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THE MALARIAL FEVERS,

HAEMOGLOBINURIC FEVER

AND

THE BLOOD PROTOZOA OF MAN

BY

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ILLUSTRATED BY FOUR COLORED PLATES
TWENTY-FIVE CLINICAL CHARTS
AND TWENTY-EIGHT PHOTOMICROGRAPHS AND DRAWINGS

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OF

THE MEDICAL CORPS

OF THE

UNITED STATES ARMY,

THIS BOOK IS AFFECTIONATELY

DEDICATED BY THE AUTHOR

PREFACE.

While several excellent works dealing with the laboratory side of the subject have appeared within recent years, no complete treatise upon the malarial fevers has been printed in English since the author's work entitled "The Aestivo-autumnal (Remittent) Malarial Fevers," published in 1901. Thayer's excellent monograph upon this subject in Allbutt and Rolleston's "System of Medicine" and the author's in Osler's "Modern Medicine" consider the subject but briefly from necessity, and the many important discoveries made in the etiology of these fevers, and the advances made in the prophylaxis of malarial disease during the past ten years are such as to justify us in the publication of the present work. The author has endeavored to record in this work all important advances and facts of interest to the student and clinician, and to this end has consulted a mass of literature, the most important papers being noted in the literary reference found at the end of each chapter. For many of these references I am indebted to the extensive bibliographies in Thayer and Hewetson's "Malarial Fevers," of Baltimore, and Zieman's monograph upon malaria in Mense's "Handbuch der Tropenkrankheiten." In every case the author has tried to give proper credit for the observations quoted, and if he has failed it has not been intentionally.

The work is very largely the result of personal experience gained in the United States military hospitals in this country, Cuba, and the Philippines, and, as such, embodies the results of over ten years of investigation, and the study of thousands of cases of malarial fever. The importance of a thorough understanding of malarial disease cannot be overrated, and with the acquisition of the Philippine Islands and of Porto Rico it is more imperative than ever that the American physician be able to distinguish these fevers, and properly treat them. The author has never changed his opinion that infinite suffering could have been avoided and scores of lives saved in our camps during the Spanish War had our physicians been thoroughly familiar with the malarial fevers, especially the aestivo-autumnal infections. Further experience has only confirmed his opinion that every physician practising in malarial localities should be able to recognize the malarial plasmodia in the blood and that blood examinations should be relied upon in the diagnosis of malarial disease.

In addition to the consideration of the malarial fevers, the author has thought it best to add chapters treating of haemoglobinuric fever and the blood protozoa of man. While he is of the opinion that haemoglobinuric fever is a disease *suis generis*, the fact that it occurs in malarial regions and often compli-

cates malarial disease renders a consideration of the condition necessary in any complete work upon the malarial fevers. The chapters dealing with the blood protozoa have been included in order to make the work complete as regards the examination of the blood, of so much importance in the diagnosis of malaria. As the protozoa described occur in regions in which the malarial fevers abound and as these organisms might be found in the blood while examining this fluid for the plasmodia, the author deemed that a brief description of the blood protozoa of man would prove of service in a work devoted primarily to the malarial fevers.

The author would indeed be ungrateful were he to omit expressing his gratitude to the many officers of the Medical Corps of the United States Army, who have aided him, directly or indirectly, in the preparation of this work. Brigadier-General George H. Torney, Surgeon-General, U. S. Army, has, by his support and encouragement, placed the author under many obligations, which he can never hope to repay, but which are here thankfully acknowledged; to Major-General Robert M. O'Reilly, and Brigadier-Generals Sternberg and Girard, the author is indebted for opportunities afforded for the study of the malarial fevers; to Colonels G. B. Girard and Byrne, and Lieutenant-Colonels Richard, Crosby, Carter, and Harris, the author's thanks are due for encouragement and assistance. The author also desires to express his gratitude to Colonel Wm. B. Leishman, of the Royal Army Medical Corps, to whom he is indebted for literature and specimens, and to Professor Novy, of Ann Arbor, for many favors.

The photomicrographs were taken at the Bureau of Science, in Manila, and to this institution, and its director, Dr. Paul Freer, and the director of the biological department, Dr. Richard P. Strong, the author desires to express his gratitude and appreciation. It is the earnest hope of the author that this volume may be of value in the elucidation of the fevers of tropical and subtropical countries.

CHARLES F. CRAIG.

New York, April 10, 1909.

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PART I.

THE ETIOLOGY OF THE MALARIAL FEVERS.

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CHAPTER I.

Synonyms; Definition; Historical; Geographical Distribution of the Malarial Fevers.

Synonyms.—ENGLISH: Intermittent and Remittent fevers, Tertian, Quartan and Aestivo-autumnal fevers, Estivo-autumnal fever, Paludal fever, Climatic fever, Ague, Marsh fever, Jungle fever, Coast fever, Mountain fever, Hill fever, Swamp fever, Cold fever, Paludism, Gnat fever, Haemamoebiasis, Cameroon fever. GERMAN: Wechselfieber. DUTCH: Koorts. FRENCH: Paludisme, Fièvre paludiene, Maladies palustres, Febbre intermittente, Fièvre pernicieuse.

Definition.—By the term "the malarial fevers" we mean a group of specific fevers due to infection of the red blood-corpuscles of man by closely related animal parasites belonging to the Protozoa, class *Sporozoa*, genus *Plasmodium*.

Zoologically considered, the malarial parasites belong to the Protozoa, class *Sporozoa*, order *Haemosporidia*, genus *Plasmodium*. From a biological standpoint the name *Plasmodium*, given by Marchiafava and Celli as a generic term for the organisms causing the malarial fevers, is most unfortunate, as they are not inhabitants of the blood plasma exclusively, but pass the greater portion of their life cycle in man within the erythrocytes. For this reason the generic name, *Haemamoeba*, suggested by Grassi, is preferable, but the term "*Plasmodium*" will have to be retained because of the law of priority.

The same objection may be raised to the name "malarial" first used by the Italians, and meaning "bad air." This term was applied to these fevers because of the supposed relations of miasmatic conditions to their causation, but in the light of our present knowledge of the etiology of this class of fevers, the name is erroneous and, according to some writers, should be abandoned. However, the name has become so firmly established in medical nomenclature that, in the opinion of most authorities, it will have to be retained.

The malarial fevers occur epidemically or endemically and are accompanied by a symptom-complex, which is more or less characteristic of each variety. Periodicity is one of the most marked clinical phenomena, and is due to the growth and sporulation of the plasmodia. All varieties of malaria are distinguished by yielding to quinin, which is also the most efficient of prophylactics. Biologically, the malarial fevers may be divided into tertian, quartan, and aestivo-autumnal; clinically, into intermittent, remittent and continuous, but the latter classification is not scientific as it does not indicate disease entities, but only the type of fever which may be present. The malarial fevers are all transmitted by mosquitoes belonging to the *Anophelinæ*, and as far as we at present know this is the only method of transmission.

Historical.—The history of the malarial fevers may be divided into four periods, as follows:

First Period. From the earliest historical time to the discovery of cinchona bark.

Second Period. From the discovery of cinchona bark to the discovery of the plasmodia.

Third Period. From the discovery of the plasmodia to the discovery of the method of transmission by the mosquito.

Fourth Period. From the discovery of the method of transmission to the present time.

First Period.—It is more than probable that the ancient Egyptians possessed some knowledge of what are now termed the "malarial fevers," for, according to W. Groff, the annual recurrence of malaria is indicated in inscriptions upon the temple ruins at Denderah. In the fifth century B. C., Hippocrates gave a clear description of these fevers, distinguishing them from other continued fevers and dividing them into tertian, quartan, quotidian, and semitertian. He recognized that the malarial fevers are most frequent in the summer and autumn and in the vicinity of bodies of water. Celsus, in the first century A. D., distinguished the pernicious forms of malaria, as well as the forms described by Hippocrates. His description of the malignant tertian fever proves beyond doubt that this form of malaria was well known at the time he wrote. He says:

> "But of tertians there are two sorts. One commencing and terminating like the quartan, with this difference only that it affords one day's interval, and returns on the third; the other, far more dangerous, returning, it is true, on the third day, but generally occuping by the accession six-and-thirty out of the forty-eight hours, sometimes even more or less; nor does it entirely subside in the remission, but only becomes mitigated."

Varro, Columella, Avicenna, and Palladius all described the forms of malarial fever observed by them, and regarded the emanations arising from swamps and the swarms of minute animals present in swamp water as probable causes of certain forms of malaria. During the years of Roman sovereignty enormous aqueducts were constructed and drainage works undertaken for the sole purpose of rendering Italy free from the terrible scourge of malaria, and that many of these operations were successful is proven by the ruins of once populous cities in localities which to-day are uninhabitable on account of the prevalence of these fevers.

During the darkness and superstition of the Middle Ages no additions were made to our knowledge of malaria and it was not until the middle of the 17th century, when cinchona bark was introduced into Europe, that an impetus was given to the study of these fevers.

Second Period.—Cinchona bark was introduced into Europe in 1640 by the Viceroy del Cinchon, who had observed its action in Ecuador in natives, and Europeans suffering from malaria. The introduction of this drug greatly stimulated the study of the malarial fevers, as by its use it was possible to distin-

guish these fevers from other diseases, and to Morton, Sydenham, Lancisi, and Torti, we owe much of our knowledge regarding the clinical symptoms of these fevers. Morton, of London, in 1697, described minutely the pernicious fevers of malarial origin, recognized the specific action of cinchona bark, and believed that the emanations from swamps and marshes had much to do with their causation. Lancisi, in 1717, published an elaborate study upon the etiology of the malarial fevers, in which he considered that they were due to inorganic and organic substances found in the air of marshy districts, and even suspected that insects, such as mosquitoes, might transmit these fevers. In 1723, Sydenham described the intermittent forms of malaria and recognized the specific action of cinchona. Torti, in 1753, published a classical treatise upon these fevers in which, for the first time, the term "malaria," destined to distinguish these infections, was used. Meckel, in 1847, described the pigmented leucocytes so often observed in malarial blood, while Frerichs and Virchow confirmed his results. It is very probable, from their descriptions, that the latter investigators actually saw the malarial plasmodia, but did not recognize their true nature.

With the perfection of the compound microscope there was rendered visible to the eye of man a hitherto invisible world of living creatures and a new era began in the study of the etiology of disease. While the theory that the malarial fevers might be due to parasitic infection was very ancient, Varo, (B. C. 129-118) having conjectured that the cause might be minute animal life in some form, the only observer who had definitely declared his belief that invisible organisms were the cause of malaria was Lancisi, and it was not until 1849, when J. K. Mitchell suggested that certain spores occuring in marshy districts might be the etiological factor, that attention was forcibly directed to the relation micro-organisms might bear to these fevers.

Following Mitchell's suggestion, Salisbury, in 1866, described certain small vegetable cells of the family *Palmella*, which he found in the soil of malarial localities upon the banks of the Ohio and Mississippi Rivers, and which he believed to be the cause of malaria. He claimed that these spores rose into the air at night and fell to the ground at sunrise, thus explaining the danger of night air, and the inocuousness of the air during the day in malarial regions. He also claimed to have demonstrated the same spores in the urine and perspiration of persons suffering from malaria, and for a considerable period his observations were accepted, and the spores of *Palmella* were regarded as the cause of these fevers.

In 1879, after the results of Salisbury had been shown to be erroneous, Klebs and Tommasi-Crudeli announced their discovery of the *Bacillus malariæ*, a bacillus found in the water and soil of malarious regions, capable of cultivation upon ordinary culture media, and producing, when injected in man, in pure culture, undoubted symptoms of malarial infection. The observations of these investigators, while never confirmed by careful workers, were accepted as true by a large proportion of the scientific world, and such authorities as

Marchifava and Cuboni claimed to have found this bacillus in the blood of their malarial patients. The final discovery, in 1880, of the true cause of malaria, although not generally admitted until 1884, proved that the bacillus of Klebs and Tommasi-Crudeli stood in no causative relation to the malarial fevers, and affords us an illustration of the fallibility of human judgment in scientific research.

THIRD PERIOD.—In 1880, Laveran, a French army surgeon, working in Constantine, Algeria, described certain parasites occurring in the blood of malarial patients which he considered to be the cause of the disease. His first communication was made to the Academy of Medicine in Paris, and was followed in 1881 by a more detailed description of the organism. He described three forms of the parasite. The first consisted of oval or crescentic bodies with hyaline protoplasm containing pigment, arranged either in clumps or in a wreath-like form. This was undoubtedly the crescentic form of the aestivo-autumnal plasmodium. The second form described consisted of small hyaline bodies containing pigment, and from these bodies there arose occasionally long, thin, hyaline filaments which possessed the property of motion. This form was undoubtedly the flagellate form of the plasmodium. The third form described by him consisted of spherical, slightly granular bodies, with motionless pigment, which were evidently degenerative forms of the two foregoing classes.

Richard, a French army surgeon serving at Philippeville, Algeria, confirmed Laveran's discovery, and recognized the young, hyaline, intracorpuscular plasmodia, but for over four years Laveran's plasmodium was regarded with but little scientific interest, the bacillus of Klebs and Tommassi-Crudeli being believed to be the true cause of the malarial fevers. However, in 1885, Marchiafava and Celli described carefully the hyaline intracorpuscular parasites and proposed the name "*Plasmodium malariæ*" for the organisms. In the same year, Golgi proved that quartan malaria depended upon a specific form of the plasmodium, and shortly afterward he demonstrated and described the parasite causing tertian fever. He also called attention to the probably distinct type of the crescentic and ovoid forms of the plasmodium, and to him we owe the discovery that the malarial paroxysm always coincides with the segmentation or sporulation of a group of parasites. Occurring every forty-eight hours, the segmentation causes a tertian fever, while if it occurs every seventy-two hours a quartan fever results. Marchiafava and Celli had been strong supporters of the bacterial causation of the malarial fevers, and when, in 1885, these authors admitted that they were mistaken, and, although they had previously regarded Laveran's parasites as degenerative changes in the red blood-corpuscles, became enthusiastic advocates of their parasitic nature, their descriptions of the plasmodia attracted wide attention, and were soon confirmed by numerous observers, as Councilman and Abbot, Sternberg, Osler, Dock, Grassi and Feletti, Antolisei, Bastianelli and Bignami, Mannaberg, and many others. During this period the morphological structure of the plasmodia was carefully

studied, and from this study of the morphology of the plasmodia there arose two distinct schools, one believing in the unity of all forms of the plasmodia, the other believing that the plasmodia of malaria are divided into distinct species. The first school, represented by Laveran, believes that the malarial plasmodium is a single organism occurring in many forms; while the second school believes that there are several species of plasmodia, each producing its characteristic type of fever, and each easily distinguished by differences in morphology and in its life cycle.

The minute study of the plasmodia resulted in the description of the life cycle of all the species, and the demonstration of the occurrence in the blood of certain forms, spherical, ovoid, and crescentic in shape, that did not sporulate, but under favorable conditions became flagellated, the nature of which was vainly guessed at until it was shown that these forms were intended to continue the life of the plasmodia outside of the human body. Although by Laveran's great discovery the diagnosis of malaria was placed upon a scientific basis, but little was known regarding the means of transmission of the plasmodia; while Gerhardt, Mariotti, Marchiafava, Celli, Bignami, Bastianelli, Baccelli, Sacharov, Elting, and others had proved that the malaria fevers may be transmitted by direct inoculation from man to man, and that the type of paraseti injected is found again in the blood of the inoculated individual, yet until the researches of Ross we possessed no definite knowledge of how infection occurred in nature or of the life cycle of the plasmodia outside of the human body.

Fourth Period.—To the brilliant work of Ross, Bignami, Bastianelli, and Grassi the world is indebted from the elucidation of the method of transmission of the malarial fevers. That malaria may be transmitted by insects is by no means a modern conception, for Varro and Columella both suggested that these fevers might be transmitted in this way, while Lancisi mentioned the mosquito as an agent in the spread of the disease. In more modern times Nott (1848) considered this method of transmission as already proven, and King (1882) advocated the same method of transmission and adduced some evidence in its support. In the Goulstonian lectures of 1894, Manson elaborated the theory of mosquito transmission, awakening renewed interest in this phase of the study of malaria. In 1895, Ross of the Indian Army Medical Service studied the changes occurring in the aestivo-autumnal plasmodia within certain species of mosquitoes, and in 1897 observed the encysted forms of these plasmodia within the stomach wall of mosquitoes of the genus *Anopheles*. Ross continued his observations upon birds infected with *Halteridium*, the parasite of avian malaria, demonstrating that in *Culex fatigans* which have bitten infected birds, the parasites become encysted in the stomach wall, and undergo a series of developmental changes resulting in the formation of multitudes of sporozoites which accumulate in the cells of the salivary glands and reinfect susceptible birds when the insect bites. MacCallum, in 1898, studying the same parasite, observed that two forms of the fully developed halteridium occurred in the infected birds, one of which is

flagellated and the other non-flagellated. He observed that the flagella, breaking away from the flagellated form, penetrated the non-flagellated organisms, and after penetration a motile body resulted which moved about among the blood-corpuscles. Later he observed the same phenomena in studying the aestivo-autumnal parasites, and considered that this process was one of fertilization. MacCallum's researches have been confirmed by Bastianelli, Bignami, and Grassi, who, working with the parasites of human malaria and with mosquitoes of the genus *Anopheles*, have demonstrated that fertilization occurs in the stomach of the mosquito and is followed by encystment in the stomach wall. Their observations proved that the plasmodia undergo the same developmental cycle in *anopheles* mosquitoes that the *halteridium* undergoes in *Culex fatigans*.

In 1898, Bignami was successful in producing an attack of aestivo-autumnal malaria in man by allowing mosquitoes which had bitten an infected individual to bite a patient who had never had malaria. In the same year, Bastianelli, Bignami, and Grassi were successful in producing a double tertian infection in man by the bites of infected *Anopheles*. In February, 1899, they were for the first time successful in infecting *Anopheles maculipennis* with quartan parasites, and traced the developmental stages of this organism in the mosquito. They were also successful in producing aestivo-autumnal malaria by the bites of infected mosquitoes. These results have been confirmed by numerous observers and prove beyond question that the malarial fevers are transmitted by mosquitoes and that there are at least three species of malarial plasmodia.

Geographical Distribution.—The malarial fevers are world-wide in their distribution, but certain localities are entirely free from malarial infection. In the Eastern hemisphere such infections are rare above 62° N. Latitude, while in the Western hemisphere they are but rarely found above 45° N. Latitude. They are most common and most severe in low-lying coast regions, mountainous countries being comparatively exempt. The deltas of large rivers, especially the rivers of tropical countries, are hot-beds of malarial disease, and this is also true of all bodies of water situated in such localities. As we approach the equator we meet less often with the benign forms of malarial infection, the prevailing types being the severe and often fatal aestivo-autumnal infections.

While the aestivo-autumnal fevers are thus more strictly bounded as regards distribution than are either the tertian or the quartan forms of malaria, they are yet so widely spread as to make their recognition of the first importance to American practitioners, for they not only occur in the semi-tropical regions of the United States, but are very prevalent in our colonial possessions, such as the Philippine Islands and Porto Rico and along the line of the Panama Canal. In these regions the aestivo-autumnal fevers are endemic, and have proven to be the greatest obstacle to colonization by the white race. Malaria is a greater foe to civilization in the tropics than is any other one factor, and Koch justly says: "Malaria is met with everywhere; the officer in his bureau, the traveler in the

interior, the soldier upon the march, all must recognize that soon or late they are to become the victims of malaria."

The distribution of the malarial fevers depends upon the presence of mosquitoes belonging to the Anophelinæ; the presence of infected individuals; proper climatic conditions as to temperature and moisture; and susceptibility of the individual bitten by infected mosquitoes to malaria. Unless all of these factors be present the malarial fevers will not be found except as imported cases, and the country so fortunate as to be thus unsuitable to the propagation of malaria will remain free from the disease. The presence of species of the Anophelinæ does not presuppose the existence of malaria, as some of the Anophelinæ are incapable of transmitting malaria, while even in localities where the right species are present no malaria will be found unless an infected individual has entered the district and infects the mosquitoes.

Given all of the factors mentioned, the malarial fevers may be endemic in certain regions, or may become epidemic in regions ordinarily free from such infections. Extensive pandemics of malaria are described by many writers, one of which, in 1558, covered all of Europe, while many epidemics have occurred, the last between 1866 and 1872, spreading over much of Europe and a large portion of India and North America. Local epidemics of malaria are often observed in places which may have been free from infection for many years. An instance of this kind occurred under my observation in a city in Connecticut. Some years before the Spanish-American War this city occasionally reported the presence of tertian malarial fever, but the cases were few in number and no other form of malaria was ever observed. After the return of a company of militia at the close of the war mentioned, several cases of remittent fever were observed which upon investigation were found to be infections with the aestivo-autumnal malarial plasmodia. The introduction of this organism was traced to the returning soldiers, some of whom had suffered from this form of malaria while in Cuba upon special service. In this instance the conditions necessary for the spread of the disease were all present in the city with the exception of the infected individuals; the right species of *Anopheles*, warmth and moisture, and a susceptible people, awaited only the returning soldier infected with the aestivo-autumnal plasmodium, and thus a form of malaria never before observed in the State of Connecticut became prevalent in this city. Such instances could be multiplied and well illustrate the facility with which malaria may be introdcued into localities previously free from these fevers.

The most important places in which malaria is endemic are the following:

North America.—In North America malaria occurs rarely above the forty-fifth parallel. Along the entire Atlantic coast line these fevers are observed, the New England States showing the fewest and the mildest cases, the disease increasing in severity as the Southern States are reached, where the aestivo-autumnal fevers not infrequently result fatally. The most severe forms prevail along the low regions of the southern coast line, and especially in the swamps of the Gulf States. Texas, Georgia, and Florida are badly infected

in some portions with aestivo-autumnal malaria; this form is also common along the southern portion of the Mississippi and its tributaries and there are regions in the delta of the Mississippi that are uninhabitable because of the prevalence of the most deadly forms of aestivo-autumnal infection. Along the Missouri and Arkansas Rivers the malarial fevers are very prevalent, and the disease is common in the States of Mississippi, Missouri, Arkansas, Kansas, Oklahoma, and certain parts of New Mexico. The States of North and South Carolina, Virginia, Maryland, and West Virginia are all infected, but to a less extent. Ohio, Indiana, Illinois, Michigan, Minnesota and Wisconsin are infected with the benign tertian type of malaria, but only in limited localities, and to a much smaller extent than are the Southern States. Of the Western States, Wyoming, Utah, Arizona, and California are more or less malarial, and in the valleys of the Sacramento and San Joaquin in California, pernicious forms of aestivo-autumnal malaria are not uncommon, while the benign tertian infections are very prevalent. The regions about the Great Lakes are almost free from malaria except in certain localities about Lake Michigan and Lake Ontario, while Canada appears to be free from these fevers except in the most Southern portions bordering upon the Great Lakes, and the infections are all of mild character.

Almost all of the islands of the West Indies are badly infected with the malarial fevers, especially Cuba, where aestivo-autumnal malaria is most prevalent and fatal in character. Barbados and St. Vincent are said to be free from malaria, and in Porto Rico the benign intermittents are the most common forms observed.

Mexico and Central America are hot-beds of the most deadly forms of aetsivo-autumnal infection, and the low-lying coast lines of these countries are among the most dangerous of the lurking places of this form of disease. The dreaded Chagres fever of Panama is a form of aestivo-autumnal infection, and, together with yellow fever, compelled the French to abandon the digging of the Panama Canal.

In South America malarial infections are common in the northern part of Brazil, in Uruguay, Paraguay, Bolivia, Venezuela, Guiana, and Colombia. The Argentine Republic, Peru, and Ecuador suffer less from malaria, but all are infected.

Europe.—Great Britain may be said to be entirely free from malarial infection, imported cases being the only ones observed in that country. In Germany, malarial infections occur along the coast of the Baltic, and they are not uncommon in the swamps of Hanover and Westphalia, and along the Rhine and its tributaries. In Holland and Belgium malaria is endemic in the river bottoms and in marshy regions. In France these infections occur along the Loire and Rhone, the West Coast, the river Brenne, and the Sologne. In these regions only the benign forms are observed, and this is also true of the malaria of Germany.

In Spain the valleys of the Tago and the Quadalquivir are infected, and

pernicious forms occur in all the countries bordering upon the Mediterranean; in Greece, Crete, Italy, Sicily, and Turkey, aestivo-autumnal infections are common, as are also the tertian and quartan fevers; in Italy, especially, occur the most malignant forms in the regions around the Roman Campagna and the Pontine marshes, as well as in the valley of the Po and along the entire West Coast. Sardinia and Corsica are also infected with the pernicious forms of aestivo-autumnal malaria. In Austria-Hungary malarial infections are present in Galicia, in the valley of the Danube, and along the Adriatic. In Turkey severe infections occur along the Danube; in Russia malarial infections are prevalent in the valleys of the Volga, Dniester, and Dnieper, and they are also common along the coast lines of the Black and Caspian Seas and the Sea of Azov.

Asia.—Asia Minor, Persia, Arabia, India, and Ceylon, as well as portions of China and nearly all of the islands of the Malay Archipelago are infected with the malarial fevers. The valleys of all of the great rivers, such as the Indus and the Ganges, are heavily infected, and pernicious forms are common; even upon the lofty tablelands of the Himalayas malarial infections are often met with, and the region of jungle country known as the Terai, at the foot of the Himalayas, is considered one of the most dangerous of malarial districts. Java and Sumatra are badly infected with malaria, as are certain parts of Borneo. The Philippine Islands, until quite recently considered as being comparatively free from malaria, have been proved to be badly infected, the islands of Luzon, Samar, Mindoro, and Mindanao showing infection with all the species of malarial plasmodia. In the island of Luzon, the foot hills of the Zambales Mountains and the part of the great Pampangan Plain in the region of the foot hills, are infected with the most pernicious forms of aestivo-autumnal malaria, while there are certain regions in the islands of Samar and Mindoro that are shunned by the natives on account of the deadly malarial infections which are present.

Africa.—In Africa are some of the most dangerous lurking places of malarial infections, the worst areas being those along the West Coast, and the valleys of the Senegal, Congo, and Niger rivers, as well as the regions around the great lakes and the jungles and lake shores of Abyssinia. In Egypt the only infected districts are situated in the delta of the Nile; Tunis, Tripoli, Algiers, the oases of the Sahara, and the East Coast are infected with all forms of the malarial plasmodia, but aestivo-autumnal infections are most common. The islands of St. Helena, the Seychelles, and Rodriguez are free from malaria, and the same is true of Cape Colony, the Orange Free State, and of German Southwest Africa. Madagascar, Mauritius, and Reunion are infected with malaria, pernicious forms occurring in all of these islands. The continent of Australia is free from malaria, as are most of the islands of Polynesia.

The résumé given indicates the most important regions in which the malarial fevers are endemic, but there are numerous districts in which a few sporadic cases occur at rare intervals, but which at any time may become

endemic foci, provided certain species of the Anophelinæ are present, together with individuals harboring the malarial plasmodia. In our own country the return of hundreds of our soldiers from the Philippine Islands infected with the various forms of malaria so prevalent there, especially the aestivo-autumnal, will inevitably result in the infection of localities hitherto free from malarial disease, and unless these infections be promptly recognized, such localities will become endemic foci of the malarial fevers.

A knowledge of the geographical distribution of these fevers is of much practical value, as localities known to be infected can thus be avoided, and those who travel through them, or reside within them, can take the proper precautions to prevent infection. A knowledge of the distribution of these fevers is also of great assistance in the diagnosis of unusual or obscure forms of fever and in the prophylaxis of malaria. The blood of every patient coming from a malarial region should be examined, and if the plasmodia are found, quinin should be administered and the proper measures taken to protect the community from the infection.

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CHAPTER II.

Etiology; Classification of the Parasites of the Malarial Fevers; Morphology and Biology of the Malarial Plasmodia in the Blood of Man.

Classification of the Malarial Parasites.—From the time of the discovery by Laveran of the malarial plasmodia to the present, much attention has been devoted by zoologists to the proper classification of these organisms, and many different opinions have been advanced concerning their exact zoological position. Laveran proposed the name "*Oscillaria malariæ*" for the parasite, but later accepted Osler's name of "Haematozoon." In 1887, Metchnikoff placed the organisms among the Sporozoa, and proposed the name "*Haematophyllum malariæ*" for the malarial parasite of man. To Danilewsky we owe the new division of the Sporozoa into a group known as the *Haemosporidia* in which he placed the malarial plasmodia. The genus "*Plasmodium*" was created by Marchiafava and Celli, and all the plasmodia of man placed in this genus by these authors. At the present time, then, it is conceded by all zoologists that the parasites causing the malarial fevers belong to the Protozoa; order *Sporozoa;* sub-order *Haemosporidia*, and genus *Plasmodium.*

The existence of distinct species of plasmodia associated with equally distinct types of malarial fever has been abundantly demonstrated by many careful observers, and the work of Marchiafava and Bignami, Celli, Grassi, Golgi, and others has resulted in the separation of at least three species of plasmodium, differing in their morphology and life history as well as in the effects they produce in man when blood containing them is inoculated or when infected mosquitoes are allowed to bite susceptible individuals.

Laveran and his followers believe that the parasite producing malarial fever is a polymorphous organism, assuming very great differences in morphology under differing conditions of environment, and that, in Laveran's words, "there does not exist a constant relation between the forms under which the haematozoa appear in the blood and the clinical manifestations of paludism; one can only say that certain forms of the parasite are more often seen in certain cases, the crescents, for instance, in relapses and in malarial cachexia." Some of Laveran's followers even claim to have observed interchangeability of the various species which have been described, but their observations still await confirmation, and the great weight of evidence to-day, both morphological and experimental, is in favor of the existence of several species of malarial plasmodia. The existence of at least three species of plasmodium, the *tertian*, *quartan*, and *aestivo-autumnal*, has been accepted by every investigator in America, England,

Germany, Italy, and in tropical regions, as India and Africa, but considerable uncertainty exists as to the species concerned in the production of the various forms of aestivo-autumnal infection. The Italian authorities, together with nearly every investigator who has studied malaria in the tropics, have made a subdivision of the aestivo-autumnal parasite into at least two varieties, the quotidian and the tertian, and a great amount of labor has been expended in differentiating these varieties and in endeavoring to demonstrate their specific characteristics. From personal experience I have no hesitation in stating that the tertian and quotidian aestivo-autumnal plasmodia can be as easily differentiated as the benign tertian and quartan plasmodia, when suitable material is available for study, and while I cannot accept the existence of a pigmented and unpigmented quotidian aestivo-autumnal parasite, I believe that the aestivo-autumnal infections are produced by two distinct organisms, the quotidian and the tertian aestivo-autumnal plasmodium.

Several of the classifications proposed for the parasites of malaria are of interest and will be briefly noticed.

LABBE'S CLASSIFICATION.—Labbe placed all of the blood parasites belonging to the Protozoa in the Sporozoa, dividing them into two classes: *Haemosporidia* and *Gymnasporidia*, in the latter division placing the malarial parasites of man as well as the *Halteridium* and *Proteosoma* of birds.

KRUSE'S CLASSIFICATION.—Kruse divides the Sporozoa into four orders, placing the malarial parasites in the Gregarinida, sub-order *Haemogregarinidæ;* genus *Plasmodium*, the generic term first given by Marchiafava and Celli.

GRASSI AND FELETTI'S CLASSIFICATION.—These authors placed all of the malarial parasites in two genera: *Haemamoeba* and *Laverania*. In the genus *Haemamoeba*, they mention four species of malarial parasites as occurring in man: *H. malariæ* (quartan), *H. vivax.* (tertian), *H. praecox.* (pernicious), and *H. immaculata* (pernicious). In the genus *Laverania*, they place the crescentic parasites, giving them the specific name "*Laverania malariæ.*" Neither the generic or specific name in this instance can stand, as both were founded upon the belief that the crescents were a distinct species of parasite.

MANNABERG'S CLASSIFICATION.—Mannaberg divides the malarial parasites as follows:

1. Malarial parasites that sporulate, but do not form *syzygies* (crescents).
   a. Quartan plasmodium.
   b. Tertian plasmodium.
2. Malarial parasites that sporulate and form *syzygies* (crescents).
   a. Pigmented quotidian plasmodium.
   b. Non-pigmented quotidian plasmodium.
   c. Malignant tertian plasmodium.

THAYER AND HEWETSON'S CLASSIFICATION.—In their classical work upon the malarial fevers Thayer and Hewetson divide the parasites of malaria into three species, the tertian, quartan and aestivo-autumnal parasites.

SACHAROFF'S CLASSIFICATION.—Sacharoff divides the plasmodia into two

genera, *Haemamoebæ* and *Laverania;* in the first genus he includes three species, as follows:

Haemamoeba praecox (aestivo-autumnal). Grassi.
Haemamoeba febris tertianae (tertian). Golgi.
Haemamoeba febris quartanae (quartan). Golgi.

In the second genus, *Laverania*, he includes one species, characterized by a crescentic shape. In this Sacharoff followed Grassi and Feletti, believing that the crescents were a distinct species of parasite.

ZIEMAN'S CLASSIFICATION.—Zieman divides the malarial plasmodia into four species, the tertian, quartan, pernicious (aestivo-autumnal), and pernicious —varietas Africana.

LÜHE'S CLASSIFICATION.—The classification of Lühe, accepted by many authorities, divides the malarial parasites into two genera, *Laverania* and *Plasmodium*. In the genus *Laverania* he places the aestivo-autumnal parasite, while in the genus *Plasmodium* he places the tertian and quartan parasites, as well as those occurring in warm-blood animals other than man, and in birds. According to Luhe, the three parasites of man should be thus classified:

Genus, *Laverania*.
Species, *Laverania malariae*. Gr. et Fe. 1890.
Genus, *Plasmodium*. Marchiafava and Celli.
Species, *Plasmodium malariæ*. Marchia et Celli. Quartan parasite.
Plasmodium vivax. Gr. et Fe. Tertian parasite.

As has been stated, the generic name "Laverania" can not be retained and the generic name "Plasmodium" should be substituted for it.

SCHAUDINN'S CLASSIFICATION.—The classification of the parasites of malaria most generally accepted by zoologists and students of malaria has been that of Schaudinn, who divided the organisms into three species as follows:

1. *Plasmodium vivax*. Gr. et Feletti. Tertian parasite.
2. *Plasmodium malariae*. Marchiaf et Celli. Quartan parasite.
3. *Plasmodium immaculatum*. Gr. et Fe. Aestivo-autumnal parasite.

The specific name "immaculatum" can no longer be retained, however, for the aestivo-autumnal plasmodium, for Blanchard has shown that Grassi previously used this name for a parasite occurring in birds, thus preventing its use for the human parasite. This fact renders the specific name proposed by Welch "falciparum" the proper name for the aestivo-autumnal plasmodium, and Blanchard's classification, which follows, the most recent and generally accepted of the many which have been mentioned.

BLANCHARD'S CLASSIFICATION.—This classification divides the parasites of malaria into three species, as follows:

1. *Plasmodium malariae*. Marchiaf. et Celli. Quartan parasite
2. *Plasmodium vivax*. Gr. et Fe. Tertian parasite.
3. *Plasmodium falciparum*. Blanchard. Aestivo-autumnal parasite.

While almost all authorities now admit the existence of three species of malarial plasmodia, the tertian, quartan, and aestivo-autumnal, the question of

the existence of more than one species of the latter organism is still an undecided one. By many authorities the aestivo-autumnal plasmodia are divided into two varieties, a tertian and quotidian, while by some the quotidian is subdivided into a pigmented and unpigmented quotidian parasite. Other authorities maintain that there is but one aestivo-autumnal plasmodium, the variations observed in the temperature curve being due to variations in the time of the developmental cycle, which may be 24 or 48 hours in length. Personally, as I have stated, there is no doubt in my mind that the two varieties of this parasite first described by Marchiafava and Bignami, tertian and quotidian, are distinct species and are distinguishable upon both morphological and clinical grounds. I have arrived at this conclusion after the careful study of the plasmodia found in many hundred cases of aestivo-autumnal fever and after years of study of malarial infections in both tropical and temperate regions. These plasmodia can be differentiated morphologically, and the infections produced by them are, when uncomplicated, clinically distinct. Anyone who can differentiate the tertian and quartan plasmodia morphologically should have no trouble in distinguishing between the tertian and quotidian aestivo-autumnal plasmodia if blood from the spleen, obtained by puncture, be examined. To one who has had the opportunity of studying a large number of aestivo-autumnal infections the two parasites can be readily distinguished by the forms occurring in the peripheral blood.

The argument that the tertian and quotidian temperatures observed in aestivo-autumnal malaria are due to the sporulation of a parasite which at one time completes its developmental cycle in the human body in 24 hours and at another time in 48 hours would appear to be illogical, and can as well be used in the case of the tertian and quartan plasmodia by those who still maintain that there is but one species of malarial plasmodium.

I have not been able to demonstrate the existence of a pigmented and an unpigmented quotidian plasmodium as specifically distinct forms, for while it is not uncommon to observe only unpigmented quotidian plasmodia in the peripheral blood upon a cursory examination in aestivo-autumnal infections, the spleen invariably shows pigmented organisms, and, as a rule, an extended search will reveal pigmented organisms in the peripheral blood.

In view of the division of the aestivo-autumnal plasmodia into two species, I would suggest the following classification of the malarial plasmodia:

Division, *Protozoa*.
Class, *Sporozoa*.
Sub-class, *Telosporidia*.
Order, *Haemosporidia*.
Genus, *Plasmodium*.
Species I.—*Plasmodium malariae*. Marchiaf. et Celli. (Quartan malarial parasite.)
II.—*Plasmodium vivax*. Grassi et Feletti. (Tertian malarial parasite.)

III.—*Plasmodium falciparum.* Blanchard. (Tertian aestivo-autumnal parasite.)

IV.—*Plasmodium falciparum quotidianum.* Craig. (Quotidian aestivo-autumnal parasite.)

Morphology and Biology of the Malarial Plasmodia in the Blood of Man.

General Considerations.—The malarial plasmodia are found in man within or upon the red blood-corpuscles and are essentially parasites living at the expense of these cells. In this situation they destroy the red corpuscles, producing the well-known anaemia peculiar to the malarial fevers, together with the pigmentation, or melanaemia, which is due to the destruction of the haemoglobin of the infected cells. Owing to the researches and discoveries of Ross, Grassi, Marchiafava, Celli, and others, it is now necessary in describing the malarial plasmodia to consider the forms present in two life cycles, that within man and that within mosquitoes belonging to the Anophelinæ. The life cycle completed within man, the *intermediate* host, is known as the *endogenous* or *asexual* cycle, and the growth and sporulation of the parasites is called *shizogony;* the cycle completed within the mosquito, or *definitive* host, is known as the *exogenous* or *sexual* cycle, and the process of development of the parasites as *sporogony.* In this chapter will be considered the morphology and biology of the forms of the malarial plasmodia concerned in *schizogony*, together with those forms concerned in *sporogony* which may be demonstrated in the blood of man. Following the classification of Schaudinn the forms observed in *schizogony* are known as the *schizont* and the *merozoite*, the first term being applied to the parasites from their earliest development in the red blood-corpuscles to the time of sporulation, while the latter term is applied to the liberated spore; these forms occur only in the blood of man and are unable to develop *outside* of the human body. The forms of the plasmodia observed in human blood, and which are intended to undergo development in the body of the mosquito, are known as *gametes*, and are sexually differentiated, the female *gamete* being known as the *macrogamete* and the male as the *microgametocyte.* These, in turn, are unable to undergo development *in* the human body, it being necessary that they reach the stomach of the mosquito before further development can occur. Under certain conditions simulating those that are present in the stomach of the insect, the *microgametocytes*, while still present in human blood which has been *removed* for examination, undergo further development and liberate active filaments, the *microgametes*, which penetrate the *macrogametes* and fertilize them; this process occurs normally within the mosquito, but inasmuch as it can be observed in specimens of blood, I shall describe the forms concerned in this chapter, together with the forms concerned in *schizogony.*

All varieties of the malarial plasmodia appear at first within the red blood-corpuscles as hyaline disks or ring-like bodies devoid of motion. The forms which undergo *schizogony* gradually acquire amoeboid motility and develop a certain amount of pigment, at the same time enlarging and encroaching more and more upon the cell containing them. The pigment is derived from the haemoglobin of the red cell which is destroyed by the growth of the plasmodium within it. After a certain period of growth the plasmodia divide into numerous minute spores which are liberated by the rupture of the red corpuscles containing them, and which invade other corpuscles and repeat the process of development briefly described. Among the spores, however, which are liberated at the time of sporulation, there are some that do not undergo *schizogony*, but after penetrating the red blood-corpuscles develop into forms intended to undergo their life cycle within the mosquito. These forms do not sporulate, but grow at the expense of the red cell and are finally found free in the blood plasma from which they escape when the blood is removed by the mosquito. These bodies may be differentiated into two varieties, as has been mentioned, and are incapable of further development in man, although Schaudinn believed that the female form, or *macrogamete*, if not removed from the blood by the mosquito, after a certain period of time underwent parthenogenesis, giving rise to numerous young spores which entered the red corpuscles and developed as in *schizogony*. Schaudinn thus explained the occurrence of relapses in malaria, but his observations still await confirmation.

In describing the malarial plasmodia as observed in the blood of man, I shall describe each species separately, first giving the morphology of the forms concerned in *schizogony*, the *schizont* and the *merozoite*, and then the forms concerned in *sporogony*, which are demonstrable in human blood, namely, the *macrogametes*, the *microgametocyte* and the *microgamete*.

The Morphology and Biology of Plasmodium Vivax (the tertian malarial parasite). *Schizogony* (human or asexual cycle).

Plasmodium vivax or the tertian malarial parasite completes its development in the blood in 48 hours and produces the well-known type of malarial fever associated with a chill and fever occurring upon every second day. This type of malaria is the most common type in temperate regions and in many subtropical and tropical localities, and has been more thoroughly studied than has any other form of the disease. The organism causing this variety of malaria is the most easily recognized of the malarial plasmodia and is the one which should be selected for study by those who desire to acquire proficiency in the recognition of the various stages in the development of the human plasmodia and the forms to be observed in the peripheral blood.

Historical Summary.—The tertian plasmodium was first described as a distinct species by Golgi in 1886. He called attention to differences in the morphology of this plasmodium as compared to the quartan plasmodium, and noted that sporulation occurred every 48 hours instead of every 72, as in the latter parasite. He also called attention to the rapid amoebid motion of this

plasmodium; the light red color of the pigment and the smallness of the grains; the great enlargement of the infected red cells and their rapid loss of haemoglobin; and the difference in size of the two organisms, the tertian when fully grown being much larger than the quartan. He described the greater number of segments or spores in the tertian plasmodium, their smaller size, and irregular arrangement. Golgi stated that a quotidian fever might be due to a double infection with the tertian plasmodium, each group sporulating upon successive days.

The observations of Golgi were soon confirmed by those of Antolisei and Bastianelli and Bignami, and have since been confirmed by every student of this type of malaria.

Unstained Preparations.—The tertian malarial plasmodium, or *Plasmodium vivax*, appears first within the red blood-corpuscle in *schizogony* as a small, non-motile, hyaline disk or "ring," the *trophozoite*, measuring about 2 microns in diameter; its outline is very indistinct and in many instances the organism at this stage of its development is overlooked by reason of the absence of amoeboid motion and because of its delicate, veil-like appearance. As the

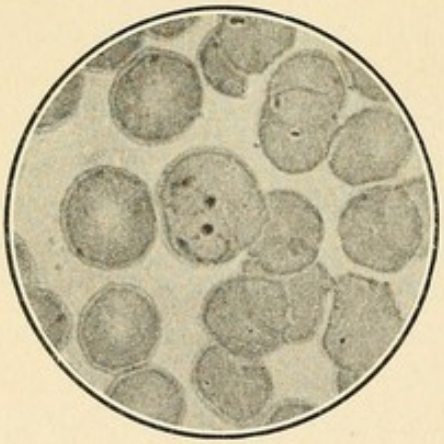


FIG. 1.—Plasmodium vivax. (Tertian plasmodium.) Double infection of red corpuscle with "ring forms." Photomicrograph, × 1200.

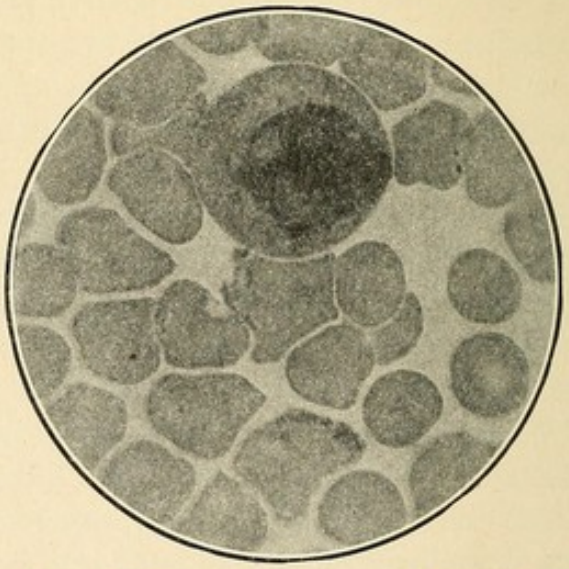


FIG. 2.—Plasmodium vivax. (Tertian plasmodium.) Young amoeboid forms. Photomicrograph, × 1200.

parasite grows older, becoming the *schizont*, it develops very marked amoeboid activity, constantly changing its shape, but is still indistinct in outline, requiring very careful examination to distinguish it in the infected red corpuscle.

In the course of from six to eight hours minute granules of a reddish-brown pigment develop within the hyaline cytoplasm and the outline of the organism becomes more clearly distinguishable. The pigment is of a peculiar reddish-brown color, and in the form of very fine granules arranged irregularly throughout the protoplasm, and is in very active, dancing motion, produced by currents within the protoplasm. As development proceeds amoeboid

motion becomes less pronounced, and when the organism is fully grown no amoeboid motion can be detected. The pigment, at first small in amount, increases gradually as the organism enlarges, is actively motile until just before sporulation, and is always in the form of fine granules pretty evenly distributed throughout the cytoplasm until just prior to segmentation when it collects in larger masses or in a single irregular mass (see Fig. 3).

In the beginning of its development the plasmodium occupies but a small portion of the red corpuscle, but as it continues to grow it encroaches more and more upon the infected corpuscle, until when full-grown it entirely fills the cell which is much swollen and decolorized. The growth of the plasmodium is gradual, covering 48 hours, at the end of which time it divides into a number of small segments or spores.

At the end of 24 hours the plasmodium fills more than half of the red corpuscle, contains much actively motile pigment, and varies greatly in shape, due to the marked amoeboid motion of the organism. Very often at this stage of development multiple infections of the red cell may be suspected by reason of the appearance of two or more spherical pigmented bodies in the same red corpuscle, but careful examination will reveal the fact that the pigmented spherical bodies are but portions of the amoeboid pseudopodia of a single organism, the remainder of the organism being situated deeper within the infected cell, and thus rendered invisible for the time being. The infected red cell at this stage is considerably larger than normal and lighter green in color (see Fig. 3).

At the end of 36 hours the plasmodium has attained its greatest size and almost fills the infected corpuscle. The amoeboid motion is sluggish, but the pigment, which has still further increased in amount, is very actively motile, and is distributed in the form of fine granules throughout the protoplasm; the outline of the plasmodium is well defined, contrasting well with the light green border of the red corpuscle which surrounds it. The infected red cell is almost twice as large as are the uninfected cells and much lighter in color (see Fig. 4).

At the end of 48 hours segmentation or sporulation occurs; the pigment becomes collected at the center or to one side of the plasmodium in the form of a compact clump, and fine radial striations are observed extending from the center toward the periphery of the plasmodium, dividing it into several avoid segments or spores. As a rule, these spores are arranged in two rows, one row surrounding the center of the plasmodium and another surrounding the first row; but very often the spores are arranged irregularly; they are always devoid of pigment, and vary in number from 12 to 24, the average being about sixteen. They are called *merozoites*. In the fresh specimen the *merozoite* when free in the blood plasma, measures from 1.5 to 2 microns in diameter, is oval in shape, almost colorless, and presents a spherical, refractive center, and a less refractive mass of protoplasm surrounding it. The *merozoites* are capable of penetrating the red blood-corpuscles and thus the human life cycle or *schizogony* of the plasmodium is continued (see Fig. 5).

Staining Reactions of Plasmodium Vivax.—In preparations of blood containing *Plasmodium vivax* stained by the Romanowsky method or any of its modifications the exact structure of the parasite can be easily demonstrated. The staining methods which are of value in the study of the malarial plasmodia will be fully described in a later chapter of this work; by their use the plasmodia are shown to consist of a mass of protoplasm, and a vesicular nucleus, rich in chromatin. This is true of all species of the plasmodia, but the structure can be more easily studied in *Plasmodium vivax* because it exceeds the other species in size and because all stages of its development can be observed in the peripheral blood.

Historical Summary.—The first observations upon the structure of the malarial plasmodia in stained specimens of blood were made by Celli and Guarnieri, who used methylene blue as the staining reagent. They described a deeply stained ectoplasm and a dimly stained endoplasm, the latter forming the center of the parasite. In the "ring-forms" they described a deeply stained spot situated between the ectoplasm and the endoplasm, which later observers have demonstrated to be the chromatin of the nucleus.

Grassi and Feletti, as the result of their study of stained malarial parasites, considered that the dimly stained endoplasm described by Celli and Guarnieri was in reality a large vesicular nucleus, containing nuclear juice, a nuclear network, and chromatin, and having a delicate, generally invisible, nuclear membrane; they also described contractile vacuoles in the protoplasm of the plasmodia and note that it is only the protoplasm that contains the pigment granules.

Romanowsky, using his now well-known staining method, demonstrated that the plasmodia consist of an outer, deeply stained portion, the protoplasm, and an inner unstained portion, the nucleus. The latter is spherical or oval in shape and presents at some portion of its periphery a deeply stained mass, the chromatin of the nucleus, the remainder of the nucleus being unstained and consisting of nuclear juice. This description applies only to the young plasmodia, as in the older organisms he found that the vesicular nucleus disappeared and that the chromatin became distributed in the protoplasm of the plasmodia.

The observations of Romanowsky regarding the structure of the malarial plasmodia have been again and again confirmed, and but little has been added to our knowledge in this direction by subsequent observers, with the exception of the differentiation of those forms concerned in *sporogony*. It may be stated that the staining reactions are similar for all species of human plasmodia, and that they prove that these organisms consist of a mass of protoplasm, containing at some period of development more or less pigment and a vesicular nucleus rich in chromatin.

With Wright's modification of the Romanowsky stain, which I habitually use, and which I have found most satisfactory in staining these organisms, the chromatin is the only portion of the nucleus which takes the stain, the young *schizont* consisting of a deeply stained mass of chromatin, surrounded by an unstained space, which in turn is surrounded by the deeply stained protoplasm. As development advances the chromatin of the nucleus divides, becomes distributed in the protoplasm where it stains in a characteristic manner, increases

in amount, and finally becomes collected into small masses forming the chromatic portion of the nucleus of the *merozoites*.

In *schizogony*, if Wright's method of staining be employed, *Plasmodium vivax* presents the following staining reactions during its various stages of development:

The youngest *schizont*, which develops from the *trophozoite* shortly after the latter infects the red blood-corpuscle, presents the so-called "ring-form," consisting of a spherical mass of chromatin stained a brilliant red or violet, surrounded by an unstained spherical or oval area; this area often presents a milky white color and is in contact at one portion of its periphery with a spherical, unstained area, considerably larger than the milky area, which appears to be stained in the same manner as the red blood cell. The milky zone, as it is called, represents the unstained portion of the vesicular nucleus, while the larger area, stained apparently in the same way as the red cell, represents a vacuole which has developed by the side of the nucleus. Immediately surrounding the vacuole and the vesicular nucleus is a ring-like mass of protoplasm stained a deep blue; this ring of protoplasm is very thin at one portion of its periphery where it almost comes in contact with the chromatin which is situated eccentrically in the nucleus. The appearance of the plasmodium at this stage is that of a blue ring of protoplasm surrounding an area of the color of the red cell, at one portion of which is a spherical milky area containing a bright red mass of chromatin (see Fig. 1).

In those *schizonts* in which limited amoeboid motion was present at the time of fixation of the specimens, many forms of the "ring" may be observed, due to minute pseudopodia arising from the protoplasm of the plasmodium. In very many instances it will be observed that the protoplasm is thicker at certain portions or very delicate filaments of blue-stained cytoplasm may be seen connecting various portions of the periphery of the "ring"; in such instances the chromatin mass may be situated at any portion of the protoplasmic filaments, very often at their extremity, or at the point of attachment to the body of the plasmodium. The vacuole in such plasmodia cannot be distinguished (see Fig. 2).

As the *schizont* becomes larger and pigment begins to appear we observe that the latter is situated in the cytoplasm of the parasite, which, by reason of their active amoeboid motion, present in stained specimens many bizarre forms. The unstained vesicular nucleus is still present and contains the chromatin, which has divided into delicate filaments and dots, staining pink, but less intensely than when it was collected in a compact mass. The nuclear vacuole may be present after pigment formation, but at a later period of development both it and the vesicular portion of the nucleus disappear, and the chromatin becomes distributed in the cytoplasm in the form of minute filaments and granules, which may stain intensely, but generally very dimly. At a certain period of development the chromatin divides into very fine filaments and only prolonged staining will demonstrate its presence. In those plasmodia in which

the vacuole is present, it appears as a round or oval, unstained area, surrounded by the blue-stained cytoplasm.

As the time for sporulation approaches this plasmodium presents very marked changes in its structure. The cytoplasm increases in amount, stains a deep blue, and is heavily pigmented. The chromatin also increases in amount, is collected in irregular clumps, and stains an intense red or violet; the filamentous structure of the chromatin has disappeared and it now consists of large grains and compactly formed masses arranged irregularly throughout the protoplasm. The vesicular portion of the nucleus has disappeared.

In the presegmenting plasmodia, the protoplasm, containing the pigment granules, stains a well-defined blue, the pigment being arranged in irregular masses staining a peculiar greenish-brown. The chromatin, staining an intense red, is collected into roughly spherical masses, arranged more or less regularly in the cytoplasm, which as yet shows little evidence of division.

In the segmenting or sporulating plasmodia the chromatin is collected in compact, deep red spherical masses, each surrounded by an unstained area, in turn surrounded by a small mass of cytoplasm; the pigment is collected into a single clump or in irregular masses situated in a small portion of residual protoplasm. When the infected red cell disintegrates, the segments or *merozoites* are liberated, the pigment and residual protoplasm are engulfed by leucocytes, and the *merozoites* again infect red blood-corpuscles.

Each *merozoite*, when stained by Wright's method, is seen to consist of a mass of protoplasm stained a deep blue, enclosing an unstained oval area which contains a spherical dot of chromatin stained a deep red or violet. The chromatin is placed eccentrically and the protoplasm is much thicker at that portion of the parasite furthest removed from the nucleus. The *merozoites* measure from 1.5 to 2 microns in diameter.

The description of *Plasmodium vivax* which has been given refers only to the forms concerned in the human cycle of development or *schizogony*, the development of the plasmodium having been traced from its entrance into the red blood-corpuscle to sporulation. Schizogony is initiated in nature by the entry into the red blood-corpuscles of *sporozoites* introduced into the blood of man by the bite of an infected mosquito. After entry into the red cells the *sporozoites* become *trophozoites* and are of two varieties, those which develop into *schizonts* and continue the infection in man, and those which develop into *gametes*, intended to continue the infection in the mosquito. The *trophozoites* which are destined to become *schizonts* are characterized by the "ring-form," and such forms always greatly out-number the *trophozoites* which develop into *gametes*.

Changes in the Infected Blood-corpuscles.—The changes which occur in the red blood-corpuscles infected with *Plasmodium vivax* are of great importance from a diagnostic standpoint, as these changes alone will suffice to differentiate this plasmodium from either the quartan or aestivo-autumnal plasmodia.

The red corpuscle infected with *Plasmodium vivax* is always larger than normal, even when the parasite is in the earliest stages of development. Not only is the red cell enlarged, but it is paler in color than normal, and in examining the blood for the tertian plasmodium it is often most easily discovered by selecting the red cells which appear larger and paler than normal and carefully

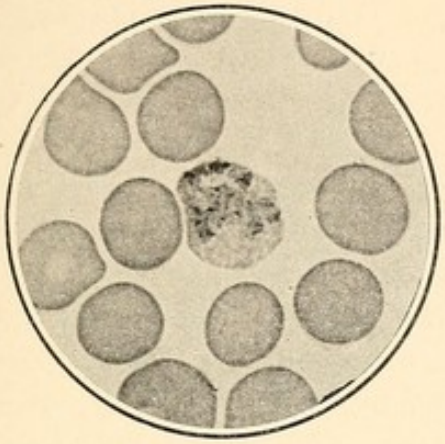


FIG. 3.—Plasmodium vivax. (Tertian plasmodium.) Half-grown parasite. Photomicrograph, × 1200.

FIG. 4.—Plasmodium vivax. (Tertian plasmodium.) Presegmenting parasite. Photomicrograph, × 1200.

examining them. While the enlargement is not marked before the plasmodia become pigmented, the red cell enlarges rapidly after pigmentation occurs, and when the plasmodium is fully developed is generally twice as large as an uninfected corpuscle, and almost devoid of color. In the stained specimens the enlargement is very noticeable and the corpuscle is often much distorted in

FIG. 5.—Plasmodium vivax. (Tertian plasmodium.) Sporulating parasite. Photomicrograph, × 1200.

shape. A very important degenerative change occurring in red cells infected with the tertian plasmodium leads to the occurrence of small refractive granules situated within the protoplasm and which stain a reddish color when the Romanowsky stain or any of its modifications are used. With Wright's stain this red stippling of the infected red corpuscle is well marked, and such cells are

known as "stippled cells," and the granules as Schuffner's granules or dots. In those cells containing the youngest "ring-forms" Schuffner's dots may not be present, but after pigment appears almost every infected corpuscle will show this form of degeneration in stained specimens.

The occurrence of these granules is of great importance in making a differential diagnosis between the tertian plasmodium in its early stages of development and similar stages of development of the quartan plasmodium. While I have *very rarely* seen Schuffner's dots in cells infected with undoubted quartan plasmodia, contrary to the statements of certain authorities who believe that this form of degeneration occurs *only* in tertian infection, the occurrence is of such great rarity as to be of no practical importance, and malarial infections in which Schuffner's dots are found in the infected red cells may practically always be diagnosed as tertian infections, provided, of course, that a double infection with some other species of plasmodium be not present.

The occurrence of these granules in cells containing the "ring-forms" is conclusive proof that these rings are of the benign tertian variety, for Schuffner's granules never occur in cells infected with "ring-forms" of the quartan or aestivo-autumnal plasmodia.

The characteristic changes occurring in the red blood-corpuscle infected with *Plasmodium vivax* are the following: *enlargement* at every stage of development of the plasmodium; *decolorization* progressive with the growth of the plasmodium; *changes in shape*, and the occurrence of *Schuffner's granules* or *dots* in the protoplasm of the cell. As it is probable that this form of degeneration of the protoplasm of the infected red cell is due to certain poisonous products elaborated by the plasmodium during its development, and as these granules occur almost exclusively in infections with *Plasmodium vivax*, it is evident that this organism elaborates certain poisonous materials differing from those elaborated by the other species of plasmodia.

The Morphology and Biology of Plasmodium Malariae. (the quartan malarial parasite). *Schizogony* (human or asexual cycle).

Plasmodium malariae, or the quartan malarial parasite, completes its development in the blood of man in 72 hours, producing that type of malarial fever characterized by a chill and a rise in temperature at the end of every third day. This is the most uncommon form of malarial infection, and in some localities is so rare as to be observed but a few times in many thousand cases of malarial disease. All stages of development common to *schizogony* occur in the peripheral blood, and the organism is easily differentiated from the other species of malarial plasmodia.

Historical Summary.—The description of this species of human plasmodium marked the first attempt to divide the plasmodia into distinct species, and to Golgi, who, in 1886, described very fully this organism, we owe the recognition of it as a definite species. He studied 22 cases of quartan fever and followed the complete cycle of the development of this plasmodium in the blood of the cases studied. He called attention to the relation of sporulation to the clinical

EXPLANATION OF PLATE I.

Tertian Plasmodium. (*Plasmodium vivax.*) Unstained specimens.

1. Normal red blood-corpuscle.
2. Hyaline "ring form."
3, 4, 5. Young pigmented forms.
6. Pigmented form, nearly half-grown.
7. Three-quarters grown pigmented form.
8. Full grown pigmented plasmodium.
9, 10. Sporulating plasmodium.
11. Macrogamete.
12. Microgametocyte. (Flagellated body.)

(Note the gradual enlargement of the infected red blood-corpuscle, and the diminution in the hæmoglobin.)

Quartan Plasmodium. (*Plasmodium malariæ.*) Unstained specimens.

1. Normal red blood-corpuscle.
2. Hyaline plasmodium.
3. Young pigmented plasmodium.
4 to 11. Various stages in the growth of the pigmented plasmodia.
11. Full-grown pigmented plasmodium.
12, 13. Sporulating plasmodia.
14. Macrogamete.
15. Vacuolated macrogamete.
16. Microgametocyte. (Flagellated body.)

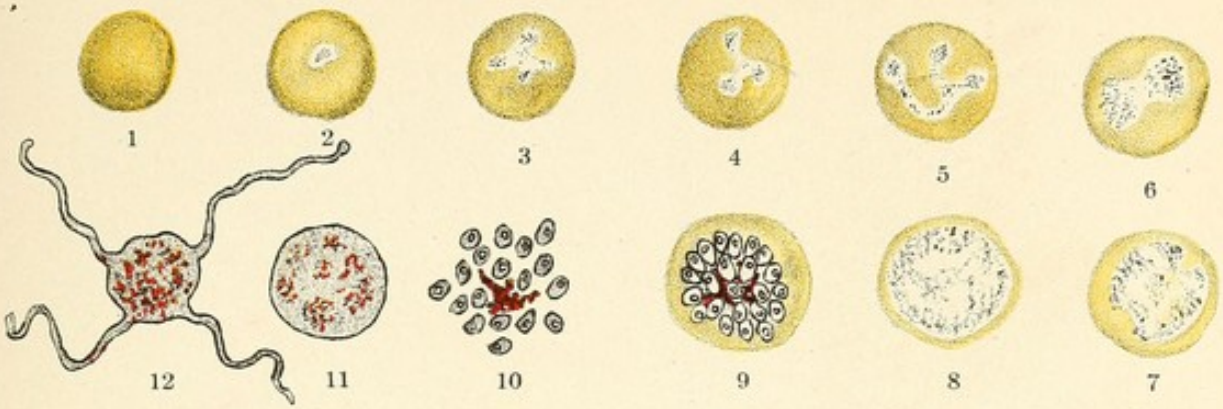
Quotidian Aestivo-autumnal Plasmodium. (*Plasmodium falciparum quotidianum.*) Unstained specimens.

1. Normal red blood-corpuscle.
2 to 8. Various hyaline "ring forms" of the plasmodium.
8, 9, 10. Pigmented forms of the plasmodium.
11. Intracorpuscular crescent. (gamete.)
12 and 13. Sporulating plasmodia.
14. Macrogamete. (Female crescent.)
15. Microgametocyte. (Male crescent.)
16. Flagellated form of microgametocyte.

Tertian Aestivo-autumnal Plasmodium. (*Plasmodium falciparum.*)

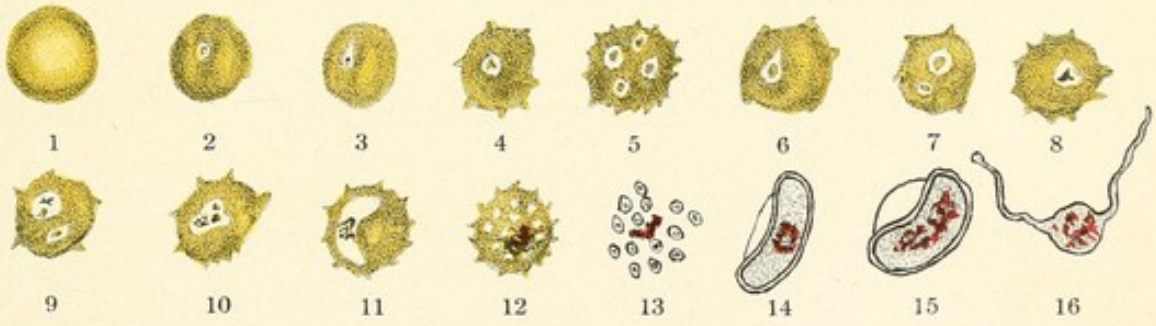
1. Normal red blood-corpuscle.
2. Hyaline "ring form."
3, 4, 5. Pigmented "ring forms" of the plasmodium.
6, 8, 9, 10, 11. Pigmented forms of the plasmodium.
12. Sporulating form of the plasmodium.
13. Macrogamete.
14. Microgametocyte.
15. Ovoid macrogamete.
16. Flagellated form of microgametocyte.

