage must be used over the deep-seated intra-muscular injection, and subsequent hot applications made. If, however, quinine aggravates the hemoglobinuria it should be withdrawn temporarily and the expectant treatment be used for a few days. Even when the parasites are not present, and the fever and the hemoglobinuria persist, it is often wise to try the hypodermic administration of quinine, as the absence of parasites is no proof that the organisms are not active in the deep seated tissues.

When no impending danger to the patient's life exists, generally it is best to use the expectant treatment, giving a milk diet for a few days. We favor the use of some mild ferruginous preparation, such as Basham's Mixture, to help supply the necessary elements for red cell reproduction; later we give Fowler's Solution.

The great majority of our patients get no quinine until such time in the course of the disease as convalescence is established. Occasionally at this time a paroxysm of fever occurs and parasites are found. Quinine is then indicated and may or may not produce hemoglobinuria. If it does, the further administration of the drug is postponed for a few days; for, as has been pointed out, quinine may produce hemoglobinuria at one time and have no such effect subsequently.

Just as in the case of cytolysis above reported, in malaria, patients come several times to the hospital, take quinine without untoward results, and are discharged, only to return later with an attack of hemoglobinuria apparently the result of quinine administration; and then return later with malaria, when quinine is safely administered without the development of hemoglobinuria.

Syphilis plays a very important part in the etiology of chronic and recurring malaria, and for this reason its presence should be looked for

in cases of hemoglobinuria and proper treatment instituted, if it is present. This disease may play some part in the direct etiology of hemoglobinuric fever, as evidenced by the great preponderance of both diseases among the European laborers. This class is heavily infected with hereditary and acquired lues.

We believe, however, that the chief influence of syphilis is exerted in the production of recurrences and cachexia in malaria, and in this way predisposes to hemoglobinuria. It is a frequent observation here that malaria and syphilis flourish together, both exerting a debilitating effect on the host, and both have to be treated simultaneously if the patient is to be relieved. In this combination of malaria and syphilis, the physical and blood findings sometimes resemble so closely those of liver abscess that a diagnosis is particularly difficult, and the former condition has led here occasionally to an exploration for the latter. We have dwelt upon this concurrence of syphilis and malaria, for in hemoglobinuric fever this conditions is sometimes present, and if one would prevent a recurrence of hemoglobinuria, under such circumstances, it is necessary to treat the patient for malaria and any other condition which militates against a normal resistance. Therefore, the treatment of hemoglobinuric fever often resolves itself into the treatment of malaria and the complications of the latter. It is well known that many cases of malaria improve on rest and good food without medication, when the natural resistance is sufficient. In those fortunately rare cases in which quinine cannot be administered on account of the amblyopia and optic atrophy that sometimes follow the exhibition of this drug, such means as absolute rest and nutritious food are our only resources. In such cases the temperature alone should not be the guiding factor in this treatment, but careful examinations of the blood, liver, and spleen are also necessary.

Similarly, a number of patients who have hemoglobinuric fever also recover without the use of quinine, but in such cases, as in similar ones in malaria, the danger of a relapse, with fatal consequences, must be always kept in mind. The reader will remember the case of the young Frenchman which we described, in whom the administration of quinine always was followed by hemoglobinuria. This man died subsequently of the disease.

Sometimes thirty grains of quinine a day is insufficient to bring about convalescence in hemoglobinuria complicated with malaria, and forty-five grains daily, or even more, is necessary before the temperature will yield.

Again, some cases necessitate the use of quinine hypodermically. The reason for this appears to depend upon localization of the parasites,

a condition so frequently seen in this country. Parasites may localize in any part of the body, and interfere with tissue function; and in the brain such localization may produce cerebral symptoms of every known kind; aphasia, hemiplegia, local paralyses, tics, neuralgias, mania, delirium, stupor, coma, convulsions, hyperesthesia, and other affections are all simulated. Such symptoms, due to localization in the systemic circulation, necessitate the administration of quinine hypodermically.

When quinine is given by the mouth, or rectum, before it reaches the systemic circulation apparently the metabolic action of the liver modifies the effect of the drug, as happens with several well known alkaloids. Such a process may account for those cases in which hemoglobinuria ensues after the drug has been administered by the mouth for several days. The hypodermic use of quinine would therefore be indicated if the patient were not making satisfactory progress toward recovery, and no other constitutional cause were present to prevent convalescence.

The nephritic complications must be cared for as in any other severe nephritis, acute or chronic.

The practical importance of determining the relationship of prior malarial infection to hemoglobinuric fever is obvious. In those cases of malaria, particularly among women, in which quinine cannot be administered, such knowledge is indispensable if proper prophylaxis against blackwater is to be instituted. In our series, four cases, three of which were fatal, occurred as the result of a neglected malaria in women.

In a malarial country, the physician who has in his care patients who cannot or will not take quinine should not fail to acquaint them with the grave danger of a subsequent pernicious malarial attack, or with the ever present possibility of the eventuation of hemoglobinuric fever, or both, and he should use every persuasion to induce such patients to leave the country. Anyone who has witnessed the distressing combination of optic atrophy and amblyopia following the necessary administration of quinine in a pernicious malaria, or who has seen a fatal hemoglobinuric fever supervene during the treatment of a neglected malaria, cannot fail to be impressed by a result which the exercise of common sense on the part of his patient would have prevented.

We are indebted to Drs. A. B. Herrick, Wm. Shaw, and R. C. Connor, of Ancon Hospital, for case reports and to Col. W. C. Gorgas, M. D., U. S. A., for permission to publish this paper.

SUMMARY.

1. Hemoglobinuric fever is a manifestation of malarial toxicity, for the most part brought about by repeated attacks of malaria.

2. It may appear coincidently with an acute malarial paroxysm.

3. It may be determined by any depressing influence.

4. It may be induced by the administration of quinine.

5. Quinine alone, nor malarial infection alone, do not cause hemoglobinuria, but one or both of these conditions, plus the toxin eventuated during the course of one or more malarial attacks.

6. Syphilis is a predisposing factor, because of its influence in the production of malarial recrudesences.

7. The treatment varies with the condition present.

8. To insure against recurrent attacks of malaria, with the subsequent production of hemoglobinuric fever, it is necessary to raise the patient's resistance to a maximum, and to eradicate the malaria, by a thorough course of treatment with quinine.

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In this paper Brem reports 162 cases of blackwater fever that occurred in Ancon Hospital from 1904 to April, 1910. These cases include those reported by Connor and Gorgas, and are included also in our case reports in Appendix A. At the end of Brem's paper are given the admission numbers of the 162 cases reported by him.

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APPENDIX A.

CASE REPORTS.

These case reports include all cases of hemoglobinuric fever upon which our statistics are based.

Under the head of "History" the temperature records are shown. The temperature was taken twice a day when two records are shown; at 8 a. m., 12 noon, 4, and 8 p. m., when four records are shown; and every four hours otherwise.

All dates are inclusive when shown as follows: 24–28th.

Under the head of treatment we have shown only whether or not quinine was given, and in what doses. I. and Q. Tonic is a preparation of iron and quinine in which there are ten grains of quinine to the dose. It was given three times a day. All quinine was given by the mouth, and mostly in liquid form, unless otherwise indicated. Quinine, grs. X, hypo, four doses, means that on the date or dates included quinine was given every four hours, hypodermically, for four doses, etc.

Most of the hemoglobin estimates were taken with Dare's instrument. When the amount of albumin is shown in percentage, the heat and acetic acid test was used, and the albumin estimated in the proportion that it occupied of the total amount of urine in the tube. In other cases the cold nitric acid test was used, and the amount estimated as plus, and in various degrees of traces.

The following abbreviations are used:

Ad	Date of admission.
Alb	Albumin in the urine.
Disc	Date of discharge.
E. A	Estivo-autumnal.
Ft	Faint.
Grs	Grains.
Hb	Hemoglobin estimation.
Hbg	Hemoglobinuria.
Mal	Malaria.
Mal. Clin	Malaria, clinical.
Pra	Previous admissions.
Prf	Previous attacks of fever.
Rbc	Number of erythrocytes per cubic millimeter.
Res	Length of residence in the Canal Zone.
T	Tertian.
Tr	Trace.
Wbc	Number of leucocytes per cubic millimeter.
Z	Ounce.

CLASS I.

Hemoglobinuria before admission and not subsequently.

Case number.	Hospital number.	Days of duration of hbg.	Previous illness.	History and Symptoms.	Urine findings.	Treatment and Result.	Blood findings.
76	54380	1	12 pra.....	American; age, 27; res., four and one-half years; ad. Feb. 13, 1909; ill, two days; fever, chills, and headache. Two days prior to admission passed hbg. for one day. No fever after admission. No record of quinine prior to hbg. Previous admissions, 11/9, '04; mal. clin., 1/18,'05; mal. E. A., 8/30, '05; mal. E. A., 1/7, '09. Hbg. fever.	2/14, neg.; 2/15, neg.; 2/16, ft. trace; 2/17, neg.	14th, quinine, grs. XXX daily; 15th, quinine, grs. XX daily to discharge on 27th. This is the second attack of hbg.	Ad., neg.; 2/13, wbc, 8,000, rbc., 3,000,000 hb., 48 per cent. 2/17 hb. 39 per cent. 2/24, hb., 59 per cent.
78	58158	(?)	1 pra.....	Austrian; age, 31; res., 18 mos.; ad., May 13, 1909; ill three weeks, irregular chills, fever. Eight days prior to ad. passed hbg. for (?) days. Had taken quinine grs. XV per day for several days prior to admission. On ad. tem. 101 degrees. Slight fever on 15th, 18th, and 19th.	Neg.....	14th, quinine, grs. X, t. i. d.; 15th, quinine grs. XV, t. i. d.; 16th quinine grs., X, t. i. d. to discharge on 25th.	Neg.
105	18418	(?)	5 pra.....	Spaniard; age, 19; res., 7 mos.; ad. Sept. 8, 1906. History of having passed hbg. (?) days prior to ad. Two days fever after ad. No record of quinine prior to hbg.	9/11, trace; 9/12 neg.	Ad. quinine grs. X, and one hypo. grs. V; 11th, two X grs. hypos. From 13th to disc. on 23d, grs. XX per day	Neg., 9/13, hbg. 40 per cent.
109	57632	3	2 pra.....	Spaniard; age, 37; res., 33, mos.; ad. April 29, 1909; ill six days, fever, headache and chills. Hbg. for three days prior to ad. Slight irregular temperature while in hospital; had taken quinine in large doses every day prior to ad. Previous ad., 2/5, '08; mal. clin., 9/16, '08, mal. clin.	4/30, trace; 5/19 trace.	Quinine, grs. X, t. i. d. to discharge on May 26th.	Neg. Hb.; 4/30, 25 per cent; 5/4, 38 per cent; 5/9, 52 per cent; 5/13; 51 per cent, 5/23, 66 per cent.
146	68701	2	2 pra.....	Spaniard; age, 21; res., 27 mos., ad. Nov. 27, 1909; ill two days; chill, fever, and sweat; hbg. cleared morning of admission. Tem. on ad. 100.5 degrees; Dec. 1, 99.5 degrees; otherwise normal. Had five pills of quinine prior to ad.	11/28, brown gran. casts and alb., trace, 11/29, trace, 12/2, neg.	On ad. quinine grs. X stat., and grs. V., q. i. d.; 11/30, quinine grs. X, t. i. d. to disc. Dec. 4.	Neg.

148	49716	1	2 pra.....	Spaniard; age, 28; res., 21 mos.; ad. Nov. 24, 1908; ill four days; fever and chills. Two days prior to ad. passed hbg. for one day. No fever after admission. No record of previous quinine. 9/30, '07, mal. clin.	11/26 trace; 12/0 neg.	On ad. quinine grs. XX; when the drug was discontinued and no more given. Disc. (?).	Neg.; 11/25 hb., 25 per cent. rbc. 1,500,000; 11/28, hb., 30 per cent.
149	49776	1	1 pra.....	Spaniard; age, 41; res., 6 weeks; ad. Nov. 25, 1908; ill three days; fever, chills; hbg. for one day prior to ad. Very slight irregular fever to Dec. 1, and normal to disc. No record of previous quinine.	11/26, neg.; 11/28 neg.; 2/4, neg.; 2/19, neg	On ad. quinine grs. XX; no more quinine. Disc. Dec. 17.	Neg.; 12/3, hb., 49 per cent, 12/12, 42 per cent; rbc., 1,472,000.
151	53877	4	7prf.....	Spaniard; age, 42; res., 16 mos.; ad. Feb. 3, 1909; ill four days, with hbg. fever and chills. No fever after ad. No record of previous quinine.	2/4, neg.; 2/9, neg.	I. and Q. tonic, z s s. t. i. d. to disc. on Feb. 27.	Neg.; hb., 2/3, 17 per cent; 2/6, 27 per cent; 2/11, 45 per cent. 2/15, neg Hb., 2/20, 40 per cent; 2/26, 45 per cent.
170	37697	(?) 2	0.....	Italian; age, 28; res., 15 mos.; ad. Feb. 19, 1908; ill four days; severe chill, followed by fever. He took quinine on the first day of his illness, with resulting hbg. which lasted but a while. On ad. tem. 100 degrees; 20th, 99 degrees; 21st, 99 degrees; p. m. 22d, 101 degrees; p. m., 23d, 101 degrees; a. m., 24th, 102.5 degrees; p. m., 24th, 100 degrees; followed by irregular temperature until March 3, when there was no more fever.	Neg.....	On ad. quinine grs. X, and grs. X t. i. d.; 24th and 25th, four X grain hypos. per day. 26th and 27th, grs. X, q. i. d. 28th to disc. on March 10 grs. X, t. i. d. NOTE.—The fever rose while the large doses of quinine were administered. This fever may have been due to a mild typhoid.	Neg.

CLASS I.—*Hemoglobinuria before admission and not subsequently.*—Continued.

Case number.	Hospital number.	Days of duration of hbg.	Previous illness.	History and Symptoms.	Urine findings.	Treatment and Result.	Blood findings.
175	54341	3	3 pra.....	Spaniard; age, 36; res., 27 mos.; ad. Feb. 12, '09. Admitted to Culebra Hospital Feb. 4, '09, with subnormal temperature, and had then been ill four days, with persistent vomiting and fever; 5th and 6th tem. subnormal. Urine almost suppressed, black, and on boiling, almost solid albumin. On 5th, quinine grs. XX, hypo. On the 6th, the urine cleared. No parasites were found. Transferred to Ancon Hospital on 12th. Temperature subnormal until 17th, when there was a rise to 101.5 degrees, and at death on 18th, 100.5 degrees. Persistent vomiting and suppression until death. Previous illness, 9/14, '07, mal. clin.; 7/23, '08, mal. clin.	2/12, alb+. 2/17 alb+.	On ad. quinine grs. XX, 13th to death; I. and Q tonic z s s, t. i. d.	Neg.
176	52192	2	1 pra.....	Spaniard; age, 43; res., 26 mos.; ad. Jan. 7, 1909; ill eight days, chills and fever; hbg. began on 5th and cleared on morning of 7th. Tem. normal until 14th. 14th–20th slight continued tem. 21st, normal; 22d, a. m., 99 degrees; p. m., 103 degrees. Normal on 23d, and to disc., on Jan. 30th. Claims one previous attack of hbg. Subsequent admission. 8/11, '09, mal. E. A.	1/8, neg.; 1/10, neg.	No quinine until rise of tem. on 22d; 22nd, two X gr. hypos; 23d, I. and Q. tonic z s s. until disc. on Jan. 30. Note the development of the malarial paroxysm on the 22d, and prompt control of the fever with quinine.	Neg.; hb., 1/8, 15 per cent; 1/10, 20 per cent; 1/13, 28 per cent; 1/15, 35 per cent; 1/17, 40 per per cent. 1/22 E. A.
184	33222	1	2 pra.....	Spaniard; age, 23; res., 20 mos.; ad. Oct. 14, 1907; ill three days, fever and chills; on 13th had hbg. On ad. tem. 101 degrees, subnormal to 15th. 16th, 99 degrees; 17th, 98, 100, 99, and 100 degrees; 18th, 98, 100.5, 99.5 and 102 degrees; 19th, 101.5, 98, 101 and 98.7 degrees; 20th, 99.5, 104, 102 and 100.5 degrees; 21–23d, irregular quotidian fever rising to 100.5 degrees. 24th to disc. on Nov. 9 irregular fever. Had quinine prior to ad.	10/15, alb+. 10/20, neg.	14th, two X gr. hypos. of quinine; 15th, four X gr. hypos; 16, 17, and 18th, four X gr. hypos. 19th, two XX gr. doses 20–22d, grs. X, t. i. d. 23d, grs. X, q. i. d. 24th–30th, grs. X, t. i. d.; 31st–6th discontinued; 7th to disc. on 9th, grs. X, t. i. d.	Neg.; 10/16, wbc. 7,500; 10/21, wbc., 15,000, hb. 10 per cent; rbc. 1,200,000 m e g aloblasts. 10/24, wbc. 8,600, hb. 10 per cent, rbc. 1,200,000. 11/5 hb., 46 per cent.

197	55463	1	Much fever	Spaniard; age, 38; res., 2 years; admitted March 9, 1909; has had fever and chills at intervals for one month. Two days prior to ad. passed hbg. for one day. No fever until March 23, when there was a slight irregular tem. until 24th. On 31st, rise in temperature, and slight irregular fever until disc. on May 30. On Jan. 11, 1909, this patient was in Ancon Hospital with hbg. fever. See case No. 168.	3/10, alb+.; 3/12, trace.	No quinine until March 31 when grs. X, t. i. d. were given until April 6. April 6 to disc. on May 30, I. and Q. tonic z s s., t. i. d. Note the development of the tertian paroxysm on March 31.	Neg.; hb., 3/15, 20 per cent; 3/23, 33 per cent; 3/26, 29 per cent. 3/31, T. Hb., 4/1, 27 per cent; 4/2, 30 per cent; 4/14, 26 per cent; 4/16, 24 per cent, wbc. 8,600, rbc. 2,720,000 hb., 5/30, 60 per cent.
206	75536	(?)	3 prf.....	Spaniard; age, 43; res., 22 mos.; admitted May 14, 1910. On April 22, 1910, this patient was admitted to Ancon Hospital with hbg. fever. On May 10 he was sent to Taboga, and developed hbg. while there. Hbg. cleared before his return. See case No. 210, Class II.	Neg.....	No quinine while in hospital.	Neg.
214	39341	1	2 pra.....	Spaniard; age, 31; res., 16 mos.; admitted April 21, 1908; ill one day; chills, fever and hbg. On ad. tem. 102 degrees; irregular fever to 26th, with rise to 104.5 degrees on that date and similar rise on 29th. Subsequent hbg., 11/5, '08.	4/22, trace; 5/21 neg.	Ad. quinine grs. XX, and grs. X, t. i. d. to 29th, when four hypos, grs. X each, per day to May 2, when grs. X q. i. d. to 8th. 8th–12th grs. X, t. i. d.; 12th–26th, grs. V, t. i. d.	Neg.; nucleated reds.

CLASS II.—SERIES A.— *Hemoglobinuria on admission.*

Case number.	Hospital number.	Days of duration of hbg.	Previous illness.	History and Symptoms.	Urine findings.	Treatment and Result.	Blood findings.
2	20222	2	2 pra..... Prf. several	Grenadian; age, 26; res., 8 mos.; admitted Nov. 8, 1906; ill one month; irregular chills and fever. Hbg. began on the 8th and cleared on the 9th. Ran an intermittent fever for 9 days, as high as 101.5 at times. No record of previous quinine.	11/9, alb. hemin crystals, z 51; 11/10 trace, z 60; 11/11, tr'ce, z 73; 11/13, neg.	No quinine until 13th. 13th–17th, grs. XX per day, hypo. 19th to disc. on 29th, I. and Q tonic, z s s, t. i. d. Disc. Dec. 7.	Neg. Hb., 11/10, 10 per cent; 11/15, 20 per cent; 11/20, 31 per cent; 12/6, 68 per cent.
8	13459	No record..	See report..	Jamaican; age, 23; res., 3 mos.; admitted May 24, 1906. No record of duration of illness. Hbg. cleared about 25th; intermittent fever 24th–25th; continued fever, 26th–30th; normal to discharge. Subsequent hbg. fever, August 5, 1906.	5/25, alb., 3 per cent.	On admission, quinine, grs. XX. Discontinued until 27th. 27th–28th, grs. X, t. i. d.; two hypos of grs. XX each. 30th to June 3, grs. X, t. i. d., 4th–7th, grs. X per day. Discharged, June 7.	Neg. Hb., 5/24, 55 per cent; 5/28, 38 per per cent; 6/5, 60 per cent.
10	17018	Not recorded	1 pra.....	Jamaican; age, 24; res., 7 mos.; admitted Aug. 5, 1906; ill several days; persistent vomiting and hbg. On ad. tem. 105 degrees; 6th, 102 degrees; normal on 7th. Slight fever, to 99.5 degrees for next five days. No record of previous quinine; previous ad- in May, 1906, with hbg fever. See case No. 8 above.	8/5, hemin crystals and alb.; 8/20, neg.	On ad. quinine, grs. XX, hypo. 6–10th, grs. XX per day; 11th to disc. on Sept. 2, grs. XV per day.	Neg.
14	66976	+2	1 pra.....	Barbadian; age, 40; res., 3 years; admitted Oct. 27, 1909; ill three days; fever and chills. Hbg., 27-29 inc. in hospital. On ad. tem. 102 at 2 p. m., normal at 8 p. m. Normal to 31st; slight fever 31st to Nov. 15, reaching about 100 in the p. m. and gradually falling to normal. No record of previous quinine. Subsequent hbg., Feb 17, 1910.	10/27, hemin crystals, alb. and casts; 10/30, neg.	On admission, quinine, grs. XX stat. No more quinine.	Neg. Hb., 10/27, 45 per cent; wbc., 13,200; hb., 11/1, 40 per cent; 11/27 90 per cent.
15	69516	3	1 pra.....	Barbadian; age, 34; res., 4 years; admitted Dec. 13, 1910; on Dec. 12, had severe chill, followed by hbg. Hbg., 12th–14th. On ad. tem. 100.5 degrees; 14th–15th, normal; 16th–17th, slight fever, and normal to disc. on Dec. 21. Had quinine on 10th, 11th, and 12th.	12/13, hemin crystals, alb. casts.	On ad., quinine, grs. XX, stat. 18th to dsc. on Dec. 21, I. and Q. tonic t. i. d.	Neg. Hb., 12/15 50 per cent.

16	57617	2	4 pra.....	Barbadian; age, 32; res. two and one-half years; admitted April 29, '09; hbg., 29th–30th; ill one day; chills, fever and vomiting. On ad. tem. 104 degrees; 30th, 102 degrees; normal afterwards to May 5, when slight remittent fever until 14th. On 15th, chill, tem. 102.5 degrees; normal, 16th; 17th, tem. 103.5 degrees, and normal to discharge on May 25. No record of previous quinine. Previous illness, 4/7, '07; fever; 10/19, '08, mal. E. A.	4/29, hemin crystals and albumin.	On ad. quinine, grs., XX, stat. May 17th, grs. XX, hypo. 18th–25th, I. and Q. tonic, z s s., t. i. d. No blood examination was made on the 15th and 17th.	Neg.
19	72431	Not recorded	3 pra.....	Barbadian; age, 40; res., 4 years; admitted Feb. 17, 1910; ill two days; fever, chills and hbg. On ad. tem. 102 degrees; 18th, 101 degrees; 19th, 100.5 degrees; 20th, 100.5 degrees; 21st, 99.5 degrees; slight fever to discharge. Previous illness, hbg. fever on Oct. 27, '09. See case 14 above.	2/18, hemin crystals, alb.	No quinine.....	Neg. Hb., 2/15 47 per cent.
20	14369	Not recorded	(?).....	Barbadian; age (?); res., (?); admitted June 12, 1906; comatose on admission; suppression of urine; retraction of neck, and positive Kernig sign. Admitted at 6 p. m., and died at 11 p. m.	Hemin crystals and alb.	On ad., quinine, grs. XX, hypo. Post mortem record "malaria." Died June 12.	Neg. Filaria; wbc., 30,000.
23	34115	Not recorded	(?).....	Barbadian; age, 30; res., 18 mos.; admitted Nov. 3, 1907; stupid and dull; ill two weeks; heavily jaundiced; severe vomiting. On ad. tem. 102.5 degrees; 4th, 100.5 degrees; 5th, 100 degrees; before death, 97.3 degrees. Semi-comatose; continual vomiting; died, Nov. 6. No record of previous quinine.	11/3, hemin crystals and alb., 40 per cent; 11/5, alb. 25 per cent; 11/6, alb., 25 per cent. No casts.	On ad., quinine, grs. XX; 4th, four hypos, grs. X each; 5th two hypos, grs. XX, each; hbg. was clearing at time of death. Died Nov. 6.	Neg.
24	23320	See report..	1 pra.....	Barbadian; age, 22; res., 7 mos.; admitted Jan. 30, 1907; semi-comatose. On ad. tem. 103 degrees; 31st, normal until death on Feb. 2. Suppression and hbg. until death; continued vomiting. Previous illness, 9/19, '06, mal. E. A.	1/30, hemin, crystals and alb.	On ad., quinine, grs. XX. Died, Feb. 2.	Neg.

CLASS II.—SERIES A.— *Hemoglobinuria on admission*—Continued.

Case number.	Hospital number.	Days of duration of hbg.	Previous illness.	History and Symptoms	Urine findings.	Treatment and Result.	Blood findings.
26	20158	4	1 pra	Barbadian; age, 36; res., 15 mos.; admitted Nov. 6, 1906; stupid; nausea and vomiting; tem. subnormal and remained so. Hbg. on admission, began on 5th and cleared on 8th.	11/6, hemin crystals and alb.; 11/8, alb. trace; 11/9, alb., 1 per cent; 11/10, alb. trace; 11/11, alb. trace; 11/12, neg.; 11/13, neg.	No quinine until 12th, when I. and Q. tonic, z s s., t. i. d., to discharge.	Neg. Hb., 11/10, 45 per cent.
28	18109	(?)	2 pra	Barbadian; age 21; res., 2 years; admitted Aug. 30, 1906; comatose. Died Sept. 2, at 1.45 a. m. Continued fever, 105–102 degrees until death. Hbg. until death. This man was in Ancon Hospital from Aug. 9 to Aug. 25, 1906, with clinical malaria.	No record except hbg.	On ad., quinine, grs., XX; 31st, grs. X, t. i. d., and one hypo. grs. XX. Died 1.45 a.m., Sept. 2.	Neg.
30	16979	3	Prf. many times. Pra. 2.	Barbadian; age, 55; res., 2 mos.; ad. Aug. 4, 1906, chill every night since July 27. Hbg. began on morning of Aug. 4, and continued to death. Intense jaundice and severe vomiting. On ad. tem. at 4 p. m., 102.3 degrees; 8 p. m., 99.8 degrees; 12 p. m., 101.5 degrees; 5th, 4 a. m., 100.5 degrees; 8 a. m., 98 degrees; 4 p. m., 100 degrees; 8 p. m., 98 degrees. No record of previous quinine.	8/4, hemin crystals and alb. 60 per cent.	On ad., quinine, grs. XX, hypo. and grs. X, hypo, Q. 4h. to death on Aug. 6.	Hb., 8/4, 65 per cent; 8/6, 42 per cent.
31	31457	(?)	(?)	Costa Rican; age, 19 yrs. 3 mos.; admitted Sept. 10, 1907; ill 14 days; chills and fever; no record of when hbg. began. Hbg. cleared on 12th. On ad. tem. 102.5 degrees; 11th from 100 to 102.5 degrees, and normal at night. Slight remittent fever to 15th; on 16th, 102.5 degrees with fever until 20th; on 24th, 102 degrees and normal to disc. on 27th. Severe vomiting 10th–14th.	9/10, hbg., 9/12, alb. +, urine clear; 4/14, alb. +; 9/20, alb. trace; 9/24 alb. trace and casts.	On ad., quinine, grs. XX; 11–12, two XX gr. hypos. per day; 13–17, grs. X, t. i. d.; 18th, two XX gr. hypos.; 19–22, grs. X, t. i. d.; 23d to disc. on 27th, I. and Q. tonic, z s s., t. i. d. Note rises in temperature while quinine was being administered.	Neg.

35	2721	4	(?).....	Greek; age, 39; res., 5 mos.; ad. June 3, 1905; had been ill 7 days with fever chills and nausea. Denied hbg. but record shows black urine on admission. On ad. tem. 103.5 degrees; 4th a. m., normal; p. m., 101.5 degrees; continued fever between 100 and 101.5 degrees until 7th; when tem. was normal; 9th and 10th, fever rose to 101.5 degrees, and intermittent fever between 99.5 and 101.5 degrees from 11th–23d inc.; 25th to July 9th slight intermittent fever, sometimes as high as 100 degrees. Clinical course resembles mild typhoid; bedside notes indicate disease was not severe. Hbg. cleared on 7th.	6/3, alb., 9.5 per cent; 6/4, z/2 alb. 12 per cent; 6/5, z 36, alb., 14 per cent; 6/6, z 27, alb., 12 per cent; 6/7, z 12, alb., 6 per cent; 6/8, z 12, alb., 1 per cent.	4th–5th, grs. XX hypo. per day; 6th–11th, grs. XX daily; 12th, grs. XXX; 13th–14th, grs. XX daily; 15th–17th, X, t. I. d.; 18th–24th, grs. XX daily; 24th July 1, grs. X, t. i. d.; 2d to 9th, grs. XX daily; 10th to disc. on 24th, I. Q. and S. tonic, z j, t. i. d. All of this quinine had no effect on the fever which ran for three weeks; patient had soft diet with extras from June 8 to July 2, after which he was placed on full diet.	6/3, E. A.
36	36249	2 +	(?).....	Greek; age, (?); res., (?); admitted Jan. 7, '08; semi-comatose; vomited continually until death. On ad. tem. 102 degrees, at death, 100 degrees.	Alb. + +; hbg.	On ad., grs. XX hypo.; 8th, grs. XX hypo. Died on 8th.	E. A.
37	51578	3	5 prf; 1 pra.	Italian; age, 31; res., 2 years; admitted Dec. 31, 1908; ill several days; fever and chills. Hbg. began on 30th and cleared on Jan. 1; on ad. tem. 100 degrees; Jan 1–3, normal; 4th–15th, intermittent fever gradually increasing until p. m.; temperature on Jan. 12th, it was 102 degrees, and normal each a. m. No fever after 15th until disc. on 22d; severe vomiting on 31st and 1st. No record of previous quinine.	12/31, alb., and hbg.; 1/1, alb. and hbg.; 1/6, neg; 1/19, alb.	On ad., quinine, grs. XX; on 11th, I. and Q. tonic, z s s., t. i. d., to disc. on 22nd; on 12th, grs. XX hypo. were given. From 4th–12th, K. I. grs. X, t. i. d. was given.	Neg.; hb., 1/2, 80 per cent; 1/6, 59 per cent; 1/12, wbc., 12,000.
39	1401	2	(?).....	Italian; age, 34; res., 34 days; history of 12 years' residence in tropics; admitted Jan. 25, 1905; ill 5 days; fever, chills, sweats, and severe vomiting. Hbg. cleared on 27th. On ad. tem. 102.5 degrees. 26th, a. m., normal; p. m., 100 degrees; 27th, normal; 28th, 100 degrees, and normal to discharge. No record of previous quinine.	1/26, alb., 22 per cent; 1/27, alb. trace; 1/28, neg; 1/29, neg.	26th, six V gr. hypos.; 27th, two V gr. hypos.; 28th, grs. V, t. i. d.	E. A. and T.

CLaSS II.—SERIES A.—*Hemoglobinuria on admission*—Continued.

Case number.	Hospital number.	Days of duration of hbg.	Previous illness.	History and Symptoms.	Urine findings.	Treatment and Result.	Blood findings.
41	36162	(?)	1 pra.....	Italian; age, 35; res. 1 year; ad. Jan. 5, 1908; ill four days; chills, fever, and headache; hbg. and jaundice. Duration of hbg is not stated. On ad. tem. 103 degrees; irregular remittent fever to Jan. 19, after which irregular subnormal tem. to disc. No record of previous quinine.	1/5, hbg. and alb.	5th–7th, grs. X, hypo., four times per day; 8th grs. X hypo. for five doses; 9–11th, grs. X, four times per day; 12th to disc. on Feb. 1, grs. X, t. i. d. For a week after admission the urine averaged z 20 per day.	Neg.
43	9372	3	1 pra.....	American; age, 31; res., 13 mos.; ad. Jan. 18, 1906; ill a week; hbg. began at noon on Jan. 17, and cleared on 19th, p. m. On ad. tem. 100 degrees; 19th, 100 degrees; 20th, 100.5 degrees; fell slowly to normal on a. m. of 24th. 24th, p. m., 100.5 degrees. Gradually decreasing remittent fever 25th to 30th; vomited continually on night of 18th, and on 19th; slight fever, 1st and 2d.	19th, am., alb., 90 per cent; p. m., alb., 60 per cent; 20th alb.trace;21st, alb.trace;22d, alb. trace; 23d alb. neg.	18th, two hypos., grs. X each; 19th, one hypo., grs. X; 23d–28th, grs. X, t. i. d.; 29th to disc. on Feb. 3, grs. XX daily.	Neg.
45	7110	* 5	4, fever....	American; age, 36; res., 4 years; ad. Nov. 15, 1905; ill three days; fever and chills; hbg. on admission, and for five days subsequently. On ad. tem. 99.5 degrees; a. m., 19th, 99.5 degrees; p. m., 101.5 degrees; a. m., 20th, 103.5 degrees; p. m., 101.5 degrees; normal until disc. on 26th. No record of taking quinine prior to ad.	19th, a. m., 29 per cent, alb.; p. m., 20 per cent, alb;20th, a. m., 20 per cent, alb; p.m. 15 per cent alb.; 21st 20 per cent alb.; 22d, 20 per cent, alb;24th, 1 per cent alb.; 25th neg.	19th, quinine, grs. X, hypo four doses; 20th, quinine, grs. XV, hypo. four doses; 21st, quinine, one XV gr. hypo., and four V gr. doses by mouth; 22d–26th, grs. V, four times a day.	E. A.