Plate I

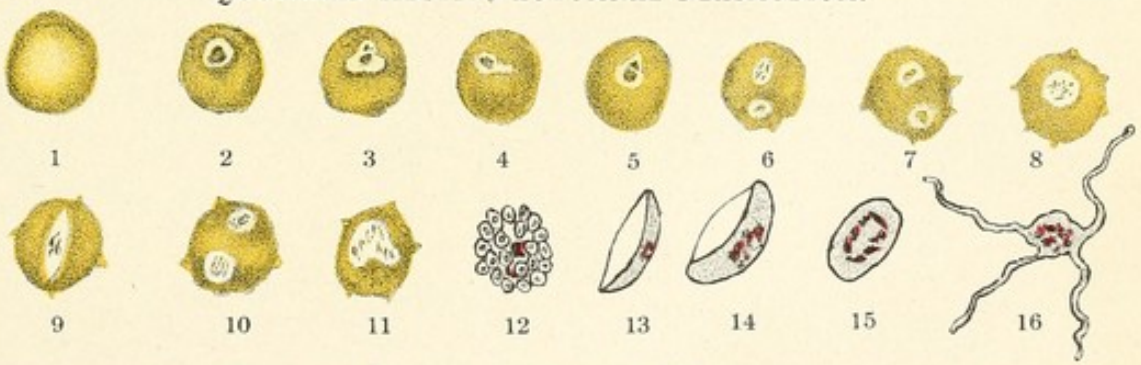


Tertian Plasmodium.

Quartan Plasmodium.



Quotidian Aestivo-autumnal Plasmodium.



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Tertian Aestivo-autumnal Plasmodium.

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symptoms, the chill and fever occurring at the end of every 72 hours, at which time segmentation of the plasmodia always occurred. He described very carefully the morphology of the organism during its various stages of development, noted that the more severe the clinical symptoms the greater the number of plasmodia in the blood, and that infection with three groups of this plasmodium resulted in a quotidian fever

Golgi's observations regarding *Plasmodium malariae* were confirmed by Osler in same year and by Antolisei in 1890, and this species has been accepted by almost every observer who has had the opportunity of studying quartan malarial infections.

Unstained Preparations.—Like the tertian plasmodium, the organism causing quartan malaria, or *Plasmodium malariæ*, appears at first within the red blood-corpuscle as a small amoeboid body called the *trophozoite*. It is sluggishly amoeboid as compared to the benign tertian plasmodium, and is hyaline in appearance. Those trophozoites which are to undergo schizogony soon develop into *schizonts*, while those intended to undergo development in the mosquito develop into *gametes*. The quartan *schizont* is a small, sluggishly amoeboid, hyaline body, measuring about 1.8 to 2.5 microns in diameter, at its earliest stage of development. Although at this period of development these organisms are believed to be indistinguishable from similar forms of the benign tertian plasmodium, there is, in reality, but little difficulty in distinguishing them, the quartan *schizont* being much more sharply cut and refractive and the infected red cell not enlarged and slightly more greenish in color.

Within a few hours the quartan plasmodium begins to develop pigment in the form of a few rather coarse granules of a dark brown color, situated at the periphery of the organism and possessing but very little motility, thus differing from the pigment in *Plasmodium vivax*, which is in the form of very minute reddish-brown granules, very actively motile. At this early pigmented stage the plasmodium is very sluggish in its amoeboid movements, and is generally of a spherical or triangular shape, filling about one-quarter of the red corpuscle, which is not in the least enlarged.

The plasmodium slowly increases in size, and in doing so loses its amoeboid motility; the pigment increases in quantity and becomes collected at he extreme periphery of the organism in the form of large, very dark brown grains which are absolutely immotile. The protoplasm of the plasmodium is very distinct and appears to be of greater consistence than the protoplasm of *Plasmodium vivax*. The infected red corpuscle is normal in size and slightly darker in color.

In 24 hours the distinguishing features of the quartan plasmodium are fully developed. The organism is sharply outlined, is very refractive, and its protoplasm often presents a peculiar, very finely granular appearance; the pigment is dark brown in color, in the form of coarse granules, and is generally collected around the edge of the plasmodium, sometimes forming an almost

complete wreath around it; the pigment is motionless. The shape of the plasmodium at this stage of development is usually triangular, ovoid, or round, and it occupies about one-half of the infected red cell. Amoeboid motion is generally absent. The invaded corpuscle is smaller, if anything, than the healthy ones and is of a darker green color (see Fig. 6).

At the end of 36 hours all of the phenomena noted are more pronounced, the organism filling about two-thirds of the corpuscle, which appears to be retracting about it; the pigment is increased in amount, is motionless, and collected in rough masses at the border of the plasmodium. Amoeboid motion is entirely absent. The growth of *Plasmodium malariae* from this time on is very slow, and it is not until about eight hours before sporulation that presegmenting forms are to be seen in the peripheral blood. Such plasmodia are spherical in shape, bordered by a thin greenish layer representing the remains of the infected red corpuscle. Numerous clumps of dark brown, sometimes almost black, pigment are present in the protoplasm, not now confined to the periphery of the plasmodium, but scattered through the protoplasm in an irregular manner. The pigment is not motile nor is amoeboid motion present in the plasmodium. The infected red cell is slightly smaller than the normal corpuscles and distinctly darker in color (see Fig. 7).

In many instances segmentation or sporulation occurs before the red corpuscle is completely filled by the plasmodium, the pigment collecting toward the center of the plasmodium and six or more segments or spores appearing within the corpuscle. More commonly, however, at the end of 72 hours, the plasmodium entirely fills the invaded cell and sporulation occurs in the following manner: the pigment becomes collected at the exact center of the plasmodium in a solid, almost black, spherical mass, or in a star-like arrangement distributed from the center, and about the same time all trace of the infected red corpuscle disappears, the plasmodium being apparently extracellular; in a short time radial striations are observed shooting out from the pigmented center, and these, joining at their extremities, form from six to fourteen oval segments or spores, the *merozoites*. As a rule, the number of spores does not exceed ten. The spores are generally arranged in a perfectly symmetrical manner around the central pigment in a single row, giving the so-called daisy or "Marguerite" appearance to the plasmodium at this stage. The number and the beautifully regular arrangement of the *merozoites* would alone serve to distinguish this stage of the quartan from the corresponding stage of the tertian plasmodium, but the quartan *merozoites* are also more oval in shape, more refractile and somewhat larger, measuring about 2.5 microns in diameter (see Fig. 8).

When segmentation is complete each *merozoite* becomes free in the blood plasma and, in the human cycle, again invades the red corpuscles, some becoming *schizonts*, while others become *gametes*.

At the time of sporulation the pigment and the residual protoplasm containing it is liberated and most of it is engulfed by phagocytic leucocytes,

some of the pigment, however, remaining free in the blood for a considerable time. There is a slight difference in size between individual sporulating bodies, even in the same individual, and rarely sporulation may be observed in plasmodia that do not occupy more than two-thirds of the red corpuscle, but as a general

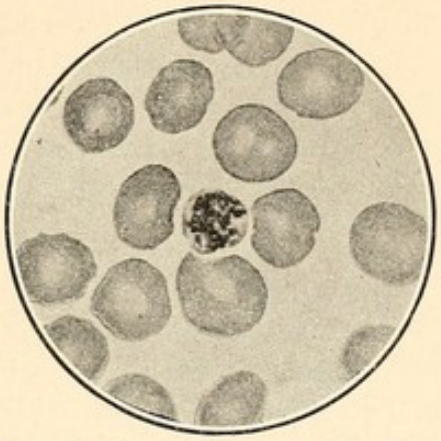


FIG. 6.—Plasmodium malariæ. (Quartan plasmodium.) Presegmenting parasite. Photomicrograph, × 1200.

rule there is not as much variation in the size of the sporulating forms of *Plasmodium malariae* as there is in the same forms of *Plasmodium vivax*. The star-like arrangement of the pigment between the segments, which Thayer considers so characteristic, is generally observed, but I have observed exactly

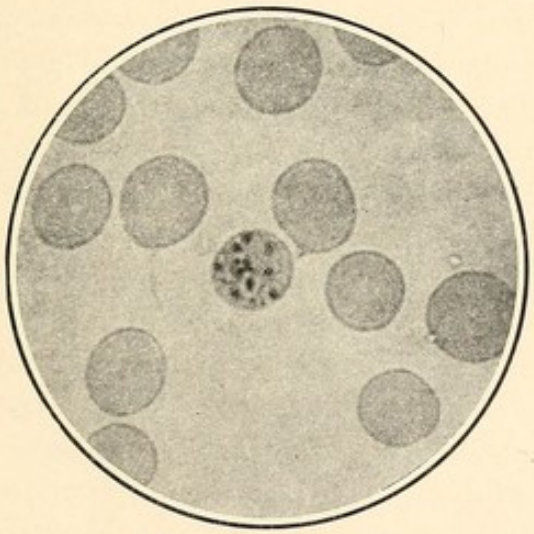


FIG. 7.—Plasmodium malariæ. (Quartan plasmodium.) Sporulating parasite. Photomicrograph, × 1200.

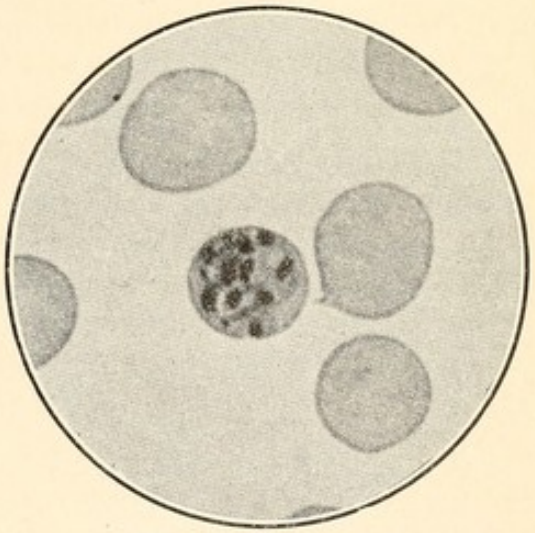


FIG. 8.—Plasmodium malariæ. (Quartan plasmodium.) Sporulating parasite Photomicrograph, × 1800.

the same arrangement of pigment in tertian segmenting forms; it is probably of accidental occurrence, doubtless more common in the quartan plasmodium, but not at all peculiar to the species.

Staining Reactions of Plasmodium Malariae.—The structure of *Plasmodium malariae*, the quartan malarial parasite, as shown by Wright's

method of staining, is similar to that of *Plasmodium vivax*, the benign tertian parasite, in that it consists of a small amount of protoplasm surrounding a vesicular nucleus rich in chromatin, but certain differences exist in the staining qualities of the protoplasm and nucleus of the plasmodium, and of the infected red corpuscle which are of service in differentiating this species from the plasmodium of tertian malaria or the plasmodia of the aestivo-autumnal infections.

The youngest *schizont* when stained is larger than the *schizont* of the tertian plasmodium, but exhibits the same ring-like appearance, consisting of a blue ring of protoplasm surrounding a milky spherical zone containing the red chromatin and a vacuole, developed at one side of the nucleus. The protoplasm of the plasmodium of quartan fever stains a deeper blue than does that of the tertian organism, and the chromatin, which stains a very dark red, is situated nearer the center of the milky or vesicular portion of the nucleus. The vacuole, which causes the "ring" at this stage of development is only observed in those plasmodia that are destined to become *schizonts*.

The staining reactions during later stages of development are like those of *Plasmodium vivax*, already described, the vacuole disappearing and with it the "ring-form," the organism spreading out into the red cell, finally filling it. The protoplasm throughout development stains more intensely blue than that of the tertian plasmodium, and the chromatin a more intense red. The latter, when distributed throughout the protoplasm, is in the form of larger, thicker filaments, in more definite clumps than is the chromatin of *Plasmodium vivax*, and in the presegmenting and segmenting forms the chromatin is in more compact clumps or masses and stains a darker red in color. Around each mass of chromatin in these fully developed forms there is an unstained milky area, representing the vesicular portion of the nucleus of the developing *merozoites*. Because of the deeper staining and circular form of the quartan plasmodia, their outline is much more distinct in stained preparations than in the case of the tertian plasmodium, and in the nearly full-grown forms the red cell is very plainly visible as a narrow rim of pink-stained protoplasm surrounding the perfectly circular plasmodium.

If stained preparations be made during the second day of development the very characteristic "band forms" of the *Plasmodium malariae* can be observed, consisting of a band of deep blue protoplasm stretching across the infected red corpuscles, enclosing a mass of chromatin stained an intense red color. I have never observed such "band forms" in any other variety of malarial infection, and a diagnosis of quartan malarial fever is justified when such forms are present.

The *merozoites* or spores consist of a deep blue mass of protoplasm and of a compact mass of dark red chromatin situated eccentrically in relation to the protoplasm. The chromatin in most instances is surrounded by a very small unstained area, the vesicular portion of the nucleus.

The pigment in the quartan plasmodium is but little affected by the stain, appearing a dark brown in color, although in those instances in which it is

collected in loosely arranged masses the stain gives it a very well-defined greenish-brown tinge.

Changes in the Infected Blood-corpuscle.—The changes observed in the infected red blood-corpuscle in quartan malarial fever are less marked than those occurring in tertian infections, but are fully as characteristic. A study of such infections as regards the blood will convince the most skeptical that *Plasmodium malariae* produces an entirely different effect upon the cells invaded by it than does *Plasmodium vivax*. It will be remembered that the red corpuscles invaded by the latter organism increased greatly in size, due to their distention by the growing parasite, and became much paler in color. In infections with *Plasmodium malariae* the red cell instead of enlarging remains normal in size, or more often becomes smaller than the uninfected cells, and instead of becoming paler in color is darker green than the healthy red cells. It would appear that in quartan malaria the plasmodium causes a shrinkage of the red corpuscle about it during its development instead of expanding the red cell as does the tertian plasmodium.

I have already spoken of the occurrence of Schuffner's granules or dots which are observed within the cytoplasm of the invaded red corpuscles in tertian infections; such a form of degeneration is probably never present in quartan infections, although in a very few such infections I have observed a stippling indistinguishable from that produced by Schuffner's dots in invaded red blood-corpuscles. However, such an appearance occurs so rarely that it is of no practical importance and does not alter the fact that the presence of Schuffner's dots in a red corpuscle infected with a malarial plasmodium indicates that the organism present is *Plasmodium vivax*.

The lack of enlargement of the infected red blood-corpuscle, its darker green color, and the absence of Schuffner's dots serve to differentiate *Plasmodium malariae* and *Plasmodium vivax*, the red cells infected with the quartan plasmodium exhibiting all of the characteristics mentioned, but are of no value in differentiating *Plasmodium malariæ* from the plasmodia of the aestivo-autumnal infections which produce very similar changes within the red corpuscles. In the latter infections, however, other changes occur within the red cells which serve to make the distinction possible.

As in the tertian infections, certain of the *merozoites* produced by the sporulation of the quartan plasmodium, and certain of the *sporozoites* introduced by the bite of the infected mosquito do not develop into *schizonts* and undergo *schizogony*, but develop into *gametes*, which undergo *sporogony* within the mosquito. These forms will be described after we have considered the *schizogony* of the aestivo-autumnal plasmodia.

The Plasmodia of Aestivo-autumnal Malarial Fevers.—As I have already stated I believe that the plasmodia causing the aestivo-autumnal malarial fevers are divided into two distinct species, which differ from one another in morphology, in their period of development, and in the pathogenic conditions they bring about in the infected individual. Many observers hold

that there is but one aestivo-autumnal plasmodium, which varies in its morphology and the period of time required for its development, but from over ten years' study of malarial infections of this type I am forced to conclude that these authorities are mistaken and that two forms of aestivo-autumnal fever occur, each form due to a specific plasmodium. That quotidian and tertian forms of aestivo-autumnal malaria exist has been abundantly proven by Marchiafava and Bignami, Bastianelli, Caccini, Mannaberg, James, Manson, Jackson, and myself, as well as others, and the plasmodia concerned in their etiology have been carefully studied and described.

Historical Summary.—Golgi, in 1885, was the first to call attention to the probably distinct type of the crescentic and ovoid parasite, and suggested the possibility of its being a distinct species of the malarial plasmod . : but to Councilman we owe the first statement of the diagnostic value of these forms. In 1887 he says: "The character of these bodies (the malarial parasite) varies in different, forms of the disease. Although they seem in some cases to run into one another, still, in general, we can say that where the plasmodia inside the red corpuscles are seen (large pigmented forms) the patient has intermittent fever, and where the crescentic and elongated forms are found he has either some form of remittent fever or malarial cachexia. We are not only able to diagnose the disease as such, but in most cases the particular form."

Golgi, in 1889, was the first to observe that the small, hyaline, intracellular rings and the crescent and the ovoid pigmented bodies were associated with malarial fevers of remittent character with long intervals between the paroxysms. He believed that the ring forms were the first stages of the crescent and ovoid forms.

The type of fever in which these plasmodia are found, and which is now known as aestivo-autumnal fever, differs very materially from the ordinary intermittent (tertian and quartan) fevers met with in northern latitudes. Under the term "aestivo-autumnal fever" is included the majority of the cases of so-called pernicious malarial fevers, and in this class of cases, which are especially prevalent in the malarial districts around Rome where they studied, Marchiafava and Celli, in 1889, discovered and described very minutely the appearance and life history of the parasites concerned in their etiology. About the same time Canalis published the results of his investigations upon the parasites associated with irregular and remittent malarial fevers, and although his interpretation of some of the phenomena observed differed widely from those of Marchiafava and Celli, the morphological descriptions of the parasites were very similar, and confirmed Golgi's theory of the existence of a separate species of the malarial parasite causing remittent malarial fever. A brief summary of the investigation of the above-mentioned authors is here given:

Marchiafava and Celli's observations may be summed up as follows: For some time before the onset of a paroxysm of fever, three forms of the aestivo-autumnal parasite may be seen in the blood, *i.e.*, minute round or ring forms, having a small, dark center, composed of pigment or haemoglobin; intracellular, minute amoeboid, hyalin parasites, containing one to three small pigment gran-

EXPLANATION OF PLATE II.

Tertian Plasmodium. (*Plasmodium vivax.*) Stained by Oliver's Modification of Wright's Stain.

1 to 6. "Ring forms" of the plasmodium.
6. Amoeboid, unpigmented form of the plasmodium.
7. Two "ring forms" in corpuscle showing Schuffner's dots.
8. Amoeboid "ring form" in corpuscle showing Schuffner's dots.
9 to 17. Various stages in the development of the pigmented plasmodium.
17. Microgametocyte.
18. Nearly full-grown plasmodium, showing minute division of the chromatin.
19, 20, 21. Presegmenting plasmodia.
22, 23, 24. Sporulating plasmodia.
25. Microgamete. (Flagellum.)
26. Sporozoites.

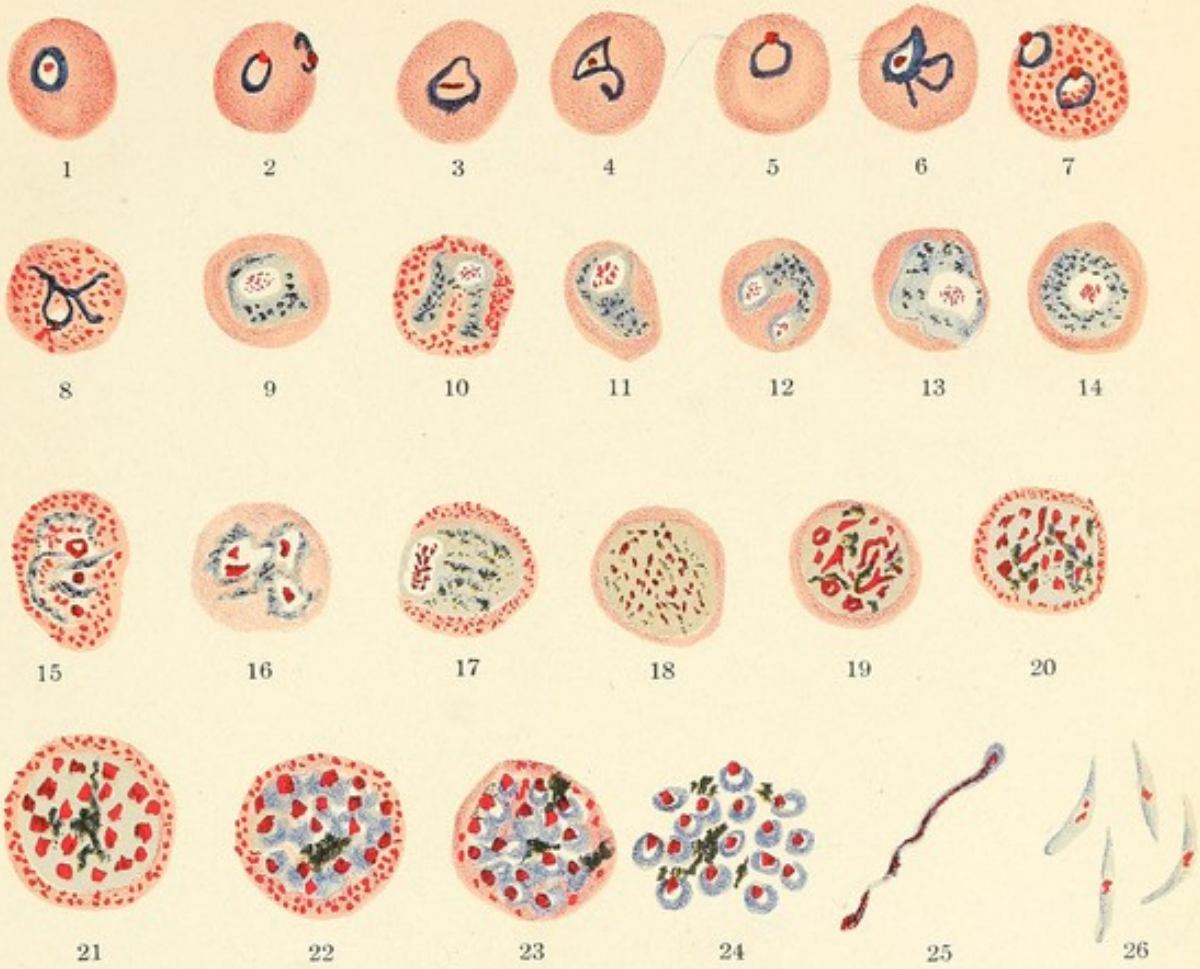
Note.—With this stain the chromatin of the nucleus stains crimson, the protoplasm blue, while the vesicular portion of the nucleus remains unstained.

Quartan Plasmodium. (*Plasmodium malariæ.*) Same stain as the tertian plasmodium.

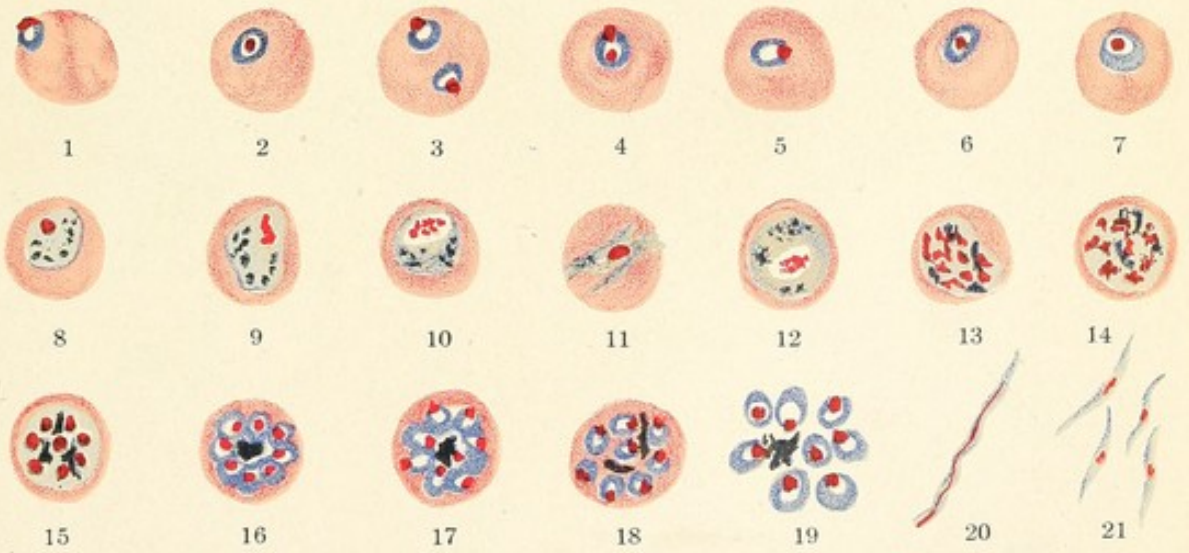
1 to 8. "Ring forms" of the quartan plasmodium.
8 to 13. Pigmented forms of the plasmodium. At 11 a so-called "band-form" is shown.
13, 14, 15. Presegmenting plasmodia.
16, 17, 18, 19. Sporulating quartan plasmodia.
20. Microgamete.
21. Sporozoites.

Note the presence of Schuffner's dots in the infected red corpuscle in tertian malaria; the larger size of the tertian plasmodium; the difference in the character of the pigment, and the greater number of spores or segments.

Plate II



Tertian Plasmodium.



Quartan Plasmodium.

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C. F. CRAIG. DEL.

ules, and somewhat larger round bodies having a block of pigment at some portion within them. The red corpuscles containing the parasites were smaller than the normal corpuscles, darker green in color, and crenated, while the haemoglobin was often seen to be retracted from the periphery of the corpuscle for a whole or part of its circumference. Segmenting bodies were very rarely seen in the circulating blood, but were found in large numbers in the internal organs, especially the spleen and the capillaries of the brain. They observed that sporulation always occurred before the onset of a paroxysm, and that the parasites pursued a developmental cycle of 24 hours or less. At the time of the paroxysm, and for some time afterward, the small amoeboid hyalin parasites, which comprise the new generation, may be seen in the blood. They describe the crescentic organisms and also intervening forms between the intracellular bodies and the crescents. They note the minuteness of the æstivo-autumnal parasite as compared with the tertian and quartan forms. They found the crescents in greater number in the spleen, but observed many cases without the formation of crescents. No segmentation of the crescents was ever noted, and neither is the development of the pigment always to be observed. In those fevers in Rome showing daily paroxysms only the small, hyalin, amoeboid, intracellular parasite is observed in the peripheral blood, and only in those cases showing a longer interval between the paroxysms is the parasite with the few pigment granules to be observed.

Canalis' contribution is a very extensive one. He divided the cycle of development of these parasites into two phases: a rapid cycle and a slower cycle in which the crescentic forms appear. The rapid cycle he considers to be of about two days' duration, though it may be only 24 hours in length. During the first hours the parasites are intracellular, amoeboid, hyalin, occupying one-sixth of the red corpuscle, the outer portion of the parasite being clear, while the center appears shaded or greenish, presenting the appearance of a nucleus. The outer portion may be very refractive. The blood-corpuscles which are invaded are very often smaller than normal and are greenish in color. As the parasite grows it becomes more amoeboid, and a few fine particles of reddish-brown pigment may be seen within the outer ring-like portion. The parasite gradually grows larger, the ring-like appearance disappears, the amoeboid movement ceases, the pigment granules melt into one small solid block at the center or one side of the parasite, and a faint radial striation appears, and from six to ten ovoid or round segments are eventually produced. They are much smaller than the segments of tertian or quartan plasmodia. The containing corpuscle may be entirely disintegrated or may appear as a dim, shadowy sphere surrounding the segments. Segmenting bodies are very rarely seen in the peripheral blood, but free pigment and pigmented leucocytes are common.

The second, or slow cycle, in which crescents develop, according to Canalis, may occur in connection with the rapid cycle or where the course of the disease has been interfered with by some drug, especially quinin. Canalis always found that crescents were not developed until some time after the onset of the fever, generally not until fifteen days had elapsed. The small, intracellular, amoeboid forms were observed to become oval in shape, while the pigment collected toward the center; a crescentic form was gradually acquired; the red corpuscle disappeared, and the now fully developed crescent was set free in the blood. He observed the double outline of the crescent, and considered that it was due to an enveloping membrane. The crescents were afterward observed to acquire an oval form and finally become perfectly round. In the crescentic and ovoid forms the pigment was always motionless, but in the round form it often became very mobile and was arranged in a perfect circle. He describes a

process of sporulation as occurring in the crescents and also observed the development of flagellate bodies from the round bodies, of which he says: "They represent, assuredly, one of the last stages in the development of the parasite, for I have never seen them appear in the blood before the formation of the round bodies." Canalis considered that the length of this cycle varied, the period from the amoeboid stage to the crescentic lasting from three to four days, the round bodies taking a day longer.

In this truly admirable paper it is unfortunate that the author committed himself to the sporulation theory of the crescents, for in the light of our present knowledge such a theory is untenable, unless Schaudinn's observations concerning the parthenogenesis of the *macrogamete* be confirmed.

That a distinct species of plasmodium is always associated with the aestivo-autumnal fevers has been confirmed by nearly every student of the subject, and Bignami, Sanfelice, Plehn, Mannaberg, Dock, Thayer, Hewetson, and others have confirmed much that appeared in the articles of Marchiafava and Celli and Canalis. However, it was not until the observations of Marchiafava and Bignami were published that attention was directed to the fact that *two* species of plasmodia are associated with these fevers instead of a *single* species. Their observations are briefly as follows:

These investigators very thoroughly studied the parasites occurring in the aestivo-autumnal fevers, and, as the result of their studies, have separated these parasites into two species, one causing a paroxysm every 24 hours, the other every 48 hours, approximately, which they have termed the quotidian and malignant tertian aestivo-autumnal parasites. The fever due to the quotidian parasite may be regular and resemble the ordinary double tertian curve, but more often the temperature curve shows evidence of anticipation or retardation, being irregular, and the symptoms vary much in their severity. A continuous of slightly remittent fever is not unusual. The quotidian parasite, as described by them, is a very small amoeboid, hyalin, ring-like, intracorpuscular body in the peripheral blood, which prior to segmentation develops a small number of minute pigment granules. Segmentation generally occurs within the red cell, and almost always in the internal organs, especially in the spleen. The rings are very pale and often very careful search is required before they are discovered; they are actively amoeboid, and never exceed one-third of the corpuscle in size. The infected corpuscle has a greenish, brassy color, is often shrunken, and the haemoglobin retracted. After some days crescentic and ovoid bodies appear.

Marchiafava and Bignami's malignant tertian parasite produces a febrile paroxysm lasting practically 48 hours, and often the temperature curve shows such variations, caused by the anticipation and conjunction of paroxysms, as to present a continued fever. According to them, the febrile curve presents, in the majority of cases, the following characteristic points: a rapid and sudden rise, a stationary stage, with slight remissions, a slight pseudocrisis, a pre-critical rise, marked often by the highest temperature, and at last a sharp crisis during which the temperature often falls far below normal.

The malignant tertian parasite, as described by these authors, resembles the quotidian very closely, but is larger and presents a greater amount of pigment within the protoplasm. It is often one-half the size of the red corpuscle. Like the quotidian, segmentation occurs mostly within the vessels of the internal

organs. The infected corpuscles are almost invariably shrunken, dark green in color, and often crenated and degenerated. Crescents and ovoid forms appear after a few days. The differences between the quotidian and malignant tertian aestivo-autumnal plasmodia as given by Marchiafava and Bignami are as follows:

1. The length of the cycle of development: 24 hours in the quotidian and 48 hours in the malignant tertian parasite.

2. The larger size of the malignant tertian parasite in all stages of development and the greater amount of pigment in the pigmented forms of the tertian organism.

3. The greater amoeboid activity of the malignant tertian parasite, which is retained for a longer period of time in the large pigmented forms.

4. The length of the amoeboid unpigmented stage which in the malignant tertian parasite may last for 24 hours.

Mannaberg distinguishes three varieties of the aestivo-autumnal plasmodia; an unpigmented quotidian, a pigmented quotidian, and the malignant tertian parasite. This classification is also accepted by Manson, and Grassi and Feletti also describe the pigmented and unpigmented quotidian parasites.

In 1893 Golgi published an important paper giving the results of his researches regarding the plasmodium of aestivo-autumnal infections, in which he vigorously combated the existence of more than one variety of the aestivo-autumnal organism, and stated that the forms found in the peripheral blood were chiefly accidental, the infection being present almost entirely within the internal organs.

At the present time almost all authorities who have studied thoroughly the aestivo-autumnal malarial fevers and who have had sufficient clinical material agree with Marchiafava and Bignami in describing more than one species of aestivo-autumnal plasmodium; all accept a quotidian and tertian variety, and some believe that an unpigmented quotidian plasmodium occurs in certain localities. From personal observation I have not been able to confirm the existence of an unpigmented quotidian organism, but neither can I deny it, as such infections may not occur in the regions in which I have studied malarial fever. I am of the opinion, however, that only one quotidian plasmodium occurs in these infections, and that the species of plasmodia concerned in the etiology of aestivo-autumnal malaria are two in number, namely, *Plasmodium falciparum* and *Plasmodium falciparum quotidianum*.

The Morphology and Biology of Plasmodium Falciparum Quotidianum (the quotidian aestivo-autumnal parasite).—*Schizogony* (human or asexual cycle).

Unstained Preparations.—*Plasmodium falciparum quotidianum* completes its cycle of development in man in twenty-four hours, and appears at first within the red blood-corpuscle as a very small (0.8 to 1 micron in diameter) amoeboid, hyalin body, "ring"-shaped or circular in contour, the *trophozoite*. In those individuals which undergo *schizogony*, the *trophozoite* quickly becomes a *schizont*, enlarging slightly and occupying about one-sixth of the red corpuscle. At the earliest stage of the quotidian *schizont* the outline of the organism is very indistinct, and were it not for its active amoeboid motion, it would be very easily overlooked. As the organism enlarges the outline becomes much more

distinct. When fully grown it is very clear cut and the entire plasmodium is very refractive. The spherical forms are perfectly hyalin in appearance, but the "ring forms" consist of a narrow hyalin ring of protoplasm enclosing a small oval or circular area showing the yellowish-green color of the blood-corpuscle. Most authorities attribute this appearance to the fact that the center of the parasite is much thinner than the periphery, thus allowing the normal color of the corpuscle to show through; the true explanation of the "ring form" is that the center of the "ring" is composed of a nutritive vacuole. When in motion the "ring forms" often appear triangular in shape, the movement consisting of a rapid, wavy motion of the border of the plasmodia and the shooting out of minute protoplasmic elongations which are retracted almost as quickly as they are thrown out. The amoeboid motion is very rapid and the organism has to be carefully watched in order to be distinguished. Sometimes the "ring form" is lost, the organism becoming a pale hyaline disk. The movement is very erratic, and there are long periods of repose during which the ring form is retained. The invaded corpuscle, even at this early stage in the development of the plasmodium, is generally smaller than those which are normal, presents a shrunken, wrinkled appearance, and is dark green in color. Crenation is often observed and double or triple infections of the red cell. The so-called "signet-ring" appearance, so common at this stage of development in the aestivo-autumnal tertian plasmodium, does not occur in this species. In the peripheral blood the hyalin, round, or ring-shaped plasmodia, just described, are the ones commonly observed, although a small number of pigmented forms are not uncommon in most cases of infection with this plasmodium.

Just prior to pigmentation the plasmodium becomes a little larger, loses its ring form, becomes more refractive and sharply defined, much more so than is the malignant tertian plasmodium at the same stage of development. In this species of plasmodium I have never observed a pigmented ring form, so common in the malignant tertian species, the pigmented bodies always being oval or round in shape with a homogeneous protoplasm. The pigment appears as a single, or at most two granules, either in the center or at one side of the plasmodium, and is always perfectly motionless. Sometimes the pigment appears as a rather coarse irregular block situated at the center of the parasite, and such forms I consider to be presegmenting organisms. The pigment is almost black in color and is never distributed throughout the protoplasm, as in *Plasmodium vivax*, or arranged about the periphery of the organism, as in *Plasmodium malariæ*. In very rare instances the pigment may consist of three or four very fine granules, but they are always in intimate association with one another. At this stage of its development the plasmodium is never larger than one-fourth of the invaded corpuscle, which is always shrunken, dark green in color, and much smaller than the normal red cells. As a rule, the invaded corpuscles exhibit marked crenation and areas of retraction of the hemoglobin. From the very peculiar color of the invaded cells, they have been called "brassy

corpuscles," and it is in this form of malarial infection that the brassy color of the infected red cell is most marked.

Segmentation occurs but very rarely in the peripheral blood, but may be easily observed in blood obtained by splenic puncture or, at postmortem, in blood from the spleen, liver, brain, and especially the bone-marrow. Segmentation occurs at the end of twenty-four hours, the plasmodium at this time not occupying more than one-fourth of the red cell, thus differing from the benign tertian and quartan plasmodia which fill the corpuscle. In the segmenting forms the pigment is collected in a solid granule or small block at the center of the parasite, while the protoplasm of the organism appears slightly granular. As segmentation commences, fine radial striations can be detected, starting from the center, and soon the plasmodium breaks up into from six to eight very minute round or oval segments, the *merozoites*. The beautifully regular segmenting forms so often observed in quartan infections are but rarely observed. Segmentation always occurs within the red blood-corpuscle, and because of the small size of the segments and their limited number, the red corpuscle is only partially filled by the young plasmodia. Shortly after segmentation is complete the red cell disintegrates, thus liberating the *merozoites* which invade normal red corpuscles and so continue the infection. As in tertian and quartan infections, the *merozoites* are of two kinds, those intended to undergo *schizogony* and those which undergo *sporogony*. The forms developing from the latter will be described in considering the mosquito cycle of these parasites.

Staining Reactions of Plasmodium Falciparum Quotidianum.—As the staining reactions of this species of plasmodium are identical in large measure with those of *Plasmodium falciparum*, I will describe them in dealing with the latter organism.

Morphology and Biology of Plasmodium Falciparum.—(The tertian aestivo-autumnal parasite. Malignant tertian or subtertian parasite of some authors.) *Schizogony* (human or asexual cycle).

This is the most common species of aestivo-autumnal plasmodium and is the one which has been most frequently observed and studied. The majority of infections with aestivo-autumnal malaria are due to this parasite, and even in those limited regions where the quotidian plasmodium has been observed the latter is very rare in comparison with the tertian species. In many instances of quotidian aestivo-autumnal infection a combined infection exists with the malignant tertian plasmodium and this has caused much confusion in the description which have been given of the aestivo-autumnal plasmodia by various observers. In those cases, however, in which the two organisms occur alone, they may be readily differentiated by their morphological characteristics and their cycle of development.

Unstained Preparations.—Like the quotidian species, the tertian aestivo-autumnal plasmodium, or *Plasmodium falciparum*, appears first within the infected red corpuscle as a round or oval hyalin ring or disk, but even in the

earliest stage of development of the *schizont* important differences are to be noted between this and the quotidian species. The young tertian plasmodia are considerable larger than those of the quotidian species, occupying from one-quarter to one-third of the infected red cell, which, while smaller than the normal cells surrounding it, and greenish in color, is not shrunken and wrinkled at this early stage of development as in quotidian infections. The "ring forms" are irregular in outline, one portion of the "ring" being broader than the remainder, giving rise to the so-called "signet-ring" appearance, never observed in quotidian infections. The organism is more highly refractive and sharply outlined, and the amoeboid motion is more sluggish and more easily observed. The ring form is often lost, a clear, hyalin disk resulting.

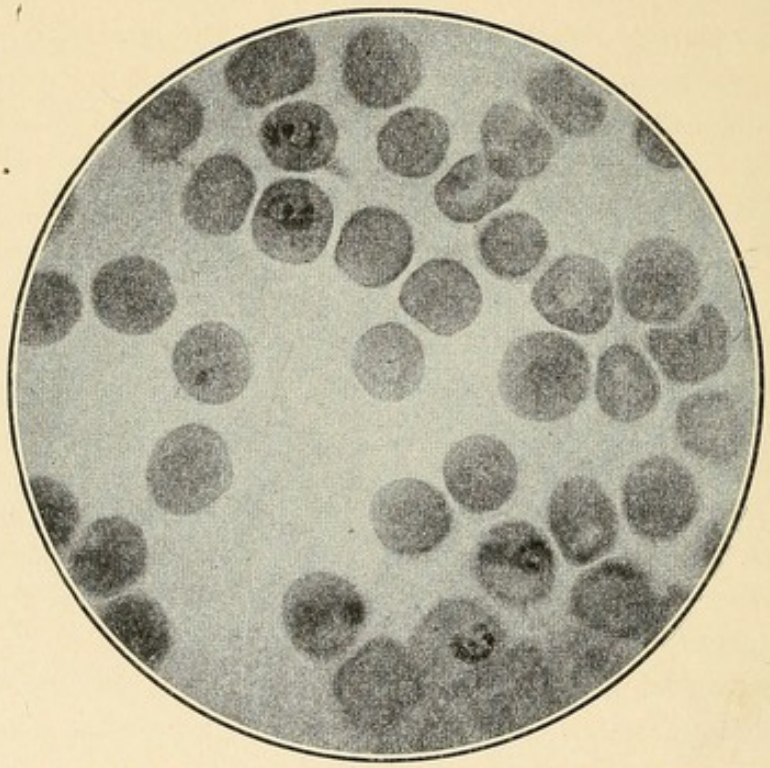


FIG. 9.—Plasmodium falciparum tertianum. (Aestivo-autumnal tertian.) Two "ring forms" and two young *gametes*. Photomicrograph, × 1200.

Very rarely is more than one parasite seen in a single corpuscle, except when intracorpuscular conjugation, a process common to all malarial plasmodia, is present. The changes in the outline of the plasmodium are very marked, and it is much more easily recognized than is the quotidian plasmodium (see Fig. 9).

In the course of from 20 to 24 hours the hyalin forms become pigmented, the pigment occurring in the form of very fine, reddish-brown granules somewhat resembling those found in the benign tertian plasmodium. The pigment is in larger amount than in the quotidian plasmodium, is sluggishly motile, and makes its appearance while the plasmodia are ring-shaped, being situated within the enlarged area, thus giving the organisms a still greater resemblance to a signet ring. The organism gradually loses the ring-form and becomes

larger, sometimes filling one-half of the corpuscle; at the same time it becomes more clearly defined, its protoplasm more refractive and faintly granular in appearance. The amoeboid motion still continues, though very sluggishly, and the pigment tends to collect in a solid block, which has a marked vibratory movement. The pigmented form is more common in the peripheral blood than is the pigmented form of the quotidian plasmodium, but is rare as compared with the tertian or quartan pigmented forms.

In this plasmodium segmentation occurs at the end of 48 hours in the vast majority of infections, although rarely segmentation may occur two or three hours earlier. At this time the plasmodium has grown to be one-half to two-thirds as large as the red corpuscle, the pigment has become motionless and collected in a solid block near or at the center, and distinct radial striations are visible starting from the center of the organism, dividing it into from 10 to 15 segments or *merozoites*. In some instances as many as 24 *merozoites* have been counted. The *merozoites* are larger than those of the quotidian species, are oval in shape, and appear very refractive. Segmentation occurs within the red blood-corpuscle, but its situation is not so easy to distinguish in this species as in the quotidian. The sporulating forms occur very rarely in the peripheral blood, and I have observed but one case in which such forms occurred in blood removed from the peripheral circulation in the thousands of cases of tertian aestivo-autumnal infection which I have studied.

The young *merozoites* are liberated in the blood plasma by the disintegration of the red blood-corpuscle and infect normal red cells, thus continuing the human cycle of the plasmodium. Besides the *merozoites* which continue the human cycle of development there are others which enter the red corpuscles and develop into *gametes*, thus rendering possible the infection of the mosquito.

Staining Reactions of Plasmodium Falciparum and Falciparum Plasmodium Quotidianum.—The staining reactions of these two species of malarial plasmodia are similar in most respects to the staining reactions of the benign tertian and quartan plasmodia, when Wright's method of staining is employed. These plasmodia are seen to consist, in the unpigmented and early pigmented stages, of a ring of blue-stained protoplasm surrounding a large nutritive vacuole, at one side of which is situated a small, vesicular, milky appearing nucleus containing one or two small masses of chromatin stained a deep red or violet. In the aestivo-autumnal "rings" the chromatin is often seen to project outward from the periphery of the blue-stained ring of protoplasm, an appearance never observed in *Plasmodium vivax* and *Plasmodium malariae*. The blue-stained protoplasm in the quotidian ring forms is very small in amount, forming a very delicate thin ring, while in the malignant tertian plasmodium the blue-stained protoplasm is thicker and at one portion of the circumference of the ring spreads out into a very definite enlargement in which the pigment, if it be present, is generally situated.

Changes in the Infected Red Blood-corpuscles.—I have already described the changes observed in the infected red blood-corpuscles in tertian

and quartan malarial fevers. It will be remembered that in infections with *Plasmodium vivax*, the invaded red corpuscle enlarges, becomes pale, and a peculiar form of degeneration occurs which results in the appearance in stained specimens of the so-called Schuffner's dots; while in infections with *Plasmodium malariae* the invaded red cells generally became slightly smaller, deeper green in color, and stained specimens show the absence of Schuffner's dots. The red blood-corpuscles when invaded by either species of the aestivo-autumnal plasmodia become much smaller than the normal red corpuscles, and much darker green in color. In infections with the quotidian species the red cells are greatly shrunken, appear wrinkled, are brassy in color, and are almost always much crenated; in infections with the malignant tertian plasmodium these changes are not so marked, the red cell being smaller than normal, but seldom presenting a wrinkled appearance, and is less often crenated. Brassy appearing corpuscles are very common, however, in malignant tertian infections, although the reduction in the size of the red corpuscle is less marked than in infections with the quotidian plasmodium. In neither type of infection do the invaded red cells show the presence of Schuffner's dots, although many of them present deeply stained, bluish granules, which have been called Marshall's dots or granules by some authorities, and which are undoubtedly due to some form of degeneration of the cytoplasm of the cells, caused by the aestivo-autumnal plasmodia.

So far as the changes in the infected red blood-corpuscles are concerned, the aestivo-autumnal plasmodia resemble the quartan plasmodium rather than the benign tertian, but in the aestivo-autumnal infections the invaded red corpuscles are much smaller than are the corpuscles infected with *Plasmodium malariae* and much deeper green in color, while the wrinkling and crenation of the corpuscles, so common in aestivo-autumnal infections, especially the quotidian, are very seldom if ever observed in the cells invaded by the quartan plasmodium.

The Sporogenic Forms of the Malarial Plasmodia Occurring in Human Blood.—I have so far described the forms of the various species of malarial plasmodia occurring in the blood of man which are concerned in *schizogony* only, but there occur other forms which do not sporulate in human blood and which are intended to continue the existence of the malarial-plasmodia in mosquitoes. It is a question whether these latter forms, which may be called sporogenic forms as they are concerned in *sporogony*, are introduced into the blood of man by the bite of the infected mosquito or whether they are elaborated during the development of the plasmodia in human blood. By some it is considered that the *sporozoites* introduced by the infected mosquitoes are of two varieties, those which develop into *schizonts* and those which develop into *gametes*, while other authorities believe that all of the sporozoites injected by the mosquito develop into *schizonts*, and that after a certain period of time certain of the *merozoites* produced by the sporulation of the *schizonts* become differentiated into forms which develop into *gametes*. According to Schaudinn, the

stimulus to the production of the *gametes* or *sporonts* is due to the reaction of the host, man, upon the plasmodium, and that such forms occur only after the infection has lasted for some time appears to be conclusive proof of this theory. Personally, I believe with Schaudinn that the *gametes* are produced only after the plasmodia have undergone sporulation for some time, and that, therefore, they are of human origin, being differentiated during the process of *schizogony*, and not introduced as such by the infected mosquito. In other words, all of the *sporozoites* introduced by the insect develop into *schizonts*, the *gametes* or *sporonts* developing from the *schizonts* after a certain time, some of the *merozoites* being thus differentiated. The development of the *merozoites* into *gametes* is much slower than into *schizonts*, taking, according to Schaudinn, twice as long. In his work upon *Plasmodium vivax* he found that the development of the *gamete* from the *merozoite* took 96 hours, while, as is well known, the development of the *merozoite* into the sporulating *schizont* occupies only 48 hours. Ruge does not agree with Schaudinn in this, but believes that the *gametes* develop coincidently with the sporulating *schizonts*, and that the majority of the *gametes* perish during apyrexia. I cannot agree with the theory of Ruge for it is well known that the *gametes* (crescents) of aestivo-autumnal fever may exist for months in the blood, during which time apyrexia has been practically constant.

The *gametes* are invariably of two kinds, male and female. They can be differentiated from one another and occur in varying proportions, the male organisms being the most numerous. Stephens and Christophers found in aestivo-autumnal infections, 53 *microgametocytes* (males) to 33 *macrogametes* (females), but Ruge found, in benign tertian infections, that the proportion varied very greatly in different cases, some infections showing equal numbers of male and female *gametocytes*, while in others he found only 1 *microgametocyte* to 50 *macrogametes*. It is very probable that the proportion varies somewhat in every case, due to the conditions favoring development brought about by the reaction of the system to infection.

The differentiation of the intracellular *gametes* from the *schizonts* is not difficult in most instances, if the following morphologic data be remembered:

1. Absence of "ring form" in all cases, the chromatin in the youngest stage or *trophozoite*, being situated in the center of the organism, surrounded by the protoplasm. Thus there is an absence of the nutritive vacuole which produces the ring-like appearance in this stage of the *schizont*.

2. The cytoplasm in the male *gamete* is more dense, and stains a deeper blue, than in the schizont, while in the female *gametes* it is less dense and stains very faintly.

3. The pigment is larger in amount in the *gametes* and more rod-like in form or in larger granules.

4. In benign tertian and in quartan infections the mature intracellular *gametes* are larger than the mature *schizonts*, there being a difference of from 2 to 6 microns in the diameter of the organisms.

5. In aestivo-autumnal infections the *gametes* are crescentic in form and are thus easily distinguished from the full-grown *schizont*.

Ruge states that any small unpigmented plasmodium showing the chromatin situated within the blue-stained protoplasm, with no unstained area between it and the protoplasm, should be considered as a *gamete*. Maurer describes the young *gamete* as circular in form, and composed of a broad, blue-stained band, enclosing a small amount of achromatic substance in which lies a large granule of bright red chromatin. In very deeply stained specimens a thick deep red border surrounds the organism, which is especially prominent in the crescentic *gametes*. As growth proceeds the disk form is lost, the achromatic substance disappears, the chromatin becomes broken up into small threads, and very coarsely granular pigment is developed. In the crescentic *gametes* a deep red border is observed surrounding them, which Maurer calls the capsule of the crescent. Maurer's description applies to specimens stained by Romanowsky's method, and I have confirmed all that he says many times in specimens stained by the method of Wright.

Schaudinn claims that in benign tertian infections, the male *gametes* or *microgametocytes* gradually disappear after the attack of fever has ceased, until in from three to six weeks only the female *gametes* or *macrogametes* can be found in the blood. I have not found that this is the case in aestivo-autumnal malaria, for in such infections I have observed both male and female *gametes* in the blood for weeks after the active symptoms had ceased, and in practically the same numbers during the entire period of observation.

In considering the forms of the malarial plasmodia, which may be observed in the blood of man, and which are intended to undergo development within mosquitoes belonging to the Anophelinæ, we have to consider, for each species of plasmodium, the *gametes* in general, and the *macrogamete*, the *microgametocyte*, and the *microgamete* in particular. The development of these forms will be considered in the next chapter of this work.

The Sporogenic Forms of Plasmodium Vivax Occurring in the Blood of Man.—In the study of the blood of benign tertian cases it will be observed that a certain number of the fully developed pigmented plasmodia do not sporulate, but become free in the blood as spherical bodies which are of two kinds, those which produce flagella or *microgametes*, and which are called *microgametocytes*, and those which do not form flagella, which are called *macrogametes*. The first are the male organisms, the second the female. In the stomach of the mosquito the *microgametes*, liberated from the *microgametocyte*, penetrate and fertilize the *macrogametes*, thus producing a *sporont*. In very rare instances this process of fertilization may be observed in blood which has been removed from the body for some time, and it is very common to observe the process of flagellation, as it is called, and the liberation of the flagellum or *microgamete*. In fresh specimens of tertian blood, the *gametes* cannot be distinguished until they are fully developed, but in stained specimens they can be distinguished without much difficulty in all stages of development.

EXPLANATION OF PLATE III.

Quotidian Aestivo-autumnal Plasmodium. (*Plasmodium falciparum quotidianum.*) Stained with Oliver's Modification of Wright's Stain.

1 to 11. "Ring forms" of the quotidian plasmodium.
11, 12. Pigmented forms of the quotidian plasmodium.
13. Presegmenting plasmodium.
14. Sporulating plasmodium.
15. Microgametocyte.
16. Macrogametes.

Chromatin, red; protoplasm, blue; vesicular portion of nucleus, unstained.

Tertian Aestivo-autumnal Plasmodium. (*Plasmodium falciparum.*) Same stain.

1, 2. "Ring forms" of the tertian aestivo-autumnal plasmodium.
3. Pigmented "ring form."
4, 5, 6, 7. Pigmented forms of the plasmodium.
8. Young gamete.
9. Nearly full-grown form, showing peculiar chromatin border.
10. Full-grown form.
11, 12. Sporulating pla modia.
13. Microgametocyte.
14. Macrogamete.

Group A. Gametes of *Plasmodium Vivax.* (Tertian plasmodium.)

1. Young microgametocyte.
2, 3. Fully grown microgametocytes.
4. Young macrogamete
5, 6. Fully grown macrogametes.
7. Extracellular macrogamete.
8. Flagellated microgametocyte.

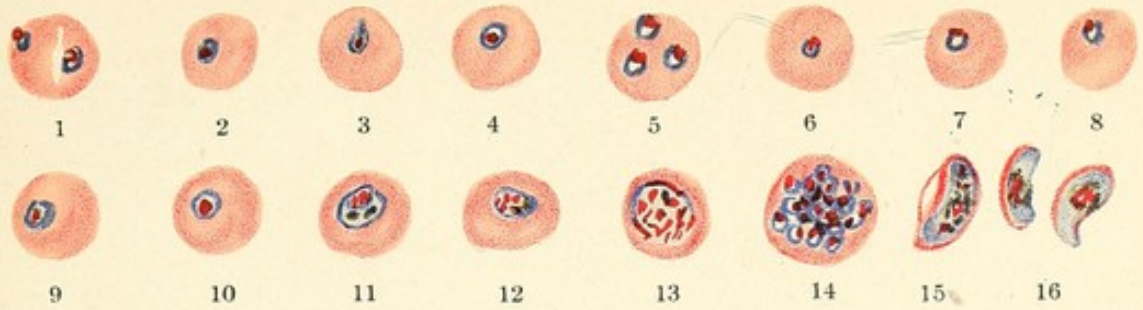
Group B. Gametes of *Plasmodium malariæ.* (Quartan plasmodium.)

1. Young microgametocyte.
2, 3. Fully grown microgametocytes.
4. Young macrogamete.
5, 6. Fully grown macrogametes.
7. Extracellular macrogamete.
8. Flagellated microgametocyte.

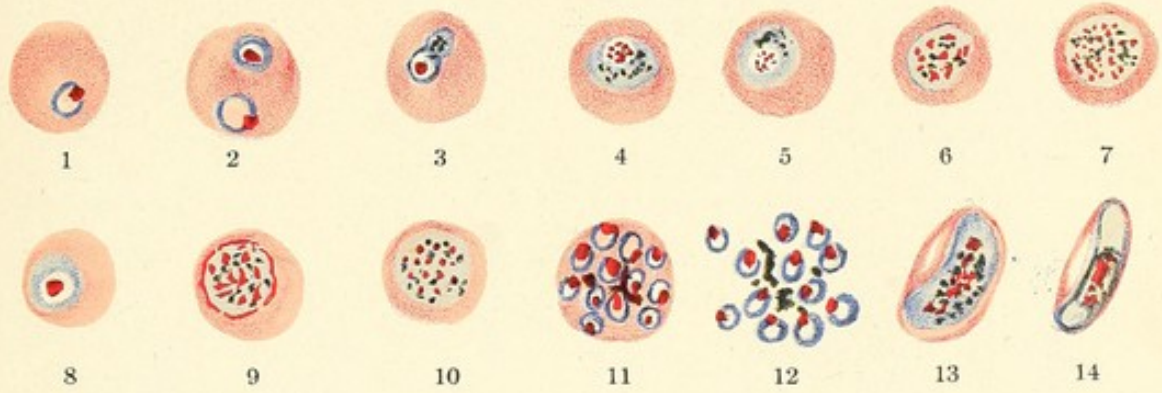
Group C. Gametes of *Plasmodium falciparum.* (Tertian aestivo-autumnal plasmodium.)

1. Young gamete.
2. Microgametocyte.
3. Macrogamete.
4, 5. Microgametocytes. (Crescents.)
6, 7. Macrogametes. (Crescents.)
8. Ookinetes.
9. Sporozoites.

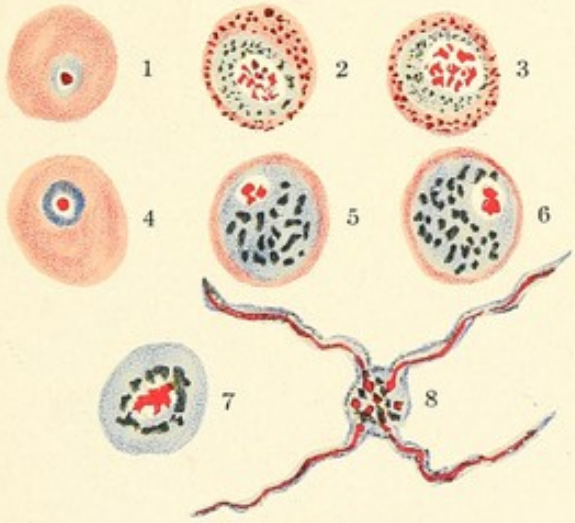
Plate III



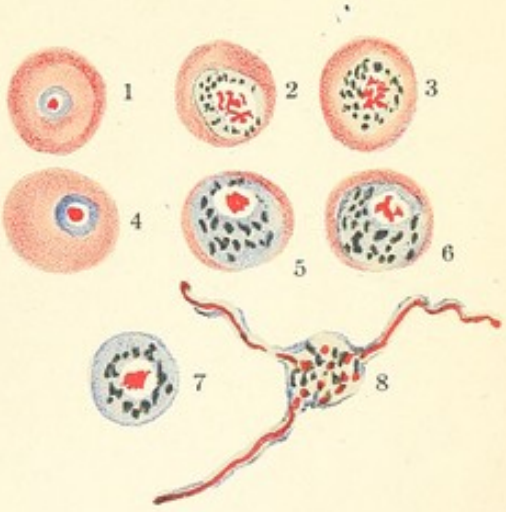
Quotidian Aestivo-autumnal Plasmodium.



Tertian Aestivo-autumnal Plasmodium.



Group A.



Group B.

Group C.

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C. F. CRAIG. DEL.

Fresh Preparations.—The Gametes.—In fresh specimens of blood the *gametes* of *Plasmodium vivax* cannot with certainty be distinguished as such until they are fully developed and liberated in the blood plasma by the disintegration of the red cell in which they have developed. At this time they can be easily differentiated into two forms, the *macrogamete* and the *microgametocyte*.

The Macrogamete.—The tertian *macrogamete* is a large, pigmented organism, measuring from 9 to 11 microns in diameter; the protoplasm appears slightly granular, and the pigment is in the form of large granules or clumps, arranged about the periphery of the organism, or commonly in a wreath-like form some distance from the periphery. The pigment is not motile, and exflagellation never occurs in the forms presenting this arrangement of the pigment granules. In rare instances a flagellum may be seen attached to the circumference of the *macrogamete*, and such an appearance always indicates an attempt at fertilization, and may be observed in the blood much more frequently than is generally supposed. Sometimes more than one flagellum or *microgamete* may be seen attached to the *macrogamete*, and their movements are peculiar and characteristic. Instead of the rapid serpentine lashings seen in the *microgametes*, when attached to the *microgametocyte*, the movements are of an entirely different character. The *microgametes* appear to straighten and then relax, revolving apparently very rapidly upon their axes; sometimes they may be seen to pull themselves loose from the *macrogamete* and again become attached to it. In the meanwhile the pigment within the *macrogamete* has maintained its circular arrangement, and is at most very slowly motile. The movements observed are produced by the efforts of the *microgamete* to penetrate the *macrogamete*, a process which normally occurs within the stomach of the mosquito.

The Microgametocyte.—The *microgametocyte* of *Plasmodium vivax* measures from 8 to 10 microns in diameter, is spherical in outline when fully developed, and free in the blood plasma, and contains a large amount of pigment in the form of large and small granules, distributed throughout the protoplasm. When first liberated from the red blood-corpuscle in which it has developed, the pigment is sluggishly motile, but in those *microgametocytes* in which *microgametes* are developing, the pigment soon becomes very actively motile, much more so than in any other form of malarial plasmodium, while the protoplasm of the organism also appears to be in motion, marked undulations of the periphery being often apparent. In those instances in which the pigment is immotile it is collected in small, irregular clumps throughout the protoplasm instead of about the periphery or in a wreath-like arrangement, as in the *macrogamete*. If a *microgametocyte* in which the pigment is in active motion be watched, in a variable length of time,—from five minutes to half an hour or more—the pigment will be seen to collect toward the center of the protoplasm, the motility becoming somewhat lessened, and suddenly, as though an explosion had occurred within the organism, there appear at certain portions of the

periphery long, thin, colorless, thread-like, actively moving filaments, which vary in number from two to six, and which undulate rapidly, lashing about among the red corpusles to which they often impart a perculiar spinning motion. These filaments are the *microgametes*.

There may now occur one of several things: either the *microgametes* may break loose from the parent plasmodium, which is the normal procedure, or, unable to do so, may become motionless and degenerate, or the *microgametocyte* may undergo degeneration before the *microgametes* have succeeded in freeing themselves. In the first instance, after the *microgamete* has lashed about among the red blood-corpuscles for a variable length of time, seemingly trying to free itself from the *microgametocyte*, it at last succeeds, and moves off in a serpentine manner among the red cells. In some instances the efforts of the *microgamete* to free itself are very vigorous, resulting in its pulling the *microgametocyte* about for appreciable distances in the microscopic field. After it becomes free the serpentine motion may be retained for a long time, even an hour or more. If it chances that only a single *microgamete* arises from the *microgametocyte*, the latter quickly degenerates after the liberation of the *microgamete*.

In those instances in which the *microgametes* are unable to free themselves from the plasmodium, after a time they become motionless, and the entire organism shrinks, becomes vacuolated, and finally disintegrates. In rare instances the *microgametocyte* undergoes degeneration before the *microgametes* are extruded or before they are able to free themselves from the parent body; in such instances the *microgametocyte* undergoes fragmentation, each fragment containing pigment. Careful observation will show that these fragments remain attached to one another for a long time by very delicate threads of protoplasm; if *microgametes* have developed before fragmentation, they become motionless and disintegrate, but the fragments containing the pigment may persist for a long time, and have been mistaken for new parasites of the blood. In one instance the pigment in one of these fragments was observed to be in active motion after a period of eight hours at room temperature.

The *microgametocyte*, after the *microgametes* have been liberated, quickly degenerates, either becoming vacuolated, or breaking up into small spherical bodies containing pigment. Not infrequently the entire organism remains as an irregular mass of cytoplasm containing the pigment in the form of irregular clumps collected toward the center, and absolutely motionless.

The Microgametes.—In fresh specimens of blood the tertian *microgamete* appears as a very slender, thread-like body, perfectly colorless, and having a serpentine, undulating motion, enabling it to progress among the blood-corpuscles which are displaced or moved about by its motions. A careful study of *microgametes* shows that considerable variations occur in individual specimens as regards appearance. I have already spoken of the variation in number and of the manner in which they free themselves from the *microgametocyte*. While still attached to the latter they often present a clubbed extremity, which changes its form, sometimes appearing blunt, sometimes pointed; after liberation of the

organism the extremities both appear pointed, and are difficult to distinguish. The *microgametes* measure from two to four times the diameter of the microgametocyte, but it is not uncommon to observe *microgametes* that are from five to eight times as long as the diameter of the parent organism. Besides the clubbed extremity that is often present, the *microgametes* sometimes show small nodular swellings along their course in which are a few pigment granules derived from the body of the *microgametocyte*. After liberation the *microgametes* appear to extrude this pigment and at the time they fertilize the *macrogametes* they are entirely hyaline in appearance. In rare instances short, very thick forms are observed, which have a very sluggish serpentine motion.

Stained Preparations.—In stained preparations of blood infected with *Plasmodium vivax* all stages in the development of the *gametes* can be easily recognized. During their intracorpuscular development they can be distinguished from the *schizonts* during the *trophozoite* phase somewhat more easily than during later stages of development, but after they have become extracorpuscular they can be distinguished without difficulty in nearly every instance of infection. The *merozoites* which are destined to develop into *gametes* cannot be differentiated even in stained preparations, from those destined to become *schizonts*.

The Gametes.—The *gametes* of *Plasmodium vivax*, in their earliest stage of development, when stained by Wright's method, consist of a perfectly circular mass of blue-stained protoplasm, in the center of which is a spherical dot of chromatin stained a deep red or violet. The achromatic zone, or nutrient vacuole, which gives the "ring" appearance to the young *schizont*, is not present in the *trophozoites* which become *gametes*, and the organism at this stage of development is larger than is the *schizont*. In those *gametes* which have become pigmented, the pigment is greater in amount than in the *schizonts*, and is distributed throughout the protoplasm. In such *gametes* the protoplasm stains blue and the chromatin, which is arranged in fibrils throughout the protoplasm, stains a pinkish red, and is not collected in masses at any stage in the development of the *gamete* while it is intracorpuscular. The *gametes* are always circular in shape at every stage of intracorpuscular development.

The following observations are of diagnostic importance in differentiating the benign tertian *gametes* from the *schizonts*.

1. The *gamete* is larger throughout its development than is the *schizont*.

2. It is much less amoeboid, and, therefore, is circular in contour in every stage of development in the red corpuscle.

3. No nutritive vacuole is present in the young *gametes*, and thus they are not "ring-like" in form. In stained preparations there is no achromatic zone surrounding the chromatin dot as in the *schizont*.