51	12383	3	Much fever.	American; age, 29; res., 6 years in tropics and 19 months on Isthmus; ad., April 23, 1906; ill two days; chills and fever; hbg. began at 2 p. m. on 22d; cleared night of 23d. For three or four months had taken grs. IX per day of quinine, but 8 days prior to ad. had omitted it. On 21st, grs. XII; on 22d, grs. XXV. On ad. tem. 103.5 degrees; normal on 24th; slight rises on 25th and 26th; normal to discharge on 30th. On afternoon of 25th a slight paroxysm with hbg.; 2/18, '08, malaria, clinical.	23d, 25 per cent, alb; 24th, a.m, 19 per cent alb.; p. m. trace; 25th, a. m., neg.; p. m., 50 per cent, alb.; 26th, a.m., 10 per cent, alb.; p. m., neg. Urine until disc. varied between neg. and trace.	23d, quinine, grs. X; 24th quinine, grs., XX, hypo.; same on 25th–26th; 27th, grs. XXX per day until disc.	Neg. Hb. Sahli 24th, 67 per cent; 25th, 52 per cent; 26th, 43 per cent; 28th, 38 per cent.
56	21975	3	Several attacks of fever.	American, female; age, 47; res., 14 mos.; ad. Dec. 30, '06; ill four days; severe chill, with fever and vomiting; hbg. began three days prior to ad. and cleared on night of 30th. Had several doses of quinine prior to ad. Tem. on ad. normal; slight rise on 31st, and normal to disc. on Jan. 11; 4/10, '06; malaria, E. A.	30th, 16 per cent alb.; 31st, 10 per cent, alb.; 1st, neg.	On ad., quinine, grs. X, and grs. X, t. i. d., until disc.	Neg. Hb., 30 and 25 per cent, dates not given.
60	18363	(?)	Much fever.	American; age, 26; res., 28 mos.; ad. Sept. 9, '06; ill two days; fever, chills, headache and vomiting; marked jaundice. On ad. tem. 102.5 degrees; 10th, a. m., normal; p. m., 100 per cent; 11th, a. m., normal; p. m., 100.5 degrees; 12th, a. m., 100.5 degrees; p. m., 101.8 degrees; 13th, a. m., normal; p. m., 101 degrees; slight fever on 14th; normal on 15th; 16th, a. m., normal; p. m., 101 degrees. Slight irregular fever to 24th, then normal to disc. on 28th. Vomiting was excessive during the first four days after ad. 7/29, '04, malaria, E. A., with hbg, see case No. 58; 12/1, '04, malaria, double tertian; 6/21, '05, malaria, E. A.; 10/26, '05, malaria, E. A., with hbg. See case No. 59.	9th, 20 per cent, alb.; 10th, 20 per cent alb.; 11th, 10 per cent, alb.; 12th, 20 per cent, alb.; 13th, 5 per cent, alb.; 14th, neg.	9th, quinine, grs. X, hypo two doses; 10th, quinine, grs. X, hypo, one dose; 11th, quinine, grs. XXX; 12th–14th, quinine, grs. XX per day, hypo.; 15th–19th, quinine, grs. XXX per day; 20th, to disc. quinine, grs. XX per day. Urine was clear on 14th; hbg. on 16th; clear on 17th; hbg. again on 18th, and subsequently clear.	Neg. 13th, hb., 20 per cent 15th, hb., 20 per cent; 20th hb., 20 per cent; 23d, hb. 18 per cent.

CLASS II.—SERIES A.—*Hemohlobinuria on admission*—Continued

Case number.	Hospital number.	Days of duration of hgb.	Previous illness.	History and Symptoms.	Urine findings.	Treatment and Result.	Blood findings.
61	64680	7	Not given..	American; age, 42; res., 4 years; ad. Sept. 20, '09; ill four days; headache, chills, and fever; hbg. began on second day of illness, and cleared on night of 25th; had taken no qinine prior to ad. On ad. tem. 104 degrees; 21st, normal and normal until death on 26th; patient had persistent nausea and vomiting until death. 6/1, '09, infected finger and abscess of breast.	Alb. hemin crystals.	20th, quinine, grs. XX, hypo., two doses; no more quinine. Suppression of urine from admission.	E. A.; 22d, hb., 60 per cent; 23d, hb. 45 per cent.
63	53031	4	4, fever.....	Italian; age, 28; res., 9 mos.; ad. Jan. 20, '09; ill two days; fever, chills and vomiting; hbg. began on afternoon of 19th, and cleared on 22d. No record of previous quinine. On ad. tem. 102 degrees; irregular fever to 100–102 degrees, until death on 27th.	Albumin + each day.	No quinine was given; suppression of urine until death.	Neg. 22nd, rbc. 1,224,000; 23d, hb., 25 per cent.
65	47661	(?)	(?)	American; age, 48; res., (?); ad. Oct. 18, '08; semi-comatose on admission and until death on 20th. Hbg. until death. Tem. 18th, 103.8 degrees; continued fever until death.	Hemin crystals alb. ++	18th, quinine, grs. X, hypo., three doses. Suppression of urine until death.	
68	24912	+3	Much fever.	Barbadian; age, 24; res. 2 years; ad. May 13, '07; ill ten days with fever, chills and vomiting. No record of previous quinine nor of the date of beginning of hbg. Urine clear on 15th. No fever subsequent to admission. 2/13, '07, malaria, clinical; 9/20, '07, malaria, quartan; 4/12, '09, malaria, clinical; 10/20, '09, malaria, E. A.	Alb. +	13th, quinine, grs. X, hypo., six doses; 14th–31st, quinine, grs. X, t. i. d. Discharged on 31st.	Neg.
73	1162	3	Much fever.	Jamaican; age, 46; res., 11 mos.; admitted Dec. 29, '04; ill seven days; fever and chills. Dec. 28, hbg. began, accompanied by diarrhea and vomiting. Urine cleared on 30th; six tablets of quinine, 27th–28th, prior to appearance of hbg. Tem. on ad. 99 degrees; and there was a very slight fever until disc. on Jan. 5.	Alb. +; 31st, 3 per cent alb. 1st, neg.	No quinine while in hospital.	E. A.

77	72743	4	2 pra.....	Panamanian of German parentage; age, 21; res., lifetime; ad. Feb. 24, 1910; ill five days; chills, fever and headache. Hbg. began on p. m. of 23d, and cleared on 26th. No record of prior quinine administration. No fever after admission.	25th, alb. H. T.; 26th, alb. F. T.; 27th, alb. neg.; 28th, alb. F. T.; 10th, neg.	No quinine after admission. Disc. on March 10.	Neg.
81	45092	3	(?)	Ireland; age, 33; res. (?); Admitted Sept. 1, 1908. Patient was a private in the U. S. Marine Corps, stationed at Camp Elliot; was admitted to Camp Elliott Hospital, and hbg. began shortly after ad. History does not state whether or not quinine had been given prior to hbg. On Aug. 31, received quinine, grs. CX, hypos., at Camp Elliott. On ad. tem. 101 degrees; irregular remittent fever 2d–3d, and between 99.5 and 102 degrees; 4th to 7th; normal on 7th to disc. on 19th.	Alb. and casts.	Sept. 3, quinine, grs. X, hypo.; 4th–14th, grs. XV, daily. Had four days of fever in Ancon Hospital while taking quinine.	Neg.
84	47802	4	2 pra.....	Italian; age, 23; res., 23 mos;. ad. Oct. 20 1908; ill three days; fever, chills, headache and vomiting. Hbg. began on 18th, and cleared on 21st; slight fever on 20th, afterward normal tem. to disc. on Nov. 6.	20th, alb., hemin crystals; 26th, neg.	20th, quinine, grs. XX; 21st–25th, grs. X, t. i. d.; 26th–27th, quinine discontinued; 28th–6th, I. and Q. tonic, one-half ounce t. i. d.	Neg. 22d, hb., 60 per cent; 3d, hb., 65 per cent.
88	23728	7	(?)	American; age, 35; res., 4 mos. on Isthmus and three years in Cuba; history of hbg. in Cuba. Ad. Feb. 10, '07; ill a week; pain in abdomen and scrotum; had been passing hbg. five days. No fever while in hospital; hbg. began on 6th, and cleared on 12th; disc. 17th.	10th, alb. and casts; few red blood cells on 12th and 14th.	11th–13th, quinine, grs. XV, t. i. d., 14th–17th, quinine, grs. XX, daily.	Neg.
89	34125	3	(?)	American, female; age, (?); res. 3 mos.; ad. Nov. 4, '07; ill one month with daily fever. Hbg. began on 3d, and continued to death on 5th. Tem. on ad. 104 degrees; 5th, tem. q. 4 h. 100, 99.8, 100, 102, and 103 degrees. Died at 7 p. m. on 5th.	Alb. and casts.	4th, quinine, grs. X, hypo. at 3, 7, and 12 p. m.; 5th, quinine grs. V, hypo., at 8.30 a. m., and 4.30 p. m.	E. A. rings and crescents.

CLASS II.—SERIES A.—*Hemoglobinuria on admission*—Continued.

Case number.	Hospital number.	Days of duration of hbg.	Previous illness.	History and Symptoms.	Urine findings.	Treatment and Result.	Blood findings.
92	47605	+2	3 pra.....	Spaniard; age, 26; res., 15 mos.; ad. Oct. 16, '08; comatose on ad.; ill two days; fever and headache; hbg. began on 15th, and cleared about 16th. Tem. on ad. 101 degrees; 17th, a. m., 102.3 degrees; p. m., 102.5 degrees; 18th, a. m., 100 degrees; p. m., normal, and normal to disc. on Nov. 2. 7/23, '08, malaria, clinical; 9/7, '08, malaria, E. A. and tertian; 10/5, '08, malaria, E. A.; 10/11, '08, malaria, E. A.	Alb., 29th neg..	16th, quinine, grs. XX, hypo; 17th, quinine, grs. XX; 23d–2d, I. and Q. tonic, t. i. d.	E. A. and tertian.
96	56137	4	1 pra.....	Spaniard; age, 29; res., 22 mos; ad. March 25, '09; ill three days; chills, fever; hbg. began on night of 24th, and cleared on 28th. On ad. tem. 102 degrees; irregular fever every day to 100 degrees until 8th, when 101.5 degrees; normal afterwards until disc. on April 23.	Alb. and casts; 29th, neg.; 4/8 neg.; 9th, alb. and casts.	No quinine until April 7th, when I. and Q. tonic; 8th, quinine, grs. V, t. i. d.; 9th–23d, grs. X, t. i. d.	Neg. 3/31, neg. 30th, hb., 34 per cent; 8th, 69 per cent; 13th, 62 per cent; 19th, 60 per cent.
97	56550	4	Fever (2)...	Spaniard; age, 36; res., 2 years; ad. April 3, '09; ill three days; fever and chills; no vomiting; jaundice marked; hbg. began on April 1, and cleared on 5th. On ad. tem. 101 degrees; continued fever between 99.5 and 101.5 degrees to 8th, and on 9th and 10th, reaching 102 in p. m.; slight continued fever between 99 and 100 degrees, until 23d; slight intermittent fever at intervals until disc. on May 29. 3/17, '08, malaria, E. A.; 8/20, '08, malaria, clinical.	Alb. and casts..	April 6, quinine, grs. XX, hypo; 8th, quinine, grs. V, t. i. d.; 10th, quinine, grs. X, t. i. d.; 15th, quinine, grs. V, t. i. d.; 17th, quinine, grs., XX, hypo.; 28th–5th, I. and Q. tonic.	Neg. 11th, hb., 29 per cent; 16th, rbc. 2,600,000; wbc. 6,000; 17th, hb. 24 per cent; 28th hb., 50 per cent; 5/5, 68 per cent.
98	55822	4	2 pra.....	Spaniard; age, 24; res. 14 mos.; admitted March 18, '09; ill four days; chills, fever and jaundice; hbg. began on 16th and cleared on 19th. On ad. tem. 101 degrees; slight fever to 22d, and normal afterwards to disc. on April 3.	Alb. and casts; 28th, neg. April 2, neg.	18th, quinine, grs. XX. No more quinine.	Neg. 19th, hb. 63 per cent; 23d, hb. 50 per cent.

99	55732	4	2 pra.....	Spaniard; age, 29; res., 28 mos.; ad. March, 17, '09, ill two days; fever and chills; hbg. began on 15th and cleared on 18th. On ad. tem. 100 degrees; normal afterwards to disc. on April 8. 2/9, '07, malaria clinical.	Alb. and casts; 18th, alb. +; 22d, neg.; 28th, neg.	April 6–7, I. and Q. tonic.	Neg. 19th, hb., 48 per cent; 4/4, hb., 82 per cent.
104	18918	+3	Fever (4)...	Spaniard; age 29; res., 4 mos.; ad. Sept. 27, 1906; ill three days; headache, fever and vomiting; hbg. on ad. and for two days after. On ad. tem. 105 degrees; later, 103 degrees; 28–29th, slight fever, afterwards normal to disc. on Oct. 6. 12/15, '06, malaria E. A.; 6/18, '07, malaria, T.	27th, alb., 25 per cent and 10 per cent; 28th, alb. 20 per cent; 29th, alb., 10 per cent; 30th, neg.	27th, quinine, grs. X, and two hypos., grs. X, each; 28th, quinine, grs. X, three hypos.; 29th–6th, grs. X, t. i. d.	Double tertian.
106	10502	+3	Not given..	Spaniard; age, 26; res., 8 mos.; ad. Feb. 21, 1906; had been ill six days; history states hbg. on ad. but omits duration. Urine was neg. on 24th; slight fever 21-22, afterwards normal to disc. on March 1. Patient was very ill on admission, with severe vomiting and incontinence of urine. Had taken some quinine prior to ad.	21st, alb.; 24th, neg.	21st., quinine, grs., X, hypo.; 22d, quinine, grs. XX, hypo.; 23d, grs. XXX; 24th-25th, quinine, grs. XX daily; 26th-March 1, grs. X, t. i. d.	Neg.
107	9004	5	Much fever.	Spaniard; age, 29; res., 16 mos.; ad. Jan. 5, '06; irregular fever for several weeks; Jan. 4, had chills, fever and passing of bloody urine; urine cleared on 8th. On ad. tem. 99–100 degrees; 6th, 98, 101.5, 100 and 101 degrees; 7th, 99.5, 100, 98, and 101 degrees; 8th, 100, 98.7, 100, and 101.5 degrees; 9th, 102, 102, 100, and 102 degrees; 10th, 100, 99.5, 101, and 102 degrees; 11th, 101, 100, 101, and 103 degrees; 12th, 101.5, 101, 101.5, and 101.5 degrees; from 13th-17th tem. fell gradually to normal; nd remained so until disc. on 27th. Very severe case; vomiting and restlessness very severe on 6th and 7th.	5th, alb., 90 per cent; 5th, alb. 90 per cent; 6th, alb., 90 per cent; 6th, alb. 95 per cent; 7th, alb. 40 per cent; 7th, alb., 10 per cent; 8th, alb. 7 per cent; 8th, alb. 1 per cent; 10th-15th, alb trace; 16th neg.	5th, quinine, grs. X, hypo; 6th, quinine, grs. X, hypo., four doses; 7th-9th, quinine, grs. V, hypo., four doses; 10th quinine, grs. XV, hypo. two doses; 11th, quinine, grs. V, hypo., four doses; 12th-15th, quinine, grs. XXX per day; 16th-27th, quinine, grs. XX, per day.	Neg.
110	53646	(?) 4	1 pra.....	Spaniard; age, 38; res., 23 mos.; ad. Jan. 30, '09; ill four days, hbg. began Jan. 28, and cleared about Feb. 1; chills and fever; no fever after admission. 11/20, '08, malaria, clinical.	Alb. and casts...	30th, quinine, grs. XX; Feb. 6th-8th, I. and Q. tonic.	Neg.; 31st, hb. 55 per cent; 4th, hb. 55 per cent.
111	53479	4	Fever.....	Spaniard; age, 26; res., 6 mos.; ad. Jan 27, '09; chills, fever and headache for several days; hbg. began on 26th and continued to death on 29th. On ad. tem., 2 p. m., 98.7 degrees; 3.30 p. m., 102.8 degrees; normal and subnormal afterward until death.	Hemin crystals, alb. and casts.	No quinine was given....	Tertian.

CLASS II.—SERIES A.—*Hemoglobinuria on admission*—Continued.

Case number.	Hospital number.	Days of duration of hbg.	Previous illness.	History and Symptoms.	Urine findings.	Treatment and Result.	Blood findings.
112	53681	2	Fever (4)...	Spaniard; age, 30; res., 18 mos.; ad. Jan. 31, '09; ill three days; chills, fever and vomiting; history of prior hbg. in Colon Hospital three mos. previously; hbg. began on 30th and cleared on 31st. Slight fever on ad. and normal afterward until disc. on Feb. 11. 10/14, '08, malaria, E. A.	Alb. and casts...	No quinine until Feb. 7, when I. and Q. tonic until disc.	Neg.
113	54202	6	Not given..	Spaniard; age, 33; res., 5 mos.; ad. Feb. 9, '09; ill three days; chills and fever; hbg. began on 6th and cleared on 11th. On ad. tem. normal; 10th, 102 degrees; normal to a. m., 14th; p. m., 100 degrees; 15th, a.m., normal; p. m., 103.2 degrees; normal to disc. on March 1.	Alb. and casts...	9th, quinine, grs. XX; 15th, I. and Q. tonic; 24th–1st, I. and Q. tonic.	Neg.; 18th, hb., 35 per cent; 26th, hb., 54 per cent; 1st, hb. 65 per cent.
114	47525	2	2 pra.....	Spaniard; age, 29; res., 18 mos.; ad. Oct. 15, '08; ill four days; fever, chills and headache; hbg. began on 15th prior to ad. and cleared on 16th. On ad. tem. normal; 18th-19th, slight fever; normal to 7th, when there was a rise to 102 degrees in p. m.; normal afterwards until disc. 16th. On the 7th tertian parasites were found. 8/22, '07, malaria, E. A.; 1/21, '09, malaria, T.; 10/25, '09, Inguinal adentis.	Alb. and casts; 18th, neg.; 19th, alb. trace; 21st, neg.	5th, quinine, grs. X; 7th–16th, I. and Q. tonic.	Neg.; nucleated red cells; 26th, hb. 33 per cent; 7th, hb., 51 per cent; 7th, tertian.
116	55104	3	3 pra.....	Spaniard; age, 25; res., 3½ years; ad. March 1, '09; ill three days; chills and fever. On ad. tem. 100; slight fever on 2d; when normal until p. m. of 10th; when chill followed by rise to 105 degrees; 11th, a. m., 102.5 degrees; p. m., 99.5 degrees; normal 12th,13th; normal to disc. on April 5. Following chill on 10th, a mixed infection of tertian and E. A. parasites was found. 5/27, '05, malaria, E. A. and iritis; 8/18, '05, malaria, E. A.; 1/7, '08, malaria, E. A.	Alb. and casts; 3d, neg.; 11th, alb. trace; 29th, neg.	1st, quinine, grs. XX; 9th–10th, I. and Q. tonic; 11th–17th, quinine, grs. X, t. i. d.; 18th–30th, I. and Q. tonic.	Neg.; 2d, hb., 60 per cent; 6th, 60 per cent; 19th, 48 per cent; 23d, 48 per cent; 3d, 54 per cent; Mar. 11th, tertain and E. A.

118	54500	4	Many.....	Spaniard; age, 28; 2 years; ad. Feb. 16, '09; ill two days; slight chill on 15th, followed by hbg. severe vomiting, persistent hiccough; very anemic and jaundiced; hbg. began on 15th and cleared on 18th; patient died on 21st. Previous hbg. six months previously. On ad. tem. 101 degrees; 17th, 98.7, 100, 100.5, and 99.5 degrees; 18th, normal; 19th to death on 21st, continued fever between 100.5–102.5 degrees. 12/13, '07, malaria, tertian; 6/23, '08, hbg. fever.	Alb. and casts; 19th, alb., neg	16th, quinine, grs. XX.	Neg.; 17th, hb., 14 per cent; 20th, less than 10 per cent.
119	54349	3	1 pra.....	Spaniard; age, 25; res., 26 mos.; ad. Feb. 14, '09; ill three days; chills, fever, and headache; hbg. began on 13th and cleared on 15th. On ad. tem. 102.3 degrees, afterwards normal to disc. on March 5. Had quinine prior to hbg. 9/7, '07, malaria, clin.	Hemin crystals; alb. +; 22d, neg; 27th, alb. and casts; 3d, neg.; 4th, neg. some casts.	No quinine until 22d, when I. and Q. tonic to disc.	Neg.
121	56729	5	1 pra.....	Spaniard; age, 37; res., 10 mos.; ad. April 7, '09; ill six days; fever, chills; hbg. began on 4th, and cleared on 8th; patient died on 22d. There was frequent and severe vomiting during hbg. and from 13th until death. On ad. tem. 103; fell gradually until normal on 10th. No suppression of urine, which was passed abundantly until death. Temp. subnormal from 10th until death.	Hemin crystals; 8th, hemin crystals; 21st alb. and casts.	No quinine until 19th, when I. and Q. tonic was given. Heavy stimulation, 20th–21st.	Neg.; 8th, hb. 38 per cent; 16th, rbc., 2,688,000 wbc., 8,600; 22d, 40 per cent.
123	21304	(?)	1 pra.....	Spaniard; age, 30; res., one month; ad. Dec. 14, '06; no record of duration of previous illness; hbg. on ad., cleared on 16th. On ad. tem. 100.4 degrees; normal 15th–20th; 21st–25th, continued fever between 100–100.5 degrees; 26th–Jan 8, slight continued fever. Hypo. abscess opened on Jan. 10. Tem. remained normal afterwards to disc. on Feb. 10. 5/24, '09, hbg. fever.	Hemin crystals; 14th, alb., 50 per cent; 16th, alb. 2 per cent; 19th, alb. trace.	14th, quinine, grs. XX, and three XX, gr. hypos.; 15th–19th, grs. XX, hypo. per day; 19th to disc., grs. X, daily.	Neg.; 14th, hb. 30 per cent; 15th, hb., 10 per cent; 19th, hb., 10 per cent; 24th, hb. 25 per cent; Jan. 1, hb., 40 per cent.

CLASS II.—SERIES A.—*Hemohlobinuria on admission*—Continued

Case number.	Hospital number.	Days of duration of Hbg.	Previous illness.	History and Symptoms.	Urine findings.	Treatment and Result.	Blood findings.
127	36534	(?)	3 pra.....	Spaniard; age, 26; res., one year; ad. Jan. 17, '08; ill three days; history of irregular fever for some time; hbg. on admission, but no further data. Irregular intermittent fever, sometimes as high as 103 degrees until Feb. 3, when it remained normal until disc. on Feb. 17. Fever yielded abruptly on Feb. 2.	Hemin crystals; alb. and casts.	17th, quinine, grs. X and four hypos, grs. X each; 18th, quinine, grs. X, hypo., five doses; 19th, quinine, grs. X, for five doses; 21st–22d, quinine, grs. X, t. i. d.; 23d–24th, quinine, grs. X, hypo. four doses; 25th, quinine, grs. X, four doses; 26th–27th, quinine, grs. X, t. i. d.; 28th–29th, quinine, grs. X, hypo., four doses; 30th–Feb. 4, grs. X, t. i. d.; 4th–7th, I. and O. tonic.	Neg.
129	47788	(?)	1 pra.....	Spaniard; age, 28; res., 9 mos.; ad. Oct. 20, '08; ill three days; headache, chills, fever and vomiting; no record of when hbg. began, but it was present on ad. 20th–22d, high continued fever 101.5–102 degrees; 23d, normal and normal until disc. on Nov. 3. Hbg. cleared on 21st.	Alb. and casts; 27th, neg.	20th, quinine, grs., XX, 21st, quinine, grs. X, four hypos.; 26th–Nov. 3, quinine, grs. X, t. i. d.	E. A. + + 29th, hb., 60 per cent.
134	49317	4	5 pra.....	Spaniard; age, 28; res., 23 mos.; ad. Nov. 17, '08; ill six days; fever, chill and headache; hbg. two days prior to ad. On ad. tem. 102 degrees; 18th, 101, 101, 102, and 102 degrees; 19th, 100.5, 100, 101, 100, 98.7, and 99.5 degrees; 20th, 100, 100, 100.5, 100.5, 99, and 99 degrees; 21st, 98, 100, 100.5, 101, and 102 degrees; death. Severe vomiting the last three days, delirium, no suppression. Hbg. began on 16th and cleared on 19th.	17th, alb. and casts; 20th, clear.	No quinine, but stimulation. Autopsy showed malarial pigment.	Neg.; 17th, hb., 49 per cent. 17th, later hb.; 19 per cent; rbc., 1,880,000; 20th, hb., 20 per cent; rbc., 1,112,000.

138	68873	4	3 pra.....	Spaniard; age, 27; res., 26 mos.; ad. Nov. 30, '09; ill three days; fever, chills, vomiting; hbg. for three days. On ad. tem. 102–103 degrees; very irregular intermittent fever until Dec. 5, with two rises a day to 100 or 101 degrees; 5th and 6th, normal; 7th, chill, with rise to 102 degrees; irregular fever to 10th, p. m. of 10th, chill, with rise to 104.5 degrees; slight irregular fever 11th and 12th; chill on 12th, with rise to 101.6 degrees; normal to disc. on Dec. 25. Hbg. began on Nov. 28 and cleared on Dec. 1. 1/6, '08, double inguinal adenitis and chancroids; 2/11, '09, hbg. fever, and tertian malaria; 9/23, '09, malaria clinical.	30th, hemin crystals; 2d, alb. trace; 3d, neg; 7th, neg; 11th, neg.	No quinine until 9th, when grs. X, four times a day were given and continued on 10th; 11th, grs. X, four doses, hypo.; 12th-25th, grs. V, t. i. d. to discharge.	Neg.; 30th, hb., 13 per cent; 15th, hb., 11 per cent; 9th, blood neg.; 11th, blood neg; 20th, blood neg.
141	63364	(?)	2 pra.....	Spaniard; age, 38; res., 16 mos.; ad. Aug. 25, '09; ill three and one-half days; chills and fever; hbg. began on 23d, and there is no record when it cleared, but hemin crystals were found on admission in the urine. No tem. after ad. Disc. Sept. 4.	25th, hemin crystals; 9th, neg.	No quinine was given...	Neg.
144	68273	(?)	2 pra.....	Spaniard; age, 21; res., 4 years; ad. Nov. 20, '09; ill eight days; fever, chills, headache and vomiting; chart notes hbg. on ad. but does not state when it began. On ad. tem. 100, 102 and 104 degrees; 21st, 104, 103, 104 and 105 degrees; 22d, 4 a. m., 104 degrees; death. Severe vomiting until death; no suppression. Urine, 132 oz., was passed in the 24 hours preceding death.	21st, hemin crystals.	On ad. quinine, grs. XX. Malarial pigment at autopsy.	Neg.; 21st, hb., 45 per cent.
150	52110	4	2 pra.....	Spaniard; age, 26; res. 20 mos.; ad. Jan. 6, '09; ill three days; fever, chills and headache. On ad. tem. 102 degrees; normal until p. m. of 13th, when 101 degrees; 14th, 98 and 100.5 degrees; normal until disc. on 26th. Hbg. began on 4th and cleared on 7th. Severe chill on p. m. of 6th; some suppression on 7th.	6th, alb. and casts; 9th, alb 12th, alb. trce; alb. 18th, neg.	On ad. quinine, grs. XX; 7th–20th, quinine, grs. X, t. i. d.; 20th–26th, I. and Q. tonic.	Neg.; 12th, hb., 25 per cent.

CLASS II.—SERIES .'.—*Hemoglobinuria on admission*—Continued.

Case number.	Hospital number.	Days of duration of hbg.	Previous illness.	History and Symptoms.	Urine findings.	Treatment and Result.	Blood findings.
157	51607	3	1 pra.....	Spaniard; age, 23; res., 5 mos.; ad. Dec. 29, '08; chills and fever for two days; hbg. after first chill, cleared at 5 p. m. on 30th. On ad. tem. normal; 30th, 98.7 and 102 degrees. Irregular fever to 100–100.5 degrees on 30th and 31st; normal and subnormal from Jan. 1 to disc. on 14th.	30th, hemin crystals.	On ad. quinine, grs. XX; 30th–3d, quinine, grs. X, t. i. d.; 8th–14th, I. and Q. tonic.	Neg.; 30th, hb., 20 per cent; 2d, hb., 25 per cent; 19th, hb., 58 per cent.
158	51753	+5	2 fever.....	Spaniard; age, 43; res., 26 mos.; ad. Dec. 31, '08; ill two days; fever, chill diarrhea, eneurisis. On ad. tem. 100 degrees; normal to Jan. 4, when 100 degrees, p. m.; normal to death on 6th. Suppression of urine from ad. to death. Hbg. began on 30th, and urine was black on 3d. 1/20, '07, malaria, E. A.	31st, hemin crystals.	On ad. quinine, grs. XX..	E. A.; 2d, hb., 30 per cent.
159	57731	3	4 fever.....	Spaniard; age, 31; res. 28 mos.; ad. May 1, '09; ill three days; April 30, chills followed by hbg. which cleared on 2d. On ad. tem. 100.5 degrees; very slight irregular fever until 7th, afterwards normal to disc. on 20th. Vomited first four days in hospital; some quinine prior to ad. 6/18, '08, malaria, E. A.; 10/16, '08, malaria, E. A.	1st, hemin crystals.	No quinine until 10th, when I. and Q. tonic until disc.	Neg.; 3d, hb., 39 per cent; rbc., 2,760,000; wbc, 6,520; 8th, hb, 41 per cent; 13th, hb. 53 per cent.
160	58065	(?)	See report..	Spaniard; age, 41; res., 30 mos.; ad. May 10, '09; history sheet missing; had hbg. on ad., and from evidence on chart it lasted in the hospital about three days. Irregular tem. to 15th; 15th, p. m., 102.5 degrees; 16th, a. m., 102.5 degrees; normal afterwards until disc. on June 5. 12/14, '06, malaria, clinical.	(?).....	No quinine until May 24, when grs. V, t. i. d. until 28th; 28th–5th, I. and Q. tonic.	(?)

165	59664	7	Many pra..	Spaniard; age, 27; res., 29 mos.; ad. June 16, '09; chills and fever every other day for a month; on 15th had chill, followed by fever, vomiting and hbg.; urine was clearing on 22d, prior to death. On ad. tem. 98 and 100.5 degrees; subnormal to 20th, when 100.5 degrees, p. m.; continued at this until 12 noon on 22d, and later rose to 104 degrees prior to death. Severe vomiting every day, increasing jaundice, and suppression until death. 9/10, '07, malaria, E. A.; 9/5, '08, malaria, E. A.; 4/25, '09, acute gonorrhea.	Alb. and casts.; 22d, alb.	No quinine until 22d, when grs. XX, hypo., at 9.30 a. m.	Neg.; 22d, neg.; 17th, hb., 30 per cent; rbc., 3,920,000; later, 2,776,000.
166	59622	4	First ad....	Spaniard; age, 41; res. 11 mos.; ad. June 15, '09; ill two days; on 14th had chill, followed by hbg. On ad. tem. 100 degrees; 16th, 101 degrees, 99 degrees; 17th, 99.5 degrees; slight intermittent fever to 20th, afterwards normal to disc. on July 6. Had taken quinine as a prophylactic prior to hbg.	15th, hemin crystals.	On ad., quinine, grs. XX; July 2, quinine, grs. X, t. i. d.; 3d–6th, quinine, grs. V, t. i. d.	Neg.; 19th, hb., 30 per cent; rbc., 1,829,000; 21st, hb. 26 per cent; 23d, hb., 35 per cent; 28th, hb. 54 per cent; 1st, hb., 48 per cent.
167	59766	4	2 pra.....	Spaniard; age, 32; res., 3 years; ad. June 18, '09; ill three days; chills and fever; hbg. began on 17th, and cleared on 20th. On ad. tem. 102 degrees, 99 degrees, p m.; normal until disc. on July 8. Patient had taken quinine before onset of hbg.	Alb. and casts..	No quinine until June 29 when four doses, grs. V each; 30th–8th, grs. X, t. i. d.	Neg.; 23d, hb., 30 per cent; 29th, hb. 42 per cent.
169	63274	3	1 pra.....	Spaniard; age, 24; res. 25 mos.; ad. Aug. 24, '09; ill one day; fever, chills, vomiting and headache; hbg. began on 23d, and cleared on 26th. On ad. tem. 100.5 degrees; normal afterwards until disc. on Sept. 18. Patient had taken quinine before onset of hbg.	25th, hemin crystals; 7th, casts; 10th, neg.	No quinine until Sept. 3, when grs. X, t. i. d.; 4th, quinine, grs. XV, t. i. d.; 9th, quinine, grs. V, t. i. d.; 14th–18th, quinine, grs. X, t. i. d.	Neg.; 25th, hb., 50 per cent; 11th, hb., 68 per cent.
171	13820	4	7 fever.....	American; age, 41; res., 14 mos.; ad. June 1, '06; ill four days; fever, chills and vomiting; hbg. began on 30th, and cleared on 3d. On ad. tem. normal; 4th, p. m., 100 degrees; 5th–6th, slight fever, and normal to disc. on 12th.	1st, alb. +; 2d, 12 per cent alb.; 2d, 10 per cent, alb.; 3d–6th, alb. trace; 7th, neg.	On ad. quinine, grs. XX, and grs. X, t. i. d. until disc.	Neg.; 2d, hb., 45 per cent.

CLASS II.—SERIES A.—*Hemoglobinuria on admission*—Continued.

Case number.	Hospital number.	Days of duration of hbg.	Previous illness.	History and Symptoms.	Urine findings.	Treatment and Result.	Blood findings.
179	52479	4	First ad....	Spaniard; age, (?); res. 19 mos.; ad. Jan. 12, '09; ill three days; fever, chills and vomiting; hbg. began on 11th and cleared on 14th. On ad. tem. 101.5 degrees; 13th, 100.4, 101.5 degrees; 14th 99 and 100 degrees; afterwards normal to disc. on Jan. 23	12th, hemin crystals; 16th neg.	On ad. quinine, grs. XX..	Neg.; 16th, hb., 34 per cent.
181	54016	3 or 4	Many pra...	Spaniard; age, 28; res. 19 mos.; ad. Feb. 5, '09; ill two days; chills, fever, and headache; hbg. began on 4th and cleared about 6th or 7th. On ad. tem. 101 degrees; afterwards mal to disc. on 13th. 8/5, '08, malaria, E. A.	6th, hemin crystals.	No quinine.....	Neg.; 6th, hb. 43 per cent; 11th, hb., 55 per cent.
183	53052	4	1 pra.....	Spaniard; age, 20; res., 2 years; ad. Jan. 20, '09; ill three days; fever and headache; hbg. began on 18th and cleared on 21st. On ad. tem. normal; slight fever 21st–24th; normal afterwards to disc. on Feb. 4; 8/7, '07; malaria, clinical.	Alb. and casts; 23d, neg.	On ad. quinine, grs. XX; Feb. 1–4, I. and Q. tonic	Neg.; 22d, hb., 25 per cent; 25th, hb., 30 per cent; 27th, hb., 40 per cent; 1st, hb., 60 per cent.
185	49539	4	.....	Portuguese; age, 26; res., 15 mos.; ad. Nov. 21, '08; ill three days; headache, chills, fever and vomiting; hbg. began on 19th, cleared on 22d; recurred on 30th and cleared on 31st. On ad. tem. 100, 100.5 and 99.5 degrees; 22d, 100.5, 100, and 98.7 degrees; normal afterwards until 1st, when a. m., 101.5 degrees; p. m., 100.8 degrees; normal until 10th, when p. m., 101.5 degrees; normal until 12th, when p. m. 101.8 degrees, and normal to disc. on Dec. 19.	Hemin crystals; 22d, alb.; 26th neg.; 30th, hemin crystals; 2d, neg.	On ad. quinine, grs. XX; 12th–19th, quinine, grs. X, t. i. d. NOTE.—This case showed recurring hbg. without quinine. Of interest are the E. A. paroxsyms on the 10th and 12th.	Neg.; 12th, E. A.; 17th, hb. 52 per cent.
186	53409	4 2	1 pra.....	Italian; age, 31; res. 2 years; ad. Jan. 26, '09; ill five days; claims to have had hbg. nine days previously; hbg. began on 25th and cleared on 28th; recurred on 7th and cleared on 8th. On ad. tem. 102 degrees; 27th, 100 and 99 degrees; normal to 5th, when 101 and 102 degrees; normal on 6th; 7th, 100.5 and 101.5 degrees; and normal to disc. on 13th.	26th, hemin crystals; 29th neg.; 6th, alb. trace; 7th, hemin crystals; 8th, neg.	On ad. quinine, grs. XX; 4th–7th, I. and Q. tonic. Note recurrence of hbg. 7th, following I. and Q. tonic.	E. A., 29th, hb., 70 per cent; 8th, hb., 60 per cent.

187	50017	5	1 pra.....	Spaniard; age, 41; res., 4½ mos.; ad. Nov. 30, '08; ill five days; fever, chills and headache. On ad. slight fever, and same on Dec. 1; normal until Dec. 17, when 100, 104, 102, and 103.5 degrees; 18th, chill, and irregular fever to 101.5 degrees. Hbg. began on 27th and cleared on 1st. Recurrence on a. m. of 17th, and urine was clear at 4 p. m. Disc. on 31st.	30th, hemin crystals; 17th hemin crystals.	30th, quinine, grs. XX; 14th, I. and Q. tonic; 15th to 17th, a. m., quinine, grs., X. t. i. d.; 17th–19th, I. and Q. tonic. Note recurrence of hbg. after the renewal of the quinine.	Neg.; 18th, neg. rbc., 4,000,000; wbc., 5,800; hb., 49 per cent.
192	66610	(?)	See report..	Spaniard; age, 39; res., (?); ad. Oct. 21, '09; patient semi-comatose on ad. and no history obtainable. On ad. tem. 101, 103.5, and 104 degrees. Died at 3 a. m., Oct. 22. 6/2, '08, malaria, clinical; 7/7, '09, malaria clinical.	Hemin crystals; alb. + and casts.	21st, quinine, grs. XX, 4 and 8 p. m. Autopsy showed pernicious E. A. infection.	E. A. +
194	11991	+9	First ad....	Jamaican; age, 27; res. 6 weeks; ad. April 9, '06; semi-comatose; ill five days; chills, fever and severe headache. Hbg. on admission and until death. Temperature of a continued fever between 102 and 105 degrees until death on 17th.	10th, alb., 11 per cent; 11th alb., 25 per cent; 12th, alb., 20 per cent; 13th, alb., 10 per cent; 14th, alb., 12 per cent; 15th, alb., 15 per cent; 16th, alb., 20 per cent; 17th, alb., 25 per cent.	On ad. quinine, grs. XX. 10th–13th, quinine, grs. XXX per day, hypo. Widal on 12th, neg. Nosuppression of urine. Autopsy. hbg. fever and malarial pigment. No typhoid or pneumonia.	Neg.; 9th, neg.; 13th, rbc., 2,208,000; wbc. 17,600; poly., 89 per cent. lym., 10 per cent; megaloblasts; normoblasts.
198	71244	3	Many pra..	West Indian negro; age, 24..res., over 3½ years; ad. Jan. 22, '10; ill two days; headache, chills and fever; hbg. began on 21st and cleared on 23d. On ad. tem. 100.5 degrees; 23d, 99, 100.5, 100, and 100 degrees; 24th, 99 and 100 degrees; normal until disc. on Feb. 9. 6/1, '06, malaria, clinical; 9/27, '06, infected wound of testicle; 7/5, '08, typhoid fever; 8/24, '09, choroditis, retinal; 10/18, '09, specific iritis; 11/5, '09, malaria, E. A.	Alb. and casts..	No quinine until 25th, when grs. X, t. i. d. until disc.	Neg.; 22nd, hb., 30 per cent.

CLASS II.—SERIES A.— *Hemoglobinuria on admission*—Continued.

Case number.	Hospital number.	Days of duration of hbg.	Previous illness.	History and Symptoms.	Urine findings.	Treatment and Result.	Blood findings.
199	72075	3	Fever.....	Spaniard; age, 40; res., 4 mos.; ad. Feb. 10, '09; ill eight days; headache, fever and vomiting; hbg. began on 9th and cleared on 11th. On ad. tem. 102, 100 and 99 degrees; slight irregular fever until 17th, afterwards normal to disc. on 26th.	Hemin crystals; alb. and casts; 12th, alb., trace; 13th, alb. trace +; 14th, neg.	No quinine at any time; 13th, differential blood count. Polynuclear, 65 per cent; large lymphocytes, 7 per cent; small lymphocytes, 25 per cent; eosinphiles, 3 per cent.	Neg.; hb. 45 per cent; 12th, rbc., 3,450,000; wbc. 7,000; hb. 45 per cent.
200	72117	5–1–1	Fever.....	Spaniard; age, 40; res., 16 mos.; ad. Feb. 11, '10; ill three days; fever, chills, headache and vomiting; hbg. began on 10th and cleared on 14th; recurred on 18th, cleared on 19th; recurred on 20th, cleared same day. On ad. tem. 101, 99, and 100.5 degrees; 12th, 98, 102.5, 98.7, 103, 99, and 98.7 degrees; 13th, 100.5, 99, 101.3, and 98.7 degrees; afterward normal until 18th, when a severe intermittent fever, resembling in type the paroxysms of E. A. malaria began and continued until the 28th, with an irregular temperature between normal and 105 degrees. Severe vomiting and hiccough during this time. After the 28th there was an irregular fever to March 6, when there was a chill, with tem. 103 degrees; normal afterwards to disc. on 16th. Patient had not taken quinine prior to onset of hbg.	11th, hemin crystals; 14th, neg.; 17th, neg.; 18th, hemin crystals; 19th, alb. trace; 20th, a. m., alb. trace; 20th, p. m., hemin crystals; 21st, alb. trace; 22d, neg.	No quinine until 21st; 21st, quinine, grs. XV, hypo., three doses; 22d, quinine, grs. X, hypo., four doses; 23d, quinine, grs. X, hypo., three doses; 24th–March 10, quinine, grs. X, four times per day; 10th–28th, quinine, grs. X, t. i. d. Differential blood count on 12th. Polynuclears, 63 per cent; large lymphocytes, 7 per cent; small lymphocytes, 28 per cent; 15th, polynuclears, 55 per cent; large lymphocytes, 12 per cent; small lymphocytes, 32 per cent. This case is of interest, in that two recurrences of hbg. without quinine are shown.	Neg.; 12th, neg., hb., 55% per cent; rbc., 3,900,000; wbc., 7,500; 13th–18th, neg. 15th rbc., 2,637,000; wbc., 7,500; hb 30 per cent; 19th, neg., 21st rbc., 974,000; wbc., 5,240; hb 10 per cent; 23d, rbc., 970,000; wbc., 7,400, hb., 10 per cent.
201	73511	3	5 pra.....	Spaniard; age, 32; res., 4 years, ad. March 12, '10; ill one day; had taken quinine for fever, and hbg. followed. On ad. tem. 102 degrees, and normal afterward until disc. on 31st. Hbg. began on 12th and cleared on 14th. 10/13, '06, malaria, E. A.; 1/18, '08, malaria, E. A.; 3/19, '09, malaria, E. A.	Hemin crystals; 13th, alb. trace; 14th, alb. trace; 16th, alb. neg.	No quinine after admission. Differential blood count on 13th. Polynuclears, 45 per cent; large lymphocytes, 16 per cent; small lymphocytes, 35 per cent.	Neg.; 13th, rbc. 3,440,000; wbc., 7,600; hb., 55 per cent.

203	73738	5	Firs ad....	Spaniard; age, 36; res., 6 mos.; ad. March 17, 1910; ill four days; fever, chills and vomiting; hbg. began on 15th and cleared on 19th. On ad., and 18th, slight irregular fever, normal to 22d, when slight fever, increasing each day until 25th; 25th–31st, continued fever between 100 and 101 degrees, afterwards normal until disc. on April 19.	Hemin crystals; 19th, alb., trace; 20th, alb. trace; 21st, neg.	26th–10th, quinine grs. X, t. i. d. Blood culture on March 30 was negative.	Neg.; 26th, neg. 30th neg.; Feb. 18th, rbc., 3,000,000; wbc., 8,000; hb., 40 per cent.
204	74742	3	No record..	Spaniard; age, 9; res. 3 years in Cuba and six mos. on Isthmus; ad. April 6, '10; ill three days; fever, chills and vomiting; hbg. began on 5th and continued until death on 7th. History of hbg. two months previously. On ad. tem. 102. and 101.5 degrees; 7th, 100 and 98 degrees. No suppression of urine. In the peripheral, blood was the heaviest tertian infection we have hitherto witnessed; almost every corpuscle appeared to be infected.	Hemin crystals; alb. and casts.	On the 6th five hypos, grs. X each, and on the 7th, one hypo., grs. XV were given. These doses apparently had no effect on the parasites.	Tertian +
205	74776	1, 3	1 pra.....	Italian; age, 32; res., 3 years; ad. April 7, '10; ill three days; fever, chills and vomiting. On ad. tem. 100 degrees; normal until 20th, when p. m., 101.5 degrees; 21st, normal; 22d, 103 and 102.5 degrees; 23d, 99 and 101.5 degrees; normal afterwards until disc. on May 12. Hbg. began on 6th, and cleared on 9th; recurred on 23d and cleared on 25th. Had quinine before hbg.	Hemin crystals; alb. and casts; 23d, hemin crystals, alb. +; 24th, hemin crystals; 25th, neg.	5th–6th, quinine, grs. X, t. i. d.; 22d, quinine, grs. XX, 8.45 p. m.; 23d, quinine, grs. XV, hypo., and grs. X, three doses. 24th, quinine grs. XV, hypo., two doses; 25th–27th, quinine, grs. XV, hypo., one dose; 2d–12th, quinine, grs. V, t. i. d. The fever on the 22d was due to a manifestation of the tertian infection. Note how the hbg. followed the administration of quinine on the 22d, after the prior chill without hbg. on the 20th.	Neg.; 22d, double tertian; 24th, double tertian
210	76656	3	2 pra.....	Spaniard; age, 43; res., 22 mos.; ad. April 22, '10; ill two days; fever, chills and vomiting. Tem. normal on ad. and remained normal until disc. on May 10. Hbg. began on 21st and cleared on 23d. 5/13, '09, hbg. fever. See Case No. 161, Series B.	23d, hemin crystals; alb. + and casts; 24th, alb. trace +; 25th neg.	No quinine while in hospital. The patient was sent to Taboga on May 10; while there he was given quinine grs. X, twice a day, and developed hbg. on May 14. See Case No. 206, Class 1.	Neg

CLASS II.—SERIES A.—*Hemoglobinuria on admission*—Continued.

Case number.	Hospital number.	Days of duration of hbg.	Previous illness.	History and Symptoms.	Urine findings.	Treatment and Result.	Blood findings.
211	77314	5	1 pra.....	Spaniard; age, 31; res., 26 mos.; ad. May 25, '10; comatose on ad.; ill two days; fever and chills; hbg. began on 23d and continued until death on 27th. On ad. tem 101 and 99 degrees; 26th, 99 and 101 degrees; 27th, 102, 104, and 101.5 degrees.	Hemin crystals; alb. and casts.	No quinine was given. Since E. A. parasites were present on ad. and at autopsy, probably quinine should have been given.	E. A.; 26th, hb., 13 per cent; 27th, neg.
212	42769	4	1 pra.....	Spaniard; age, 31; res. 20 mos.; ad. July 21, '08; ill four days; headache and fever; hbg. began on 20th and cleared on 23d. Very slight irregular fever until disc. on Aug. 11. 1/21, '09, hbg. fever. See Case No. 152, Class 3.	Hemin crystals; alb + and casts; 24th, neg; 31st, neg.	No quinine while in hospital.	Neg.; 26th, hb.; 18 per cent; 28th, hb., 28 per cent; 1st, hb., 49 per cent; 10th, hb. 51 per cent.
213	44569	4+	2 pra.....	Spaniard; age, 27; res. 15 mos.; ad. Aug. 23, '08; headache, fever and vomiting; hbg. began before ad. and cleared on 26th. On ad. tem. 101 degrees; 24th, 98.7 and 102.5 degrees; normal to 29th, when irregular fever, to 100 degrees until 5th, when normal to disc. on 11th. 12/13, '07, malaria, tertian; 2/16, '09, hbg. fever. See Case No. 118, Class 2, Series A.	Hemin crystals; 25th, alb., 3 per cent, Esbach; 29th, trace; 1st, trace.	23d, quinine, grs. XX. Blood on admission showed many nucleuated red blood cells.	Neg.; 28th, hb. 10 per ceni; 29th, hb., 12 per cent; 30th; hb., 14 percent 1st, hb., 21 per cent; 4th, hb. 35 per cent.
215	77524	4+, 1, 1	First ad....	Jamaican; age, 9; res., (?); ad. May 29, '10; ill one month with chills and fever; hbg. before ad. and cleared on June 1; recurred on June 7, and 27. On ad. tem. 104 degrees; remittent fever between 100 and 103 degrees until June 10; June 11, normal a. m.; 102.5 degrees p. m.; normal on 12th; slight fever to 16th, with rise to 102 degrees on that date; slight fever to 27th, when 103 degrees; slight fever from 27th to July 11; continued fever between 101.5 and 103 degrees, July 11 to 17; and normal until disc. on July 24.	Hemin crystals; 30th, alb. +; 1st, neg.; 3d, alb. and casts.	On ad. quinine, grs. X, June 2d–7th, quinine, grs. X, t. i. d.; 7th, quinine, grs. X, hypo.; 27th to disc. grs. V, t. i. d.; June 19, quinine abscess opened. July 15, blood culture neg. for typhoid.	Neg.; 6/7, hb., 29 per cent; 6/19, hb., 58 per cent.
217	78420	4	First ad....	Barbadian; age, 27; res., 10 mos.; ad. June 13, '10; ill three days, fever, chills and headache; hbg. began on 12th and cleared on 15th. On ad.	Alb. and casts; 18th, alb. ft. trace; 20th, few casts;	On ad. quinine, grs. XX; 17th–23d, quinine, grs. X, t. i. d.; 24th, quinine, grs. XV, hypo.;	Neg.; July 6, hb. 95 per cent; July 12, hb., 95 per cent.

				tem. 101.6 degrees; irregular fever, sometimes as high as 102, until July 4, afterwards normal until disc. on July 27. Nausea and vomiting during first week in hospital and part of second.	25th alb., ft. trace; 7/25, alb. ft. trace.	25th, quinine, grs. XV, hypo., two doses; 1st–22d, quinine, grs. X, t. i. d.; 23d–27th, quinine, grs. V, t. i. d.	
220	79463	5	4 pra.....	Italian; age, 30; res., 40 mos.; ad. June 27, '10; ill three days; headache, fever chills and vomiting; hbg. began on 26th, following three doses quinine, and lasted until death on July 1. Very slight fever from ad. until death; suppression of urine until death.	Hemin crystals; alb. + and casts.	30th–31st, quinine, grs. XV, hypo., two doses.	Neg.; 27th, hb., 95 per cent; rbc., 5,000,000; 28th, neg.
223	79950	3+	(?)	Spaniard, (female); age, 43; res., (?); ad. July 3, '10; ill four days; fever, chills and vomiting. Ad. with hbg. which cleared on 5th; remittent fever between 100 and 103 degrees from admission until death on 9th.	Hemin crystals.	7th–9th, quinine, grs. V, t. i. d.	Neg.; 3d, hb., 25 per cent; 4th, hb., 20 per cent; 5th–6th, hb., 10 per cent.
224	80327	6	1 fever.....	Spaniard; age, 33; res., 8 mos.; ad. July 8, '10; ill three days; chills, fever and vomiting; took quinine on 6th and 7th; hbg. began p. m. of 7th and cleared on 12th. On ad. tem. 101 degrees; slight afternoon rise at intervals until disc. on July 22.	Hemin crystals; alb. + and casts.	On ad. quinine, grs. XX. 9th–10th, quinine, grs. X, t. i. d.	Neg.
226	81633	3, 2	1 fever.....	Spaniard; age, 26; res. 3 years in Cuba, 6 mos. on the Isthmus; ad. July 26, '10; ill two days; fever, chills and headache; hbg. began on 26th, and cleared on 28th; recurred on Aug. 11, and cleared on 12th. On ad. tem. 101.5 and 102.5 degrees; 27th, 99 and 103 degrees; 28th, 101.6 and 100 degrees; normal afterwards until Aug. 11, when p. m., 101 degrees; 12th, 99.5, 100, 99.5, and 98.7 degrees; and normal until disc. on August 30.	Hemin crystals; alb. + and casts; 27th, alb. +; 29th, alb. trace; 5th, neg.; 12th, hemin crystals; 15th, neg. 25th, neg.	July 28, quinine, grs. XV, hypo.; 29th, quinine, grs. V, four doses; On Aug. 9, thymol was given, three doses of grs. XL each.	Neg.; 27th, rbc., 3,280,000; hb., 70 per cent; 5th, neg; 11th, neg.; rbc., 3,260,000; hb., 65 per cent.
227	82387	4	8 pra.....	Barbadian; age, 32; res., 41 mos.; ad. Aug. 5, '10; ill three days; fever and chills; hbg. began on 4th and cleared on 7th. On ad. tem. 100 and 100.5 degrees; and normal afterwards until disc. on August 27.	Hemin crystals; alb. + and casts; 10th, alb. ft. trace; 11th, alb. ft. trace; 16th, neg.	On ad. quinine, grs. X, and grs. X, t. i. d. to disc. on Aug. 27. Note the regeneration of the hemoglobin before the increase in the erythrocytes.	Neg.; 6th, a. m., rbc., 1,536,000 p. m., 1,296,000; hb. 35 per cent; 9th, rbc., 2,408,000, hb. 5 per cent; 11th, rbc., 3,408,000; 13th, rbc., 3,680,000, hb., 55 per cent; 26th, rbc., 3,560,000, hb., 95 per cent.

CLASS II.—SERIES A.— *Hemoglobinuria on admission*—Continued.

Case number.	Hospital number.	Days of duration of hbg.	Previous illness.	History and Symptoms.	Urine findings.	Treatment and Result.	Blood findings.
230	82982	4	5 pra.....	Barbadian; age, 26; res., 5 years; ad. Aug. 16, '10; ill two days; fever, chills, headache and vomiting; hbg. began on 15th and cleared on 18th. Irregular tem. between 98 and 100 degrees until 22d, when normal until disc. on 29th.	Hemin crystals; alb. + and casts; 27th, neg.	On ad. quinine, grs. XX; 25th – 29th, quinine, grs. X, t. i. d.; 19th, rbc., 2,456,000; hb., 40 per cent; 20th, rbc., 2,296,000; hb., 40 per cent; 21st, rbc., 2,500,000; hb., 50 per cent; 22d, rbc., 2,192,000; hb, 40 per cent; 27th, rbc., 2,072,000; hb., 50 per cent.	Crescents; 17th, rbc., 3,200,000 hb., 60 per cent; 18th, rbc., 2,440,000 hb., 45 per cent.
231	83096	2	(?)	Spaniard; age, 24; res., 29 mos.; ad. Aug. 18, '10; ill three days; headache, fever, and chills; hbg. began on 17th and cleared on 18th. On ad. tem. 100 degrees, and normal to disc. on 29th.	Hemin crystals; alb. + and casts; 19th, alb., trace; 20th, neg.	No quinine.	Neg.

CLASS II—SERIES B.—*Cases with hemoglobinuria occurring on or about day of admission and prior to entrance to hospital.*

2	20222	2	2 pra.....	West Indian negro, Grenada; age, 26; res., 8 mos.; ad. Nov. 8, '06; ill several days; fever, chills and headache; hbg. began on 8th and cleared on 9th. Intermittent fever as high as 101.5 degrees at times until 17th; normal until 22d; 22d–29th, slight remittent fever; normal afterwards to disc. on Dec. 6.	Hemin crystals; alb. + and casts; 10th, alb. trace; 11th, alb. trace; 13th, neg.	13th–18th, quinine, grs. XX, hypo., per day; 19th–6th, I. and Q. tonic; 9th, urine 51 oz. 10th, 60 oz.; 11th, 73 oz.	Neg.; 10th, hb., 10 per cent; 15th, hb., 20 per cent; 20th, hb., 31 per cent; 6th, hb., 68 per cent.
8	13459	(?)	No record..	Jamaican; age, 23; res., 3 mos.; ad. May 24, '06; irregular fever for two weeks; hbg. began on 24th, but chart does not state when it cleared; 24th–25th, intermittent fever; 26th 28th, 99.5 to 103 degrees; fell to normal on 31st, and remained normal until disc. on June 7. 8/5, '06, hbg. fever. See case No. 10, below.	25th, alb. 2 per cent.	On ad. quinine, grs. XX; 27th–28th, quinine; grs X, t. i. d.; 29th, quinine, grs. XX, two doses, hypo.; 30th–3d, quinine, grs. X, t. i. d.; 4th–7th, quinine, grs. X, daily.	Neg.; 24th, hb. 55 per cent; 28th, hb., 35 per cent; 5th, hb., 60 per cent.

10	17018	(?)	1 pra.....	Jamaican; age, 24; res., 7 mos.; ad. Aug. 5, '06; ill two days; fever, persistent vomiting and jaundice. On ad. tem. 105 degrees; 6th, 102 degrees; 7th–12th, very slight fever; normal until disc. on Sept. 2. Hbg. began on 5th, no record of duration. Previous hbg. in May. See Case No. 8, above.	Alb. 30 per cent; 20th. neg.	On ad. quinine, grs, XX, hypo.; 6th–10th, quinine, grs. XX, per day; 10th-2d, quinine, grs. V, t. i. d.	Neg.
30	16979	3	Much fever, 2 pra.	Barbadian; age, 55; res., 4 mos.; ad. Aug. 4, '06; ill eight days; chill every night; intense jaundice, severe vomiting, and continued to death on 6th. On ad. tem. 102.3, 99, and 101.5 degrees; 5th, 100.5, 98, 100 and 98.7 degrees; drop to sub-normal before death on morning of 6th.	Hemin crystals; alb., 60 per cent.	On ad. quinine, grs. XX, hypo., and two hypos., grs. XV each, at intervals of four hours later; 5th, quinine, grs. XV, hypo., six doses.	Neg.; hb., 65 per cent; 5th, 42 per cent.
35	2721	5	No record	Greek; age, 39; res., 5 mos.; ad. June 3, '05; ill seven days; fever, headache and chills; hbg. began on 3d and cleared on 7th. On ad. tem. 103.5 degrees; 4th, 98.7 and 101.5 degrees; fever between 100 and 101.5 degrees, until 7th, when tem. was normal; 8th, p. m., 99 degrees; 9th, p. m 100 degrees; 10th, p. m., 101.5 degrees, and continued fever between 99 and 101.5 degrees until 23d; 25th to July 9, slight intermittent fever. Bedside notes indicate that the febrile process was mild, and indeed the patient was on a soft diet from June 8 to July 2, when he was put on full diet. Disc. on July 24.	3d, alb., 9.5 per cent; 4th, alb., 12 per cent; 5th, alb., 14 per cent; 6th, alb., 12 per cent; 7th, alb., 6 per cent; 8th, alb., 1 per cent; 9th, alb. trace.	4th–5th, quinine, grs. XX, hypo., daily; 6th–11th, quinine, grs. XX, daily; 12th, quinine, grs. X, t. i. d.; 13th–14th, quinine, grs. XX, daily; 15th–18th, quinine, grs. X, t. i. d.; 18th–24th, quinine, grs. XX, daily; 24th–July 1, quinine, grs. X, t. i. d.; 1st–9th, quinine, grs., XX, daily; 10th–24th, I., Q. and S., t. i. d	E. A.
48	10163	7 +	Much fever	Greek; age 42; res., 3 years; admitted February 12, 1906; ill 4 days; chills and fever. On ad. chill, and tem. 104 degrees. Tem. fell gradually until normal on morning of 14th. 14th., p. m. 101 degrees. Normal and subnormal until death on 19th. Vomiting severe until death. Hbg. was present on ad. and continued until death. Patient had taken small doses of quinine prior to hbg. Suppression of urine until death.	Alb + and casts; 12th, alb. 55 per cent; 13th, alb. 50 per cent; 14th, alb. 12 per cent; 15th, alb. 2 per cent; 16th, alb. 10 per cent; 17th, alb. 5 per cent; 18th, alb. 5 per cent; 19th, alb. 5 per cent	On ad., quinine, grs. XV, and grs. X; 13th, quinine, grs. XX, hypo.; 14th-17th, quinine, grs. X hypo., two doses; 18th-19th, quinine, grs. X hypo., one dose; urine was obtained with catheter as follows: On ad., 12 oz.; 13th, 8 oz.; 14th, 1 oz.; 15th, 8 oz.; 16th, 8 oz.; 17th, 12 oz.; 18th, 15 oz.	Neg.

CLASS II.—SERIES. B—*Cases with hemoglobinuria occurring on or about day of admission and prior to entrance to hospital*—Continued.

Case number.	Hospital number.	Days of duration of hbg.	Previous illness.	History and Symptoms.	Urine findings.	Treatment and Result.	Blood findings.
52	12271	2	Much fever	American; age 27; 6 years in Tropics and 8 mos. on Isthmus; Admitted Apr. 19, 1906. Irregular fever for two weeks Had XXV grain dose of quinine prior to inset of hbg. Hbg-began on 19th and cleared on 20th On ad. tem. 102 degrees; until May 3rd had a typhoid-like tem. between 99 degrees and 103 degrees. From the 3rd to the 10th. tem. fell gradually to normal on 10th, and remained normal until disc. on May 22nd. Patient passed an abundance of urine during attack of hbg. Widal on May 10th was negative for typhoid. 1st June, 1910 malaria, clinical'	Hemin crystals; alb. 50 per cent; 20th, a. m., alb. 27 per cent; p. m., alb. 12 per cent; 21st, a. m., alb. 3 per cent; p. m., alb. trace; 22-25th, alb. trace; 26th, neg.	On ad., quinine, grs XV., and 2 hypos. grs. X; 20th–22d, quinine, grs. X, hypo, 2 doses daily; 23rd, quinine, grs. XXV.; 24th, quinine, grs. X, t. i. d. hypo; 25th, quinine, grs. X hypo. 2 doses; 26th, quinine, grs. X hypo., 3 doses; 27th–May 3d, quinine, grs. X, t. i. d.; 4th–7th, quinine, grs. XX, daily; 7th-16th, quinine, grs. X, daily	Neg. Hb. estimated with Sahli's instrument: 20th, hb., 42 per cent; 21st, hb., 28 per cent; 22nd, hb., 22 per cent; 24th, hb., 24 per cent; 28th, hb., 24 per cent; 2nd, hb. 19 per cent; 5th hb., 17 per cent; rbc., 900,000; 9th, hb., 25 per cent, 11th hb., 31 per cent, rbc., 1,500,000 22nd, hb., 60 per cent, rcb., 3,000,000.
59	6418	4	Several pra.	American; age, 24; res., 15 mos; admitted October 26, 1905; Ill 1 month; irregular fever. In July, 1904, had E. A. malaria and hbg. fever. Severe vomiting on admission, jaundice, and headache. On ad. tem. 104 degrees; 27th, 99.5 degrees, 101.5 degrees; and normal until disc. on Nov. 3rd. 7/29 '04, hbg. fever, and malaria E. A., case No. 58; 12/1, '04, malaria tertian; 21/6, '05, malaria E. A.; 9/9, '06, hbg. fever, case No. 60.	26th, alb. 90 per cent; 27th, alb. 35 per cent; 28th, a.m., 15 per cent; p.m., 10 per cent; 29th, alb. trace	27th, quinine, grs. XX; 28th-29th, quinine, grs. XX hypo per day; 30th-31st, quinine, grs. XX per day; 1st, quinine, grs. XXV; 2nd–3rd, quinine, grs. XX.	E. A.
72	2803	(?)	1 fever.....	West Indian negro; age, 22; res., 5 mos.; admitted June 8, 1905; Ill several days. There was hbg. on admission, but further data are lacking. No fever while patient was in hospital. There were probably recurrences of hbg. Disc on July 13th. 3/15, '05. Malaria E. A.	Alb. 100 per cent; 13th, alb 100 per cent; 15th, alb. 50 per cent; 18th, alb. 75 per cent; 21st, alb. 50 per cent; 22d, alb. 66 per cent	Patient had several doses of quinine, but the chart is incomplete, and no definite statement can be made.	E. A. hb., 35 per cent.

94	55468	2	3 pra.....	Spaniard; age, 28; res., 20 mos., admitted March 9, 1909; ill 2 days; chill, fever, vomiting and headache. Hbg. began a. m. of 9th, and cleared p. m. of 10th. On ad. tem. 101.6 degrees; 10th, 100.5 degrees; 100 degrees. Slight P. M. rises 12th-15th. Normal afterward to disc. on April 15th. 1/31, '09; malaria E. A.	Hemin crystals; 11th, alb. + and casts; 12th, alb. +; 13th, alb. +; 24th, trace; 1st, neg.	On ad., quinine, grs XX; 23rd–5th, quinine, grs. V, t. i. d.; 6th–15th, I. and Q. tonic	E. A. 12th, hb., 25 per cent; 18th, hb., 32 per cent; 25th, 44 per cent; 2nd., 60 per cent.
95	55348	2	Much fever	Spaniard; age, 20; res., 18 mos. admitted March 6, 1909; ill 2 days; chills, fever. Patient was admitted at 2 p. m. and stated that prior to ad. he had passed no black urine, but urine on ad. was dark. This case may belong to Class 3. Very slight irregular fever at intervals to disc. on March 27th.	Hemin crystals; alb. + and casts	On ad., quinine, grs. XX; 12th–27th, I. and Q. tonic	Neg. 7th, hb., 65 per cent; 8th, hb., 53 per cent; 18th, hb., 70 per cent.
122	56717	2	Many pra..	Spaniard; age, 25; res., 7 mos., admitted April 7th, 1909; ill 3 days; chills, fever, headache; Hbg. began on 7th and cleared on 8th. On ad. tem. 104 degrees, 100.2 degrees, 101 degrees; 8th, 101.5 degrees, and fell gradually to normal on 9th, and remained so to disc. on 24th.	Alb. + and casts 12th, neg.	On ad., quinine, grs. XX; 15th–24th, I. and Q. tonic	Neg. 8th, hb., 49 per cent; 13th, hb., 46 per cent; 18th, hb., 40 per cent.
124	38349	3	3 pra.....	Spaniard; age, 27; res., 25 mos.; admitted March 11th, 1908; ill 1 day; fever, chills and headache. Previous hbg. 16 mos. ago. Hbg. began on 11th, and cleared 13th. On ad. tem. 102 degrees, normal afterward until disc. on 24th. Had quinine prior to hbg. 6/20, '07, malaria, clinical.	Hemin crystals; 14th, neg.; 21st, neg.	On ad., quinine, grs. XX hypo.; 12th–14th, quinine, grs. X, hypo., 5 doses; 15th, quinine, grs. X, 5 doses; 16th, quinine, grs. X, 4 doses; 17th, 24th, quinine, grs. X, t. i. d.	Neg. 14th, neg.
126	38711	3	16 pra.....	Spaniard; age, 19; res., 2 years; admitted March 24, 1908; ill 3 days, chills, fever and jaundice. Hbg. began on 24th and continued to death on 26th. On ad. tem. 104 degrees, 25th 101 degrees, 101-5 degrees, 102 degrees, 100 degrees; 26th 99 degrees, 97 degrees, 98.3 degrees, 100.6 degrees, when death ensued. Severe vomiting and suppression of urine until death. 1/8, '07, malaria, E. A. and tertian.	Hemin crystals; alb. + +	On ad., quinine, grs. XX; 25th grs. X, hypo. 5 doses.	Tertian.

CLASS II.—SERIES B.—*Cases with hemoglobinuria occurring on or about day of admission and prior to entrance to hospital*—Continued.