4. The *gametes* show very little amoeboid motion at any stage of their development.

5. The pigment in the *gametes* is much greater in amount and earlier developed than in the *schizonts*. It is present in almost the earliest forms, and

in the fully developed *gamete* is still motile, while it is motionless in the fully grown *schizont*.

6. The chromatin divides earlier in the *gamete* than in the *schizont*, is loosely arranged, and never separates into distinct masses.

7. The period of development within the red corpuscle is almost twice as long for the *gamete* as for the *schizont;* hence the greater amount of pigment in the former and its larger size.

After development, the *gametes*, if they are not ingested by mosquitoes, degenerate, and disappear after some weeks, although Schaudinn claims that the female *gamete* or *macrogamete*, under such circumstances, may undergo parthenogenesis and thus produce new generations of *schizonts*, leading to a relapse of the infection.

In stained specimens the *gametes* may be differentiated into male and female forms, the *microgametocytes* and the *macrogametes*.

The Macrogametes. (Female gametes.) In stained specimens the protoplasm of the *macrogametes* stains an intense blue, much darker than does the protoplasm of the *schizonts*. The nuclear chromatin is small in amount at all stages, consisting in the earliest stage of development of a minute dot and later of a few small dots or rods situated near the periphery of the organism, stained a bright red in color. The pigment is very dark, almost black in color, and is in the form of large rods, as much as 1 to 3 microns in length, in the fully developed *macrogametes*. It is very sluggish in motion and is apt to be collected in irregular masses toward the periphery or the center of the organism. It is very often observed arranged in a wreath-like manner close to the border of the organism. The *macrogametes* are always circular in contour.

The *macrogametes* may be distinguished from the *microgametocytes* by:

1. In the fresh specimen, a granular protoplasm containing much nutrient material, visible as large refractive granules. When stained, by the dark blue color of the protoplasm.

2. The *macrogamete* has a smaller amount of nuclear chromatin, sometimes only a few dots, situated about the periphery of the organism.

3. A longer period of development and greater persistence in the blood of man after the active symptoms of malaria have ceased.

4. Larger size, measuring from 13 to 16 microns.

5. Darker colored pigment, consisting of large rods measuring from 1 to 3 microns in length. The benign tertian *macrogamete* is the only form of the malarial plasmodia presenting such large rods of pigment.

6. Less active movement of the pigment and its arrangement in a wreath-like formation.

The Microgametocytes.—The *microgametocytes* of *Plasmodium vivax*, in their various stages of development, differ somewhat in the appearances they present in stained specimens. During their earliest intracorpuscular stage they are distinguished from other forms by the pale blue staining of their protoplasm, which, in the larger forms, sometimes appears hyaline even in stained prepara-

tions. The chromatin is large in amount and stains an intense red. In the fully developed form, just before the development of the *microgametes* or flagella, the chromatin is seen to be divided into from four to eight masses, which are collected at the periphery of the organism. In those organisms which are stained while undergoing exflagellation, the chromatin may be traced into the flagella, and when the process is complete the body of the *microgametocyte* is generally entirely free of chromatin. In such forms the protoplasm stains a pale blue, while the pigment, in the form of minute dots or very slender, short rods, stains a greenish-blue in color. The pigment is larger in amount than in the *macrogamete*.

In the *microgametocytes* the chromatin is much larger in amount than in the *macrogametes*, sometimes comprising from one-third to one-half of the parasite; it is often collected into large irregular masses or in well-defined fibrils, some of which are of considerable thickness. According to Zieman, the proportion of chromatin to plasma in the *microgametocytes* is from 1 to 1 to 1 to 4, while in the *macrogometes* it is from 1 to 8 to 1 to 12.

In stained specimens the shape of the *microgametocytes* is oval or circular prior to the development of the *microgametes*, and they are smaller than the *macrogametes*, and are seldom larger than the fully developed *schizont*.

The following points serve to differentiate the *microgametocyte* of *Plasmodium vivax* from the *macrogametes:*

1. The pale blue staining of the protoplasm.
2. The larger amount of chromatin and its arrangement in masses.
3. In the fresh specimen the lesser amount of amoeboid motion.
4. In fresh specimens the greater amount of pigment which is much more motile and greenish in color. The movement of the pigment which has aptly been characterized as a "swarming motion" serves to distinguish the *microgametocyte* from either the fully developed *schizont*, in which the pigment is motionless, and from the *macrogamete*, in which the pigment is either motionless or very slightly motile and generally arranged in a wreath-like manner.
5. The presence of flagella or *microgametes*.
6. The smaller size of this form of the plasmodium.

The Microgametes.—The *microgamete* of *Plasmodium vivax* in stained preparations of blood is seen to consist of a mass of pale blue stained protoplasm containing a considerable amount of brilliant red chromatin, in the form of threads, granules, or irregular masses. The shape of the organism is thread-like with pointed ends, and it may well be likened to a spirochaete devoid of an undulating membrane. Most of the *microgametes* consist very largely of chromatin, only a small amount of protoplasm being visible, but occasionally the chromatin is small in amount or even absent. Where no chromatin is present it is certain that the *microgametes* are sterile. The above description applies to the free *microgametes*, the appearance of those still attached to the parent body having already been noticed.

The Sporogenic Forms of Plasmodium Malariae Occurring in Human

Blood.—The *gametes* of *Plasmodium malariae*, the quartan malarial plasmodium, are very similar to those of *Plasmodium vivax*, in both fresh and stained specimens of blood, and I shall describe them but briefly, as much that has been said regarding the gametes of *Plasmodium vivax* is equally true of the *gametes* of *Plasmodium malariæ*.

The Gametes.—The *gametes* resemble very closely those of *Plasmodium vivax* in all stages of intracorpuscular development, and can only be distinguished by their smaller size and the absence of swelling of the infected red blood-corpuscle. After becoming fully developed and extracorpuscular, male and female forms may be distinguished, the *microgametocytes* and the *macrogametes*.

The Macrogametes.—The *macrogametes* of *Plasmodium malariae* are very hard to distinguish from the *schizonts*, as the quartan plasmodium is always round in form and lacks amoeboid motion after the development of pigment. In the earliest stage the absence of the nutritive vacuole, or achromatic zone, in stained specimens, is distinctive of a *gamete*, but the quartan *schizont* also loses the achromatic zone at an early stage of development, and the distinction becomes impossible. In the fully developed *macrogamete* the granular, solid appearing protoplasm and the greater amount of very coarse pigment renders the distinction less difficult. In stained specimens the free *macrogametes* are distinguished by their large size (11 to 12 microns in diameter) and smaller amount of undivided chromatin.

The Microgametocytes.—The description already given of the *microgametocyte* of *Plasmodium vivax* is true, in most respects, of the *microgametocytes* of the quartan plasmodium. There is the same pale staining protoplasm, the large amount of chromatin, the swarming pigment, and the development of *microgametes* or flagella, which are formed in the same manner, and present the same appearances in both fresh and stained specimens of blood. They differ from the tertian *microgametocytes* in their smaller size and less motile pigment, which is in larger granules.

The Microgametes.—The description given of the *microgametes* of *Plasmodium vivax* is equally true for the *microgametes* of the quartan plasmodium and, so far as I am aware, we have no data sufficient to distinguish this form of the two plasmodia.

The Sporogenic Forms of Plasmodium Falciparum and Plasmodium Falciparum Quotidianum Occurring in Human Blood.

The sporogenic forms, or *gametes*, of the aestivo-autumnal plasmodia are distinguished from similar forms of other human malarial plasmodia by their crescentic shape, a peculiarity which makes their differentiation easy and possible to even the tyro in the examination of malarial blood. As the differences between the *gametes* of the malignant tertian and the quotidian aestivo-autumnal plasmodia are merely differences in size and in shape, I shall not

describe these forms separately, but shall consider the general morphology of the aestivo-autumnal *gametes* in both fresh and stained specimens of blood, noting the differential points between the two species as suggested by the general description.

The crescents occur only in the blood of aestivo-autumnal infections, and only after the infection has persisted for some time. Canalis claims that he has never but once seen crescentic bodies in the peripheral blood before the fifteenth day of the disease, but, in most instances, they may be found in cases after the disease has been active for something over a week, twelve days being the average time for their development. They persist in the blood for weeks after the active symptoms of infection have ceased and gradually disappear unless new infection occurs. They are not affected by quinin, nor do we know of any drug that is capable of destroying this form of the plasmodia. This is also probably true of the *gametes* of the benign tertian and quartan plasmodia.

Although the crescentic shaped *gametes* develop in a considerable proportion of aestivo-autumnal infections, it is by no means true that every such infection shows these forms, and from personal observation, both in the tropics and in this country, I believe that not over 50 per cent. of such infections present crescents in the peripheral blood. If blood from the spleen be examined or smears of the bone-marrow, crescents will be observed in a greater proportion of cases, but in many aestivo-autumnal infections the formations of *gametes* appears to be entirely absent. Manson believes that crescents are more frequently observed in cases of malaria which have been contracted in the tropics, but have returned to temperate regions, and that in the tropics it is much more rare to observe this form of plasmodia. I do not agree with this, for I have found that the percentage of cases showing crescents in the tropics is practically the same as in temperate regions. It often requires a long and patient search to demonstrate the presence of crescents in the blood of individuals who have suffered from aestivo-autumnal infections, and, while I believe that a prolonged search would show crescents in 50 per cent. of such cases, still in the study of several hundred cases I have only been able to demonstrate this form in a little over 33 per cent. Rogers found that crescents were present in only 10 per cent. of the cases he observed in Europe.

The crescentic *gametes* of the aestivo-autumnal plasmodia, like the *gametes* of the benign tertian and quartan plasmodia, develop within the red corpuscle, and, when fully grown, can be differentiated into male and female forms, the *microgametocytes* and the *macrogametes*. Their after-development is similar, the *microgametocyte* developing *microgametes* which become free and fertilize the *macrogametes*. The process of *microgamete* formation, or flagellation, as it is called, may be observed in blood which has been removed from the body for some time and in which a sufficient amount of moisture is present, and does not differ from the same process as observed in the *gametes* of tertian and quartan plasmodia, which has already been described. The crescentic *microgametocyte* becomes oval and later round in form, after which

the *microgametes* or flagella are developed as in the other malarial plasmodia (see Fig. 10).

Fresh Preparations.—The crescentic *gametes* of the aestivo-autumnal plasmodia are developed within the red corpuscles and during their intracorpuscular stage are distinguished from the *schizonts* by their limited amoeboid motion, the early development of a greater amount of pigment within them, the crescentic or ovoid form acquired during the latter stages of intracorpuscular development, and their longer period of development. Their protoplasm is more opaque and granular in appearance and the pigment is darker in color. Just before the *gametes* are liberated from the red corpuscles they have become definitely crescentic in shape and may be differentiated into male and female forms. The red cell has shrunk about the parasite, forming a membrane-like covering, one portion of which, that connecting the poles of the crescent,

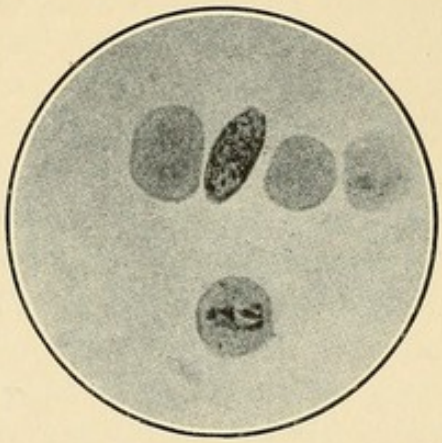

FIG. 10.—Tertian aestivo-autumnal "ring form" and *microgametocyte*. (Ovoid form.) Photomicrograph × 1200.

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forms a hemispherical projection, the so-called "bib" of the crescent. In the youngest crescentic forms the pigment is distributed throughout the protoplasm, but in the older forms it becomes collected at the center or toward one of the extremities. The border of the crescent is sharply defined, being represented by a single or double refractive outline, often of a bright green color, due to the color of the red corpuscle which forms an enveloping membrane. The pigment in the crescentic *gametes* is generally immotile, but in a few instances I have observed sluggish motility.

The Macrogamete.—The *macrogamete*, or female crescent, in both species of aestivo-autumnal plasmodia, is distinguished from the *microgametocyte*, or male crescent, by its slender form, the arrangement of pigment, and the fact that it does not develop *microgametes* or flagella. This form measures from 11 to 15 micra in length by 2 to 3 micra in breadth. The pigment is dark brown in color, immotile, and either concentrated in the center of the crescent in a dense mass or arranged in a wreath-like manner near the center of the parasite. The protoplasm is opaque and granular in appearance. After becoming extracellular, which normally occurs within the stomach of the mosquito, but which may often be observed in human blood, the *macrogamete*

becomes first ovoid and then circular in shape, having a clear-cut hyaline border, a granular protoplasm, and the pigment arranged in a wreath-like manner about the center of the organism. Not infrequently the pigment is divided into small, almost black dots, arranged in a perfect circle midway between the center and the periphery of the parasite.

The *macrogametes* of the quotidian aestivo-autumnal plasmodium are distinguished from those of the tertian by their smaller size, the pointed extremities of the crescent, the smaller amount of pigment, and its division into fine granules instead of into rods, the less granular protoplasm, and the absence, at any time, of a double outline. The quotidian *macrogamete* never measures more than 8 or 9 microns in length, while the malignant tertian generally exceeds 12 microns.

The Microgametocyte.—The *microgametocytes* of both species of aestivo-autumnal plasmodia are shorter and plumper in appearance than are the *macrogametes*, being kidney-shaped rather than crescentic. They measure 7 to 10 microns in length by 3 to 5 microns in breadth, and may have a double or single border of a greenish color. The protoplasm is less opaque and granular than in the *macrogametes* and the pigment is in finer particles and distributed throughout the protoplasm or collected at the poles of the crescent. As in the other malarial plasmodia, the *microgametocytes*, when liberated from the corpuscle in which they have developed, produce *microgametes* or flagella. This process is often observed in properly collected specimens of human blood and is essentially the same as the like process already described in the benign tertian and quartan plasmodia. The crescentic or kidney-shaped *microgametocyte* becomes ovoid and then round, the pigment becomes very actively motile, the entire protoplasm of the organism appears violently agitated, and soon one or more slender filaments are projected from the periphery of the organism and lash about among the surrounding blood-corpuscles. These filaments are the *microgametes*. The *microgametocytes* of the quotidian aestivo-autumnal plasmodium are distinguished from those of the malignant tertian plasmodium by their small size, seldom measuring over 7 microns in length, and by their very plump appearance which often renders them ovoid rather than crescentic in shape. The pigment is also smaller in amount and less motile.

The Microgametes.—In fresh specimens of blood the *microgametes* of the aestivo-autumnal plasmodia appear as very delicate, hyalin filaments, having an active serpentine motion, enabling them to move about among the blood-corpuscles. The *microgametes* cannot be distinguished from those occurring in quartan and tertian infections, nor can the *microgametes* of the two species of aestivo-autumnal plasmodia be distinguished from one another.

Stained Preparations.—The staining reactions of the aestivo-autumnal *gametes* are essentially similar to those of the tertian and quartan *gametes*, when Wright's stain is used, the protoplasm staining blue, the chromatin red, the achromatic zone surrounding the chromatin in the *schizont* being absent in these forms.

The Gametes.—In their earliest stages of development, the aestivo-autumnal *gametes* are distinguished from the *schizonts* by their spherical shape, by the deep blue staining of their cytoplasm, by the situation of the chromatin within the center of the parasite instead of at one side, and by the presence of a deep red line surrounding the exterior of the *gamete*, in some instances. In stained specimens the signet-ring appearance so frequently observed in aestivo-autumnal *schizonts* is not observed in the *gametes*.

The Macrogamete.—In stained specimens the protoplasm of the *macrogamete* is colored a deep blue, most intense at the poles of the crescent; the chromatin stains a brilliant red and is situated at or near the center of the crescent. The pigment stains a greenish-brown and often surrounds the chromatin as a distinct wreath, or is collected in small circular masses near the chromatin. The remains of the red blood-corpuscle surrounding the crescent are stained a salmon or bright pink and not infrequently a deep red band may be observed surrounding *macrogametes* which are apparently free in the blood plasma. The pink stained remains of the red blood-corpuscle often appear as an irregular, jagged rim around the crescent, and the "bib" as a faintly staining mass occupying the concavity of the *macrogamete*, having a brightly stained, pink border.

In stained specimens of blood the aestivo-autumnal *macrogametes* present the following features which enable us to distinguish them from the *microgametocytes:*

1. The long slender shape of the crescent.

2. The situation of the chromatin in a dense mass at or near the center of the crescent.

3. The deep blue staining of the protoplasm.

4. The concentration of the pigment in little masses or in a wreath-like manner about the chromatin.

The Microgametocyte.—The protoplasm of the *microgametocyte* stains a delicate blue, and in many instances it is almost impossible to stain it at all. The chromatin stains a delicate red and is in the form of a loose network spread over the greater portion of the crescent. The pigment is granular in appearance and is distributed throughout the crescent. The amount of stained protoplasm is very small as compared with the protoplasm of the *macrogamete*, and the chromatin is often almost invisible on account of the delicate fibrils of which the chromatin network is composed. The staining of the red blood-corpuscle surrounding the *microgametocyte* is similar to that already described for the corpuscle containing the *macrogamete*. In stained specimens containing the oval and round forms of the *microgametocyte*, the chromatin is found to be collected in irregular masses, staining a deeper red, and situated toward the periphery of the plasmodium. The following features enable us to distinguish the aestivo-autumnal *microgametocyte* from the *macrogamete* in stained specimens of blood:

1. The plump kidney shape of the crescent.

2. The pale blue staining of the protoplasm.

3. The pale red staining of the chromatin, which is arranged in a loose network, occupying a large portion of the crescent.

4. The distribution of the pigment throughout the protoplasm of the crescent.

There are no essential differences in the staining reactions of the *macrogamete* and *microgametocytes* of the quotidian and malignant tertian aestivo-autumnal plasmodia.

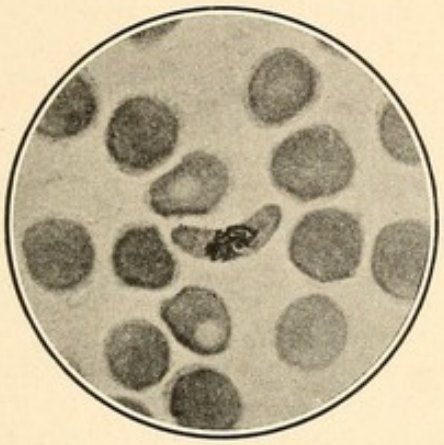

FIG. 11.—Aestivo-autumnal tertian *macrogamete*. Note slender form. Photomicrograph, × 1200.

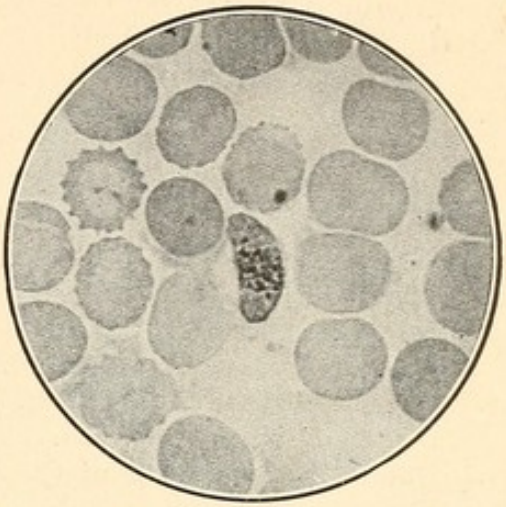

FIG. 12.—Tertian aestivo-autumnal *microgametocyte*. Note plump form. Photomicrograph, × 1200.

The Microgametes.—As in the quartan and benign tertian plasmodia, the *microgametes* of the aestivo-autumnal plasmodia are seen to consist, in stained specimens, of a filamentous mass of chromatin, enclosed by a small amount of protoplasm. No essential differences are noted in the *microgametes* of any of the malarial plasmodia, so far as staining reactions are concerned.

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CHAPTER III.

Development of the Malarial Plasmodia Within the Mosquito: Mosquitoes; Structure; Ova; Larvae; Pupae; Habits; Distribution; Classification. Mosquitoes Proven to Transmit Malaria; The Relation of Number of Infected Mosquitoes to Malarial Infection in Various Localities.

Development of the Malarial Plasmodia within the Mosquito.—In the previous chapter I have described the forms of the malarial plasmodia destined to undergo development within the mosquito and which may be observed in the blood of man. Thus I have described the *macrogametes*, the *microgametocytes* and the *microgametes*, and also the fertilization of the *macrogamete* by the *microgamete*, a process which may be observed in human blood after it has been removed from the body, but which normally occurs in the middle intestine of the mosquito. In this chapter I shall describe the changes occurring after the fertilization of the *macrogamete* and trace the cycle of development of the plasmodia within the mosquito.

Historical Summary.—The conception that mosquitoes transmit malaria is by no means a recent one, such a theory having been held by the early Roman observers, Varro, Columella, and Vitruvius. Many of the people of both civilized and uncivilized nations have believed that these fevers are due to the mosquito, and Koch is authority for the statement that in German East Africa the native name for malaria, Mbu, is also the native name for the mosquito, and that the people firmly believe that the fever is due to the bite of these insects. In 1848, Nott, of New Orleans, in a paper upon yellow fever, speaks of the transmission of malaria by the mosquito as a fact, and in 1883, King, of Washington, advocated this theory very vigorously, and compiled a great mass of evidence in its favor. After the appearance of King's paper, numerous writers published arguments in favor of such a method of transmission, chief among whom may be mentioned Laveran, in 1884; Flügge, in 1891; Pfeiffer, in 1892, and Manson, in 1894.

In 1896, in his Goulstonian lectures, Manson anew directed attention to this subject, and while some of his deductions have been proven to be erroneous, it is unquestionably true that to this author we owe the stimulation of interest which resulted in the discovery of the true relation of the mosquito to the malarial fevers. Manson stated in these lectures his belief that the crescentic and flagellated parasites are the extracorporeal sporulating homologues of the intracorporeal sporulating plasmodia, and that, as the mosquito had been proven to remove from man *Filaria nocturna*, acting afterward as a host of this parasite, so the same insect might remove these extracorporeal bodies of the malarial parasites and constitute the host for these particular bodies. Manson did not, at that time, believe that the mosquito inoculated malaria into man, but that the insect removed from man certain stages of the plasmodium which afterward underwent development within the mosquito, and which were then liberated in the water and dust and thus infected man.

To Ross, a Surgeon-Major of the Indian Army Medical Service, we owe the discovery of the true relation of the mosquito to the malarial fevers. Stimulated by Manson's theories regarding this subject, this investigator, in 1895, studied the development of the parasites of aestivo-autumnal fever in the mosquito, and proved that the crescents underwent definite changes within the stomach of the insect, flagella developing in the same manner as has been described when this process occurs in the blood of man. Later this investigator, in 1897, described the large cyst-like bodies situated in the outer layer of the stomach wall, and considered that these were developmental forms of the plasmodia within the tissues of the mosquito, and that he had at last been successful in finding the mosquito in which the malarial plasmodia underwent their extra-corporeal cycle of development.

In 1896 Bignami stated it as his belief that the mosquito inoculated malaria in man during the act of biting, the organisms being introduced with the saliva of the insect, and that this method of transmission of the disease is of greater importance than transmission by air or water.

In 1898 Ross studied very carefully the malaria of birds, due to *proteosoma* and *halteridium*. In mosquitoes which had been allowed to bite birds infected with *proteosoma*, he found in the stomach wall large pigmented bodies similar to those observed previously in mosquitoes which had bitten malarial subjects; he found that these bodies increased in size until they protruded from the stomach wall of the insect, and that there developed within them a large number of delicate thread-like bodies, which, after rupture of the cyst in which they had developed, were liberated into the body-cavity of the insect. He was able to trace these bodies to the cells and ducts of a gland located in the thorax, and which possesses an efferent duct leading into the proboscis. This gland Ross considered as a venemo-salivary gland, and he then advanced the theory that the thread-like bodies were injected into the bird when the insect bit, and that they began anew the life cycle of the proteosoma in the bird. He proved this theory experimentally by allowing infected mosquitoes to feed on healthy birds, and found that "1. Out of 28 originally healthy sparrows subjected to the bites of gray mosquitoes previously fed on diseased sparrows, 22, or 79 per cent., became infected, all with a very large number of parasites, in from five to eight days. 2. Out of two crows and four weaver-birds, one of the crows and all of the weaver-birds showed a copious proteosoma infection within nine or ten days of being bitten by gray mosquitoes fed previously on sparrows with proteosoma." Ross was thus able to prove beyond question that the malaria of birds is transmitted by the mosquito, and he stated it as his belief that what had been found true of bird malaria would also be found true of human malaria.

In 1897 MacCallum, in studying the development of halteridium, a blood parasite of birds, observed that the fully developed extracellular *halteridium* consisted of two forms, one of which was flagellated, the other non-flagellated. He observed that the flagella, breaking away from the flagellated form, penetrated the non-flagellated organisms, and that after penetration a motile body resulted which moved about among the blood-corpuscles, and which was capable of penetrating and destroying them. His observation was confirmed later by Ross, Koch, and Marchoux. The discovery of MacCallum explained the occurrence of pigment within the cystic bodies in the stomach of the mosquito and also demonstrated that the development of these organisms is sexual in nature, and that the flagella alone are incapable of development.

The demonstration, experimentally, that mosquitoes transmit malaria to man we owe to Italian investigators who, following the work of Ross and MacCallum, endeavored to produce malaria in man by allowing infected mosquitoes

to bite healthy individuals. In 1898, in Rome, Bignami endeavored to produce malaria in man in this way, but was not successful, probably because he did not use the right species of mosquito in his experiments. Later in the same year this observer was successful in producing an attack of aestivo-autumnal malaria in man by allowing mosquitoes which had bitten an infected individual to bite a patient who had never had malaria. In the same year, Bastianelli, Bignami, and Grassi were successful in producing a double tertian infection in man by the bites of infected *Anopheles*. In February, 1899, they were successful in infecting *Anopheles maculipennis* with quartan plasmodia, and were able to trace the developmental stages of this species of plasmodium in the mosquito. They were also able to report a second successful experiment with the benign tertian plasmodium and another with the aestivo-autumnal plasmodium. In April, 1899, Bastianelli and Bignami reported three successful inoculation experiments, the first, a double tertian infection; the second, a tertian infection, and the third, an infection with one of the aestivo-autumnal plasmodia. The experiments of the Italian observers have been again and again confirmed by numerous investigators whose results will be considered fully in the chapter of this work dealing with the methods of transmission of the malarial fevers.

General Description of the Mosquito Cycle (Sporogony).—I have already described the process of flagellation, as it is called, and the fertilization of the *macrogamete*, or female plasmodium, by the *microgamete*, or male plasmodium. This process occurs in nature in the middle intestine of the mosquito, after the insect has bitten an infected individual. The result of this fertilization is known as the *zygote* or *sporont*. After a certain period of time the *zygote* becomes elongated and finally motile and is then known as the *ookinete*. The *ookinete* penetrates the wall of the middle intestine and eventually becomes situated on the outer side of the epithelium and the basement membrane of the intestine between the adipose tissue and the muscular wall. Here the organism becomes spherical in shape and forms a cyst known as the *oocyst*. At this stage the protoplasm is granular and reticular in appearance, the pigment is reduced in amount, and the entire organism is enclosed within a well-defined capsule. The *oocyst* is formed at about the third or fourth day after infection of the mosquito. About the fifth or sixth day the *oocyst* enlarges and within it are formed spherical refractive bodies known as *sporoblasts*. At this stage the organism is increased so much in size that it projects from the intestinal wall. Besides the *sporoblasts*, the cyst contains some pigment and minute granules which resemble fat. At the end of a week the *sporoblasts* have produced a large number of delicate filaments having pointed extremities and containing a small amount of nuclear chromatin. These filaments are the *sporozoites*, measure about 14 microns in length, and are arranged in a ray-like manner about a central mass which may contain pigment. At this stage the capsule of the *oocyst* is very distinct. The *sporozoites* are finally liberated by the rupture of the *oocyst* and gradually make their way to the cells and tubules of the salivary glands of the insect. When this has occurred the mosquito, in the act of biting, will inoculate the *sporozoites*, which, penetrating the red blood-cells, develop into *merozoites*, and the human cycle of the plasmodium begins. The entire

cycle of development in the mosquito is completed in from 10 to 14 days, so that the insect may bite two or three times before it is infectious.

The following biological terms are applied to the forms of the malarial plasmodia concerned in *sporogony*, or development within the mosquito.

1. *Macrogamete*, in tertian and quartan infections the female spherical bodies, and in aestivo-autumnal infections the female crescent.

2. *Microgametocyte*, in tertian and quartan infections the male spherical bodies, and in aestivo-autumnal infections the male crescent.

3. *Microgamete*, the liberated flagellum of the *microgametocyte*.

4. *Zygote* or *sporont*, the result of the fertilization of the *macrogamete* by the *microgamete*.

5. *Ookinete*, the motile stage of the *zygote* or *sporont*.

6. *Oocyst*, the cystic stage of the *ookinete*.

7. *Sporoblasts*, developed within the *oocyst*.

8. *Sporozoites*, bodies developed within the *sporoblasts* and liberated by the rupture of the *oocyst*, which are introduced into man by the mosquito, and which are capable of beginning the human life cycle, or *schizogony*, of the plasmodia by infecting the red blood-corpuscles.

The cycle of development within the mosquito has been studied in all species of malarial plasmodia, and infection of man by the mosquito has been demonstrated with all species of the plasmodia.

Detailed Description of Sporogony of the Plasmodia of Malaria.—A great amount of study has been devoted to the changes occurring in the plasmodia of malaria during *sporogony*, and it may be stated that every stage of this life cycle has been thoroughly investigated and described by numerous writers upon the malarial fevers. The following description is derived partly from personal observations and partly from the observations of others, notably those of Schaudinn, Grassi, Bastianelli, and Bignami.

Previous to the formation of the *microgametes*, the *microgametocytes* undergo certain changes which are of interest. The nucleus gives off a large amount of chromatin, which becomes arranged about the periphery of the organism, and which enters into the formation of the thread-like *microgametes*. It would appear that this chromatin is taken up by the *microgametes* just before the latter emerge from the body of the *microgametocyte*, for in stained specimens it is but seldom that any chromatin is observed in the residual body immediately after the appearance of the *microgametes*.

The only change observed in the *mac ogamete* prior to fertilization concerns the nucleus, a portion of the substance of which is claimed by Schaudinn to be eliminated.

When fertilization occurs, the *microgamete* penetrating the *macrogamete*, the chromatin of the former constitutes a pronucleus which fuses with the female pronucleus of the *macrogamete*, and a fertilization spindle is thus formed, which is often very well defined in properly prepared specimens. The organism resulting from the union of the *micro-* and *macrogamete*, or the *zygote*, does not

encyst, but develops into an elongated vermicule or *ookinete*. This body is somewhat oval in shape, the anterior extremity being very narrow and pointed while the posterior extremity is broad and rounded in appearance. The nucleus is situated a little posterior to the middle of the body and is composed very largely of chromatin, which takes a deep red stain with Wright's method of staining. The pigment is collected in a loosely arranged mass near the posterior extremity and later in the development of the *ookinete* may be extruded or may be retained until the formation of the *sporozoites*, when it is liberated together with a portion of residual protoplasm. The movements of the *ookinete* are very active, consisting of contractions of the body and of a rapid progressive motion, gliding in character, no satisfactory explanation of which has as yet been given. Schewiakoff believes that the gliding progressive motion is due to the secretion and extrusion of a gelatinous thread which pushes the organism forward as it is formed, while Crawley thinks that the motion is due to wave-like contractions of the protoplasm. However the motion is produced, it enables the *ookinete* to force its way through the epithelial lining of the mosquito's stomach and reach that portion of the stomach wall immediately beneath the epithelial lining where it rests and the *oocyst* is formed. When it reaches this locality the *ookinete* becomes spherical in shape and secretes a delicate covering membrane, continuing to grow until it projects from the stomach wall toward the body cavity of the insect.

The nucleus divides and each daughter nucleus is surrounded by a portion of protoplasm, forming the *sporoblasts;* the *sporozoites* are developed within the *sporoblasts* by the repeated division of the nucleus of each *sporoblast*, the small nuclei thus produced accumulating upon the surface of the *sporoblast* and forming delicate protoplasmic prolongations, each consisting of a little protoplasm and a clump of chromatin, eventually forming the *sporozoites*. When development is complete, the cyst is filled with a multitude of *sporozoites* together with some residual protoplasm, and in many instances considerable pigment. When the cyst ruptures, the *sporozoites* are liberated in the body cavity of the insect and are carried by the blood to the salivary glands, from which they pass down the proboscis to the blood of man when the mosquito bites. The *sporozoites* are actively motile, spindle-shaped, and measure about 14 microns in length.

The time consumed in *sporogony* has been variously estimated at from 10 to 14 days, the average being 10 to 12 days. It varies, in all probability, with each species of plasmodium, but never exceeds 14 days.

The fertilization of the *macrogamete* by the *microgamete*, first observed in human malaria by MacCallum, has been observed by Koch, in Africa, and by Ashburn and myself, in the Philippine Islands, in blood from malarial cases removed for some time from the body.

To those who are interested in tracing the development of the malarial plasmodia within the mosquito, the following description, arranged in periods of time may prove useful.

First and Second Days After Ingestion of Malarial Blood.—The fusiform and spindle-shaped *ookinetes* penetrate the epithelial lining of the insect's stomach and reach the muscular layer, where they encyst and form the *oocyst*. In stained specimens the *ookinete* presents at or near the center a deep red chromatin mass, representing the nucleus, the chromatin being in the form of short, very delicate threads or granules. The pigment is collected in a dense clump at the posterior end or is distributed throughout the protoplasm; the

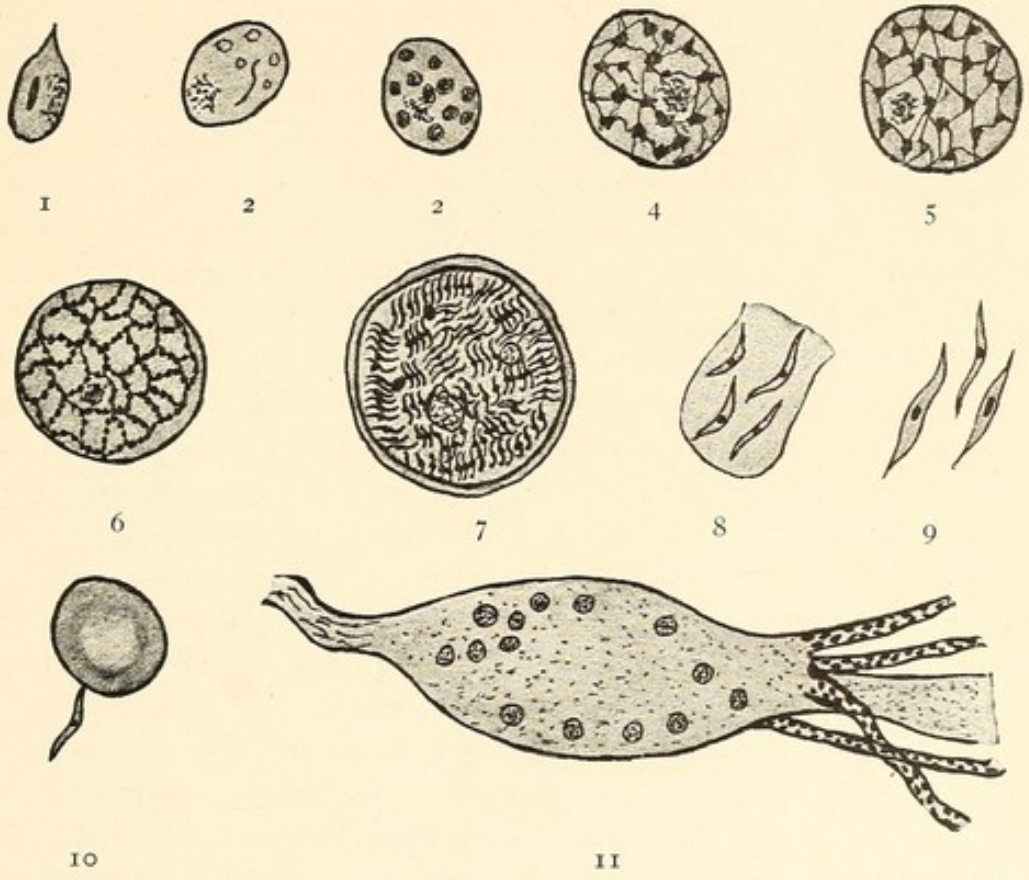

Fig. 13.—Development of Plasmodium vivax within the Mosquito.
1, Ookinete; 2, Oocyst; 3, 4, 5, Oocysts showing the development of sporoblasts; 6 and 7, Oocyst showing development of the sporozoites, which are fully formed in 7; 8, Sporozoites within a cell of the salivary gland; 9, Sporozoites; 10, Entrance of sporozoite into a red blood-corpuscle; 11, Middle intestine (stomach) of mosquito, showing several oocysts in the wall of the organ.

protoplasm contains numerous vacuoles and stains a light blue color. The *oocyst* at the end of two days is about the size of a red blood-corpuscle, contains considerable pigment distributed throughout the protoplasm, and the chromatin is found in small granules or in minute irregular masses, collected toward the center of the organism.

Third and Fourth Days.—During the third and fourth days the *oocyst* increases to twice its original size, and develops a well-marked cyst wall. The pigment is not increased in amount, and is collected in small masses; the protoplasm is vacuolated and the chromatin is distributed throughout it in fine granules or delicate threads.

Fifth and Sixth Days.—At the end of the sixth day the cyst has increased very greatly in size, measuring from 35 to 75 microns in diameter, and projects from the wall of the stomach outward toward the body cavity of the insect. The protoplasm appears granular, and large, very refractive spherical bodies may be distinguished within it, the *sporoblasts*. The pigment has not increased in amount and, owing to the great increase in size of the organism, appears to have greatly diminished; in some instances the cyst, at this stage, is devoid of pigment. The chromatin is collected in the sporoblasts and stains red, while the protoplasm stains a very pale blue.

Seventh to Eighth Days.—Under favorable circumstances, and in some species of *Anophelina*, the cysts have attained their full growth in eight days. At this time a well-marked double outlined membrane surrounds them, which is perfectly smooth in contour; the *sporoblasts* form common centers from which radiate multitudes of delicate, elongated, spindle-shaped, or thread-like bodies, the *sporozoites*. The *sporozoites* appear to originate from the outer layers of the *sporoblasts*, each *sporozoite* being attached by its inner extremity to a small portion of the residual protoplasm of the sporoblast. When isolated and stained each *sporozoite* measures from 12 to 14 microns in length, and contains one or more masses of chromatin imbedded in the light blue protoplasm. When fully developed the *sporozoites* become detached from the *sporoblasts* and the cyst is then observed to be filled with multitudes of these delicate filamentous organisms.

The above description applies to the tertian aestivo-autumnal plasmodium, but practically the same appearances are observed in the mosquito cycle of the benign tertian and quartan plasmodia. It should be remembered that in any one insect all of the plasmodia are not in the same stage of development at the same time, some being more advanced than others, but the periods as given are true for the vast majority of aestivo-autumnal plasmodia, in most species of Anophelina. Unless the temperature be suitable, the development may be delayed to 12 or even 14 days, and in *Myzomyia funesta*, a very common malaria carrier, the cycle of development at 80° F. always takes 12 days.

After the *sporozoites* are liberated into the body cavity of the insect by the rupture of the cyst wall they may be observed in fluid from any portion of the body of the insect, and if the cells of the salivary glands be examined numerous *sporozoites* will be seen within them, as well as within the salivary ducts.

Mosquitoes.

A good working knowledge of the structure, habits, distribution, and classification of mosquitoes is essential to the student of malaria and to the practitioner of medicine, especially in tropical countries, where these insects are responsible for the spread of some of the most prevalent and dreaded infections of man. We have already reviewed the relation of mosquitoes belonging to the *Anophelinae* to malaria; in addition we now know that *Filaria bancrofti* is

transmitted by *Culex fatigans*, as proven by Manson and others; *Filaria philipinensis* by *Culex fatigans*, proven by Ashburn and myself; that dengue is transmitted by *Culex fatigans*, as shown by Graham and Ashburn and the writer; and that yellow fever is alone transmitted by *Stegomyia calopus*, as conclusively proven by the U. S. Army Board composed of Reed, Carroll, Lazear, and Agramonte. It is not improbable that further research will show that these insects are responsible for the transmission of still other diseases, but enough is known of their activity in this respect to make a knowledge of them of great importance to the medical practitioner. In the preparation of this summary of our knowledge regarding mosquitoes I am greatly indebted to the works of Theobald and Giles and much of the material included is copied almost *verbatim* from their contributions.

Of the *Culicidae*, the sub-family *Anophelinae* is the only one of interest to the student of malaria, as only mosquitoes belonging to this sub-family have been proven to transmit malarial fevers.

General Description of Anophelinae.—The following description applies to mosquitoes in general, as regards anatomical structure, and includes only those points of value in diagnosis or that are essential to a clear understanding of the relation of these insects to the transmission of malaria.

External Anatomy of the Mosquito.—The mosquito is divided into three well-marked areas for purposes of description: the head, the thorax, and the abdomen.

THE HEAD.—The head varies somewhat in form in different species, and presents upon each side a prominent compound eye, larger in the males than in the females. The space separating the eyes above is known as the *occiput*, and that separating the eyes in front the *vertex;* the back of the head is the *nape* or neck. The occiput and vertex are of importance in classification on account of the scales and bristles with which they may be covered. A process projects forward from the head which is called the *clypeus*, and which varies in structure in different species. The mouth, or *proboscis*, is prolonged forward into a hollow tube, fitted both for piercing and sucking, and is composed of the *labrum*, *epipharynx*, or upper lip; two sharp lancets or *mandibles;* the *hypopharynx;* and the *labium* or lower lip, which terminates in two jointed organs known as the *labella*.

The hypopharynx and the labrum form the sucking tube through which the blood is drawn when the insect feeds; the hypopharynx is pierced by the salivary duct through which the saliva flows into the sucking tube and thence into the wound. The *palpi* arise close to the proboscis, one on either side, and vary in size, shape, and the number of segments composing them. In the *Anophelinae* they are as long as the proboscis in the female, thus serving to distinguish them from the mosquitoes of the sub-family *Culex*, in which the palpi in the female are very short. The antennae also arise from the head, beside the palpi, and are long jointed structures surrounded by hairs in the female, but in the male terminate in minute plumes.

THE THORAX.—The thorax is situated between the head and the abdomen, and is composed of the *mesothorax*, the *scutellum*, the *prothoracic lobes*, and the posterior portion or *metathorax*. The greater portion of the thorax is comprised in the mesothorax, having posteriorly a small area called the scutellum, which n the *Anophelinae* has a rounded border, while in the other families it is trilobed. The prothoracic lobes are placed laterally, while the metathorax is situated most posteriorly, is rounded in contour, and placed beneath the scutellum. The thorax is of importance in classification because of the character of the scales which cover it.

THE WINGS.—The wings arise from the upper portion of the thorax, are two in number, and their venation is of great importance in classification. Fig. 15 gives the venation of the wing common to all mosquitoes, and the fork cells, A and B, are of the greatest importance in distinguishing sub-families and genera.

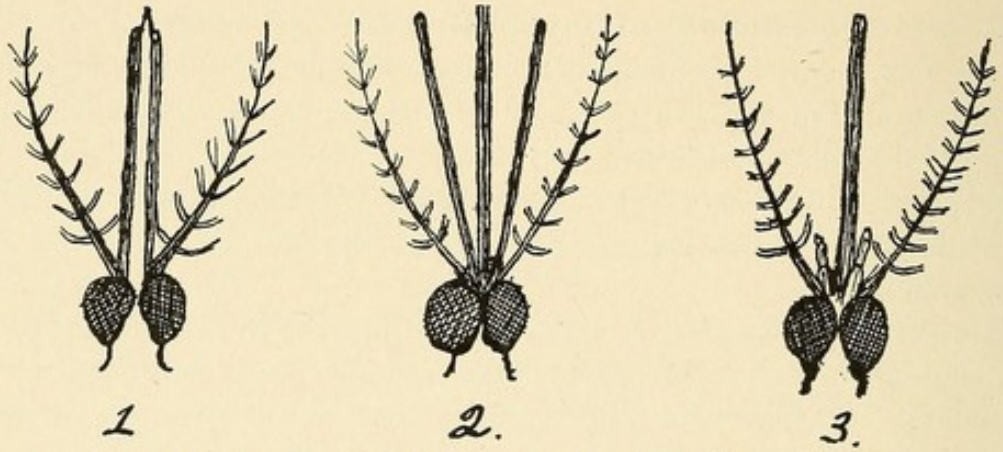

FIG. 14.—Comparison of head of female *Anopheles* and *Culex*.

1, Head of *Anopheles*, showing the palpi closed along the proboscis; 2, Head of *Anopheles*, showing the equal length of the palpi and the proboscis; 3, Head of *Culex*, showing the short palpi.

THE LEGS.—The legs arise from the pro-, meso-, and metathorax, and are six in number. They are of but little value in classification and will not, therefore, be further described.

THE ABDOMEN.—The abdomen is composed of eight well-defined segments. In the male the last segment terminates in the genital organs, and in the female in two lobes. Scales clothe this portion of the insect in most species, and their shape and arrangement are of great value in differentiation and identification of various species.

Internal Anatomy.—To the student of malaria the chief points of interest in the internal anatomy of the mosquito are situated in the alimentary canal, which may be said to commence at the distal end of the proboscis, terminating at the anus. The salivary glands, really appendages of the alimentary canal, have also to be considered in this relation.

THE ALIMENTARY CANAL.—Commencing with the sucking tube of the

proboscis, which has opening into it the salivary duct, and proceeding backward, the following structures are successively reached:

1. The true mouth, situated just behind the clypeus.

2. The buccal cavity.

3. The pharynx, or pumping organ, by which the insect is enabled to suck blood or other fluids.

4. The oesophagus, extending from the pharynx to the eosophageal valve; three blind tubules or sacs diverge from the oesophagus and serve as receptacles for food.

5. The oesophageal valve, which acts as a valve between the oesophagus and the mid-gut or middle intestine.

6. The mid-gut, a straight tube which terminates in a dilatation.

7. The "stomach." The portion of gut between the "stomach," which is situated at the level of the 6th abdominal segment and the anus, is known as the hind gut.

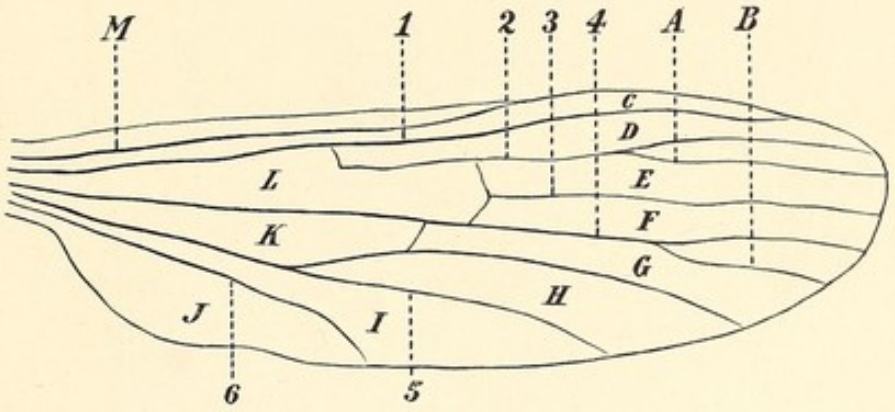

FIG. 15.—Venation of Wing in Anophelinæ.

1 to 6, First to six longitudinal veins; A, first sub-marginal cell (first fork-cell); B, second posterior cell (second fork-cell.); C, sub-costal cell; D, marginal cell; E, second sub-marginal cell; F, first posterior cell; G, third posterior cell; H, anal cell; I, auxiliary cell: The fork-cell; A and B, are of especial importance in classification. (Modified from Theobald.)

The Malpighian tubes, arising from the hind-gut, as well as the ovaries in the female, and their appendages, and the genital organs of the male will not be described, as they are of little interest in classification or in the differentiation of species.

THE SALIVARY GLANDS.—The salivary glands are of great interest because through them are transmitted the *sporozoites* causing malarial infection in man. As has been stated, the groove in the sucking tube is connected with the salivary glands by the salivary duct; at the base of the hypopharynx is placed a pumping organ controlled by voluntary muscles, and it is by means of this organ that the saliva is forced into the proboscis and thence into the wound. The common salivary duct passes backward underneath the buccal valve and divides into two tubes which pass backward through the neck into the thorax where they connect the two salivary glands. Each of the salivary glands consists of three

blind caeca, lined with large, granular cells, and possessing a central, well-defined canal, opening into the thoracic branches of the common duct, previously mentioned. It is in these cells that the malarial *sporozoites* are found at the termination of the mosquito cycle of development of the plasmodia.

Life History of the Anophelinae.—The *Anophelinae*, in common with all mosquitoes, pass through a larval and pupal stage before development into the perfect insect and these stages in their life history are always passed in water so far as we at present know. I have several times observed *Anopheles* larvæ in semi-fluid mud, and it is probable that development can occur in such an environment, provided enough moisture is retained by the soil.

The Ova.—The eggs of the *Anophelinae* are deposited upon the surface of water, and are arranged separately, and not in boat-shaped masses as in *Culex*. The *Anopheles* ova are easily recognized by their lateral floats, some of which are very beautiful. The ova are oval in shape, and hatch in from one day, as in *Myzomyia ludlowii*, to several days, as in other species.

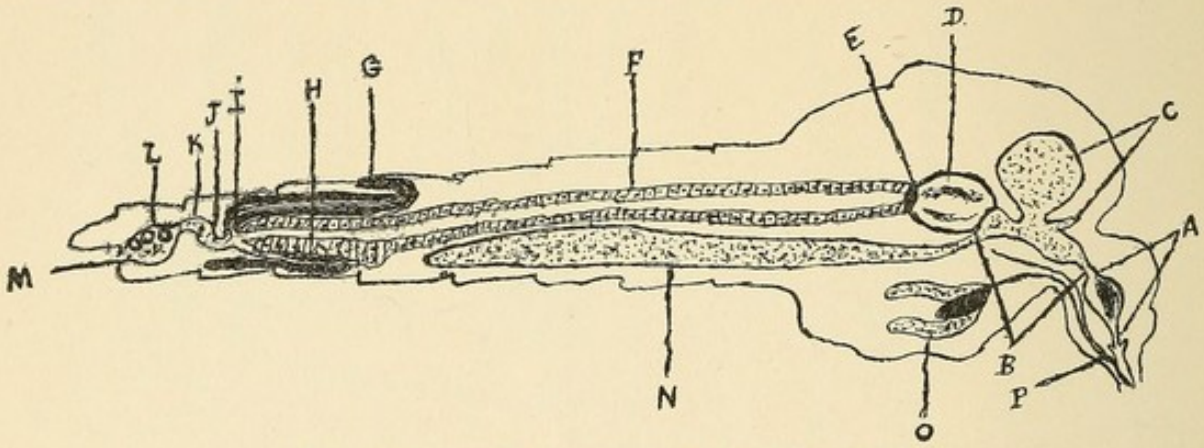

Fig. 16.—Internal Anatomy of the Anophelinæ.

A, Pharynx; B, oesophagus; C, dorsal reservoirs; D, oesophageal valve; and caeca; E, beginning of mid-gut; F, mid-gut; G, Malpighian tube; H, stomach; I, mid-gut ends; J, ileum; K, colon; L, rectum; M, anus; N, ventral reservoir; O, salivary glands; P, salivary duct. (After Nuttall and Shipley.)

The Larvae.—The larvae of all mosquitoes are either siphonate or asiphonate. The asiphonate larvæ always belongs to the *Anophelinae*, and live only in water, either fresh or salt. It may be said with certainty that any of the larvae of the *Anophelinae* will develop in any collection of water, although certain species breed by preference in certain localities. Theobald states that "practically all kinds of collections of water are acceptable to the larvae; some prefer rain-water barrels, cisterns, and the water in tins, calabashes, and jam-pots; others ponds, slow-running streams, and along the banks of large rivers; others live in the water collected in bromelias, and in the water that collects in hollow bamboos, gaining their entrance through exit holes left by boring insects. The domestic forms which are best known usually choose barrels and cisterns. The importance of the sylvan species is, however, just as great, as it is by means of these that fever is contracted in the jungle as well as in the habitations of man."

At Camp Stotsenburg, the most malarial post in the Philippine Islands, *Anophles* larvae were repeatedly found in hollow bamboo posts, as well as in small stagnant collections of water around the native huts, thus proving conclusively that the old idea that *Anopheles* breed only in clear, running water is incorrect. It is noteworthy, however, that *Anopheles* larvae were only found in bamboo posts which allowed the ingress of sunlight by reason of being open at the top, while in posts in which the opening was so placed as to exclude sunlight only *Culex* larvae were found.

The larvae, like the adult insect, is divided into three main portions, the head, the thorax, and the abdomen. While in *Culex* the head is larger than the thorax and projects laterally, in the *Anophelinae* the head is smaller and the thorax projects laterally beyond the boundary of the head. The thorax presents upon each side bunches of bristles and is unsegmented. The abdomen is composed of nine segments. While in *Culex Stegomyia*, etc., the eighth

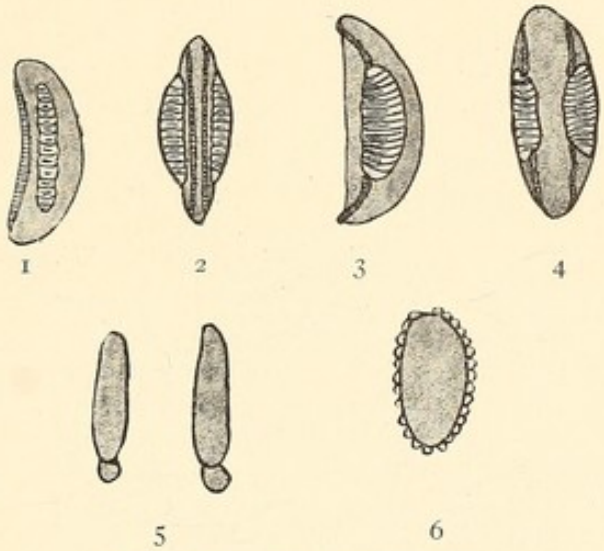

FIG. 17.—Ova of Mosquitoes.

1 and 2, Ova of *M. culicifacies* (Anopheles); 3 and 4, Ova of *N. maculipalpis* (Anopheles). (Note the lateral floats on the Anopheles ova); 5, Ova of *Culex;* 6, Ova of *Stegomyia.*

abdominal segment presents upon its dorsal surface a well-marked respiratory siphon, in the *Anophelinae* this is represented by two slightly raised openings, which are used for respiration, but which do not in the least resemble the siphon of *Culex* or of other species. The arrangement of the respiratory aparatus of the *Anophelinae* forces the members of this sub-family to lie horizontal to the surface of the water during respiration, instead of at an angle, as in *Culex*, and this serves as an easy method of differentiating them. An exception to this rule has been noted in a few *Culicinae*. The color of the larvae is usually gray, brown, or greenish. Anopheles larvae are not very resistant and are usually short lived although a few species have been known to hibernate through a long winter. The length of the larval stage varies in the different species. In *Myzomyia ludlowii* the larval stage occupies from 9 to 10 days.

THE PUPAE.—The pupal stage lasts from a few hours to several days, depending upon the temperature. During this time the pupae are very active, constantly coming to the surface of the water to breathe, but as they are not easily differentiated from the pupae of *Culex*, a detailed description is not considered necessary. Fig. 19 gives a good general idea of the structure of the pupa.

THE IMAGINE.—When the time has arrived for the emergence of the imagine or adult insect, the pupa rises to the surface of the water, the skin over

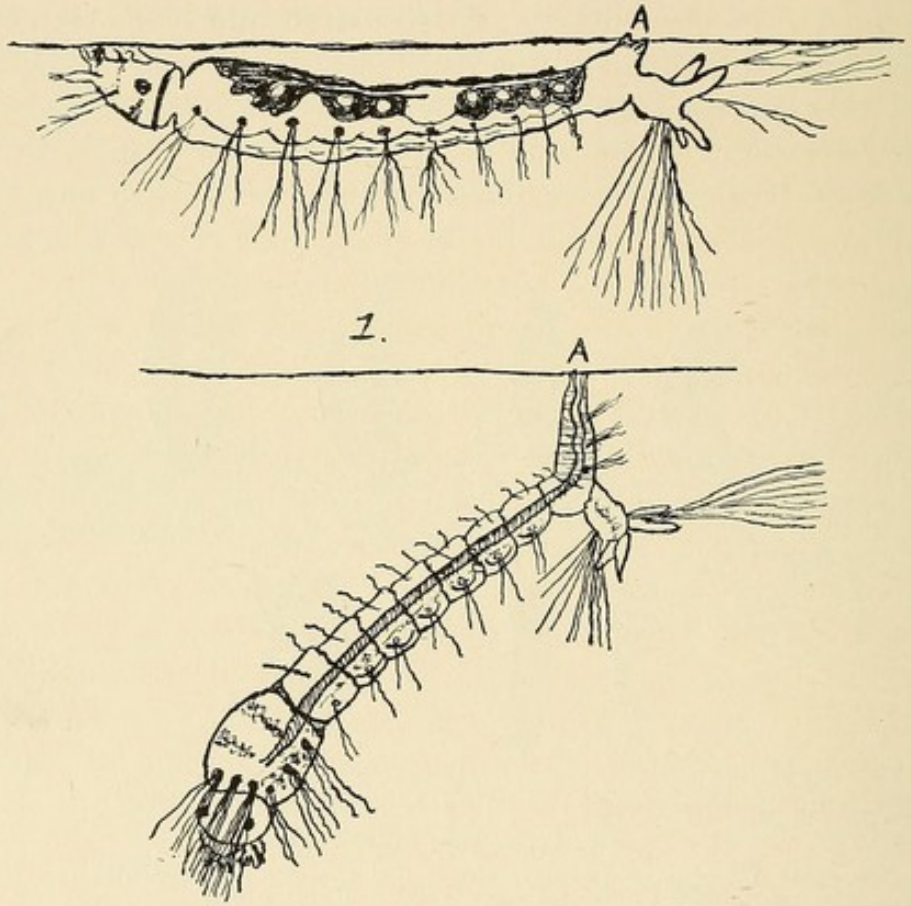

FIG. 18.—Larva of *Anopheles* and *Culex*.
1, Larva of Anophelinæ. Note horizontal position in reation to surface of the water, and the absence of syphon (A). Larva of Culex. Note angular position in relation to surface of the water, and presence of the syphon, at A. (Fig. 1, after Howard; 2, after Theobald.)

the thorax breaks open, and the perfect insect gradually emerges from the pupal case, which serves as a resting place for it until its wings are dried and it is able to take flight.

HABITS OF THE ANOPHELINAE. FEEDING.—As a rule, all *Anophelinae* are night feeders, but it is not at all unusual to observe *Anopheles*, of various species, feeding in the late afternoon, and I have often seen *Myzomyia funesta* biting in the early morning and even at noon in the tropics. During the daytime most *Anopheles* hide in the woods or beneath the leaves of bushes and small trees or in dark corners of houses or native huts in the tropics. I have observed hundreds of *Myzomyia ludlowii* and *Myzorhynchus barbirostris* around the base-

board of toilet sinks and upon clothing in dark closets during the daytime in the Philippines. It is undoubtedly true that the vast majority of mosquitoes never attack man, feeding upon fruit and vegetable juices, especially upon the juices of fruits, as the banana, and upon flowers, only attacking man as the opportunity offers and when convenient. The males are not blood suckers, but subsist entirely upon the juices of fruits and flowers. As the females alone feed upon blood it was for a long time supposed that this was essential to the laying of eggs, but later observations have shown that this is not so, and Theobald says: "it may therefore safely be said that mosquitoes breed mainly without the stimulus of human blood." Many species have been observed sucking the blood of invertebrates, such as insects.

Flying Distance.—Mosquitoes do not cover very great distances in flying. Formerly it was supposed that the limit of flying distance for mosquitoes was a half-mile, but it is now known that this distance is exceeded very commonly, and Theobald gives the average flying distance as one mile. I am sure, from personal observation in the Philippine Islands, that *Anopheles* mosquitoes often fly from two to two and a half miles in search of food, for at Camp Stotsenburg no breeding places of *Anopheles* existed in the post proper, so far as we could determine, and the nearest breeding places discovered were at least two miles away; yet, at times, Anopheles were very numerous in the post and malaria was very prevalent.

Resting Position.—The position assumed by the insect while resting has always been used as a differential point in the classification of mosquitoes. Regarding this it may be said that all of the *Anophelinae* (with the exception, according to Giles, of *Myzomyia culicifacies*) when at rest form a complete angle to the resting surface, the proboscis, head, thorax, and abdomen, being in a straight line, while in *Culex* the proboscis, head and thorax, form an angle with the abdomen, thus giving the insect a hunchback appearance (see Fig. 20).

Hibernation.—In the tropics mosquitoes breed throughout the entire year, but are much less numerous in the dry than in the rainy season. In temperate and cold regions they may pass through the cold season as fully developed adults, as larvae, or even in the ova. According to Theobald, the fertilized females of *A. maculipennis* hibernate in the adult stage in cellars, outhouses, stables, etc., while *A. bifurcatus* and *A. nigripes* exist throughout the winter in the larval stage even under thick ice. If a warm spell occurs during a winter some of the hibernating mosquitoes emerge from their hiding places and bite, thus causing outbreaks of malaria during the winter season. It is also true that the ova of some species of *Anopheles* will withstand a considerable amount of drying, and I have not infrequently observed the development of larvae in dry mud which has been placed in water and protected from outside contamination. In the tropics I believe that many species of *Anopheles* would disappear if it were not for the resisting powers of the ova to drying and sunlight, and that it is this property which enables these insects to exist through the dry season in areas in which water is almost absent. Just as in the temperate

and cold regions these insects are able to resist freezing, so in the tropics nature has provided them with ample resisting powers against drying and the effects of the tropical sun.

Classification.—The classification adopted in this work is that of Theobald, a classification which has been accepted by nearly every scientific worker upon mosquitoes, such as Blanchard, Daniels, Ludlow, Graham, Lutz, and Goeldi. This classification is based largely upon the character of the scales which clothe the head, thorax, wings, and abdomen of the insects. Fig. 21 illustrates the shape and variation in these scales as given by Theobald, and also gives the nomenclature applied to them.

The general characteristics of the sub-family *Anophelinae*, as given by Theobald, are as follows: Head, numerous upright forked scales. Thorax scaly or hairy, metanotum always nude, scutellum always simple, with scales or hairs. Abdomen hairy or scaly. Palpi in the female as long as the proboscis. Wings, long fork cells, the first submarginal longer than the second posterior cell. Up to the present time Theobald has described 18 genera of *Anophelinae*, but, while it is probable that each genus contains species which are able to transmit malaria, only a few of the genera are at present of interest to us in this relation. Of the 18 genera, eight are represented by but a single species, and none of these have been proven to transmit malaria. These genera are *Feltinella; Bironella; Aldrichia; Chagasia; Chrystya; Kerteszia; Myzorhynchella* and *Lophoscelomyia*.

For the differentiation of the other genera Theobald gives the following table:

A. Fork cells long.
  a. Thorax and abdomen with hair-like curved scales.
    a. Head with upright forked scales only.
      1. Wing scales large and lanceolate, wing unspotted, or if spotted the spots due to collections of similarly colored scales. Genus, *Anopheles*. Meig.
      2. Wing scales small, narrowly lanceolate, the wings with spotting of varied color. Genus, *Myzomyia*. Bl.
      3. Wings with patches of large inflated scales. Genus, *Cycloleppteron*. Theo.
    β. Median area of head with some flat scales. Genus, *Stethomyia*. Theo.
  b. Thorax with narrow curved scales; abdomen hairy; wing scales small and lanceolate. Genus, *Pyretophorus*. Bl.
  c. Thorax with hair-like curved scales and some narrow ones in front; abdomen with apical lateral scale tufts and scaly venter; no ventral tuft; wing scales lanceolate. Genus, *Arribalzagia*. Theo.
  d. Thorax with hair-like curved scales; no lateral abdominal tufts; a distinct apical ventral tuft and dense scales palpi in the female; wings with dense, large, lanceolate scales. Genus, *Myzorhynchus*. Bl.
  e. Thorax and abdomen with scales; thoracic scales narrow-curved

or spindle-shaped; abdominal scales as lateral tufts and dorsal patches of flat scales. Genus, *Nyssorhynchus*. Bl.

f. Abdomen nearly completely scaled with long irregular scales and with lateral scale tufts. Genus, *Cellia*. Theo.

g. No lateral tufts and smaller wing scales. Genus, *Neocellia*. Theo.

The following brief descriptions of the principal genera of interest to students of malaria are largely those given by Theobald, to whom I am indebted for much that appears in this chapter upon mosquitoes.

Genus, *Anopheles*. MEIGEN, 1818. Occurs mostly in temperate regions, although certain species occur in tropical countries, especially in the hill regions. This genus is found in Europe, the United States, North Africa, hill districts of India, in Australia, West Indies, West Africa, all of North America. Fifteen species are included in this genus, the type species being *A. maculipennis*, a common species in Europe and North America. Some of the species have been

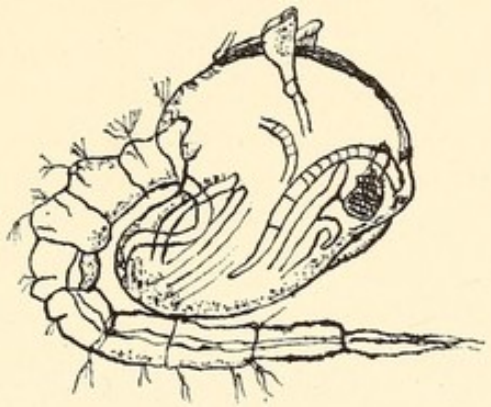

FIG. 19.—Pupa of Anophelinæ. (After Nuttall and Shipley.)

proven to transmit malaria, as *A. maculipennis* and *A. algeriensis*. The larvae of *A. maculipennis* occur in water barrels and pools, others in small natural collections. Adult *A. maculipennis* hibernate. Theobald believes that all species may act as the hosts of the malarial plasmodia.

Genus, *Myzomyia*. BLANCHARD, 1902. This genus occurs in Europe, Africa, Asia, the Philippine Islands, but does not occur in North or South America, the West Indies, or Australia. The type species is *M. funesta* Giles, one of the most common of malarial carriers in tropical regions in Asia and Africa. Five of this genus have been proven to transmit malaria, namely, *M. listonii* Liston; M. *funesta* Giles; *M. turkhudii* Liston; *M. culicifacies* Giles, and *M. nili* Theobald. *M. culicifacies* is of especial interest, as its resting position is like that of non-malarial mosquitoes. *M. rossii* Giles has been proven incapable of transmitting malaria. These mosquitoes vary greatly in their breeding habits, some breeding around human habitations, while others are sylvan species. Recently *M. ludlowii* Theobald, a common species in the Philippine Islands, has been proven a host for the aestivo-autumnal plasmodia. About twenty-one species occur in this genus.

Genus, *Stethomyia*. THEOBALD, 1902. Contains but two species, *S. nimba* Theobald and *S. fragilis* Theobald. The former is probably the transmitter of jungle malaria in South America. The latter occurs in the Federated Malay States.

Genus, *Pyretophorus*. BLANCHARD, 1902. Occurs only in Asia, Africa, and Australia. They are all large mosquitoes and have beautifully spotted wings. The larvae live in puddles, streams, pools, rice fields, and in flowing water. Three species have been proven to transmit malaria: *P. costalis* Loew; *P. chaudoyei* Theobald, and *P. ardensis* Theobald. Over twenty-six species have been described.

Genus, *Arribalzagia*. THEOBALD, 1902. Only one species belongs to this genus, *A. maculipes* Theobald. This species occurs in the Brazils and is probably a transmitter of malaria.

Genus, *Myzorhynchus*. BLANCHARD, 1902. This genus is distinguished by the densely scaled palpi, hairy thorax, and densely scaled proboscis. They are all large dark insects, breeding in swamps, and beneath tropical vegetation. They occur in South Europe, Asia, Africa, and Australia. Four species have been found in the Philippine Islands.

Genus, *Nyssorchynchus*. BLANCHARD, 1902. About twenty species occur in this genus. Mosquitoes of this genus are generally house breeders or develop in pools or puddles in close proximity to human habitations. They occur in India Africa, Australia, and in the Philippine Islands. *N. stephensii* has been proven to act as a host for the malarial plasmodia.

Genus, *Cellia*. THEOBALD, 1903. Seven species occur in this genus, the most marked characteristics being the scaled abdomen with dense lateral tufts, and the heavily scaled wings. The larvae live in any open water and some species are commonly found in human habitations. The following species have been found to harbor the malarial plasmodia. *C. argyrotarsis*, *C. albimanus*, and *C. pharoensis*.

For a detailed description of the species mentioned in the foregoing summary the reader is referred to Theobald's monographs upon the *Culicidae*.

Geographical Distribution of Mosquitoes.—Mosquitoes occur wherever malaria does, but it does not follow that malaria is always present even though mosquitoes are abundant. In order that the malarial fevers may spread in any locality, the right species of mosquitoes must be present, together with individuals infected with some species of the plasmodia. To the student of malaria, the geographical distribution of mosquitoes resolves itself into the determination of the distribution of the *Anophelinae* only, and, as has been said, the distribution of malaria and that of mosquitoes belonging to this sub-family exactly coincide, and the amount of malaria in any country, or in any given locality is an index of the number of *Anopheles* present. This fact is of importance from a prophylactic standpoint, as the determination of the species of mosquito present in any locality enables us to avoid those inhabited by *Anopheles* or to take the proper precautions against infection. In the selection of camp sites of a more or less permanent character or of the sites for permanent military posts, a preliminary "mosquito survey" will often prove of inestimable value, both as regards the future health of the camp or post and the cost of maintaining it. The same is true of the selection of building sites of any character where mosquitoes and malaria are apt to be present. I have already spoken of the geographical distribution of the malarial fevers, and it is not, therefore, necessary to give in detail the countries in which the malarial mosquitoes

occur, as to do so would be but a repetition of what has already been said regarding the distribution of malaria. It may be of value, however, to mention those species of the *Anophelinae* which have been proven by experiment to transmit the malarial fevers, and to mention the countries in which such species occur, with special reference to the West Indies, the United States, and the Philippine Islands.

The following members of the sub-family *Anophelinae* have been found experimentally to transmit the malarial fevers or to act as hosts of the malarial plasmodia:

Genus, *Anopheles*. *A. maculipennis*, MEIG; *A. bifurcatus*, LINN; *A. algeriensis*, THEO.; *A. jasoensis*, TSUZUKI; *A. formosaensis*, DONNE; *A. cohaesus*, DONNE; *A. quadrimaculatus*, SAY; *A. albipes*, GILES; *A. vagus; A. vincenti; A. martini; A. pursati*. 12 species.

Genus, *Myzomyia*. *M. listoni*, LISTON; *M. funesta*, GILES; *M. turkhudii*, LISTON; *M. culicifacies*, GILES; *M. nili*, THEO.; *M. hispaniola*, THEO.; *M. ludlowii*, THEO.; *M. lutzii*, THEO. 8 species.

Genus, *Stethomyia*. *S. nimba*, THEO. 1 specie.

Genus, *Pyretophorus*. *P. costalis*, LOEW; *P. chaudoyei*, THEO.; *P. ardensis*, THEO.; *P. superpictus*, GRASSI; *P. jeyporensis*, THEO. 5 species.

Genus, *Arribalzagia*. *A. maculipes*, THEO. 1 specie.

Genus, *Myzorhynchus*. *M. sinensis*, WIED; *M. barbirostris*, VAN DER WULP; *M. pseudopictus*, GRASSI; *M. paludis*; THEO.; *M. mauritianus*, GRANDPRE AND CHARMOY; *M. coustanii*, LAV. 6 species.

Genus, *Nyssorhynchus*. *N. fuliginosus*, GILES; *N. stephensii*, LISTON; *N. maculipalpis*; GILES, *N. theobaldii*, GILES. 4 species.

Genus, *Cellia*. *C. argyrotarsis*, ROBINEAU-DESVOIDY; *C. pharoensis*, THEO.; *C. albimanus*, WIED. 3 species.

From the above summary it will be seen that no less than forty species of the *Anophelinae* have been proven experimentally to be hosts of the malarial plasmodia. The geographical distribution of these species is as follows:

West Indies.—*Cellia argyrotarsis. Cellia albimanus.*

Canada.—*Anopheles maculipennis.*

United States.—*Anopheles maculipennis. Anopheles quadrimaculatus. Cellia argyrotarsis.*

Central and South America.—*Anopheles albipes. Arribalzagia maculipes. Pyretophorus lutzii. Cellia argyrotarsis. Myzomyia lutzii. C. albimanus.*

Europe.—*Anopheles maculipennis. Anopheles bifurcatus. Myzorhynchus pseudopictus. Pyretophorus superpictus. Myzomyia hispaniola.*

Asia.—India.—*Myzomyia culicifactes. Myzomyia listonii. Myzomyia turkhudii. Pyretophorus jeyporensis. Myzorhynchus barbirostris. Myzorhynchus sinensis. Nyssorhynchus theobaldi. Nyssorhynchus stephensii. Nyssorhynchus fuliginosus. Nyssorhynchus maculipalpis.*

Japan.—*Anopheles jesoensis. Anopheles formosaensis. Anopheles cohaesus.*

Africa.—*Myzomyia funesta. Myzomyia nili. Pyretophorus costalis. Pyretophorus ardensis. Pyretophorus chaudoyei. Myzorhynchus barbirostris. Myzorhynchus mauritianus. Myzorhynchus paludis. Cellia pharoensis.*

Madagascar.—*Myzorhynchus coustanii.*
Mauritius.—*Myzorhynchus mauritianus.*

The Philippine Islands.—The following malarial mosquitoes have been found in the Philippine Islands by Ludlow, Whitmore, Banks, and the writer: *Myzomyia funesta. Myzomyia ludlowii. Myzorhynchus barbirostris. Myzorhynchus sinensis. Nyssorhynchus fuliginosus.*

Further observation will undoubtedly demonstrate that other species occur in these islands.

Number of Infected Mosquitoes in Malarial Regions.—The number of mosquitoes showing infection in malarial regions will depend upon the number of infected individuals present, the season of the year, certain atmospheric conditions, and the amount of care exercised by the inhabitants in protecting themselves from these insects. Thus the figures given by various observers differ very greatly in this respect, as would be expected.

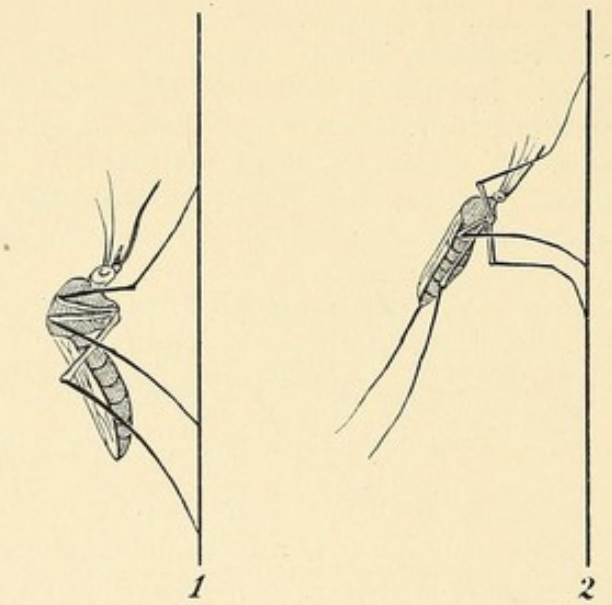

FIG. 20.—Comparison of Resting Position of *Anopheles* and *Culex.*

1, Resting position of *Culex*, on vertical surface; 2, resting position of *Anopheles* on vertical surface. (The resting position upon a horizontal surface may be observed by turning the page so that the vertical line becomes horizontal.)

Celli, in Italy, found that of the *Anopheles* examined by him, 2.5 per cent. were infected with the malarial plasmodia; A. Plehn, in Kamerun, examined 860 *Anopheles* and found 2.2 per cent. infected; La Monaco examined 1,420 *Anopheles* and found 1 in 164 infected during August, and 3 in 103 infected in September; Sargent, in Algiers, found 1.6 per cent. of the *Anopheles* which he examined infected, and Zieman, in Africa, found that of the mosquitoes collected in the huts of the natives no less than 16.6 per cent. showed infection with malarial plasmodia.

At Camp Stotsenburg, in the Philippine Islands, during the height of the malarial season, as high as 35 per cent. of the *Anopheles* examined have shown

infection, but at other times the percentage has been very small, sometimes less than 1 per cent.

Daniels found that 47.5 per cent. of the mosquitoes which he allowed to bite malarial patients became infected.

It is now a well-established fact that certain of the *Anophelinae* are incapable of acting as hosts to the malarial plasmodia, and the following observations of Stephens and Christophers and of Hirshberg are of interest in this connection.

Stephens and Christophers, at Mian Mir, India, dissected 259 *Myzomyia culicifacies*, and found 12 or 4.6 per cent. infected with malarial *sporozoites;* of 496 *Myzomyia rossii* dissected by them not one was found infected. At

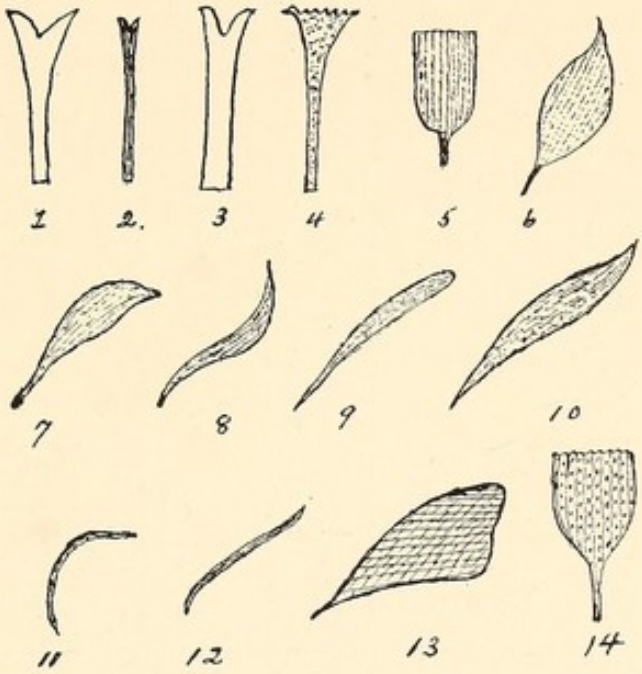

FIG. 21.—Character of Scales upon Mosquitoes.

1, 2, 3, and 4, Upright forked scales; 5, spatulate scale; 6, spindle scale; 7 and 8, broad and narrow curved scales; 9, linear scale; 10, lanceolate scale; 11 and 12, hair scales: 13, broad asymetrical scale. 14; ordinary butterfly scale.

Enur, in India, the same observers dissected 69 *Myzomyia culicifacies* and found 6 or 8.6 per cent. infected with *sporozoites;* of 364 *Myzomyia rossii* dissected at the same time not one was found infected.

Hirshberg, in his experiments, found that out of 58 *Anopheles punctipennis*, none developed malarial *sporozoites*, while of 48 *Anopheles maculipennis*, eight were positive for *sporozoites*.

Not only are some of the *Anophelinae* unable to act as hosts for the plasmodia, but some species can only act as host for a certain species of plasmodia; this fact has been proven again and again and serves to explain why certain types of malaria are limited to certain localities. In Japan it has been found that *Anopheles formosaensis* and *Anopheles cohaesus* can only transmit the aestivo-autumnal infections, while *Anopheles jesoensis* is able to act as a host for both

the benign tertian and the aestivo-autumnal infections. On the other hand, *Anopheles maculipennis*, the most common mosquito occurring in temperate regions, is able to transmit tertian, quartan, and aestivo-autumnal malaria.

While at the present time the malarial mosquitoes are more or less localized in their distribution and certain types of malaria are thus confined to limited regions, the increase of transportation facilities and of commerce will inevitably lead to a more general distribution of these insects, and thus regions free from

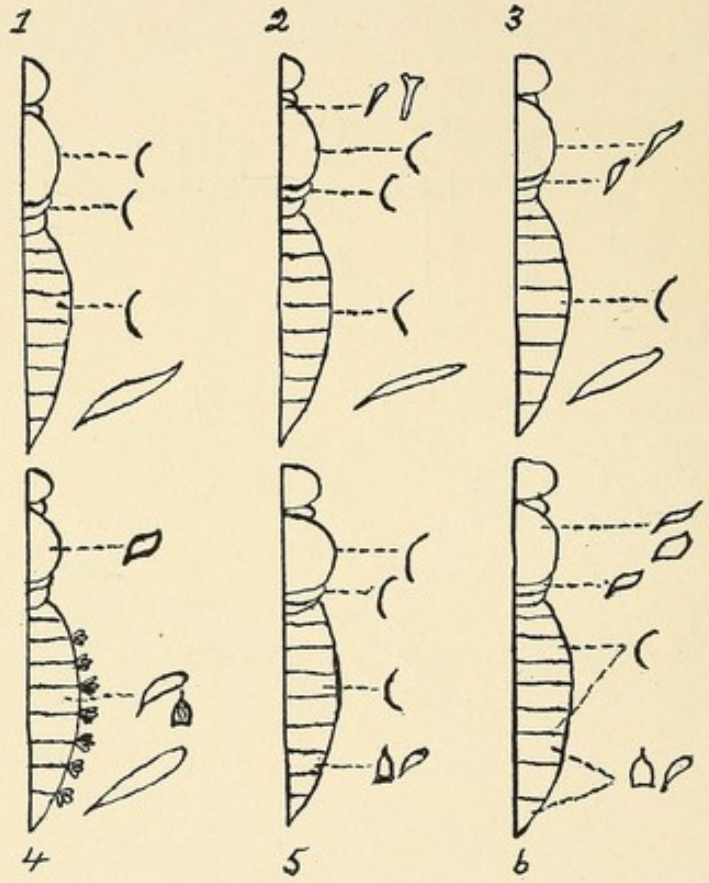

FIG. 22.—Showing characteristics of Scales on various portions of body of different species of the Anophelinæ, which have been proven to transmit malaria.

1, Anopheles; 2, Myzomyia; 3, Pyretophorus; 4, Cellia; 5, Myzorhynchus; 6, Nyssorhynchus. (Arranged from Theobald.)

malarial infection will become infected, and the more severe types of malaria, the aestivo-autumnal, will invade territory hitherto infected with the benign tertian type.

Number of Species.—Nearly 1000 species of mosquitoes have been described, of which the *Anophelinae* number some 150 species. Most of these insects are wood dwellers and do not come in contact with man, but it is probably true that most, if not at all, of the *Anophelinae* which are capable of transmitting the malarial fevers are semi-domesticated species, and prefer to live within reach of human habitations.

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CHAPTER IV.

Methods of Transmission of the Malarial Plasmodia: By the Atmosphere; By Water; By Inoculation of Malarial Blood; By Inoculation by the Mosquito; Cultivation of Malarial Plasmodia; Immunity.

Up to within very recent times it was held by many students of malaria that the disease might be transmitted to man in one of three ways, either by the air, by water, or by the bite of an infected mosquito. The theories of the transmission of malaria by the air or by water are very ancient, and, until the rôle played by the mosquito in the transmission of these fevers was discovered, both had ardent advocates, although there was but little experimental evidence upon which to base either theory, and that little of no scientific value. The only method of the transmission of malaria that has been proven scientifically is that by the bite of an infected mosquito, and at the present time this is the only known method of transmission. While it would, perhaps, in the light of our present knowledge, be rash to assert that the malarial fevers can be transmitted only by the mosquito, the fact remains that no other method of natural transmission has been discovered, and, therefore, that as far as we can see, the malarial fevers *are* only transmitted to man by the bite of mosquitoes belonging to the *Anophelinae*. Before considering the experimental evidence upon which the mosquito theory of the transmission of malaria is based, a short review will be given of the air and water theories of transmission.

Transmission by the Atmosphere.—This is the most ancient of all of the theories of malarial transmission, and it was the belief in this method that led to the term "malarial" as applied to these fevers. The advocates of this theory believed that the malarial germs reached man through the respiratory tract, being inhaled, as in dust, or from the infected air of malarial regions. This theory was accepted by multitudes of observers, yet never had a single experimental fact that proved it or that was of sufficient importance to serve as a logical argument in favor of such a method of transmission. On the contrary, there are many facts, well known to the strongest adherents of this theory, that conclusively prove such a method of transmission to be impossible. Among these may be mentioned the strictly local character of malarial infection; the protection afforded by heights; the greater prevalence of the disease in moist regions and during the rainy season, when dust is not present; the fact that these fevers are not carried by the wind; and the protection afforded the crews of ships when the ships are anchored at some distance from the shore. To this theory we owe the common opinion that the air of malarious localities is poisonous; that the vapors and fogs arising from marshes and lowlands are laden

with malaria; and numerous other fanciful opinions, which, even though we now know them to be false, are yet held by many, and in some localities constitute a stumbling-block whenever measures looking to the prophylaxis of malaria are a subject for discussion.

The strictly local character of malarial infections has long been used as an argument against the transmission of the disease by the air. Almost every authority has agreed that malaria spreads but a little way in a horizontal or vertical direction. Celli quotes a typical example of this given by Marchiafava and Spadoni. In Celli's words:

> "Near Sinigaglia there is a canal between the river Misa and the sea; the water stagnating there was, up till a little time back, the *fomites* of malarial infection. The inhabitants of the nearest houses and more especially of the houses with the doors and the windows looking on this canal, suffered from malaria, while those of the houses a little more distant remained immune."

There are very numerous instances of this kind in the literature upon malaria; Bignami instances that while the hospital of San Michele di Ripa Grande is free from malaria, there are most dangerous malarial foci in the immediate neighborhood and that the inhabitants of Sezze who live near a marsh suffer greatly from malaria, while those living near the hills in the vicinity do not suffer from the disease. Marchiafava and Bignami instance certain cities, as Genzano and Albano, situated between the Pontine Marshes and Rome, as disproving the theory of transmission by air, because, while receiving the emanations from the most deadly malarial localities in these marshes, they are entirely free from malarial fevers.

It has long been known that ships anchoring a goodly distance off the most malarial coasts escape infection, which would not occur if the germ of the disease were carried by air currents. During the campaign in Madagascar, according to Vincent and Burot, the troops operating upon shore were almost decimated by malaria, while the crews of the war ships, hardly 300 feet from shore, did not suffer at all from these fevers.

During an investigation of latent malaria in natives living about Camp Stotsenburg, in the Philippine Islands, I found that the little barrios or villages differed greatly in the amount of malarial infection present in them. The percentage of infected children varied from as high as 60 per cent. to as low as 5 per cent., yet all of the barrios were situated within a radius of two miles. Such a variation could not occur were the malarial fevers transmitted by the atmosphere. Not only did the barrios vary in the number of infections, but certain portions of individual barrios were most malarious, while other portions were free from infection.

It has long been known that malaria does not develop in high regions in some instances, even though such regions be surrounded by the most highly infected territory; in other words, the infection of malaria does not travel far in a vertical direction. For centuries the inhabitants of the Pontine marshes have protected themselves from malaria by sleeping in elevated shelters, and the inhabitants of all malarial regions recognize that the upper stories of houses

are less apt to be infected with these fevers than are the lower. Tomassi-Crudeli found that at Girgento, the custodians of the temples suffer greatly from malaria, while people sleeping in houses a short distance away, but upon higher ground, do not suffer at all; Celli instances the case of the workers in the marshes at the foot of the Lepini Mountains, who at night go up into the foot-hills to sleep and who thus escape malarial infection. The town of Norma is built upon the summit of an almost perpendicular mass of rock, 343 meters high, and the inhabitants are free from malaria. According to Celli, the town of Ninfa, situated at the foot of the rock upon which Norma is built, and which was once a flourishing Papal seat, now consists of ruins, the only inhabited house being a mill, where malaria is so severe that the workers have to be changed every week during the malarial season. While, as a rule, malaria is not met with upon highlands, there are many exceptions, and in the Philippines one of the worst malarial foci in all the islands is situated in the foot-hills of the Zambales Mountains. Height is only protective when conditions are present preventing the development of *Anophelinae*, and the mere fact that a country is elevated should not be considered as proving that it is free from malaria.

It would appear that the most convincing argument against the transmission of malaria by the air is the fact that the disease is not conveyed by winds, for it is impossible to believe that if the malarial germ were present in the air it would not be carried by the wind. The malarial fevers are strictly local infections, being confined within certain well-defined limits, even in infected localities.

Transmission by Water.—The believers in the theory that water is capable of transmitting malaria have instanced numerous occurrences which appear to support their contention. The oft-quoted *Argo* incident, used so often as an almost impregnable argument in favor of such a mode of transmission, is of little scientific value in the light of our present knowledge. Boudin reported this epidemic, which occurred upon the French transport "Argo," in 1834. In July of that year, three French transports sailed from Bona, Algiers, bound for Marseilles, and loaded with French soldiers. While upon two of the transports the troops continued in good health, upon one, the "Argo," there occurred a severe epidemic of what was regarded as malarial fever, thirteen of the crew dying, while 98 were admitted to the hospital when the ship reached Marseilles. The cause of the epimedic was supposed to be a number of barrels of water from a swamp, shipped at Bona, where malaria was prevalent. A review of the facts in this celebrated case show that it is almost impossible that any of the patients suffered from malaria, for the incubation period was shorter than has ever been observed; every man of the 120 constituting the crew was affected; in every case the symptoms were described as pernicious in character, and in no case was there a recurrence of the disease. It is very evident that these men suffered from some form of acute poisoning, perhaps due to the swamp water, but more probably due to some article of food. The

simultaneous occurrence of the disease in every one of a crew of 120 men is positive proof that it could not have been due to the malarial plasmodia.

Other similar epidemics have been reported as occurring upon ships, but none of them are of any scientific value as proof of the transmission of malaria by means of water.

As an instance of the erroneous conclusions that may be drawn from appearances, the following description of an epidemic of malaria, noted by Davidson, is of interest: The troops stationed at Tilbury Fort suffered greatly from malaria, while those residing about the railway station, and the coast guards, were in excellent health. The water-supply of the fort came from a neighboring swamp, while that of the station and of the coast guards was from a spring. While the water tanks at the fort were being repaired, the soldiers also used the spring water, and the malaria disappeared. Hence the inference was clear that the swamp water produced the malaria, and at that time such an inference was justifiable, but how easily, at the present time, the disappearance of malarial fever at this station can be explained. The tanks which were uncovered served as breeding places for mosquitoes; while the tanks were being repaired the mosquitoes could not breed and malaria disappeared.

Numerous investigators have endeavored to produce malaria in man by the use of water from malarial districts, but all such experiments have ended in failure. Celli was the pioneer in this line of research and his experiments are given in the following table:

Method	No. experimented on	Duration of experiment	Water from	Result.
By ingestion.	6	8–15 days.	Pontine marshes.	Negative.
	12	12–21 days.	Sicily.	Negative
	30	5–30 days.	Tuscan Maremma.	Negative.
	25	6–24 days.	Vallomonica.	Negative.
By inhalation.	16	2–15 days. Twice a day. 20–30 minutes.	Pontine marshes.	Negative.
By enteroclysm.	5	2–14 days.	Pontine marshes.	Negative.

Some of the above experiments were undertaken by Zeri at Celli's suggestion, and all of them were negative so far as the production of malaria was concerned. Since the discovery of the transmission of malaria by the mosquito, it has been suggested that perhaps the plasmodia, after passing through their life cycle in the mosquito, may exist in water in the form of resistant spores, or that the eggs of the mosquito, when ingested in water, may be capable of conveying the infection. Nunmerous observers have shown, however, that the malarial plasmodia are not present in the eggs of infected mosquitoes, and no form of the plasmodia has ever been found in the water of malarious regions. Laveran, and later Manson, suggested that water might become infected by the dead bodies of infected mosquitoes, and Ross undertook to prove this hypothesis. He gave a native water containing the dead bodies of mosquitoes infected with malarial plasmodia, the ingestion of which was followed in eleven days by an attack of fever, with plasmodia in the blood. The experiment was of no positive value as it was carried out in a malarial region, and, although repeated in many individuals, was never again successful.

Transmission by Inoculation of Malarial Blood.—While the direct inoculation of the blood of a patient suffering from malaria into a healthy individual probably occurs very rarely in nature, it is well known that the malarial fevers may be easily transmitted in this way. These fevers have been successfully reproduced in this way by Gerhardt, Mariotti, Marchiafava, Celli, Bignami, Bastianelli, Baccelli, Sacharoff, Elting, and many others. It has invariably been found that the species of plasmodium in the blood injected is found again in the blood of the individual so infected, and is followed by the clinical symptoms of that type of fever usually produced by the species of plasmodium experimented with. For instance, the subcutaneous inoculation of blood from a person suffering from a benign tertian infection into a healthy individual is followed by the occurrence of tertian fever in that individual, and the appearance in his blood of *Plasmodium vivax*. This fact proves conclusively that there are different species of malarial plasmodia, each capable, and capable only, of producing the characteristic clinical symptoms with which it is always associated.

Gerhardt, in 1884, was the first to successfully inoculate malarial fever in man, and his work was soon confirmed by that of others. Antolisei and Angelini produced typical tertian fever in two cases by the inoculation of the blood of a patient suffering from this form of fever, while Gualdi and Antolisei produced quartan fever in the same way; in 1889 the same observers inoculated a man with blood containing hyaline and crescentic forms of the aestivo-autumnal plasmodia, and on the ninth day afterward typical "ring" forms of the organism were found in the blood, and an irregular fever developed. Crescentic forms appeared upon the tenth day after the onset of the fever.

Calandrucio inoculated himself from a case of quartan malaria, produced by inoculation, and in 18 days developed a typical quartan fever, the plasmodia being found in his blood. Bein produced tertian fever, with characteristi:

paroxysms, in four cases, by the inoculation of blood containing the tertian plasmodium withdrawn by leeches, and in one case produced a tertian attack by the inoculation of blood from an experimental case of tertian malaria.

An experiment of Di Mattei is of interest, both because two types of fever were produced at different times in the same case, and because he claimed to have produced an aestivo-autumnal fever by the inoculation of blood containing only the crescentic form of the plasmodium. The patient experimented upon had suffered from quartan malaria for some time previously, but had recovered. He was inoculated with blood from a case of irregular fever, which showed only crescents at the time of inoculation. About eight days after inoculation the patient's blood showed non-pigmented, hyalin parasites. No fever occurred until sixteen days after inoculation, and it was nine days after the onset of the fever before crescents were found in the blood, or 25 days after inoculation. Di Mattei followed this experiment by injecting into the same patient blood from a case of quartan malaria, and in fifteen days quartan fever appeared, and quartan plasmodia were present in large numbers in the blood. While Di Mattei considered that the blood inoculated contained only crescents, it is evident, from what we know of the development of the malarial plasmodia, that he must have inoculated asexual forms of the organism.

Sacharoff produced aestivo-autumnal malaria in himself by the inoculation of infected blood which had been removed from the body for four days. He allowed leeches to suck the blood of a case of pernicious malaria whose blood contained immense numbers of hyalin, non-pigmented "ring" forms of the aestivo-autumnal plasmodia. The leeches were kept upon ice for four days, at the end of which time he injected 1 c.c. of blood from one of them into his arm. At the end of 12 days he had a malarial paroxysm, accompanied by a chill, which was repeated upon the following day, and an examination of his blood demonstrated the presence of numerous typical "ring" forms of the aestivo-autumnal plasmodia.

From the foregoing it is evident that the malarial fevers may be inoculated from man to man by the injection of infected blood and that the species of plasmodium inoculated is always found in the blood of the infected individual.

Transmission by the Mosquito.—The one method of the transmission of malaria which has been confirmed by abundant experimental evidence, and which to-day is accepted by all authorities, is that by the bite of infected mosquitoes. I believe that this is the only way in which these fevers are naturally transmitted, and certainly it is the only way which has been actually proven and which is, therefore, worthy of our belief. In a most convincing manner Marchiafava and Bignami refute the arguments of the air and water theorists, and sum up in favor of the transmission of the disease by the mosquito as follows:

"Thus, admitting that malaria in man is the result of inoculation by mosquitoes, it is not difficult to explain why it is practically not carried by the wind; it is also easy to understand why the danger of acquiring malaria is greatest in

the evening and the night. We see at once why the infection does not rise far above the ground; we comprehend readily the danger of sleeping in malarious districts; and finally this theory explains perfectly the well-known prophylactic efficiency of mosquito-nets in regions where malaria prevails. Also this agrees with what we know of the habits of mosquitoes in malarious countries, which sting especially at evening and during the night, do not fly far from marshes, or places where the proper conditions of their existence prevail, are in hiding during the day out of the way of the winds, are most numerous in places where malaria prevails, disappear from places where works of sanitation have removed the conditions necessary to their existence, do not fly to any great height above the ground," and many other arguments.

Nuttall, in an elaborate review of the evidence in favor of the transmission of malaria by the mosquito, mentions the following facts, which I have tabulated below:

1. **The Malarial Season.**

A. Corresponds to a period of warmth and moisture, conditions most favorable for the development of mosquitoes.

B. Develops after the first rains, which form pools in which mosquitoes may develop.

C. Malaria often ceases after excessive rains, when such pools are flooded and washed out, thus destroying the mosquito larvae.

D. Malaria is most prevalent in wet years, when mosquitoes are most numerous.

2. **The Malarial Country.**

A. Malaria is most common in low, moist countries, swamps, jungles, low sea-boards, river deltas and valleys, and in such places mosquitoes most abound.

B. Malaria becomes more common as the equator is approached, which is also true of the abundance of mosquitoes.

3. **Conditions Affording Protection from Malaria and Mosquitoes.**

A. Protection of the body, such as is afforded by closing the windows and doors at night and using mosquito-nets, gauze, veils, curtains, etc., has long been recognized by the inhabitants of malarial countries as protective against the malarial fevers.

B. Thickly built houses exclude malaria. Malarial fever seldom penetrates far into cities, as mosquitoes are stopped by walls, hedges, etc., and are attracted by the lights in the suburbs.

C. Intervening woods and expanses of water protect from malaria, the woods by obstructing the passage of the mosquitoes, acting as a sort of screen; the bodies of water because the mosquitoes perish in them or do not attempt to cross them, as these insects are incapable of prolonged flight.

D. Cultivation of the soil: Malaria is often prevented by cultivation of the soil, due to the fact that this destroys the stagnant pools and swamps, or "mosquito nurseries."

E. Flooding the land will prevent malaria by destroying the breeding places of the mosquitoes.

F. Avoidance of sleeping out-of-doors at night or exposure after sunset: The mosquitoes bite mostly at night, and when asleep the individual is bitten frequently, thus increasing the chances of infection.

G. Use of fires: Fires indoors or out protect against malaria because the mosquitoes are attracted by them, and fly into them and perish before reaching the person.

H. Immunity of persons working in sulphur mines in malarious regions due to the fact that mosquitoes are driven away by the smell of sulphur.

4. **Influence of Occupation.**—The more exposed a person is to the night air in malarial regions, by reason of his occupation, the more liable is he to contract malaria, as he is thus exposed to the bites of mosquitoes.

5. **Effect of Turning Up the Soil.**—Malaria often follows the turning up of the soil, as in extensive excavation works, and this is due to the fact that the inequalities of the excavated land gives rise to small pools, which form suitable breeding places for mosquitoes.

6. **Elevation and Malaria.**—Malaria is most dangerous near the ground, and people living in the upper stories of houses suffer much less severely from these fevers than those living upon the ground floor. Mosquitoes fly low, and the nearer the ground one is the more apt is he to be bitten.

7 **The Coincidence of Malaria and Mosquitoes.**—Wherever there is malaria there we may be sure of finding mosquitoes belonging to the *Anophelinae*.

It is evident from the above that the epidemiological data concerning the malarial fevers present strong presumptive evidence in favor of the transmission of the disease by the mosquito, but we do not have to deqend upon this evidence alone, for we are now possessed of a mass of experimental evidence which proves beyond all doubt that the malarial fevers are inoculated into man by the mosquito. To the brilliant work of Manson, Ross, Bignami, Bastianelli, Marchiafava, and Grassi the world is indebted for the elucidation of one of the most important of etiological questions.

I have already considered the development of the malarial plasmodia within the mosquito and have given a brief historical summary of the growth of our knowledge concerning this question; here it is my purpose to give in detail the most interesting of the experimental evidence proving that the mosquito transmits the malarial fevers.

Bignami was the first to succeed in producing malaria by the bites of infected mosquitoes. His patient, one Sola, who had been an inmate of the Santo Spirito Hospital for six years, suffering from a nervous disorder, but who had never had malaria, offered himself voluntarily as a subject for the experiment. The mosquitoes used were from Maccarese, an intensely malarious locality, and the following is Bignami's record of the experiment:

"Sola slept in the room in which the infected mosquitoes had been liberated from September 26 to the end of October. During the latter part of October the patient complained of malaise and headache. On the afternoon of October

31, he had a slight elevation of temperature to 37.2° C. (99° F.). On November 1, at about 3 P. M., he was taken with a severe chill which lasted until 5 o'clock, the temperature rising rapidly to above 39° C. (102.2 F.). Between 9 and 10 o'clock a feeling of cold was again experienced. The fever continued all night, falling in the early morning (November 2) to 38.2° C. (100.8° F.), and rising again that evening to 39.3° C. (102.7° F.). The patient was restless and complained of severe headache, but there were no grave symptoms. In the night, about 11 o'clock, he had another chill of short duration. During this night the temperature remained above 39° C. (102.2° F.), and on the morning of November 3 rose above 40.4° C. (104.7° F.), the patient being very restless and complaining of much suffering. The fever broke in the afternoon with a gentle perspiration.

"At quarter after five in the afternoon a hypodermic injection of one gram of quinine was given and repeated at night. The fever fell, and at 8 A. M., on November 4, the temperature was 36.7° C. (98° F.). The administration of quinine was continued during the following days, the patient continuing to have slight elevations of temperature which did not reach 38° C. (100.4° F.) except once, on November 6. From November 7 onward the patient was entirely without fever, and rapidly regained his appetite and strength.

"An examination of the blood made with the greatest care on November 2 gave negative results, no malarial parasites being found. On the morning of November 3 a few young annular parasites, motile and discoid, without pigment, and presenting the characteristic appearance of the parasites of aestivo-autumnal fever were found. These forms increased in number during the day, and were quite numerous during the afternoon hours. In some there was a beginning pigmentation at the border consisting of very fine granules of pigment.

"We see, therefore, that there was produced experimentally in Sola a grave malarial fever with a temperature curve such as is frequently seen in a primary aestivo-autumnal infection. The fever began briskly, continued with slight remissions from November 1 to 3, and began to fall on the evening of the latter day when the specific remedy was administered. The parasites found in the blood belonged to the aestivo-autumnal species.

"This is perhaps the first time that, in the primary aestival infection acquired in the natural way, examinations of the blood have been made from the beginning of the fever. We find that after forty hours the parasites begin to be found, at first in small numbers, but rapidly becoming more and more numerous.

"According to the opinion of all who followed this experiment, it was conducted in such a way as to silence all objections. Sola is a robust individual, notwithstanding his nervous malady, who has never in his life had malarial fever, and who has not been outside of the Santo Spirito Hospital for six years. The room where the experiment was conducted was an annex of the San Carlo ward, in which, within the memory of the hospital physicians, there has never been an autochthonous case of malarial fever, nor has there ever been any malaria in the neighboring houses.

"Now in a room in the San Carlo ward of the Santo Spirito Hospital (Rome) Sola acquired a malarial infection produced by aestivo-autumnal parasites, with a well-marked fever and symptoms so grave as to call for the prompt administration of quinine. The fever, indeed, was exactly such a one as is ordinarily caught by laborers in the Roman Campagne in the summer and autumn months, a fever beginning with the typical curve of the aestivo-tertian or sometimes with a continued curve. This identical fever, such as prevails at Maccarese, was taken by Sola in a place where there was of Maccarese neither the water nor the soil nor the air, but the mosquitoes alone. We are then forced to the

conclusion that the fever was acquired by inoculation by the mosquitoes. While in this case there could be no doubt that the mosquitoes were responsible for the fever, it was not definitely determined just what species of mosquitoes was concerned, as there were three different species liberated in the room. After this experiment Grassi, Bastianelii, and Bignami worked with *A. maculipennis*, and never failed to produce the disease when they were used. The following, a successful experiment performed by Bastianelli and Bignami, and quoted in their own words, is of interest in many ways:

"A patient suffering from a relapsing aestivo-autumnal infection, in whose blood were many crescents and round and flagellated bodies, slept, from December 10 to 18, in a room in which had been set free about 50 individuals of *A. maculapennis*, brought from Maccarese. The temperature of the room was maintained at from 18° to 22° C. (64.4° to 71.6° F.). Most of the mosquitoes stung the patient, and became infected with crescent bodies, and subsequent examinations showed in the middle intestine the characteristic forms in process of development. But it was also observed that the mosquitoes remaining in the room at the given temperature during the last days of December did not have in the intestines mature sporozoa with *sporozoites*, but only the growing forms. Evidently at a temperature of from 18° to 22° C. the life cycle of the parasite is completed very slowly. But these same mosquitoes, confined for a few days in an incubator at a temperature of 30° C. (86° F.), were found to contain forms of a later development. There were noted, enclosed in the intestines, typical capsules filled with *sporozoites*, and also broken and empty capsules, and in the salivary glands were numerous *sporozoites*.

"When this fact was noted, three mosquitoes of this group were kept in an incubator at 30° C. for two days, and on January 2 they were made to sting a new subject, A. R.——, who lent himself knowingly and willingly to the experiment. It is needless to say that this man had never had malaria. On January 5 two of the same mosquitoes were made to sting the same person again, who then had been stung in all five times by three specimens of *A. maculapennis*.

"After this part of the experiment, the three mosquitoes were dissected, and examined under the microscope, with the following results: *A. maculipennis*. No 1. In the intestines were found many capsules with *sporozoites*, and some capsules which had been ruptured and completely emptied of their contents. In the salivary glands were found two infected tubules; in one the cells were swollen, of ovoid form, and filled with granules of uniform size. When pressure was made on the preparation there issued a very large number of *sporozoites* of typical form, uniform in appearance, and all of equal length; in the other tubule were also seen cells. containing filiform *sporozoites* of characteristic appearance.

"*A. maculipennis*. No. 2. In the intestine were very numerous capsules, some still whole and filled with *sporozoites*, others ruptured and shrunken, and containing a granular residuum of a pale yellow color. In some of these ruptured capsules were seen brown bodies of various size and shape, some elongated, others short and deformed. In the salivary glands all the tubules were infected except one or two. In them were seen cells containing typical *sporozoites*, cells filled with granules similar to those described in *A. maculipennis*, No. 1, and cells filled with round hyaline bodies of variable size. In addition there were also found typical filiform *sporozoites* along the excretory ducts of the gland.

"*A. maculipennis*. No. 3. The intestine was filled with mature sporozoa. Many capsules were broken and shrunken, and contained a pale yellow detritus; others contained a large central body of granular aspect, surrounded by a hyaline halo and without any recognizable structure. These were possibly mature sporozoa in process of degeneration. The salivary glands were not found infected.

"From the results of these examinations we may conclude that of the three specimens of *A. maculipennis* employed, only two had inoculated the patient with malaria.

"On the evening of January 10, the patient had a sense of heat and a headache, but the temperature was normal. On January 11, 12, and 13, there was no fever and the patient felt well. On January 14, that is, after from 9 to 12 days' incubation, there was no fever until 8 o'clock in the morning, but then the temperature began to rise rapidly and reached 39.5° C. (103.1° F.) at noon. From this time the fever remained continuous up to January 18. The temperature fell to normal in the morning of the eighteenth. (Two grams of quinine were given hypodermically on the sixteenth, and repeated on the seventeenth, and recovery was complete and rapid.

"On examination of the blood on the morning of January 16, there were found scanty aestivo-autumnal parasites with very fine pigment granules at the periphery. There were found also plasmodia without pigment and with granules in normal red blood-corpuscles and in brassy bodies. The parasites disappeared after the exhibition of quinine on January 17. Thus the infection was rapidly cut short and no crescent bodies were seen.

"We have in this case a typical example of aestivo-autumnal infection, beginning with a continued fever, as is usual with this group of malarial infections. The course of the disease was in every respect identical with that in the first case of malarial fever experimentally produced by the stings of mosquitoes (the Sola case, described by Bignami)."

From the above it will be seen that in this case the disease was caused by the bites of only two insects, and this is not surprising when one considers the immense number of *sporozoites* in the infected salivary glands of a single mosquito. There i no reason to doubt but that one mosquito may infect a large number of individuals.

One of the most striking confirmations of the truth of the mosquito theory of the transmission of the malarial fevers is found in the experiments of Sambon and Low. These investigators spent an entire summer at Ostia, a most malarious region in the Roman Campagna, residing in a mosquito-proof hut. During the day, the time was spent mostly out of doors, but early in the evening the observers retired to their hut and there spent the night. Neither investigator developed malaria, although many individuals, residing in the same locality, without protection from mosquitoes, suffered severely from the disease. Ostia is so malarious that it was formerly said that to spend one night at that place would result in a malarial paroxysm, and this was proven recently when of sixteen police officers who spent one night at Ostia, all developed malaria within two weeks; yet Sambon and Low lived through an entire summer at this place and did not suffer from malaria, because they spent the nights in a mosquito-proof hut. As showing the manner of life of the laborers in the Roman Campagna and how severely they suffer from malaria, the following quotation from an editorial in the British Medical Journal of December 8, 1900, describing the experiments at Ostia is of interest:

"Ostia, like all other malarious districts in the Roman Campagna, has no indigenous population. The little wretched town of mean buildings gathered

round the old mediaeval castle is inhabited by a fluctuating population, which comes there from all parts of Italy, but chiefly from the south. In winter a large number of laborers come to plough the fields and sow the corn, but they leave before the end of June. In summer other workman come for short periods to harvest the corn and maize. The life of these laborers is wretched in the extreme; they may well be called 'white slaves.' They suffer fearfully from malaria. They were sometimes met returning bare-footed to their distant homes, under the scorching sun, delirious from fever. They often fall by the roadside, and many have died in the ditch in sight of the great gray cupola.

"They work from dawn to sunset closely watched by overseers on horseback, who drive them like beasts. If they dare complain an infantry regiment is called out to keep them in order. Their food is dry bread. Those who can afford it add a morsel of cheese or an onion to the fare. They sleep in little huts made of boughs and straw. Many have no covering between themselves and the starry heavens. The people who gather reeds at the mouth of the river live in huts built on piles, which look exactly like the tree houses or pile dwellings of the New Guinea Papuans."

Can any one reading this description of industrial conditions in "sunny Italy" wonder at the terrible mortality from malaria that has ever been characteristic of that country.

In 1900, Manson, believing that the experiments of the Italian investigators, while conclusive to the scientific world, were vitiated in the public mind by the fact that they were performed in a malarial country, conceived the idea of having infected mosquitoes sent from Italy to him in London and using these mosquitoes to produce malaria in a healthy individual, in that city, where malaria is unknown, unless it is imported in the person of an infected patient. Accordingly, Sambon sent Manson some mosquitoes fed upon a case of benign tertian malaria in Rome, and these mosquitoes were used in an experiment upon Manson's son, the late Dr. P. Thurburn Manson. The experiment is given in the latter's own words:

"I am twenty-three years of age, was born in China, but have lived in this country (England) since I was three; have never been abroad since, nor in any district in this country reputed to be malarial. I am healthy.

"The first consignment of mosquitoes arrived at the London School of Tropical Medicine on July 5. Only some half-dozen had survived the journey. They were in a languid condition and would not feed satisfactorily. One may have bitten me. By July 7, they were all dead. The second consignment arrived on August 29. They had been infected in Rome on August 17, 20, and 23, by being fed upon a patient with a double benign tertian infection. The patient was reported to have had numerous parasites, including many *gametes* in his blood. On arrival twelve insects were lively and healthy looking. I fed five of them on August 29, three on August 31, one on September 2, and one on September 4. They bit my fingers and hands readily. The bites were followed by a considerable amount of irritation, which persisted for two days.

"The third consignment arrived on September 10. They had been fed in Rome on September 6 and 7 on a patient suffering from a simple tertian infection but with very few parasites in his blood. There were some 50 to 60 mosquitoes in good condition. Twenty-five bit me on September 10 and 10 on September 12.

"Up till September 13, I had been perfectly well. On the morning of the thirteenth I rose feeling languid and out of sorts with a temperature of 99° F. By midday I was feeling chilly and inclined to yawn. At 4.30 P. M. I went to bed with severe headache, sensation of chilliness, lassitude, pains in the back and bones and a temperature of 101.4° F. Repeated examinations failed to discover any malarial parasites in my blood.

"September 14.—I slept fairly well, but woke at 3 A. M. with slight sweating and a temperature of 101°. During the day my temperature ranged between 101° and 102°. The symptoms of September 13 were exaggerated and anorexia was complete. Several examinations of the blood were made again with negative results.

"September 15.—Woke at 7 A. M. feeling distinctly better, with a temperature of 100.4°. No malarial parasites were discovered on repeated examinations of my blood by my father. About 2 P. M. I commenced to feel slightly chilly; this soon wore off, and I became hot and restless. By 4.30 P. M. temperature was 103.6°. It remained about 103° till 9 P. M. when profuse sweating set in. I am told there was some delirium.

"September 16.—I woke at 8 A. M. feeling quite well; temperature 98.4°. I made several blood examinations and found one doubtful half-grown tertian parasite. In the afternoon and evening there was a recurrence of fever (temperature 102.8, relieved by sweating.

"September 17.—Again felt quite well on waking after a good night's sleep; temperature 99°. At 10 A. M. several half-grown parasites, a *gamate*, and two pigmented leucocytes were discovered in the first blood film examined. During the day many tertian parasites were found. Their presence was confirmed by my father and others. About 2 P. M. the sensation of chilliness returned. Temperature 101.8°. By 5 P. M. temperature had reached 103°. There was then copious sweating. The edge of the spleen could be felt on deep inspiration, and there was a slight feeling of discomfort in the region of that organ. Dr. Frederick Taylor and Mr. Watson Cheyne confirmed the presence of splenic enlargement. By 9 P. M. the temperature had fallen to 99.2°, and I was feeling better. Quinine (10 grains) was given.

"September 18.—Woke after a good night, feeling perfectly well (temperature 97°). Ten grains of quinine were taken and subsequently five grains every eight hours. I continued perfectly well all day. A few three-quarters grown tertian parasites and some *gametes* were found during the forenoon and afternoon. At 10 P. M. the parasites had disappeared, the last being found at 5 P. M.

"September 19.—No parasites discovered. Temperature normal. Feeling quite well. There is no splenic enlargement, and no tenderness. Appetite returns.

"September 25.—In good health. No recurrence of malarial symptoms. A second experiment with mosquitoes sent from Rome and infected with the benign tertian plasmodium was performed upon another individual in London, and was successful. In both Dr. Manson's case and in the latter, relapses occurred and tertian plasmodia were always easily demonstrated in the blood."

In 1899, Grassi, Bignami, and Bastianelli found that over 75 per cent. of *Anopheles* caught in rooms occupied by malarial patients showed developmental forms of the plasmodia within them, and they were successful in infecting A. *maculipennis* with the quartan plasmodium.

The experiments given comprise but a small portion of these which demonstrate beyond all doubt that the malarial fevers are transmitted from man to

man by the mosquito, and while it is not yet proven that this is the only mode of transmission, it is but reasonable to suppose that this is the case. Schaudinn claimed to have traced developmental forms of the plasmodium in the eggs of mosquitoes and thus considered that the disease might be transmitted by the adult insect to its progeny through the eggs and larvae, as in the case of Texas fever and relapsing fever. His researches have not been confirmed and the experiments of Marchiafava and Bignami would appear to indicate that such hereditary transmission of the plasmodia does not occur. Neither the eggs or the larvae of infected *Anopheles* showed the presence of any form of the plasmodia, nor were *Anopheles*, born in the laboratory, the progeny of infected insects, able to produce malaria in man, although six individuals were thus experimented with. At the present time the only known method of the transmission of the malarial fevers is through the bite of infected mosquitoes, and the plasmodia are not present in the ova of these insects.

Cultivation of Malarial Plasmodia.—No one as yet has been able to cultivate the malarial plasmodia in artificial media outside of the human body. Coronado, a Spaniard, is the only investigator who has claimed to have been successful in the cultivation of the plasmodia, but his experiments have been repeated by other observers, none of whom have been able to confirm his results. He claimed to have cultivated the plasmodia in unsterilized water. In tubes of such water containing mud from the bottom of the supposedly infected pool, a small amount of malarial blood was placed, and in 24 hours Coronado claimed that cultures developed, and the entire life cycle of the plasmodia could be followed. His description of this life cycle is at variance with that occurring either in man or in the mosquito, and it is evident that his results are erroneous, and that he observed some other organism in the grossly contaminated water.

The plasmodia, however, have been kept alive outside of the human body for several days. Sacharoff was the first to be successful in such experiments, finding that in malarial blood obtained by leeches, from the human subject, the plasmodia remained alive for over a week, provided the leeches were kept upon ice. No reproductive changes occurred during this time. He also found that the aestivo-autumnal plasmodia remained actively amoeboid for seven days, and capable of causing malaria for four days; under such conditions, the benign tertian plasmodium remained amoeboid for only forty-eight hours. Rosenbach found that the benign tertian plasmodium remained alive in the blood of leeches or forty-eight hours, and he considered that during this time growth occurred, and possibly multiplication.

Blumer, experimenting with blood containing aestivo-autumnal plasmodia, found that the small hyaline parasites continued present for over a week in the leech if it were kept upon ice, but he was not able to demonstrate amoeboid motion, nor could any evidence of growth or reproduction be discovered.

Hamburger and Mitchell have performed similar experiments, which are described by Thayer, as follows:

"Mr. Hamburger took the blood from a case of aestivo-autumnal fever with quotidian paroxysms at a time when only small amoeboid and ring-shaped, non-pigmented hyalin bodies were present. During the next several days he was able to distinguish a slight increase in size, with the accumulation, in nearly every organism, of a few small, motile pigment granules. On the eight day the organisms were distinctly visible, each with a small group of slightly motile granules in the middle or at some point on the periphery of the parasite. Specimens stained on the eighth day showed characteristic ring-shaped bodies. The experiment of Hamburger, which I was able to follow, furnishes the first demonstration of the actual growth of the parasite and the accumulation of pigment outside of the human body. (This was written before the discovery of the development of the plasmodia within the mosquito.)

"Mr. Mitchell placed a leech upon an individual suffering with a combined aestivo-autumnal and double tertian infection. The blood showed two groups of active tertian organisms and a few crescentic and ovoid forms. In the body of the leech the tertian organisms were to be made out for ten days. The pigment was active for four days, but no amoeboid movement was to be made out in the parasites. The crescentic and ovoid bodies remained unchanged; no flagellate forms were observed."

In the light of our present knowledge concerning the transmission of these fevers by the mosquito, it is interesting to note that in the leech the cre cents and ovoids underwent no further development, and that flagellated parasites were entirely absent.

In view of Roger's successful efforts in the cultivation of *Leishmania-donovani* in citrated blood, I have endeavored to cultivate the plasmodia of malaria in a similar manner, the method pursued being as follows:

The patient's arm is corded above the elbow and sterilized. A large superficial vein is selected and five cubic centimeters of blood is removed from it with a sterilized glass syringe, and added to tubes containing from 1 to 2 c.c. of citrate solution, the tubes being then kept at room temperature, at blood temperature, and at a temperature of 22° C. I experimented in th s way with blood containing the *gametes* (crescents) of the aestivo-autumnal plasmodia, and with blood containing tertian *gametes*, but was unable to observe any indications of development in the organisms beyond flagellation, which occurred soon after the blood was added to the citrate solut on. The intracellular plasmod a underwent no developmental changes, but soon degenerated, although some could be distinguished in the red corpuscles as long as three days after removing the blood from the patient. There appeared to be no difference, as regards appearance, in the organisms kept at room temperature, in the incubator, or at 22° C.

Immunity.—There has for years been considerable question as to whether immunity to the malarial fevers exists in individuals or races. There can be no doubt that both *natural* and *acquired* immunity to the malarial fevers is possible, and that the presence of immunity against these fevers is not so very uncommon in individuals residing in malarial localities. Koch firmly believes that immunity to malaria exists because of the common occurrence of sponta-

neous recovery and the freedom from the disease observed in certain groups of people, as the coast negroes of East Africa, and the Chinese coolies of Sumatra. In these people the immunity is undoubtedly acquired during a long residence in malarial localities.

In considering this portion of our subject it will be convenient to do so under the following divisions: *Natural immunity*, absolute and relative, and *acquired immunity*, absolute and relative.

Natural Immunity.—By natural immunity we understand an immunity occurring naturally, the individual never having suffered from the disease. Natural mmunity is generally *hereditary*, and, in most instances, is *absolute*, but occasionally is *relative*, the individual, under certain conditions, succumbing to infection. An *absolute* natural immunity against malaria is sometimes observed in individuals and families, but it is never a racial characteristic. Maurel concluded from his exhaustive studies upon racial immunity that no human race is immune from malaria, although many races have an acquired immunity. A natural *relative* immunity is often observed in the descendants of the inhabitants of very malarial communities, an immunity which is protective until unusual exposure or hardship so undermines the natural resistant powers that an infection results. An *absolute* natural immunity is observed in rare instances, and almost every writer upon malaria has given examples of such immunity. Celli instances the case of four individuals, living at Sezze, in the Pontine marshes, a most malarious region, who have resided there for years, have never taken any precautions against malaria, yet who have never suffered from the disease. "They work very laboriously, have insufficient and bad food, frequently sleep on the marshes, in the open air and in such a manner as to be continually bitten by mosquitoes; still they have never had malaria, are very healthy, have a rosy color, and their liver and spleen are normal in size."

Marchiafava and Bignami note an interesting case of natural absolute immunity in a family residing in one of the worst malarial portions of the Roman Campagna. The grandfather, the father, and the two sons, although exposed continually to infected mosquitoes, have never had malaria, although almost every one living in the same place for any length of time develops the disease.

I have observed a few instances of natural immunity among American soldiers, both in Cuba and in the Philippine Islands. These men, although living in most malarial regions and taking no precautions against infection, never suffered from the disease, while their companions, even those who were cautious regarding exposure to mosquito bites, one by one developed paroxysms of fever with the plasmodia in the blood.

We thus see that an *absolute* natural immunity is present in some individuals, and while it is comparatively rare yet I believe that more extended observation will demonstrate that it is much more common than is generally supposed. My experience with the malarial fevers as they occur among our troops would appear to show that a not inconsiderable proportion of the men possess a natural

immunity to these fevers, probably *relative* in character, in most instances, but *absolute* in a goodly number. Natural immunity is never a racial characteristic, for no race of men is immune, as a race, to the malarial fevers.

Acquired Immunity.—By the term "acquired immunity" we understand an immunity acquired through an attack or attacks of a disease. It is somewhat doubtful if an *acquired* immunity against the malarial fevers is ever *absolute* in character, although many sufferers from these fevers never have more than one attack. In the vast majority of instances an immunity acquired against malaria is *relative* in character, being overcome by many factors, such as exposure, starvation, mental or physical strain, an unusually large amount of the infective principle, or excessive changes in temperature. The immunity acquired by repeated attacks of malaria is always *relative* in character.

Long residence in a malarious country will, undoubtedly, if the individual survives repeated attacks of the disease, confer upon him a *relative* immunity to malaria. In other words, the malarial poison produces certain changes in the human organism which render it at least partially immune to further attacks. This immunity, however, is often gained at the expense of the vitality of the individual, and the penalty inflicted is a chronic malaria cachexia, which markedly lowers the health of these immunes. The history of acquired immunity is simply that of repeated attacks of malarial fever, each one a little less severe than the preceding, until at last a spontaneous cure is effected which is permanent. It should not be forgotten that in many individuals supposed to be immune to malaria, the immunity consists in the absence of symptoms only for the examination of the blood of such individuals will often reveal malarial plasmodia undergoing *schizogony*. In these individuals, the condition present might perhaps better be called an *increased tolerance* to the plasmodia rather than an immunity in the restricted sense in which the word is often employed. This subject will be considered more fully in the chapter dealing with latent and recurrent malarial infections, as in such instances the malarial infection is really latent in character.

It is a well recognized fact that the inhabitants of malarial countries are often more resistant to the infection than are new-comers, and in most instances this immunity, which is relative, has been acquired through repeated attacks of the disease. The black races in some portions of Africa, although not naturally immune to malaria, enjoy a relative immunity, and even when they contract malaria suffer much less severely from it than does the European. Plehn has demonstrated that the Kamerun negroes rarely have malarial fever, and generally recover spontaneously; whereas Europeans suffer very severely in the same locality. The same is said of the Malays and the Chinese by Martin, while Tommasi-Crudelli has noticed differences in the resisting power of the inhabitants of certain localities in Italy.

The natives of the Philippines, living in the most malarial localities, enjoy an increased resistance to these fevers, a resistance which may be broadly 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. It is probable, however, that a very large proportion of the natives would have been found infected had their blood been examined; hey had simply acquired, from repeated attacks, an immunity to the malarial poison and therefore presented no symptoms of the disease.

The apparent immunity of native races to malaria was unexplained until Koch made his observations in Africa regarding the occurrence of malaria in native children. He proved conclusively that in malarial regions a very large proportion of infants and children show the malarial plasmodia in their blood, even though no symptoms of the disease be present, while, in the majority of instances, the blood of adults does not show any trace of malarial infection. From his findings he concluded that the adult natives, in the tropics, are immune to malaria because of having suffered from repeated attacks in infancy and childhood.

In West Africa Koch found that 100 per cent. of children under two years of age showed malarial plasmodia in their blood and that the percentage of infections decreased with advancing age; thus, children from two to five years of age showed 48 per cent. infected, and from 5 to 10 years 23.5 per cent. infected, while those over ten years of age were free from infection. In Kaiser Wilhelm's Land (New Guinea) his findings were as follows.

Place	Age	No. examined	Percentage infected.
Bogadjine	Under 2 years	10	8 cases or 80%
	2 to 5 years	12	5 cases or 41.6%
	5 to 55 years	86	0 cases or 0%
Bongn.....	Under 2 years	6	6 cases or 100%
	2 to 5 years	13	6 cases or 46.1%
	5 to 10 years	17	4 cases or 23.5%
	10 to 40 years	39	0 cases or 0%

In Java, according to Koch, of 297 children examined under one year of age only 66, or 22.1 per cent., were found infected, while of 429 children over one year of age 47, or 10.9 per cent., were infected. It will thus be seen that the percentage of infections in children varies in different localities, but he claims that the adult ratio is practically zero in tropical countries where malaria is very prevalent.

Koch's results have been confirmed by Stephens and Christophers and by James. Stephens and Christophers, at Accra, West Africa, found from 23 to 90 per cent. of babies infected; up to eight years of age 20 to 57 per cent., up to 12 years of age 28 to 30 per cent.; and after the twelfth year infection was found to be rare. At Lagos, of children under two years of age 50 to 100 per cent. were infected; from two to five years, 40 to 75 per cent., and from five to ten years 25 per cent.

James, in India, found that the percentage of malarial infection among native children varied greatly in different localities, being zero in some places and as high as 86 per cent. in others. Thus, at Mian Mir, children up to three years of age showed 80 per cent., infected; up to five years, 66 per cent ; up to ten years, 50 per cent., while after ten years none were infected. At Ennur, children up to three years of age showed 65 per cent. infected; up to five years, 51 per cent.; up to ten years, 46 per cent.; and up to fifteen year , 16 per cent. He found no infection in natives over fifteen years of age. He also states that in the most malarious localities the immunity of the adult is very apparent, but in those localities in which the malarial ratio is low, an immunity of the adult does not appear to be established.

The truth of Koch's assertions regarding the immunity of adult natives in malarial regions has been seriously injured by the observations of numerous investigators, and it may safely be said that adult natives, in most malarial regions, show plasmodia in their blood in a considerable percentage of those examined.

Hope, in Pabna, found that while 922 adult natives showed plasmodia in their blood, only 862 children examined at the same time presented them; in other words, that the adult malarial ratio was larger than the malarial ratio in children.

Annett, Dutton, and Elliot, working in Nigeria, obtained the results given below:

Age of child	Per cent. infected
0 to 1 year,	27.3%
1 to 2 years,	63.0%
2 to 3 years,	63.0%
3 to 4 years,	51.0%
4 to 5 years,	48.8%
5 to 6 years,	34.8%
6 to 7 years,	6.6%
7 to 8 years,	27.5%
8 to 9 years,	25.0%
9 to 10 years,	14.0%
10 years and above,	10.0%

It will be observed that these investigators found 10 per cent. of adults infected.

The following rules governing immunity in malarial regions may be said to be fairly well proven by the observations of many investigators:

1. In severely infected regions, provided conditions are favorable for the propagation of malaria, a relative immunity is generally observed in the adult population, and is more promptly acquired, as more reinfections occur in childhood.

2. In slightly infected regions a relative immunity is not rapidly acquired, as fewer children are infected and reinfections are less common.

3. In countries in which seasons, such as winter, occur which are unfavorable to malaria, an acquired immunity to the disease is rarely observed, as reinfections are thus rendered less numerous.

In this connection the observations of Panse in East Africa (Tonga) are of great interest as they serve to show that in some regions the above rules do not hold good. He examined 2,227 natives in a highly malarious locality with the following results:

Age	No. examined	No. infected	Per cent. infected
Under 1/2 year	16	6	37.5%
Between 1/2 and 1 yr.	9	6	66.6%
1 year of age	25	22	88.0%
2 years of age	20	17	85.0%
3 years of age	28	25	89.2%
Between 4 and 5 yrs.	48	34	70.8%
Between 6 and 7 yrs.	84	52	61.9%
Half-grown children	314	125	39.4%
Adults	1683	258	15.3%

Summary: Of children under 1 year of age, 48 per cent. were infected.
Of children between 1 and 3 years, 87.6 per cent. were infected.
Of children between 4 and 7 years of age, 65.1 per cent. were infected.

The results given by Panse agree with my own in the examination of native Filipinos, and they seem to me to be more nearly correct than those of Koch, for while they undoubtedly show a gradual diminution of the number of cases of infection with advancing age, they also show that only a certain proportion of the adult population acquire an immunity, which I believe will be found to be true of the population of most malarial communities. It certainly is not often found to be the case that all the adults in such a community are immune to malaria, and, indeed, it is impossible to believe in any such wide-spread immunity following attacks of malaria; yet Koch and others have claimed absolutely negative results in the examination of the blood of adults in malarial

regions. I think it is evident that such results must be very exceptional, and require the most careful confirmation before they can be accepted as true of malarial regions in general.