Case number.	Hospital number.	Days of duration of hbg.	Previous illness.	History and Symptoms.	Urine findings.	Treatment and Result.	Blood findings.
131	48384	2	3 fever.....	Spaniard; age, 32; res., 18 mos.; ad. Nov. 1, '08; ill 1 day; fever and chills, headache. Hbg. following chill on 1st and clearing on 2nd. Tem. on ad. 103 degrees; 2nd 101.5 degrees, 100 degrees; 3rd 98 degrees, 101.5 degrees; 4th normal; 5th 98.7 degrees, 101.5 degrees; 6th 100 degrees, 98.7 degrees; normal until 9th. 9th 99.5 degrees, 103 degrees; normal to 17th. 17th, 100 degrees, 101 degrees, and normal to disc. on 25th.	Alb. + and casts; 6th, neg; 19th, neg.	On ad., quinine, grs. XX. 7th–25th, I. and Q. tonic.	Neg.; 9th, crescents; 2d., hb., 37 per cent; nucleated red cells; 12th, hb., 38 per cent; 13th, rbc., 4,256,000; wbc., 8,200, 16th, hb., 50 per cent; 24th, hb., 55 per cent.
142	66966	2, 2	2 pra.....	Spaniard; age, 28; res. 3 years; admitted Oct. 27, 1909; ill 1 day: chills and fever; on 29th had chills and fever. Hbg began on 27th and cleared on 28th. Recurred on 29th and cleared on 30th. On ad. tem. 98.7 degrees. Very slight fever 29th–30th, and normal to disc. on Nov. 13th. Vomiting on 28th and 31st. 1/12, '09; malaria, E. A. 2/23, '09, mal., E. A.	Hemin crystals; 29th, neg.; 30th, alb.; 31st, neg.	29th, quinine, grs. V at 10 a. m., followed by hbg. at 10.50; 31st, quinine, grs. V, 3 doses; 1st–6th, quinine, grs V. t. i. d.; 7th–13th, I. and Q. tonic.	Neg.; 28th, neg.
156	51364	3	1 pra.....	Spaniard; age, 28; res. 2 years; admitted Dec. 24, 1908; ill 2 days, chills, fever, headache. Hbg. began at 7 p. m. on 24th and cleared on 26th. On ad. tem. 101 degrees. Irregular fever between 99.5 degrees and 100.5 degrees until 30th, afterward normal until disc. on Jan. 9th. One hypo. of quinine on 23rd, prior to onset of hbg.	Alb. + and casts	On ad. quinine grs. XX, 25–4th; I. and Q. tonic.	Neg.; 30th, hb., 35 per cent; 2d, hb., 45 per cent.
161	58157	2, 1	3 pra.....	Spaniard; age, 43; res. 10 mos.; admitted May 13, 1909; ill 2 days; chill on night of 12th, followed by hbg. 6 a.m. on 13th, which cleared on 15th. On ad. tem. 100 degrees, 103 degrees, 104 degrees; 14th, 103.5 degrees, 101 degrees, 102 degrees, 101 degrees, 101.5 degrees, 99.5 degrees; normal from 15th to 30th, when 100 degrees, p. m. with hbg., which	Hemin crystals; 14th, alb., 50 per cent; 24th, alb., trace; 9th, alb. trace	22–30th, quinine, grs. X, t. i. d.	Neg.; 14th, hb., 39 per cent; rbc. 2,950,000, wbc., 6,250; 16th, hb., 20 per cent; rbc., 1,800,000; 24th, hb., 19 per cent; rbc., 1,240,000;

				cleared on that day, and normal to disc. on June 22nd. 10/28, '08, malaria, E. A.; 4/22, '10, hbg. fever. See case No. 296. 5/14, '10, hbg. fever. See case No. 210			29th, hb., 30 per cent; 4th, hb., 37 per cent; 9th, hb., 42 per cent; 17th, hb., 53 per cent.
162	58252	3	1 fever.....	Spaniard; age, 34; res. 27 mos.; admitted May 17, 1909; ill 2 days; chills, fever. Hbg. began about 7 p. m. on 16th and cleared on 18th. No fever on ad. 31st-4th, slight irregular intermittent quotidian temperature to 100 degrees p. m. of each day; normal to disc. on June 8th. Had quinine about 4 or 5 on 16th, prior to onset of hbg. 9/28, '08, malaria, clinical.	Hemin crystals; alb. + and casts; 6th, neg.	21–23d, quinine grs. V, t. i. d.; 24–8, I and Q. tonic.	Neg.; 18th, hb., 52 per cent; rbc, 3,087,500; 26th, hb., 55 per cent; 2d, hb., 68 per cent.
163	58413	4, 1	1 pra.....	Spaniard; age, 30; res. 21 mos.; admitted May 19, 1909; ill 1 day; fever, chill, on night of 18th, followed by hbg. which cleared on 21st. Recurred for one day on 26th. On ad. tem. 103 degrees, 104 degrees; 20th, 102.5 degrees, 100 degrees, 104 degrees; afterwards fell gradually until normal on a.m. of 24th, after which a gradual rise until 26th, 101.5 degrees, 103 degrees, 100 degrees, 103.5 degrees, 100 degrees. Same type of fever on 27th, 28th and 30th, remittent quotidian type; p. m. temperatures 101 degrees, afterwards normal until June 10th, when similar fever to 14th, afterwards normal to disc. on June 29th. 3 doses of quinine on day of hbg. prior to onset.	Hemin crystals; alb. + and casts.	27th, quinine, grs. X, t. i. d.; 28th, quinine hypo. grs. XX. Blood culture on June 3d was returned as suspicious of typhoid.	Neg.; 20th, hb., 45 per cent; rbc., 3,850,000; wbc., 14,500; 2d, hb., 45 per cent; 12th, hb., 40 per cent; 22d, hb., 62 per cent.
173	53966	2	1 fever.....	Spaniard; age, 46; res., 16 mos.; admitted January 31st, 1909; ill 4 days; fever, headache, chills, vomiting. Hbg. began on 31st and cleared on Feb. 1st. No fever after ad. to disc. on Feb. 16th.	Alb. + and casts; 7th, alb. trace; 11th, alb. neg.	9–16th I. and Q. tonic.	Neg.

CLASS II.—SERIES B.—*Cases with hemoglobinuria occurring on or about day of admission and prior to entrance to hospital*—Continued.

Case number.	Hospital number.	Days of duration of hbg.	Previous illness.	History and Symptoms.	Urine findings.	Treatment and Result.	Blood findings.
189	63696	6, 3	4 pra.....	Spaniard; age, 25; res., 28 mos.; admitted Sept. 1, 1909; ill 1 day; chill and fever, a. m. of Sept. 1st, followed by hbg., which cleared on 6th. Recurred on 9th and cleared on 11th. On ad. tem. 104.5 degrees, 103 degrees, 100 degrees; 2nd 103.5 degrees, 102.5 degrees, 100.8 degrees, 101 degrees; 3rd-6th continued fever between 99.5 degrees and 100.5 degrees; 7th normal; 8th slight fever; 9th 100 degrees, 99.5 degrees; 10th 102 degrees, 100 degrees, 102 degrees, 100.5 degrees. Slight fever 11th-12th, and normal afterwards to disc. on 30th. Had some quinine prior to onset of hbg. 6/10, '08, malaria, E. A.	Hemin crystals; 7th, neg.; 8th, neg.; 9th, hemin crystals 18th, neg.	9th, quinine grs. V for three doses. Note hbg. following this quinine. Thymol treatment on 24th, without illresult.	Neg.; 1st, hb., 32 per cent; 10th, hb., 17 percent; 18th, hb., 40 per cent; 25th, hb., 52 per cent.

CLASS III.—*Hemoglobinuric fever subsequent to admission.*

1	15938	2	4 fever.....	Barbadian; age, 24; res., 1 year; admitted July 15, 1906; ill 1 day; chills and fever. Hbg. began on 17th and continued to death on 19th. 15th-16th high fever; 17th-19th normal. Two convulsions on 16th.	Alb. + and casts.	Quinine, grs. X, hypo., four doses per day.	E. A.
3	32205	2	1 pra.....	Guadeloupe; age, 18; res., 4 years; admitted Sept. 25, 1907. Hbg. on afternoon of 25th, cleared on 26th. On ad. tem. 102 degrees. 26th-30th fever fell gradually to normal. From 30th to Oct. 10th there was remittent fever, sometimes as high as 102.5 degrees. Widal on 7th, neg. for typhoid. Disc. Oct. 30th. 10/3, '08, malaria, clinical.	Guiacum test positive for hb.; 28th, neg.; 1st, neg.	On ad., quinine, grs. XX, 26th, quinine grs. X hypo., 2 doses; 30th-8th, quinine grs. XX, b. i. d.; 9th-30th, quinine, grs. X, t. i. d.	Neg.
4	52291	1, 1, 1	Fever.....	Jamaican; age, 22; res., 2 years; admitted Jan. 9, 1909; ill 3 days; chills and fever. Claims to have had hbg. one day prior to ad., but it was not evident on the 9th. Hbg. for one day on 11th, 19th, and 28th. 9th-11th slight fever. Normal to Jan.	Hemin crystals; 11th, hemin crystals; 19th, alb. + and casts.	Quinine, grs. XX; 18th, I. and Q. tonic; 27th, quinine, grs. X, t. i. d. This is an unusual case. Hbg. on 11th, when last dose of quinine had been on 9th, and	Neg.; 13th, hb., 65 per cent; 20th, hb., 58 per cent; 25th, hb., 78 per cent; 1st, hb., 90 per cent.

				19th. 19th, 98.7 degrees, 104 degrees; normal to 28th. 28th, 98.7 degrees, 104 degrees, and normal to disc. This was a case of paroxysmal hemoglobinuria. The attacks were short, lasting part of a day only. 7/10, '09, malaria, clinical.		following the administration of quinine on the 18th and 27th.	
5	15093	3	Fever.....	Barbadian; age, 20; res., 1 year; admitted June 28, 1906. Patient had infected knee, which had opened and was discharging pus. On ad. tem. 102.7 degrees; normal on a. m. of 29th; p. m. 105 degrees, with chill. 30th 105 degrees, 98.7 degrees, and remained normal until discharge on July 6th. Hbg. began on 29th and cleared on 1st.	Not examined until 30th, when it was black.	On ad., quinine, grs. XX; 29th, grs. X, t. i. d. and at night, after hbg., 4 hypos. of grs. X each. 30th-5th, quinine, grs. X, t. i. d. It is evident that the paroxysm of hbg. and the temperature on admission were in no way connected with the infective process in the knee, otherwise the temperature curve would not have been as it was.	Not examined.
6	18489	3	5 pra., with fever.	Barbadian; age, 32; res., 1 year; admitted Sept. 13, 1906; ill 1 day; fever, chill and sweat. Tem. normal until 16th.; 16th 101.5 degrees, p. m., and normal until disc. on 28th. Hbg. began on p. m. of 16th and cleared on 18th. Note the apyrexia with tne heavy E. A. infection.	Alb. and casts; 16th, black; 17th, alb., 3 percent; 18th, alb. trace; 20th, neg.	On ad., quinine, grs. X, 14–15th, quinine, grs. X, four doses; 16th, quinine, grs. X, for four doses, and grs. XX, hypo; quinine was given, grs. X, t. i. d., 17–28th.	E. A. + +; 16th, hb., 83 per cent; 19th, hb., 60 per cent; 20th, hb., 64 per cent; 23d, hb., 60 per cent.
7	26308	3	1 pra.....	Jamaican, age, 32; res., 4 mos.; admitted April 25, 1907; ill 3 days; chills, fever, and headache. On ad. tem. 104 degrees; 26th a. m. 98.7 degrees; p. m. chill and fever, which latter continued on 27th. On the night of 27th hbg. developed. 28th 8 a. m. severe chill, and another chill at 5 p. m.; chill at 3.30 a. m. on 29th. Temperature normal from 8 a. m. on 29th, when hbg. cleared; and remained normal. High fever 27th-28th with severe vomiting. Urine diminished during attack. 1/16, '07, malaria, E. A.	Alb. and casts; 26th, neg.; 27th – 30th, alb.; 28th, hemin crystals.	On ad., quinine, grs. XX, 26th–27th, quinine, grs. X, t. i. d.; 28th–29th, quinine, grs. X, hypo., 5 doses.	E. A. +; 28th, neg.

CLASS III.—SERIES A.— *Hemoglobinuric fever subsequent to admission*—Continued.

Case number.	Hospital number.	Days of duration of hbg.	Previous illness.	History and Symptoms.	Urine findings.	Treatment and Result.	Blood findings.
11	69270	1	1 pra.....	West Indian negro; age, 22; res., 30 mos.; admitted Dec. 8, 1909; ill 5 days; fever and chills. On ad. tem. 100 degrees. 9th 98.7 degrees, 100.5 degrees; normal until p. m. of 11th, when chill and rise to 104 degrees. Fever 12th-13th, and normal to disc. on 29th; hbg. followed chill on 11th, and cleared on 12th. 9/2, '09; malaria E. A. and hbg. fever.	Alb. and casts; 10th, alb. 12th, hemin crystals; 12th, alb. + and hemin crystals; 18th, neg.	On ad., quinine, grs. XX, 9th–12th, quinine, grs. X, t. i. d.; 18th–29th, I. and Q. tonic.	Neg.; 14th, hb., 47 per cent.
12	71243	1, 1	4 pra.....	Mexican; age, 28; res., 2 years; admitted Jan. 22, 1910; chill, followed by fever. Hbg. after admission on 22nd, cleared by a. m. of 23rd. Recurred on 30th and cleared same day. Irregular fever after ad. until Feb. 4th; normal afterwards to disc. on 8th. Jan 30th, chill, with rise to 104 degrees; 9/24, '09, malaria, clinical; 10/7, '09, axillary adenitis.	On ad. neg; later, hemin crystals.	On ad., quinine, grs. XX, 27th – 29th, quinine, grs. XX, daily; 30th–8th, quinine, grs. X, t. i. d.	Neg.; hb., 50 percent; 26th, hb., 75 per cent.
13	66952	2	2 pra.....	West Indian negro; age, 30; res., 18 mos.; ad. Oct. 27th, '10; ill one day; fever and headache. On ad., tem. 103 degrees; 28th, normal; 29th, 99.4; 5 p. m., chill, vomiting and hbg., which cleared on 30th; slight fever at intervals to disc. on Nov. 23rd; 1/14, '09, malaria, E. A.; 5/25 '09, malaria, E. A.	Neg.; 29th, a. m., neg; 29th, p. m., alb. + black; 31st, neg.; 1st, neg.; 3rd, neg.	On ad., quinine, grs. XX, 28th – 29th, quinine, grs., X, t. i. d.; 5th-15th, quinine, grs. X, t. i. d.; 16th–23d, I. and Q. tonic.	Neg.; 5th, neg.
17	65034	3	2 pra.....	Barbadian; age, 23; res., 2 years; ad. Sept. 24, '09; ill a week, irregular fever and chills. On ad., tem. 103.5 degrees, ran slight irregular fever to 29th, when there was a rise to 101.5 degrees; slight irregular fever to Oct. 9th, after which normal until disc. on Oct. 17th. Hbg. began on 25th and cleared on 27th; 9/9, '08, malaria, E. A.; 12/19, '08, malaria, E. A.	Alb.; 26th, hemin crystals.	On ad., quinine, grs. XX, 31st–1st, quinine, grs. X, t. i. d.; 12th–17th, I. and Q. tonic.	Neg.; 27th, hb., 45 per cent; 29th, hb., 55 per cent; 6th, hb., 20 per cent.

18	63564	4	Fever.....	Barbadian; age, 41; res., 4 mos; ad. Aug. 30, '09; ill a week, fever, chills, headache. On ad., normal; 31st, normal; 1st, a. m., 98.7, p. m., 105 degrees; no further fever to disc. on Sept. 12th; hbg. followed chill on 1st, and cleared on 4th; vomiting 3rd and 4th.	Neg.; 2d, black alb. and casts; 3d, alb. and casts; 4th, alb. trace; 6th, alb. trace; 7th, neg.	On ad., quinine, grs. XX, 31st–8th, quinine, grs. X, t. i. d.; 9th–12th, I. and Q. tonic.	E. A.; 2d, [neg.; 8th, hb., 60 per cent.
21	13879	3	6 pra.....	Barbadian; age, 23; res. 10 mos.; ad. June 2, '06; ill one day; fever, chills. On ad., temp. 100 degrees; normal on 3d; 4th, 98.7 degrees, 102 degrees; slight fever 5th and 6th; normal afterwards to disc. on 11th. Hbg. followed chill on 4th, and cleared on 6th.	Neg.; 4th, alb. 40 per cent; 6th, alb. 10 per cent.	On ad., quinine, grs. XX, 3d–11th, quinine, grs. X, t. i. d.	E. A.; 5th, hb., 85 per cent; 7th, hb., 85
22	22428	2	8 fever; 6 pra	Barbadian; age, 24; res. 16 mos.; ad. Jan. 9, '07; ill 3 days; fever, chills, and headache; on ad., tem. 101.5 degrees; 10th, normal; 11th, 98.7 degrees; 101.5 degrees; 12th, 99.5, 98.7 degrees; 13th–15th, slight fever; 16th, 97.8 degrees—101 degrees; 17th, 97.8 degrees, 101 degrees, normal to disc. on 31st. Hbg. followed chill on 11th and cleared on 12th; 6/21 '06, malaria, E. A. and gonorrhea; 10/3 '06, malaria, E. A.; 3/27 '07, suppurative arthritis of both knees.	Alb.; 12th, alb. 20 per cent; 13th, alb. 05 percent; 15th, alb. neg.	On ad., quinine, grs. XX, 10th – 11th, quinine, grs. X, t. i. d.; 12th, quinine, grs. XX, two hypos.; 13th, quinine, grs. XX, hypo. and 3 grs. XV, doses hypo.; 14th, two doses, grs. X, hypo.; 15th, quinine, grs. XX, hypo.; 16th – 30th, grs. X, t. i. d.	E. A.; 11th, hb., 72 per cent; 12th, hb., 58 per cent; 16th' hb., 56 per cent.
25	20433	3	3 fever.....	Barbadian; age, 25; res., 7 mos.; ad. Nov. 19, '06; ill one day fever, chills; on ad., tem. normal; 20th, 97.6 degrees, 102 degrees; 21st, 99 degrees, 104 degrees; normal afterwards to disc. on Dec. 1st. Hbg. followed rise on 20th, and cleared on 23d.	Neg.; 21st, alb.+	20th, quinine, grs. X, t. i. d.; 21st, quinine, grs. X, 4 doses, hypo. Considerable diminution of urine during attack.	E. A. +; 26th, hb., 42 per cent.
27	20231	8	2 fever.....	Barbadian; age, 19; res. 4 mos.; ad. Nov. 8, '06; ill 3 days; chills, fever and vomiting. On ad., tem. 101 degrees; subnormal until 12th; 12th–15th, slight remittent fever; 16th–17th, subnormal; death on 17th. Hbg. developed late on 9th, or early on 10th, continued to death, and was followed by almost complete suppression of urine.	Alb.; 10th, black; alb. 75 per cent; 11th, alb. 75 percent; 12th, alb. 75 per cent; 17th, alb.+++	On ad., quinine, grs. XX; 9th, quinine, grs. X, 4 doses hypo; 10th, quinine, grs. X, 2 doses hypo. Urine was from 2 to 4 oz. per day.	E. A.; 8th, hb. 80 per cent;, 11th, hb., 50 per cent; 17th, hb., 35 per cent.

CLASS III.—SERIES A.—*Hemoglobinuric fever subsequent to admission*—Continued

Case number.	Hospital number.	Days of duration of hbg.	Previous illness.	History and Symptoms.	Urine findings.	Treatment and Result.	Blood findings.
29	16525	2	3	Barbadian; age, 27, res. (?) ad. July 25, '06. No record of symptoms on ad., slight fever to Aug. 1st; normal to Aug. 5th; Aug. 5th, p. m., 101.5 degrees; normal 6th–7th; 8th, severe chill at 9.15 a. m., 10.30 a. m., 102.5 degrees, 103.5 degrees; 9th, 100.5 degrees and normal to disc. on 14th. Hbg. on 8th and 9th; 12/18 '05, malaria clinical; 6/16, '06, acute otitis media; 7/5, '06, malaria, E. A. + and crescents +	8th, hbg.; 9th, hbg.	On ad., quinine, grs. X; 26th — 7th, quinine, grs. X, t.i.d.; 8th, quinine, grs. X, 3 doses hypo; 10th–14th, quinine, grs. X, t. i. d. On 28th, quinine, grs. XV, 2 doses hypo.	E. A.
32	15945	1, 2, 1	None.....	French; age 32; res., 3 mos.; ad. July 15th, '06; ill 3 days; chills, fever, and took quinine, grs. XV daily. Denies previous malaria or illness. On ad., tem., normal; 16th, normal; 17th, 97.8 degrees, 102 degrees; 18th, normal; 19th–20th, 102 degrees, 101 degrees; 21st, normal; slight fever, 22nd–23d; normal afterwards to disc. on Aug. 3d. Hbg. for one day on 17th, recurred on 19th–20th, and for one day on 25th.	15th, neg.; 17th, black; alb. 40 per cent; 18th, alb. trace; 19th, black; alb. 40 per cent; 20th, black; alb. 20 per cent; 21st, a. m., trace; p. m., neg.; 22–25 a. m. neg.; 25th, p. m., black; alb. 15 per cent; 27th, neg.	On ad., quinine, grs. XX, 16th–28th, quinine grs. X, t. i. d.; 29th–3d., quinine, grs. XX, daily.	Neg.
33	56969	1, 1, 1	2 pra.....	Greek; age, 25; res. 2; years; ad., Apr. 14th, '09; ill 4 weeks, irregular fever, chills, pain in back and limbs. On ad., tem. 99.8; 15 th normal; 16th, fever a. m., normal p. m.; 17th, slight fever; 18th–25th, normal; 26th, 100 degrees, 101.5 degrees; 27–28th, normal; 29th, 98.7 degrees, 103 degrees; normal afterwards to disc. on May 20th; 16th, vomiting severe. Hbg. on 16th for one day; 26th for one day, 29th for one day.	Neg.; 16th, hbg. alb. +; 26th, hbg. alb.; 29th, hbg. alb.; 16th, hemin crystals; 26th, hemin crystals; 29th, hemin crystals.	On ad., quinine, grs. XX, 15th, quinine, grs. X, t. i. d.; 23d–28th, I. and Q. tonic; 4th–8th, quinine, grs. V, t. i. d.; 13th–20th, I. and Q. tonic.	Neg.; 18th, hb., 40 per cent; 21st, hb., 58 per cent; 25th, hb., 54 per cent; 27th, hb., 51 per cent; 28th 48 per cent; rbc. 2,815,000 7th, hb., 52 per cent; 14th, hb., 58 per cent.

34	55189	1	9 pra.....	Greek; age, 28; res. 21 mos.; ad. Mar. 3d, '09; ill 2 days; fever, chills, eneurisis. On ad., tem. 100.6 degrees; 4th, normal; 5th, 100.8 degrees, 100.5 degrees; normal afterwards to disc. on 17th. Hbg. on 5th for one day only.	Neg.;5th, black, a. m.; clear, p. m.; 7th, neg.	On ad., quinine, grs. XX, and grs. X, t. i. d. on 4th; 13th–17th, I. and Q. tonic.	E. A.; 6th, hb., 60 per cent; 15th, hb., 63 per cent.
38	68759	2	1st. ad.....	Italian; age, 29; res. 3 years; ad. Nov. 29, '09; ill one day; headache, fever; diarrhea for 3 weeks. On ad., tem. 101 degrees; normal until Dec. 3d.; 3d, 98.7 degrees, 103 degrees; normal afterwards to disc. on Dec. 15th; severe vomiting on 3d. Hbg. began on 3d and cleared on 4th.	Neg.; 3d, black, alb, +; 4th, hemin crystals; 5th, clear, alb. +; 6th, alb. trace; 7th–10th, neg.	On ad., quinine, grs. XX, 30th–2d, quinine, grs. X, t. i. d.; 3d, urine, 30 oz.; 4th, 35 oz.; 5th, 56 oz.	Neg.; 7th, hb., 50 per cent.
40	22762	3	3 fever.....	Italian; age, 30; res. 5 mos.; ad. Jan. 17, '07; ill 3 days; chills, fever. On ad., tem. 104 degrees; 18th, normal; 19th, 103.5 degrees, 102 degrees, 101.5 degrees, 102 degrees, 98.7 degrees; 20th, 98.7 degrees, 102 degrees; 21st, 98.7 degrees, 100.5 degrees; 22d–24th, slight fever; normal afterwards until disc. on Feb. 19. At 7.15 p. m. on 18th, had severe chill and vomiting. Vomited continually, 19th—21st. Hbg. began on night of 18th and cleared on 20th.	Neg.; 18th, p. m., black; 19th, alb. ½ per cent; 20th; alb. trace; 21st, alb. trace.	On ad., quinine, grs. XX, 18th, quinine, grs. X, t. i. d.; 19th, quinine, grs. XX, three doses, hypo.; 20th, quinine, grs. XX, two doses, hypo.; 21st–22d, quinine, grs. XX, one dose, hypo.; 23d, quinine, grs. XV, t. i. d.; 24th, quinine, grs. X, t. i. d.; 25th–19th, I. and Q. tonic.	Neg.; 21st. hb., 40 per cent; 26th, hb., 56 per cent; 2d, hb., 45 per cent; 7th, hb., 53 per cent; 13th, hb., 65 per cent; 18th, hb., 79 per cent.
42	23831	1	Several attacks of fever and hbg.	French; age, 27; res. 6 years; ad. Feb. 14th, '07. This case is one of hbg. following quinine in a small dose. Slight, continuous fever to 21st. See page (?) for full report.	See report	See report	Not examined on ad.; 21st, hb., 70 per cent.
44	8823	3	None.....	American; age, 40; res. 2 mos.; ad. Dec. 30, '05. Denies previous malaria; ill 4 days; fever, chills and headache. Had been taking quinine for past 3 days. On ad., tem. 100.4 degrees; 31st, 100 degrees, 100 degrees; normal until disc. Hbg. began on 31st, and cleared on 2d; 6/30, '06; malaria, clinical.	Alb. and casts; 31st, hemin crystals; 31st, a. m., alb. 30 per cent; p. m., alb. +; 1st, alb. 5 per cent; 2d, alb. 1 per cent; 3d, 2 per cent	On ad., quinine, grs. V, four doses; 31st, quinine, grs. X, two doses, hypo.; 1st, quinine, grs. V, four doses.	Neg.

CLASS III.—SERIES A.—*Hemoglobinuric fever subsequent to admission*—Continued.

Case number.	Hospital number.	Days of duration of hbg.	Previous illness.	History and Symptoms.	Urine findings.	Treatment and Result.	Blood findings.
46	10474	3	Much fever	American; age, 38; res. 7 years in tropics and 2 mos. on Isthmus; ad. Feb. 21, '06; ill 2 days, chills, fever; had quinine one day prior to ad. On ad., tem. 102.5 degrees, 105 degrees; 22d, 100.5 degrees, 102.5 degrees, 102.5 degrees, 102.5 degrees; 23d, 100 degrees, 102 degrees; fell gradually until normal on 26th; 26th, 98.7 degrees, 100 degrees; 27th, 98.7 degrees, 100 degrees; slight fever at intervals until disc. on March 13th. Severe chill after ad.; vomiting until p. m. of 24th. Hbg. began on 22d and cleared on 24th.	Neg.; 22d, alb. 22 per cent; 23d, alb. 30 per cent; 24th, alb. 3 per cent; 25th, neg.	On ad., quinine, grs. XV, 22d–25th, quinine, grs. X, hypo., two doses; 26th–4th, quinine, grs. X, t. i. d.; 4th–13th, quinine, grs. X, b. i. d.	Not examined.
47	8408	3	3 fever; 2 pra	American; age, 28; res. 7 mos.; ad. Dec. 18, '05; ill 2 days; fever, chills, vomiting. Took about 40 grs. quinine prior to ad. On ad., tem. 101 degrees; normal on 19th; 20th, 98.7 degrees, 102.5 degrees; 21st, 102.5 degrees, 103 degrees; 22d, 98.7 degrees, 102 degrees; 23d, 98.7 degrees, 102 degrees; 24th, 100.5 degrees, 102 degrees, 100.5 degrees; 103.5 degrees, and death. Very severe vomiting entire time, delirious 48 hours before death. Hbg. began on 20th, p. m., and cleared on 22d, p. m.; 6/23, '05, malaria, E.A.; 11/2, '05, malaria, tertian.	Neg.; 21st, black, alb. 40 per cent; hemin crystals; 22d, alb. 10 per cent; 23d, alb. 5 per cent; p. m., alb. 3 per cent	On ad., quinine, grs. V, 4 doses; 19th–20th, quinine, grs. V, 2 doses; 21st, quinine, grs. XV, 4 doses, hypo.; 22d, quinine, grs. XV, 2 doses, hypo.; 23d, quinine, grs. XV, 1 dose, hypo.; 24th, quinine, grs. XV, 1 dose, hypo. Urine, 20th, 18 oz.; 21st, 4 oz.; 22d, 30 oz.; 24th, 14 oz.	Neg.
49	9925	3	Much fever	Italian; age, 47; res. 22 years; ad. Feb. 3, '06; had been ill two weeks with fever and chills; no quinine until ad. Tem. on ad., 101 degrees; 4th, 98 degrees, 104 degrees; 5th, 100.5 degrees, 101 degrees; 6th, 98 degrees, 103 degrees; slight irregular fever to p. m. of 11th, when 102 degrees; remittent fever, a. m., normal, p. m., 101 degrees; 103 degrees until 16th; 17th, normal; 18th, 98.7 degrees, 104 degrees; 19th–20th, 100 degrees; 21st, 98.7 degrees, 102 degrees; fell	Neg.; 6th, alb. 15 per cent; hemin crystals; 7th, alb. 12 per cent; 9th, neg.; 10–11th, alb. +; 12th, alb. 4 per cent; 13–16th, alb. trace.	On ad., quinine, grs. XV, 4th–6th, quinine, grs. X, t. i. d. and grs. X, hypo on 6th; 7th–8th, quinine, grs. X, hypo, 2 doses; 9th–10th, quinine, grs. X, t. i. d.; 11th, quinine, grs. X, 4 doses; 12th–16th, quinine, grs. X, t. i. d. and grs. X, hypo. on 13th; 17th, quinine, grs. X, t. i. d.; 17–	Neg.; 17th, hb., 30 per cent.

				gradually until normal on 24th; chills were frequent during febrile accesses. Hbg. began on 6th, 5 p.m. and cleared on 8th.		disc., quinine, grs. X, t. i. d., and on 17th, grs. X hypo; 19th, grs. XV, hypo; 20th, grs. X, hypo; 21st, grs. XX, hypo. Date of disc. not given.	
50	12653	5	3 fever.....	American; age, 25; res. 2 years in tropics and 6 mos. on Isthmus; ad. May 2, '06; ill 3 days; chills and fever; had some quinine prior to ad. On ad., tem. 99.5 degrees; 3d, 98.7 degrees, 104 degrees, and normal afterwards to disc. on 12th. Following chill on 3d, hbg. began and cleared on 7th. Vomiting on 3d–4th.	Neg.; 3d, alb., 55 per cent; 4th, a. m., alb., 60 per cent; p. m., alb., 75 per cent; 5th, alb., 50 per cent; 6th, alb., 25 per cent; 7th, alb., 13 per cent; 8th, alb., trace; 10th, neg.	On ad., quinine, grs. XV, 3d, quinine, grs. X, t. i. d.; 4th, quinine, grs. X and grs. XX hypo.; 5th–6th, quinine, grs. X, 3 doses, hypo.; 7th–12th, quinine, grs. X, t. i. d. Note: Comparative slight loss of blood.	Neg.; 3d, hb., 95 per cent.; 4th, hb., 95 per cent.; 5th, hb., 86 per cent; rbc., 4,200,000; 9th rbc., 3,400,000 7th, hb. 76 per cent.
53	400	6	Much fever	English; age, 39; res., nearly all of life; ad. Sept. 14, '04. On ad., 99.5 degrees; 15th–21st, normal; midnight of 21st, had chill; 21st, 101 degrees, 104 degrees; 22d, 98 degrees, 103 degrees, 99 degrees; 23d–24th, irregular fever, 100.5 degrees, 101 degrees, and normal afterwards to disc. on Oct. 2d. Had some quinine prior to ad.; chills and vomiting during hbg.; hbg. followed chill on 21st and cleared on 26th; 6/14, '05, malaria, E. A.	Neg.; 21st–26th, black.	17th, quinine, grs. X, 22d–25th, quinine by hypo., but amount not stated.	Tertian.
54	25362	5	No record..	American; age, 37; res., 14 mos.; ad., Mch. 25, 1907; ill 4 days. On 23d, noticed hbg. but urine was clear on ad. On ad., tem. normal; 26th, p. m., chill 27th, 99 degrees, 103 degrees; 2d–8th, continued fever between 100 degrees and 101.5 degrees; death on 8th. Severe vomiting after chill on 26th; 27th, better; 28th–29th, severe vomiting; 30th, vomiting and delirium; 1st–2d, delirium and vomiting; 3d–5th, better; 7th–8th, vomiting and delirium. Hbg. followed chill on 26th, and cleared on 30th.	Alb., trace; 26th, hemin crystals; 26th – 30th, black; 30th; alb., trace; 31st, neg.	On ad., quinine, grs. X, t. i. d.; 27th, quinine, grs. XX, 3 doses, hypo.; 28th, quinine, grs. XX, hypo.; 29th–30th, quinine, grs. XX, 2 doses, hypo.; 31st, quinine, grs. X, t. i. d.; 1st, quinine, grs. XX, hypo.; 2d–8th, quinine, grs. X, t. i. d. Suppression at death.	Neg.; 27th, neg. hb. 20 per cent; 2d, hb., 10 per cent.

CLASS III.—SERIES A.—*Hemoglobinuric fever subsequent to admission*—Continued.

Case number.	Hospital number.	Days of duration of hbg.	Previous illness.	History and Symptoms.	Urine findings.	Treatment and Result.	Blood findings.
55	25304	5	3 pra.....	American; age, 26; res., 16 mos.; ad. Mch. 23, '07; ill 3 days; chills and fever. On ad., tem., 101 degrees; 24th, 102 degrees, 104 degrees; normal afterwards until disc. on Apr. 5th. Hbg. began on 26th, and cleared on 30th; 1/12, '06, malaria, clinical; 10/16, '08, malaria, clinical; 7/12, '09, malaria, clinical.	Neg.; 26th, alb. +, casts.	On ad., quinine, grs. X, and grs. X, t. i. d. to disc. on May 5th.	E. A.; 27th, hb., 55 per cent; Apr. 1st, hb., 40 per cent.
57	13463	1, 1, 1, 1	Much fever	American; age, 40; res., tropics 20 years, on Isthmus, 2 years; ad. May 24, '06; no history of fever at this time; complained of loss of use of right arm. Although this patient denied fever, note tem. on ad. and parasites in blood. On ad., tem. 101 degrees; 25th, 99.5 degrees, 102.5 degrees; 26th, 100 degrees, 105 degrees, 105 degrees, 104.5 degrees, 100.5 degrees; 27th, 99 degrees, 104 degrees, 103.5 degrees, 99 degrees; 28th, 98.7 degrees, 102.5 degrees; 29th, 97.8 degrees, 100 degrees, and normal to disc. on June 4th. Following chill on May 26th, hbg. clearing at night; same on 27th, and 28th; hemin crystals on 30th, and hbg. for one day on 31st; 4/27, '05, concussion of spine; 6/4 '05, malaria, E. A; 1/12 '06, malaria, clinical.	Neg.; 26th, a. m., alb., trace; 1 p.m., alb., 60 per cent; 4 p.m., alb., 30 per cent; 9.30 p. m., alb., trace; 27th, a.m., neg.; 1 p.m., alb., 40 per cent; 4 p.m., alb., 8 per cent; 8 p. m., alb., trace; 28th, a. m., neg.; 1 p. m., alb., 25 per cent; 4 p.m.alb.,4 per cent; 8 p.m., alb., trace; 29th, a.m., neg.; p.m., alb., 1 per cent; 30th, trace; 31st, alb. ,+ black; 1st neg.	25th, quinine, grs. X, two doses; 26th, quinine, grs. X, three doses, and grs. X, hypo.; 27th–29th, quinine, grs. X, t. i. d.; 31st, quinine, grs. X, t. i. d.; 2d–4th, quinine, grs. X, b. i. d.	E.A.;31st, hb., 50 per cent.

58	98	2	Fever.....	American; age, 23; res., 2 mos.; ad. July 29, '04; no record of symptoms prior to ad. Tem. on ad., 103 degrees; 30th, 105 degrees, 100.5 degrees; 31st, 100.5 degrees, 102 degrees; 1st, 103 degrees, 105 degrees, 102 degrees; 2nd, 102 degrees, normal, and normal to disc. on Aug. 25th. Intense jaundice. Hbg. began on Aug. 1st and cleared on 2d; 12/1, '04, malaria, tertian; 6/21, '05, malaria, E. A.; 10/26, '05, hbg. fever. See case No. 59, Class 2-B; 9/9 '06, hbg. fever. See case No. 60, Class 2-A.	Neg.; 1st, black	30th, quinine, grs. X, 4 doses; 31st, quinine, grs. IJ, 7 doses, hypo.; 1st, quinine, grs. IJ, 2 doses, hypo.; 2d, quinine, grs. IIJ, and 4 hypos., dose not given; 3d–25th, quinine, grs. vj, t. i. d.	E. A.
62	52206	3, 1	12 pra.....	American; age, 27; res., 4½ years; ad. Jan. 7, '09; ill 4 days; fever, chills, and headache; had taken quinine; previous hbg. in December. On ad., tem. normal; 8th, 98.7 degrees, 104.5 degrees, 9th, 103 degrees, 97.8 degrees; 10th, 98.7 degrees, 103.5 degrees; 11th, 98.7 degrees, 103.5 degrees; 12th, 98.7 degrees, 102.5 degrees; 13th, 98.7 degrees, 100 degrees; 14th, 98.7 degrees, 102.5 degrees; 15th, 98.7 degrees, 101 degrees, and normal to disc. on Feb. 5th. Chills on 8th, 10th-12th; vomiting first seven days, and delirium at intervals; hbg. followed chill on 8th and cleared on 10th; recurred for one day on 13th; 8/6, '04, infected foot; 11/9, '04, malaria, clinical; 1/18, '05, malaria, E. A.; 8/30, '09, malaria, E. A. and neuritis; 2/13, '09, hbg. fever. See case No. 76, Class 1.	Alb. and casts; 8th, alb. +; 9th, alb.; 10th, alb., trace; 11th–12th, alb., trace; 19th, alb., trace; 20th, neg.	On ad., quinine, grs. X, 8th, quinine, grs. X, t. i. d.; 12th, quinine, grs. X, hypo., 2 doses, and grs. X; 13th–14th, quinine, grs. XX, 2 doses, hypo.; Feb. 3d–5th, quinine, grs. V, t. i. d. Casts persisted for two weeks in the urine.	Neg.; 8th, hb., 24 per cent. 7th, hb., 17 per cent; 19th, hb., 26 per cent; 28th, neg.; 2d, neg.
64	19329	1	6 pra.....	English; age, 30; res. 3 mos.; ad. Oct. 9, '06; ill a week; chills, fever, and vomiting. On ad., tem. 98.7 degrees, 101 degrees; slight fever on 10th, and a.m. of 11th, normal afterwards until disc. on 16th. Hbg. for one day, on 10th, 9/10, '06, malaria, E. A.	10th, alb., 30 per cent.	On ad., quinine, grs. XX, 10th, quinine, grs. X, t. i. d.; 12th–16th, quinine, grs. X, b. i. d.	E. A.

CLASS III.—SERIES A.—*Hemoglobinuric fever subsequent to admission*—Continued.

Case number.	Hospital number.	Days of duration of hbg.	Previous illness.	History and Symptoms.	Urine findings.	Treatment and Result.	Blood findings.
66	25282	3	1st ad.....	Norwegian; age, 28; res., 14 mos.; ad. Mch. 23, '07; ill 5 days; chills, fever and headache; had hbg. on 21st, which cleared on 22d. On ad., tem. normal; 25th, 98.7 degrees, and intermittent quotidian fever to Mch. 30th; 30th, 98.7 degrees, 100.8 degrees; 31st, 100 degrees, 100.5 degrees; 1st, 98.7 degrees, 100.5 degrees; 2nd, 100 degrees, 102 degrees to Apr. 14th, daily fever, with remissions, and afterwards normal to disc. on 22nd. Hbg. began on 24th and cleared on 26th.	Neg.; 24th, alb., 25 per cent; 25th, alb., 10 per cent; 26th, alb., neg.	On ad., quinine, grs. X, 23d-31st, quinine, grs. X, t. i. d.; 1st–2d, quinine, grs. X, b.i.d.; 13th – 19th, quinine, grs. XXV, daily; 20th–22d, quinine, grs. V, t. i. d.	Neg.; 27th, hb. 30 per cent; 4th, hb., 20 per cent; 12th, hb., 35 per cent.
67	13445	1, 1	2 fever.....	Denmark; age, 40; res. 3 mos.; ad. May 24, '06; ill 3 days; fever, chills, and headache; claims to have had hbg. before ad.; quinine, grs. XXX per day for three days prior to ad. On ad., tem. normal and remained normal until May 30th, when patient had a severe chill in p. m. with tem. 104 degrees; normal until June 3d when chill and fever, 103 degrees; fever on 4th; normal from 5th to disc. on 9th. Hbg. for one day on 30th and again on 3d.	Neg.; 31st, a. m., alb., 12 per cent; hemin crystals; p. m., neg., 3d., a.m., alb., 10 per cent; p. m., neg.	25th, quinine, grs. X, t. i. d.; 26–9th, quinine, grs. X, b. i. d.	Neg.; 25th, hb., 40 per cent; 2d, hb., 35 per cent; 6th, hb., 27 per cent.
69	3747	2	Much fever	German; age, 31; res., 3 weeks; ad. July 17, '05. Ill 2 days; fever and chills; had not taken quinine. On ad., tem. 104.5 degrees; normal afterwards until p.m. of 21st; 21st–26th, continued fever between 101–103 degrees, due to a malarial relapse; normal after to disc. on Aug. 3d. Hbg., 18th–19th.	18th, hb., 6 per cent; 19th, hb., 8 per cent; 20th, neg.	17th–20th, quinine, grs. XX, daily; 23d–31st, quinine, grs. XX, daily.	E.A.; 26th, E.A.+
70	10521	1	1 fever.....	Denmark; age, 24; res., 6 mos.; ad. Feb. 22, '06; ill 6 days; fever, vomiting and chills; some quinine prior to ad. On ad., tem. 99 degrees, 102.5 degrees; 23d, fever; normal afterwards until disc. on 25th; hbg. on 23d for one day.	Alb.; 23d, black.	On ad., quinine, grs. XX, 23d, quinine, grs. XX, hypo.; 24th–25th, quinine, grs. X, t. i. d.	Double tertian.

71	3707	2	2 pra	German; age, 27; res., 4 mos.; ad. July 15, '05; ill 2 days; fever, chills and headache. On ad., tem. 102.5 degrees; 16th, 98.7 degrees, 105 degrees; normal afterwards until disc. on 21st. The patient had 2 prior mala ial attacks, one in May, and one in June, due to quartan infection. There is some reason to believe that this attack was due to quartan infection also. Hbg. 16th–17th.	Alb. and casts; 16th, black;	16th, quinine, grs. XX, 17th – 18th, quinine, grs. X, t. i. d.; 19th–21st, quinine, grs. XXV.	Double tertian.
74	3933	(?)	Much fever	West Indian negro; age, 35; res. 3 mos.; ad. July 24, '05. Chart record is missing, but history states hbg. as beginning on 25th.	.....	Quinine, grs. X, t. i. d.	Tertian.
75	3791	3	1.....	West Indian negro; age, 28; res. 6 mos.; ad. July 18, '05; claims that this is first illness; no quinine; ill one day, fever and chills. On ad., tem. 103.5 degrees; 19th, 100 degrees, 101.8 degrees; 20th, 101.5 degrees, 103 degrees; 21st, 101 degrees, 100.5 degrees; normal afterwards to disc. on 26th; hbg. began on 19th and cleared on 21st. Despite his claim, the same patient was in the hospital in June with clinical malaria.	19th, alb.; 20th, alb.; 21st, alb.; 22d, neg.	On ad., quinine, grs. XV, 19th – 26th, quinine, grs. X, b. i. d.	E. A.
79	62474	1	(?)	Italian; age, 42; res. 2 years; ad. Aug. 9, '09; ill one day; severe chill, fever and vomiting. On ad., tem. 101 degrees; 10th, normal; 11th, 101 degrees, p. m. and normal afterwards until disc. on Sept. 4th; hbg. occurred after ad. on 9th and lasted one day.	9th, black; hemin crystals.	On ad., quinine, grs. XX, 10th, quinine, grs. X, t. i. d.; 11th, quinine, grs. V, t. i. d.; 21st–24th, quinine, grs. X, t. i. d.; 25th, quinine, grs. XV, t. i. d.; 26th–28th, quinine, grs. V, t. i. d.	E.A.; 10th, hb 75 per cent.
80	3980	1	None.....;	Columbian; age, 22; res., 2 mos.; ad. July 25, '05; ill 2 days; chills, fever and headache. On ad., tem. 105 degrees; 26th, 98.7 degrees, 99.5 degrees; normal afterwards to disc. on 29th. Hbg. on night of 25th, clearing on 26th. Patient had had quinine, grs. X, prior to ad.; 8/10, '05, malaria, E. A.; 1/15, '06, malaria, E. A.	26th, p.m., neg.	On ad., quinine, grs. XV, 26th – 29th, quinine, grs. X, b. i. d.	E. A

CLASS III.—SERIES A.—*Hemoglobinuric fever subsequent to admission*—Continued.

Case number.	Hospital number.	Days of duration of hbg.	Previous illness.	History and Symptoms.	Urine findings.	Treatment and Result.	Blood findings.
82	48455	2	4 pra. fever.	Irish; age, 35; res., 13 mos.; ad. Nov. 2, '08; ill one day; chills, fever and headache; had been taking quinine. On ad., tem. normal; 3d, 97 degrees, 102 degrees, 101.5 degrees, 98.7 degrees and normal to disc. on 17th. On 3d, and again on 5th, much nausea. Hbg. began on 5th and cleared on 6th.	Trace; 5th, alb. +.	On ad., quinine, grs. X, 3d–5th, quinine, grs. XX, hypo., 2 doses; 13th – 17th, quinine, grs. X, t. i. d.	Neg.
83	3911	2	4 pra.....	English; age, 22; res., 6 mos.; ad. July 22, '05; ill 3 days· chills, fever and headache; had taken quinine, grs., X per day for several days. On ad., tem. 102 degrees; 23d, 100.5 degrees, 101.5 degrees; 24th, 99 degrees, 100 degrees; 25th, 99 degrees, 99.5 degrees; normal to disc. on 28th. Hbg. began on 25th and cleared on 26th.	23d, neg.; 24th, neg.; 25th, alb. +; 27th, neg.	On ad., quinine, grs. XV, 23d–28th, quinine, grs. X, b. i. d.	E. A.
85	5810	2	1 fever.....	American; age, 43; res., 4 mos.; ad. Oct. 7, '05; ill 3 days; fever, chills, and headache. Tem. on ad., 98 degrees, 101.5 degrees, 104.5 degrees; 8th, 100.5 degrees, 104 degrees; 9th–10th, normal; 11th, 101.5 degrees, 102 degrees; normal afterwards to disc. on 14th. Hbg. began on night of 10th and cleared on 11th; 8/16,05, malaria, E. A.; 8/19, 07, multiple ulcers of skin; improved under specific treatment.	7th, neg.; 8th, neg.; a. m., neg.; trace; 9th, p. m., alb. trace; 10th, a. m., alb., trace, p. m., black; 11th, a. m., alb. trace; p. m., neg.	On ad., quinine, grs. X, hypo., 2 doses; 8th–9th, quinine, grs. XX, hypo.; 10th–12th, quinine, grs. X, t. i. d.; 13th–14, quinine, grs. X, b. i. d.	Tertian.
86	3975	3	None.....	American; age, 33; res., 6 weeks; ad. July 25, '05; ill 3 days; fever, chills, and headache, diarrhea, 12–15 stools daily. On ad., tem. 100.5 degrees; 26th, 99.5 degrees, 98 degrees; 27th, 100 degrees, 101 degrees; 28th, 102.5 degrees, 101.8 degrees; 29th, 103.8 degrees, 104.8 degrees; 30th, 101.5 degrees, 100 degrees; 31st, 99 degrees; died a. m. of 31st. Severe vomiting during entire attack; marked hiccough; no diarrhea while in hospital. Hbg. began on 29th and continued to death.	26th, alb., trace, 27th, neg.; 28th, alb., trace; 29th, a. m., alb., trace: p. m.; black; 30th, alb., 15 per cent; 31st, alb., 10 per cent.	On ad., quinine, grs. XV, 27th – 31st, quinine, grs. X, b. i. d.; on 31st, 2 X grs. hypos. Urine: 27th, 54 oz.; 28th, 25 oz.; 29th, 49 oz.; 30th, 45 oz.; no suppression.	E. A.

87	3728	2	No record..	American; age, 30; res., 1 mo.; in tropics 5 years ago; ad. July 16, '05; ill 3 days; chills, fever and vomiting. On ad., tem. 104 degrees; 17th, 101.5 degrees, 104 degrees; 18th, 100 degrees, 99 degrees; 19th, 98.7 degrees, 100 degrees; 20th, 98.7 degrees, 100 degrees; 21st, 99.5 degrees, 100 degrees, and normal to disc. on July 23d. Had taken quinine, grs. XXX, on 14th and 15th. Hbg. began on 18th and cleared on 19th.	17th, alb., trace; 18th, black; 19th, black.	On ad., quinine, grs. X, 17th–23d, quinine, grs. X, b. i. d.	E. A.
90	5773	1	1 fever.....	Chilean; age, 40; res., 4 mos.; ad. Oct. 6, '05; had taken some quinine; ill 6 days; fever and chills. On ad., tem. 102 degrees, 104 degrees; 7th, 98 degrees, 105 degrees, 101 degrees; normal afterwards to disc. on 12th. Hbg. one day on 10th.	7th, alb., trace, 8th, alb., trace; 9th, alb., trace; 10th, hbg.; 11th – 12th, neg.	On ad., quinine, grs. XX, 7th, quinine, grs. X, b. i. d.; 8th, quinine, grs. X, t. i. d.; 10th–12th, quinine, grs. X, b. i. d.	Double tertian.
91	47423	2	1 pra.....	Spaniard; age, 38; res., 4 mos.; ad. Oct. 19, '08; ill 3 days, fever, chills, and headache. On ad., tem. 101 degrees; 15th, 98.7 degrees, 100 degrees; normal afterwards to disc. on 29th. Hbg. on 15th, clearing on 16th.	Alb.; 15th, hbg.	On ad., quinine, grs. XX, 25th–29th, I. and Q. tonic.	E. A.; 15th, hb., 48 per cent; rbc.; 2,760,000; 16th 3,304,000; 21st, hb., 70 per cent; 22d, hb., 60 per cent; 26th, hb., 71 per cent.
93	47637	2	1 pra.....	Spaniard; age, 32; res., 19 mos.; ad. Oct. 17, '08; ill one day; fever, chills and headache. On ad., tem. 102.5 degrees; 18th, 97, 101.5 degrees; 14th–20th, normal; 21st, 100.5 degrees, 101 degrees; normal afterwards to disc. on Nov. 1st. Hbg. began on 21st and cleared on 22d.	Neg.; 21st, black.	On ad., quinine, grs. XX, 16th – 21st, quinine, grs. X, t. i. d.; 28th–1st, I. and Q. tonic.	E. A.; 22d, hb., 29 per cent; rbc., 2,456,000; wbc., 6,000; 28th, alb. 54 per cent; 1st, alb. 59 per cent.
100	72169	2	2 pra.....	Spaniard; age, 29; res., 2½ years; ad. Feb. 12, '10; ill 2 days; fever, chills. On ad., tem. 99.5 degrees; normal afterwards until 21st; 21st, 99.5 degrees, 100 degrees; 22d, 98.7 degrees, 102 degrees; 23d, normal; 24th, 98.7 degrees, 103.5 degrees; 25th, 101 degrees, 99.5 degrees, 100 degrees; 26th, 100 degrees, 105.7 degrees; 27th, 99.5 degrees, 103.5 degrees; irregular fever to March 4th; normal afterwards to disc. on 14th. Severe vomiting 22d–27th. Hbg. began on 26th and cleared on 27th; 1/19, '08, malaria, clinical; 2/9, '09, gonorrhea.	Neg.; 26th, hbg.; 27th, p. m., neg.	15th–4th, quinine, grs. X, t. i. d.; 27th, quinine, grs. XV, hypo., 2 doses.	Neg.; 18th, hb., 15 per cent.

CLASS III.—SERIES A.—*Hemoglobinuric fever subsequent to admission*—Continued.

Case number.	Hospital number.	Days of duration of hbg.	Previous illness.	History and Symptoms.	Urine findings.	Treatment and Result.	Blood findings.
101	69850	2	Many pra.	Spaniard; age, 28; res., 28 mos.; ad. Dec. 20, '09; history of hbg., 11 days prior to ad. No fever while in hospital. Hbg. on 24th, clearing on 25th. Disc. Jan. 4th; 2/6, '08, malaria, clinical; 6/15, '08, malaria, clinical; 9/22, '08, malaria, tertian; 10/28, '09, chancroids and adenitis; 5/9, '10, malaria, clinical.	21st, alb., trace, 22d, alb., trace; 23d, alb., neg.; 24th, black; 25th, alb., trace; 26th, neg.	Thymol, grs. XI, three doses was given on 23d. Hbg. began on 24th; 26th–4th, quinine, grs. X, t. i. d.	Neg.; 21st, hb. 68 per cent.
102	3985	2	2 pra.	Spaniard; age, 29; res., 2 years in Cuba, 2 mos. on Isthmus; ad. July 26, '05; ill 2 days; fever, chills and sweat. On ad., tem. 103 degrees, 104 degrees, 27th, 100.2 degrees, 100 degrees; 28th, 99.5 degrees, 101.5 degrees; 29th, 104.2 degrees, 101 degrees; normal afterwards to disc. Hbg. began on 27th and cleared on 28th; 12/23, '05 malaria, E. A.; 1/11, '06, malaria, clinical; 8/25, '06, malaria, E. A.; 12/7, '06, malaria, clinical; 1/12, '07, acute gastritis; 11/2, '08, malaria, clinical; 11/8, '09, acute gastritis.	27th, alb., 1 per cent; 28th–30th, alb., trace.	On ad., quinine, grs. XX, and grs. X, b. i. d. to disc. Two typical, E. A. paroxysms. This case is interesting, in that much subsequent malaria without hbg.	E. A.
103	48607	3	6 pra.	Spaniard; age, 29; res., 2 years; ad. Nov. 5, '08; ill 3 days; fever, chills, and headache. On ad., tem. 101 degrees; normal afterwards to disc. on Dec. 5th. Hbg. began on 18th and cleared on 20th; 4/21, '08, hbg. fever. See case No. 214, Class 1.	Neg.; 8th, alb., trace; 18th, alb. +.	On ad., quinine, grs. XX, and grs. X, t. i. d. to 13th; 13th – 17th, I. and Q. tonic.	E. A. 10th, hb. 54 per cent; 18th, hb., 45 per cent; rbc., 3,840,000.
108	6970	4	Fever.	Spaniard; age, 37; res. 33 mos.; ad. Nov. 10, '05; ill 1 day; chills, fever, vomiting. On ad., tem. 100.5 degrees; 11th, 99.3 degrees, 101.5 degrees; 12th, 99.5 degrees, 99 degrees; 13th–14th, normal; slight fever at intervals until disc. on 21st. Hbg. began on a. m. of 11th and cleared on 14th; vomiting, 12th–13th; 8/3, '05; malaria, E. A.	11th, alb., a.m., 20 per cent; p. m., 30 per cent; 13th, alb., a. m., 25 per cent; p. m., 10 per cent; 14th, neg.	On ad., quinine, grs. XX, 11th, quinine, grs. X, t. i. d. and beginning with 4 p. m., grs. X, hypo., Q. 4 H. for 6 does; 12th, quinine, grs. XV, hypo., Q. 6 H. for 3 doses; 13th–21st, quinine, grs. V, four doses per day.	Not examined until 11th 11th, neg.

115	55111	3	3 pra.....	Spaniard, age, 32; res., 7 mos.; ad. Mch. 1st, '09; ill 2 days, fever, chills, and headache. On ad., tem. normal; 2d, 98.7 degrees, 100 degrees; 3d, 98.7 degrees, 100 degrees; 4th, 101.5 degrees, 103 degrees; 5th, 100 degrees, 102.5 degrees, 103.5 degrees, 102 degrees; 6th, 100 degrees, 100 degrees, 103 degrees, 102.8 degrees, 101 degrees, 99.5 degrees; 7th, 99.5 degrees, 98.7 degrees, 100 degrees, 101.5 degrees, 104 degrees, 102 degrees; normal afterwards to disc. on Apr. 5th. Hbg. began at 2 a. m. on 4th and cleared on 6th; 8/6, '08, malaria, E. A.	Alb.; 2nd, alb., 4th, hbg.	On ad., quinine, grs. XX, 2d-3d, quinine, grs. X, t. i. d.; 27th–5th, quinine, grs. X, t. i. d.	Tertian, +; 5th, neg.; 6th, hb. 42 per cent; 7th, hb., 30 per cent; 19th, hb., 30 per cent; 23d, 69 per oent; 2d, 92 per cent.
117	54956	1	4 pra.....	Spaniard; age, 44; res., 25 mos.; ad. Feb. 25, '09; ill 2 days; slight fever, headache, and backache. On ad., tem. 99.5 degrees; 26th, normal; 27th, 101 degrees, 99.5 degrees; normal to disc. on Mar. 1st. Hbg. on p. m. of 26th, cleared on a. m. of 27th; 8/6, '08, malaria, E. A.	Neg.; 26th, hbg. hemin crystals; 28th, alb. trace.	On ad., quinine, grs. XX, 26th, quinine, grs. X, t. i. d.	Neg.; 1st, hb., 59 per cent; 6th, neg.
120	57473	3	7 pra.....	Spaniard; age, 21; res., 23 mos.; ad. Apr. 26th, '09; ill 2 days; fever, chills, headache. On ad., tem. normal, and normal to p. m. of 29th, when chill and fever; 30th, 101.5 degrees; 99.5 degrees, 101.5 degrees, 100 degrees, 99 degrees, 98.7 degrees, and normal to disc. on May 15th. Hbg. followed chill on 29th and cleared p. m. of May 1. Severe vomiting during hbg.	27th, alb.; 30th, hemin crystals.	On ad., quinine, grs. XX; 27th–28th, quinine, grs. X, t. i. d.; 29th, I. and Q. tonic; 3d–10th, quinine, grs. X, t.i.d.; 11–15th, I. and Q. tonic.	Neg.; 30th, hb., 41 per cent; rbc., 2,500,000; wbc., 8,650; 1st, hb., 42 per cent; 12th, hb., 62 per cent.
125	38735	2	6 pra.....	Spaniard; ad. Mch. 25, '08; ill one mo.; irregular chills and fever. On ad., tem. 102 degrees; 26th, 98.7 degrees, 102 degrees; 27th, 97 degrees, 101.5 degrees; normal afterwards to disc. on Apr. 23d; chill at 10 a. m. on 27th, followed by vomiting and hbg., which latter cleared on 28th.	26th, alb.; 27th, hemin crystals; 2d, neg.	On ad., quinine, grs. XX; 27th, quinine, grs. X, t. i. d.; 28th, quinine, grs. X 5 doses. hypo; 29th, quinine, grs. X, 5 doses; 30th, quinine, grs. X, 4 doses; 1st–23d, quinine, grs. X, t. i. d.	E. A. and tertian
128	47781	2	1 pra.....	Spaniard; age, 35; res., 3 mos.; ad. Oct. 20, '08; ill 2 days; fever, chills, and claims to have had hbg. on 18th. On ad., tem. 103 degrees; 21st, 98.7 degrees, 106 degrees; very slight irregular fever to 26th, and normal to disc. on Nov. 5th. Following chill at 2.30 p. m. on 21st, hbg. developed, which cleared on 22d; 8/27, '08, malaria, tertian.	21st, hemin crystals; alb+and casts.	On ad., quinine, grs. XX, 21st, quinine, grs. X, t. i. d.	Tertian.

CLASL III.—SERIES A.— *Hemoglobinuric fever subsequent to admission.*

Case number.	Hospital number.	Days of duration of hbg.	Previous illness.	History and Symptoms.	Urine findings.	Treatment and Result.	Blood findings.
130	48075	3	1 pra.....	Spaniard; age, 29; res., 30 mos.; ad. Oct. 26, '08. On ad., tem. 101.6 degrees; 27th–28th, normal; 29th, 103.7 degrees, 98.7 degrees; 30th–31st, slight fever, and normal to disc. on Nov. 11th. Hbg. began late on 28th, after chill, and cleared on p. m. of 30th.	Alb.; 30th black.	On ad., qninine, grs. XX; 26th–28th, quinine, grs. X, t. i. d.; 7th–11th, I. and Q. tonic.	Tertian; 24th, neg.; hb., 30 per cent; rbc., 3,320,000; wbc., 9,400; 30th, hb., 19 per cent; wbc. 6,000.
132	49146	2	1 pra.....	Spaniard; age, 24; res., 17 mos.; ad. Nov. 14th, '08; ill one day; fever, chills, headache; no fever after ad. to disc. Hbg. began on 15th and cleared on 17th; 1/12, '09 malaria, E. A	Neg.; 16th, hemin cyrstals; 17th, p. m., neg.; 23d, neg.	On ad., quinine, grs. XX, 21st, disc. I. and Q. tonic.	Neg; 16th, hb., 67 per cent; rbc., 5,320,000; 20th hb., 39 per ct.; rbc., 3,000,000.
133	49303	2	1 pra.....	Spaniard; age, 43; res., 18 mos.; ad. Nov. 17, '08; ill 2 days; fever, chills, vomiting and headache. On ad., tem. 101.5 degrees; normal until p. m. of 25th, when 100.5 degrees; 26th, 98.7 degrees, 101 degrees, 103.5 degrees, 99.4 degrees; 27th, 100 degrees, 99 degrees; slight fever on 28th, and normal to disc. on 10th. Hbg. began after chill on 25th and cleared on 26th.	18th, alb. trace; 26th, hemin crystals; alb. +	On ad., quinine, grs. XX, 18th-19th, quinine, grs. X, t, i. d.; 20th–24th, I. and Q. tonic; 8th–10th, I. and Q. tonic.	E.A.; 26th, hb., 50 per cent; rbc., 4,880,000; wbc. 8,800; 27th, rbc., 2,600,000; hb., 29 percent; 29th, hb., 38 per cent; rbc. 2,230,000 Dec. 1st, hb. 50 per cent.
135	49419	1	3 pra.....	Spaniard; age, 28; res., 17 mos.; ad. Nov. 19, '08; ill 5 days; fever, chills, and vomiting. On ad., tem. normal and remained normal to disc. on Dec. 9th. Hbg. on 21st for one day; 8/5, '08, malaria, E. A.	20th, alb. trace; 21st, black; 22d, neg.	On ad., quinine, grs. XX; 20th, quinine, grs. X, t. i. d.; 30th–9th, I. and Q. tonic.	E. A.; 21st, crescents; 27th, hb., 40 per cent; 6th, hb., 68 per cent.
136	18981	3, 1	1 pra.....	Spaniard; age, 36; res., 8 mos.; ad. Sept. 28, '06; ill several days; cough, cold, fever. Tem. on ad., normal; 29th, a. m., normal; chill at 11 a m.; noon 104.8 degrees, 101.5 degrees; 30th, 100.5 degrees, 100 degrees, 97 degrees, 98.7 degrees; 1st, 98.7 degrees, 97 degrees, 98.7 degrees, 100.5 degrees, 99 degrees; 2d, 98.7 degrees, 98.7 degrees 102.5 degrees, 103 degrees, 102.5 degrees, 101 degrees; 3d, 98.7 degrees, 100 degrees; 4th,	Hbg. on 29th; 30th, alb., 6 a. m., 10 per cent; 9.50, 40 per cent; 11, 25 per cent; 1.50 p. m., 35 per cent 3d, neg.	On ad., quinine, grs. XV; 29th–12th, quinine, grs. X, t. i. d.	Neg.; 2d, hb. 20 per cent.

				100 degrees, 98.7 degrees; 5th, 97 degrees, 100 degrees, and normal afterwards to disc. on Oct. 16th. Following chill on 29th, hbg., which cleared on a. m. of 1st and recurred in p. m.			
137	49446	4	4 pra.....	Spaniard; age, 34; res., 15 mos.; ad. Nov. 19, '08; ill 10 days; fever, chills, vomiting and headache. On ad., tem. normal; chill on 20th, at 5 a.m., severe; 20th, 101 degrees, 100 degrees, 101 degrees, 100 degrees, chill, 101.5 degrees; 21st, 99.5 degrees, 99 degrees, 99.5 degrees, 99 degrees, 100 degrees, 99 degrees, 100 degrees; 22d; 98 degrees, 98 degrees, 100 degrees, 98.7 degrees, and subnormal to death on 23d, a. m. Hbg. followed chill on morning of 20th, and continued to death. No suppression; 22d, passed urine, 55 ozs.; 8/10, '07, malaria, E. A.; 10/5, '07, malaria, clinical.	19th, alb. trace; 21st, alb. + + 22d, alb. + + Hemin crystals.	On ad., quinine, grs. XX.	Neg.; 21st, hb., 35 per cent; rbc., 1,180,000, wbc., 7,000.
139	68716	1	1st ad.....	Spaniard; age, 44; res., 15 mos.; ad. Nov. 27, '09; ill 4 days; fever, chills, headache; for five days ran an irregular fever between 98.7 degrees and 100 degrees; Dec. 2d–3d, normal; irregular fever to 100 degrees to Dec. 9th; slight fever to 99 degrees at intervals to disc. on 22d. Had taken quinine for four days prior to ad. Hbg. on one day only.	Neg.; 3d, neg.; 4th, alb. trace; 5th, alb. trace, casts; 7th, alb. trace; 8th, neg.; 9th, hemin crystals; 10th, alb. trace; 11th, neg.	On ad., quinine, grs. X; 28th–8th, quinine, grs. X, t. i. d.	Neg.; 3d, neg.; 4th, hb. 39 per cent; 12th, hb. 28 per cent.; 21st, hb. 45 per cent.
140	23719	3	4 pra.....	Spaniard; age, 24; res., 1 year; ad. Feb. 9, '07; ill 3 days; chills, fever, headache. On ad., tem. 101 degrees at 9.45 p. m., chill, and vomiting; irregular fever, falling by degrees to normal on 14th; 16th, a. m., normal, 1 p. m., chill, 104.5 degrees; 17th, 100 degrees, 100 degrees; irregular fever, sometimes to 100.5 degrees, to March 2d; 3d–7th, intermittent fever, 100.5 degrees, 101 degrees each p.m.; normal afterwards to disc. on 20th. Hbg. began on 9th, after chill, and cleared on 11th; 4/2, '06, malaria, clinical.	9th, 11 p.m., alb. 5 per cent; 10th, alb. 8 per cent; 12th, neg.; 24th, alb.	On ad., quinine, grs. XX, later, grs. XV, hypo; 10th, grs. XV, hypo, 2 doses; grs. XX, 2 doses; 11th, grs. XX, 2 hypos; 12th, grs. XX, hypo; 13th–15th, I. and Q. tonic; 16th, grs. XX, 2 hypos; 16th–19th, I. and Q. tonic; 20th–24th, grs. XX, hypo; 25th, grs. X, b. i. d.; 26th, grs. XV, t. i. d.; 28th–3d, grs. XV, 4 doses per day; 4th, grs. XX hypo, 2 doses; 5th–7th, grs. XX, b. i. d.; 8th–20th, grs. X, t.i.d.	Neg.; 9th, hb. 10 per cent; 14th, hb. 30 per cent.

CLASS III.—SERIES A.—*Hemoglobinuric fever subsequent to admission*—Continued.

Case number.	Hospital number.	Days of duration of hbg.	Previous illness.	History and Symptoms.	Urine findings.	Treatment and Result.	Blood findings.
143	66828	3	8 pra.....	Spaniard; age, 25; res., 3 years; ad. Oct. 25, '09; ill 3 days; fever and chills every other day. On ad., tem. 101.5 degrees; 26th, 98.7 degrees, 99 degrees, 104.5 degrees, 102 degrees, and normal to disc. on Nov. 15th Hbg. began on night of 26th and cleared on 28th. Although this patient's former admissions could not all be distinguished from those of another of the same age, name, and length of residence, it is certain that he was in the hospital several times with E. A. malaria; 8/6, 10, malaria, E. A.	Neg.; 27th, hemin crystals,alb.;28th, alb. trace +; 29th, neg.	On ad., quinine grs. XX; 27th, quinine, grs. X, t. i. d.; 30th–15th, quinine, grs. V, t. i. d.	Tertian. 27th, neg.; 28th, neg.
145	68703	4	2 pra.....	Spaniard; age, 24; res., 32 mos.; ad. Nov. 27, '09; ill 4 days; fever, chills and headache. On ad., tem. 100 degrees and normal afterwards to p. m. of 30th,when rise to 100.5 degrees; normal afterwards to disc. on 10th. Hbg. began on 30th and cleared on 3d; 10/10, '07, orchitis; 10/5, '09, cellulitis; 1/18, '10, malaria, clinical.	28th, alb. trace +; 30th, hemin crystals; 3d, alb. +; 7th, alb.; 8th, neg.	On ad., quinine, grs. XX; 27th–1st, quinine, grs. X, t. i. d.; 7th–10th, quinine, grs. V, t. i. d.	Tertian.
147	63727	4	1 pra.....	West Indian negro; age, 24; res., 27 mos.; ad. Sept. 2, '09; ill 1 day; headache, fever, chills. On ad., tem. 99.5 degrees; normal on 3d; 4th, 101.5 degrees, 102.5 degrees; 5th, 99.5 degrees, 100.5 degrees; 6th, 99.5 degrees, 100.5 degrees; 7th, 98 degrees, chill, 102 degrees; 8th, 99 degrees, 101.5 degrees; irregular intermittent fever to 14th, and slight fever afterwards at intervals to disc. on 23d. Hbg. began on 7th, after chill, and cleared about 10th. Subsequent hbg., 12/8, '09.	3d, alb. trace; 7th, hemin crystals.	On ad., quinine, grs. XX; 3d, quinine, grs. X, t.i.d.; 4th–5th, quinine, grs. XV, t. i. d.; 9th–11th, quinine, grs. X, t. i. d.	E. A. 4th, hb. 60 per cent; 8th, hb. 35 per cent; 12th, hb. 45 per cent; 17th, hb. 60 per cent.

152	53139	3	3 pra.....	Spaniard; age, 31; res., 26 mos; ad., Jan. 21, '09; ill one day, fever and headache. On ad., tem. 99.5 degrees; 22d, 97 degrees, 100 degrees; 23d, 97.5 degrees, 101 degrees; normal afterwards to disc. on 30th. Hbg. began on 23d and cleared on 25th; 6/21, '08, hbg. fever; 9/30, '08, malaria, E. A.	22d, alb. trace; 24th, black; 26th, neg.	On ad., quinine, grs. X; 22d–23d, quinine, grs. X, t. i. d.; 29th–30th, I. and Q. tonic.	E. A. 29th, hb. 60 per cent.
153	51969	1	1 pra.....	Spaniard; age, 39; res., 18 mos; ad. Jan. 4, '09; had been disc. from hospital on 3d, with a diagnosis of tubercle bacilli in the urine. These bacilli were found on several examinations but no systemic leisons were demonstrated. On night of 3d, patient had chill and fever. The parasites found on ad. on 4th, indicate that this was a relapse, as the patient had been some time previously in the hospital. On ad., 101.5 degrees, 5th, 100 degrees, 99.5 degrees; normal afterwards to disc. on 16th. Hbg. on 5th, one day only.	Neg.; 5th, a. m., hbg., black, p. m., clear; 9th, alb. trace; 12th, alb. trace.	On ad., quinine, grs. XX; 11th–16th, I. and Q. tonic. Note the absence of fever, 6th–11th, without quinine, although parasites were present on ad.	E. A. 6th, neg.
154	51971	1	7 pra.....	Spaniard; age, 20; res., 19 mos.; ad. Jan. 4, '08; ill 3 days; chills, fever, and headache. On ad., tem. 101.5 degrees; normal afterwards to 7th; 7th, 100 degrees, 99.3 degrees; normal afterwards to disc. on 16th. Hbg. followed rise in tem. on 7th, and urine was clear a. m. of 8th; 10/9, '08, malaria, E. A.; 11/30, '08, tonsillitis.	Neg. 7th, black; 8th, neg.	On ad., quinine, grs. XX; 5th–6th, quinine, grs. X, t. i. d.; 14th–16th, I. and Q. tonic.	E. A. 7th, hb., 45 per cent.
155	50980	1	3 pra.....	Spaniard; age, 31; res., 2 years; ad. Dec. 17, '08; ill 6 days; fever, chills and vomiting. On ad., tem. normal and remained normal until 3.30 p. m. on 19th, when chill, and rise to 103 degrees; normal on 20th and normal afterwards until disc. on Dec. 31st. Hbg. began on 19th and cleared on 20th; duration, about 16 hours; 8/19, '07, malaria, E. A. and tertian.	18th, alb. trace; 19th, p. m., hemin crystals; 20th, p. m., neg.	On ad., quinine, grs. XX; 18th, quinine, grs. X, t. i. d.; 19th, quinine, grs. X, 2 doses; 26th–31st, quinine, I. and Q. tonic.	Neg.