In one of the most malarial localities in the Philippine Islands (Camp Stotsenburg) I examined the blood of 45 adults and 180 children, all Filipinos, and all of whom at the time of examination were free from symptoms of malaria. I was able to obtain the exact age in but 147 of the 180 children, and only this number is included in the table of results which follows:

Age	No. examined	No. infected	Per cent. infected
1 to 5 yrs.....	40	30	72.5%
5 to 10 yrs.....	54	20	37.0%
10 to 15 yrs.	53	13	24.5%
Adults.....	45	28	62.2%

In my examinations it will be noticed that of the 45 adults examined, no less than 62 per cent. showed infection with the malarial plasmodia, despite the fact that my examinations of the blood of children demonstrate that the percentage of infections diminished with advancing age; this apparent contradiction I cannot explain, but it is probable that a study of the blood of a larger number of adults would materially reduce this great percentage of infections. From the results obtained, however, it is very evident that the adult Filipino in this locality has developed but little immunity to the malarial fevers, and I think it is probable that these people possess little or no immunity to malaria, although in malarial localities such adults have from childhood suffered from repeated attacks of the disease. I have notes upon several native adults of this region, who, within two years, have been admitted to the hospital from 8 to 16 times with malarial infection. This lack of immunity to malaria in the native adults of the Philippines appears to me to be a very significant and important fact from the standpoint of social economy, for it is invariably true that a people suffering from long-continued malarial infection are poor producers, especially along agricultural lines, where strength and endurance are demanded. It is a fact that will have to be taken into account in our endeavors to make this people prosperous, for I am convinced that malarial infection is very prevalent among them, often in an insidious form, and that it offers a serious barrier to effort upon their part. The gratuitous distribution of quinine to the people of certain districts of the Philippines would do much toward increasing their capacity for labor.

From what has been said it is evident that an acquired relative immunity against the malarial fevers is not uncommon under certain conditions and in some localities, and that it is always due to repeated attacks of malarial infection.

The efforts that have been made to produce an artificial immunity to malaria will be mentioned in speaking of the serum treatment of the disease.

My results concerning the proportion of infected adults in malarial regions in the tropics have recently been confirmed by A. Plehn, whose investigations were conducted in Kamerum, West Africa. He found as follows:

Age	No. examined	No. infected	Per cent. infected
Under 2 years	18	17	94%
Between 2 and 5.....	26	24	92%
Between 5 and 10.....	40	34	85%
Adults.....	43	26	60%

He concludes as the result of his researches that the adult West Coast African negro is not *immune* to malaria, but has established a *tolerance* to the plasmodia, as shown by the fact that the attacks are so mild as to present no characteristic symptoms. In this way these natives are relatively immune to malaria because they have established an immunity to the malarial toxin or toxins.

The Theories of Immunity as Applied to Malaria.—As is well known, there are two theories of immunity that are supported by medical scientists, that of Ehrlich and that of Metchnikoff, and each theory has many able supporters. Both schools believe in the various antibodies, Metchnikoff and his followers believing that all are produced by the leucocytes, while the school of Ehrlich does not designate any specific body cell as producing them; Ehrlich believes that there are many different *complements*, while Metchnikoff believes that there are but two, *microcytase* and *macrocytase*, both produced entirely by the phagocytes, and liberated by phagolysis or destruction of the phagocytes. *Complement* has been extracted from the leucocytes by the followers of both theories, so that some *complement*, at least, is produced by the leucocytes. The most enthusiastic of Ehrlich's followers, however, believe that *complement* only occurs in normal blood serum. Metchnikoff also believes that antitoxins when introduced into the body act by stimulation of the phagocytes, leading to increased absorption of the toxin and consequently to its destruction. He is positive in the belief that immunity in every disease depends upon the phagocyte.

The immunity in malaria must depend upon certain reactions between the cells of the tissues and the plasmodia or their toxins; the exact *modus operandi* is not known, but may be explained theorotically by ether Metchnikoff's or Ehrlich's conception of the cause of immunity. The fact that no malarial toxin has as yet been discovered does not militate against Ehrlich's theory as applied to this disease, but it is probable that immunity in malaria depends not only upon antibodies evolved in the blood serum, but also upon substances liberated during phagolysis, and, to a marked degree, upon the process of phagocytosis.

Whether the antibodies evolved are antiplasmodial, that is, capable of destroying the plasmodia, or antitoxic in nature, or both, is entirely problematical.

Causes of Natural Immunity to Malaria.—Natural immunity to the malarial fevers is comparatively rare and is individual in character. It probably depends upon factors which are operative in other infections, but I am inclined to believe that phagocytosis is of greater importance in malaria than it is in most other acute infections. The chief factors concerned in natural immunity against the malarial fevers are probably the following:

1. Antiplasmodial and antitoxic substances in the blood serum.
2. Antiplasmodial and antitoxic substances in the leucocytes, which are liberated by phagolysis.
3. Phagocytosis.
4. Absorption of toxic material by the leucocytes.
5. Absence of specific cell receptors.
6. Distribution of the cell receptors in non-vital organs.

Any one or all of these factors may be concerned in natural immunity in malaria, and it is not necessary to discuss here the manner in which they act; it should be remembered that the whole subject of the production of immunity in malaria is theoretical, and we can only reason from analogy with other infectious diseases.

Causes of Acquired Immunity in Malaria.—As has been shown, repeated attacks of the malarial fevers result in an acquired relative immunity to the disease, and this immunity may be more or less racial in character. This condition may be brought about by complex factors, the chief of which are probably:

1. Production of antiplasmodial and antitoxic substances in the blood serum.
2. Phagolysis of leucocytes, and consequent liberation of antiplasmodial and antitoxic substances.
3. Overproduction and excretion of such substances by the polymorphonuclear leucocytes.
4. Resorption of toxin by the leucocytes.
5. Phagocytosis.

The immunity observed in individuals after repeated attacks of malaria is probably an *acquired active antitoxic immunity*, as shown by the fact that the plasmodia may be present and undergo normal *schizogony*, but no symptoms of malaria are produced. As I have shown, this form of immunity consists in a relative tolerance to the presence of the plasmodia and their toxins, thus strongly indicating that such malarial toxins exist and that it is possible for antitoxic substances to be produced in the blood of patients suffering from this disease.

The antiplasmodial substances may consist, I believe, in both plasmodicidal and plasmodilytic agents, for it is not uncommon, during malarial attacks, to observe numerous extracellular plasmodia in the blood serum undergoing

marked degenerative changes, such as vacuolation and fragmentation. To these phenomena the term "plasmodiolysis" might well be applied.

While antiplasmodial substances may be of great importance in the production of immunity against malaria, it cannot be denied that phagocytosis is very common in this disease, and undoubtedly plays a very important part in the defense of the organism against the infection.

The question is often asked: Does one form of malaria protect against another? We have but very little data upon this point, although we do know that various forms of the infection may occur together or may follow one another. The question is only of importance when an immunity has become established to one form of the disease, and regarding this we have Koch's observations in the Bismarck Archipelago. Only one form of malaria, the quartan, occurs in this Archipelago, and many of the natives have acquired an immunity to this form. In numerous instances, however, Koch observed the development of tertian and aestivo-autumnal malaria in these quartan immunes when they visited places in which these forms of malaria were present.

This observation would appear to prove conclusively that immunity to quartan malaria does not protect against either the benign tertian or the aestivo-autumnal fevers. This fact agrees with out conceptions of the specificity of the various malarial plasmodia, and would appear to be a conclusive argument against the unity of the species which have been described.

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CHAPTER V.

Predisposing Causes, General and Local; Period of Incubation of the Malarial Fevers; Congenital Malaria.

Predisposing Causes.—While the malarial plasmodia are the direct cause of the malarial fevers and while the transmission of these fevers depends entirely, so far as we at present know, upon infected mosquitoes belonging to the *Anophelinae*, there are certain factors which enter indirectly into the etiology of malarial disease, either by favoring the development of the plasmodia within man or the mosquito or by favoring the development of mosquitoes capable of transmitting the disease. Such factors are known as predisposing causes and may be divided into *general* and *local*.

General Predisposing Causes.—General conditions predisposing to the malarial fevers are climate, locality, altitude, time of day, moisture, character of the soil, winds, rain, season, and atmospheric conditions.

Climate.—A careful examination of the geographical distribution of the malarial fevers convinces us that climate is of immense importance in the etiology of these fevers. These infections are most common and pernicious in tropical regions, so that heat may be considered as an essential predisposing cause of the malarial fevers. The mild tertian and quartan infections, while common in all malarial localities, are peculiarly the fevers of the temperate malarial zones, while the more severe and often pernicious aestivo-autumnal infections are most common in tropical countries. Thus climate influences not only the amount of malaria in a locality, but also the type of infection. In temperate climates malaria occurs only during the warmer seasons, while in the tropics it occurs throughout the year, although cases are more numerous during certain periods. All climatic conditions favoring the development of mosquitoes of the genus *Anopheles* act as predisposing causes of the malarial fevers, provided infected individuals are present, otherwise climate has no effect whatever upon the prevalence of these fevers, except a local effect in provoking an attack in already infected individuals.

Locality.—This portion of our subject has already been considered under the geographical distribution of the malarial fevers and in the chapter dealing with immunity. It has been shown that the prevalence of malaria is greatly influenced by locality, and that certain types of infection are present most frequently in certain limited regions. Not only are tertian and quartan infections most common in temperate regions, but even in such localities the two types vary in prevalence, while the prevailing type in most tropical regions

are the aestivo-autumnal infections. Climatic influences are not the only ones which operate in thus limiting the varieties of malarial infection in certain localities, for it is probable that the variety of *Anopheles* present is of much greater importance in regions in which all the types of malarial infection are present. Thus it will be found, that in regions in which the benign tertian infections are most prevalent, especially if such regions be situated in the tropics, the prevailing type of *Anopheles* present is one that transmits *Plasmodium vivax*. As showing the influence of locality upon the type of malarial infection, the following instance may be of interest:

At Camp Stotsenburg, Pampanga Province, Luzon, P. I., during five months, I observed 386 cases of malaria in which the plasmodia were demonstrated in the blood. Of these cases 98 were infected with the benign tertian plasmodium (*Plasmodium vivax*); eight with the quartan plasmodium (*Plasmodium malariae*), and 272 were infected with the aestivo-autumnal plasmodia, of which 258 were infected with the tertian aestivo-autumnal plasmodium (*Plasmodium falciparum*) and 14 with the quotidian aestivo-autumnal plasmodium (*Plasmodium falciparum quotidianum*). There were eight combined infections with the benign tertian and tertian aestivo-autumnal plasmodia.

At Camp Gregg, 40 miles distant from Stotsenburg, where the climatic conditions were exactly similar, Captain Chamberlain, of the Army Medical Corps, during twelve months observed 162 cases of malaria in which the type of plasmodium was recognized. Of the 162 cases, 83 were infected with the benign tertian plasmodium, 4 with the quartan plasmodium, and 75 with the aestivo-autumnal plasmodia. At Camp Gregg the quotidian aestivo-autumnal infections were more prevalent than at Camp Stotsenburg, no less than 16 of the 75 aestivo-autumnal infections being of this type.

From the above it will be seen that while at Camp Stotsenburg the aestivo-autumnal infections greatly outnumbered other types, at Camp Gregg the benign tertian infections were greatest in number, although climatic conditions were practically the same. Similar variations in the type of malarial infection have been noted by numerous observers and can best be explained by the occurrence in such localities of certain species of *Anopheles* which transmit only a certain species of the malarial plasmodium. Thus at Camp Stotsenburg the mosquitoes most prevalent were those that transmit the aestivo-autumnal plasmodia, while at Camp Gregg the tertian transmitting mosquitoes were most numerous.

ALTITUDE.—The malarial fevers occur especially in lowlands along the coast and rivers of warm countries. This is an etiological fact which has been observed since the very earliest study of malarial infections. Mountainous regions are generally free from malaria, although there are many exceptions to this rule. In the Philippine Islands certain valleys are almost free from malaria, while the hills in the vicinity are notoriously infected. In Italy, while there are numerous examples of the protection afforded against malaria by residence upon hills surrounding malarious districts, Grassi has found

malaria present at a height of 8,400 feet, while in the Rocky Mountains malaria has been observed on the eastern slope at a height of over 6,000 feet. It should be remembered, however, that many cases diagnosed as malaria in the Rocky Mountains, or as mountain fever, are really cases of typhoid fever.

In South America, in the Andes, malarial fevers have been observed at an elevation of 10,000 feet. Elevation is a protection against malaria only when mosquitoes and the conditions favoring their existence are absent, and where these infections do occur at high elevations it will invariably be found that the climatic and telluric conditions are favorable to the development of these insects. Relapses of malarial infections acquired elsewhere are common in high cool regions and this should not be forgotten, as pointed out by Thayer, when malaria is reported in a district supposed to be free from the disease. Thayer has reported a case, in which a relapse of a benign tertian infection occurred while the individual was traveling in a healthy portion of the Alps, 18 months after the last attack of the fever.

It has been observed that persons living in malarious localities and sleeping in the lower stories of houses are more apt to become infected than those sleeping in the upper stories. For a long time this was held to be due to the low-lying, noxious "malarial" vapors which penetrated the lower floors but did not rise to the upper stories of dwellings. The true explanation is that mosquitoes do not fly, as a rule, to any great height, and thus those persons sleeping in the lower stories of dwellings are more frequently bitten.

Time of Day.—It has always been observed that there is much more danger of contracting malaria at night than during the day, a fact formerly attributed to the malarial gases and vapors which arise over damp ground during the hours of night. In the light of our present knowledge of the method of transmission of these fevers the fact is easily explained, for the mosquitoes that transmit the disease are nearly all night feeders, and do not bite, as a rule, until after dark or during twilight.

Moisture.—Moisture is absolutely essential for the propagation of malaria, as water is necessary for the development of the ova of mosquitoes. Marshes and low-lying damp regions are usually conducive to malaria, and where malaria is most prevalent there moisture is found in abundance. Even in the most malarial of tropical regions a short wet season is followed by a great decline in malarial infection and a total disappearance of the disease when there is a prolonged draught. The influence of moisture is explained by the fact that mosquitoes are most numerous and breed most abundantly in moist regions.

Character of the Soil.—The geological formation of the soil is of very great importance in the prevalence of malaria. An impervious subsoil is a predisposing cause of malaria in that it favors the production of stagnant pools and collections of water in which mosquitoes may breed. Tropical jungles, low marshy lands, or lands covered with stagnant pools of water are most apt to be malarious not because of the character of the soil, but because, as Mar-

chiafava well says, "beneath a more or less thick stratum of humus there is an impervious layer" which gives rise to pools of water and general moisture of the soil. From the days of the earliest Romans, who constructed extensive drainage canals, up to the present time, it has been recognized that thorough drainage of a malarial region resulted in the disappearance of the disease, but it was not until the discovery of the relation of the mosquito to malarial transmission was announced that we had any adequate explanation of this fact.

While the porosity of the soil is obviously of great importance, the conformation of the soil is of still greater, as this determines the regulation of the moisture. Even though pools be formed, if the conformation is such that they can be quickly drained, malaria may not be prevalent, as the ova of the mosquitoes do not have time to develop; on the other hand, if the conformation be such that water collects in pools and hollows which cannot be drained, then malaria may become prevalent.

While moisture and the collection of water in pools sufficiently large to enable the larvae of mosquitoes to breed is essential to the prevalence of malaria, these fevers may occur in regions in which, at first glance, the character of the soil would indicate that such an occurrence would be impossible. Lutz has proven that certain species of Anophelinae may develop in collections of water formed between the leaves of trees or plants in tropical and subtropical regions, and that extensive malarial infection may exist where the common breeding-places of these mosquitoes are absent. In many localities noted for the prevalence of malaria the soil may be dry and no breeding places of mosquitoes be apparent, but close inspection will reveal the fact that *Anopheles* are present, breeding probably at some distance from the infected locality, in small jungle pools or in artificial collections of water about the quarters of the natives living in the vicinity. This is the case at Camp Stotsenburg, in the Philippine Islands, where malaria was so prevalent that it had to be abandoned as a brigade post. The soil is volcanic in nature, and even after the heaviest rains, becomes perfectly dry in a few hours. There is no stagnant water within one mile of the post, and no breeding-places of *Anopheles*. Still these insects are numerous at times and as they must fly at least a mile before reaching the post, it will be seen that in this instance the prevalent idea that they fly but a short distance is disproved. It was invariably found that when the grass about Camp Stotsenburg was allowed to grow to any length the number of mosquitoes increased, with a coincident rise in a number of cases of malarial infection; on the other hand, when it was cut, both mosquitoes and malaria diminished very appreciably.

In this instance, while the soil of the infected region could not be considered as a predisposing factor in the prevalence of malaria, the soil of the region surrounding the Camp and the carelessness of the natives regarding the artificial collections of water about their houses resulted in severe infection of an area in which mosquitoes could not breed but which they could reach by flying.

The building of canals, railways, harbors, and extensive military works;

plowing and ditching; the clearing of land and the construction of highways, have often been followed by outbreaks of malaria among the workmen and the inhabitants of the surrounding country. This was formerly attributed to the turning up of the soil and the consequent liberation of "malarial" gases, but we know now that such operations favor malaria only inasmuch as suitable breeding-places for mosquitoes are formed, water collecting in the holes and hollows inevitably produced during extensive work involving the digging up of the soil. In regions where neither the suitable mosquito or infected individuals are present, such operations are never followed by the appearance of the disease.

The character of the soil is of little importance so long as breeding-places for mosquitoes are not present, the question of soil in relation to malaria depending entirely upon the relation which it bears to the propagation of the malarial mosquitoes.

WINDS.—Some authorities have considered that the malarial fevers may be transmitted by the winds, Scheube stating that "when they blow over marshes or other sources of malaria they may carry the disease to fever-free spots. I believe that such an occurrence is so rare as to be of no practical importance, as it is obvious that winds can only transmit malaria by blowing infected mosquitoes to uninfected localities, and it is a well-known fact that these insects hide in the grass and beneath foliage when winds are blowing. A few instances are recorded where winds appear to have transmitted malaria by transmitting infected mosquitoes. Thus Brunnhoff mentions an epidemic of malaria upon a German ship lying two miles away from a malarial coast, although none of the crew had visited the shore. Such an epidemic can only be explained by supposing that infected mosquitoes reached the vessels, presumably by action of the wind, as two miles is a much longer distance than these insects usually fly.

If is probable, however, that winds exercise a considerable protective influence against malaria, as mosquitoes do not fly about when the wind is blowing. It is a common observation in the tropics that on windy days mosquitoes are seldom troublesome, whereas in the same locality, upon still days, these insects may be so numerous as to render life a burden.

RAIN.—Rain favors the production of malaria because it favors the breeding of mosquitoes. Added to this, rainy weather, by diminishing the resisting powers of the individual, favors the development of the disease in that individual after he has become infected by the mosquito. In the tropics the malarial fevers are especially prevalent during and immediately after the rainy season, and in the temperate zones a dry spring is followed by a decrease in the number of cases of malaria in an infected locality. In many regions, however, where abundant rains occur, malaria is rare, even though the Anophelinae are present. This is explained by the fact that in such regions the rains are so heavy and continued that the breeding places of mosquitoes are washed out and the ova and larvae do not have a chance to develop, or that no infected individuals are

resident in the locality. In the former instance an unusually heavy rainfall may act as a protection against malaria.

SEASON.—Malaria may justly be considered as a seasonal disease. This is so because the insects transmitting these fevers require a certain amount of heat and moisture in order to develop, and these conditions are fulfilled only during certain seasons of the year. Added to this we know that the malarial plasmodia will undergo development only in the stomachs of mosquitoes living under proper conditions as regards temperature, it having been proved by Jancso that the *oocysts* develop best at a temperature of between 20° and 30° C., while if the temperature be lower than 16° C. the organisms perish.

In temperate regions initial attacks of the malarial fevers occur only during the warm months, while in the tropics these fevers occur throughout the year, although even in such regions a marked seasonal variation is observed. Not only does the season of the year profoundly influence the number of cases of malaria observed in a given locality, but it also influences the type of infection present at various times. In temperate regions the benign tertian fever occurs in the spring and early summer months almost alone, the quartan and aestivo-autumnal fevers beginning to appear in July and August, and being most numerous during September and October, at which time the benign tertian fever cases have diminished in number. In the tropics this difference in type as related to season is not so marked, although the aestivo-autumnal types are more common in the late summer and autumn months than at other seasons. In both temperate and tropical regions cases of malaria are observed throughout the year, but the cases occurring in the early spring are almost without exception instances of relapse, and most of those occurring in the tropics during the latter portion of the dry season are of the same character.

The seasonal variation in malaria observed in different countries is remarkable and at first sight difficult of explanation until we remember the method of transmission of these fevers, which in each locality depends entirely upon local conditions as regards climate and other factors influencing the propagation of malarial mosquitoes.

As illustrating the influence of season upon the prevalence of these fevers in different localities the following tables are given: In Baltimore this subject has been thoroughly studied by Thayer and the following table given by him illustrates the effect of season upon the total number of cases of malaria occurring in that city, and also the variation in the type of malarial infection.

Type	Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
Tertian	12	12	28	51	76	68	131	161	153	168	54	17
Quartan	3	1	0	1	0	0	3	0	2	1	4	2
Aestivo-autumnal	5	1	2	5	2	3	37	99	191	203	63	22
Combined	0	1	1	0	0	1	3	3	4	11	6	2
Total	20	15	31	57	78	72	174	263	350	383	127	43

From the table it will be seen that the malarial season is at its height in Baltimore during the months of August, September, and October, the great increase in the number of cases at this time being due to the aestivo-autumnal fevers. It will also be noted that the benign tertian type occurred during the spring and early summer months.

The following table given by Celli includes 93,000 cases of malaria observed in hospitals in Rome and well illustrates the seasonal variation of these fevers in Italy. As in Baltimore, the greatest number of cases was observed during the months of August, September, and October, but a marked decrease occurred during the months of June, which is not true of the fevers of Baltimore. Celli concludes, and I think rightly, that most of the fevers occurring up to June are relapses, with the exception of the benign tertian cases, and concludes "the true malarial season is in the second half of the year; its duration varies in different years; relapses occur during the whole of the first six months of the following year, gradually declining from January to June."

Months	Years													Total
	1864	1865	1873	1874	1877	1878	1892	1893	1894	1895	1896	1897	1898	
January....	284	195	853	595	638	661	240	189	249	236	314	129	90	4673
February...	228	198	681	528	519	543	177	125	163	175	243	94	58	3732
March.....	189	170	711	747	544	502	231	119	125	165	244	98	61	3906
April.....	168	151	653	675	564	576	223	148	157	180	235	115	76	3921
May.....	112	114	669	584	480	504	244	119	159	165	229	120	76	3575
June.....	83	88	409	331	339	375	205	119	138	150	155	88	73	2553
July.....	439	340	1135	865	1858	398	608	553	813	582	502	320	431	8844
August.....	1492	570	2824	2647	2373	1604	694	741	1298	1181	939	410	905	17678
September..	1056	476	2185	2019	1995	1896	586	761	984	1357	684	505	799	15203
October....	775	437	1761	1732	1460	1495	500	911	855	1191	532	403	703	12755
November..	431	475	1280	1186	795	1245	404	831	678	898	361	215	732	9531
December..	271	205	777	773	695	1193	311	427	427	767	252	137	386	6621
Total ..	5528	3419	13938	12682	12260	10992	4423	5043	6046	6947	4690	2634	4390	92992

In tropical regions the seasonal variation of malaria is as marked, as regards the number of cases, as in temperate regions, but not as regards the type of malaria, the aestivo-autumnal fevers being predominant in most localities throughout the year. The seasonal variation in the tropics depends upon the character of the wet and dry seasons and varies considerably in different localities, and in different years. The following table illustrates the seasonal variation in malaria at Camp Stotsenburg, Island of Luzon, Philippine Islands, while the two tables following show the variation at Camp Gregg, forty miles from Stotsenburg.

Table showing seasonal variation in cases of malaria at Camp Stotsenburg, Luzon, P. I.

Year	Month	Number of Cases
1904	August	24
	September	57
	October	24
	November	58
	December	75
1905	January	76
	February	27
	March	20
	April	10
	May	14
	June	17
	July	11
	August	29
	September	31
	October	43
	November	54
	December	126
Total		386

Tables showing the seasonal variation in malaria at Camp Gregg, Luzon, P. I. Compiled by Major Chamberlain, U. S. Army.

TABLE A.

Year	Month	No. of Cases
1904	January	2
	February	4
	March	6
	April	6
	May	1
	June	2
	July	6
	August	20
	September	23
	October	33
	November	41
	December	18

TABLE B.

Year	Month	No. of Cases
1903	January	27
	February	21
	March	8
	April	12
	May	9
	June	11
	July	16
	August	13
	September	14
	October	8
	November	3
	December	6

In considering the table of malarial infections at Camp Stotsenburg, it will be observed that while the malarial fevers are present throughout the year, they begin to increase in September, that the greatest number of cases occur during the months of November, December, and January, and that a marked decrease commences in Februrary and March. The increase commences toward the latter portion of the rainy season in this part of the Philippines, and the greater number of cases occur just following this season, and at this time mosquitoes are most numerous. At Camp Gregg the malarial season differs from that at Camp Stotsenburg, as shown by Tables A and B, and this difference must be due to local conditions, as the seasons are the same in both places. It will thus be seen that we should be conservative in drawing conclusions regarding the seasonal occurrence of malaria in different regions based upon the occurrence of malaria in any particular region, as these fevers are local diseases and what is true regarding their occurrence in one locality may be very erroneous in another.

However, I believe, from observations made both in this country and in the tropics, that the aestivo-autumnal infections are most numerous in the late summer and autumn months, and that even in the tropics these fevers observe a seasonal variation almost as marked as in temperate regions. While in the tropics of the aestivo-autumnal types occur throughout the year, it has been my exeprience that, at least in Cuba and the Philippine Islands, these fevers begin to increase in number during August, and reach their maximum during December and January, most of the cases observed during the early spring and summer being relapses rather than initial infections.

Atmospheric Conditions.—Certain atmospheric conditions act as predisposing causes of malaria in so far as they encourage the propagation of mosquitoes or deplete the health of infected individuals. In considering the relation of climate, season, winds, and rains to malaria, some of the more important of these conditions have been mentioned, but certain of them deserve a more extended notice.

As mentioned, *temperature* exercises a marked influence upon the prevalence of malaria, these fevers being most abundant during the warm months of the year. While this is so, the correlation between malaria and temperature is a complex problem and there are exceptions to the general rule that are difficult of explanation. Celli calls attention to the fact that in the province of Rome during 1879 malaria was more prevalent than for eight years, but the mean temperature was the lowest of these years; the rainfall in the months of March, April, and May was the highest of these years, and it is probable that mosquitoes were more numerous. Many apparent contradictions to the influence of temperature are explained by the habits of the various species of malaria transmitting mosquitoes and by certain local conditions affecting their development.

Atmospheric depressions, by producing moisture of the ground, are of importance in the etiology of the malarial fevers, for, as has been

mentioned, these fevers are most common where the soil is moist, thus affording opportunities for the breeding of the malarial mosquitoes. It should be remembered, however, that no condition of the atmosphere *per se* is capable of producing malarial infection, but that the atmosphere is of importance only as a predisposing factor in the presence of infection or as it favors the propagation of the insects transmitting the disease.

Local Predisposing Causes of the Malarial Fevers.—Among local conditions which may act as predisposing causes of the malarial fevers may be mentioned the following:

1. RACE.—The occurrence of these fevers in regard to different races has been discussed in the chapter dealing with immunity, and there it has been shown that the relative immunity enjoyed by certain dark-skinned races in malarial localities is the result of repeated infections during childhood and early adult life. That people inhabiting malarial regions are less susceptible to infection than new-comers is a fact that cannot be disputed, but the examination of the blood of such persons will often result in the demonstration of the plasmodia, although no symptoms of infection are present. In this case there is no immunity to the plasmodia, but rather to the *effects* of the parasites. Thayer and Hewetson have shown in the United States that the negro is relatively less liable to malaria than the whites, the relative susceptibility of the negro being nearly two-thirds less. According to Hirsch, the Caucasian race is more susceptible to malaria than any other, and it is undoubtedly true that the white man recently arrived in malarial regions of the tropics develops the disease promptly while the dark-skinned races escape for long periods of time. It is probable that the thicker skin of the negro and of the Malay, as well as the use of grease or oil, together with the natural odor of the skin, may be of importance in protecting these races from the bites of mosquitoes.

Those individuals residing in a malarial locality present the more chronic forms of infection, while new arrivals present the acute and severe types. Scheube claims that in Europeans the quotidian or remittent types of malaria are most common, while the natives, or less predisposed races, show the benign tertian and quartan forms of fever. This has not been my experience in Cuba or in the Philippines, for I have observed aestivo-autumnal infections as frequently in the natives as in Americans, and the tertian and quartan fevers more frequently in newly arrived American soldiers.

2. SEX.—When equally exposed both sexes present the same ratio of infection, but, as a matter of fact, malaria is more common in men than in women, as the latter are not as often exposed to the bite of the mosquito. In those countries in which the women work in the fields and are exposed during the late afternoon and the night to the bites of these insects, malaria is as common in the women as in the men, while in the case of babies and young children there is no appreciable difference as regards sex. Parturition has been regarded by some as a predisposing cause of malaria, but the evidence is not satisfactory, although I have observed cases in which the strain of this period has made

manifest an already existing infection. In malarial regions the appearance of fever after childbirth should always lead to the examination of the blood, and not infrequently it will be found that the symptoms are due to malaria. Pregnancy exercises no protective influence against malaria and a severe attack of any of the malarial fevers in the later months of pregnancy may be followed by miscarriage.

While under similar conditions *sex* has no influence as regards malarial infection, it is of some importance in the prognosis of these fevers. It has been my experience, as well as that of Davidson, that in native races more fatal cases of malaria are observed among women than among men, and among female children than among male children. In the Philippine Islands I observed that almost all of the children dying from malarial infections were females and that male children presented less marked symptoms than female.

3. Age.—Children are more susceptible to infection than adults, and the younger the child the more susceptible it is. This has been well proven by the observations of Koch, Stephens and Christophers, Annett, Dutton, and Elliott, and others, in their studies of malarial infection among the natives of various regions. My own observations in the Philippines also show that young children are more susceptible than older ones, but that in this instance the adults suffer from malaria as much, or even more, than do the children. Old age is protective in malarial localities because of the development of a relative immunity due to repeated attacks in childhood and early adult life.

4. Occupation.—The occupation of man becomes a predisposing factor in the production of these fevers in proportion to the chances that occupation gives him of infection by the mosquito. Laborers working at ditching, railway building, and other occupations which necessitate exposure to the night air and, therefore, to mosquitoes, are especially liable to contract these fevers. An instance of this was the terrific mortality from aestivo-autumnal malaria during the French work upon the Panama Canal.

5. Social and Hygienic Conditions.—The poor are the greatest sufferers from malaria because they are not as well nourished and are not, as a rule, protected from the bites of mosquitoes. This is well illustrated in tropical countries where the native suffers greatly from malaria in the same locality in which the well-to-do white escapes by reason of better hygienic conditions and measures taken to prevent mosquito bites. Celli has studied this phase of the subject very thoroughly in Italy and has shown that the social condition of the Italian peasant is indirectly responsible for the ravages of malaria in that country. Because of improper food, miserable housing, insufficient and bad clothing, and excessive work, the unfortunate peasant of Italy falls an easy victim to malaria, and what is true in that country is equally true of every region where these fevers are prevalent and poverty exists.

Bad sanitary conditions predispose to malaria by depleting the health and encouraging the propagation of the mosquito which acts as the agent of transmission. A careful police of private grounds in malarial regions should be

insisted upon, and particular attention should be paid to the character of habitations and the food supply of the people. Malaria is purely an economic question, and can be controlled by any community willing to spend the time and mnoey necessary for the accomplishment of this end.

6. Other Conditions Influencing Infection.—There are numerous other factors that contribute to the production of malarial fevers, among which may be mentioned previous ill health and all those conditions which lower the individual's resisting powers, such as exposure to heat, cold, and excessive moisture; dissipation, overeating, overwork, either mental or physical; loss of sleep, severe operations, and in short, anything which interferes with the normal physiological processes. There can be no doubt that an infection with a small number of malarial plasmodia is overcome in a great many instances by the healthy individual, but should the normal resisting powers be lowered such an infection would result in the symptoms of the disease.

The Occurrence of Malaria in Uninhabited Regions.—Certain instances are of record in which malaria has been reported as prevalent in regions uninhabited by man. Such regions have been reported in Africa and India, and a number of theories have been evolved in order to account for the malaria of these regions. The discovery by Dionisi of a plasmodium in the blood of bats very closely resembling human plasmodia, and by Koch of a plasmodium in monkeys almost identical morphologically with the benign tertian plasmodium of man, has led some observers to consider that the human plasmodia are capable of existence in certain other animals, and that man is infected by mosquitoes who have acquired their infection from these animals. Manson suggests the possibility that the malarial plasmodia may pass from mosquito to mosquito through the infection of the mosquito egg by the *sporozoites*, and that the cycle thus established may continue indefinitely, thus accounting for the development of malaria in regions uninhabited by man.

While it is perhaps too early to be dogmatic upon this subject, I believe the concensus of opinion is that malaria can only be transmitted to man by the bite of an infected mosquito that has derived its infection from man, and that the occurrence of malaria in regions in which infected man is absent is not proven, and so far as our present knowledge goes would appear to be impossible.

The Incubation Period of the Malarial Fevers.—We possess but little definite knowledge of the incubation period of the malarial fevers when naturally acquired, but it is safe to say that it must vary very greatly in individual cases. We know from experience that the plasmodia may be demonstrated in the peripheral blood for days, and even weeks, before the development of symptoms of the disease, and that such instances of latency are not uncommon. We do possess, however, a considerable mass of data regarding the incubation period of these fevers after the direct inoculation of infected blood, and after experimental infection by the bites of mosquitoes.

The Incubation Period after the Direct Inoculation of Infected Blood.—In a previous chapter I have shown that the malarial fevers are in-

oculable from man to man by the injection of blood from an infected individual into a healthy one. The period of incubation of the various types of malaria following this procedure is given in the table that follows, together with the name of the observer and the species of plasmodium inoculated.

Observer	Species Inoculated	Period of Incubation	Type of Fever
Antolisei and Angelini.	Tertian.	11 days.	Tertian.
Antolisei and Angelini.	Tertian.	11 days	Tertian.
Bein.	Tertian.	12 days	Tertian.
Bein.	Tertian.	12 days	Tertian.
Baccelli	Tertian.	6 days.	Tertian.
Mannaberg.	Tertian.	21 days.	Tertian.
Gualdi and Antolisei.	Quartan.	10 days.	Quartan.
Gualdi and Antolisei.	Quartan.	12 days.	Quartan.
Gualdi and Antolisei.	Quartan.	15 days.	Quartan.
Di Mattei.	Quartan.	18 days.	Quartan.
Di Mattei.	Quartan.	11 days	Quartan.
Calandrucio	Quartan.	18 days.	Quartan.
Baccelli.	Quartan.	12 days.	Quartan.
Gerhardt.	Aes. autumn. quotid.	7 days.	Aes. autumn. quotid.
Gerhardt.	Aes. autumn. quotid.	12 days.	Aes. autumn. quotid.
Bignami.	Aes. autumn. tertian.	6 days.	Aes. autumn. tertian.
Bignami.	Aes. autumn. tertian.	10 days.	Aes. autumn. tertian.
Bastianelli and Bignami.	Aes. autumn. tertian.	3 days.	Irregular type.
Bastianelli and Bignami.	Aes. autumn. tertian.	4 days.	Irregular type.
Bastianelli and Bignami.	Aes. autumn. tertian.	5 days.	Irregular type.
Bastianelli and Bignami.	Aes. autumn. tertian.	4 days.	Irregular type.
Panichi.	Aes. autumn. tertian.	5 days.	Irregular type.

From a consideration of the above table it will be observed that the incubation period after direct inoculation of malarial blood varies within narrow limits for each type of malaria, the longest incubation period observed being 21 days in a case of tertian fever, while Elting records the shortest period in aestivo-autumnal fever, the symptoms developing 33 hours after inoculation. While the period of incubation observed after such experiments is of scientific interest it should be remembered that the data is obtained by the inoculation of the disease in an unnatural manner, for we have no evidence of the direct

transmission of malaria in nature. It is obvious that in such a method of transmission only the forms concerned in the human cycle of the plasmodium undergo development and therefore that we can draw no conclusions regarding the period of incubation of malaria following the bite of infected mosquitoes from such experiments. Fortunately, we possess data concerning the period of incubation after the bite of infected mosquitoes, and while the natural period of incubation is undoubtedly very variable, it is probable that in most instances it approximates that observed in experimental cases of malaria produced by infected insects.

The Incubation Period after Experimental Inoculation by the Mosquito.—In the inoculation of blood containing only the forms of the malarial plasmodia belonging to the human cycle, it is reasonable to suppose that the period of incubation will be shorter than that observed when the mosquito transmits the sporozoites to man. That this is so has been proven experimentally by Marchiafava and Bignami, Grassi, Bastianelli, Bignami, Manson, Jancso, and other observers.

Marchiafava and Bignami mention one instance in which the period of incubation after the bites of mosquitoes infected with the aestivo-autumnal plasmodia was from nine to twelve days, and one in which the period of incubation after the bites of mosquitoes infected with the tertian plasmodium was between sixteen and nineteen days. Grassi, Bignami, and Bastianelli report a case in which the incubation of aestivo-autumnal fever after the bite of infected mosquitoes was from twelve to thirteen days, and Bastianelli and Bignami, a case in which the incubation period of aestivo-autumnal fever was from nine to twelve days, and also another case in which tertian fever developed in 18 days after the bites of mosquitoes infected with this species of plasmodium. In quartan infections, the period of incubation is longer, averaging from two to nearly three weeks.

From these observations it will be seen that the period of incubation of the malarial fevers after the bites of infected mosquitoes varies considerably according to the type of infection, but is always longer than when the blood of an infected individual is injected directly into a healthy person. The following summary well illustrates this point:

Incubation after Direct Inoculation.—In six cases of tertian fever, the average period of incubation was 12 days.

In seven cases of quartan fever the average period of incubation was 13.5 days.

In nine cases of aestivo-autumnal infection the average period of incubation was six days.

Incubation after Inoculation by the Mosquito.—The incubation in tertian fever averages 14 days; in quartan fever, nearly three weeks; in aestivo-autumnal infections, 10 to 12 days.

Incubation Period after Natural Infection.—It is obvious that the period of incubation after natural infection is generally a very difficult problem,

and can only be determined in a very small proportion of cases; the literature contains very scanty information upon this phase of our subject, the most satisfactory data we possess being furnished by Marchiafava and Bignami, Celli, and Jackson.

Marchiafava and Bignami were so fortunate as to observe three cases in which they could be sure of the period of incubation. These cases are here given in the words of the authors:

"Case I.—A robust young man, twenty-five years of age, living in the central part of Rome, had never had malarial fever. On November 4, 1894, he was obliged to go to Sermonetta, a notoriously malarious town near the Pontine marshes. He arrived in the city at 10 o'clock, slept that night, tormented by swarms of mosquitoes, in a house on the outskirts of Sermonetta, and in the morning returned to Rome, where he resumed his usual occupation. For six days he was in good health, then he had two days of malaise, and on November 13th, that is to say, *nine days* after his stay in Sermonetta, he was taken down with an aestivo-autumnal tertian fever, the parasites of this form being found in the blood.

"Case II.—An engineer, living in Rome, who had never suffered from malaria, was constrained by the duties of his calling to pass a day, in October, 1895, in a place in the Pontine marshes, and he slept that night in a cabin in poor repair in which were many mosquitoes. At the end of *ten days* an aestivo-autumnal infection, with irregular fever developed, of which he had several relapses, extending up to the following spring.

"Case III.—A lady, who for many years, had enjoyed good health, passed a week at Fiumicino in the month of October, 1894. Three days after her return to Rome an aestivo-autumnal malarial fever declared iself, and not being promptly treated, developed into a choleraic pernicious attack; following this the patient remained profoundly anaemic, with a sanguinolent diarrhoea, and died at the end of a few weeks."

In the last case the period of incubation was probably from nine to ten days.

Jackson gives a most interesting instance in which a limited epidemic of malaria occurred in a troop of United States Cavalry, under circumstances in which the period of incubation could be accurately determined. Out of 45 men belonging to a troop of the 6th U. S. Cavalry, exposed at the same time and under similar conditions to infection, 18 developed tertian aestivo-autumnal fever, the incubation period in all varying between *ten* and *eleven* days.

In two cases Zieman noted an incubation of 10 and 11 days in aestivo-autumnal fever, and Navarre describes an incubation of 12 days in certain sailors who went ashore in a malarious locality for three hours and sailed immediately afterward.

It will be observed that in all of these instances the period of incubation of naturally acquired aestivo-autumnal infections agrees exactly with the period of incubation as observed in cases experimentally produced by the

bites of infected mosquitoes. But though the period of incubation for these infections, as well as for tertian and quartan infections, in the vast majority of cases, is as has already been noted, instances do occur in which the incubation is greatly prolonged. Sternberg quotes the instance of certain sailors who were infected while their ship lay for two days in a malarious port, and who developed the disease, one after 48, the other after 184 days after leaving the port. The following instances, observed by myself, well illustrate the variation in the length of the period of incubation in the malarial fevers:

In August, 1899, a surgeon of the United States Army was stationed in a malarious locality a few miles from Havana, Cuba, remaining at this station until September, when he returned to New York, and was then ordered to San Francisco. While at the station in Cuba he enjoyed good health until a day or two before leaving, when he felt somewhat indisposed but no definite symptoms developed. After reaching San Francisco he remained well until March, 1900, but during that month suffered at times from malaise and diarrhea. On April 1st. he had a slight chill and his temperature rose to 106.2° F. His blood showed numerous hyalin and pigmented forms of the tertian aestivo-autumnal plasmodium, and though this attack was quickly overcome by quinine, he has had several relapses.

In this instance it is undoubtedly true that his infection occurred in Cuba, as aestivo-autumnal malaria does not occur in either New York or San Francisco and he was in no other places than these after leaving Havana. In this case, then, the incubation period was at least seven months. It is probable that had he remained in Cuba, the incubation period would have been greatly shortened, but the change to more favorable climatic conditions and the consequent benefit to his general health delayed the onset of the symptoms.

In another instance two officers of the Army, stationed at a malarious post in the Philippines, never suffered from malaria while there, but one, one month after returning to the United States, developed an attack of tertian malaria, while the other, four months after his return, developed an attack of tertian aestivo-autumnal malaria. Neither of these officers had been in malarious regions after leaving the Philippines. These officers were both five weeks in making the journey from the Philippine Islands to their station in the United States, so that in the case of the one infected with tertian fever, the incubation period must have been at least nine weeks, while in the aestivo-autumnal infection, the incubation period must have been at least twenty-one weeks.

I might give many more instances proving that the incubation period in the malarial fevers varies very greatly at times, but these will suffice. The cause of this variation may be sought in the number of *sporozoites* inoculated by the mosquito, the resistance of the individual inoculated, the character of the *sporozoites* as regards infectivity, and natural conditions favoring the development of the plasmodia within the infected individual. Certain it is that in a large proportion of the cases presenting long periods of incubation, the theory

first advocated by Thayer is true, namely, that while no symptoms are produced the parasites multiply and perform their life-cycle in small numbers. I am the more convinced of this as it is borne out in the examinations of the blood of soldiers returning from the tropics. While serving at the United States Army General Hospital at the Presidio, I examined the blood of every case admitted for the malarial plasmodia, without regard to the presence of symptoms. This routine practice led to the surprising discovery that nearly 40 per cent. of the men showing malarial parasites in their blood presented no symptoms of the disease, and further observations embracing 1,297 cases of malaria in Americans have shown that 307, or nearly 24 per cent., presented parasites in the blood but no symptoms of infection. In many of these cases I have observed the plasmodia for days and even weeks in small numbers in the peripheral blood, and in tertian and quartan infections followed the normal life-cycle in man, and during this time no symptoms of malaria have developed. It is evident that the long period of incubation in such cases depends upon the small number of the plasmodia, and this in turn, upon the resistance of the individual. It is not too much to say that if this routine practice of examining the blood of every individual in malarious districts or of those coming from such districts could be followed, our ideas regarding the period of incubation in malaria and the relation of these fevers to other diseases would be greatly modified.

The question arises, How long may a susceptible individual live in a malarious country before acquiring the disease? It is, of course, impossible to answer this question for all cases; but in the great majority of instances a susceptible individual living in a region infected with the tertian or aestivo-autumnal types of the disease will acquire the fever in from three to six weeks, while it is probable that quartan infection is not acquired under two to four months. Marchoux states that recruits arriving in Senegal develop the disease in from 14 to 16 days after arrival (aestivo-autumnal fever) and of the hundreds of cases of malaria occurring in our soldiers in Cuba and in malarious regions in the Philippines, almost 95 per cent. of those whom I questioned gave a history of having resided in these countries for from two to six weeks before the onset of the disease. One month was the most common period given by the men as intervening between landing in Cuba and the first chill, and the same is true of cases observed in the more malarial portions of the Philippine Islands.

Congenital Malaria.—For many years it was believed that malaria could be transmitted through the placenta and that in some instances babies were already infected with the disease at birth. Before the discovery of the malarial plasmodia this theory was generally accepted and served to explain the large infant mortality from these fevers in badly infected regions. The fact that severe malarial attacks were capable of producing abortion or, more frequently miscarriage, appeared to give added weight to the placental transmission of these fevers, and the cases reported by the older writers upon apparently sufficient clinical grounds, led many observers to regard this method of transmission as proven and of great practical importance in malarial countries. The dis-

covery of the malarial plasmodia, and the method of transmission of the fevers produced by these parasites, rendered most of the evidence in favor of placental transmission of little scientific value, as none of the cases reported had been examined as to the presence of the plasmodia in the blood or tissues, and the large infant mortality was fully accounted for by the facility with which infected mosquitoes bite the youngest infants.

A few of the older reported cases deserve some credit, however, such, for instance, as that of Duchek, in which the babe showed marked splenic enlargement, and at autopsy, three hours after birth, much pigmentation in this organ and free pigment in the blood of the portal vein. This case cannot be considered as conclusive since similar appearances of the spleen and of the blood might be produced by other infections. In a few instances malarial plasmodia have been found in the blood of newly-born babes, but in all such instances the interval elapsing between the birth of the children and the examination of the blood has been sufficient to allow of postnatal infection. Such cases have been reported by Bein, Bouzian, Peters, and a few other observers.

Opposed to the inconclusive evidence offered in favor of congenital malarial infection we have the observations of many noted students of this disease which prove, I believe, that the malarial fevers cannot be transmitted to the foetus through the placenta. The placental blood of malarious mothers, the blood of infants born to such mothers, and the blood of infants whose mothers have aborted by reason of malarial infection, has been examined by many competent investigators, and not one has reported the presence of malarial plasmodia in such blood except in instances in which infection of the child might have occurred after birth. Bignami examined the blood of a foetus of three months and of another of six months from women who had aborted because of pernicious attacks of malaria, with a negative result in both instances; in a third case, that of a pregnant woman, who died of pernicious malarial fever, the autopsy showed the lesions usually found in such cases, and the blood contained multitudes of plasmodia, but the blood of the foetus was free from plasmodia, and the organs showed no lesions of malarial character. Similar cases have been reported by Bastianelli, Caccini, and Schaudinn. Bignami has demonstrated that the malarial plasmodia cannot develop within the nucleated red blood-cells of the foetus, and believes that this is also true as regards the young red corpuscles.

In an elaborate study of this subject, Sereni concludes that placental transmission of the malarial plasmodia is impossible. He has never observed the plasmodia in newly-born children of malarial mothers, although he states that the placenta contained numerous parasites. Zieman, in Kamerum, has never observed plasmodia in the blood of newly-born negroes, although in four cases the mothers were suffering from malaria at the time of giving birth. He believes that the placenta offers an impassable barrier to the plasmodia. A most interesting case reported by Thayer supplies conclusive evidence that the transmission of malaria through the placental circulation does not occur.

A woman, suffering from a severe quartan infection, gave birth to a seven months' foetus during an attack of the fever. The blood of the child did not show any plasmodia nor did a malarial infection develop later, but an examination of the placenta developed the interesting and significant fact, which bears out Zieman's conclusion, that while upon the maternal side numerous plasmodia could be demonstrated, there was a complete absence of them upon the foetal side of the organ. From the evidence at hand I believe that we are justified in stating that placental infection with the malarial plasmodia does not occur, and, therefore, that congenital malaria does not exist.

Literature upon Predisposing Causes, Period of Incubation, and Congenital Malaria.

Predisposing Causes of Malaria.

For the literature and data concerning the predisposing causes of the malarial fevers consult the monographs of Marchiafava and Bignami, Thayer, Mannaberg, Zeiman, Laveran Celli, and Craig, which have already been mentioned.

The Incubation Period of the Malarial Fevers.

Consult the monographs above mentioned, the list of references given at the end of Chapter IV, as regards the period of incubation after direct inoculation of malarial blood, and the references given under the "Transmission of malaria by the Mosquito," for the work of Grassi, Bastianelli, and Bignami.

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PART II.

THE GENERAL AND SPECIAL PATHOLOGY OF THE MALARIAL FEVERS.

CHAPTER I.

The General Pathology of the Malarial Fevers; Morphological Changes in the Erythrocytes and Leucocytes; Anaemia; Differential Blood Count; Phagocytosis; Melanaemia; The Urine; The Etiology of the Fever.

Primarily, malarial infections exert the most marked effect upon the blood, as the plasmodia live at the expense of the red blood-corpuscles, and probably elaborate toxins which materially affect all of the elements of this fluid. The pathological changes which occur in the blood as the result of malarial infections are due to primary and secondary causes. The primary cause is the infection of the erythrocytes with the plasmodia and the changes brought about by such infection; the secondary is the anaemic condition which is the inevitable result of all malarial infection.

Morphological Changes in the Erythrocytes and Leucocytes.—Certain morphological changes occur in the cells of the blood as the result of the invasion of the red corpuscles by the plasmodia, and these changes vary with the species of plasmodia concerned. The chief changes occurring in the erythrocytes are:

Changes in Size.—As I have already noted the red blood-corpuscles when invaded by *Plasmodium vivax*, the tertian parasite, become swollen, and as the parasite increases in size the red corpuscles also enlarge until, when the parasite is fully developed, the red cell is twice or three times as large as the uninvaded cells surrounding it. This is a characteristic change in tertian infections. In cells invaded by *Plasmodium malariae*, on the other hand, there is no increase in size, but the invaded red cell is of the same size as the normal cells, or, in a few instances, somewhat smaller. In infections with the aestivo-autumnal plasmodia, the invaded red cell is always smaller than the normal cells, a change which is as characteristic of these infections as the enlarged erythrocyte is of tertian malarial infection.

Changes in Form.—The red corpuscle invaded by the tertian plasmodium is generally somewhat distorted in shape when the parasite is fully grown, but is never crenated. In quartan infections the shape of the red cell is preserved, as it generally is in aestivo-autumnal infections, but in the latter crenation of the cell is very common, especially in the quotidian aestivo-autumnal infections.

Changes in Color.—In tertian infection the color of the infected red cells is much paler than normal, and when the parasite is fully developed the red cell may be almost colorless; even in newly invaded cells the color is much less marked than in the normal red corpuscles, and this serves as a diagnostic

feature in differentiating this plasmodium from quartan and aestivo-autumnal organisms. In the latter infections the color of the red cell invaded by the parasite is not diminished, but, especially in the aestivo-autumnal infection, increases. In infections with the quartan parasite the color of the infected red cell is normal or else it is slightly more greenish than normal; in the aestivo-autumnal infections the infected red cell is generally darker green in color than normally, and may appear "brassy," the cell being smaller and appearing shrivelled. This change is most marked after a paroxysm, when the parasites have become pigmented, and the dark olive-green color of the invaded cells is generally present after the administration of quinine, which appears capable of producing this change in the infected corpuscles in both aestivo-autumnal and quartan infections. Marchiafava and Bignami believe that the "brassy" appearance indicates necrosis of the red cell and that after this occurs the plasmodium within the cell perishes. I believe that while the increase in color may indicate necrosis of the red cell, this necrosis is the essential result of its invasion by the plasmodium, and that the latter does not die, but undergoes sporulation in such cells. This is easily demonstrated in smears of blood from the spleen in aestivo-autumnal infections, in which many brassy red corpuscles may be seen to contain sporulating plasmodia. The "brassy" cells are most numerous in quotidian aestivo-autumnal infections.

Retraction of Haemoglobin (Partial Decolorization of the Erythrocyte.)—Many infected red corpuscles, especially in aestivo-autumnal infections, show a retraction or concentration of the haemoglobin at some portion the periphery of the cell or within it, small areas being colorless. In many instances this haemoglobin membrane, as it may be called, is retracted about the contained parasite, and it is to this change in the red cell that the "bib" and double outline of the crescent or *gamete* is due. In malarial infections the uninvaded red cells often present colorless areas, or vacuoles, which are many times mistaken for hyaline parasites by the novice in blood examinations, and the almost colorless center of anaemic red cells, so often observed in malaria, is not infrequently mistaken for a plasmodium.

Changes in the Staining Reactions of the Erythrocytes.—In tertian infections, and rarely in quartan and aestivo-autumnal infections, specimmens of blood stained by one of the modifications of Romanowsky's method, show reddish-stained granules in the protoplasm of the invaded red cells, known as Schuffner's dots. I have already spoken of the diagnostic significance of these dots as regards tertian infections and stated that this change in the staining reaction of the red cell is characteristic, generally, of such infections. As is well known, many of the erythrocytes in severe cases of malarial infection present the phenomena described as polychromasia and basophilic degeneration. This is evidenced by areas in the red cell or the whole cell staining a brownish color or the cell is filled with granules which are basophilic in character. This condition, however, is not characteristic of malaria, for it occurs in all severe anaemias and in many other diseases, as has been shown by many observers, notably Maxi-

mow, Askanazy, Litter, Bloch, Fish, Cabot, Ewing, Schwalbe and Solley, Grawisz, and Stengel, White and Pepper.

The exact nature of polychromasia and basophilia is as yet a matter of controversy, some authorities regarding the process as degenerative in nature, while others maintain that it is not of necessity a regressive process. It is not advisable here to consider the arguments as to the significance of these basic staining granules, but it would appear that so far as the study of the process in malaria is concerned, the evidence all points to its degenerative nature.

The only observations regarding the significance of basophilia of special interest to the student of malaria are those of A. Plehn. He suggests that the granules which are basophilic in character and which are observed in the red cell in malaria, are in reality latent forms of the plasmodia. He believes that multiplication of these latent forms occurs in the blood, followed by destruction of the red cells, which process continues until conditions are favorable for the development of the large amoeboid plasmodia. He also states that after the disappearance of the amoeboid forms these latent bodies remain, continuing as the latent form of the plasmodium.

The observations of Plehn have not been confirmed by any observer, while, on the other hand, all those who have studied the subject unite in considering the basophilia of malaria as identical with that occurring in other diseases. Solly, from his studies of tertian malarial blood, found granulations of the red cell in only two out of thirty cases, and concludes that there is no evidence that the granulations are latent malarial plasmodia. I have observed basophilia in a very great number of specimens of malarial blood, and agree with Solley that there is no evidence whatever that the granulations are a form of the malarial plasmodium. To believe that the erythrocyte contains at the same time a growing amoeboid plasmodium and multitudes of latent forms (the dots) is impossible, and when it is remembered that the same process is observed in the erythrocytes in other diseases, I believe that Plehn's hypothesis is untenable, and unsupported by any evidence of value. No morphological changes of importance occur in the *leucocytes* in malaria with the exception of those observed in phagocytosis, which will be discussed later in this chapter.

Malarial Anaemia.—Every malarial infection, whether acute or chronic, is accompanied by anaemia, the inevitable result of the destruction of the red cells by the invading plasmodia, and, to a lesser extent, by the action of the toxins liberated in the blood by the escape of the parasites from the red cells. In no disease is the destruction of the red corpuscles more rapid than in malaria and in no other class of infections is anaemia of greater diagnostic importance, especially if it has appeared suddenly and is accompanied by chills and fever. The anaemia of malaria affects both the red and white corpuscles and the haemoglobin, and has been thoroughly studied by nearly every writer upon these fevers, but to Kelsch we owe the first exhaustive study of this subject, and his

work, completed in 1876, stands to-day almost alone in its thoroughness and scientific accuracy.

The Red Corpuscles.—No matter how slight an attack of malaria we may be observing, we shall invariably find a reduction in the number of red blood-corpuscles, and the more severe the attack may be the greater will be the reduction in these cells. In severe aestivo-autumnal infections, and even in tertian and quartan infections of extraordinary severity, the red corpuscles may fall from normal to 3,000,000 per cu. mm. within 48 hours, and in pernicious attacks the reduction may be even greater. Turk describes a loss of 1,000,000 red cells in one day; Mannaberg, 1,000,000 in two days, and Kelsch, 2,000,000 in two days, in acute aestivo-autumnal infections. I have observed a loss of nearly 2,000,000 red cells in thirty-six hours in a case of tertian aestivo-autumnal malaria. Marchiafava and Bignami state that in a case of quotidian malaria the red cells were reduced 1,000,000 within 24 hours, and Dionisi found that in an acute attack of tertian aestivo-autumnal fever which had lasted three days the red blood count showed only 2,625,000 red cells per cu. mm. In pernicious attacks of aestivo-autumnal malaria Kelsch states that in one day the red cells may be reduced to 1,000,000 per cu. mm. in initial attacks, while if the patient has already suffered from malaria and is thus anaemic, a pernicious attack generally reduces the red cells to from 1,000,000 to 2,000,000 per cu. mm. In a case of pernicious quotidian aestivo-autumnal malaria, which proved fatal, I found that the red blood-corpuscles only numbered 860,000 per cu. mm. a few hours before death, the attack having lasted about five days. In this case there was no rise in the temperature until just before death, so that the anaemia produced was not dependent upon high temperature.

A reduction in the number of red blood-corpuscles follows every paroxysm for a certain period of time, but it will always be observed that while during the first few days of an initial infection the reduction is marked, the continuance of the disease, after a certain amount of anaemia has been produced, is not characterized by a further reduction, but the number tends to remain at a certain level, no matter how long the infection may last. In each recurrence it will be found that the reduction in the number of red corpuscles is less and less marked, and in chronic infections, while there is more or less anaemia, there is but a slight reduction of red cells after a paroxysm.

The return to the normal number of red corpuscles after mild or even severe attacks of tertian and quartan fever which have been promptly stopped by treatment is usually fairly rapid, but cases untreated, or in which many relapses have occurred, are followed by a chronic and persistent anaemia, which is one of the most marked characteristics of people inhabiting malarial regions. In aestivo-autumnal infections the return to the normal number of red cells is much slower than in tertian and quartan infections, and after a moderately severe attack it will be found that the normal number of red cells is not reached, as a rule, before the end of two months, although in rare instances recovery is rapid. In one case under my observation the red cells fell to 690,000

per cu. mm. in three days, and increased to 2,100,000 per cu. mm. in three weeks, after treatment, and it was several months before the normal number of red corpuscles was regained.

Dionisi has contributed some very valuable data concerning the anaemia of the aestivo-autumnal infections and his conclusions are here given:

"1. In aestivo-autumnal fever, the reduction in the number of the red blood-corpuscles bears a direct relation to the number of the organisms. Where the parasites are numerous there is a constant reduction of from 200,000 to 1,000,000 with each febrile paroxysm; where the parasites are scanty the reduction is less.

"2. When crescentic bodies are present in addition to the other forms, they seem to exert no influence on the blood changes.

"3. When, after a paroxysm, the number of corpuscles has suffered a sudden and very marked diminution, the suceeding paroxysms may be followed by but a slight reduction only, or even by an increase.

"4. In relapses, the reduction per paroxysm is less than in a primary infection.

"5. In infections determined by the amoeboid forms (acute aestivo-autumnal infections) there is, during apyrexia, no complete return of the red corpuscles to their normal number. Some attempts at restitution may be seen during the first several days of apyrexia, while after this, during perhaps eight to fifteen days, there may be a steady reduction of from 100,000 to 500,000 red blood-corpuscles without the appearance of any parasites in the blood.

"6. Only after marked and continuous reductions following each paroxysm does there occur in the afebrile period a relative restitution of the red blood-corpuscles; this may be slow or rapid.

"7. If the increase in the corpuscles has begun, the presence of crescents has no deleterious effect.

"8. In tertian and quartan fevers the same changes are observed, excepting that in the afebrile period there is a rapid and almost complete restitution of the red blood-corpuscles."

My observations upon the reduction in the red blood-corpuscles in aestivo-autumnal fevers confirm those of Dionisi in all essential particulars, but I believe that the reduction observed after the disappearance of the symptoms, and which lasts for a few days, is due to plasmodia whch have escaped destruction by quinine, which, while not numerous enough to produce symptoms, destroy a certain number of red corpuscles. This may also serve to explain the slow restitution of the red blood-corpuscles in this class of infections, for, as I shall demonstrate, many individuals harbor the aestivo-autumnal plasmodia for weeks without presenting any definite symptoms of malarial infection.

The Leucocytes.—In acute malarial infection the leucocytes are reduced in number, both absolutely and relatively to the red blood-corpuscles. Thus the malarial fevers, like typhoid, dengue, kala-azar, and trypanosomiasis, are characterized, as a rule, by a marked leucopenia, only the pernicious forms showing a leucocytosis. During the first hours of an acute attack of any of the forms of malaria there may be a more or less marked leucocytosis, sometimes only visible during the first fifteen or twenty minutes, at others still

demonstrable until the decline of the fever. Generally the leucocytosis is only observable for a short time at the onset of the paroxysm, soon giving place to the characteristic leucopenia. Kelsch found that the leucocytes gradually decreased in number as the paroxysm continued and that after the attack the leucocytes number from a half to a third of the normal number. After recovery the leucocytes increase very gradually until the normal number is reached, but this increase is very slow as compared to the rapidity of the decrease during the active stages of the infection.

In tertian, quartan, and in ordinary aestivo-autumnal infections the leucocytes during the attack number from 3,000 to 5,000 per cu. mm. as a rule, although many cases are observed in which these cells number from 2,000 to 2,500 per cu. mm.

In the pernicious forms of malaria, generally due to the aestivo-autumnal plasmodia, a marked leucocytosis is often observed. Kelsch first noted this fact, and gives instances in which he found 20,000, 25,000, and as high as 35,000 leucocytes per cu. mm. I have never observed a case of pernicious malaria in which there was not a marked leucocytosis, and in one instance, due to the quotidian plasmodium, the leucocytes numbered over 40,000 per cu. mm. When recovery occurs, the leucocytosis quickly disappears, but in fatal cases it perists to the end, so that the occurrence of a marked leucocytosis, which tends to increase, is a bad prognostic sign in pernicious malaria.

The Differential Leucocyte Count.—Recently much attention has been paid to the changes occurring in the relative proportion of the various leucocytes in acute malarial infections. Rogers called attention to the relative increase in the mononuclear leucocytes, and his observations have been confirmed by numerous investigators. Stephens and Christophers state that there is always an increase in the large mononuclears, and they consider this increase of great diagnostic importance. Billet found a marked increase in the mononuclears and considers that an increase in the polynuclears indicates a complication. Poch, in his studies of the blood in tertian and quartan infections, found a marked initial increase in the polynuclears, succeeded by an increase in the mononuclears. Zieman describes a polynuclear increase at the beginning of the febrile attack, which, at the height of the fever, disappears rapidly, and is succeeded by a relative increase in the large mononuclears. These changes occur in initial attacks and in recurrences, but not in cachexia. From my own observations, I believe that in all forms of malarial infection, during acute attacks, whether initial attacks or recurrences, there occurs a relative increase in the mononuclear leucocytes, chiefly the large mononuclears, and that this increase occurs in the vast majority of the cases, but not in all. An increase in the polynuclear leucocytes is often observed during the onset of the febrile paroxysm, especially when the leucocytosis is marked, but a polynuclear increase occurring during the subsidence of the fever or in the apyrexial period indicates a complication. The following differential blood counts illustrate those commonly obtained in malarial infections:

Polynuclears,	52.0%	Count in tertian malaria.
Small mononuclears,	16.3%	
Large mononuclears and transitionals,	32.4%	
Eosinophiles,	.3%	
Polynuclears,	55.0%	Count in quartan malaria.
Small mononuclears,	20.6%	
Large mononuclears and transitionals,	22.2%	
Eosinophiles,	3.0%	
Polynuclears,	45.0%	Count in aestivo-autumnal infections.
Small mononuclears,	18.4%	
Large mononuclears and transitionals,	5.0%	
	35.6%	
Eosinophiles,	1.0%	

The above counts are intended merely to illustrate those obtained in malarial disease and it should not be expected that all counts will show as large an increase in the mononuclear leucocytes, although in the majority of instances the large mononuclears will constitute from 15 to 20 per cent. of the leucocytes observed. The greatest increase is observed during apyrexia, the least during the height of the fever. The differential leucocyte count is of some value in differentiating the aestivo-autumnal remittent fevers from typhoid, as in the latter there is no increase in the large mononuclear cells, although there is a leucopenia and an increase in the small mononuclears. Rodgers has contributed several valuable studies upon the diagnosis of malaria and typhoid by means of the differential blood count, and where the plasmodia cannot be found or the Widal test applied this method may be of great assistance in differential diagnosis. It is of but little value, however, in differentiating between malaria and such diseases as kala-azar, dengue, or trypanosomiasis, as in the latter a large mononuclear increase is often observed. While in something over 50 per cent. of cases of malarial infection a relative increase in the large mononuclear leucocytes is observed it has not been my experience that very much weight can be given in diagnosis to a mononuclear increase in malarial infection.