CLASS III.—SERIES A.— *Hemoglobinuric fever subsequent to admission*—Continued.

Case number.	Hospital number.	Days of duration of hbg.	Previous illness.	History and Symptoms.	Urine findings.	Treatment and Result.	Blood findings.
164	58637	2	5 pra.....	Spaniard; age, 42; res., 32 mos.; ad. May 24, '09; ill 4 days; chills and fever. Claims to have passed hbg. on 21st–22d. On ad., tem. 100 degrees; 25th, 99 degrees, 100 degrees; 26th, 99 degrees, 101.5 degrees; slight irregular fever to June 5th, afterwards normal to disc. on June 22d. Hbg. began at midnight of 25th and cleared on 27th	Neg. 26th, black	On ad., quinine, grs. XX.	Neg. 25th, hb. 39 per cent; 27th, neg.; 30th, hb. 40 per cent; 5th, hb. 46 per cent; 17th, hb. 60 per cent.
168	63139	1	1 pra.....	Spaniard; age, 29; res., 5 years; ad., Aug. 21, '09; ill 8 days; fever and chills; patient had taken much quinine prior to ad. On ad., tem. 102 degrees; 22d, 99.5 degrees, 102 degrees and normal to disc on 28th. Hbg. began on night of 21st and cleared on 22d; 8/24, '08, malaria, clinical.	22d, hemin crystals.	On ad., quinine, grs. XX.	Neg.
172	53806	3	1 pra.....	Spaniard; age, 28; res., 23 mos.; ad. Feb. 2, '09; ill 3 days; chills, fever, headache. Claims to have passed hbg. 2 days prior to ad. On ad., tem. 102 degrees; 3d–4th, 100 degrees; 5th, 97 degrees, 99 degrees, 6th–8th, 100 degrees; 9th, 102 degrees, 100 degrees, 100.5 degrees, 99 degrees; 10th, 99.5 degrees, 101 degrees; normal afterwards to disc. on Mch. 4th. Hbg. began on 5th and cleared on 7th.	Alb.; 5th, black; 9th, neg.; 10th, trace; 2d, neg.	On ad., quinine, grs. XX; 3d-4th, quinine, grs. X, t. i. d.; 21st–4th, I. and Q. tonic.	Neg. 8th, neg. wbc. 8,400.
177	52454	1	1 pra.....	Spaniard; age, 30; res., 17 mos.; ad. Jan. 12, '09; ill one day; slight fever; no fever after ad. to disc. on Jan. 23d. Hbg. began on night of 13th, and cleared on 14th.	Neg.; 14th, a.m., hbg.	On ad., quinine, grs. XX; 13th, quinine, grs. X, t. i. d.; 21st–23d, I. and Q. tonic.	E. A. 14th, hb. 65 per cent; 20th, hb. 56 per cent.
178	52386	1	1 pra.....	Spaniard; age 27; res., 14 mos.; ad. Jan. 11, '09; ill 3 days; fever, chill, vomiting and headache. On ad. tem. 100 degrees; and no more fever to disc. on 23d. Hbg. began on night of 13th, and cleared on 14th; 8/24, '08, malaria, clinical; subsequent hbg., 8/21, '09.	12th, alb. trace; 14th, dark.	On ad. quinine, grs. XX; 12th–13th, quinine, grs. X, t. i. d.; 19th–23d, I. and Q. tonic.	E. A. 15th, hb. 50 per cent; 17th, hb. 55 per cent; 21st, hb. 60 per cent; 26th, hb. 70 per cent.

181	52496	2	1 pra.....	Spaniard; age 22; res., 20 mos.; ad. Jan. 12, '09; ill 4 days; chills, fever, and vomiting. On ad. temp. 99 degrees; 13th, 100 degrees; chill, 105.2 degrees, 103.5 degrees, 101.5 degrees; normal afterwards to disc. on Jan. 22d. Hbg. began on 13th, after chill, and cleared on 14th.	13th, a. m., alb. trace; 14th, Hemin crystals.	On ad. quinine, grs. XX; 13th, quinine, grs. X at 7 a. m.	Neg. 14th, hb; 54 per cent' 20th, hb. 60 per cent.
182	53055	2	2 pra.....	Spaniard; age 34; res., 2 years; ad. Jan. 20, '09; ill 3 days; fever, chills, and headache. On ad. tem. 100 degrees; 21st, normal; 22d, 97.5 degrees; 10 a.m., chill, 101.5 degrees, 101 degrees; normal afterwards to Feb. 2d, when 100.5 degrees a.m.; irregular fever at intervals afterward to disc. on Feb. 7th. Hbg. followed chill on 22d, and cleared on 23d; 9/7 '07, malaria, clinical; 2/22 '08, synovitis of wrist.	Neg.; 26th, neg.; 31st, neg.	On ad. quinine, grs. XX; 21st, quinine, grs. X, t. i. d.; 31st–2d, I. and Q. tonic.	Tertian.
188	23573	2	5 fever.....	Spaniard; age 30; res. 1 year; ad. Feb. 6, '07; ill 3 days; headache, chills, fever, and vomiting. On ad. tem. 102.5, normal until 8 p.m. on 8th, when chill, with rise to 103.5 degrees; 9th, 102 degrees, 100 degrees, and normal until 18th, when p.m. 102 degrees; 19th, 100.7 degrees, 101.3 degrees; 20th, 98.7 degrees, 98.7 degrees, 100 degrees, 103 degrees; and normal to disc. on March 16. Hbg. began after chill on 8th, and cleared on 10th; 12/21, '06, malaria, E. A.	Neg.; 10th, alb. 3 per cent; 11-12th, alb. +; 13th, alb. trace; 14th, alb. neg.; 21st alb., trace; 23d, neg.	On ad. quinine, grs. XX; 7th–8th, quinine, grs. X, t. i. d., and on 8th, p. m., grs. XX, hypo., two doses; 9th, quinine, grs. XX, hypo., three doses; 10th–11th quinine, grs. XX, hypo. 12th–16th, quinine, grs. X, t. i. d.; 13th, quinine, grs. XX, hypo.; 16th–20th, I. and Q. tonic; 20th, quinine, grs. XX, hypo.; 24th–28th, quinine, grs. XV, t. i. d.; 1st–3d, quinine grs. X, t. i. d.; 4th–5th, quinine, grs. XV, t. i. d.; 6th–12th, quinine, grs. X, t. i. d.; 12th – 16th, quinine, grs. XV, t. i. d.	Neg. March 6, hb. 70 per cent; 9th, hb. 54 per cent; 12th, hb. 48 per cent.

CLASS III.—SERIES A.—*Hemoglobinuric fever subsequent to admission*—Continued.

Case number.	Hospital number.	Days of duration of hbg.	Previous illness.	History and Symptoms.	Urine findings.	Treatment and Result.	Blood findings.
190	6875/	2, 1	1 pra.....	Spaniard; age 25; res. 1 year; ad. Nov. 29, '09; ill 3 days; chill, fever, and headache. On ad. tem. normal; 30th, 100.5 degrees, 100.5 degrees, 99.5 degrees, normal until Dec. 11th, 6 p.m., when chill, 8 p. m. 104 degrees, 12 p.m. 98.70; 12th, 103 degrees, 100.5 degrees, 99 degrees, 97.5 degrees; and normal to disc. on Dec. 21st. Hbg. began on 30th, ond cleared on 1st. Relapse on 11th for one day; 7/12 '08, malaria, clinical.	Neg.; 30th, hemin crystals; 1st, alb. +; 23d, alb.; 4th, neg; 6th, neg; 8th, neg.; 11th, hemin crystals; 13-15-17th, neg.	Onfad. quinine, grs. XX; 11th, quinine, grs. X, two doses.	Neg. 3d, hb. 43 per cent; 9th, hb. 54 per cent; 12th, hb. 48 per cent.
191	55218	(?) 4	14 pra.....	Spaniard; age, 26; res., 27 mos.; ad. March 3, '09; ill for 2 months; irregular chills, fever, and headache. On ad. tem. normal; normal until p.m. of 7th, when 102 degrees; 8th, 98 degrees, 102 degrees, 101.5 degrees, 98 degrees, and afterwards subnormal until death on 19th. Hbg. began on 7th. Chart does not state how long it continued, but notes a recurrence on the 15th, which continued to death. Suppression from 15th to death.	Neg.; 7th, hemin crystals; 15th, hemin crystals.	On ad. quinine, grs. X; 4th–7th, quinine, grs. X, t. i. d.; 12th, quinine, grs. X, hypo., two doses; 14th, quinine, grs. X, hypo., two doses; 15th, quinine, grs. X, hypo.	Tertian. 6th, hb. 70 per cent; 12th, hb. 37 per cent; 16th; 30 per cent; wbc. 22,600.
193	25575	3	7 fever.....	West Indian negro; age, 26; res., 6 mos.; ad. April 3, '07; with fractured thigh; tem. was normal until p.m. of 7th, when 100.5 degrees; 8th, 100 degrees, 99.5 degrees; 9th, 99 degrees, 100.5 degrees, 101.5 degrees; 10th, 99.5 degrees, 103.8 degrees, 103.5 degrees; 11th, to May 19th, slight fever; 20th, 99.5 degrees, 101 degrees, and normal afterwards to disc. on June 13th. Hbg. began on 10th, and cleared on 12th; 9/26, '07. Heminhoids.	4th, neg.; 10th, hbg.	9th, quinine, grs. XV; 10th, quinine, grs. X, t. i. d.; 11th–24th, quinine, grs. X, four times per day; May 20, quinine, grs. X, t. i. d. to 25th. Note the E. A. paroxysm developing in the ward, with subsequent hbg.	April 10, E. A
195	542	(?)	No record..	Jamaican; age, 6; res., (?); ad. Oct. 9, '04; ill a week; slight fever after ad. to 14th; normal afterwards to disc. on 29th. Hbg. began on 10th, but chart does not state when it cleared.	10th. black.	Quinine, grs. i j four times a day while in hospital.	E. A.

196	16183	(?)	2 pra.....	Jamaican; age, 13; res., 5 mos.; ad. July 18, '06; ill a week; temperature chart missing. Diagnosis hbg. fever, 5/20 '06 malaria, clinical; 1/23 '07, malaria, E. A.	(?).....	(?).....	Neg.
202	73688	3	2 fever.....	Spaniard; age, 32; res. 4 years; ad. Mar. 16, '10; ill two weeks, irregular chills, fever, and headache. On ad. tem. 98.7 degrees, 100.5 degrees; 17th, 98.7 degrees, 101.5 degrees; 18th, 98.7 degrees, 103 degrees; 19th, 98.7 degrees; 101.5 degrees. Slight irregular fever until Apr. 1st, when normal to disc. on Apr. 19th. Patient had taken some quinine for three days prior to ad. Hbg. began on 19th and cleared on 21st; 8/29, '08, malaria, E. A.; 12/2 '08, malaria, E. A.	Neg.; 19th, hemin crystals; 21st, p. m., neg.	On ad. quinine, grs. X; 17th – 18th, quinine, grs. X, t. i. d.; 28th, grs. XX, hypo.; 29th–11th, quinine, grs. X, t. i. d.; 11th–19th, quinine, grs. V, t. i. d.	Tertian. 21st, hb. 50 per cent, rbc. 2,500,000; wbc. 6,600; 9th, hb. 83 per cent.
207	76347	3	5 pra.....	Barbadian; age, 49; res. 4 years; ad. May 9, '10; ill 4 days, chills, and fever. On ad. tem. normal, and normal until 3 p. m. on 12th, when 104 degrees; 4th, 99, 100 degrees, and slight irregular fever to 13th; normal afterwards to disc. on 24th. Hbg. began on p. m. of 12th and cleared on night of 14th.	Neg.; 10th, neg.; 13th, hbg.	On ad. quinine, grs. XX; 10th–24th, quinine, grs. X, t. i. d.	E. A.
208	75546	3	No record..	West Indian negro; age, 40; res. 10 mos.; ad. Apr. 22, '10; ill 5 days, chills, fever, and headache. On ad. tem. 101.5 degrees, and normal afterwards to disc. on 7th. Hbg. began on 26th a.m.; and cleared on 28th, p. m.	23d, neg.; 26th, hemin crystals.	On ad. quinine, grs. XX; 23d–25th, quinine, grs. X, t. i. d.	E. A. 30th, hb. 90 per cent.
209	76601	4	Fever.....	Spaniard; age (?); res. 5 mos. on Isthmus first time, 8 mos. in Cuba, and 8 mos. on Isthmus this time. Ad. May 13, 1909; ill two days, severe fever, chills, and vomiting. On ad. tem. 97.5 degrees, 99 degrees, 102 degrees; irregular continued fever between 100 degrees, and 102.5 degrees until 18th; 18-19th, 100 degrees; 20-25th, 99; and normal until disc. on June 22nd. Hbg. began after ad. on 13th and cleared on 17th. Associated with it was a very heavy E. A. infection.	14th, hemin crystals.	On ad. quinine, grs. XX; hypo, two doses; 14th, one hypo., grs. XV, and three hypos., grs. XX; 15th–17th, grs. XV, hypo., two doses per day; 18th, grs. XV, hypo.; 19th, grs. XV, hypo., and grs. V, t. i. d.; 20th–1st, grs. V, four times per day; 2d–22d, grs. V, t. i. d.	13th, E. A.; 14th, E. A.; 15th, E. A.; 16th, neg.; 31st, hb. 65 per cent; June 16, hb. 100 per cent.

218

78543

78010

Hospital number.

1st ad.....

Days of duration of hbg.

3

Much fever

4.....

Previous illness.

CLASS I

Hemoglobinuric fever subsequent to admision—Continued.

			and Symptons.	Urine findings.	Treatment and Results.	Blood findings.
			0; res. 3 years; ad. ill four days; fever, ٢. On ad. tem. 98 rees; 8th, 102, 100.5, rees; 9th, 101, 98, 102 degrees; 10th, 3.5, 104 and 104 degrees. Death Hbg. began on ıth.	7th, alb.; 8th, hemin crystals.	On ad. quinine, grs. XX, and grs. XV, hypo.; 8th, grs. XV, hypo., two doses; 9th, grs. XV, and grs. XX, hypo.	Neg.; 8th, 1,024,000.
			. 4 years; ad. fistula in ano. on June 16th, legrees p.m.; 9.5 degrees. ..5 degrees, degrees, 98.7 de- .. fever on 20th; 21st, ..ıth rise to 104 degrees; ir- ..gular fever, not over 100 degrees, until June 28th, when normal afterwards to disc. on June 28th. Hbg. began on 17th, p.m., and cleared on 20th.	18th, hemin crystals.	17th, quinine, grs. X, t. i. d.; 18th, quinine, grs. XV; 19th, quinine grs. XV at 1 a. m., grs. XX hypo. at 9 p. m.; 21st, grs. XV, hypo. at 9 p. m.; 22d, grs. V, four times per day until 26th, when grs. X, t. i. d. to disc.	Not examined until 18th, when neg.; 19th, hb; 20 per cent; rbc. 2,000,000.
3	1 pra.....		Jamaican; age, 14; res., 6 mos.; ad. June 20, 1910; ill 4 days; fever, chills, and vomiting. On ad. tem. 102, normal on 21st; irregular subcontinued fever, between 99 degrees and 101 until 26th; from 26th to July 2nd, continued fever between 100 degrees and 102 degrees; July 2nd to 6th, fever fell by lysis to normal, and remained normal to disc. on August 5th. Hbg. began on 20th, after ad., and cleared about the 24rd; blood culture on June 30th was negative for B. typhosus and allied strains.	20th, hemin crystals; 23d, neg.	On ad. quinine, grs. XX; 21st, quinine, grs. XX, hypo, two doses; 23d, quinine, grs. X, hypo., three doses; 24th, quinine, grs. XV, hypo., two doses; 25th–July 10, quinine, grs. X, t. i. d.; 25th–Aug. 5th, quinine, grs V, t. i. d.; The hb. estimates were carefully made, and each one was verified. Thymol, grs. LX, on July 25.	E. A. 22d, hb. 55 per cent; rbc. 3,840,000; 23d, hb. 60 per cent; 24th, hb; 40 per cent. 25th, hb. 55 per cent; 28th, hb. 45 per cent; 30th, hb. 35 per cent; 1st, hb., 45 per cent; 6th, hb. 55 per cent; 14th, hb. 90 per cent.

221	79515	4, 3	Much fever	Greek; age, 28; res., 3 years; ad. June 27, 1910; ill several days; fever, chills, and headache. On ad. tem. 102 degrees; 28th, normal; 29th, chill at noon, 103 degrees; 30th, 99.5 degrees, 99 degrees; normal until 6th, when chill, 104 degrees, 7-9th, 100 degrees, 100.5 degrees; normal afterwards to disc. on 22d, except for slight fever on 14th. Hbg. began on 29th, and cleared on July 3d; recurred on July 7th and cleared on 10th.	Neg.; 29th, hemin crystals; July 2d, alb. trace; 3d, alb. trace; 4th, neg.; 7th, hemin crystals.	On ad. quinine, grs. XX; 28th–6th, quinine, grs. X, t. i. d.; 9th, quinine, grs. V, four doses.	E. A. 7th, neg.; 8th, hb. 35 per cent; rbc. 1,376,000.
222	79827	2	4 fever.....	Italian; age, 42; res., 3 years; ad. July 1, 1910; ill 10 days, fever, chills, and headache. On ad. tem. normal, and normal to 9th; when p.m. 102.5 degrees; 10th, 98.7 degrees, 101.5 degrees, and normal afterwards to disc. on 20th. Hbg. began on 9th, and cleared on 11th; hbg. in 1908.	Neg.; 9th, black.	On ad. quinine, grs. XX; 2d–10th, quinine, grs. X, t. i. d.	Neg. 11th, hb. 98 per cent; rbc. 4,872,000.
225	81819	5	No record..	Barbadian; (female) age, 25; res., 12 mos.; ad. July 28, '10; ill 6 days; fever, chills, and headache; 6 mos. pregnant; tem. normal until 31st, when chill at 7.30 a.m.; 31st, 102.5 degrees, 104.5 degrees, 102 degrees, and subnormal afterwards until death on Aug. 3d. Hbg. began on 31st, and was clearing at death.	Neg.; 31 - 3d, hemincrystals.	29th–2d, quinine, grs. X, t. i. d., with grs. XX, hypo., on 31st; aborted on 31st, and although but few parasites were found in the peripheral blood, in the placenta was the heaviest infection we have hitherto witnessed.*	E. A. 31st, E. A.; 1st, neg.; 2d, neg.
228	82830	5	3 pra.....	Barbadian; age 26; res., 30 mos.; ad. Aug. 13, 1910; ill 3 days; fever, chills, and headache. On ad. tem. 101 degrees, 104.5 degrees, 101.5 degrees; 14th, 98.7 degrees, 98 degrees, 97.5 degrees, 97.5 degrees, 104 degrees, 103.8 degrees; 15th, 102.5 degrees, 100 degrees, and normal to disc on Aug. 29th. Hbg. began on 14th, on 18th cleared.	Alb.+; 15-18th, hemin crystals; 19th, alb. trace; 23d, neg.	On ad. quinine, grs. XX, and four grs. X doses; 14th–16th, grs. X, four times per day; 17th–19th, grs. XV, t. i. d.; 20th–29th, grs. X, t. i. d.; 15th, a. m., hb. 95 per cent, rbc. 5,470,000; wbc. 9,200; p. m., hb. 90 per cent; rbc. 4,808,000; wbc. 15,600; 17th, hb. 85 per cent; rbc. 4,228,000; 18th, hb. 85 per cent; rbc. 4,384,000; 20th, hb. 85 per cent; rbc. 4,000,000.	E. A. 14th, E. A.; 15th, E. A.

*No evidence of malarial infection was found in the foetus. In five cases we have had opportunity to examine foetal blood and organs, when the mother had a malarial infection, and in each case no evidence of malaria was found.

APPENDIX B.

A CONSIDERATION OF THE ARGUMENTS IN FAVOR OF AND AGAINST MALARIA AS A FACTOR IN THE ETIOLOGY OF HEMOGLOBINURIC FEVER.

I.

THE HISTORY OF HEMOGLOBINURIC FEVER.

In the discussion of the various hypotheses as to the etiology of hemoglobinuric or blackwater fever, we stated that—

> Our inquiry is limited to the etiology of hemoglobinuric fever in the Canal Zone; and we shall not say at present how far the conclusions derived by us will apply to the hemoglobinuric fever of other countries. See p. 55.

We have since searched the literature available here, which is not inconsiderable, for information as to the etiology of the disease in different countries, and in this Appendix it is our purpose to compare the results obtained by us with those of other observers. Although we are dependent upon the literature, and not, as we would wish, upon personal experience for our knowledge of the conditions under which blackwater fever obtains in other regions, we cannot believe the etiology and epidemiology of so striking a clinical picture differ to any extent in widely separated lands. So that if the conclusions reached by us in regard to hemoglobinuric fever in the Canal Zone be correct, they may be used as criteria in considering the conflicting hypotheses and data advanced elsewhere.

In a recent article Craig[1] has collected the views of the leading exponents of the hypothesis that hemoglobinuric fever is a disease due to infection with a specific organism other than the malarial parasite, and has advanced these and his own arguments as evidence against the influence of malaria in the etiology of the disease. His paper is an excellent presentation of the various conflicting hypotheses; and is, as far as we have been able to ascertain, the most complete summary of the opinions of those who agree with him as to the etiology of blackwater fever. For these reasons we will refer frequently to his statements.

We think it better to take up singly the problems concerned in the etiology of the disease, and to review as carefully as possible the evidence that has been adduced. The hypothesis, with various modifications, that hemoglobinuric fever is in some way dependent for its etiology on malarial infection represents the opinion of most of those who have studied the two diseases clinically and epidemiologically;

the hypothesis that it is due to infection with a specific organism has the support of those who cannot agree that the arguments in favor of its malarial origin apply with sufficient force to justify the conclusions derived therefrom. For convenience, we shall refer to these hypotheses as the "malarial" and the "specific."

One of the arguments used most frequently by the advocates of the specific hypothesis is that if hemoglobinuric fever has its origin in malarial infection, then the former disease should have prevailed at all times in countries where the latter is endemic to a great degree. They point out that malaria has been endemic in tropical and subtropical countries since the dawn of medical history, while blackwater fever is of recent discovery in such localities. From these premises they infer that the home of the latter malady is in tropical Africa, where it was first discovered, and from there has slowly spread during the past fifty or sixty years until at present it is found in many malarious regions from which it was formerly absent. That it was absent from these places, they claim to demonstrate by stating that the disease, had it been present, by reason of its "striking" symtomatology could not have been overlooked by good observers. Blackwater fever has been reported from India, for instance, in the last twenty years only, and it is unreasonable to suppose that it escaped the notice of such men as Maclean, Carter, or Fayrer, had it existed there.

This argument, if proven, would be very strong evidence against the malarial hypothesis. But before it can be accepted, its advocates must demonstrate that in countries from which the disease has been reported only recently, its symptomatology had not been confused previously with that of malaria. The extension of the malady into such countries must be proven in a manner that excludes the possibility of its presence prior to its recognition. Moreover, since hemoglobinuric fever seldom chooses natives of a country in which intense malaria is endemic for its victims, the presence or arrival of persons non-immune against malaria, their number and manner of living, must be carefully considered. So that a very thorough study of the history of the disease, more thorough than by Craig, for example, is necessary before this argument can be refuted or upheld. To such a study it is essential that one should add experience gained by personal knowledge, in order to appreciate the observations of others.

Deaderick[2] gives the period from 1850 to 1853 as the time when blackwater fever was first reported:

> Lebeau, Daulle, and Leroy de Mericourt, physicians in the French Navy, who observed it in Madagascar, and especially on the Island of Noisse Be, on the northwest coast of the former island.

It will be noted that although the French observers were almost alone for several years in reporting the disease, it was recorded by them between 1853 and 1863 as prevailing in countries so widely separated as Senegal and French Guiana, and Madagascar and the French possessions in the West Indies. As far as we can ascertain, these early observers did not claim to have discovered a new disease, but that the symptoms described by them should distinguish the disease in which they occurred from yellow fever and some forms of malaria. This is well shown by A. Plehn,[3] who states:

> It was first of all by the reports of Berenger-Feraud from Senegambia during the sixties of last century that the attention of the pathologists of the scientific world was called to the fact that a well characterized group of illnesses, which he called "fiévre bilieuse mélanaurique" must be separated from those diseases in which the condition is that of continued high fever, which up till then had been called yellow fever, both on the West Coast of Africa, and the east coast of tropical America, as well as in the East Indies, and which also differed from yellow fever in its endemic aspect.

Plehn states also that this illness never led to any particular epidemics like yellow fever, and transfer from man to man was never observed.

Hemoglobinuric fever was next reported from Greece, in 1858, and from Louisiana in 1859. The reason for this latter is clear when one recalls the close association that prevailed for many years between New Orleans and France, an association quite as close as that between France and some of her Colonial possessions. As soon as the knowledge that the symptomatology of blackwater fever was to be distinguished from that of yellow fever came to the physicians who practiced in parts of Louisiana where both diseases were endemic, the former was immediately recognized, not as a recently imported disease, but as one which previously had been confused both with malaria and yellow fever.

The war of 1861-65 put an end for the time to further investigation in the South; but after the restoration of peace numerous cases of hemoglobinuric fever were reported from that part of the world. It was the consensus of opinion among observers between 1866 and 1875 that the disease was not a new importation, nor of recent recognition, but had been endemic in the South for many years, at least as far back as the time when it was first reported from Africa. The evidence adduced by Deaderick,[2] a part of which we present below, is conclusive as to the endemicity of the disease in the Southern States for a considerable period prior to the time when it was first distinguished therein as blackwater fever.

> Dr. Elliotson, in 1832, mentioned a case of ague accompanied by a discharge of bloody urine during the cold stage.[2]

Faget treated the disease as early as 1859, and states that cases with hematuria and hematatmesis had frequently been seen in New Orleans, and mistaken for yellow fever. Inasmuch as Faget considered hemetamesis a common symptom of yellow fever, it is possible that he himself confounded the two diseases in some instances.[2]

Dr. A. G. Mabry, in a report of a case of intermitting icterode hematuric fever in 1870, says, "It is a mistake to suppose that this is a new form of disease. More than twenty-five years ago I treated, in the vicinity of Selma, Alabama, cases of intermitting fever, presenting in a marked degree all the symptoms characteristic of these cases at the present day."[2]

These statements, based on the authority of physicians who observed the disease, both before and after its classification as an entity, do not permit of doubt as to its occurrence prior to its recognition in the Southern States.

The same is true of the disease in Africa:

Berenger-Ferraud pointed out that this fever had been observed in Dakar and Gorree since 1820.[3]

And A. Plehn states also:

Owing to mistaken ideas, blackwater fever was always called "sporadic endemic yellow fever."[3]

A definition, in view of recent epidemiological studies of the latter disease, that would not at present be tenable. Moreover—

The few cases in Europe and in the tropical colonies of the civilized world, which came under the attention of individual doctors, were looked upon as malarial fever in the worst form, and excited no attention when they occurred on yellow fever coasts.[3]

Christophers and Bentley state:

It had been previously thought that blackwater fever was due to the presence of blood or bile in the urine.[4]

A study of such early literature as we have been able to obtain, shows plainly that long before the symptoms of blackwater fever were thought of otherwise than those of severe malaria or yellow fever, marked jaundice, hiccough, and *blood* or *bile* in the urine were noted by keen observers to occur in the urine of severe malarial cases. These early writers considered this appearance of *blood* or of *bile* as a concomitant symptom of malaria, and did not attempt to distinguish an intermittent or remittent fever so accompanied from one in which the urine was normal in color, except to note that the disease was more severe in the former instance. It is in recent years only that diseases are distinguished by reason of factors other than clinical observation, a circumstance to which we shall refer later. So that Sydenham,[5] when he observed that in intermittent fever the color of the urine was red, but not as red as in those cases that manifested also a jaundice, never thought that possibly the cases with jaundice and a deeper colored urine might be what we now term blackwater fever.

Stokes and Bell quote Shields, who when he wrote of the endemic fever of Batavia in Johnson's "Diseases of the Tropical Climates," stated:

> A great proportion (of patients) changed in a few days to a bright yellow, some to a leaden color; other cases terminated fatally, in a very rapid manner, too, without the slightest alteration in that respect. Generally, however, the alteration in color indicated great danger.[6]

Unless the "endemic fever of Batavia" was a disease that has passed from the knowledge of physicians of to-day, Shields' description strongly suggests that he observed not only pernicious malaria, but hemoglobinuric fever as well.

Cleghorn, quoted by the same authors, when he wrote of the prognosis in the congestive form of remittent fever, said:

> But the utmost danger is to be apprehended, if a few drops of blood fall from the nose, if black matter like coffee grounds be discharged upwards or downwards, if the urine is of a dark hue, or strongly offensive smell, if the whole skin is tinged with a deep yellow, etc.[7]

And Bell himself, in his account of of pernicious intermittent fever, observed:

> There are cases of intermittent fever in which the jaundice takes place very suddenly, and disappears very slowly, to which the name *icteric fever* has been applied.[8]

This information is in a work published in 1842. Cleghorn, Shields, and Bell all were familiar with the malaria of tropical countries. At that time yellow fever had been separated from other diseases, and typical cases of typhoid fever were being recognized by competent observers. So that these symptoms were very probably correctly referred to as malarial attacks. We do not claim that the symptoms as described are conclusive proof that hemoglobinuric fever was the malady to which they were due; but anyone whose knowledge of that disease has been acquired by clinical experience will readily recognize a "striking" similarity between these symptoms as they occurred years ago in intermittent and remittent fever, and those that are typical to-day of blackwater when it supervenes during an attack of malaria.

In 1858 various Greek physicians reported the occurrence of hematuria after the administration of quinine in malarial fever. One of these published a paper on "Hemorrhages, and Particularly Hematuria, in Intermittent Fever,"[9] and opposed the hypothesis that quinine was the cause of the symptoms. Deaderick states that the credit for "first directing attention to the etiologic relation between quinine and hemoglobinuric fever"[2] belongs to these physicians, and not to Tomaselli, whose observations were not published until 1874. It should be noted that the Greek physicians, and others, at this time believed

that the color of the urine was due to blood or bile, and it was not until 1882 that "Corre and Karamitsas proved that the process was a hemoglobinuria and not a hematuria,"[2] although Christophers and Bentley[4] assert that the early French observers differentiated hemoglobinuria from hematuria. It is, however, evident from these reports that blackwater fever was endemic in Greece at the same time that it was reported from Africa and America.

In 1874 Tomaselli reported hemoglobinuric fever in Sicily.

> Almost immediately, interest being aroused, the disease was shown to occur in Sardinia and Southern Italy.[4]

About the same time the Dutch physicians in the East Indies, in Java and New Guinea, and in Guiana, in South America, wrote of the malady as prevalent in these colonies.[4]

In 1890 the Germans began to report the disease. Schilling, writing of malaria, also described blackwater fever, and noted its occurrence in Kaiser Wilhelm's Land, in the northwestern part of New Guinea. As Christophers and Bentley observe: "Coincident possibly with the stimulation of German colonial activity, we find numbers of investigators of that nation recording the disease"[4] from countries separated so distantly as the West Coast of Africa, German East Africa, and New Guinea, parts of the world from which it had been previously reported by the French and Dutch physicians.

In their careful summary of the dates on which blackwater fever was first observed in various parts of the world, Christophers and Bentley note that until 1895 "little or nothing had been reported concerning the disease from the British tropical and sub-tropical dependencies, although surrounded by areas of French and German colonies in which the disease prevailed extensively."[4] The slowness of the British observers to recognize the malady is not, in our opinion, a valid argument against the prevalence of the disease prior to its recognition in their colonies. Those who do not believe in the malarial hypothesis lay great stress upon what they call the recent appearance of hemoglobinuric fever in India; and if India were the only British tropical dependency where the disease was late in appearing, the argument, "that had it been present it would have been recognized," would have great force. This argument, as stated by Manson, is:

> Before 1885, strange to say, no Indian writer had mentioned hemoglobinuria as a feature in the pyretology of Hindustan or of the East. Apart from the possibility of its having been overlooked, there may be another explanation for this singular silence; the disease may have been confounded with bilious remittent. It is difficult to believe, however, that the large number of acute observers who have studied Indian diseases so carefully, and for so many years, could have systematically ignored this striking disease. Possibly, therefore, it is of recent introduction into India. Such

an idea is countenanced by the fact that certain medical men practising in Africa, good observers, declare that blackwater fever is of recent introduction there; and, moreover, that it is yearly becoming more common in that country. In certain States of the American union it seems to have been only recently introduced. Meeks says that it first appeared in Texas in 1886.[10]

There are several errors in this statement, if the authority of those who have made a careful study of the literature of the disease is to be accepted. Christophers and Bentley state that the first case of hemoglobinuric fever was recorded in the British literature in 1892.[4] Deaderick, quoting the page and volume of the journal from which he derived his information, says that the disease was endemic in Texas in 1866.[2] And certainly it is not of recent introduction into Africa, if the statements of the early observers are to be accepted. But the true reason why blackwater fever was not sooner reported from India is not that it was not endemic there, on the contrary, it was, as we shall presently show, but like other observers, the British physicians did not differentiate the malady until they had become familiar with descriptions of it in the literature. The following excerpt from Christophers and Bentley shows this very clearly:

It is noteworthy that up to this time (comparatively recently) little or nothing had been reported concerning the disease from the British tropical and sub-tropical dependencies, although surrounded by areas of French and German colonies in which the disease prevailed extensively. So that India was not alone in lacking reports of the disease. Crosse and Manson recorded cases in 1892, the earliest recorded observations by the English to our knowledge, and although from time to time a few isolated articles had appeared in the English medical journals, the disease had not been given a place in English literature or text-books available to the majority of British physicians practising abroad. But in 1898, as an immediate result of Manson's and Ross's great discovery, a sudden and extraordinary awakening of interest in tropical disease was aroused throughout the British Empire, and within the next half-dozen or so years blackwater fever was recorded by British observers from places so widely remote as British Central Africa, India, Rhodesia, Ugunda, Nigeria, East Africa, the Soudan, China, British Malaya, Burmah, British Honduras, and also from the neighborhood of Jerusalem. It is obvious that the recent introduction of the disease (simultaneously) into these countries is most unlikely.[4]

This history of the finding of hemoglobinuric fever in the British Empire exactly parallels that of its discovery in the Dutch, French and German colonies, and the recognition of it in the Southern States; in fact, it may be said of the finding of the disease that it was not until a description of it appeared in the medical literature of a country in such a manner as to be accessible to practitioners in the tropics and sub-tropics, that it was recognized by the physicians of that country.