The Haemoglobin.—Besides the reduction in the number of the red and white blood-corpuscles, there is generally a marked reduction in the haemoglobin in all malarial infections, but especially in the aestivo-autumnal infections. This reduction is usually proportionate to the loss in red corpuscles, but in some cases the haemoglobin is less than normal in proportion to the loss in the red corpuscles, and in pernicious cases, the loss of haemoglobin may be rapid and great, from 10 to 40 per cent. being lost in two or three days. However, little weight can be given to the reduction in haemoglobin as regards the prognosis of individual cases, for in some of the most pernicious forms of malaria that I have observed, there has been but a slight reduction in the

haemoglobin, while in many mild tertian infections there is often a very marked reduction.

Rossoni has thoroughly investigated the effect of malarial infections upon the haemoglobin index of the blood and his conclusions, which have been confirmed by numerous investigators, are as follows:

"1. No acute infection results in as active a deglobulization as does malarial fever.

"2. In all cases of malarial fever there is an immediate diminution in the number of corpuscles and in the amount of haemoglobin. This loss generally bears a direct relation to the duration of the infection. In pernicious cases, however, a diminution of as much as two-thirds of the total amount may take place in from one to three days.

"3. The gravity of pernicious cases does not always bear a direct relation to the extent of the loss in haemoglobin.

"4. The destruction of haemoglobin and corpuscles bears, generally, a direct relation to the number of parasites in the blood. Occasionally, however, cases with high fever and marked losses in haemoglobin and corpuscles may show but few parasites in the circulating blood. A long continued diminution of haemo. globin is often associated with the presence of crescents.

"5. The loss in haemoglobin and corpuscles is rarely evident during the paroxysm, but begins with apyrexia and may continue for several days afterward.

"6. Recovery from malarial anaemia is slower than from the other acute anaemiae.

"7 Usually the haemoglobin and corpuscles are equally diminished, but sometimes the haemoglobin is a valuable point in differential diagnosis between malarial fever and enteric fever or pneumonia.

"8. The restitution of the haemoglobin in malarial anaemia is often incomplete, and individuals living in malarial districts have often a slightly smaller percentage of haemoglobin than those living elsewhere."

Phagocytosis.—In examining the blood of patients suffering from malarial infections, it will almost invariably be noticed that many of the leucocytes contain brown or blackish pigment, portions of plasmodia, or even whole plasmodia. These leucocytes are the so-called phagocytes which can always be demonstrated in malarial blood at some time during the infection. These pigment-containing cells were observed and described as occurring in the blood before the plasmodia of malaria were discovered, and Laveran, Marchiafava, Celli, Golgi, Metchnikoff, Bignami, Osler, Barker, Dock, and Thayer have all added to our knowledge of these cells. In the tertian and quartan infections phagocytes were observed to be most numerous during or just after the paroxysms, while in the aestivo-autumnal infections these cells appeared at less regular intervals. Marchiafava and Celli first proved that the phagocytes are capable of engufilng and destroying living plasmodia, Laveran having held that the pigment observed in these cells was engulfed only after the fragmentation and death of the plasmodia. That Marchiafava and Celli were right in their observations may be proven by any one interested, for one of the most interesting and instructive phenomena visible under the microscope, is the engulfing of extracellular malarial plasmodia by the phagocytic leucocytes.

Golgi, as the result of his researches upon phagocytosis in tertian and quartan malaria, and Marchiafava, Bignami, and Bastianelli, as the result of theirs in aestivo-autumnal fevers, have demonstrated that phagocytosis occurs most commonly during the early hours of a malarial attack, and that during apyrexia this process almost disappears. Golgi considered that to phagocytosis we owe spontaneous recovery in malaria, and his opinion agrees with that of Metchnikoff, who believes that these cells, either by engulfing and digesting the plasmodia or by excreting products inimical to their growth, bring about recovery in most cases of malarial infection.

The Phagocytic Cells.—The cells which act as phagocytes in malaria are: the large mononuclear and transitional leucocytes, as well as certain of the polynuclear cells; the endothelium of the liver and Kupffer's cells; the cells of the splenic pulp, and the uninuclear leucocytes in the bone marrow. The small mononuclears and the eosinophiles have been said, by some observers, to be phagocytic, but these cells are not generally so. In one or two instances, I have observed entire plasmodia within coarsely granular eosinophiles, so it is impossible to deny that, under certain conditions, these cells may become phagocytic, but they are not so normally.

The large mononuclears and the transitionals in the peripheral blood, and to a lesser degree the polynuclears, are the chief phagocytic agents in all malarial infections, and while the total number of leucocytes in these infections is decreased, it will be noted that the phagocytic cells are relatively increased, thus adding support to Metchnikoff's theory that to these cells we owe spontaneous recovery in malaria.

The endothelial cells of the liver are found in the peripheral circulation acting as phagocytes in only the most pernicious cases of malaria, but in the liver these cells, as well as the cells of Kupfer, are actively phagocytic, showing within them pigment, plasmodia, and even red blood-cells containing the plasmodia. In fatal cases, these cells are often observed lying free in the capillaries, crowded with pigment and parasites, and even those cells still attached to the vessel walls contain much pigment and fragments of plasmodia.

The cells of the splenic pulp are very actively phagocytic and here we find immense cells, from 10 to 20 times the size of the small mononuclear, containing great blocks of pigment, plasmodia in various stages of development, and even entire infected red blood-corpuscles. These large cells are known as *macrophages*, and are characteristic of malarial infection. The splenic vessels, in fatal cases of malaria, are crowded with these macrophagi, with free malarial pigment, and degenerated cellular material, and, as Marchiafava and Bignami suggest, it is probable that many of the melaniferous cells observed in the vessels of the liver are really derived from the splenic pulp.

Degenerative Changes in the Phagocytic Cells.—In pernicious cases of malaria there occur in the peripheral blood numerous phagocytic cells which are evidently undergoing degeneration, and sections of the liver, the

spleen, and smears of the bone marrow, in such cases, show numerous degenerating phagocytes. The forms of degeneration occurring in these cells comprise vacuolization, fatty degneration, and fragmentation of the nucleus. Such forms of degeneration occur rarely in leucocytes which present no evidence of phagocytosis. The degenerative changes are most common and marked in the large mononuclear leucocytes and in the macrophages. Bignami has claimed that the malarial spores are capable of developing after the necrosis of the phagocyte which has engulfed them, but his theory has never been proven and it is extremely doubtful whether any form of the malarial plasmodia is capable of development after it has once been engulfed and acted upon by the phagocytic cell.

Time of Occurrence of Phagocytosis.—In tertian and quartan malarial fevers phagocytosis is most marked during or directly after the chill, and this is true also in uncomplicated cases of tertian and quotidian aestivo-autumnal malaria during an acute attack. If, however, the disease has persisted for some time or there is a double infection, the cyclical appearance of phagocytosis cannot be demonstrated without repeated observations and most careful study, and often not even then. In pernicious cases phagocytes are, as a rule, very numerous, especially the large mononuclear variety, and the macrophages. Quinine tends to increase phagocytosis, especially in pernicious cases. In many instances of severe aestivo-autumnal infection an examination of the blood at any time will show a marked phagocytosis, due in all probability to the rapid and irregular multiplication of the plasmodia.

Substances Engulfed by the Phagocytes.—In malarial infections the following are found within phagocytic cells: first and most common, free pigment; second, extracellular plasmodia, many of which are flagellated; third, shrunken and degenerated red corpuscles, both with and without parasites (these occur only within macrophages); fourth, segmenting plasmodia (common in blood from the spleen); fifth, crescentic and ovoid forms (very rarely). The amount of pigment and cellular detritus absorbed by the phagocytes is enormous, and there can be no doubt that these cells are of inestimable value to the organism in taking from the capillaries and small vessels this material which might so easily occlude them. In this way alone phagocytosis in malaria is of the very greatest importance, for without it we would observe pernicious symptoms in the majority of our cases.

The Significance of Phagocytosis.—The fact that the phagocytes not only engulf and clear the vessels of pigment and cellular deteritus, but that they can, and do, engulf and destroy large numbers of living plasmodia proves that this process must be one of vital significance. It is undoubtedly true that the sporulation of the plasmodia acts as the stimulating factor to phagocytosis, for, as I have shown, this process is most marked during a malarial paroxysm, and this fact would appear to indicate that phagocytosis is an important, if not the most important, means of defense possessed by the organism against malarial infection. Two theories have been advanced regarding the signifi-

cance of this process, one, advocated by Metchnikoff and his followers, that phagocytosis in malaria is an active protective process and is the cause of spontaneous recovery; the other, advocated by Bastianelli, that it has but little to do with spontaneous recovery, and that the facts are not sufficient to prove that the phagocyte is, as Metchnikoff believes, an active enemy of the malarial plasmodia.

We believe that there can be no doubt in the mind of a careful observer that the phagocytic cells perform a very active part in the destruction of living malarial plasmodia, and that, therefore, the phagocyte is an active enemy of these organisms. We believe that it is also clear that this process exercises an important mission in enabling the organism to recover from the infection, but we doubt that phagocytosis is the *direct* and *only* cause of spontaneous recovery. The immense value of the process in ridding the vessels of the viscera the bone marrow, and the peripheral capillaries of free pigment, cellular detritus, and degenerated plasmodia must be admitted, for after pernicious attacks of malaria, only a few days supervene before the body is practically cleansed of the results of the infection, such as pigment, degenerated red cells and leucocytes, and fragmented and moribund plasmodia.

In many malarial infections, especially the aestivo-autumnal fevers, phagocytosis has considerable prognostic value. From my own observations I would say that the following rule will hold true in almost every case of aestivo-autumnal malaria: The greater the phagocytosis the more severe is the infection and the more grave the prognosis. Especially is this true if in the peripheral blood occur numerous large mononuclear phagocytes or macrophages. I am convinced that a marked phagocytosis in aestivo-autumnal malaria, far from being a feavorable sign, is almost typical of a pernicious infection, and if no cyclical course can be traced after repeated examinations, is absolutely typical, and should be the signal for the institution of the most energetic therapeutic measures.

It would appear, from the evidence at hand, that phagocytosis is one of the weapons possessed by the organism which enable it to overcome malarial infection, both by the property possessed by the phagocyte of engulfing and destroying the living plasmodia, and by removing from the organism the pigment and cellular detritus which would otherwise accumulate and injure the tissues. This process cannot be considered as the cause of spontaneous recovery, acting alone, but it is one of the most important factors concerned in such recovery, and may be the principal factor in many instances. It is certainly true that Metchnikoff is correct in considering the phagocyte as an active agent in ridding the body of malarial plasmodia, and it may well be that in the phagocyte we have the true explanation of malarial immunity.

Melanaemia.—The occurrence within the blood of malarial pigment, either free or enclosed within the leucocytes, is known as melanaemia, and, next to the occurrence of the plasmodia within the red corpuscles, is the most characteristic change occurring in the blood n malarial infections, and is the one

which has been longest known to the students of these fevers. This pigment may be brown, brownish-yellow, or black in color, and may occur in the form of blocks, granules, rods, grains, irregular clumps, fine needles, or cylindrical, polyhedral, circular or irregular masses. This condition is only present in malarial infections, and is often of great service in diagnosis where the parasites are few in number or in chronic malarial poisoning.

Historical.—The history of the discovery and explanation of pigment in the blood in malaria is of interest, but we can only touch upon it in this contribution. Meckel, in 1847, was the first to describe pigment as occurring in the blood in malaria, and his observations were soon confirmed by those of Virchow and Frerichs, and these authorities considered that the pigment was derived from the spleen or liver, although Frerichs believed that it originated in the spleen alone, being due to the destruction of the blood in that organ. Meigs and Colin wrote excellent descriptions of this condition, but to Arnstein we owe the discovery that the pigment originates in the circulating blood during the malarial paroxysm, being deposited afterward in the liver, spleen, bone marrow, and other viscera. He, together with Kelsch, came to the conclusion that the destruction of the red blood-cells in malaria gave rise to the pigment, which remained in solution in the blood until the latter became saturated, when it was precipitated in granules which were then engulfed by the leucocytes. This theory was accepted until the investigations of Laveran, Marchiafava, and Celli, who demonstrated that the pigment is not formed after the disintegration of the red corpuscles, but is formed during the growth of the malarial plasmodia within them, being, in fact, the changed hemoglobin of the corpuscles absorbed by the plasmodia during their growth. The true malarial pigment, or *melanin*, is elaborated during the development of the plasmodia within the infected cell and is liberated when sporulation of the parasites occurs.

Varieties of Pigment.—Two varieties of pigment are present in the blood in malarial infections: one, *melanin*, the true malarial pigment, is black in color, and is found in both the blood and tissues; the other, *haemosiderin*, is yellow in color, and is found only in the tissues. The first gives no reaction for iron; the second does.

As regards the origin of the two varieties, I am fully in accord with Bignami, who says: "The melanaemia, index of an acute infection, is derived only from the direct transformation of haemoglobin into melanin through the action of the parasites within the red corpuscles, as Marchiafava and Celli have demonstrated; that the melanosis of the viscera, spleen, liver, bone-marrow, etc., index of a previous infection, has a double origin. In chief part it is derived from the melanaemia, that is, from the deposition in the viscera of the black pigment formed during the acute infection in the circulating blood; in part it has a local origin, that is, it is derived from the slow transformation of the blocks of ochre-colored pigment which are deposited or formed in the spleen and in the other viscera from the enormous quantity of altered red blood-corpuscles,

which, in grave infections, die before the direct action of the parasites has transformed their haemoglobin into black pigment."

Chemical Characteristics of Melanin and Haemosiderin.—*Melanin* (the black pigment) is not acted upon by strong acids, but is decolorized by the potassium and ammonium salts; it is very soluble in sulphide of ammonium, but insoluble in strong acids. No trace of iron has ever been demonstrated in melanin, but this fact does not prove that it is not present. In all probability, melanin is closely allied to haematin, as is held by Carbone, who believes that it is identical with the latter.

Haemosiderin (the yellow pigment) is insoluble in strong acids, caustic potash, alcohol and water; turns black when treated with sulphide of ammonium, and gives a blue color when treated with ferrocyanide of potassium and hydrochloric acid. Thus it will be seen that this pigment, unlike melanin, gives an iron reaction.

Distribution of Melanin and Haemosiderin.—*Melanin* occurs in the blood and tissues in the form of minute granules of a dark brown or nearly black color, which tend to accumulate in small irregular clumps when situated in the viscera. In tertian infections the melanin is generally of a golden-brown color, while in quartan and aestivo-autumnal infections it is darker, generally almost black. This pigment, formed, as has been said, within the red cells or, more properly, within the body of the plasmodium, is liberated with the segments during sporulation, and is taken up by the leucocytes or is deposited in certain tissues, especially in the brain, spleen, liver, and bone-marrow. This pigment is engulfed by the large mononuclear leucocytes, the polynuclear leucocytes, and rarely by the eosinophiles, but not by the endothelial cells of the liver and spleen, or by Kupfer's cells in the liver. In the tissues this pigment may often be seen in large quantities, much of it having reached this locality by diapedesis of leucocytes containing the pigment or by the rupture of capillary vessels which have become occluded by phagocytic leucocytes and masses of melanin. This pigment occurs free in the blood plasma, but, while used as a diagnostic evidence of malarial infection, such free pigment cannot be relied upon in diagnosis, as extraneous particles of dirt, so common in blood specimens, cannot be differentiated morphologically from melanin. Pigmented leucocytes, provided the pigment contained within them is dark brown or black in color, are of value in diagnosis. In pernicious malaria melanin occurs in considerable amount in the kidneys and the lungs, as well as the muscular wall of the heart, and in cases characterized by intestinal irritation this pigment is common in the villi of the intestine.

The yellow pigment, or *haemosiderin*, occurs within the tissues, never in the peripheral blood. In the liver and spleen, and in smaller quantity in the bone-marrow, kidneys, and other viscera, this pigment occurs in the form of fine grains, larger masses of an amber color, and large blocks or masses of a golden-yellow color. It is especially abundant in fatal cases of pernicious aestivo-autumnal fevers, occurring in such cases chiefly in the liver and spleen.

This pigment is also derived from the haemoglobin of the red corpuscles, but from corpuscles which have not been invaded by the plasmodia. Unlike melanin, this pigment is observed within the endothelial cells of the viscera and in Kupfer's cells, as well as in the cells of the spleen and within the epithelium of the kidney tubules. Melanin occurs chiefly in the phagocytic cells in the capillaries of the viscera, while haemosiderin occurs most frequently within the tissue cells of the viscera.

There is some evidence which goes to prove that melanin may be derived from haemosiderin, under certain conditions, and Bignami believes that this change occurs after the acute infection in haemosiderin formed during the paroxysms of the fever.

Summary of Blood Changes.—Summing up our knowledge as regards the changes in the blood in the malarial fevers, it may be briefly stated as follows: A marked reduction in the number of red corpuscles, both by parasitic invasion and as the result of poisons elaborated by the plasmodia during their development, as well as changes brought about in the blood-forming glands by the malarial infection; a corresponding reduction in the number of white cells, with, in most cases, a relative increase in the large mononuclear leucocytes; a marked reduction in the haemoglobin, and the presence in the blood of black and brownish-yellow pigment, in greater or lesser amount.

The Urine in Malarial Infections.—In most malarial infections the urine shows some departure from the normal, and in aestivo-autumnal infections, and the more severe tertian and quartan infections, very grave pathological conditions may be present. A number of observers have studied the urine in malaria and have described the conditions present, notably Rem-Picci, Thayer, Celli, and Botazzi and Pensuti.

Quantity.—In tertian and quartan infections the amount of urine passed in 24 hours is generally increased, while in aestivo-autumnal infections the quantity is normal or decreased. In certain cases of aestivo-autumnal infection the quantity is greatly increased. During the malarial paroxysm a large amount of urine is often passed, due to the increased vascular tension present during the cold stage; the smallest amount of urine passed is generally during the interval between the paroxysms.

Polyuria is not infrequently observed during convalescence from all malarial infections, but especially in the convalescence of tertian and quartan cases. Rem-Picci observed it in 60 of 150 cases, and I would even put the percentage higher, as I have found it present in at least 80 per cent. of all cases in which special attention was paid to the urine. Polyuria, however, is not confined to the stage of convalescence, for it is observed during the attacks or immediately following each paroxysm of the fever. It may last a few days or several weeks. I observed an interesting case in which the patient recognized the impending occurrence of a malarial paroxysm by the greatly increased amount of urine he passed just before the onset of the chill. The daily amount of urine passed when polyuria is present averages from two to three liters, but may be much

greater. One patient under my observation, after a tertian aestivo-autumnal attack, passed from 20,000 to 25,000 c.c. of urine per day, for several weeks. This is a very unusual occurrence, however, especially in aestivo-autumnal infections, in which polyuria is not as common as in tertian and quartan infections.

Specific Gravity.—During the attack the specific gravity is increased, although the amount of urine passed may be excessive. After the attack, the specific gravity is generally normal, unless polyuria be present, when it varies with the amount excreted, but is generally low. In cases presenting polyuria during convalescence, the specific gravity of the urine is low, varying between 1.005 and 1.010. In many cases of mild infection there is no variation from normal in the specific gravity.

Color.—As in all febrile diseases the color of the urine is increased during the attack, being usually reddish and smoky in appearance. It generally deposits a considerable sediment of urates or phosphates upon standing. The color of the urine in the polyuria of convalescents is usually a pale lemon-yellow.

Reaction.—The urine, both during the attack and in convalescence is acid in reaction, the acidity being greatly increased during the paroxysms when the urine is diminished in amount. The acidity is normal when the urine is excreted in normal quantity.

Total Solids.—The total solids are increased, especially during a malarial attack.

Urea.—The amount of nitrogen excreted in the 24 hours is increased above normal, this increase being greatest during the fever. Sometimes the increase is most marked before the fever, while after the paroxysm, in the afebrile period, the amount of urea eliminated is lowest, but is not below normal. In rare instances the greatest amount of urea is excreted during the afebrile period. The increase in nitrogen and urea eliminated during malarial attacks is undoubtedly due to increase of tissue waste brought about by the action of the infection upon the organism.

The urine in cases of malarial polyuria following the paroxysms generally shows a decreased amount of urea.

Uric Acid.—According to Rem-Picci, no special law controls the excretion of uric acid during attacks of malaria, but an increase during the fever is rarely observed in aestivo-autumnal infections, in my experience.

Phosphates.—This subject has been studied by Rem-Picci, Bernasconi, Rosenstein, Gee, and Freund, and all agree in stating that at the beginning of the paroxysms there is a marked decrease in the phosphates in the urine, followed, during apyrexia, by a marked increase in the excretion of phosphoric acid, thus proving that during the fever there is a retention of phosphates in the body. The amount of phosphates excreted during the 24 hours by malarial patients is greater than normal. The phosphates are generally increased in the urine of patients suffering from the polyuria of convalescence.

CHLORIDES.—The chlorides are markedly increased during the fever, but decrease in the afebrile period, the decrease beginning during the decline in the temperature. In convalescence we rarely observe an increase in the chlorides.

SODIUM AND POTASSIUM.—The amount of sodium and potassium eliminated, as well as the period of elimination, varies considerably in different patients. Rem-Picci found that about one half of his cases showed diminished sodium and potassium during pyrexia, while the other half showed a diminution during apyrexia. More sodium was eliminated during pyrexia in one half, while in the other half more sodium was eliminated during apyrexia. The increased excretion of sodium may be peculiar to malaria, but the lack of careful observations upon the urine of other fevers due to protozoa leaves this matter still in doubt.

IRON.—Colasanti and Iacoangelini have demonstrated that more iron is present in the urine of malarial patients than that of other fevers, and that the quantity of iron is greater after than during the paroxysm. The increase in iron is greatest in the most severe infections.

ALBUMIN.—Albuminuria occurs with varying frequency in malarial patients depending upon the type of infection and upon the locality. In the tropics albuminuria is much more common in malaria than in the temperate zones, and even in the tropics it is more common in certain severely infected regions. Albumin appears in the urine of a certain proportion of cases of the more severe tertian and quartan infections, and in the majority of cases of aestivo-autumnal fevers. In the latter infections hyaline, epithelial, and granular casts are not infrequently observed, and it can be stated as a rule that all fatal cases of malaria show albuminous urine before death. This subject will be further discussed in the chapter dealing with the complications of malaria.

PEPTONE is found very rarely in the urine after the decline of the temperature as reported by Botazzi and Pensuti.

NUCLEO-ALBUMIN has been found in the urine of malarial patients by Mannaberg, *urobilin* by Kieweit de Jonge.

INDICAN.—In severe aestivo-autumnal infections, especially those accompanied by severe irritation of the gastrointestinal canal, the urine shows a a marked increase in the amount of indican excreted.

THE DIAZO-REACTION.—The diazo-reaction occurs not so very infrequently in cases of malaria, especially in long-continued aestivo-autumnal infections. Thayer and Hewetson, Mannaberg, Zieman, and the writer have all observed this reaction in the urine of malarial patients, and it is generally acknowledged that this test is untrustworthy in the diagnosis between malaria and typhoid. Horcicka found this test positive in 7 per cent. of the tertian cases, in 12 per cent. of quartan cases, and in 33 per cent. of the aestivo-autumnal infections observed by him.

TOXICITY OF THE URINE.—Several observers have endeavored to ascertain

whether the toxicity of the urine is increased in malarial infections, much good work in this line having been accomplished by Brousse, Roque and Lemoine, and Botazzi and Pensuti.

Brousse's conclusions from his work are as follows:

"1. The urotoxic coefficient calculated by Bouchard's formula, the mean coefficient being 0.464, rises during the paroxysm, and the physiological effects observed are those which usually follow the injection of urine-dyspnoea, myosis, fall of temperature, exophthalmos, and, furthermore, convulsions.

"2. This toxicity is diminished during the period of convalescence in intermittent fever very much below that of the urine during the paroxysm, and, moreover, below that of normal urine."

On the other hand, Botazzi and Pensuti, following the method of Brousse in injecting malarial urine into animals, do not agree with the latter observer, but conclude that the experiments do not prove the existence of a specific toxin in malarial urine. Their conclusions, which are deserving of the greatest consideration, are as follows:

"1. That in the malarial fevers the febrile urine is less toxic than that passed during the apyretic stage.

"2. That the urine emitted during the period of apyrexia is more toxic than normal urine.

"3. That the toxicity of the urine of malarial patients augments constantly with the succession of febrile attacks, though in some cases this augmentation appears in the form of unexpected and irregular exacerbations.

"4. That, as there is nothing specific in the course of the intoxications produced in rabbits with malarial urine, there is no need to suppose the presence of specific toxins or substances of the nature of leucomaines, for the salts of potassium, phosphoric acid, the urinary pigments, the peptones—all of which substances are eliminated in increased quantities—are a sufficient explanation.

"5. That the injection of febrile urine is followed by a slower intoxication, characterized by sopor, by increased diuresis, by diarrhoea, and mydriasis, while the apyretic urine produces a more acute effect, sometimes fulminating, characterized by clonic and tonic spasms, myosis, "*exorbitisme*," spastic expiration.

"6. That to explain this different picture one may suppose that with febrile urine the polyuria and diarrhoea are due chiefly to the increased richness in urea, while the peptones may contribute to the production of sopor. In the afebrile urines the salts of potassium, the phosphoric acid, the urinary pigments, and especially the urobilin, manifesting themselves as substances essentially convulsive, determine an hypertoxicity.

"7. Finally, besides the haemocytolysis, the destruction of the cellular elements of the tissues, and the formation and elimination of toxic substances, there must exist intermediate factors which account for the absence of increased toxicity after the first febrile paroxysms, and the irregular elevation and diminution in the urotoxic coefficient in some other cases."

The work of Botazzi and Pensuti would appear to show that while the urine in malarial cases has an increased toxicity at certain times, this toxicity is not due to a specific toxin, but to the products of tissue waste and haemolysis. Up to the present time no one has succeeded in demonstrating a specific malarial toxin in the urine of patients suffering from the disease.

Etiology of the Fever.—In the regularly intermittent malarial fevers, it is well known that the onset of the fever is coincident with the sporulation of the plasmodia. The same is true in the more irregular aestivo-autumnal infections, although the time of sporulation of the plasmodia is not so easily recognized, as segmenting forms do not usually occur in the peripheral blood. In these cases, however, blood from the spleen, obtained by puncture, will also show a preponderance of segmenting forms at the onset of the fever.

To what is the fever due? Many and various have been the theories held by scientists regarding this question. Laveran believed that the febrile attack was due to nerve irritation; Richard, that it is the index of the reaction of the human organism to the malarial plasmodia; Golgi, that the febrile paroxysm is due to the invasion of the red blood-corpuscles by the young plasmodia, while Antolisei concluded that the invasion of the red cells by the plasmodia had little to do with the rise of temperature, which he believed to be due to the setting free in the blood-plasma of the newly-born plasmodia at the time of segmentation.

To Baccelli, however, we owe the most reasonable theory of the rise of temperature in malaria, and the one which is to-day accepted by most authorities. He suggested that during sporulation, and the consequent liberation of the young plasmodia in the blood plasma, certain toxic products, evolved during the growth of the plasmodia, were also liberated, and that these produced the rise in temperature and the characteristic symptoms of a malarial paroxysm. The toxic products he considered to be chemical poisons of unknown nature, the amount liberated depending upon the number of plasmodia reaching the stage of sporulation. This theory has been accepted by Marchiafava, Bignami, Golgi, Thayer, Zieman, and many other students of malaria. I believe that this theory explains most rationally the rise in temperature in the malarial fevers, by a probable direct action of the toxin upon the heat centers and upon the vasomotor system, and reasoning from analogy, it is impossible to believe otherwise than that the fever of malaria is due to the liberation of toxic products in the blood during the sporulation of the plasmodia.

While we must admit that as yet we have no positive proof of the existence of a specific malarial toxin or toxins, yet certain facts have been ascertained which go far toward establishing this theory upon experimental evidence. That toxic products are eliminated in the urine in malaria I have already shown, although no specific toxin has been found in this fluid. The same is true of the perspiration at the time of the paroxysm, as shown hy Queirolo, who found that such perspiration was very toxic to guinea-pigs, while the perspiration of normal individuals was not. The occurrence in the spleen, liver, brain, and other viscera of areas of focal necrosis, identical with those described by numerous observers, such as Welch, Reed, and Flexner, as occurring in other acute infections, like typhoid and diphtheria, and as due to toxic substances circulating in the blood, is almost positive proof that malaria is

a toxaemia, for Flexner has proven that such focal areas of necrosis are characteristic of a general toxaemia.

The recent experiments of Rosenau, Francis, Parker, and Beyer with filtered blood from malarial cases, would appear to indicate that the blood serum contains a toxin capable of causing the symptoms of malaria when injected into a healthy individual. They have demonstrated this toxin in the blood during the chill in tertian infection, but were unable to demonstrate it in the blood in a case of aestivo-autumnal infection during the decline of the paroxysm. They say: "While this poison reproduced the symptoms of the disease, still the data are too limited to consider it the malarial toxin." The researches of Celli, Mannaberg, Gualdi, and others regarding a malarial toxin in the blood resulted negatively, but there is some reason to believe that those of Rosenau and his confrères, conducted under modern precautions, have been successful in demonstrating the malarial toxin. However that may be, the occurrence of areas of focal necrosis, the growth of connective tissue, which follows malarial infection, the clinical symptoms of these fevers, the degenerative changes occurring in the blood and in the tissue cells, all point to a specific toxin as the etiological factor.

In the light of our present knowledge, we are forced to conclude *that the rise of temperature in all malarial fevers is due to a toxic substance or substances produced by the plasmodia during their development, and liberated at the time of sporulation of these organisms.* While it is probable that toxic materials are formed during the degeneration and breaking up of the red corpuscles in malaria, I believe that such materials have but little to do with the production of the fever and the characteristic symptoms of the disease.

The periodicity of the rise in temperature is easily explained by the intervals of time elapsing between the sporulation of the plasmodia, and in the case of continued fevers, by the fact that multiple groups of plasmodia are present which sporulate at short intervals, thus causing an almost constant discharge of toxic material into the circulation. In this way all variations in the temperature curve observed in malaria may be explained, the sporulation of the plasmodia initiating the temperature and the clinical symptoms.

If sporulation be delayed we have an anomalous temperature curve, while if a double or triple infection with various species of plasmodia occur we have an irregular or almost continuous temperature curve. Infection with two groups of tertian plasmodia produces a quotidian curve, as does infection with three groups of quartan organisms, provided both varieties sporulate at intervals of twenty-four hours. A quotidian curve is also produced by the quotidian aestivo-autumnal plasmodium while a double infection with this organism may produce an almost continuous temperature. In those instances in which two groups of quartan parasites sporulate at intervals of 24 hours, a temperature curve is produced characterized by a rise of temperature upon two days, with one day of normal temperature intervening. The temperature and the severity of the clinical symptoms vary according to the species of

plasmodia infecting the individual and the number of plasmodia present. Thus the plasmodia causing the aestivo-autumnal fevers evidently produce a toxin which is more powerful than that of the plasmodia of tertian and quartan infections, for in the former class of infections we meet with the vast majority of pernicious symptoms, and this though the plasmodia may not be as numerous as in the milder infections. In general, however, the symptoms increase in severity with the number of plasmodia present, even in the aestivo-autumnal infections.

In rare instances fatal pernicious infections are observed in which there is little, if any rise of temperature. I have observed a fatal case of aestivo-autumnal infection in which throughout the disease the temperature was normal or subnormal, yet in which the blood from the spleen showed immense numbers of sporulating aestivo-autumnal plasmodia. How can such an absence of temperature be explained? At the present time we cannot explain these cases, except to say that in malaria, as in other diseases, many exceptions are noted to the general rule, and unexplainable idiosyncrasies occur.

After a malarial infection has persisted for a considerable length of time, it is commonly observed that even though the plasmodia may be demonstrated in the blood and undergo sporulation as usual, the fever becomes modified or disappears. While we are unable to state definitely the reason for the disappearance of the fever in these infections, it is probable that the continued action of the toxin or toxins upon the organism has resulted in its acquiring a relative immunity to the fever-producing toxin, or has stimulated the production of antitoxic substances.

The subject of spontaneous recovery is a most interesting one and one that will well repay careful investigation, for in its explanation lies the secret of immunity to these fevers. If we understood the etiology of spontaneous recovery we would undoubtedly be able to devise some method of producing immunity, and eventually of ridding the world of one of its greatest scourges in the form of disease.

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Consult also the monographs upon malaria which have been mentioned in preceding chapters.

CHAPTER II.

The Special Pathology of Acute Malarial Infections.

The pathological lesions occurring in the viscera in acute malarial infections are similar in character for all species of plasmodia, although more severe lesions are usually found in aestivo-autumnal infections. The visceral pathology of malaria has been thoroughly studied by numerous observers, among whom may be mentioned Bignami, Laveran, Guarnieri, Councilman, Abbott, Dock, Bastianelli, Thayer, Barker, Monti, and Ewing. In recent years our knowledge of the changes occurring as the result of malaria in the viscera has been greatly added to by such studies, and we have come to understand better the extensive pathological lesions which often follow these infections. I cannot better introduce this portion of our subject than by quoting Marchiafava and Bignami's admirable remarks concerning the pathology of malaria. They say:

> "The malarial infection develops in the blood; here only, and chiefly within the red corpuscles, can the parasite live. From this it follows that the parasite invades the red corpuscles and nourishes itself at their expense, transforming the coloring matter of the corpuscles into black pigment (which, after the multiplication or the destruction of the parasite, is incorporated into the white cells) or otherwise injuring the red corpuscles. In consequence of this infection of the blood, we find, in addition to the destruction of the cells, a production of the detritus of the red corpuscles and of the parasites, the presence of pigmented white cells, and the penetration of erythrocytes containing parasites, and of leucocytes containing pigment, into the capillaries of all the organs. It can be understood from this primary localization of the infection how the principal changes must be found in the hematopoietic organs in addition to the blood, and how alterations are to be encountered in all the organs and tissues."

This brief summary furnishes the key to the special pathology of malaria, and it should be remembered that any of the species of malarial plasmodia may cause pernicious symptoms leading to the death of the patient, and that the pathological lesions are practically similar for all species of plasmodia.

Appearance of the Cadaver.—The skin of a patient dying of malaria has a peculiar dusky-brown, yellowish, or grayish hue, more pronounced the longer the infection has lasted, and most pronounced in patients suffering from malarial cachexia. The wasting of the tissues depends upon the duration of the disease. Rigor mortis appears early, and is only moderate in extent, but postmortem discoloration is often intense and appears soon after death. Not infrequently jaundice is present and the body resembles that of a yellow-fever cadaver externally.

The Brain.—As most patients dying of pernicious malarial infection suffer from cerebral symptoms, the brain presents marked pathological lesions. In no organ are the pathological changes more exquisitely illustrated than in the brain, especially in those patients who have died of cerebral forms of the infection. In rare cases the brain will appear almost normal.

MACROSCOPIC.—Externally the blood-vessels are generally congested, and the entire organ appears hyperaemic. Small capillary hemorrhages are often observed and oedema is generally present. In those cases in which no cerebral symptoms have been present during life there is but little evidence of hyperaemia. Externally the brain does not appear pigmented save in very rare instances.

Upon section the cut surface is generally hyperaemic, and small hemorrhages, capillary in character, may be present in the gray matter, and even in the white matter. The lateral ventricles are dilated and filled with fluid, which may be blood-stained, and the choroid plexus is markedly congested. In the majority of instances the cortex is of a brownish or chocolate color, due to melanosis, and often the gray matter is more or less pigmented. In some cases of aestivo-autumnal infection, however, the brain may not appear pigmented. Small hemorrhages are often found in the white substance and also in the cerebellum. In not a few cases of pernicious malaria the brain appears anaemic and no pigmentation can be detected. The congestion and hemorrhages are due to blocking and rupture of the capillaries by the plasmodia, free pigment, cellular detritus, and pigmented leucocytes.

MICROSCOPIC.—As a rule, the capillaries of the brain are filled with blood corpuscles, many of which contain plasmodia. The plasmodia may be found to be in various stages of development, or, which is very common, all of them at about the same stage of development. If the plasmodia contain much pigment, as in tertian and quartan infections, and in some aestivo-autumnal infections, the brain appears greatly pigmented, while the reverse is also true. The plasmodia may be so numerous that almost every red corpuscle is invaded, or they may be very few in number. In some instances they are so numerous as to occlude the lumen of the capillaries, thus forming thrombi. The small arteries and veins are less rich in infected corpuscles. In rare cases the entire cycle of development of the plasmodium may be found illustrated in one capillary. Besides infected blood corpuscles, the following structures may be observed in the capillaries:

a. Free plasmodia.
b. Macrophages.
c. Free pigment.
d. Pigmented leucocytes.
e. Endothelial cells.

(a) Free Plasmodia.—In some cases large numbers of extracellular or free plasmodia, always pigmented, are observed in the capillaries. These plasmodia are always round, oval, crescentic, or segmenting bodies, with pig-

ment in the form of a solid, minute block, situated at or near the center. These plasmodia are most numerous in tertian aestivo-autumnal infections.

(b) Macrophages.—Immense white blood-corpuscles containing free pigment and plasmodia are generally seen, often so large as to distend and entirely block the capillary in which they are situated. Most of these cells are of endothelial origin. Smaller phagocytic leucocytes are often present and may be so numerous as to occlude the capillaries.

(c) Free Pigment.—Many of the capillaries contain much free pigment, which sometimes occurs in such large quantities as to block the capillaries and form thrombi. This condition is generally present in cases which have presented marked comatose symptoms.

(d) Pigmented Leucocytes.—Most of the leucocytes present in the brain capillaries are pigmented, and often contain red corpuscles containing plasmodia. The leucocytes are usually present in small numbers.

(e) Endothelial Cells.—The endothelial cells lining the capillaries are generally swollen and are undergoing fatty degeneration; they are often pigmented, and, by reason of their distention, may occlude the capillaries. They often occur free in the capillary and may contain plasmodia.

Changes in the Nerve-cells.—To Marchiafava and Monti we are indebted for valuable contributions upon the lesions occurring in the nerve-cells (ganglion cells) as the result of pernicious malaria. These lesions occur in both the protoplasm and nucleus of the nerve-cell. In the protoplasm the chromatic bodies of Nissle disappear, and the protoplasm appears very granular, or, in the severest cases, the protoplasm appears to be disintegrated and rarefied. The nucleus in such cells may appear normal or, especially in the pyramidal cells, the nuclear membrane and nucleolus disappear as well as the chromatin, or one or the other of these elements may persist. Notable changes are observed in the branches of the cortical cells, consisting of attenuation and nodal formations along them, or they may present a beaded appearance. Sometimes very large, bleb-like swellings occur along their dendrites, connected by very slender filaments of protoplasm. In rare instances nodes are observed along the axis cylinders. All of the lesions above described are most marked in fatal cases of comatose aestivo-autumnal malaria.

Spinal Cord.—Usually the spinal cord presents no lesions of importance in malaria but in rare instances lesions similar to those described for the brain are observed.

The Retina.—Guarnieri has studied the lesions occurring in the retina in pernicious malaria and finds that they consist in congestion and hemorrhages, the congested vessels containing parasite-infected red corpuscles, macrophages, pigmented leucocytes, and free pigment. Many of the capillaries are occluded, thus leading to impairment of function.

The Lungs.—The gross pathology of the lungs in cases dying of pernicious malaria is not characteristic, there being usually, according to the stage of the disease and the severity of the infection, hypostatic congestion, oedema,

capillary hemorrhages, or areas of broncho-pneumonia present. Pigmentation is generally present but cannot be distinguished from the pigmentation of anthracosis.

MICROSCOPIC.—Sections from the lungs show the following changes: The alveolar capillaries are generally congested and often contain large numbers of pigmented or parasite-laden leucocytes which are often much degenerated. These cells are most numerous in the smaller arteries and capillaries. The polynuclear leucocytes are seldom observed. The endothelium of the capillaries is often swollen and contains small particles of pigment, but this condition is very much less marked than in the brain, liver, and spleen.

When broncho-pneumonia has occurred, the exudation into the alveoli is mostly composed of polynuclear leucocytes, and the alveolar cells, while only in rare instances are pigmented leucocytes or phagocytes observed, though the alveolar capillaries are often crowded with them. Neither is free pigment common in this exudation, but in one case I have observed parasite-infected red cells in the alveolar exudation in a case in which the symptoms were those of a severe lobar pneumonia. Marchiafava and Bignami claim that this lack of diapedesis of the pigmented leucocytes and macrophages is due to the fact that these cells are degenerated and have lost the power of amoeboid motion by which they are normally enabled to pass through the capillary walls. In certain cases areas of hemorrhage, microscopic in character, are observed in section of the lung.

When pneumonia complicates the pernicious malarial fevers it is, without doubt, due to the diplococcus of pneumonia, or streptococci, and the symptoms and lesions are influenced by the coexisting malarial infection.

The Heart.—There is but little that is characteristic in the appearance of the heart in cases of pernicious malaria. In very severe cases the organ is somewhat pigmented and the heart muscle is flabby and anaemic. The chambers of the heart, especially the right ventricle, may contain clots, in which may be demonstrated infected red corpuscles, and pigmented leucocytes and endothelial cells.

MICROSCOPICAL.—The endomysium may contain many mast cells, and rarely fatty degeneration of the muscle fibers occurs. The capillaries of the muscular wall of the heart may contain numerous plasmodia, both free and within red corpuscles, as well as pigmented leucocytes. Ewing describes a case in which cardiac failure was the most prominent symptom and in which the heart muscle contained a greater proportion of plasmodia and pigmented leucocytes than either the spleen or liver. A somewhat similar case has been reported by Benvenuti, but it is problematical whether malarial infection can so weaken the heart muscle through the engorgement of the capillaries and their occlusion as to cause the death of the patient.

The Stomach and Intestines.—Macroscopically, the only change usually observed in the stomach and intestines is more or less pigmentation, the mucous membrane being of a dull slate color or a dark brown or chocolate color. In

cases dying of the choleraic form of pernicious malaria, the lesions are more marked, consisting of hyperaemia, necrosis, and even ulceration of the mucous membrane. In such cases the mucous membrane is swollen, inflamed, and areas of capillary hemorrhage and superficial necrosis are observed. The intestine may contain blood-stained mucus. Peyer's patches, as well as the solitary glands, are often greatly swollen in severe choleraic malaria.

Microscopic.—Sections of the stomach and of the intestines show that the capillaries are distended with blood, and in the intestines, especially, the capillaries of the villi are crowded with parasite-infected corpuscles, free plasmodia and pigment, phagocytes, and endothelial cells. These may occlude the capillaries, forming thrombi, with resulting necrosis and ulceration of the mucous membrane in places. The epithelium lining the mucous membrane is often necrotic, and there may be present a very general superficial necrosis of this membrane, involving only the epithelial layer. Beneath the areas of necrosis there is a dense infiltration with leucocytes, and bacteria of various species are found in the necrotic tissue and invading the submucosa beneath the necrotic areas.

The Adrenal Glands.—Barker has carefully described the lesions of acute malaria occurring in the adrenal glands. The arteries and veins contain many plasmodia, bacteria, pigmented leucocytes, plasmodia within red corpuscles, and a few macrophages. The vessels are distended, and there occur areas of capillary and venous dilatation. Polynuclear and mononuclear leucocytes are present containing plasmodia, the polynuclear cells being present throughout the gland, the mononuclear being found between the vessel walls and the adrenal cells of the zona fasciculata. The endothelial cells of the organ act as phagocytes, as in the liver and spleen, and a few of the adrenal cells may contain pigment and infected corpuscles. Evidences of degeneration are observed in the adrenal cells, many of which are swollen, fatty, and vacuolized, and show fragmented nuclei. The changes in these glands are very suggestive of a toxaemia.

The Liver.—The lesions of acute malarial infection are generally well marked in this organ and many of them are absolutely characteristic.

Macroscopic.—The organ is generally enlarged, sometimes markedly so, but usually the enlargement is slight and sometimes not appreciable. The consistence of the organ is reduced. Pigmentation is always present, the color varying from a brownish shade to black upon section. The capsule is smooth and the lobules generally indistinct. The gall-bladder is generally distended with almost black bile, and the walls of this organ may be greatly pigmented. Upon section, the cut surface varies in color from a very dark brownish-red or a slate color to black, and is bathed in blood, as the organ is usually greatly congested. It is not uncommon to find the cut surface mottled with light yellow spots due to fatty degeneration.

Microscopic.—The lesions characteristic of malarial infection are found in the capillaries, in the liver cells, and in the connective tissue of the organ.

The capillaries contain many large macrophagi, containing much pigment, plasmodia and sometimes, red corpuscles. In many of the capillaries the lumen of the vessel is occluded by these macrophagi, or by free pigment and cellular detritus. The number of parasite-infected red corpuscles is very limited in this organ, as a rule, although I have seen sections in which they were very numerous. The endothelial cells are very active as phagocytes and large irregular masses of protoplasm, filled with pigment and degenerated plasmodia, and formed by the fusion of two or more endothelial cells, are not infrequently observed blocking the capillaries of the liver.

The cells of Kupfer form a considerable proportion of the phagocytic cells, being swollen and containing pigment and fragmented plasmodia.

The liver cells exhibit various forms of degeneration, being swollen, atrophied, necrotic or vesiculated. In many cases the liver cells contain fine granules of yellow pigment (haemosiderin) and in some instances the protoplasm is entirely replaced by this pigment. This pigmentation of the liver cells is not characteristic of malaria, and is generally most pronounced toward the center of the liver lobules. A peculiar hyaline degeneration of the nuclei of the liver cells is rarely observed in pernicious cases of malaria, which is characteristic of this class of infections.

The central veins of the lobules are dilated with corpuscles and in many places small haemorrhagic areas have been formed by the rupture of capillaries and smaller blood-vessels, and the surrounding liver tissue becomes infiltrated with infected red corpuscles, leucocytes, phagocytes and free pigment. The congestion of the capillaries causes pressure atrophy of the columns of liver cells in places, and entire liver lobules may thus be practically composed of dilated capillaries, the liver cells having completely atrophied.

Focal Necrosis.—Areas of focal necrosis, such as have been described by Reed in typhoid, and by Welch and Flexner in diphtheria, are often observed in the liver in severe pernicious malarial infections. These areas certainly indicate that a specific toxin circulates in the blood in malaria, and both Barker and Flexner believe that they are due to a general toxaemia. The areas of focal necrosis vary in size, the liver cells are undergoing hyaline degeneration, while polynuclear and mononuclear cells are present in abundance, and capillary thrombi are seen, oftentimes multiple in character. Following the necrosis there is a proliferation of connective tissue in the vicinity, starting from the portal spaces, with the formation of new bile ducts and changes in the liver cells similar to those in the early stages of cirrhosis.

The changes occurring in the connective tissue of the liver consist in an infiltration of the portal spaces by round cells and the proliferation of connective tissue following focal necrosis. The question of a malarial cirrhosis is one of personal susceptibility, in large measure, as is shown by the rarity of this condition in malarial regions and among those who have suffered from repeated attacks of the disease, but I believe that such a form of cirrhosis does rarely occur.

The periphery of the liver lobules and the portal spaces are generally much pigmented, but occasionally the pigment is scattered in irregular masses throughout the lobules being contained in macrophages within the capillaries, or in haemorrhagic areas within some portion of the lobule. In some cases the spaces between the capillary wall and the liver cells are greatly enlarged and are filled with phagocytic Kupfer's cells, containing free pigment, infected red corpuscles, free plasmodia, and even small leucocytes.

The Spleen.—The spleen presents the most characteristic lesions of malarial infection of all the viscera, and a smear from the cut surface of this organ will clinch the diagnosis of malaria in every doubtful case.

Macroscopic.—The spleen is always enlarged, sometimes enormously so. The enlargement generally depends upon the length of time the infection has lasted, the largest spleens being observed in cases which have suffered from repeated and severe acute attacks of the disease. As a rule, the organ is pigmented externally, varying in color from a light chocolate to black. The capsule is tense and smooth, and the consistence greatly diminished. The cut surface is of a chocolate, slate, or jet-black color, and in many cases the splenic pulp is so soft as to be diffluent. The Malpighian corpuscles may be invisible or visible as minute white dots scattered through the parenchyma. In cases dying from an initial pernicious attack, the spleen may not be pigmented. The enlargement of the spleen is often slight in aestivo-autumnal infections.

Microscopic.—The venous sinuses of the spleen are congested and dilated, thus hindering the circulation, and resulting in the production of irregular haemorrhagic areas in the parenchyma. The sinuses contain multitudes of plasmodia, either free or in red corpuscles, as well as enclosed in immense macrophages and smaller mononuclear or polynuclear cells. The number of infected red cells within the sinuses is often enormous, almost every corpuscle containing one or more plasmodia, and this is especially true in aestivo-autumnal infections. I have, however, observed cases in which but few red corpuscles were demonstrable in the spleen.

The cells of the splenic pulp are pushed apart by the multitudes of red corpuscles which contain plasmodia in various stages of development, the pigmented forms and the sporulating bodies being most frequently observed. Free plasmodia are less common but by no means rare. In aestivo-autumnal fever, in cases which have lasted for several days, crescents are found, but I have never observed them in large numbers and they are often absent even when they may be demonstrated in the peripheral blood.

Besides the parasite-infected red corpuscles, the sinuses contain an immense number of phagocytic cells, consisting of small cells, resembling lymphocytes, which are few in number, and immense macrophages, which are much more numerous in the spleen than in the liver. The latter cells often present evidence of degeneration, as shown by fatty changes and necrosis of the protoplasm.

The smaller vessels of the spleen are congested and filled with infected red

cells, phagocytic leucocytes and endothelial cells, and free pigment and plasmodia. Free pigment is present throughout the pulp sinuses, lying in large blocks or clumps or in the form of minute rods and granules. Here, as in the liver, two forms of pigment occur: the dark brown or nearly black malarial pigment or melanin, and the golden-yellow pigment derived from the degenerated and broken-down red corpuscles, haemosiderin.

Areas of focal necrosis, exactly similar to those described as occurring in the liver are sometimes observed in the parenchyma of the spleen, and pressure necrosis of minute areas, due to the distended or ruptured capillaries, is a common lesion.

The connective tissue of the spleen is not increased in very acute infections, but in those cases which die of an acute attack following repeated attacks of malaria, the connective tissue of the trabeculae may be increased in amount. Pigmentation of the fibrous trabeculae is almost always observed, but the Malpighian corpuscles are not pigmented, although a considerable amount of pigment generally surrounds these bodies. Thrombosis is a common lesion in the spleen. In rare instances there is but little evidence in the spleen of malarial infection, even though death has occurred from that disease. Bloombergh and Coffin report a case in which no plasmodia could be demonstrated in sections of the spleen, although the plasmodia were demonstrated in the peripheral blood, and I have observed at least two fatal cases of malaria in which the plasmodia were so few in smears from the spleen that a long search was required before they could be demonstrated.

The Kidneys.—As a rule, the macroscopical appearance of the kidney is not at all characteristic of malaria. The organs are generally slightly enlarged, the capsule smooth, the consistence decreased, while there may be marked congestion, and in rare instances, considerable pigmentation. The cut surface is generally congested, and the cortex may appear slightly thickened. The capsule strips readily. The appearances presented in an acute parenchymatous nephritis are by no means rare, accompanied by small haemorrhages in the cortex of the organ.

Microscopical.—Aside from the purely malarial lesions present, the microscopic pathology of the kidneys in pernicious malaria is that of an acute or subacute parenchymatous nephritis, but the lesions peculiar to malaria are much less marked than in the other viscera, especially the brain, liver, and spleen.

The Malpighian tufts are often found congested and the seat of small capillary haemorrhages. There is but little pigmentation, but sometimes the glomeruli appear greatly pigmented, the pigment being situated within phagocytic cells in the capillaries, and in the endothelial and epithelial cells. Plasmodia, either free or within red corpuscles, may be seen occasionally within the glomerular capillaries, but they are generally few in number. The epithelium of Bowman's capsule shows some proliferation, and the capsular space may be filled by it or by fibrinous material, in which may be imbedded pigmented leucocytes and plasmodia.

The epithelium lining the convoluted tubules presents cloudy swelling, fatty degeneration, or necrosis. The straight tubules often contain hyaline, epithelial, or granular casts. The intertubular capillaries are somewhat congested and in them free pigment in small amount is observed, as well as endoglobular plasmodia, pigmented leucocytes, and macrophages. In some instances capillary haemorrhages have occurred into the parenchyma and areas of pressure necrosis may be present.

In very rare instances the organ may appear greatly pigmented macroscopically, the cortex appearing dark gray in color, while the pyramidal vessels may be distinctly outlined by the large pigment deposits within them.

The lesions in the kidneys which result from malarial infection are undoubtedly due to a toxic poisoning, as the plasmodia are present in too small numbers to produce the grave lesions which are not seldom found in these organs.

The Bone-marrow.—MACROSCOPICALLY, the bone-marrow varies in color according to the length of time the infection has lasted. In the long bones, in recent cases, the normal yellow color of the marrow is found; while if the infection has lasted for some time the color varies from red to black. Generally in acute cases there is a chocolate color observed. There may be an extensive hyperplasia of the marrow in severe and rapidly fatal cases.

MICROSCOPIC.—In sections of bone-marrow the lesions observed are very similar to those observed in the spleen. The capillary vessels contain numerous endoglobular plasmodia in advanced stages of development, sporulating bodies, and, if the infection has persisted long enough, crescents. They also contain numerous macrophages inclosing granules and clumps of pigment, as well as red blood-corpuscles and plasmodia. External to the capillaries, in the marrow pulp, plasmodia are found in various stages of development, and numerous crescentic plasmodia or *gametes* may be present in aestivo-autumnal infections. Here are also found many large macrophages, some of which are undergoing degenerative changes. Nucleated red corpuscles are common as well as pigmented medullary cells. The leucocytes may be greatly increased in number.

The pathological changes in the other viscera are of little importance and do not merit description.

The following autopsy record of a case dying of a quotidian aestivo-autumnal infection is inserted to illustrate the lesions most commonly found in the malarial fevers.

R. G. C.—Age fifty-two years. White. Clinical diagnosis, pernicious quotidian aestivo-autumnal fever.

Body that of a man apparently fifty years of age, somewhat emaciated. Skin yellowish in color. Rigor mortis slight. Postmortem discoloration marked over dependent portion of the body. Finger-nails not congested. Pupils regularly dilated. Marked anaemia of the mucous membranes and of the skin.

Brain.—The dura mater appears normal. The amount of cerebrospinal

fluid is increased. The surface of the cerebrum is pale, and upon section the medulla appears hyperaemic, and the cortex is a dark slate color. The lateral ventricles are filled with fluid. The choroid plexus is not congested. The cerebellum, upon section appears normal.

Thoracic and Abdominal Cavities.—The pleural cavities are free from fluid. The liver reaches about one centimeter below the border of the last rib. The omentum contains a large amount of fat, and reaches the level of the umbilicus. The appendix is about three centimeters in length, and lies in the right iliac fossa; it is normal in appearance. The bladder is filled with urine. Abdominal aorta shows no sclerosis.

Liver.—The liver measures 28 x 21 centimeters. The organ is purplish-black in color externally and the capsule is smooth. The gall-bladder contains a large number of gall-stones and much inspissated bile. Upon section the cut surface of the liver is slate colored, and the lobules are ill defined. The organ is greatly congested. Weight, 1,640 grams.

Spleen.—The spleen measures 19 x 12 centimeters. The organ is almost black in color externally and the capsule is distended and smooth. Upon section the cut surface is black in color, with light gray areas scattered through it, marking the location of the Malpighian corpuscles. The consistence of the organ is very much decreased, it being almost diffluent. Weight, 440 grams.

Pancreas.—The pancreas measures 22 x 4.5 centimeters. Upon section the cut surface appears congested. Weight, 115 grams.

Kidneys.—Both kidneys appear somewhat congested. The capsule is smooth and slightly adherent. Upon section the cut surface is congested, but the cortex and pyramids are distinct, the cortex being slightly thickened. Weight of each kidney, 125 grams.

Lungs.—The lungs are crepitant throughout and appear normal.

Pericardial Cavity.—The pericardial cavity contains about 3 c.c. of clear straw-colored fluid. Both layers of the pericardium appear normal.

Heart.—The amount of extracardial fat is increased. The blood-vessels are congested. Upon section of the heart the ventricles are found to contain small clots. The muscular walls are about normal in thickness, and the valves of the heart are normal in appearance.

Microscopical Examination.—THE LIVER.—The fibrous tissue in the portal spaces is slightly increased in amount, and large numbers of small round cells are present in this tissue. All the blood-vessels in the sections are increased in thickness. The liver cells are swollen, smoky, and granular in appearance, and in many of them the nucleus has disappeared. In others the nucleus is present, exhibiting necrotic changes, as evidenced by loss of staining power, and the absence or diminished staining of the chromatin granules. The protoplasm of the liver cells contains much fine yellow pigment, but this pigment is not found within the nucleus of the cells.

The intralobular capillaries contain a great deal of black pigment, numer-

ous macrophages, and smaller mononuclear leucocytes. The free pigment in the capillaries is in the form of irregular blocks, and the yellow pigment, so common in the protoplasm of the liver cells, does not appear within the capillaries. The macrophages which crowd the capillaries contain within their protoplasm an immense amount of black pigment, evidently derived from broken-down plasmodia; they also contain infected red blood-corpuscles and free plasmodia of the quotidian aestivo-autumnal variety. The number of plasmodia present is comparatively small, but the amount of pigment is immense, and it occurs in clumps so large that many of the capillaries are occluded by it. This condition is especially noticeable in the capillaries near the portal spaces. On account of the small caliber of the capillaries the macrophages are often compressed, appearing as long, slender, pigment-bearing cells. The plasmodia present are small, round, or oval bodies, containing a few small granules or grains of pigment, generally collected at the center of the organism. Most of these are presegmenting plasmodia. No crescents (*gametes*) are present in the liver. The stellate cells of Kupfer contain black pigment and sometimes small plasmodia.

In numerous situations throughout the capillaries of the liver there occur large, bleb-like plasmodia, containing pigment, which are probably degenerating parasites. There is not a single capillary in the sections that does not contain pigment-bearing cells or a few plasmodia.

THE SPLEEN.—The Malpighian bodies are somewhat fibrous, and at their border there is a large amount of yellowish-brown pigment. The splenic pulp contains a small number of red corpuscles showing small, round, or oval plasmodia within them, all of which are pigmented. The sinuses contain numerous infected red cells, immense numbers of macrophages, and large masses of free pigment The macrophages contain the following: (1) large irregular collections of brownish-black pigment; (2) red corpuscles containing pigmented aestivo-autumnal plasmodia; (3) free plasmodia, most of them pigmented and showing signs of segmentation; (4) fine granules of a yellowish pigment which is distinct from the large amount of dark brown or black pigment present. Some of the macrophages show all of these bodies within their protoplasm, while others, and they are in the majority, show only one or two free plasmodia and irregular collections of pigment. As a rule, the macrophages are about six to eight times as large as a normal red corpuscle, but many are present which are much larger and entirely block the capillaries.

Besides the macrophages there are many mononuclear leucocytes and endothelial cells, which are free from plasmodia or pigment. The polynuclear leucocytes are comparatively few in number. Everywhere throughout the sections there are very large masses of free pigment situated in the splenic sinuses, and in many places rupture of the sinues has occurred and areas of pressure necrosis have formed.

Throughout the sections of the spleen may be seen crescentic forms of the quotidian aestivo-autumnal plasmodium, but only in small numbers. In the

spleen there are also bleb-like degenerating plasmodia, like those in the liver. The sporulating forms of the plasmodium are remarkably few in number, but many of the macrophages contain sporulating bodies.

THE KIDNEYS.—Sections of the kidneys show the lesions of acute parenchymatous nephritis and some lesions characteristic of pernicious malarial infection. The Malpighian tufts are greatly congested, the capillaries being distended with blood, some of them having ruptured, thus causing hemorrhages with Bowman's capsule. Many of these capillaries contain free plasmodia, round or oval in shape and generally pigmented. The capillaries also contain a small number of infected red corpuscles, free pigment, degenerated plasmodia, and phagocytic cells. The number of plasmodia, both free and within red cells, is very much smaller than in sections of the liver or spleen.

The epithelium of the tubules is much swollen and is rapidly proliferating while the protoplasm of the cells is smoky and finely granular in appearance, and contains in many instances pigment grains of a yellowish color. One of the most interesting features of the kidney sections is the occurrence within the tubules of collections of black pigment and here and there a few plasmodia. A few infected red cells are also present within the tubules. The intertubular capillaries contain numerous free pigmented plasmodia, infected red cells and macrophages. The walls of the capillaries are not thickened. The amount of pigment present in the kidney is very slight as compared with that present in the liver and spleen, and the same is true of the number of plasmodia.

THE BRAIN.—The changes observed in the sections of the brain may be divided into those occurring within the capillaries and those within the brain substance proper. The small capillaries of the brain, especially those of the cortex, are crowded with pigmented, free plasmodia, leucocytes containing pigment, and in some places by small collections of yellow pigment. The infected capillaries are most numerous in the cortical portion of the brain, but they are by no means rare in the medullary portion. The pigment within the capillaries is generally collected in irregular masses, is brownish-black in color, and, in some places, entirely occluded the lumen of the capillary. The plasmodia present in the capillaries are mostly free, small in size, oval or round in shape, and contain pigment, which is generally collected at or near the center in the form of a few small grains or a single black block. It is remarkable how uniform these plasmodia are in appearance and how rarely an infected red cell is observed. In some places the capillaries are occluded by immense macrophages containing much pigment and numerous plasmodia.

The changes occurring within the substance of the brain consist in a necrosis of the protoplasm of some of the cortical cells, as is evidenced by the irregular staining reactions of the protoplasm and nucleus. Sections of the heart, lungs, stomach, and intestines were not examined as they presented no evidences of malarial infection.

The above autopsy record illustrates the common findings after death from pernicious malaria, but much greater changes are often observed, changes

so characteristic that a glance suffices to diagnose the cause of death, while in rare instances the lesions of malaria may be so slight as to be of little service in diagnosis.

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CHAPTER III.

The Pathology of Latent Malarial Infections and of Malarial Cachexia.

Pathology of Latent Malarial Infections.—By a latent malarial infection we mean a malarial infection which is not manifested by any symptoms, and in which an examination of the blood may or may not show the presence of the plasmodia. The pathology of such infections has received but little attention, and if we confine the term "latent infection" only to those cases in which no symptoms are present and no plasmodia are found upon repeated examinations of the blood, it will at once be seen why the pathology of this condition has not been investigated. Such cases of malarial infection will only be discovered at autopsy, the patient having died from some other disease, and outside of the tropics and the more malarial regions of the temperate zones, such cases will necessarily be very rare. In this chapter I shall only touch upon the pathology of those cases in which no plasmodia were demonstrated in the blood and no clinical symptoms of malaria were detected before death.

During my service at the U. S. Army General Hospital at he Presidio of San Francisco I observed seven cases in which the autopsy showed latent malarial infection in which before death no symptoms of malaria had developed and no plasmodia had been detected in the peripheral blood. Three of these cases were benign tertian infections and four aestivo-autumnal infections of the tertian type.

Pathology of Latent Tertian Malaria.—The pathologic lesions present were confined entirely to the liver and spleen, and this was also true of the aestivo-autumnal infections. In numerous cases coming to autopsy from other diseases, accompanied by a latent malarial infection in which the plasmodia were found in the blood before death, but in which there were no definite symptoms of malaria, it was observed that the chief pathologic lesions of malaria were also found in the liver and spleen, but that other organs presented slight lesions. Thus it will be seen that from the mildest latent infections to the severe acute infections there is a gradual progress in the pathological lesions, first manifested in the liver and spleen and spreading, according to the extent and severity of the infection, to all the organs.

The Spleen.—In these latent infections the most marked lesions were always present in the spleen. The organ in the tertian infections was considerably enlarged and dark bluish in color externally, the capsule smooth and tense, the notches distinct, and the organ somewhat decreased in consistence. Upon section the color was a dark browish-red, but did not present that browish or black color found n well-marked acute infections; this, of course, is easily

understood from the fact that the plasmodia present were comparatively few in number and that therefore little pigment was formed.

Microscopically, the sections of the spleen showed intense congestion of the splenic sinuses, together with pigmentation, especially marked along the edges of the Malpighian bodies and along the fibrous trabeculae. The connective tissue of the organ was not increased. The cells of the splenic pulp were greatly increased in number and many of the cells showed marked division of the nucleus. Many also were pigmented and distorted in shape.

The splenic sinuses and capillaries showed the presence of numerous infected red cells and pigmented leucocytes. While these infected cells were not nearly as numerous as in acute infections or as in more advanced latent infections, still they were sufficiently numerous as to be very noticeable. The plasmodia were in about the same stage of development in each case, but it so happened that the patients had died at such a period that the entire cycle of the tertian plasmodium within the human body could be worked out from examination of the sections of the spleen from these cases. As far as could be ascertained the plasmodia presented no essential difference in their appearance from those found within the red cells in the peripheral circulation during an acute infection. The sporulating bodies were numerous in one case, the segments appearing, however, slightly more refractive and more clearly outlined than when found in the peripheral blood. Their staining reactions were exactly the same.

The chief point of importance in the pathology of these cases is that the entire human cycle of the plasmodium can be completed within the spleen, thus proving conclusively that the seat of the initial malarial infection is in this organ, for no plasmodia could be demonstrated in the blood of these cases. While this has been the opinion of nearly all authorities for several years, few observations are on record in which, as in these cases, no malarial symptoms or plasmodia could be determined during life, but the entire human cycle of the organism was found in sections of the spleen, and no where else in the body.

Besides the infected red cells, numerous leucocytes were observed containing pigment in the form of large and small granules, and a few containing malarial plasmodia. Macrophages were also present containing much pigment in large blocks, and often one or more half or nearly full-grown plasmodia. A small amount of free pigment was observed lying within the splenic sinuses.

THE LIVER.—Macroscopically, the liver did not differ in appearance from that of a normal organ, so far as the pathology of malaria is concerned. Upon section marked venous congestion was present in all of the cases. The sections of the liver showed microscopically a few pigmented leucocytes within the capillaries, some of the leucocytes containing degenerated plasmodia. There was but little pigment present in the organ, most of it being within leucocytes. No macrophages were observed, most of the pigmented leucocytes being of the polynuclear type. A very careful search was made in the sections of the liver for infected red corpuscles, but in no one of the cases was an infected

red corpuscle observed. It will thus be seen that the lesions in these latent cases were almost entirely confined to the spleen, the liver being but very slightly involved.

Pathology of Latent Aestivo-autumnal Malaria.—The pathology of latent aestivo-autumnal malarial infections differs but little from that of tertian infections and chiefly in the type of the plasmodia present.

THE SPLEEN.—Macroscopically, the spleen appeared much as the spleen in the tertian infections, save that in all cases it was not as much enlarged nor as much pigmented. Upon section the consistence was found decreased, the Malpighian bodies nearly invisible, the color a dark mahogany-red—in one case brown—the substance of the spleen being almost diffluent in two of the cases. Upon microscopical examination the same changes were found as in the tertian latent cases, the splenic sinuses being congested, the cells of the splenic pulp increased in number and showing marked division of the nucleus, considerable pigmentation present, and the presence of infected red corpuscles and melaniferous leucocytes. The infected red cells were not as numerous as in the tertian latent infections. The plasmodia observed within the red corpuscles were almost uniformly in one stage of growth, but in the sections of the spleen from the four cases all stages in the human life cycle of the aestivo-autumnal plasmodium (tertian) could be observed. The younger forms were similar in appearance to the young forms observed in the peripheral blood, being small, hyaline rings, presenting in smears from the spleen, marked amoeboid motion. The older plasmodia were disk-shaped or ring-like, and contained more or less pigment in the form of very fine reddish-brown granules, the pigment being very slightly motile. In one case numerous sporulating bodies were observed, the sporulation always occurring within the red cell. The segments varied in number, the largest number counted being 24, the smallest 12. A peculiarity about the segments was that each appeared to present the "ring-form" which is usually found in the red cell at the earliest stage of infection. This appearance was so distinct that the infected corpuscle appeared to be filled with minute "rings." The pigment in the sporulating bodies was collected either at the center or to one side, and none of the segments contained any pigment.

No crescents were observed in the sections of the spleen from any of the cases. Numerous pigmented leucocytes were observed and macrophages containing much pigment and one or two plasmodia. Considerable free pigment was present in the same localities as noted in the tertian cases.

THE LIVER.—The pathologic changes in the liver were similar to those observed in the tertian latent cases. No infected red cells were found, although a considerable number of melaniferous leucocytes were observed, together with some free pigment.

The chief point of value in the pathology of latent malaria is the demonstration that the malarial plasmodia are capable of undergoing their entire human life cycle within the spleen, thus proving the time-honored theory that the spleen is the seat of all malarial infections. Most of these cases were present

in the hospital for several weeks; repeated blood examinations were made; they were carefully studied clinically, and in none of them was malarial infection suspected. It is obvious that puncture of the spleen would probably have resulted in the discovery of the malarial infection in these cases, but this procedure is dangerous, even in experienced hands, and is certainly not advisable as a routine measure.

The Pathology of Malarial Cachexia.—Since the separation of kala-azar and malaria upon etiological and pathological grounds, the pathology of malarial cachexia is much better understood than when these two infections were confused. Almost every writer upon malaria describe marked pathological lesions in chronic malarial poisoning, but it is more than probable that many of them are due to complicating diseases rather than to the malarial infection.

The Blood.—In the majority of patients suffering from repeated attacks of malaria, in whom a cachectic condition has developed, there is present a greater or less degree of anemia, the red cells seldom numbering over 3,000,000 per cu. mm. and often not over 1,500,000 per cubic millimeter. The haemoglobin is proportionately reduced, and there is often an increase in the large mononuclear leucocytes. In severe cases nucleated red cells may be present, and poikilocytosis is often marked.

From their researches Dionisi and Bignami have separated four types of postmalarial anaemia, as follows:

"1. Anaemiae in which the examination of the blood shows alterations similar to those observed in secondary anaemia, from which they differ only in that the leucocytes are diminished in number. The greater part of these cases go on to recovery; a few, without any further change in the haematological situation, pursue a fatal course.

"2. Anaemiae in which the examination of the blood shows alterations similar to those seen in pernicious anaemia—presence of gigantoblasts. These cases end fatally.

"3. Anaemiae which are progressive, as the result of compensation by the marrow for losses brought about by the infection. At autopsy the marrow of the long bones is found to be wholly yellow, while the marrow of the flat bones is also poor in nucleated red cells.

"4. Chronic anaemiae of the cachectic, which differ from the above-mentioned types by clinical and anatomical characters, in that the special symptoms of malarial cachexia prevail, while one observed postmortem, a sort of sclerosis of the bone-marrow."

I agree fully with Dionisi and Bignami regarding the forms of anaemia following acute malaria, and have observed very severe anaemiae of the secondary type frequently A pernicious anaemia following malaria has, in my experience, been very rare, only one case being observed in over 5,000 patients.

Aside from the blood, the chief pathological lesions in malarial cachexia occur in the spleen, the liver, and the bone-marrow.

The Spleen.—In most instances the spleen is greatly enlarged, sometimes weighing several pounds; is generally greatly pigmented; the capsule more or

less roughened by adhesions; the color of the cut surface being slate, brown, or black; the Malpighian corpuscles standing out as almost white areas. The connective tissue of the organ is often increased macroscopically. Microscopically, the lesions consist in marked enlargement and fibrosis of Malpighian corpuscles, increased connective tissue along the trabeculae, which encroaches upon the parenchyma in places, enormous distention of the splenic sinuses, and the replacement of the splenic pulp by connective tissue containing large and small round cells. Pigmentation is very marked, the pigment being collected about the Malpighian corpuscles and along the fibrous trabeculae and in the walls of the blood-vessels. Hyperplasia of the cells of the splenic pulp occurs in places, especially about the enlarged follicles.

THE LIVER.—The liver may be enlarged or it may be atrophied, according to the length of time the cachexia has lasted. The perilobular connective tissue may be increased and there may be a hyperplasia of the liver parenchyma. Severe chronic venous congestion may be present and angiomata may be formed in the liver substance. The pigmentation is excessive at times, while in those patients who have suffered from cachexia for years the malarial pigmentation may have entirely disappeared. In greatly pigmented livers the outline of the lobules may be distinctly traced by the deposit of pigment, much of the pigment being extravascular.

The question as to the occurrence of cirrhosis of the liver as the result of prolonged malaria infection is still *sub judice*. While in many instances the liver in cachetics is atrophic, inquiry will generally develop the fact that the atrophy is as apt to be due to one of several causes as to the malarial infection. I am inclined to believe that in susceptible individuals severe and continued malarial infection may produce cirrhosis of the liver, but such cases are very rare, and I have never observed one in which the cirrhosis of the liver could not have been attributed to other causes.

THE BONE-MARROW.—The changes in the bone-marrow are due principally to the anaemia produced by repeated attacks of malaria. The marrow of the long bones is generally red in color and there is a marked increase in the consistence. The fatty tissue has been replaced by vascular medullary tissue, composed of large cells showing mitotic nuclei, lymphoid cells, giant cells, and normoblasts. Pigmentation may be almost absent even when the other viscera are markedly pigmented. In long-continued cases the nucleated cells are rare, and in some cases the microscopical lesions are those of pernicious anaemia.

Forms of Degeneration.—In the liver, spleen, and kidney, cloudy swelling and fatty degeneration of the cells of the parenchyma is noted and amyloid degeneration is not uncommon. While this change is not characteristic of malaria, it occurs so frequently in malarial cachexia as to be of importance. In the kidneys it is most usually observed, affecting the smaller blood-vessels and the walls of the tubules. It also occurs in the intestine in the vessels of the villi and in the spleen, affecting chiefly the capillaries of the follicles. The

liver is not as often the seat of amyloid degeneration as in other diseases, the condition being most noticeable at the periphery of the lobules.

The changes in the other viscera are not of special interest. The heart muscle is often flabby and below normal in thickness, while the anaemia present renders it pale in color. Fatty degeneration of the heart muscle is not commonly observed, and pigmentation is generally absent. The intestinal canal shows no changes of importance except amyloid degeneration in a small proportion of the cases. The lungs show no lesions characteristic of malarial cachexia.

The enlargement of the spleen, so long relied upon as indicative of chronic malarial infection, can no longer be held as of much assistance in diagnosis in regions where kala-azar is prevalent, as in such regions the spleen index is most unreliable as showing the proportion of malarial infections. It is probable that careful study of the fevers occurring in the tropics will demonstrate that enlargement of the spleen is common to many of them.

Literature upon the Pathology of Latent Malarial Infection and Malarial Cachexia.

Pathology of Latent Malaria Infection.

1903. Craig, C. F. The Pathology of Latent Malarial Infection as Observed at Autopsy. American Medicine, vol. vi, No. 4, p. 145.

Pathology of Malarial Cachexia.

The monographs upon malaria which have been referred to in previous chapters, especially those of Thayer, Marchiafava and Bignami, Ziemann, and Mannaberg.

1892–3. Bignami. Studi sull' anatomia patologica della infezione malarica chronica. Bull. dell. R. accad. med. d. Roma, xix, f. ii, p. 186.

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PART III.

THE SYMPTOMATOLOGY AND CLINICAL VARIETIES OF THE MALARIAL FEVERS.

CHAPTER I.

Clinical Classification; Tertian Malarial Fever; Quartan Malarial Fever; Aestivo-autumnal Malaria; Analysis of Symptoms; Examination of the Blood.

Clinical Classification.—It is often extremely difficult to classify the malarial fevers from a clinical standpoint. A division of these infections into intermittent, remittent, and continuous fevers, so often followed, is useful, but is at best a rough classification which does not indicate disease entities, and is confusing in many ways. It may be stated that any malarial fever may be intermittent, remittent, or continuous. For instance, while a single tertian infection is undoubtedly intermittent in type, we can conceive of a tertian infection in which several groups of plasmodia sporulating at various periods may give rise to a remittent or even continuous temperature curve, and in practice benign tertian infections remittent in type are not so very uncommon. The same holds true of quartan infections and especially of the aestivo-autumnal fevers. It is also a fact that infection with a single generation of any one of the malarial plasmodia will result in an intermittent fever. In other words, all malarial infections are intermittent in character and only become remittent or continuous when more than one generation of the plasmodium matures at different intervals of time, or when the typical character of the temperature curve is disturbed by inadequate treatment or by the natural resisting powers of the individual. While the term "remittent malaria" is generally applied to infections produced by the aestivo-autumnal plasmodia, the name is a misnomer, as the aestivo-autumnal infections are as truly intermittent as are the tertian and quartan. For this reason, I believe that classification should rest upon etiology in these infections and that clinical classification resting upon any other basis is unscientific and inevitably leads to confusion and a loose method of diagnosis. It is of the greatest importance in the treatment of malaria that we know to which species of plasmodium the fever is due, and this we can only know, in most instances, by an examination of the blood. A classification based upon the character of the temperature curve is very misleading and tends to lead to carelessness in making the blood examination or to neglect of that most important procedure. Stastistics of the type of malaria present in any locality based entirely upon the character of the temperature curve are worse than useless and should receive but little consideration in the study of malarial endemicity.

The following classification is adopted in this work, as it would appear to be the best from both a clinical and etiological point of view:

1. Tertian malaria, due to *Plasmodium vivax*.

2. Quartan malaria, due to *Plasmodium malariae.*

3. Tertian aestivo-autumnal malaria, due to *Plasmodium falciparum.*

4. Quotidian aestivo-autumnal malaria, due to *Plasmodium falciparum quotidanum.*

As I have already stated, I hold with Marchiafava and Bignami and others that there are two distinct types of aestivo-autumnal infection, both from a clinical and etiological standpoint, and I have already considered the morphological differences between the two types or species of plasmodia, but we do not have to rely solely upon such differences in distinguishing these fevers, for both varieties are distinct clinically in uncomplicated cases. I am aware that many observers have failed to recognize two forms of aestivo-autumnal malaria, but I am sure that any unprejudiced observer will admit the existence of these two forms of infection, if he studies uncomplicated cases of aestivo-autumnal fever in which quinine has not been given and in regions where these infections are endemic.

As to the relative frequency of these two forms of malaria it is undoubtedly true that the tertian aestivo-autumnal infection is altogether the most frequent. From the data I possess, comprising several thousand cases of aestivo-autumnal fever, the tertian plasmodium was found in about 75 per cent. of the cases.

The impression which prevails among many physicians, that a remittent temperature curve is characteristic of all aestivo-autumnal infections, is a false one, for irregularity or remittence is by no means confined to the aestivo-autumnal infections, which, if uncomplicated, are as truly intermittent as are either the benign tertian or quartan fevers. While it is true that irregularities of temperature are more apt to occur in aestivo-autumnal cases, because they are more resistant to treatment and are more commonly produced by multiple groups of plasmodia, it is not true that a remittent temperature curve is characteristic of them and that a diagnosis can be based upon such remittency. Any malarial fever may become irregular or remittent, from a multitude of causes, one of the chief of which is the unscientific use of quinine.

Clinically, all aestivo-autumnal fevers should be classed as *severe* forms of malarial fever, in contradistinction to the tertian and quartan types which are classed as *mild* or benign types of malarial infection. This classification of the aestivo-autumnal fevers as severe forms is of great importance. While, of course, comparatively few aestivo-autumnal infections result fatally, and while most are readily amenable to proper treatment and many are cured spontaneously, the fact remains that almost all of the pernicious malarial fevers are caused by the aestivo-autumnal plasmodia, and every case showing the presence in the blocd of these plasmodia should be considered as serious in nature and treated accordingly.

The old idea that pernicious malaria is due to a particular species of plasmodium has long ago been abandoned, and we now have upon record fatal cases of malaria due to all four species of plasmodia, although most fatal infections have been due to the tertian aestivo-autumnal parasite. In

my own experience this species has occurred most frequently in fatal infections, but the quotidian plasmodium occurs more frequently than either the benign tertian or the quartan plasmodia. The aestivo-autumnal plasmodia occurring in the blood in fatal infections differ in no way from those occurring in aestivo-autumnal infections in general, and it is probably the susceptibility of the patient and the number of the plasmodia present which determines the pernicious character of the attack rather than the species of aestivo-autumnal plasmodium present.

Some authorities have striven to establish a class of malarial infections characterized by long intervals between the paroxysms, the so-called "long-interval fevers," in which six, eight, or even ten days elapse between the attacks of fever. Such a classification is not consistent with what we know of the plasmodia causing the different types of malaria, and is undeserving of consideration. Such cases are simply relapses of a malarial infection, and are as apt to be due to the tertian or quartan plasmodium as to either of the aestivo-autumnal plasmodia. In rare instances a case is observed which apparently shows some such regularity, but the resemblance is only apparent, for an examination of the blood will demonstrate that the cycle of development of the plasmodium causing it is completed as usual, although clinical symptoms may be absent or atypical at certain times; in other words, the infection is *latent*.

Symptoms of Tertian Malarial Fever.—The paroxysms of fever in benign tertian malaria occur every forty-eight hours and are initiated by the sporulation of the tertian plasmodium or *Plasmodium vivax*. The time of the onset of the paroxysm can be accurately judged by the stage of growth of the organism as observed in the peripheral blood. The onset of the paroxysm always occurs during the segmentation of the plasmodium, and quotidian paroxysms are caused by double infections with the tertian plasmodium.

This, the most common and mildest form of malarial fever, occurs in both temperate and tropical countries, being the most common type in the temperate zones, and in certain localities in the tropics. Of 2,803 cases of malaria observed by myself in soldiers returning from the Philippines and from Cuba, 839 suffered from tertian malaria, of which 220 were double tertian infections. In Baltimore, of 542 cases of malaria observed by Thayer and Hewetson, 338 were tertian infections, while of 71 cases studied by Mannaberg in Vienna all but 10 were infected with this organism. In uncomplicated cases this type of malaria presents a typical temperature curve, showing in single infections a rise of temperature every second day; in double infections, a rise of temperature every day; while in infections with numerous groups of tertian plasmodia there may be a remittent or sub-continued temperature curve. In cases presenting quotidian paroxysms it is often possible to destroy one group of parasites by small doses of quinine, and when this is done the regular tertian paroxysm will reappear.

The paroxysm, when typical, is divided into three stages, chill, fever, and sweating. The *prodromal* symptoms are generally malaise, loss of appetite, and

more or less dull headache and slight aching in the extremities. After these symptoms have persisted for a few days (and during this period the plasmodia may often be observed in the peripheral blood in small numbers) the patient is seized with a severe chill, but although he feels extremely cold the temperature continues to rise, and at the acme of the chill has reached 103°, 104°, or even 106° F. The chill is immediately followed by a pronounced sense of heat, and in a short period of time the patient will complain as bitterly of this as he previously had of the cold. During the stage of fever, delirium may be present and there is generally severe headache. During the onset of the chill, nausea and vomiting are common, but they do not persist, as a rule, during the stage of fever. After the fever has lasted for a few hours, it rapidly declines to normal, accompanied by very severe sweating, the entire skin being bedewed with moisture, often so pronounced that the bed-clothing is saturated. The following detailed description is true of most tertian malarial paroxysms:

The Cold Stage or Chill.—As I have mentioned, there are generally some prodromal symptoms of the approaching malarial chill as evidenced by yawning, a general sense of discomfort, headache, and often nausea and vomiting. The feeling of cold usually commences at the feet and gradually progresses upward, although very often the first chilly sensations are felt along the spine. In tertian infections the chill is severe, the patient shaking very vigorously, but it is not so severe as in most quartan infections. In certain mild cases the chill may be absent, the patient complaining only of chilly sensations. The facial expression of the patient during the chill is one of cyanosis, the lips being blue and the skin bluish-red in color. The extremities are cyanotic and the skin presents the well-known condition characterized as "goose-flesh." The pulse is rapid, generally rather diminished in volume and often irregular. Headache is very often intense. During the chill the temperature rises very rapidly, reaching 104° F. or more in severe cases, but careful examination will demonstrate that the temperature had begun to rise before the onset of the chill. The urine is increased in quantity and decreased in specific gravity. The duration of this stage varies from an hour to two hours in the most serious cases.

The Hot Stage.—At the beginning of the hot stage the patient complains of flushes of heat, rapidly succeeded by cold sensations. Soon the sensations of cold are entirely lost and the patient complains bitterly of the intense heat due to the high temperature. The facial appearance is that of intense congestion, the conjunctivae being injected, and the entire surface of the body reddened, the congestion being especially marked in the hands. The pulse is full, bounding, and often dicrotic. The respirations are rapid and hurried, and there may be a slight cough due to congestion of the lungs. The headache increases and may be very intense and of a throbbing character.

In the mild tertian attacks there are no nervous symptoms present beyond a severe headache, but in the severe cases there may be marked delirium or a drowsy condition merging into semi-coma, or even coma. This condition

is almost always present in those rare cases of tertian fever which become pernicious.

The chief cymptoms complained of by the patient during the hot stage are the intense heat of the fever and the headache. The temperature may reach its highest point during this stage, but very often it is highest at the end of the cold stage. It is not uncommon during the hot stage to observe skin eruptions. Herpes is very frequently seen, especially about the lips, and urticaria and a general erythema not infrequently occur. These eruptions sometimes lead to a suspicion of some eruptive disease being the cause of the chill. Herpes of the penis may occur during the hot stage of the paroxysm or may develop later. The duration of this stage varies from four to six hours, but may be shorter or longer.

THE SWEATING STAGE.—As the fever begins to decline, it will be noticed that the perspiration appears first upon the forehead and face, and the patient at once begins to feel better, the decrease in the unpleasant symptoms being proportionate to the severity of the sweating. Commencing, as has been said, on the face, the perspiration rapidly involves the entire body and is often so severe that water may be seen trickling from the skin of the arms, thighs, and legs. The sweating stage lasts, as a rule, from two to three hours, at the end of which time the temperature has declined to normal, all of the unpleasant symptoms have disappeared, and the patient falls into a sleep which may last for several hours. As a rule, the temperature goes somewhat below normal and the decline, if rapid, as it often is, is accompanied by considerable weakness of the circulation, the pulse being slow and of low tension. In very rare cases this stage may be accompanied by collapse and death. During the sweating stage the urine may be increased in amount.

The average duration of the entire tertian paroxysm is from eleven to fourteen hours, but it should be remembered that there are paroxysms so slight as to be hardly recognized, especially in children, while, on the other hand, the length of the paroxysm may be prolonged to twenty-four hours. In young children the onset of the malarial paroxysm is often accompanied by convulsions. (Chart A.)

Physical examination of the patient will often show an enlarged and tender spleen, but this sign cannot be relied upon except in those cases which have had severe and repeated infections. An enlarged and tender spleen occurs too frequently in other acute infections to be of more than confirmative evidence in the diagnosis of malaria. Albuminuria is present in a considerable proportion of the cases of tertian infection. Of over 1,000 cases of tertian infection personally observed by the writer nearly 46 per cent. showed albumin in the urine, and it is probable that a careful examination of the urine in all such cases would result in showing a larger percentage than this. Hyaline and granular casts are found in the urine in the most severe cases, but not as frequently as in the aestivo-autumnal infections. Polyuria is very frequently observed immediately following the paroxysm, and it may persist for days and even weeks.

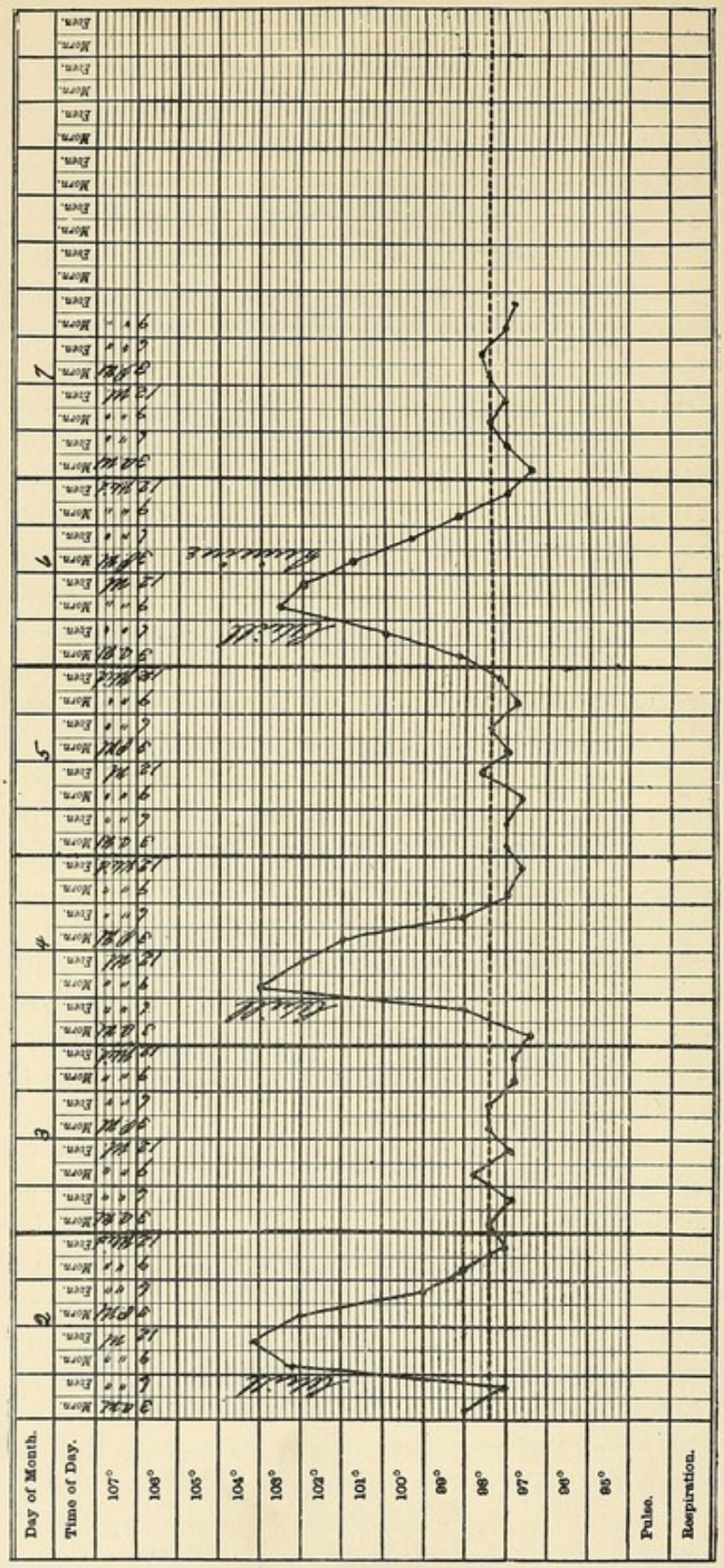

CHART A.—Tertian Malarial Fever.

Symptoms of Quartan Malarial Fever.—The symptoms of quartan malarial infection are very similar to those of tertian infections, although they are generally more severe in character.

Frequency of Quartan Infections.—This is the most rare form of malarial infection, being absent in many malarial localities, and occurring very rarely in others, while in some regions it is the prevailing type of infection. It is probably most common in temperate regions, but is not infrequently observed in the tropics together with aestivo-autumnal infections. The following table illustrates the relative frequency of this type as observed in different localities:

Observer.	No. of cases observed.	Quartan infections.
Maillot, in Algeria,	2338	26
Finot, in Blida,	4211	21
Laveran, in Algiers,	311	7
Thayer and Hewetson, in Baltimore, U. S. A.,	1680	15
Griesinger, in Tübingen,	414	3
Mannaberg, in Vienna,	144	8

In my own experience, comprising over 5,000 cases of malaria in which the plasmodia were demonstrated in the blood, only 26 cases of quartan infection were observed. Practically all of the cases were in soldiers returning from the Philippines and from Cuba, where they had contracted their infection. The percentage of quartan infection in the Philippine Islands is higher, however, than in many other tropical countries, as is shown by the fact that Koch only observed one case of this infection in tropical Africa and Zieman reports its absence from Kamerun, while I observed 18 cases in the Philippines in the course of about twelve months. In certain regions in Italy this type of infection is the prevailing one, tertian and aestivo-autumnal infections being almost unknown.

In most localities in the temperate zones quartan infections occur most frequently in the late summer and during the autumn months, but in the tropics they occur at more irregular intervals which vary with the time of the rainy season, these infections appearing several weeks after the cessation of the rains or, in other words, toward the latter part of the malarial season.

The Symptoms.—The paroxysms of quartan malaria are characterized by their regularity in uncomplicated infections, the febrile attacks occurring at the end of every 72 hours, but, here again, we may have double infections, in which the attacks occur upon two days in succession, with an afebrile day interposed, or triple infections, in which the attacks occur daily. Double and triple infections are comparatively rare. Mannaberg saw two cases of double quartan, and Thayer and Hewetson three cases of triple quartan. I have never seen a triple quartan infection and only one double infection. Irregular and sub-continued quartan infections are rarely observed, though such cases have been described by Antolisei and Feletti.

As in tertian infections the febrile paroxysm in quartan malaria corresponds with the sporulation of the quartan parasite, of *Plasmodium malariae*, and the time of the occurrence of the paroxysm may be accurately foretold by the stage of the development of the plasmodia in the peripheral blood.

The symptoms observed during a quartan paroxysm are so similar to those already described in tertian infections that a detailed account of them is not necessary. There are the same stages of chill, fever, and sweating as are seen in the tertian infections, but, as a rule, the symptoms are more severe and pernicious attacks are more common. The nervous symptoms especially are apt to be more pronounced, and slight delirium is very common. (Chart B.)

The quartan paroxysm is not as prolonged as is the tertian, lasting from eight to ten hours, but the attacks may be shorter than this or may extend over twenty-four hours. I have never observed a quartan infection in which the paroxysm lasted over 12 hours.

During the fall in temperature collapse symptoms may develop, and the temperature generally falls considerably below normal, and may remain so during the apyrexial period and for some weeks after recovery. In both tertian and quartan malaria the paroxysms are most apt to occur during the day, usually during the afternoon or late morning, but in both forms of infection the paroxysms may occur during the night. In cases of double or triple infection the febrile periods are apt to be irregular in the time of occurrence, the chill appearing one day in the afternoon and, perhaps, the next day in the morning.

Aestivo-autumnal Malaria.—The aestivo-autumnal malarial infections are caused by two distinct plasmodia, one completing its cycle of development in the human body in 24 hours and the other in 48 hours. The symptoms of the two infections differ greatly, especially the temperature, and in uncomplicated cases the tertian aestivo-autumnal infections may be diagnosed by the temperature curve alone. Either of the aestivo-autumnal plasmodia is capable of causing pernicious symptoms, but personal observations appear to show that the tertian species is the one most commonly concerned, about 75 per cent. of the pernicious cases I have observed being due to this plasmodium.

The aestivo-autumnal infections have long been distinguished by the term "remittent fevers," it being supposed that in these infections the temperature curve, instead of presenting the marked intermittency observed in tertian and quartan fevers, was remittent or irregular in character. This is not always so, however, for these fevers, when uncomplicated or uninfluenced by quinine, are as truly intermittent as are the tertian and quartan infections. It is undeniable that remittency and irregularities in the temperature curve are more common in the aestivo-autumnal fevers, but too much stress should not be laid upon this point in diagnosis.

Frequency of Occurrence.—The aestivo-autumnal infections are essentially tropical malarial infections, and it is to these forms of malaria that the

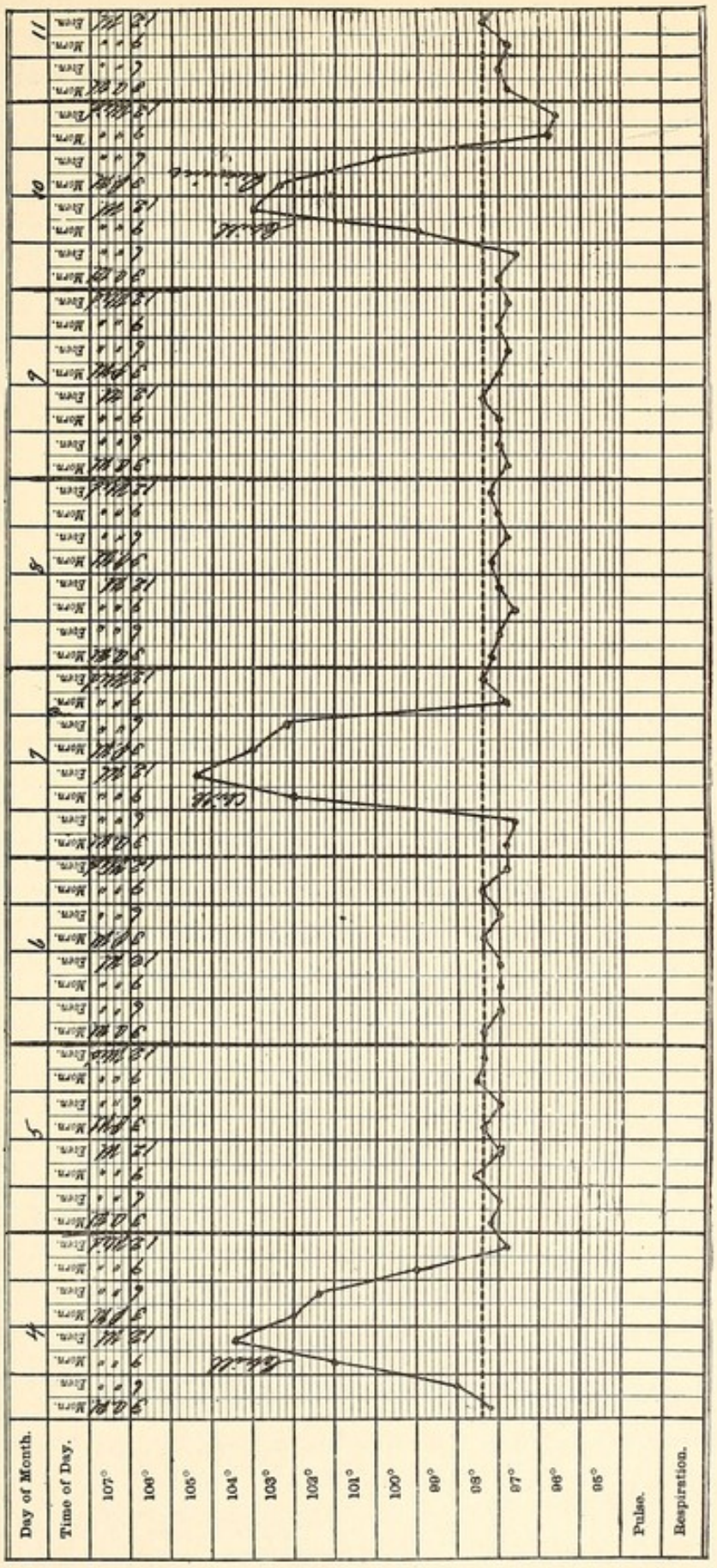

CHART B.—Quartan Malarial Fever.

term "tropical malaria" is applied by some writers. As aestivo-autumnal malaria occurs also in temperature climates, and does not differ in its symptoms from the same infection occurring in the tropics, the term "tropical malaria" should be abandoned if by it we mean a form of malaria peculiar to the tropics. It is true that in the tropics these infections are more apt to become pernicious, but this fact is not due to any difference in the plasmodia, but to the debilitated condition of the patient brought about by the tropical climate and by other factors, such as repeated infection, infection with a great number of plasmodia, and, in the case of soldiers, by exposure and overexertion beneath a tropical sun, followed by the chilling of the cool tropical evenings.

The relative frequency of the occurrence of aestivo-autumnal infections varies very greatly in different localities. In the temperate zones these infections are rare, but in the tropics they comprise the great bulk of malarial disease, but even in the tropics they are much more frequent in some localities than in others. At Camp Stotsenburg in the island of Luzon, there occurred from three to four cases of aestivo-autumnal infection to one of tertian, but at Camp Gregg, only forty miles from Stotsenburg, the prevailing type of infection was the benign tertian.

The occurrence of many cases of tertian infection in certain localities in the Philippine Islands led to the report that aestivo-autumnal malaria was infrequent there, but a more careful study of the subject has demonstrated that the Philippines are not an exception to the great rule that in the tropics the aestivo-autumnal infections are the prevailing type. In 2,000 cases of malaria in soldiers returning from the Philippines and in natives of those islands, in which the plasmodia were demonstrated in the blood, no less than 1,662 were infected with the aestivo-autumnal plasmodia. These personal observations are confirmed by those of Jackson, Chamberlain, and others, so that we may state positively that the prevailing types of malarial fever in the Philippine Islands are the aestivo-autumnal.

The tertian aestivo-autumnal infections occur very much more frequently than do the quotidian infections, the latter type being comparatively rare. Thus of 1,662 aestivo-autumnal infections, personally observed, 1,473 were due to the tertian aestivo-autumnal plasmodium and only 189 to the quotidian aestivo-autumnal plasmodium.

The aestivo-autumnal infections occur most frequently in temperate regions during the months of July, August, September, and October, but in the tropics they persist throughout the year, although they are most numerous during the latter portion of the rainy season and at the beginning of the dry season.

In describing the symptoms of the aestivo-autumnal infections I shall mention here only those observed in ordinary attacks, leaving the description of the symptoms of pernicious attacks for a succeeding chapter. The symptoms of this group of malarial fevers are very apt to be atypical and the descriptions which follow apply only to the fevers as usually observed.

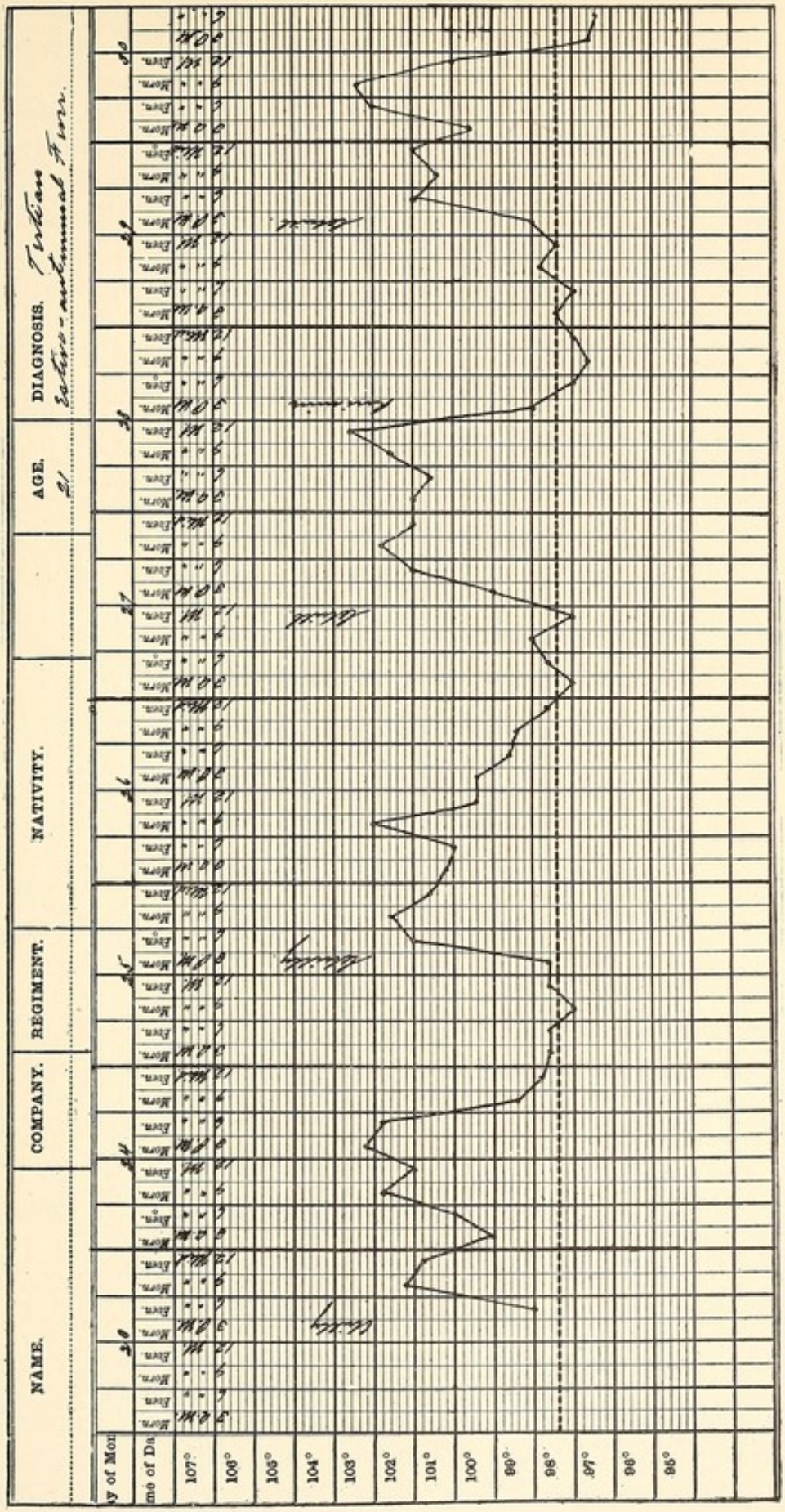

CHART 1.—Typical Temperature Curve of Tertian Aestivo-autumnal Malarial Fever.

Symptoms of Tertian Aestivo-autumnal Malaria (Non-pernicious Type).—Patients suffering from this type of malaria will generally present the following symptoms:

PRODROMAL.—The prodromal symptoms are loss of appetite, slight headache, evanescent pains in the back and legs, nervousness, increased urination, and a general feeling of malaise. In some instances the onset is sudden, the patient having felt well until the appearance of marked symptoms. As in tertian and quartan infections, three stages may be distinguished. The paroxysms occur every forty-eight hours and correspond in time with the sporulation of *Plasmodium falciparum*.

THE COLD STAGE OR "CHILL."—This is generally initiated by yawning and the patient complains of headache, slight nausea, perhaps accompanied by vomiting, and often intense nervousness. In a majority of the cases there are no distinct chills, but the patient complains of chilly "creeping" sensations along the spinal column and slight flushings of cold especially noticeable along the posterior aspect of the buttocks and thighs. At the same time the headache increases, there is present a feeling of extreme weakness, and generally profound mental depression, sometimes so great as to be the most prominent symptom. The skin presents the appearance of "goose-flesh," and it and the mucous membranes are cyanosed; the extremities are cool and feel heavy to the patient. There is severe pain and aching in the legs and back, greatest, as a rule, in the lumbar region. The pulse is generally weak and increased in frequency and may be very irregular. The respirations are rapid and rather shallow. The tongue is broad and flabby and heavily coated. During this stage the temperature gradually rises and may reach 103° F. or more. This portion of the attack does not last over half an hour in the majority of the cases, and the patient seldom shakes with the chill as in tertian and quartan infections.

THE HOT STAGE.—Gradually the patient experiences a sensation of heat, coming first as localized flushings, but soon becoming general. The facial appearance is that common to fever, the eyes being suffused and brilliant, the face red, and the skin dry and hot. Headache is intense and there is present either great mental depression or nervous excitement. The pain in the back and limbs is often agonizing in character, and in some instances there is severe pain over the abdomen, either over the spleen or in the right iliac region. The temperature is elevated and in uncomplicated cases very characteristic. Nausea and vomiting are frequently present, the vomiting sometimes being very severe. Diarrhoea is a common complication. The urine is increased in quantity and is generally albuminous. The pulse is rapid and dicrotic in character, the respirations rapid, and there may be severe dyspnoea.

THE SWEATING STAGE OR STAGE OF REMISSION.—The hot stage continues for several hours (sixteen to eighteen or twenty) and is followed by the falling of the temperature accompanied by more or less sweating. During the latter stage the symptoms gradually decline in severity and finally disappear, the

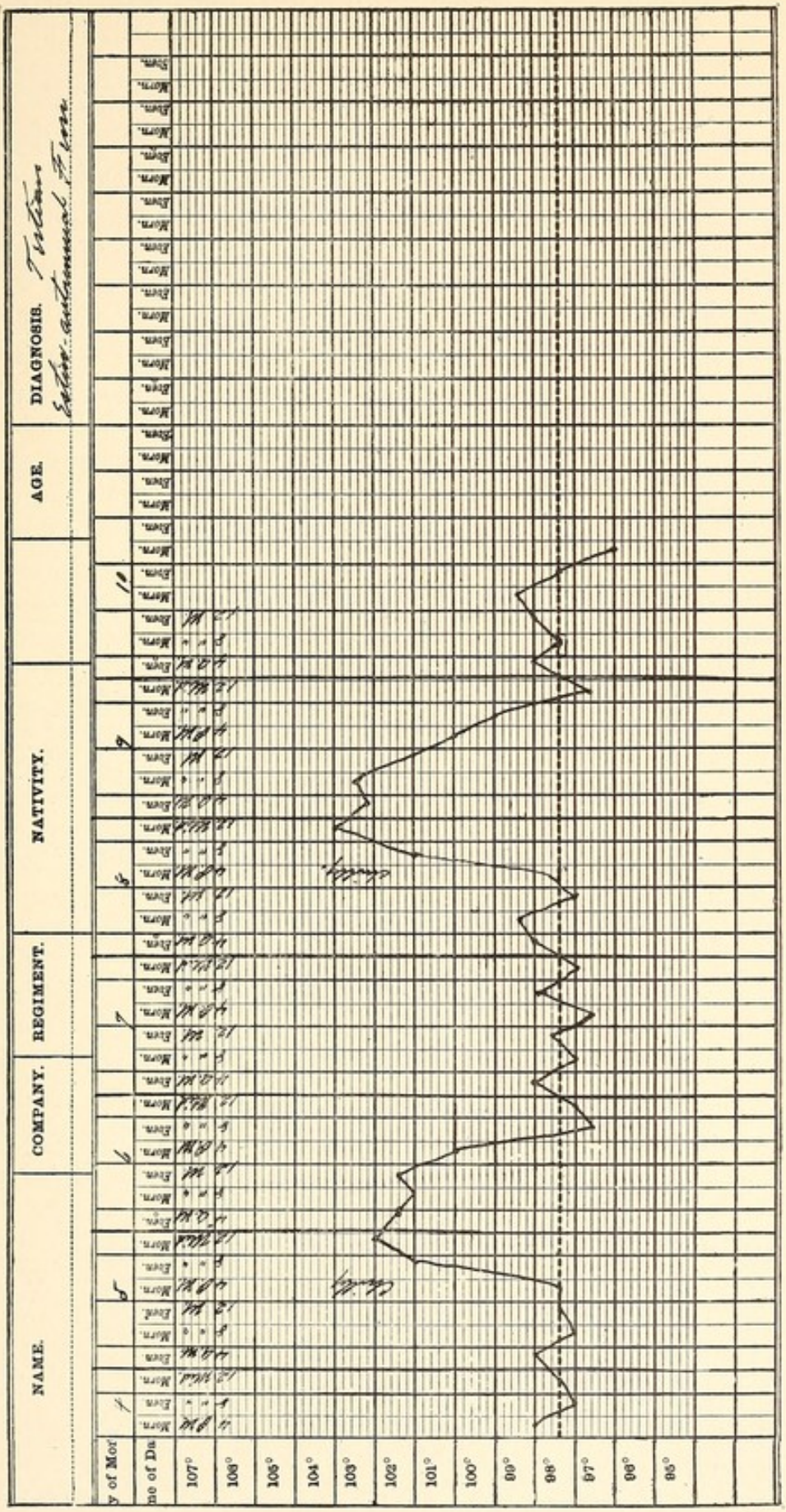

CHART 2.—Tertian Aestivo-autumnal Malarial Fever, showing short duration of the paroxysm.

temperature going a degree or a degree and a half below normal. A slight sweating is generally observed, but it is not nearly so marked as in tertian and quartan infections.

The period of normal temperature or intermission may last only two or three hours, when another paroxysm ensues. As a rule, attacks of this fever occur toward evening, extend throughout the next day, and subside during the first hours of the third day, the entire paroxysm thus lasting thirty-six hours or more and occurring every 48 hours. While the symptoms described are often more severe in this type of malaria than they are in tertian and quartan infections, there is nothing diagnostic about them except the curve exhibited by the temperature. In uncomplicated cases the behavior of the temperature is absolutely characteristic, and the temperature curve is one that is not met with in any other disease. This peculiarity of tertian aestivo-autumnal infections was first pointed out by Marchiafava and Bignami, and the writer has been able to confirm their observations in every uncomplicated case of such infection. At the onset of the fever the temperature rises suddenly to 103° or 104° F. Following the sudden rise there occur slight oscillations which cover several hours, during which time the temperature falls from one-half to one degree. This period of slight oscillation is followed by a distinct fall or pseudocrisis, the temperature dropping from one and a half to two or even three degrees. This fall in the temperature is often considered by the physician as the true crisis of the paroxysm; on the contrary, however, the fever again rises to a point higher than that before attained and then falls rapidly. This peculiar temperature curve can be divided into five stages: (1) the initial rise; (2) the period of slight remissions; (3) the pseudocrisis; (4) the precritical rise; (5) the true crisis. Another point of value in diagnosis between this type of fever and the benign tertian and quartan types is the length of the febrile period. This varies, but generally the temperature remains elevated over 24 hours, and often from 38 to 40; in other words, the paroxysm really covers two days, while the period of intermission is very short. (Chart 1.)

Symptoms of Quotidian Aestivo-autumnal Malaria.—The quotidian aestivo-autumnal fever is characterized by a febrile paroxysm occurring every twenty-four hours, corresponding to the sporulation of *Plasmodium falciparum quotidianum*. Otherwise it varies but slightly in its symptomatology from the tertian type. As in the latter form, the three stages described may generally be observed, but in the quotidian type the chilly sensations are more severe and there is often a distinct chill. Sweating is also more pronounced, but is not so marked as in the simple tertian and quartan fevers. The temperature curve is entirely different. It consists in the abrupt rise of the temperature to 103° F. or more, succeeded by as abrupt a fall. The attack lasts, as a rule, only about eight or ten hours. The temperature curve seldom remains regular for long at a time, for the attacks tend to run into one another, thus giving rise to more or less continuous fever. This is especially true of the pernicious attacks. (Chart 5.)

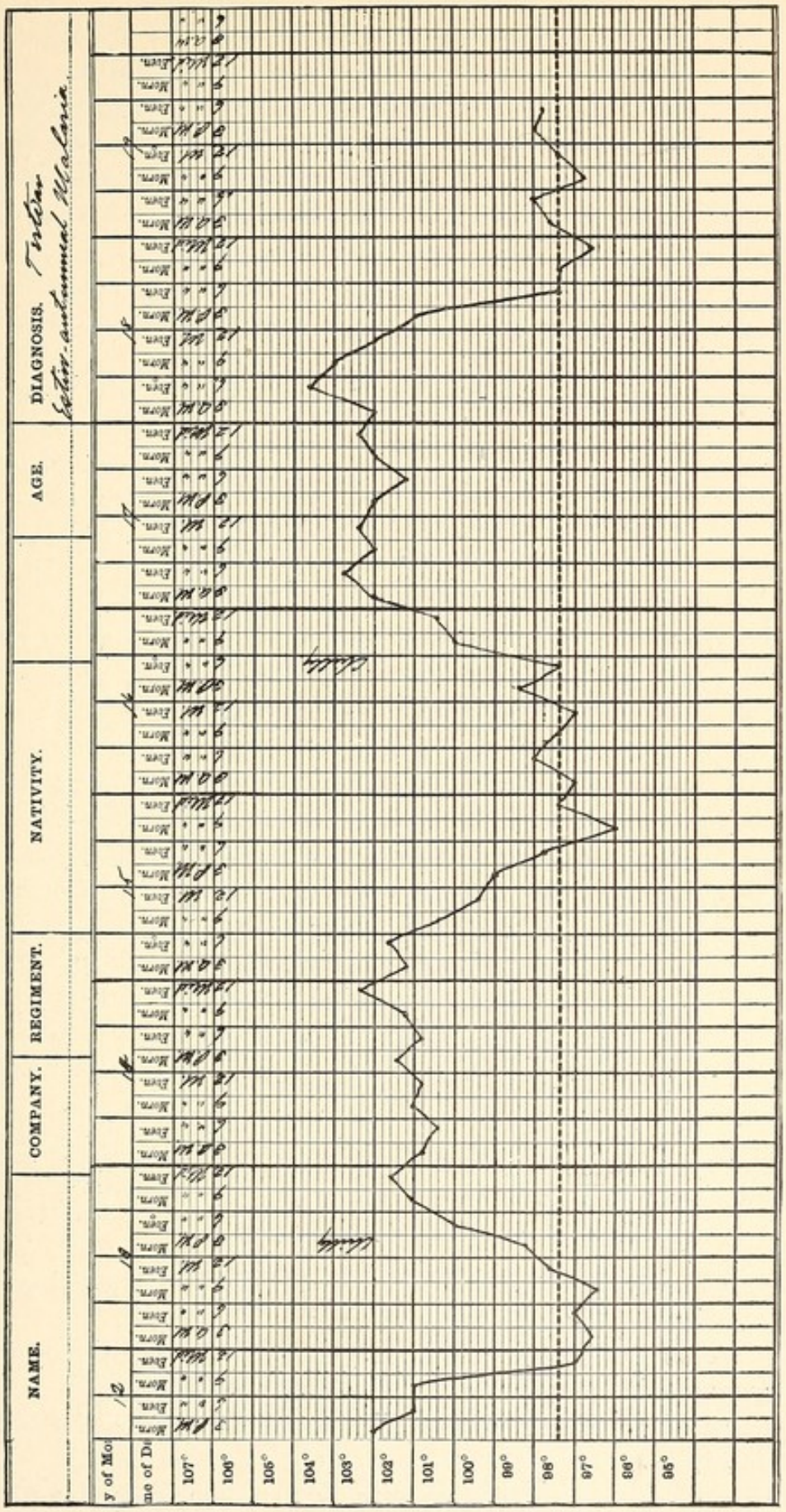

CHART 3.—Tertian Aestivo-autumnal Malarial Fever, showing long stage of slight remissions.

To one who has studied aestivo-autumnal malarial infections in regions where they are endemic and who has been so fortuate as to observe such infections uninfluenced by treatment or other complicating factors, the great difference in the temperature curves of the tertian and quotidian type is alone sufficient to distinguish them, and when we add to this difference the variation in the morphology and developmental history of the two plasmodia concerned, we must admit that aestivo-autumnal malaria is caused by two species of plasmodia, as first described by Marchiafava and Bignami.

Analysis of the Symptoms of Malarial Infections.—It will be of interest and value to consider more in detail the symptoms observed in the various types of malarial infection.

The Temperature Curves.—I have already spoken of the temperature curves exhibited by malarial infections, and, while in uncomplicated cases a diagnosis of the type of infection might be arrived at from a study of the temperature alone, there are so many variations from the typical temperature in all forms of malarial infection that it is seldom safe to depend upon this symptom in making a diagnosis. The curves presented in single benign tertian and in quartan malaria are characteristic, the febrile paroxysm in the one occurring at the end of every 48 hours, in the other at the end of every 72 hours, but in double or triple infections or in mixed infections, the temperature curve may be so altered as to be of no service in diagnosis. In the tertian aestivo-autumnal cases the temperature curve is very characteristic in uncomplicated cases, but many cases occur in which the curve is so altered as to be unrecognizable. In a large proportion of tertian aestivo-autumnal cases, the characteristic temperature curve already described will be observed, but there are many deviations from the classical type. These deviations, in all forms of malaria, are due to several factors, among the most important of which are the following: improper medication with quinine; double infections or infections with more than one species of the malarial plasmodium; anticipation of the attacks, especially common in the pernicious fevers; retardation of the attacks; slight elevations of temperature between the attacks, and complication with some other disease.

The most beautifully typical malarial temperature curve may be rendered atypical and very confusing by the administration of small doses of quinine at irregular intervals, and this is one of the most common causes of irregularity in the curve.

The most important alterations in the tertian aestivo-autumnal temperature curve produced by the factors enumerated are:

1. A curve almost identical with that of the benign tertian, produced by the short duration of the paroxysm. (Chart No. 2.)

2. A curve characterized by a long period of slight remissions, due to prolongation of the paroxysms. (Chart No. 3.)

3. A curve showing no well-marked initial elevation of the temperature, thus causing a more or less continuous fever line.

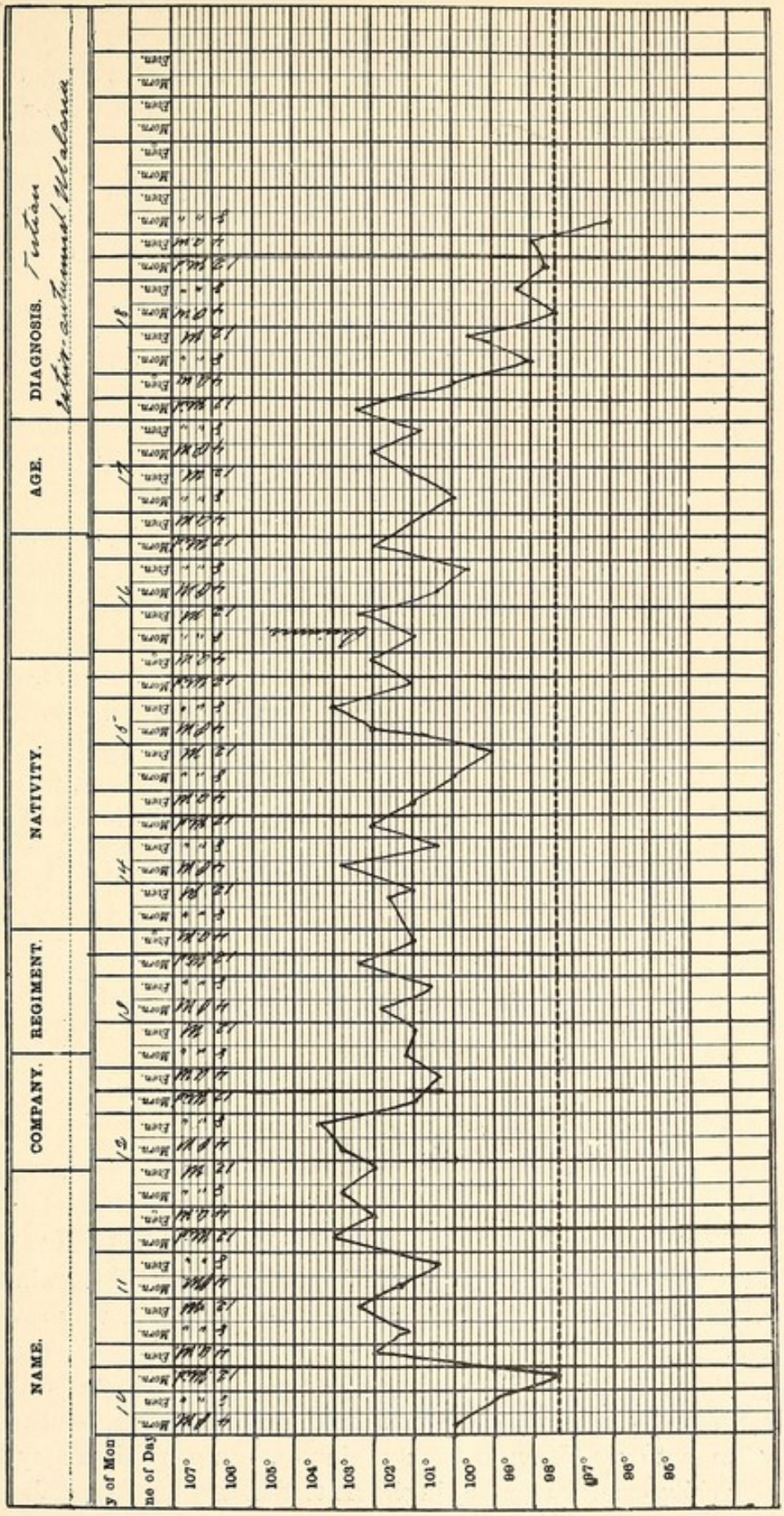

CHART 4.—Tertian Aestivo-autumnal Malarial Fever, showing continuous temperature curve.

4. A continuous curve showing only slight remissions, due to overlapping of the paroxysms. (Chart No. 4.)

5. A curve showing a very marked pseudocrisis, thus causing the fever line to resemble that of a double tertian or quotidian aestivo-autumnal infection.

6. A curve in which the five stages described are reversed.

Besides these modifications there occur many which are so complex that it becomes impossible to recognize the disease with which we are dealing without a microscopical examination of the blood.

In the aestivo-autumnal fevers a temperature chart which shows only the morning and evening temperature is worse than useless as a guide in study or diagnosis, and the use of a chart showing the temperature every three or four hours is imperative. To secure the most typical temperature curve the chart should be a three-hourly one, and only by the use of such a chart can the peculiar curve of tertian aestivo-autumnal malaria be demonstrated.

In the *quotidian* form of aestivo-autumnal malaria the temperature curve is not very characteristic. The temperature rises quickly and falls as quickly, the entire attack lasting, as a rule, about eight hours, but sometimes longer, while in the typical form the temperature, during the crisis, falls considerably below normal. This is a very marked peculiarity of the quotidian form, and in no other disease does the temperature fall so far below normal without a fatal result to the patient. I have seen many cases in which the temperature fell to 95° F. during the crisis, and several in which it fell even lower, without any symptoms of collapse developing. As the curve in this form of aestivo-autumnal infection resembles so closely that of a double tertian infection, we are forced to depend upon the microscope in order to exclude the latter, and there is no greater proof of the value of a microscopical examination of the blood than is found in the ease with which the various forms of malarial fever may be diagnosed and differentiated by it, and such an examination is often instrumental in saving life.

The Chills.—In benign tertian and in quartan infection the chills are pronounced in the vast majority of instances, although very rarely such infections are observed in which the patients complain only of chilly sensations. In the aestivo-autumnal infections, however, the chill is slight or almost absent, especially in the tertian form. In the majority of cases the patients simply complain of chilly sensations along the spinal column and seldom shake with the chill. In the quotidian infections the chill is more pronounced than in the tertian form, and in both occur cases in which the chill may be very severe and exhausting. There are also many cases in which the chill is so slight as not to attract the attention of the patient. As a rule, the chilly sensations or the chill do not last over three-quarters of an hour, and in the aestivo-autumnal infections often not over fifteen to twenty minutes. In general, it may be said that shaking chills occur commonly in simple tertian and quartan malaria, very rarely in aestivo-autumnal infections.

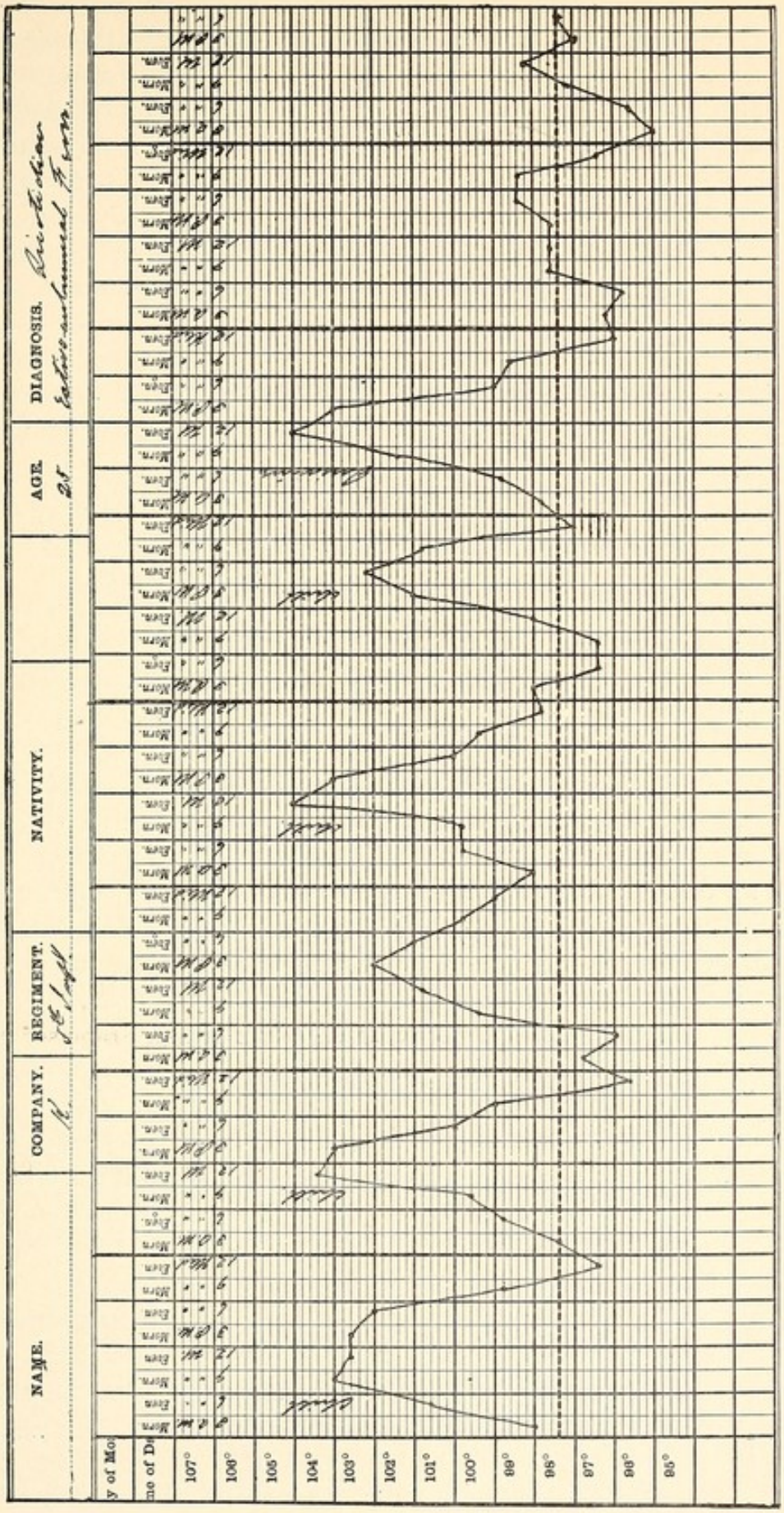

CHART 5.—Typical Temperature Curve of Quotidian Aestivo-autumnal Malarial Fever.

THE SWEATING.—In simple tertian and quartan infections the sweating which occurs during the decline of the febrile paroxysm is generally profuse and sometimes very exhausting. In these cases the entire skin is covered with perspiration, often so great in quantity that the water may be seen trickling down the trunk and limbs, saturating the bed-clothing. In the tertian aestivo-autumnal infection the sweating is not excessive, and is often so slight as not to attract attention. In the quotidian form the sweating is generally more severe, but not, as a rule, so marked as in the simple tertian or quartan infections. In both forms of aestivo-autumnal fever, however, the sweating stage may be prolonged and exhausting.