The contention of Christophers and Bentley as to the absence of reports from the British tropical possessions can be verified by anyone who will read the text-books prior to 1903. As late as 1901, Copeland,

writing in a work of no less authority than Albutt's System of Medicine, says:

> Hemoglobinuric fever is practically confined to the tropical and sub-tropical regions of Africa and America. It has appeared now and then in Java and New Guinea. A few somewhat doubtful cases have been reported from India, Assam, and Cochin China, but in Asia the disease is practically unknown. In Europe a few cases have been reported from Italy and Greece.

This is interesting, in that it shows that the author was not familiar with the literature of the disease, or he would not have overlooked the numerous cases reported by Tomaselli and the Greek physicians.

Copeland further states:

> It is an interesting point, and one worthy of note, that until comparatively recent years there existed no records of "blackwater" fever, even on the West Coast of Africa. In a report by Bryson, in 1847, on "Diseases of the African Station," there is no mention of the special symptoms so characteristic of the disease. It is very difficult to account for this: for although cases of the disease may have been less numerous fifty years ago than at the present time (1901), yet it seems unlikely that this peculiar condition of the urine should have escaped notice altogether. (Very probably the condition did not escape notice, but the proper interpretation of it did.) It is possible that the color of the urine may have been put down, in some instances, to the presence of bile, especially if the amount of pigment were so great as to render the urine quite black, but this error could hardly have been made in those cases where the color is of a decidedly red tint, as it is when the urine is quickly extruded from the bladder, or when the attack is mild.

We do not find it difficult to account for the failure of Bryson to describe the disease. He, like other observers in West Africa, may have failed to recognize it; if his work was confined to the observation on shipboard of diseases contracted on shore by the sailors under his care, it is improbable that he saw it at all. As A. Plehn says: "It was not until the traders in that region moved to the land from their hulks which hitherto had been anchored in the rivers that blackwater became prevalent."[3] As to the color of the urine, it is our experience that in malaria all degrees of red colored urine are seen, some of which cannot be distinguished from the color in blackwater when the urine is "clearing;" on the other hand, in acute biliary obstruction, due to inflammation of the bile capillaries, the urine may be, and frequently is, very dark indeed.

In their extensive review of the geographical distribution of the disease Christophers and Bentley[4] do not report it as occurring in the British possessions in the West Indies, although according to Craig[1] it is found in Trinidad and Tobago.

When a proper consideration is given to the history of hemoglobinuric fever in the British colonies, it is very clear, notwithstanding

the keeness of the English observers in other tropical diseases, that it is certain for a considerable time they overlooked this malady.

Maclean is frequently referred to as an authority on the fevers of India, whose attention so striking a disease as blackwater fever could not have escaped. Christophers and Bentley quote him as stating, in 1886, with reference to certain cases of remittent fever, that: "In some cases recorded by me there was a profuse secretion of bloody urine that lasted until convalesence set in."[11] We were so fortunate as to find his original description of these cases. In Reynold's System of Medicine, published in 1870, Maclean[12] gives the following account of some of the symptoms observed by him in remittent fever in India. It may be stated here that this author's description of the symptoms of malaria is exceedingly instructive and illuminating, and may be read with profit in this day when the use of the microscope in diagnosis has taken to a great extent the place of the former accurate clinical observation.

> Of all the symptoms, nausea and vomiting are the most constant and exhausting; the vomited matters at first consist of any food that may be in the stomach, then of a watery fluid, often surprising in quantity. Soon bilious regurgitation takes place into the stomach, and the rejected matters become of a greenish yellow color, then brown, and finally, in extreme cases, black, resembling the "black vomit" of yellow fever. The resemblance will be more striking if, as sometimes happens, the skin assumes a yellowish tinge, and a hemorrhagic tendency be evinced. I have seen two cases at Madras, both in officers of the Forest Conservancy Department, in which the hemorrhagic range was most extensive, the patients passing blood from the stomach, bowels, and kidneys. In one of the cases I had the advantage of the assistance of Dr. Cornish, the able Secretary of the Principal Inspector-General of the Madras Army, and we both agreed that the symptoms in this case came nearer in their *ensemble* to those of yellow fever than any we had seen in the whole range of our experience in the East. Hiccough is often troublesome when gastric irritability is severe, but it usually appears as the disease is passing off. In one of the cases alluded to above, it lasted several days. The state of the urine is deserving of the closest study. Many authors of great authority write of it as always scanty, high colored, and of high specific gravity. But in severe Indian remittents I have noticed the opposite condition. Dr. Cornish, I am sure, must remember that in the case we saw together there was even diuresis throughout until convalesence was established. I have notes of three other cases in which the same condition prevailed; in all four the urine was bloody.[12]

A combination of fever, jaundice, hiccough, and the passage of "bloody" urine in certain cases of malaria are prominent symptoms upon which we base a clinical diagnosis of blackwater fever. And we firmly believe that any physician who is familiar with the disease will agree with us that Maclean's description proves beyond doubt the existence of hemoglobinuric fever, or a disease resembling it so closely clinically as to be indistinguishable, in India prior to 1870.

In considering the evidence presented above, one should take into account certain other facts in regard to the disease. It is essentially one that affects newcomers and such residents who are non-immune against malaria, in a region where the latter is endemic. In newcomers, in most cases, it occurs after a residence from six months to two years. We have discussed already this phase of the etiological problem. At present we wish to call attention to the prevalence of intense malaria, as shown by a high percentage of native children infected with the disease, in certain places where non-immunes are absent, or, if resident, live protected against infection. In such places hemoglobinuric fever does not prevail, so its absence until comparatively recent times, when non-immunes have arrived, in some intensely malarious countries can be explained.

It is plain that the finding of blackwater fever in various parts of the world has depended upon the extension into them of the knowledge of the disease, and not upon the extension of the disease itself. In this respect hemoglobinuric fever differs decidedly from yellow fever, kala-azar, sleeping sickness, and dengue, which diseases have assumed at times well marked epidemic features, and whose progress from one country to another, or from one part of a country to another, has been accurately traced. The history of blackwater fever, as we have given it, in the colonies of France, Germany, and England shows this clearly. It is obvious also, as shown by the quotations from Cleghorn, Bell, and Shields, prior to the recognition of the disease, and from Maclean's description of certain symptoms which occurred in cases of remittent fever in India, that the symptoms of hemoglobinuric fever, whether or not they occurred in that disease, were familiar to physicians many years ago in places where it is claimed that the disease has appeared only recently.

When their descriptions of these symptoms are considered, that these physicians did not recognize the disease as an entity is very insufficient evidence that the malady did not exist. Hemoglobinuric fever is not the only disease, tropical or otherwise, which, prior to its recognition as a distinct symptom-complex or a distinct malady, has been confused with other endemic affections.

We assert, then, that the advocates of the specific hypothesis cannot, in view of the evidence, maintain their claims that the disease has progressed geographically by extension; or, provided a population non-immune against malaria be present, that it has been absent from intensely malarial localities; or that it is of recent importation into these. And although the "striking" symptomatology of hemoglobinuric fever was referred to other diseases, particularly in India and the East

to malaria, and to both malaria and yellow fever in America and Africa, it was not overlooked by authoritative writers on tropical medicine, between 1821 and 1870.

II.

THE GEOGRAPHICAL DISTRIBUTION OF HEMOGLOBINURIC FEVER AND MALARIA.

The advocates of the specific hypothesis argue that there are many regions intensely infected with malaria which are free from hemoglobinuric fever. In some instances this assertion is too broad, for in many localities said to be free the disease has been found. And always one must consider whether or not that prime factor in the occurrence of blackwater, the presence of persons non-immune against malaria, has been taken into account. We present a summary of the geographical distribution of the disease, compiled from the writings of Scheube,[13] Manson,[10] Christophers,[4] Daniels,[14] Stephens,[15] Bentley,[4] A. Plehn,[3] Marchiafava and Bignami,[16] Craig,[17] Deaderick,[2] and Ronald Ross.[8] This includes only localities in which the disease is endemic, and does not reckon places in which imported cases are sometimes met with.

North America—Virginia, North Carolina, South Carolina, Georgia, Florida, Alabama, Mississippi, Louisiana, Arkansas, Texas, and Tennessee.

Central America—Along the entire eastern seaboard; in British Honduras, Nicaragua, Costa Rica, and Panama.

West Indies—Cuba, Martinique, Guadaloupe, Hayti, Trinidad, and Tobago.

South America—Colombia, Venezuela, French, English and Dutch Guiana; Brazil, particularly among the laborers engaged in the construction of the railroad in the southwestern part, and Uruguay.

Europe—Spain, Italy, Sicily, Sardinia, and Greece. One case has been reported from Krakau, in Poland. Merv, Turkey, and along the banks of the Danube.

Asia Minor—Palestine.

Africa—Algeria, the West Coast from Senegal to the Orange River, Rhodesia, Uganda, Nigeria, and British, German, and Portuguese East Africa. In Madagascar, Reunion, the Comoro Islands, and Mauritius. And in some of the islands in the Gulf of Guinea.

Asia—In India; in the northeast, in Behar, between the Ganges River and the Himalayas, and in Assam and Burmah; a strip along the eastern coast, between the Godavari and the Mahandi Rivers, occupying the middle third of the coast country between Madras and Calcutta; in the north-central part, a region between Meerut and the

Indus River, and the Bengal Duars; a region around Nagpur, in Central India; and in the Canara district, around Bombay, on the western coast.

In Siam and the Malay Peninsular, Cochin China, Tonquin and other parts of French Indo-China.

East Indies and Polynesia—Sumatra, Java, Celebes Islands, New Guinea and the adjacent Bismark Archipelago, Formosa, and a few cases from the Philippines.

This distribution includes every country in the world in which intense malaria is endemic*. Some of these regions are not included in the geographical distribution given by the advocates of the specific hypothesis. For instance, Craig states:

> Even in the countries in which this fever occurs, there are as many regions intensely infected with malaria which are free from the disease, although only a comparatively short distance from the endemic foci. Such regions occur in our own country, in some of the Southern States, and in Italy hemoglobinuric fever is limited to very restricted localities, while some of the worst malarial portions of that country have never presented a single instance of the disease. The same is true of India, of the Straits Settlements, the Islands of Polynesia, the West Indies, and the countries of South America.[1]

This statement is so radically at variance with the reports of recognized authorities, that one is inclined to doubt if the author has thoroughly examined the literature. In Italy, the mortality from malaria in Sicily and in Calabria, in the South, is "double that of the Roman Campagna, and ten times that of Northern Italy."[15] The mortality from malaria in Sicily is from seven to eight in 1,000, in North Italy it is less than one in 10,000.[4] Cases of hemoglobinuric fever have been reported from the Campagna, but the disease is more prevalent in the South, where the malaria is more intense. We are unable to learn of any region in Italy where severe malaria prevails, from which hemoglobinuric fever is absent.

In India, as we shall show presently, blackwater fever occurs among persons non-immune against malaria in all places where the proportion of native children infected with malaria is high. The reports of James[19] on the prevalence of malaria in India, and of Christophers and Bentley[4] on that of hemoglobinuric fever, are sufficient to convince anyone of this.

All students of the disease agree that it occurs only in regions where malaria is intense. If the malarial hypothesis be accepted, a constant exposure to malarial infection is inferred as the necessary element for the production of blackwater fever in most persons. It is admitted

*With the possible exception of Mexico, we could obtain no data as to either malaria or hemoglobinuric fever there, other than that both prevailed on the Eastern Coast.

that blackwater may be coincident sometimes with the first malarial attack, but such cases are exceptional. If the correctness of the specific hypothesis be granted, then the climatic, meteorological, and telluric conditions necessary for the existence of the specific organism are those requisite also for the production of intense malaria. Since the advocates of this hypothesis require those who take the other view to show why intense malaria may prevail without hemoglobinuric fever, it is equally incumbent on them to show why this disease is never found in non-malarial localities so situated that all conditions favorable for the existence of this specific organism are present.

To consider thoroughly these propositions a definite understanding of the factors concerned in the production of hemoglobinuric fever must be had.

1. Since the disease occurs nowhere except in regions of "intense malaria," or, at least, in places where malaria is greatly prevalent, the term "intense malaria" should be defined.

2. If there are regions in which intense malaria prevails that are free from hemoglobinuric fever, it is necessary to ascertain whether certain conditions are absent from such regions that are present in those where the two diseases obtain proportionately. Should intense malaria be found unassociated with blackwater fever, why is not the converse also true, that the latter obtains in places which are free from the former?

1. *Intense malaria and the regions where it prevails*—It is paradoxical to assert that a malarious country is always one where intense malaria prevails. The latter term includes the former, but the proposition itself is by no means inevitable. Intense malaria obtains in countries where at all seasons the percentage of native children infected is very high; in a malarious country, though present in great intensity at intervals, the disease is sometimes absent at others. The West Coast of Africa is a region where malaria is intense; Central Italy and the Eastern Shore of Virginia are malarious districts.

Ronald Ross[18] gives a very interesting and instructive description of the conditions under which intense malaria prevails. He calculates that if, in a certain village, one-half of the inhabitants are infected, and there are 20 Anopheles to each person, the chances of becoming infected are only 5 in 100, or 1 in 20. We regret that lack of space prevents the full presentation of this writer's conclusions, for he shows plainly that in order to maintain a high percentage of infected native children, the number of anopheles mosquitos requisite is so enormous that only in certain places can the conditions essential to such propagation be found.

We have stated that for the production of blackwater fever, the presence of persons non-immune against malaria in an area where the latter disease is intense is a necessary factor. This cannot be controverted, for the occurrence of the former disease in persons immune against the latter is almost unknown. Nor do the reports of hemoglobinuric fever in natives of India or of the West Coast of Africa render this statement invalid, as we shall show. The subject of immunity against malaria is too complex to discuss in detail, but some propositions have been advanced that are now generally accepted as true.

The researches of Koch,[3] Christophers and Bentley,[4] James,[19] Daniels,[14] Stephens,[15] and others, in Africa and India, and in the East Indies, show that to acquire immunity, a native must live in a locality where the percentage of infected children, or the *infantile endemic index* (Ross) is relatively high; in other words, immunity is acquired by repeated attacks of malaria in infancy and childhood. This immunity may be interrupted by a residence in a non-malarial country, so that it would appear that occasional infections are necessary to maintain it. It has been shown also that the higher the *infantile endemic index*, the less is the proportion of infected adults, *or the adult endemic index* (Ross). So that when the former reaches 80 per cent, the latter is close to 0. On the other hand, the smaller *the infantile endemic index*, the greater is the *adult*, until all ages are affected equally, or the disease prevails no longer.

With a consideration of these facts in mind, we shall proceed to investigate the prevalence of blackwater fever and that of intense malaria.

On the west coast of Africa *the infantile endemic index* (hereafter referred to as the i. e. d.) is very high, and the *adult endemic index* (a. e. d.) is low, natives over twenty-five being practically immune. A. Plehn states that "Blackwater fever is absent in the relatively immune coast negroes if they remain in their own homes."[3] But here and there are districts in which the i. e. d. is low, and malaria obtains among the adults. When a negro from such a district enters one where the i. e. d. is high, he is liable to incur an attack of blackwater.

In Nigeria[20] an average of 39.9 per cent of native children under ten years were infected, the lowest rate was 22.9 per cent, the highest, 66.6 per cent. If the malarial hypothesis be accepted, it will explain why in some localities in Nigeria blackwater would be less prevalent than in others.

In the town of Bathurst,[21] in Gambia, the European population varied between 60 and 80, and the natives were about 15,000 in number. The i. e. d. in 1900 was 80 per cent. In 1898, when the European

population was 63, there were 23 admissions to the hospital, mostly for malaria, and 4 cases of blackwater, all in whites. In 1899, when the European population was 80, there were 57 admissions for malaria, and 3 cases of blackwater. In 1903, after a certain degree of anti-malarial sanitation had been effected, there were 48 admissions, "mostly trivial," and but one case of blackwater.

Near Bathurst[22] is the French town of Conkary, with a native population of 12,000 and a European of 400, in 1903. This town has been laid out by the French in spacious and regular streets, is kept clean, has an excellent water supply, is well drained, and possesses an excellent pail-system for the disposal of excreta. In spite of these advantages, in 1903 malaria and blackwater fever prevailed extensively among the Europeans. The Commission found that this unfortunate condition was due to the presence of numerous old wells, which had formerly been used to supply water, and since the introduction of the pipe system had not been filled. In these old wells anopheles bred in abundance. The otherwise excellent sanitation had reduced the proportion of diseases, such as typhoid and dysentery, to almost nothing. Most of the Europeans had malaria every year, and in 1900 there were 15 cases of blackwater fever among them, in 1901, 8 cases, and in 1902, 10 cases. In 1903, although the statistics for that year were not available, it was evident that neither blackwater nor malaria was decreasing. The Commission was not able to obtain definite information as to the i. e. d., but it was estimated at 80 per cent. The amount of malaria among the Europeans would have been much greater had it not been for the almost universal custom of using mosquito nets.

A very complete report on the prevalence of malaria and hemoglobinuric fever in the German possessions in East and West Africa is given by Schilling.[23] The i. e. d. is very high. About 1900 quinine prophylaxis was initiated. The tables which follow show the effect of this measure, not only on malaria, but on blackwater fever as well.

TABLE XIV.—*Compiled from Schilling.*[23]
Malaria Among the German troops in East Africa.

	1893-94	1894-95	1895-96	1896-97	1897-98	1898-99	1899-1900
Strength	.....	123	111	104	112	105	129
Cases of malaria	.....	412	414	343	318	345	386
Percentage of malaria	316	337	373	330	278	328	299
Cases of blackwater fever	.....	4	32	19	30	32	19

	1900-01	1901-02	1902-03	1903-04	1904-05	1905-06	1906-07
Strength	130	150	162	139	138	242	189
Cases of malaria	261	229	209	162	140	252	158
Percentage of malaria	200	152	129	124	101	104	84
Casesofblackwaterfever	17	12	8	9	2	6	5

TABLE XV.—*Compiled from Sshilling.*[23]

Malaria Among the German troops in West Africa (Cameroons).

	1900-01	1901-02	1902-03	1903-04	1904-05	1905-06	1906-07	1907-08
Strength	91	85	71	87	84	92	.....	89
Cases of malaria	340	151	114	104	131	131	.....	87
Percentage of malaria	370	177	162	119	165	142	.....	97
Cases of blackwater fever	20	18	21	23	8	13	.....	9

Similarly, A. Plehn,[3] in German West Africa, demonstrated that blackwater developed in only one-fourth of the persons who took quinine as a prophylactic, as compared with those who did not, and the amount taken was small in proportion to that given as a cure.

It is evident from these observations that in other countries, as in the Canal Zone, any form of prophylaxis that is efficient against malaria is efficient also against blackwater fever. The advocates of the specific hypothesis may assert, and rightly, that anti-malarial prophylaxis, consisting of complete sanitary measures, will be effective against diseases other than malaria or hemoglobinuric fever. But in the town of Conkary the sanitary methods in force have freed the Europeans there from tropical diseases other than these two. So that there the hemoglobinuric fever must depend for its cause on the same etiology as does the malaria. On the other hand, without sanitary measures, under the same climatic conditions, and in the presence of a high i. e. d., the Germans reduced by the use of quinine prophylaxis the prevalence of blackwater fever in greater proportion than they reduced the malaria rate. It is plain from this evidence that if a specific organism be the cause of hemoglobinuric fever, it must be transmitted in the same way as that of malaria, and like the latter, must yield to quinine prophylaxis. And such an hypothesis, we have previously shown, for the Canal Zone, at least, is not tenable.

The same prevalence of blackwater fever among the non-immunes, when the i. e. d. is high, obtains in the East Indies. Jones[24] states that in British New Guinea it is among those who have had repeated attacks of malaria that hemoglobinuric fever prevails.

The prevalence of malaria in India, in our opinion, has been greatly overstated. We do not assert that in this country the disease is not common; but it is true that India is not, as is Africa, a country of intense malaria. The conditions that favor intense malaria obtain in limited districts only. In the Bengal Duars, and in the Terai, which latter is a "densely wooded, damp, pestilential tract of an average breadth of twelve miles, which stretches from the Ganges along the foot of the Himalayas to Assam,"[25] the ground water that has its origin in the Sub-Himalayan mountains comes to the surface. This water

supply is continuous, taking the place of the heavy rains of tropical Africa, and produces conditions most favorable for the propagation of intense malaria. Other intensely malarial regions are the Jeypore hill district, on the eastern coast, not far below Calcutta, where there is a heavy rainfall; and near Bombay, on the western coast. James[19] gives the following data concerning the prevalence of malaria in India. The percentage figures refer to the proportion of native children infected.

In Calcutta, no infected children were found, although anopheles were plentiful. In Madras, the rate was 5 per cent, and in the plains of Bengal, from 7 to 24 per cent. In the Bengal Duars, from 28 to 72 per cent. No infected children were found in the Darjeeling hills. Blackwater fever has been reported from this district, but only in persons who had gone there for their health. Such cases were imported, and should be classed with those that occur in England or in Germany. In Mian Mur, in the Punjab, in North Central India, from 20 to 56 per cent. In this place the varying percentages were obtained in a restricted locality. In various towns in the central provinces, from 5 to 45 per cent. In the Vizagapatam district, which is halfway between Madas and Calcutta, on the east coast, from 0 to 27 per cent. In the Jeypore district, from 20 to 86 per cent. In Assam, from 5 to 85 per cent.

It is plain from these figures that not only does the intensity of malaria in India vary decidedly over different localities of large area, but in comparatively small districts also the same is true, and even in restricted limits in these. So that if a very careful analysis of the prevalence of malaria were not made, it would be easy to err, as some have done, in stating that there are large areas where malaria is intense, when the intensity is confined to a small part of these areas; or that some districts are free from the disease, when no more than a small part of the districts is free.

If a comparison is made between the intensity of malaria, as given above, and the localization of blackwater fever in India, it will be seen that the latter is distributed in proportion to the former. The Bengal Duars and the Terai are notorious blackwater regions, and it was in the Duars that Stephens "Saw more cases in a fortnight than in the same time in Africa." Since these districts are in relatively remote parts of India, and are sparsely inhabited by Europeans, it is very unlikly that the disease was carried there by extension, sparing on its way places like Calcutta, where abundant opportunities for its propagation would be present.

This exact parallel between the intensity of malaria in India, and the prevalence of blackwater fever there, has not escaped the attention of

unprejudiced observers in that country. James noted it during the progress of his investigations into the prevalence of malaria; and Stephens and Christophers, when they learned of the intensity of malaria in Canara, near Bombay, predicted, and correctly, the occurrence of blackwater in that place.

In recent years the intensity of malaria in India, when the entire country is considered, at no time has been so great as in the blackwater districts of Africa. We have shown that in the Canal Zone a certain degree of malarial intensity is necessary for the occurrence of blackwater fever. The same is true in India. In 1892, a time when no prophylactic measures of any value had been instituted against malaria there, when undoubtedly many cases of disease were termed malarial that were due to other causes, the prevalence of malaria in the army, as shown by the following table, was no greater than that in the Canal Zone in 1907, and very much less than the 370 per cent morbidity from malaria in the first part of their occupation, and the 200 per cent morbidity that prevailed later, among the German troops in East Africa.

TABLE XVI

Malaria among the troops in India.[26]

EUROPEAN ARMY, 1892.

Total strength	68,137
Admissions from intermittent fever	29,237
Deaths from intermittent fever	19
Admission rate per 1,000	420
Death rate per 1,000	.26
Admissions from remittent fever	894
Deaths from remittent fever	75
Admission rate per 1,000	12.4
Death rate per 1,000	1.05
Total admission rate per 1,000 from malaria	432.4
Total death rate per 1,000 from malaria	1.31

NATIVE ARMY 1892.

Total strength	127,355
Admissions from intermittent fever	66,989
Deaths from intermittent fever	125
Admission rate per 1,000	535.9
Death rate per 1,000	1.02
Admissions from remittent fever	1,676
Deaths from remittent fever	181
Admission rate per 1,000	13.4
Death rate per 1,000	1.44
Total admission rate per 1,000 from malaria	549.3
Total Death rate per 1,000 from malaria	2.46

If most of the intermittent fevers in the above table belonged to the tertian or quartan varieties, it is evident that estivo-autumnal malaria was very infrequent when compared with its prevalence in Africa and the Canal Zone. This is probable, for the researches of the British observers have shown that with the exception of those localities in which intense malaria prevails, the estivo-autumnal species is more infrequent than the other two, thus placing most of the malaria in India in the class that prevails in the Temperate Zone in Europe and America. As we stated in another place, while there is no positive proof that estivo-autumnal species is solely concerned in the etiology of hemoglobinuric fever, all the evidence at hand implicates this variety as responsible, and the data just quoted corroborates this belief.

Whatever may be said of regions from which the disease is absent it is certain that in those where blackwater obtains the prevalence of this disease is in exact proportion to that of severe malaria; and when the occurrence of hemoglobinuric fever in the temperate zones is considered, the same factor will be shown to obtain. The highest morbidity rate from blackwater fever that we found was that shown among the Europeans in 1896-97, in the town of Duala, in the Kameruns (Cameroons) in German West Africa. In this period 48 per cent of the Europeans acquired blackwater fever, and it is interesting to note that the malaria morbidity among them reached 391, while in certain months as many as 70 per cent were infected.[23]

Compared with the figures given for the malaria morbidity in places where blackwater obtains to a great degree, the malaria morbidity for regions of so-called "intense malaria" in the temperate zone becomes small by comparison. Here and there in Southern Italy, Greece, or our own Southern States may be obtained figures approaching somewhat those of the African morbidity. But it is obvious that any such prevalence of malaria in the temperate zones would, in a short while, depopulate the areas in which it occurred, as has been the case in some villages in Greece and in the Roman Campagna. For the Caucasian race does not acquire more than a slight relative immunity against malaria except in rare instances, and cannot exist for a long time under conditions such as obtain in the blackwater districts of Africa. As further evidence that in the temperate zones the intensity of malaria cannot begin to approach that of the tropics may be adduced the lack of places suitable for the continual propagation of the almost inconceivable number of anopheles required.

The malaria morbidity for Greece and Italy, though relatively large for temperate countries, is small when compared with that of the blackwater regions of the tropics. Undoubtedly circumscribed

areas may show a high morbidity rate, but nowhere are localities whose figures approach some of those quoted for German East Africa.

In 1901 the percentage of malaria in the Italain army was only 2.5,[27] and this was before the institution of prophylactic measures. From 1885 to 1905, 69.92 per cent of the employees of the Adriatic railways were infected, and this includes at least 50 per cent of relapses. Among the custom-house officers in 1900–'02 the malaria morbidity was 65 per cent. These two classes of employees worked in the most malarious regions in Italy, and the figures given for them are probably a maximum for such localities, except circumscribed areas. Nor was this malaria of severe type, for the Italian statistics[28] from 1901 to 1908, which include 62,758 cases, show but 37 per cent of the estivo-autumnal variety. So that in Italy intense malaria, in the sense that the word is used to indicate the prevalence of the disease in the blackwater districts of Africa and Asia, does not exist except in a few places. In 1906 the admission rate due to malaria to the hospitals for all races in the Canal Zone was 81 per cent, and for European laborers, probably slightly in excess of 100 per cent, and yet the blackwater morbidity among the latter was not over 1.5 per cent. Since these laborers have the same susceptibility to malarial infection as have the inhabitants of Italy, it is obvious that even among the heavily infected employees of the Adriatic railroads and the custom-house, blackwater would not prevail to any great degree. The highest morbidity from blackwater fever in the Canal Zone among the European laborers has never exceeded 2.5 per cent, so that even when the repeated infection in Italy is considered, the disease would not reach great proportions.

In Greece:

> The average number of cases of the disease throughout the kingdom is 29 per cent. Of the 69 provinces of the kingdom, 19 show a number of cases equal to over 40 per cent of the number of inhabitants, and of 445 communes only 29 are free from the disease, whilst the remainder are affected in a greater or smaller degree, especially in cases of 59 communes with a percentage of 41 to 50, 33 with 51 to 60 per cent, 32 with 61 to 70 per cent, 18 with 71 to 80 per cent, and 2 with 81 to 90 per cent; or 135 communes (nearly one third of the total number) with a percentage of over 40. In years of epidemic it happens that in many communes the whole of the inhabitants are attacked by malaria.[29]

There is but little difference between the climate of Greece and that of Southern Italy. But 1-68th of the surface of Greece is covered with marshes whose area exceeds 1,000 square meters, and there are numerous smaller marshes, and torrent beds full of small pools.[29] So that malaria prevails more extensively in Greece than in Italy, because there are in the former country a greater number of suitable breeding places for anopheles. As a corollary, there is also more hemoglobinuric

fever. Greece is the only country in the temperate zone where the intensity of malaria over a large area approaches that of the tropics, and in which the prevalence of hemoglobinuric fever approximates a similar proportion. Even there the prevalence of estivo-autumnal malaria does not approach that of the tropics.

We have gone into detail in this comparison between the intensity of malaria and that of hemoglobinuric fever, and have cited so much data bearing on this comparison, because we desired to show that the same climatic, meteorological and telluric conditions necessary for the production of the one are essential also to the prevalence of the other. In the light of the evidence we have adduced, it must be admitted even by those most strongly opposed to the malarial hypothesis that if any specific organism other than the malarial parasite is responsible for blackwater fever, such an organism must conform exactly in its life habits and its extra-corporeal existence to those of the malarial parasite. Since the same mechanical prophylaxis which inhibits the prevalence of malaria inhibits also that of blackwater fever, as is shown in every country in which this method is used, it follows that the specific organism responsible for the latter malady must be conveyed in the same manner as the one which produces the former. The carrier must be a winged insect; for, as every one knows who has lived in the tropics, neither wire screens and mosquito curtains, nor ditches and sewer-systems, protect against crawling insects. We shall take up later the consideration of the efficacy of quinine prophylaxis.

2. *The absence of hemoglobinuric fever from regions of intense malaria*— We shall repeat the propositions to be considered under this head "If there are regions where intense malaria prevails that are free from hemoglobinuric fever, it is necessary to ascertain whether certain conditions are absent from such regions that are present in those where the two disease obtain proportionately. And should intense malaria be found unassociated with blackwater fever, why is not the converse also true, that the latter obtains in places free from the former?"

As far as we have ascertained, there is but one country, the Philippine Islands, in which intense malaria is said to prevail, that is free from blackwater fever. That is, if by intense malaria we mean a malaria morbidity rate of at least 50 to 60 per cent per annum, due in greater part to estivo-autumnal infection. That this condition is essential, is amply shown in the preceding section. It must be admitted that if the arguments against the malarial hypothesis, based on data from the Philippines, which are advanced by Craig[1] are correct, they afford some proof for the necessity of a specific organism as the essential

factor in the etiology of hemoglobinuric fever. Now, some of the evidence either for or against the malarial hypothesis is circumstantial, and in the absence of positive testimony, that hypothesis which is supported by the stronger and better attested evidence is the more likely to be correct. This is as true in science as in law. And in view of the positiveness with which the presence of hemoglobinuric fever in certain parts of Africa, and in India, had been denied by reputable authorities, when later it was found to prevail, one is entitled to doubt if the disease is as rare in the Philippines as Craig would have one believe. If it is, then this is the only country in which a non-immune population, heavily infected with malaria, does not show hemoglobinuric fever. We shall, however, account for the absence of blackwater in the Philippines by evidence that is more positive than circumstantial. That Craig was in error in his assertion as to other regions where malaria is intense and blackwater is absent, we have already shown. He himself admits that in his very extensive experience with malaria in the United States Army, he saw but two cases of hemoglobinuria following the use of quinine, and in these "the symptomatology was very different from that of hemoglobinuric fever." And further, he says:

> The lack of periodicity in the temperature curve, the presence of an enlarged and tender liver, the repeated chills, the occurrence of marked jaundice, the leucocytosis and the hemoglobinuria, have all been instanced by Sambon and other authorities, as definitely separating the disease on clinical grounds from malarial fever.[1]

Since this author's knowledge of hemoglobinuric fever admittedly has been obtained from the literature, and not from personal experience, if this knowledge is inaccurate, in all fairness it may be said that it is possible, like many other competent and able physicians have also done, he too has overlooked the disease, or mistaken it for malaria. For the differential points in the symptomatology, as given above, are not accurate. In the first place, no one at this time claims that the symptomatology of a hemoglobinuric attack is a reason for supposing it is due to malaria; although clinically, with the exception of the hemoglobinuria, it is impossible at the onset to differentiate the two, and later, only by reason of a more constant jaundice and the hemoglobinuria in the blackwater cases. An enlarged and tender liver is a very constant feature in malaria. Repeated chills are not a prominent symptom in blackwater. Jaundice is common to both diseases, and sometimes is almost as marked in malaria as in blackwater. And the author who stated that leucocytosis is a constant factor in hemoglobinuric fever is in error. In fact, a large and tender liver, associated with jaundice, repeated chills, leucocytosis, and passage of

dark colored urine, is not infrequently seen in biliary obstruction, dependent on some septic process, due to inflammation of the bile capillaries. This condition is somewhat similar clinically to hemoglobinuric fever, and if an examination of the urine is not made, may be mistaken for this disease. And conversely, by persons not familiar with the malady, hemoglobinuric fever may be mistaken for this form of bile capillary inflammation. Certainly, the differential symptoms above attributed to hemoglobinuric fever would cause suspicion as to the accuracy of the diagnosis of this disease.

With a consideration of these facts in mind, we will take up the prevalence of malaria and blackwater in the Philippines.

It is admitted that hemoglobinuric fever has occurred in that country. One case was reported in 1905, and two others in 1906, all in members of the United States Army.[1] In the period from 1903 to 1908, inclusive, only three other cases were reported in the Army outside of the Philippines.

The following table[30] shows the relative admission and death rates per thousand of mean strength for malarial diseases in the Philippine Islands (American troops), by years, 1898–1908:

TABLE XVII.—*Malaria among the troops in the Philippines.*

	1898	1899	1900	1901	1902	1903	1904	1905	1906	1907	1908
Admission rate per 1,000	429.5	705.4	742.8	520.5	438.1	458.5	220.6	261.5	304.2	167.7	123.9
Death rate per 1,000	1.72	1.23	1.64	.9	.67	1.34	.25	.63	.55	.17	.16

A comparison of this table with those showing the morbidity rate for the German troops in Africa demonstrates at once that the malaria in the army of the Philippines is not so intense, by any means, as in the blackwater districts of Africa. In fact, on the average, the intensity is, except for the years 1899–1900, no greater than for the less malarial districts of Greece and Italy. Further, the malarial patients in the army were under competent medical supervision during the attack, and by reason of their stay for two years only and relatively low malarial rate, not exposed to the accumulative malarial infection which occurs in places of much more intense malaria, or in those where the liability to infection occurs over a long period of years. It is in malaria infected persons who have not been properly or sufficiently treated that hemoglobinuric fever for the most part occurs.

This is shown by the marked diminution in the amount of hemoglo-

binuric fever when quinine prophylaxis and treatment is intelligently used.

Malaria among the United States troops in the Canal Zone.—That prompt and efficient treatment of malaria by quinine in large doses reduces the proportion of blackwater fever to a minimum, we are able to show by positive evidence. Since early in 1903 to the present time the United States Government has stationed a battalion of marine troops on the Isthmus. This battalion is placed at Camp Elliott, adjoining the Zone town of Bas Obispo. Camp Elliott is not a particularly malarious place, as it is situated on a hill, and is well drained. For target practice, however, the troops have at different times gone into camp at Mindi and Corozal, outside the limits of sanitary improvements in these places. Each locality is within the tidal limit, the one, on the Atlantic side, the other, on the Pacific, and anopheles abound near both. Consequently the entire battalion at times has been infected with malaria, especially in 1906 and 1907.

But as soon as symptoms were evident the men were at once released from duty and quinine was given in doses of 30 or 40 grains a day. Subsequent taking of the drug was compulsory. The effectiveness of this admirable method of handling what at times amounted to a severe epidemic is shown by the mortality statistics of the battalion. *Not one death due to malaria has occurred at any time.* This is in part owing to facilities for the immediate transportation of the sick from the practice camps to the hospital at Camp Elliott, as soon as symptoms were evident, but the greater credit should be given to the system that can compulsorily place patients infected with malaria under immediate treatment and to the knowledge which renders the treatment effective.

Through the courtesy of Dr. J. G. Ziegler, U. S. Navy, who is stationed at Camp Elliott, we are able to present a table showing the amount of malaria in the battalion from 1903 to 1910, inclusive. This table is compiled from his very complete figures, showing by quarters the number of men, and the amount of primary malarial infections and of relapses. We are indebted also to Dr. Ziegler for the other information concerning the marines that is here presented.

TABLE XVIII.—*Compiled from data furnished by Dr. J. G. Ziegler.*

Malaria among the troops in the Canal Zone.

	1903	1904	1905	1906	1907	1908	1909	1910
Average annual strength	298	444	207	253	182	409	397	387
Cases of malaria	126	262	156	796	378	452	189	41
Percentage of malaria	42	59	75	331	202	173	48	10.6
Annual rate per 1,000 of malaria	422	590	753	3,315	2,022	1,733	476	10
Cases of blackwater fever	0	0	0	0	0	1	2	0

Notwithstanding the very great amount of infection in some years, *only three cases of blackwater fever are recorded in the time that the battalion has been stationed on the Isthmus.* These happened, one in 1908, and two in 1909, one in the first quarter, the other in the third.

To account for this very small prevalence of hemoglobinuric fever, it is necessary to show that some factor obtained among the troops that protected them from the disease. The malady was not overlooked, for to our personal knowledge the different surgeons who have been stationed at Camp Elliott had a full acquaintance with the symptomatology. Non-exposure to infection with a specific organism (other than the malarial parasite) will not account for it, for cases of blackwater other than the three that occurred among the marines have been reported from Mindi, Corozal, and Bas Obispo. Immunity against malaria was not responsible, for this disease prevailed among the troops more extensively than among the American employees of the Commission. To no habit of living is the cause assignable, for in their liberty hours and days the men employ themselves exactly as do the employees. It is not a matter of housing, food, or of water supply, for these are the same among the one as among the other.

There remains, then, this factor: the method of treatment of malaria. Although this disease is efficiently handled by the Commission physicians after the patients apply for treatment, they have no facilities for detecting it otherwise. It is well known that to cure malaria thoroughly and promptly, rest and large doses of quinine are essential. This treatment we cannot give when the Americans, as they sometimes do, insist on working, and take small doses of quinine, although it should be said that this is exceptional, and if the malady becomes severe, the Americans promptly seek hospital treatment. In the meantime, however, the partially controlled infection is creating a susceptibility to blackwater. For this reason hemoglobinuric fever developed more readily among the Americans than among the marines in times of severe malarial prevalence, and we cannot assign any other cause. The results obtained by the Navy surgeons stationed at Camp Elliott are possible only under military regulation, but they are none the less valuable as an indication of how malaria can be treated effectively.

If, then, under the military system of treating malaria, the prevalence of blackwater fever in the Canal Zone is kept to a minimum, it is not difficult to account for its infrequency among the troops in the Philippines, in which country the malarial rate in the Army has been very much less than that among the marines stationed here. It is true that the same percentage of malaria among the German troops in Africa as obtained among the marines in the Canal Zone in 1906–07

was productive of a high proportion of blackwater fever, but we are sure that if the methods of treatment in the two places are compared, a marked difference in the amount of quinine given and the length of time and the method of administration will be observed. We regret that we are unable to present data on this very important comparison.

The comparatively greater malarial rate among the marines is due to two causes. The figures this rate is based upon include every case of the disease, while those for the rate among the Americans include hospital admissions only. At target practice the troops lived in tents in very malarious localities, which the Americans have not done except in a few instances, when a general infection promptly followed. The reasons for the greater prevalence of hemoglobinuric fever among the civilians than among the troops are amplified in the following section.*

A very fair comparison can be made also between the intensity of malaria in the Philippines and that among Americans in the Canal Zone, and the effect of this intensity on the prevalence of hemoglobinuric fever. In making this comparison it is essential to keep in mind that our records in the Canal Zone include hospital admissions only, and do not take account of a very considerable amount of malaria treated at home and in the dispensaries, and also as a rule, only those Americans who have not been successful in having the disease cured by these methods enter the hospital; while in the Army the record includes every case of malaria that is sufficiently severe to excuse the patient from duty, which in effect means practically every case. Moreover, we are informed by Army officers in the Medical Corps who have had service in the Philippines that only in recent years has the microscope come into general use in diagnosis, and a very great part of the malaria was diagnosed clinically. As a result, it is very probable that the malaria rate, as shown in Table XVII, is somewhat high. This, of course, does not refer to Craig's own statistics, which were the result of personal observation, and we willingly concede that these are beyond dispute.

In 1905 and 1906 the malaria rate in the Canal Zone, due to hospital admissions only, was 514 and 821 respectively, Table III, Page 18.

*The valuable data furnished by Dr. Ziegler did not reach us until we had completed this Appendix. The proofs of the rest of this paper had come to hand, so the need of haste in sending the manuscript of the Appendix to the printer prevented us from altering it otherwise than to insert Dr. Ziegler's data as a separate section, without proper correlation of composition with the preceding and subsequent sections. We feel, however, that by its importance to the subject this information will compensate for the repetition we could not avoid.

There were comparatively few European laborers on the Isthmus at that time, so that these figures refer mainly to the rate for Americans and negroes. As the admission rate in 1908–'10 for Americans (Chart No. 4), was slightly higher than that for negroes, and this at a time when the former were but slightly exposed to infection, by reason of improved sanitation, it is evident that in 1905–'06 the malarial rate for the Americans was proportionately higher. Taking into account the large number of cases that did not come into the hospitals, but were treated outside, a minimum estimate of the malaria rate among the Americans for 1905 and 1906 would be at least 750 and 1,200 per thousand.

Now, if these figures are compared with those in Table XVII, it is seen that in two years only, 1899–1900, the malarial rate in the Army in the Philippines even approximated the maximum malaria rate in the Canal Zone. It should be remembered that the greater part of these malaria cases in the Philippines were promptly put under quinine treatment. In 1905 there were between 3,000 and 4,000 Americans in the Canal Zone, and 5,464 in 1906. Yet in 1905, only 10 Americans were admitted to Ancon Hospital with blackwater fever, and 1906, only 11. From 1907 to 1910, inclusive, the number of Americans employed was between 6,000 and 7,000, and the malaria rate, as shown by the hospital admissions, fell from 424 per thousand to 187 per thousand. Five cases of hemoglobinuric fever in Americans were admitted to Ancon Hospital in 1907, 3 cases in 1908, 3 cases in 1909, and 1 case in 1910.

Among the troops in the Philippines the malaria rate fell from 742 per thousand in 1900, to 123 per thousand in 1908. The rate for 1900 was the maximum. It is evident that if intense malaria is the cause of blackwater fever, but very few cases would have occurred at any time in the Army in the Philippines, and particularly in the last few years. So that, as far as the prevalence of hemoglobinuric fever in the Army is concerned, Craig's statement that "The almost complete absence of hemoglobinuric fever in the Philippines is an excellent illustration of the fact that a most malarial country may be free from the disease,"[2] fails completely as an argument against the malarial hypothesis.

Craig further states:

> At Camp Stotsenberg, in the Philippines, one of the most intensely malarial regions of which we have record, where, within six months, there were more than thirty deaths from pernicious malaria among the natives in the vicinity, a case of hemoglobinuric fever has never been known to occur, and the natives informed me that they had never heard of a single instance of the passage of bloody urine during an attack of fever.

As for this intense prevalence of malaria among the natives, if the disease obtains as severely as is shown by Craig's figures taken from the

Philippine census, some places showing a death rate from malaria between 50 and 100 per thousand *per annum*, if some degree of immunity is not established before long, the islands will be depopulated. The highest death rate from malaria in the Canal Zone was 7.8 per thousand in 1906, among the negroes, and the rate per thousand of admissions into Ancon Hospital from hemoglobiuric fever among this class was only 0.59. Although malaria is common among the children of natives of the Canal Zone, hemoglobinuric fever is almost unknown at any age, and this is, as we have shown, true also for the dark-skinned races in every country where malaria is intense. In India, the natives of the Terai and the Duars have a relative immunity against malaria, and against blackwater as well.

We cannot believe, then, notwithstanding the great prevalence of malaria among them, that the natives of the Philippines do not acquire an immunity against malaria. And, indeed, this is the opinion of Craig himself. He states in "The Malarial Fevers," page 95:

> The natives of the Philippines, living in the most malarial localities, enjoy an increased resistance to these fevers, a resistance which may broadly be called an acquired immunity, for while the plasmodia are often found in the blood, symptoms are absent or are so slight as to escape attention. This resistance to the infection is very marked when compared to the lack of resistance shown by the American troops stationed in the same locality. At Camp Stotsenburg, out of a brigade of American troops, over 600 entered the hospital in one month, suffering from initial attacks of malaria; in the native population, which far outnumbered the troops, only a very few cases of malaria were observed although the natives were living under much poorer sanitary conditions, and were much more exposed to the bites of mosquitoes.

Although there is a marked discrepancy between this statement and the idea conveyed in his paper on hemoglobinuric fever as to the severity and intensity of malaria among the natives of the Philippines, Craig evidently believes that immunity against malaria is the rule among them.

We find, then, that conditions which are present in regions where blackwater is common do not obtain in the Philippines, and that the absence of blackwater fever there confirms rather than denies the malarial hypothesis. Among the non-immune population for which figures can be ascertained, i. e., the American troops, the intensity of malaria was neither great enough nor sufficiently sustained to produce more than a small amount of hemoglobinuric fever, and three cases of the disease have been reported. Also the prompt and continued anti-malarial treatment was efficient, as at Camp Elliott, in reducing to a minimum the liability to blackwater. Among the native population and in the Philippine Scouts the absence of the malady can be attributed to the relative immunity against malaria, a result which

is paralleled in every other country whose native inhabitants belong to a dark-skinned race.

Blackwater fever has not yet been reported from a country where malaria does not prevail, although the climatic and other conditions are suitable. Until 1865 the Island of Mauritius had been free from malaria. In that year occurred an outbreak of the disease, followed the next year by an epidemic that assumed alarming proportions. In the Island of Reunion, 125 miles distant, "precisely similar events occurred at the same time."[18] Blackwater fever had never been reported from either island prior to the outbreak of malaria, although at the time of the differentiation of this disease, Reunion, which is not very far from Madagascar, was, and still is, a French possession. It is extremely unlikely that had blackwater been prevalent in Reunion prior to the invasion of that island by malaria it would have been overlooked. But since the entrance of malaria into Mauritius and Reunion, hemoglobinuric fever has been a common and fatal disease in those islands. Obviously it was introduced and propagated by the same cause that was responsible for the very great severity and continued prevalence of malaria in those islands. Ross points out that persons infected with malaria had been introduced into both islands, but in far greater numbers into Mauritius, for many years preceding the malaria outbreak, and that relapses of malaria had been noted among these immigrants, and he rightly attributes the epidemics in both islands to an increase in the anopheline factor.

Now, in the Seychelles and the Island of Rodriguez, which are in the Indian Ocean and adjacent to Mauritius, very few, if any, anopheles are found, and these islands enjoy a freedom from both blackwater and malaria, although the other diseases that obtain in Mauritius and Reunion prevail in them also. Communication between all these islands is frequent, and if blackwater were due to a specific organism other than the malarial parasite, and spread by extension, it would be difficult to explain its absence from the malaria free islands.

In the Gulf of Guinea, and in the islands of Polynesia and Oceania, blackwater fever prevails only in those islands where malaria obtains also. The same is true in the West Indies, and since in all these places other diseases are common in neighboring islands which have similar climatic and meteorological conditions, the evidence in favor of an etiological factor common to both blackwater and malaria is too strong to be denied.

We conclude, then, that there are no places from which, when the following conditions are present, blackwater fever is absent:

1. The presence of a population non-immune against malaria.

2. The prevalence of malaria in such quantity as to produce an almost constant infection in this population. (With reference to the second proposition, the infection may be continued in a population in two ways; by re-infection, and by relapse, or by a combination of the two. In regions of intense malaria, re-infection is more common, and it is in such places that blackwater prevails with greatest severity.)

3. A large proportion of estivo-autumnal malaria; for the amount of blackwater fever is in direct proportion to the intensity of this variety.

4. The neglect of prompt and continued administration of quinine, especially in primary attacks, to persons non-immune against malaria.

III.

OTHER ARGUMENTS AGAINST MALARIAL HYPOTHESIS.

The presence or absence of malarial parasites in hemoglobinuric fever.— Provided the conditions mentioned are fulfilled, we consider that the etiology of the two diseases, malaria and hemoglobinuric fever, has a common factor in the presence at some time of the malarial parasite. It is asserted by the advocates of the specific hypothesis that many cases of blackwater fever do not at any time present evidence of malarial infection, and that in countries where blackwater is endemic, other diseases also show a large percentage of past or coincident malaria. As far as the Canal Zone is concerned, we have discussed in another place the first of these propositions. Again we urge that particular attention be given to cases that have occurred during a period of several years in the same locality, rather than to isolated cases collected from many places. Cases in which the blood is not examined until after the onset of the hemoglobinuria should not be used as criteria in determining the percentage of positive bloods obtained. For the parasites vanish very quickly from the peripheral blood after the hemoglobinuria has been determined. We believe, however, that a more extensive use of the thick film method will result in finding a greater percentage of positive bloods.

We have shown that when the blood is examined before the blackwater supervenes, a very large percentage of positive bloods is obtained. In our series this percentage was 61, and at the same time the percentage of positive bloods in all cases diagnosed as malaria was 58. If it is urged that we were wrong in some of our diagnoses of malaria in cases followed by blackwater, we reply that it was only in those cases so diagnosed that blackwater occurred. In every instance when the diagnosis of malaria was made, the patient was treated for that disease

before the onset of the hemoglobinuria whether or not parasites were found. It cannot be said that we diagnosed certain cases as clinical malaria after the supervention of the blackwater, for an examination of the case records in Class III, Appendix A, will show that these cases were all under treatment for malaria. Especially in the past three years the physicians in Ancon Hospital have used every effort to diagnose as clinical malaria only those cases in which such a diagnosis is proper. The reasons for this diagnosis, the methods used to obtain it, and the explanation of the comparatively low percentage of positive bloods have been fully discussed elsewhere. That blackwater in Ancon Hospital followed in positive and clinical malarial cases only, *and in no other disease*, evinces that either our diagnosis of clinical malaria was correct, or else we included in this diagnosis some hitherto undiscovered malady, clinically indistinguishable from malaria, and like it, followed sometimes by blackwater fever. We regard this latter surmise as highly improbable.

In the consideration of those cases in the literature in which the blood was negative when examined before the attack, especial attention should be given to the method of examination, the stain used, and to whether or not quinine had been administered. Even if quinine has not been given, and the peripheral blood is examined shortly before the attack, the absence of parasites is not a proof that they are absent also from certain parts of the internal circulation. We have frequently examined the peripheral blood, in cases of estivo-autumnal malaria, on the day of admission, in patients who have had no quinine, and have found no parasites, when later these were demonstrated. In some instances splenic puncture has been used by us in an endeavor to demonstrate parasites, with negative results, when both before and after the puncture parasites were present in the peripheral blood. Even the most careful examination, as is evident from these facts, will sometimes fail to show parasites, and in view of this the small number of cases of blackwater in which the blood has been negative before the attack, although it was properly examined by competent observers, and no quinine had been given, it is of little value as evidence that no malaria was present, when compared with the very large number of cases in which, under similar circumstances, parasites have been found. It should not be overlooked that the immediate presence of parasites is not always necessary for the determination of hemoglobinuria, as is proven by those instances in which the blackwater has occurred in patients who have been taking quinine in doses of thirty grains a day for a period of a week or more. What is essential, as we have pointed out, is that at some time before the supervention of the hemo-

globinuria, the patient be infected with the malarial organism. It is not possible, in any case of blackwater fever reported in the literature, to exclude beyond a doubt a prior or coincident infection with malaria, and in a very great percentage of the cases such infection has been established with certainty. As A. Plehn[3] observes:

> It is not necessary that the fever should be severe in order that the tendency (to hemoglobinuria) should be created. On the contrary, the latent infection is sufficient, and a slight and often scarcely perceptible attack, given the opportunity, operates. Two German marine officers were known to us who were quite free from malarial fever during a year's command on West African coasts who sickened after their return to Germany with malaria, and had severe blackwater.

The possibility of overlooking a prior malarial infection is plainly demonstrated in such instances as Plehn's two cases, and it is obvious that the denial of previous or coincident malaria by a person who has been exposed to this disease and who subsequently develops blackwater, is not of itself *prima facie* evidence that such malaria can be excluded.

An argument, that would be strong if it were sufficiently sustained, against the malarial hypothesis is the reported absence of either parasites or pigment, or of both, at autopsy in cases of hemoglobinuric fever. The preponderance of evidence must be considered in the determination of this argument. The recognition of parasites, when these are few in number, in autopsy preparations requires expert knowledge, such as is attained only by long and continued experience. In these preparations the parasites, except the segmenting and crescent forms, for the most part appear in coccal shapes; when a good stain is not used, their detection is difficult. So that in estimating the value of the testimony relative to the absence of the parasites at autopsy, one must take into consideration the competency of the observers. However, this absence is of no value as evidence against a prior malarial infection; for in our personal experience and in that of others as well, parasites are not seldom absent at autopsy in hemoglobinuric fever when they were present at the onset of the disease.

The presence of malarial pigment at autopsy is of more importance, for this is found much more frequently than are the parasites. In discussing the possibility of its absence the method of search and the competency of the observers must be considered. We have no desire to question either the ability or the skill of those who have reported the absence of this pigment at autopsy in cases of blackwater, but it is just and proper, in the review of this testimony, to give the greater weight to the evidence of those who are the better qualified by practice and experience. We do not know of any place other than Ancon Hospital where so many autopsies are performed with regularity on subjects who have had prior or recent malarial infections. For more

than six years nearly every fatal case of hemoglobinuric fever has also come to autopsy. Surely the experience of our pathologists must be of great value as evidence in considering the relation of malarial infection to hemoglobinuric fever; and to this evidence must be given at least the same weight as to that of observers who do not have similar facilities for such study.

Dr. S. T. Darling, Chief of the Board of Health Laboratory in the Canal Zone, under whose direction the autopsies at Ancon Hospital are performed, informs us that he has not yet failed to find evidence of malarial infection, as shown by the presence of pigment or parasites, in each case of hemoglobinuric fever that has come to autopsy, when such evidence was properly sought for. On the other hand, this evidence is not infrequently lacking when death has not been due to malaria or to hemoglobinuric fever. This refutes the statement that in a malarial locality the organs of most patients dying of any disease would undoubtedly show a few grains of malarial pigment. Darling further states that it is essential to search most carefully *all places* where pigment or parasites may be found; the examination that does not include the liver, spleen, bone-marrow, brain, and especially the portal lymph glands is insufficient, for either pigment or parasites may be found in one of these localities when absent from the others.

From the data given in reports of many of the cases in which pigment was not found it is evident that this thorough search was omitted; in other instances inexperience may account for the negative result. Certainly the findings of Darling have more weight as evidence in this matter than those of occasional observers, however conscientious their work may have been.

We do not, as Craig[1] implies in speaking of the conclusions drawn by Whipple, nor did Whipple himself, "base a belief in the causative relation of a previous malarial infection to hemoglobinuric fever on the finding of a few grains of malarial pigment at autopsy in individuals residing in a malarial locality such as the Isthmus of Panama." The finding of evidence of prior malarial infection in all cases of hemoglobinuric fever at autopsy is but one of the many factors we have demonstrated in the relation between the two diseases. As we have stated, certain evidence for or against the malarial hypothesis is circumstantial; but the testimony in favor of it is so connected, and each part so sustains the whole, that our conclusions are not affected by arguments which, while individually strong, are not supported by mutual agreement.

The association between malaria and other diseases.—Advocates of the specific hypothesis frequently assert that the large percentage of

patients who have hemoglobinuric fever associated with malarial parasites is no evidence of a connection between the two diseases, as a similar proportion of positive bloods would be found in any other disease in a malarial country.

This assumption is incorrect if applied to diseases that occur in the Canal Zone; we were unable to obtain data for other places. It is a matter of common clinical observation in severe infectious diseases such as pneumonia and typhoid fever, that when malarial parasites are present at the onset of the malady, they frequently disappear without the use of quinine. Moreover, there are many of these cases in which quinine has been administered. For this reason we selected amoebic dysentery for comparison, a disease in which the probability of the administration of quinine prior to entrance into the hospital is small, and at the same time is one in which frequent blood examinations for the purpose of differential leucocyte counting are made, so that the chance of detecting occasional parasites would be increased. We are indebted to Dr. W. F. Shaw, of this hospital, for the following figures. He analyzed the findings in 260 cases of amoebic dysentery, which occurred in Ancon Hospital from January, 1905, to January, 1911. In 48 of these, or 18.4 per cent, parasites were found in the peripheral blood, a larger percentage than occurs in any disease other than malaria itself, except blackwater fever. Shaw investigated also 74 cases of liver abscess, another disease in which for the most part very careful blood examinations are made. In 4 of these cases the blood examination was not recorded, in the other 70, parasites were in the blood of 7, or 10 per cent. In 33 cases of typhoid fever that occurred in Ancon Hospital between June and December, 1909, we found parasites in the blood of 4, or 12.1 per cent. The percentage is about the same in tuberculosis,and lower in pneumonia, judging from an examination of the ward registers. We have not had the time necessary to examine the charts in the cases of these latter diseases.

Compared with the figures given above, the 61 per cent of blood examinations positive for malaria obtained in those cases of hemoglobinuric fever that developed in the hospital, and the 23.8 per cent when the blackwater occurred prior to admission, are evidence of the most convincing kind as to the relation between the two disease; and further, this comparison disproves entirely the statement that in a malarial country other diseases will show as high a percentage of parasites in the peripheral blood as does blackwater fever.

Malaria and other tropical diseases.—For many years kala-azar was regarded as a form of malarial cachexia. Giles, in 1889, because he found uncinaria ova in the stools of nearly every case that he investi-

gated, attributed the disease to infection with this organism. For these reasons, the advocates of the specific hypothesis assert that since the evidence in favor of the malarial etiology of hemoglobinuric fever is no greater than was the evidence in favor of malaria as a cause of kala-azar, or that of uncinariasis as a factor in the same disease, the confusion as to the etiology of kala-azar should serve as a warning to those who would attribute blackwater fever to malaria.

This is probably the weakest argument hitherto advanced against the malarial hypothesis, in that the analogy therein is entirely at fault. As soon as an effort was made to distinguish between malaria and kala-azar by means of comparative epidemiology, it was shown at once that the two diseases must have a different etiology. Rogers,[31] when he first investigated kala-azar, concluded that the epidemic cases which he saw in Assam could not be differentiated clinically from the sporadic cases seen elsewhere in India, and he attributed these epidemic cases to malaria, because he, and most of the other observers in India, regarded the sporadic cases as malarial. It is no more than just to add that Rogers had grave doubts, however, as to whether malaria really was the cause of kala-azar. Since most of his investigations, especially the blood examinations, were made in the most malarious parts of Assam, it is not singular that he was at fault in his conclusions.

But the researches of James[32] soon showed the error of assigning a common etiology to the two diseases on the ground of clinical resemblance and the finding of malarial parasites to some extent in kala-azar. This observer, as he says in his report, employed a mode of investigation essentially different from that adopted by previous workers. These studied kala-azar from the clinical resemblance between it and malaria; he worked along the line that if kala-azar were a form of malarial fever, because it is a severe and fatal form, it should occur for the most part in intensely malarial districts; and if it were endemic in localities free or nearly free from malaria, then it could not be due to this disease. His researches were brilliantly successful, for he demonstrated that kala-azar was as prevalent in places where the malarial endemic rate was high as in those where it was low or *nil*, and he showed also that the converse was true, for he found places where malaria prevailed extensively that were free from kala-azar. Moreover, he made the important observation, that there was an agreement of opinion, amidst a conflict of statements and views, that natives who had lived all their lives in the same localities, were as liable to kala-azar as were newcomers.

As for the hypothesis of Giles, Dobson[33] showed shortly after this was advanced that uncinariasis was as prevalent among those who

suffered from other diseases, and among those who were healthy, as it was among those who had kala-azar.

From this evidence it would appear that the testimony concerning the malarial etiology of blackwater fever is of an entirely different kind from that on which was based either the malarial or uncinarial hypothesis as to the etiology of kala-azar, since the former comprehends not only the association of the two diseases, the finding of malarial parasites in them, and the geographical distribution, but includes also an epidemiological study, and a comparison with other maladies.

No tropical disease other than blackwater fever corresponds to the distribution of intense malaria. Dengue, yellow fever, sleeping sickness, and kala-azar are absent from some parts of the world where hemoglobinuric fever is common. Except yellow fever, each of these diseases is as fatal among the residents as among new comers, and there is nothing whatever in the epidemiology of any one of them that would suggest a dependence upon malaria. Uncinariasis is as common among those who are susceptible to blackwater as it is among those who are immune, and the same may be said of amoebic dysentery. For example, the natives of the Canal Zone, who are practically immune to hemoglobinuric fever, are heavily infected with hookworm, while among European laborers both diseases prevail.

The presence or absence of a specific hemolysin in hemoglobinuric fever.—It is true, as Craig[1] affirms, that an hemolysin has not yet been demonstrated in hemoglobinuric fever. But as far as we are aware, neither has one been isolated in malaria. And no one who has witnessed the greater loss of red blood cells that follows a paroxysm of tertian malaria, than follows a paroxysm of estivo-autumnal or quartan when the parasites are more plentiful than in tertian, can doubt that some cause other than the mechanical destruction by the parasites destroys the erythrocytes. After a paroxysm due to any of the species of the malarial parasite, the loss in red blood cells is greater than the per cent of infected erythrocytes, but this is particularly true in tertian infections. We have seen a loss of 25 per cent of the red blood cells follow a tertian paroxysm in which not one erythrocyte in fifty was infected, and have witnessed a loss of less than 10 per cent in heavier estivo-autumnal infections. The total loss, however, is greater in the end in estivo-autumnal and quartan infections, because these relapse more readily, and are, as a rule, of longer duration.

Similarly the very great loss of red blood cells in most cases of blackwater is out of proportion to the number of the malarial parasites. It is quite true that the presence of a specific organism similar to the

piroplasmata would explain this loss, but evidence in favor of such organism, except in this particular instance, is lacking in every respect, as we have shown throughout this paper; while the hypothesis of an hemolysin, due in some manner to malarial infection, explains equally as well as does the specific hypothesis the blood destruction, and moreover, has the advantage of the testimony and analogy. The hemoglobinuria of diseases due to bacterial poisons certainly is not referred to organisms other than those associated with the maladies, and is attributed, not to the action of the bacteria themselves on the red blood cells, but to hemolysins formed by the bacteria in the course of the diseases. We have shown previously that in the production of cytolysin, specific toxin, and hemolysin the metabolic processes of malarial parasites are directly analogous to those of bacteria; and it is not unreasonable to suppose that the former under certain conditions can produce an hemolysin of sufficient potency to determine a hemoglobinuria of any degree.

Epidemics of hemoglobiniric fever.—These have all occurred on the introduction of non-immunes into a region of intense malaria, and for the most part prior to the use of any prophylactic methods against this disease. In modern times, as we have demonstrated, hemoglobinuric fever is controlled by anti-malarial prophylaxis; if, then, blackwater is not dependent on malaria for its etiology, how can the proportion between the two diseases, which varies directly according to the amount of malaria among persons non-immune against this disease, be explained?

CONCLUSIONS.

The history of hemoglobinuric fever proves that the symptomatology of the disease was recognized and recorded prior to the time when the malady was distinguished either as an entity or as a symptom-complex of malaria. There is no proof that blackwater fever has spread from one country to another, or from one part of a country to another, as have kala-azar, yellow fever, and sleeping sickness. On the contrary, the disease invariably manifests itself when certain conditions relative to the epidemiology of malaria, and to that of no other disease, are present. These conditions are:

1. The presence of a population non-immune against malaria.
2. The prevalence of malaria in such quantity as to produce an almost continuous infection in this population.
3. A large proportion of estivo-autumnal malaria; because the amount

of blackwater fever is in direct proportion to the intensity of this variety.

4. The neglect of prompt and continued administration of quinine, especially in primary artacks, to persons non-immune against malaria.

In every locality, without exception, where these conditions obtain, hemoglobinuric fever is found.

The conditions may vary from time to time in the same or in different localities, with a corresponding increase or decrease in the amount of hemoglobinuric fever. They are present in restricted areas and absent from those contiguous. When any condition varies, hemoglobinuric fever varies in proportion. In this respect the malady differs from every infectious disease other than malaria, for it does not enter a hitherto non-malarial district except by the introduction of estivo-autumnal malaria; when this malaria becomes prevalent in a region formerly free, blackwater fever follows in proportion to the intensity of malaria and the capacity of the population to acquire immunity. Also, estivo-autumnal malaria may obtain very extensively among children when in places where the adult population, by reason of continued attacks in childhood, has acquired immunity. If non-immunes do not enter such places, or if, after entrance, prompt prophylactic and therapeutical measures are instituted against malaria, blackwater fever does not prevail.

These propositions are supported by positive evidence, and do not admit of controversy. Every statement made in support of them has concrete facts and the witness of authoritative observers as its basis. The conditions necessary for the generation of hemoglobinuric fever explain clearly why the disease is absent from places where it once prevailed, or is present in those from which it was formerly absent; why it occurs in some malarious countries and not in others; why it obtains in certain areas only in a malaria infected district; and why in restricted localities, or even in certain houses, the malady may present itself, while those adjacent are free.

Although the evidence associating hemoglobinuric fever with the presence of malarial parasites is circumstantial, since it relies in great part on the skill and experience of observers, it is none the less strong and authoritative, in actuality far more so than that which implies a lack of such association. Notwithstanding the reported absence in isolated instances of proof of malarial infection in blackwater fever during life or at autopsy, the connection between the two is not materially affected thereby; for when all circumstances of the relationship are considered in their entirety, the dependency of the latter upon the former is manifested to an extent unparalleled in the etiology of in-

fectious diseases. When to the epidemiological evidence of this relationship is added these proofs: that in no other malady is malarial infection so constantly present; that in malarious countries other diseases fail to show even an approximate amount of such infection; that mechanical and therapeutical measures instituted against malaria are equally efficient against hemoglobinuric fever; that prompt and efficient treatment against the one, no matter how greatly it obtains, is successful also in reducing the prevalence of the other; either the truth of the relationship as asserted must be admitted, or the existence of an organism dependent upon the conditions enumerated must be assumed. Such an assumption is not supported in biology, either by analogy or fact, unless some vague conjecture of an improbable symbiosis be so included.

Throughout our thesis we have referred to hemoglobinuric fever as a disease, or else have used a synonomous term. We have done this, partly in deference to the present custom, and partly to avoid ambiguity. In our opinion it is better to describe hemoglobinuric fever, as Marchiafava and Bignami have done, as "a syndrome which is encountered not rarely, especially in hot climates, in the course of a malarial infection." For, although medical usage may sanction in some instances the classification of different conditions dependent upon the same etiological factor as distinctive "diseases," there is no need for such application to the description of the hemoglobinuria and associated symptoms that "occur in the course of a malarial infection."

Unlike some writers, we do not find difficulty in calling blackwater fever a syndrome. It is not necessary to assume that all malarial infections of a certain intensity are followed by hemoglobinuria; because, for such determination an individual predisposition is necessary. In most cases, but not in all, this predisposition is enhanced by repeated attacks of malaria. That is why regions of the most intense malaria produce the most blackwater fever; for the chances of very susceptible persons becoming infected with malaria are thereby made certainties, while the likelihood of determining a predisposition in less susceptible persons is correspondingly increased. Except in localities where malarial infection and repeated re-infection and relapses are continuous, hemoglobinuric fever is comparatively rare, but it is not more uncommon than are the comatose and algid types of malaria, or any one of the syndromes depending upon interference with the functioning of the nervous system, such as a paralysis or a neuritis. These, like hemoglobinuric fever, may occur at any time in the course of a malarial infection, especially in an untreated or improperly treated one, and do occur most often where malaria is most intense.

Since it is not possible to predicate the amount of infection that results in the determination of any of these other malarial syndromes, otherwise than to say that they occur in proportion to the intensity of malaria, it is illogical to assert, as some have done, that blackwater fever should invariably follow when a certain degree of personal malarial infection has been attained. One might as well say that every infection with *B. tuberculosis* is followed by the same symptoms; or that meningitis ensues when a certain number of the diplicocci of pneumonia are present.

We know that when such organisms localize in certain parts of the body, definite symptoms follow, and we believe that under certain conditions the toxins of malarial poison produce hemolysis; but why some persons are thus acted upon while others with equal amounts of infection are not, is a problem that still awaits solution, nor does our lack of knowledge in this respect affect our cognizance of the primary cause.

The primary cause in hemoglobinuric fever, is either prioror coincident malaria, or both, the immediate cause is sometimes the administration of quinine, but this never acts unless the primary cause has been or is present. With this knowledge we are able to treat the syndrome intelligently, and often to prevent its occurrence, by the removal of the primary cause; and by sending away from the source of infection those who, since by reason of personal idiosyncrasy they cannot take quinine at any time without the production of blackwater fever, should not remain in a malarious country.

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