FACIAL APPEARANCE.—In primary acute attacks of all forms of malaria the face is flushed or congested, the eyes suffused and brilliant, while an anxious expression is often present and the patient looks very sick. Exceptions to this rule are observed in which the face is pale and the patient appears indifferent or even cheerful. In cases which have suffered from relapses the face is usually brownish-yellow in color, slightly flushed and haggard looking.

THE SKIN.—In primary acute attacks of malaria there is no alteration in the color of the skin, but in the majority of patients who have suffered from relapses, especially of the aestivo-autumnal fevers, the skin assumes a grayish or yellowish hue and appears very anaemic. In some aestivo-autumnal infections, notably the so called "bilious remittent fever," the skin may be markedly *jaundiced*, so much so as to suggest yellow fever.

During acute attacks of all of the malarial fevers various skin eruptions may make their appearance, especially *urticarial* eruptions, which I have observed often in aestivo-autumnal fever. *Herpes* of the lips is a very common symptom in some localities and in some infections, but is not as common in all localities as has been supposed. Thus F. Plehn, in Africa, observed herpes only once in 714 cases of malaria, and my own experience in the Philippines is corrobative of that of this observer. Of over 500 cases of malaria observed in Luzon, P. I., I saw only about 10 cases in which herpes occurred, while at San Francisco and in Cuba this condition was much more common, although all of the cases observed at San Francisco were in the person of soldiers returning from the Philippines and who had contracted their malaria in those islands. It would thus appear that locality has much to do with the frequency of the occurrence of this symptom. Herpes of the nostrils is not uncommon, and in several cases of aestivo-autumnal malarial I have observed herpes of the penis occurring with or immediately after a paroxysm of fever.

Peeling of the skin is sometimes observed in aestivo-autumnal infections, occurring during an acute attack. I remember such a case in which the peeling was very extensive, portions of the epidermis several centimeters in diameter being thrown off.

THE MOUTH AND TONGUE.—The mouth, during the paroxysms, is dry, the tongue thickly coated with a dirty white or brownish fur, and either broad and flat or pointed and narrow. In severe cases of aestivo-autumnal fever the

tongue is dry and coated with a thick brown fur, while in pernicious cases sordes may form upon the lips and teeth as in typhoid fever.

Symptoms Connected with the Circulatory System.—The organs of circulation are generally but slightly affected during a malarial paroxysm. The *heart sounds* are usually clear, but often a slight systolic murmur may be heard over the mitral region. In many instances, however, the heart sounds are muffled or the second sound is increased in volume. During the chill, especially if it be severe, (and, therefore, more commonly in the simple tertian and quartan infections than in the aestivo-autumnal), the *pulse* is weak and rapid; during the stage of fever it is full, easily compressible, and often remarkably dicrotic. It is increased in frequency, averaging from 120 to 140 beats per minute. During the decline of the fever the pulse is full in volume and dicrotic, while it is decreased in frequency. Sometimes there is present a marked *bradycardia*. In not a few cases of aestivo-autumnal infection the pulse will be found intermittent and sometimes alarmingly irregular, and I have observed instances in which the first symptom of the malarial paroxysm consisted in temporary failure of the heart's action. In many cases the patient complains of a dull or acute precardial pain. The area of heart dullness is not altered in uncomplicated cases.

Symptoms Connected with the Respiratory System.—The respirations are always increased in frequency during an acute attack of any of the malarial fevers, and in severe cases often appear to be slightly labored. This condition is due to the greater or lesser amount of congestion present in the lungs and the high temperature. *Dyspnoea* is present in some of the more severe infections, and *acute bronchitis*, of mild character, is a very common symptom during acute attacks of aestivo-autumnal fever. In rare instances symptoms indistinguishable from those of *pneumonia* may appear, accompanied by a limited amount of blood-stained sputum.

Physical examination of the lungs may show slight areas of lessened resonance and a few râles, chiefly sibilant in character. Moist râles are sometimes heard. The physical signs of an acute bronchitis are often demonstrable.

Symptoms Connected with the Digestive System.—In all cases of malaria there is loss of the appetite, often observable for days before the onset of the febrile paroxysm. A feeling of oppression in the stomach or actual pain in that region are common symptoms during the paroxysm and sometimes for days afterward. *Nausea* is a very common symptom in all forms of malarial infection, whether acute or chronic, occurring in fully 90 per cent. of all cases, and this symptom is often very distressing and exhausting. *Vomiting* occurs in a large proportion of all cases and in some instances is so severe and persistent as to endanger the patient's life. *Diarrhoea* is another common symptom, occurring during the paroxysm or immediately afterward, and rarely may be of serious import. *Constipation* is more commonly observed, however, and may be present for days before the onset of the fever.

Pain over the stomach and abdomen is not infrequently met with and has

been the cause of many mistaken diagnoses. I have repeatedly seen cases of malaria with severe pain in the region of the appendix diagnosed as appendicitis, and in more than one instance the microscope saved the patient an operation. In some cases there is general pain over the abdomen simulating very closely that of a general peritonitis. I have observed instances in which the abdominal pain was agonizing in character, and controlled only by large doses of morphine.

Symptoms Connected with the Glandular System.—Enlargement of the *spleen* during an acute initial attack of malaria is by no means constant. While there can be no doubt but that the organ is enlarged slightly in all acute infections, the enlargement in many cases is not demonstrable, and a very large proportion of the cases do not present a palpable spleen. In cases, however, which have suffered from malarial infection for a considerable period of time, and in which there have been many relapses, the splenic enlargement is generally noticeable, the organ being plainly palpable, and often extending nearly to the umbilicus or perhaps beyond it. Laveran claims that every case of malaria shows an enlargement of the spleen, while Kelsch and Kiener, A. Plehn, and others state that this organ is often not enlarged. It is probable that much of the confusion regarding this matter is due to lack of accuracy in making the physical examination and in clearly defining the method of examination. Thus in many cases careful percussion will show enlargement of the organ, although it may not be palpable. From my own experience I have learned that palpable enlargement is much less common than has hitherto been supposed, but that in almost every case the organ will be found enlarged upon percussion. Mannaberg claims that in 88 per cent. of cases suffering from malaria, the spleen is palpable, while in the remaining 12 per cent. it is enlarged to percussion.

The spleen is palpable in aestivo-autumnal malaria more frequently than in simple tertian or quartan infections, because the aestivo-autumnal infections are more resistant to treatment and more prone to relapse. In recent infections the organ is soft and rounded and very tender upon pressure, while in old infections it is hard and presents a well-defined, rather sharp margin.

In acute infections the *liver* is often slightly enlarged and tender, especially in cases which have suffered from numerous relapses.

Symptoms Connected with the Urinary System.—In many cases of malaria *polyuria* is a prominent symptom, occurring before, during, or after a paroxysm. *Pain* in the lumbar region, over the kidneys, is a very common symptom, and direct pressure upon these organs is sometimes exquisitely painful. In a large proportion of the cases, however, the lumbar pain is not referable to the kidneys.

Symptoms Connected with the Nervous System.—While symptoms referable to the nervous system occur in all forms of malaria, it is in the aestivo-autumnal fevers that they are most frequent and most important. The malarial toxin appears to have a marked affinity for the tissues of the nervous

system and its action upon the vasomotor centers is well illustrated in the phenomena of the malarial paroxysm, *i.e.*, chill, fever and sweating. *Delirium* occurs in a fairly large percentage of cases of aestivo-autumnal malaria, and in severe tertian and quartan cases, and is usually of a mild, quiet type; active maniacal delirium is sometimes observed. *Headache* occurs in practically every case and is very often severe and most distressing. It is usually referred to the forehead and occiput, and persists throughout the paroxysm, and often in the afebrile interval. Soreness of the scalp is often complained of after the paroxysm. *Stupor* is a common accompaniment of the more severe forms of all the malarial fevers, and *coma* is common in pernicious cases. *Vertigo* and *tinnitus aurium* are common and annoying symptoms. Patients suffering from the aestivo-autumnal infections are often extremely nervous, both during and between the paroxysms, and not infrequently this condition deepens into a mild form of melancholia; such cases should be carefully watched, as suicidal tendencies are apt to develop.

Pain in the back and limbs is always present during acute attacks of malaria, and may be very severe, and is always one of the most disagreeable things the patient is called upon to bear.

The more severe nervous symptoms occasionally observed in severe malarial attacks, such as aphasia, paraplegia, hemiphegia, epileptiform convulsions, and mania will be considered in the chapter dealing with the complications of malaria.

Examination of the Blood.—I have already noted and described the blood changes occurring during malarial infection, and will consider here the blood findings as regards the plasmodia during the clinical periods of the fevers.

Simple Tertian Malaria.—During the febrile paroxysm an examination of the blood will show the presence of: 1. Sporulating plasmodia. 2. Fully developed pigmented intracellular plasmodia. 3. Young hyaline ring-forms. Examined at various hours during the afebrile period, the plasmodia may be followed in development from the unpigmented and slightly pigmented organism, filling only a portion of the infected cell, to the fully grown plasmodium, containing much pigment and filling and distending the infected red corpuscle. An hour or two before the onset of the paroxysm, the blood contains only fully developed forms and sporulating bodies.

In double infections all stages of the plasmodium can be found at the same time.

Quartan Malaria.—An examination of the blood in quartan malaria gives the same results as in simple tertian as regards the stage of development of the plasmodium.

Tertian Aestivo-autumnal Malaria.—During the febrile period, an examination of the peripheral blood shows the small, more or less amoeboid, hyaline, intracorpuscular plasmodia, from one-tenth to one-sixth the size of the red corpuscle.

During the afebrile stage the young pigmented forms are found in the peripheral blood.

Before the onset of a paroxysm the pigmented forms are more numerous and have attained their largest size, about one-fourth that of the infected red cell.

At the commencement of a paroxysm the plasmodia are generally remarkably few in number in the peripheral blood, but the young unpigmented forms appear about at the acme of the fever.

In this form of malarial infection it is but very rarely that sporulating forms are found in the peripheral blood, but blood secured by puncture of the spleen at the time of the paroxysm will show multitudes of these bodies.

Quotidian Aestivo-autumnal Malaria.—The examination of the blood in cases of quotidian aestivo-autumnal malaria gives results substantially the same as those obtained in the tertian type as given above, so far as the time of appearance of the plasmodia in the peripheral blood is concerned, so that it is unnecessary to describe them separately.

In mixed infections and in irregular aestivo-autumnal infections the examination of the blood will show the presence of the plasmodia concerned, but it is difficult in such cases to trace the cycle of development of the parasites of any one group.

Malaria in Children.—Because malarial infections in children present important differences in their symptomatology from the same infections occurring in adults, it is necessary that we should speak of such infections somewhat *in extenso*.

Frequency.—It has already been mentioned that in malarial localities the children suffer much more severely than do the adults, and that malaria tends to disappear with increasing years. It is not necessary here to recapitulate the evidence collected upon this point which has been given in a preceding chapter but the important point should be remembered that in children malaria is very often *latent* and that in malarial localities the children furnish almost all of the pernicious cases. The infantile mortality from malaria in the tropics is enormous and very largely preventable.

The *symptoms* of malarial infection in young children are so slight in many instances that for days and even weeks such an infection may be present without attracting attention. In the Philippines I have often seen children playing about the streets with a temperature of 100° to 101° F. and their blood swarming with plasmodia. In young children the onset of a malarial paroxysm is often marked by convulsions and the nervous symptoms are pronounced throughout the attack. In other cases the onset is preceded by yawning and drowsiness, or by severe headache. The chill is frequently absent or very slight, but the hot stage is marked, the temperature prolonged, and the sweating very slight or entirely absent. In many cases the only symptom of importance is the fever which may be almost continuous or very irregular, lasting from a few hours to several days. Spontaneous recovery is common and relapses are frequent.

Enlargement of the spleen is not apparent in more than half of the cases. Pain in the stomach is a common symptom in children and vomiting and diarrhoea occur very frequently. In certain cases a fatal diarrhoea may occur, and convulsions and coma are common in pernicious cases. In children over three years of age the symptoms are more like those occurring in the adult, and the diagnosis is more easily made in older children.

It is obvious that, in malarial localities especially, the diagnosis of these infections in children is of the very greatest importance from both a prophylactic and therapeutic standpoint. The atypical character of the symptoms renders a clinical diagnosis difficult, and in many instances impossible, and we have to depend upon the microscope in arriving at a diagnosis. In every malarial locality the blood of all the children should be examined and this procedure should be as much a part of the sanitary police of a locality as the proper disposal of sewage or the care of the water supply, for it will thus be possible to distinguish those infected with malaria and to institute proper measures for prevention and cure of the disease. It is not too much to expect that the enforcement of such a measure in badly infected localities will in time render them practically free from malaria.

CHAPTER II.

Clinical Illustrations of the Tertian and Quotidian Aestivo-autumnal Malarial Fevers.

Because of their interest and importance I have selected for description in this chapter a number of typical cases of tertian and quotidian aestivo-autumnal fever observed in soldiers returning from Cuba in 1898 and 1899. I have selected these cases from hundreds of others because they were studied for several days before quinine was administered, and thus all of the typical phenomena of the paroxysm were observed. From the charts shown it will be observed that these cases conformed to one of two types of fever, tertian or quotidian, and the examination of the blood demonstrated that they were due to two distinct plasmodia, which could be differentiated morphologically. I believe that the following cases prove conclusively that two varieties of aestivo-autumnal fever occur, each characterized by its own peculiar clinical course and by the presence in the blood of a specific plasmodium.

In considering these cases I have aimed to give only the salient features, both clinical and microscopical in each instance, and it should be remembered that there are many exceptions to the typical types as illustrated in this chapter. Cases occur in which the temperature curve is more or less continuous, and in which there are found multiple groups of parasites or combined infections with more than one species of malarial plasmodium. In such cases the symptoms are often atypical, and the temperature curves are most irregular and confusing. It matters not how typical the temperature curve may be, however, in a case of aestivo-autumnal fever, it can be easily made atypical by the administration of insufficient doses of quinine given at irregular intervals. Such treatment, far too common, will cause the most typical temperature curve, whether tertian or quotidian, to become irregular and often altogether unrecognizable as one of malaria, and is the most prolific source of the existing confusion regarding the classification of the aestivo-autumnal fevers. In combined infections with both the tertian and quotidian plasmodium, a more or less continued or slightly remittent temperature curve is seen, while in cases in which quinine in unsuitable doses has been given, an irregular, intermittent temperature curve is most common. Where, however, no combination of the two species of plasmodium exists and quinine has not been administered, it will almost invariably be found that either a tertian or quotidian temperature curve will be observed in aestivo-autumnal infections in which only one group of plasmodia is undergoing development.

Cases of Quotidian Aestivo-autumnal Malaria.

There is nothing peculiar about the temperature curve in this form of malarial fever, it very closely resembling an ordinary double tertian curve. It is a notable fact, however, that many cases of pernicious malarial fever present this type of temperature curve, and the blood has shown the characteristic quotidian aestivo-autumnal plasmodium. None of the cases described in this chapter were pernicious in character, as I have purposely selected those of a milder type, because they are so much more common.

Case I. Chart 6.—Hamilton. The patient, a soldier, arrived at Santiago, Cuba, in August, 1898. He was there about one month when he developed measles, which was followed by dysentery. About the middle of October he began to have chills and fever. His chills occurred, as a rule, every day, but were sometimes irregular. Besides the chills he suffered from nausea, vomiting, severe headache, and diarrhoea. Has had several attacks followed by recovery under treatment. He was feeling well on his arrival at the hospital, June 23, 1899. Upon the 26th he began to run a temperature characterized by quotidian paroxysms, but had no distinct chill until the 30th. Up to the latter date he suffered from nausea, some headache, and general pains. On the 30th he had a distinct chill, suffered from nausea, vomiting, sweating, severe frontal headache, and general pain, especially severe between the shoulders. His bowels were constipated.

Physical Examination.—Patient is anaemic and emaciated. Skin slightly yellow; face flushed; tongue heavily coated with a thick, yellowish fur, and flabby; lungs and heart normal; pulse full and bounding; spleen enlarged and tender, reaching about 4 cm. below ribs; liver normal. Some tenderness over abdomen on deep pressure, probably due to pressure on spleen.

Examination of the Blood.—The blood was examined daily at intervals until the parasites disappeared. It was found that they were most numerous in the peripheral blood during or just after a paroxysm, but at no time were they numerous enough to show more than one infected corpuscle, on the average, to the field. The parasites were typical of the quotidian aestivo-autumnal variety, and two forms were observed in the peripheral blood: the "ring" forms and the pigmented bodies. The ring forms were very small, indistinct in outline, perfectly circular when at rest, and very actively amoeboid. They never showed the "signet ring" appearance so common in the tertian variety, and were never more than one-sixth the size of the infected red corpuscle. Some infected corpuscles contained two, and a few even three plasmodia. The pigmented forms were about one-fourth the size of the infected cell, which was always shrunken, brassy green in color, and generally crenated. The outline of the pigmented forms was sharply defined, and they were perfectly circular in shape, amoeboid motion being absent. The pigment occurred in the form of one or, at most, two rather large, almost black dots, either centrally or peripherally situated. The pigment was almost motionless. No segmenting forms

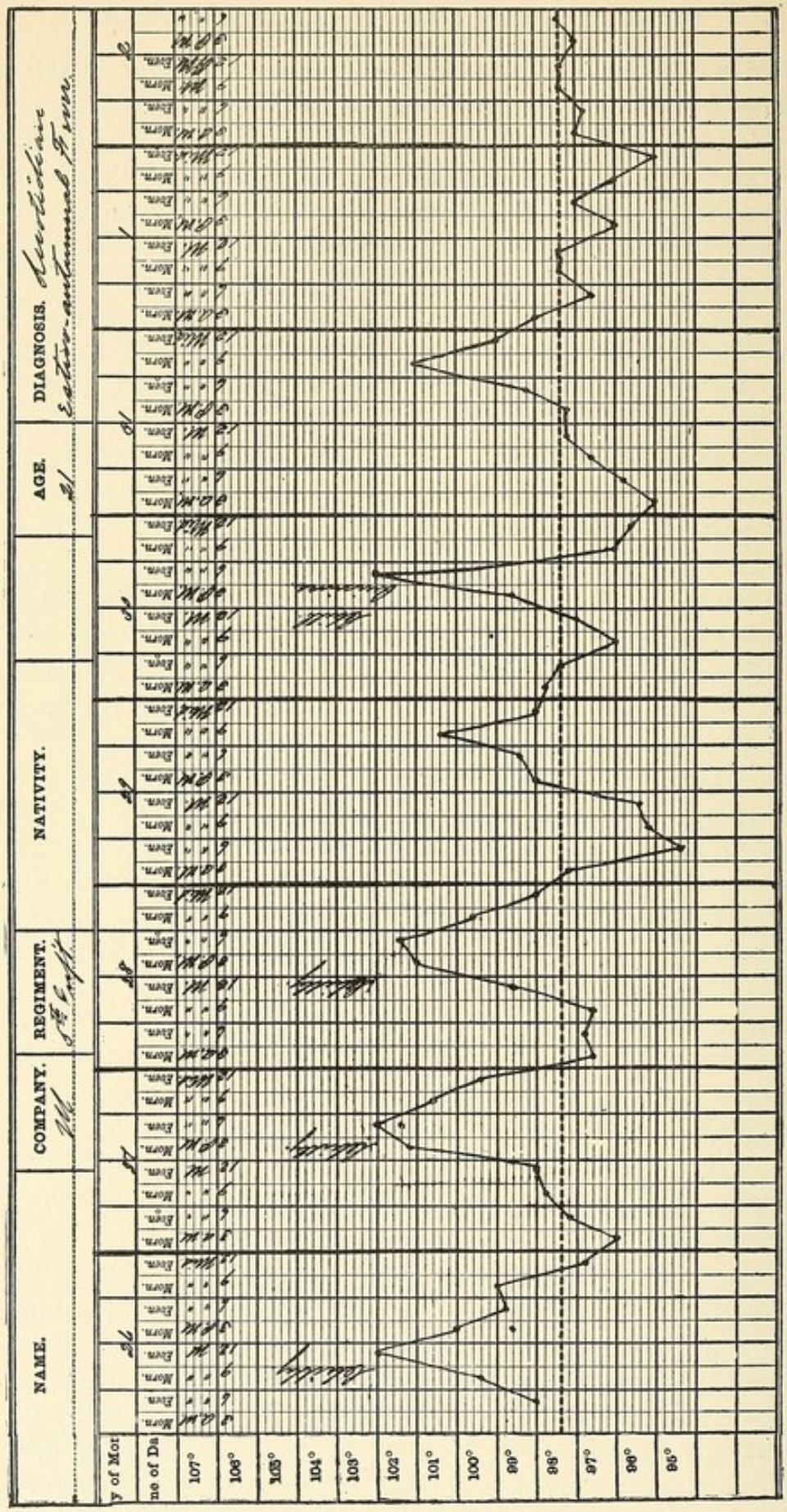

CHART 6.—Quotidian Aestivo-autumnal Malarial Fever.

or crescents (*gametes*) were observed in this case. The plasmodia disappeared from the peripheral blood two days after the commencement of the administration of quinine.

TREATMENT.—Quinine, in doses of grm. 0.325, every four hours.

Upon reference to the temperature chart it will be seen that there is nothing very distinctive about the temperature curve, beyond its quotidian character, and the fact that during the first three paroxysms the patient had no chills, suffering only from chilly sensations, while during the fourth paroxysm even the chilly sensations were absent. The first distinct chill occurred during the fifth paroxysm. The temperature curve might well be taken for that of a double tertian infection, the microscope alone being serviceable in differentiating the type of infection present. The temperature reached normal after two days' treatment. The subnormal temperature of 95.4° F. upon the 29th is worthy of notice, as it has been my experience that in no disease does the temperature so often reach low sub-normal points as in this form of aestivo-autumnal fever.

Case II. Chart 7.—S. F. S. The patient, a soldier, suffered for several weeks in Santiago, Cuba, from attacks of fever, accompanied by chilly sensations, headache, backache, slight nausea, and sweating. He grew gradually weaker and was transferred to the United States, arriving at the hospital on January 23, 1899. His temperature remained normal until the twenty-sixth, when he had a chill, which was repeated every day for four days. During this time he suffered from severe headache, with much mental depression, backache, darting pains down the legs, and nausea.

PHYSICAL EXAMINATION.—Much emaciated; skin of a peculiar grayish-yellow hue; tongue thickly coated and flabby; expression listless and depressed; heart and lungs normal; pulse rapid, full and strong; spleen enlarged and tender, reaching about 6 cm. below the border of the ribs; liver slightly enlarged; bowels constipated.

EXAMINATION OF THE BLOOD.—The blood was examined daily at regular intervals and showed very numerous quotidian aestivo-autumnal plasmodia. Ring-forms and pigmented forms were common, and upon one occasion two segmenting forms were observed in the peripheral blood. The organisms appeared to be most numerous during the latter portion of the paroxysm. The ring-forms were very minute, indistinct in outline, and actively amoeboid. The pigmented forms were circular or oval in shape, and contained one or two nearly black pigment dots. The segmenting forms were intracorpuscular and in one instance the segments numbered six, in the other eight. Numerous corpuscles showed double or triple infection.

TREATMENT.—Quinine grm. 0.65 every four hours.

The temperature chart in this case shows an unusually high range of fever for a quotidian aestivo-autumnal infection, but is not otherwise remarkable. It resembles, even more closely than that of Case I, an ordinary double tertian chart, and it would obviously be impossible to make a diagnosis of the type of

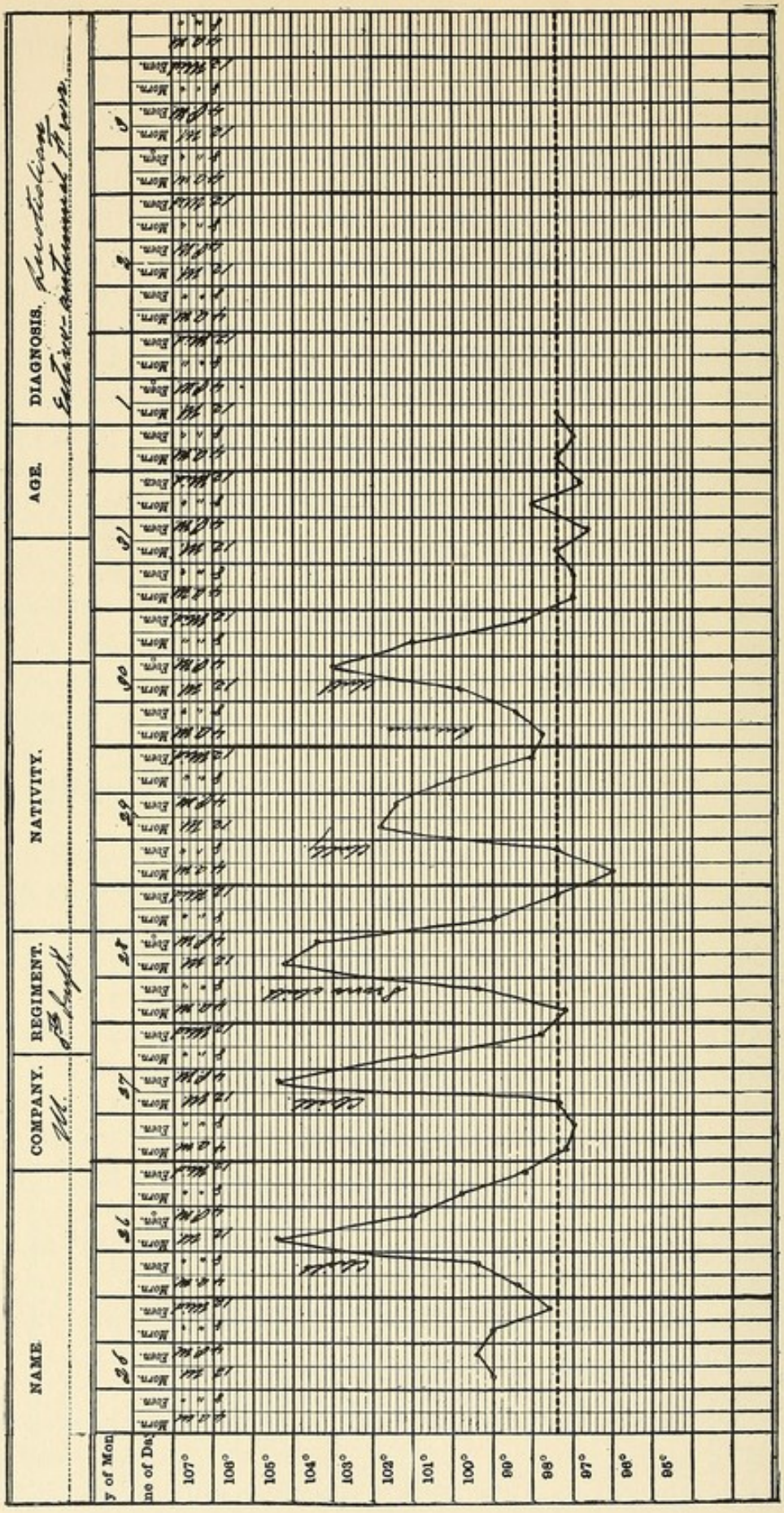

CHART 7.—Quotidian Aestivo-autumnal Malarial Fever.

infection in this case without the aid of the microscope, and this case well illustrates the importance of a microscopical examination of the blood in the diagnosis of malaria. The prompt subsidence of so pronounced an infection under large, repeated doses of quinine is worthy of attention.

Case III. Chart 8.—C. T. The history in his case is briefly as follows: The patient had never been in the tropics and his malaria was contracted at Fortress Monroe, Va. His illness began with a slight chill, nausea, vomiting, and severe headache and backache. He has slight epistaxis and complained of some abdominal tenderness. His temperature reached 103.8° after the chill.

PHYSICAL EXAMINATION showed an enlarged spleen, general abdominal tenderness, hot, dry skin, flushed face, injected conjunctivae, and a pointed, tremulous tongue thickly coated with a white fur; the pulse was full, and rather slow. The case was regarded at first as one of typhoid fever, but no Widal reaction could be obtained, and an examination of the blood showed large numbers of quotidian aestivo-autumnal plasmodia.

EXAMINATION OF THE BLOOD.—The blood showed numerous intracorpuscular "ring-forms" of the quotidian aestivo-autumnal plasmodium, and a few crescents (*gametes*). The intracorpuscular plasmodia were very small, rather dimly outlined, actively amoeboid, and corpuscules showing double infection were numerous. The infected corpuscles were smaller than normal, dark green in color, and often crenated. No pigmented forms were observed.

The *gametes* were remarkable because of their plump appearance and small size; while the male and female organisms could be distinguished, both were much more plump than the *gametes* of the tertian aestivo-autumnal plasmodium. They contained perfectly motionless, almost black pigment, in the form of short rods; their protoplasm had a peculiar refractive ground-glass appearance, and in every instance a darker colored, greenish double outline was to be seen surrounding them.

TREATMENT.—Quinine in grm. 0.40 doses, given every four hours, caused a disappearance of the fever in two days.

In this case the temperature chart is not as typical as in the other cases cited, and is therefore more interesting. During the first two days of the illness the temperature showed hardly any remission, but after that the remissions occurred as usual. It is difficult to explain this by any other hypothesis than a double infection at first, two groups of plasmodia reaching maturity within a few hours of one another, one group afterward dying out. This explanation is further strengthened by the fact that on the twenty-seventh, two paroxysms occurred, and by the presence of *gametes* in the blood, thus showing that a malarial infection must have existed in a latent condition for some time. Upon the twenty-seventh, the last paroxysm occurred immedately after the remission of the first. As a whole, however, the chart is a fairly typical one of quotidian aestivo-autumnal fever, and illustrates the value of the microscopical examination of the blood, as this case resembled so closely a case of typhoid fever that it was so diagnosed by every physician who saw it, and even the microscopical

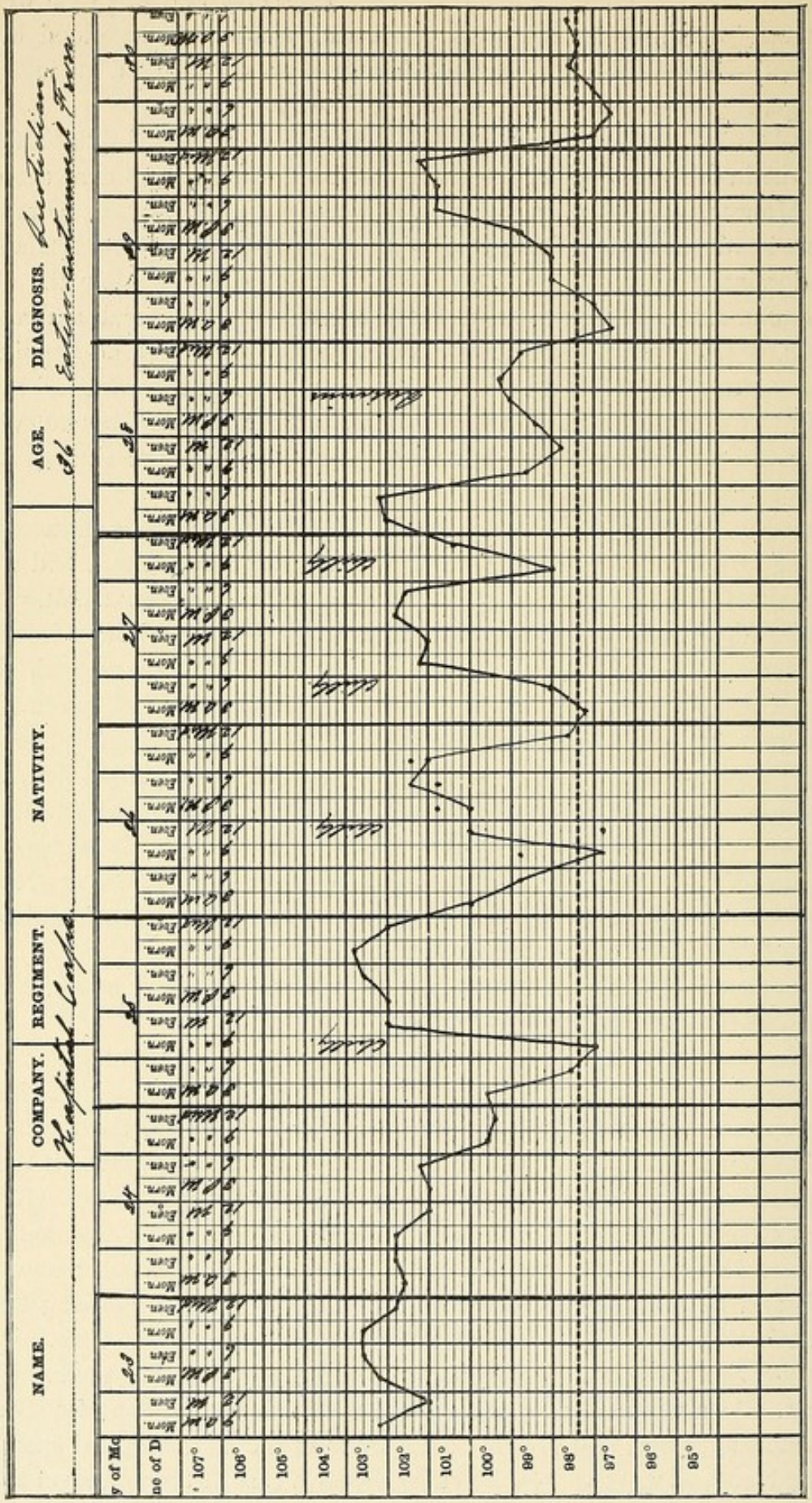

CHART 8.—Quotidian Aestivo-autumnal Malarial Fever.

examination was considered as only showing a malarial complication until the rapid disappearance of the fever under quinine proved conclusively the malarial nature of the infection.

Case IV. Chart 9.—R. S. This patient, a soldier, had been in the service for thirteen years, during which time he had enjoyed good health. He had had a slight cough at times during the past two years, but there were no physical signs and the sputum was negative for *Bacillus tuberculosis*. While in Tampa, Florida, in 1898, he suffered from chills, occurring every day, but this attack ended after four days, and he went with his regiment to Santiago. He remained there until January, 1899, and suffered from several attacks of malaria, being unfit for duty for about six weeks in all. He arrived at the hospital at Fortress Monroe on January 23, 1899. While in the hospital he developed a quotidian temperature with slight chilly sensations, rarely a distinct chill, which was considered for a while to be due to tuberculosis. At the time of the paroxysms he complained of headache, pain in the back and limbs, and slight nausea. He had no distinct sweats.

PHYSICAL EXAMINATION.—Patient somewhat emaciated and very anaemic; skin bronzed and rather moist; tongue flabby and coated; spleen enlarged; heart and lungs normal; abdomen rather tender; pulse full and rapid.

EXAMINATION OF THE BLOOD.—The blood contained numerous ring-forms of the quotidian aestivo-autumnal plasmodium and a few *gametes* (crescents). In several examinations only two pigmented plasmodia were seen.

The ring-forms were similar in appearance to those already described, being minute in size and always perfectly round. The pigmented forms were circular in shape, more sharply outlined than the "rings," and the pigment consisted of one black dot situated in the center of the parasite.

The infected corpuscles were very dark green in color. The *gametes* were small and very plump and presented a double outline. An intracorpuscular crescent was observed during one examination.

TREATMENT.—Quinine in doses of grm. 0.40 every four hours reduced the temperature promptly.

The temperature curve in this case is remarkable for its regularity, and because of its resemblance to the temperature curve often observed in pulmonary tuberculosis. This resemblance, together with an acute bronchitis which was present, led to the case being considered one of phthisis until a microscopical examination and the blood cleared up the diagnosis, and quinine cured the infection. It will be observed that the temperature fell below normal after each paroxysm.

Case V. Chart 10.—C. S. The patient went with his regiment to Santiago in August, 1898. He was there about three weeks when he was taken suddenly ill with "fainting spells," as he expressed it. He was taken to the hospital and there suffered from severe headache, slight chills, and nausea and night sweats. Was in the hospital about two weeks and was then returned to duty, but had several relapses, the last one occurring about five weeks before

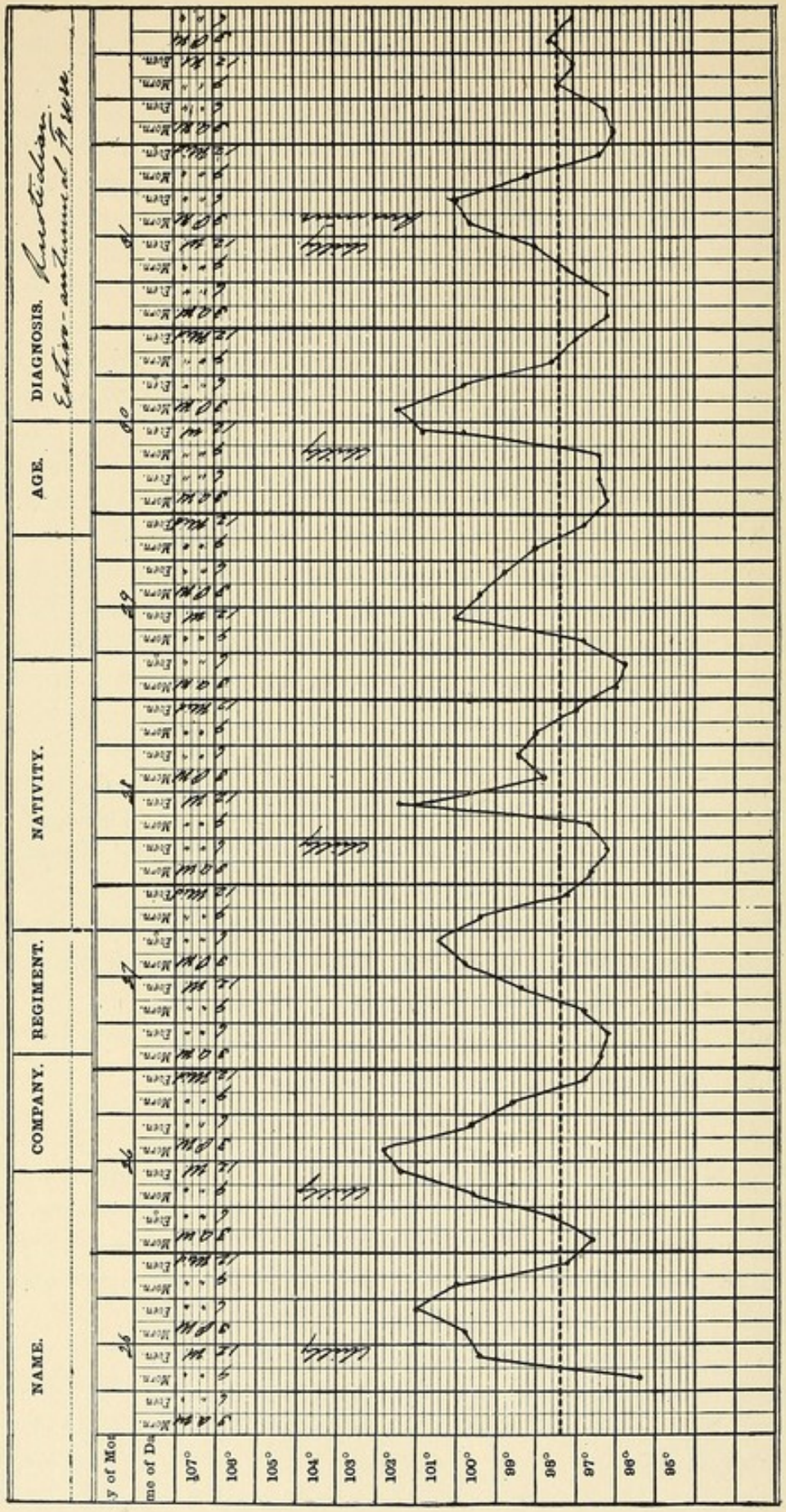

CHART 9.—Quotidian Aestivo-autumnal Malarial Fever.

arrival at the Fortress Monroe hospital where he arrived on December 11, 1898, and where I first saw him. While at the latter hospital he suffered from two attacks of fever attended with chilly sentsations, severe headache, and nausea.

PHYSICAL EXAMINATION.—Patient somewhat emaciated and very anaemic: skin yellow; tongue flabby and coated; heart and lungs normal; spleen not appreciably enlarged; liver enlarged; abdomen distended, but not tender; bowels constipated.

EXAMINATION OF THE BLOOD.—The blood contained a few typical "ring-forms" of the quotidian aestivo-autumnal plasmodium, the "ring" being small, circular in shape, actively amoeboid at times, and unpigmented. Pigmented forms were also numerous. These were more sharply defined than the "ring-forms," were less than one-fourth the size of the infected red corpuscle, and the pigment occurred as a single dot, situated at the center or one side of the parasite. The pigment was perfectly motionless and almost black in color. No amoeboid motion was noticed in the pigmented forms and the infected corpusles were always shrunken and crenated, and many "brassy" cells were observed.

TREATMENT.—Quinine in doses of grm. 0.40 every four hours soon reduced the temperature to normal.

The temperature chart in this case is that of a typical quotidian aestivo-autumnal infection, the paroxysms occurring regularly, and the chart resembling that of a double tertian infection. From the study of a large number of cases of this type of malaria, of which the five cases given are fair examples, the conclusion is inevitable that there occurs a type of aestivo-autumnal malarial infection, characterized by quotidian paroxysms, and by the occurrence in the blood of a specific plasmodium which completes its cycle of development in man in approximately 24 hours. In blood secured by puncture of the spleen all stages in the development of this plasmodium may be studied, and each stage differs markedly from the corresponding stage of the tertian aestivo-autumnal plasmodium. I have not been able to demonstrate the existence of an unpigmented quotidian plasmodium, as described by Mannaberg, Manson, and others.

Cases of Tertian Aestivo-autumnal Malaria.

In the chapters which have preceded this one I have called attention to the fact that the majority of cases of aestivo-autumnal fever present paroxysms occurring, approximately, every 48 hours. These tertian paroxysms are peculiar in that while they occur every other day, each paroxysm is prolonged so that it lasts considerably over 24 hours, and often almost 48 hours. This type of malarial fever is further characterized by a peculiar temperature curve, which was first described by Marchiafava and Bignami, and which shows the following characteristics: a rapid and sudden rise, a stage of slight remissions, a pseudocrisis, a precritical rise, during which the temperature generally reaches a higher point than it had previously, and, lastly, the true crisis, in which the temperature rapidly falls to normal or below.

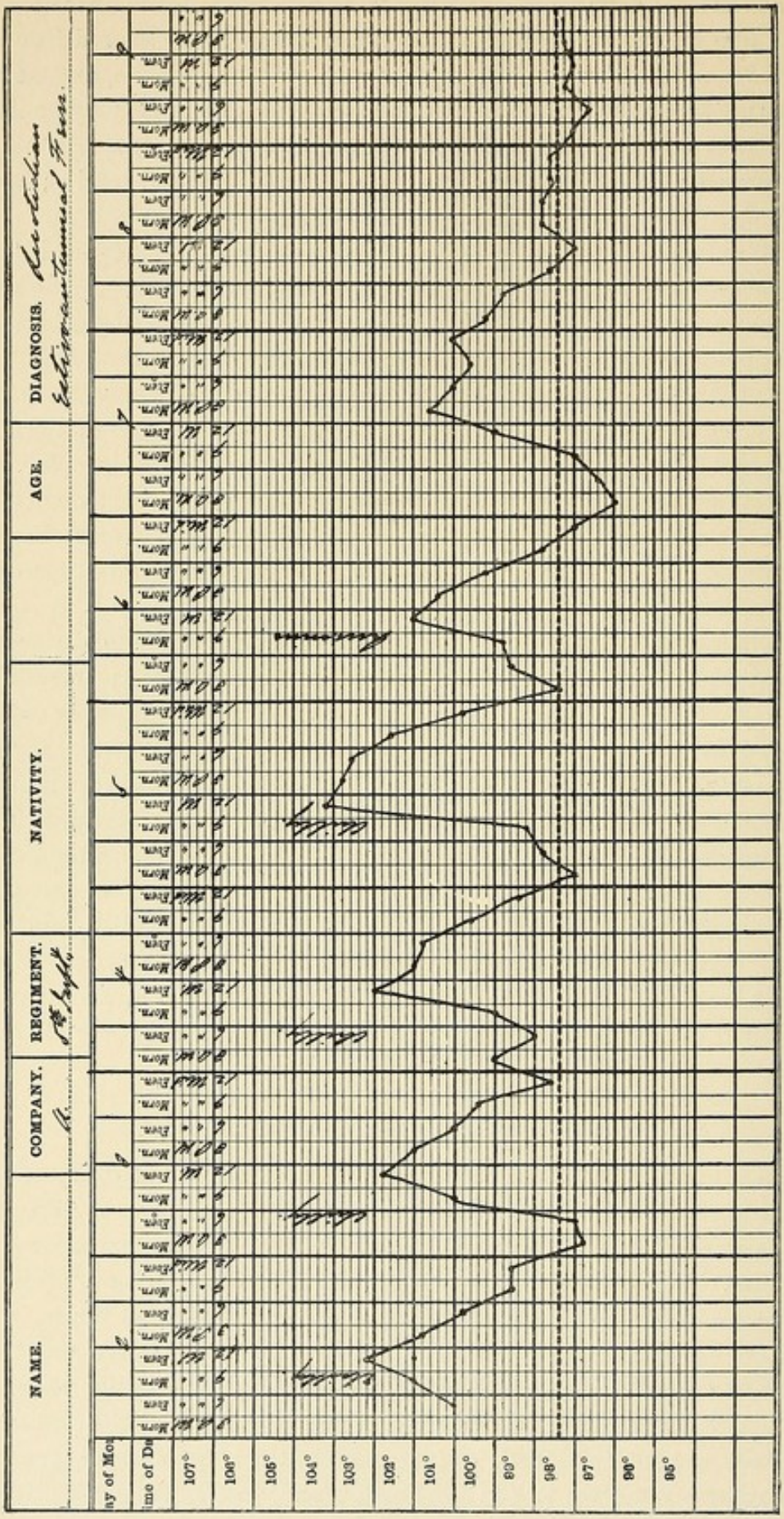

CHART 10.—Quotidian Aestivo-autumnal Malarial Fever.

This peculiar temperature curve is presented in all uncomplicated cases of tertian aestivo-autumnal malaria, where quinine has not been administered. In cases infected with two groups of plasmodia sporulating at different times or by the simple tertian or quartan plasmodium or, again, by both the quotidian and tertian aestivo-autumnal plasmodia, this peculiar temperature curve will not be observed, nor will it be in cases which have received insufficient doses of quinine or quinine at long intervals of time.

In order, then, to secure a typical temperature chart of tertian aestivo-autumnal fever, we must have a patient infected with a single group of plasmodia and must withhold quinine for several days. It is safe to say that nearly all of the confusion existing to-day regarding the types of aestivo-autumnal malaria is due to one or two factors; infection with more than one *species* of plasmodium or with more than one *group* of plasmodia, and the improper and untimely use of quinine. The first factor can only be eliminated by the microscopical examination of the blood, and the second only by an earnest scientific spirit upon the part of the physician, so strong that he will be willing to withhold quinine long enough to secure a proper knowledge of the nature of the disease which he is called upon to treat. Medicine to-day has reached the stage where the so-called diagnostic terms "intermittent" and "remittent" malarial fevers are of little exact meaning, and an earnest effort should be made to substitute for them, in medical nomenclature, the more scientific terms, tertian and quartan malaria, and quotidian and tertian aestivo-autumnal malaria.

The following cases are selected from a large number because they are typical of tertian aestivo-autumnal malarial fever, and I believe that they conclusively demonstrate the existence of this variety of aestivo-autumnal fever.

Case I. Chart 11.—S. C. Age 23. The patient arrived at Santiago, Cuba, in August, 1898. On September 20, 1898, he was taken sick with a chill, which was followed by a high temperature. He had chills every other day for several days, and suffered from nausea and vomiting, severe headache and pains in the legs, and drenching perspiration. He had several attacks during the next two months and was finally sent to the Simpson General Hospital, where he arrived upon December 11, 1898. Upon December 17, he had a rise of temperature accompanied by chilly sensations. This paroxysm was succeeded by three others, all accompanied by chilly feelings, severe headache and backache, nausea, and great nervous prostration.

PHYSICAL EXAMINATION.—Patient somewhat emaciated; skin yellowish; mucous membranes pale; cheeks flushed; eyes bright; tongue broad and coated; heart and lungs normal; abdomen rather tender; spleen slightly enlarged; bowels constipated; marked mental depression and general debility.

EXAMINATION OF THE BLOOD.—The blood was examined at frequent intervals and numerous "ring-forms," pigmented rings, and larger pigmented forms of the tertian aestivo-autumnal plasmodium were found. No segmenting forms were observed. The "ring-forms" were larger than those of the quotidian

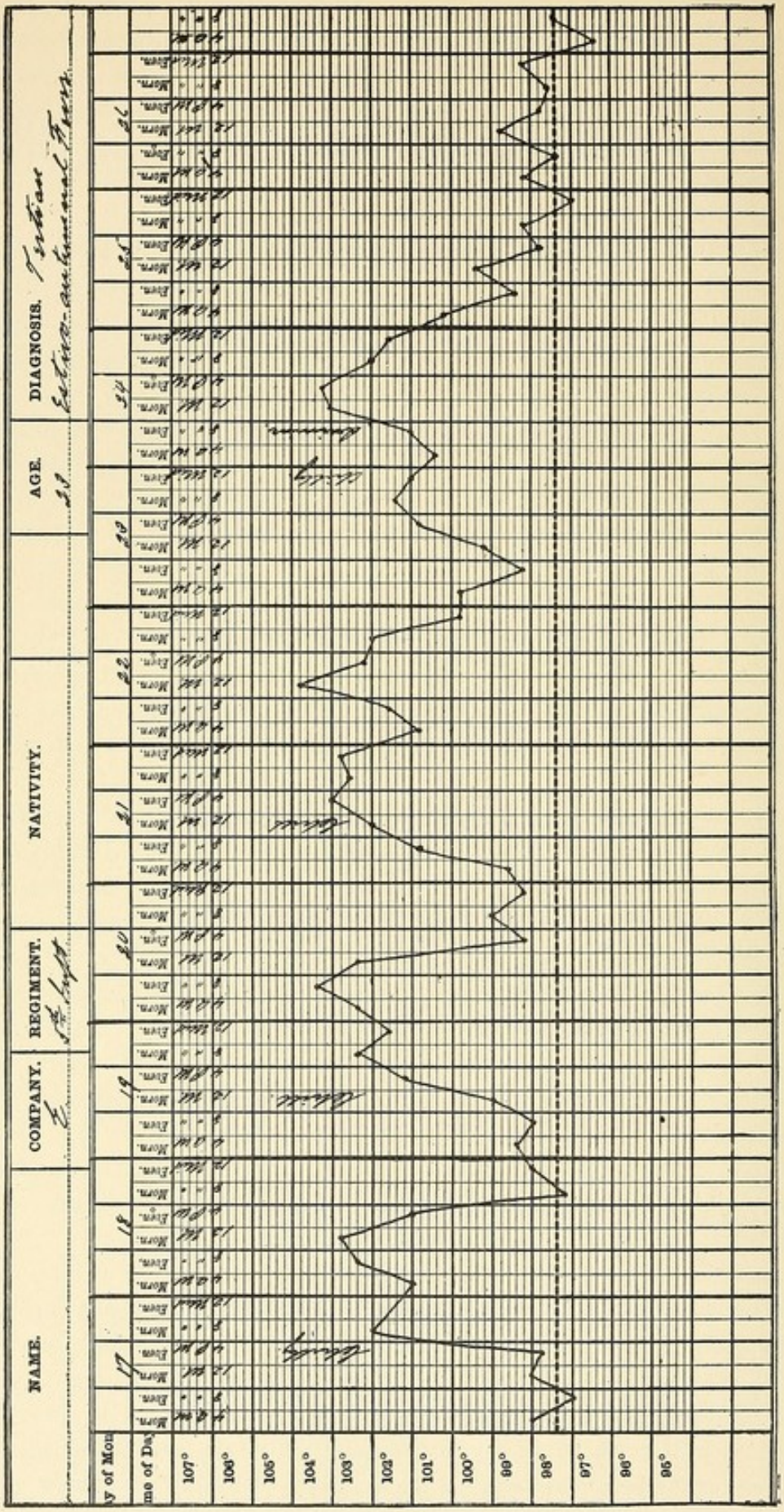

CHART II.—Tertian Aestivo-autumnal Malarial Fever.

aestivo-autumnal plasmodium, being about one-fourth the size of the infected red cell, irregular in shape, most of them presenting an enlargement at some portion of the periphery, thus causing the so-called "signet-ring" appearance. They were refractive and sharply outlined, with clear protoplasm, and having a sluggish amoeboid motion. The "ring-form" was sometimes lost during the movement of the organism, a clear, circular, hyaline disk resulting. The infected red corpuscles, while more greenish in color than the uninfected cells, was not nearly as much altered in appearance as in the quotidian infections, and was seldom crenated.

The pigmented rings and larger pigmented bodies were present in small numbers. The "rings" showed a few fine pigment granules, generally in the dilated portion of the ring, and these granules were often in rather rapid motion. These pigmented rings still showed considerable amoeboid motion.

The pigmented bodies larger than the "ring-forms" were sharply defined, the protoplasm being refractive and finely granular in appearance. The pigment was in the form of fine reddish-brown granules, and possessed a marked vibratory motion. These plasmodia were about one-half the size of the infected red corpuscle, and some of them still showed a slight amoeboid motility.

TREATMENT.—Quinine in doses of grm. 0.40 every four hours, reduced the temperature in two days, and its continued use resulted in recovery.

A consideration of the temperature chart in this case shows it to be a beautiful illustration of the peculiar temperature curve in this type of malarial fever. Quinine was withheld until the occurrence of the fourth paroxysm. It will be seen that the paroxysms occurred at intervals of approximately 48 hours, and that the temperature lasted from 36 to 40 hours, and the chart shows well the various characteristics of the curve already mentioned. Taking the paroxysm of the twenty-first, for example, we see beautifully illustrated the rise, the period of slight remissions, the pseudocrisis, the precritical rise, in which the temperature reaches the highest point, and, lastly, the crisis, in which the temperature rapidly fell to nearly normal. The intervals between the paroxysms were short, and two of the paroxysms were accompanied by chills. As a general rule, the temperature goes to normal or below, during the intervals, but in this case it did not always do so.

Case II. Chart 12.—P. R. H., Age 21. Patient arrived in Cuba on December 17, 1898. Was taken sick March 13, 1899, with severe pain in the head, chill, high fever, and nausea and vomiting. Was supposed to be suffering from typhoid fever, but felt better after a week in the hospital and was up and about. On April 6, the day before he boarded the steamer on his way to Fortress Monroe, the fever returned, accompanied by the same symptoms, He arrived at the Simpson Hospital upon April 12. He had four chills after arrival, occurring every other day, but not very severe, accompanied by nausea and vomiting, headache, and pain in the back and legs.

PHYSICAL EXAMINATION.—Patient looks very ill. Greatly emaciated;

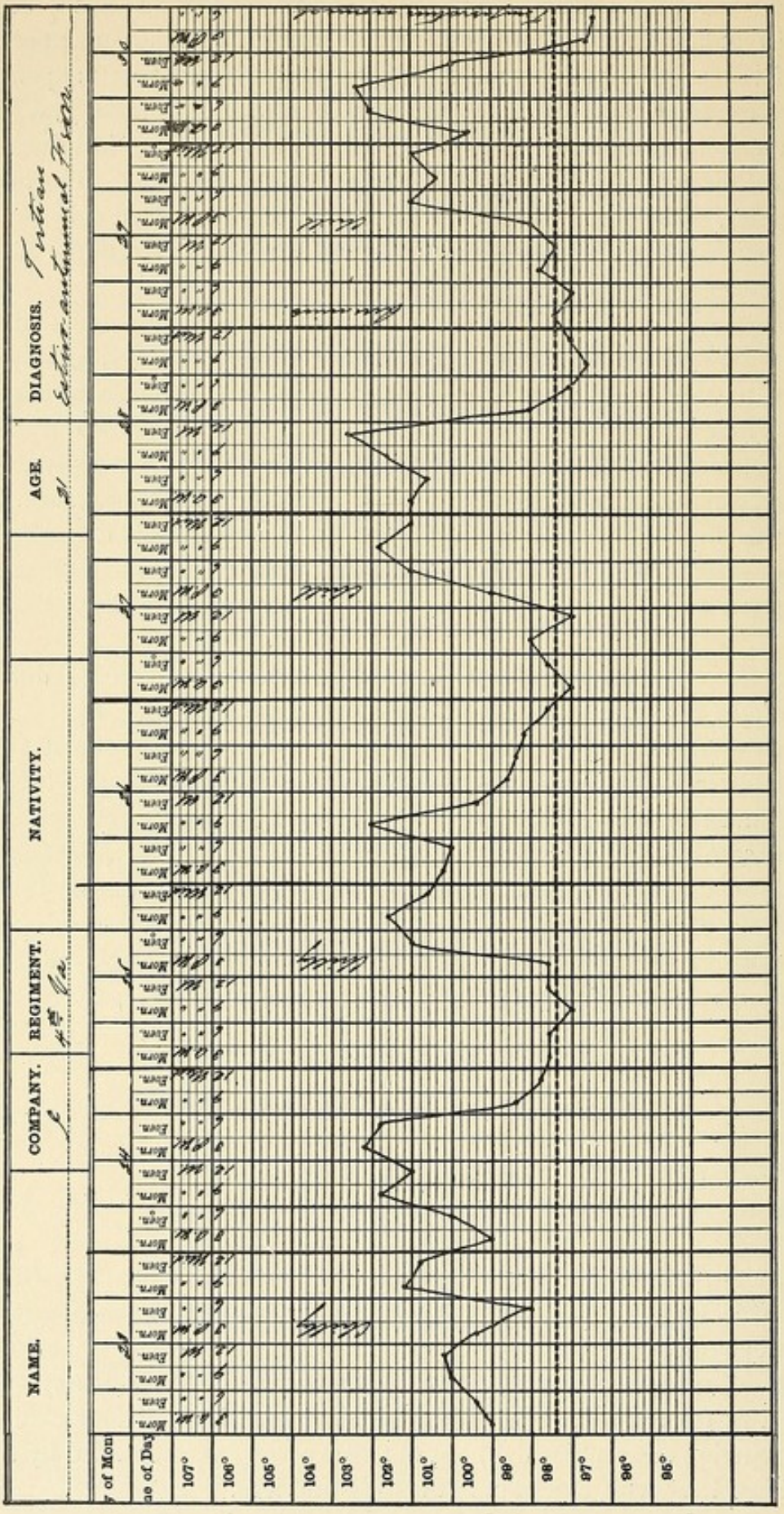

CHART 12.—Tertian Aestivo-autumnal Malarial Fever.

skin yellow; face congested and eyes bright; tongue broad and coated with a yellow fur; pulse rather weak and very rapid; heart and lungs normal; spleen slightly enlarged; liver normal; abdomen rather tender; bowels constipated.

EXAMINATION OF THE BLOOD.—The blood was examined at frequent intervals and always showed "ring-forms" and pigmented ring-forms of the tertian aestivo-autumnal plasmodium, similar in every respect to those described in the preceding case. No segmenting forms or crescents were found in the peripheral blood. The parasites were most numerous just before the paroxysms.

TREATMENT.—Quinine, grm. 0.50 every six hours. Recovery.

The temperature chart in this case is a typical one of tertian aestivo-autumnal fever. It will be seen that there were four paroxysms in all, and that each paroxysm showed the characteristic temperature curve, although the paroxysm of the twenty-third is slightly atypical, in that after the pseudo-crisis there occurred a slight remission before the final rise and crisis. In no other malarial fever will a temperature chart like this be observed, and it is actually diagnostic of the type of infection which it occurs in.

Case III. Chart 13.—A. H. H. The patient, while in Santiago, suffered from malarial fever, having chills nearly every other day, accompanied by high fever, severe headache and backache, and nausea. He arrived at Fortress Monroe on January 23, 1899, and after admission to hospital had several paroxysms of fever, accompanied by chilly feelings, but no distinct chill; severe headache and backache, some nausea, and general muscular pain.

PHYSICAL EXAMINATION.—The patient does not look very sick. There is some anaemia; the tongue is coated; the heart, lungs, and liver are apparently normal. The spleen is enlarged, reaching half-way to the umbilicus. There is much mental depression.

EXAMINATION OF THE BLOOD.—The blood was examined frequently and numerous pigmented and unpigmented tertian aestivo-autumnal plasmodia were found, most numerous just before or some time after the paroxysm. No sporulating parasites were observed.

TREATMENT.—Quinine, grm. 0.40 every four hours. Recovery.

In this case the temperature chart is again typical of tertian aestivo-autumnal infections, and would easily be recognized as such upon simple inspection. The occurrence of the paroxysm upon every third day; the length of the individual paroxysm; the peculiar curve exhibited—all prove conclusively the type of malarial fever present, even without the aid afforded by the microscope in detecting the characteristic plasmodium.

Case IV. Chart 14.—S. The patient arrived at Santiago, Cuba, in August, 1898. He was there about two weeks when he was taken suddenly ill, having a chill, high fever, nausea and vomiting, and great mental depression. Chills recurred every other day and were always accompanied by intense headache and fever. Arrived at the Simpson U. S. Army General Hospital on December 11, 1898, and on the sixteenth, had chilly sensations and a rise of

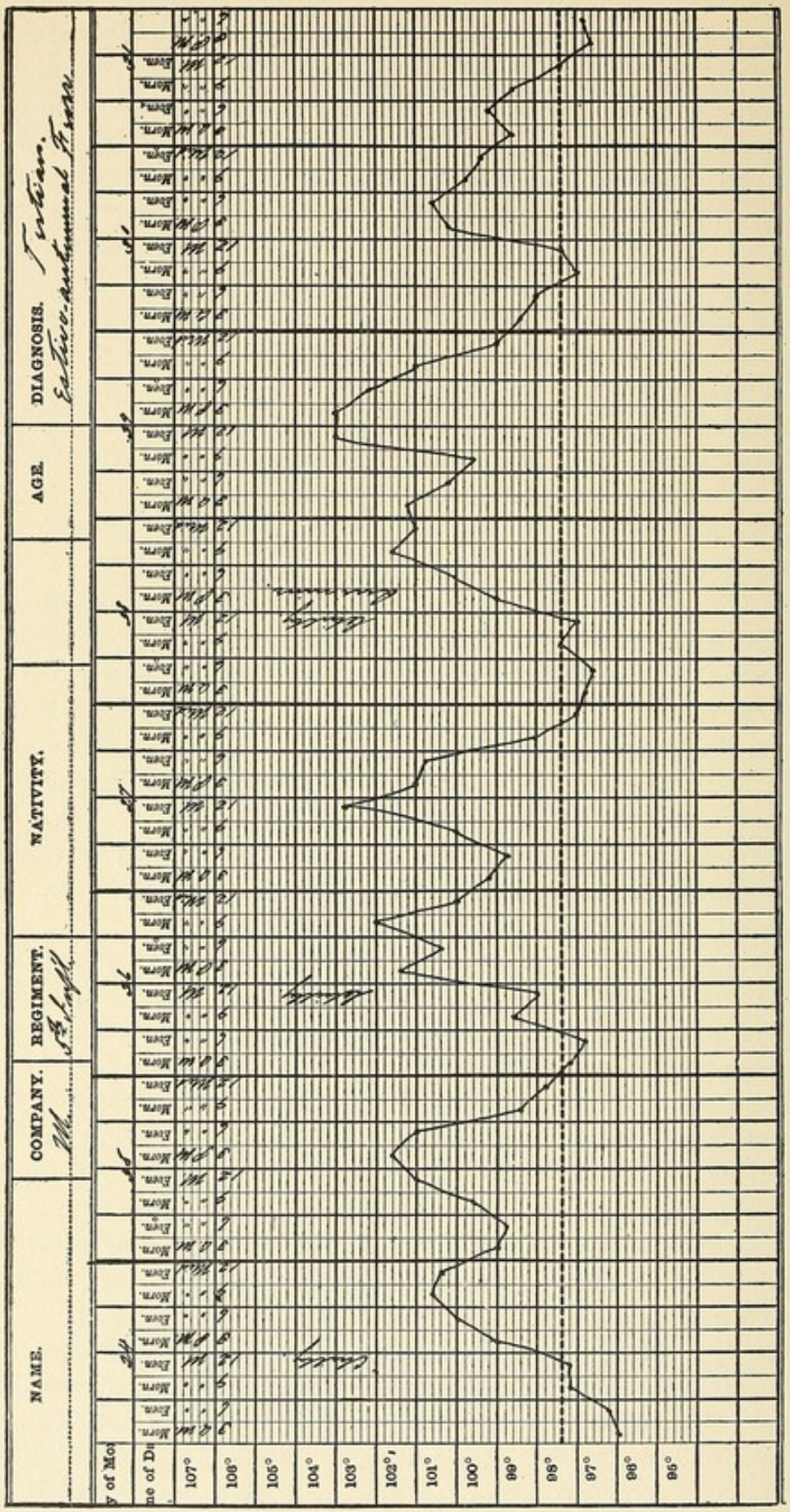

CHART 13.—Tertian Aestivo-autumnal Malarial Fever.

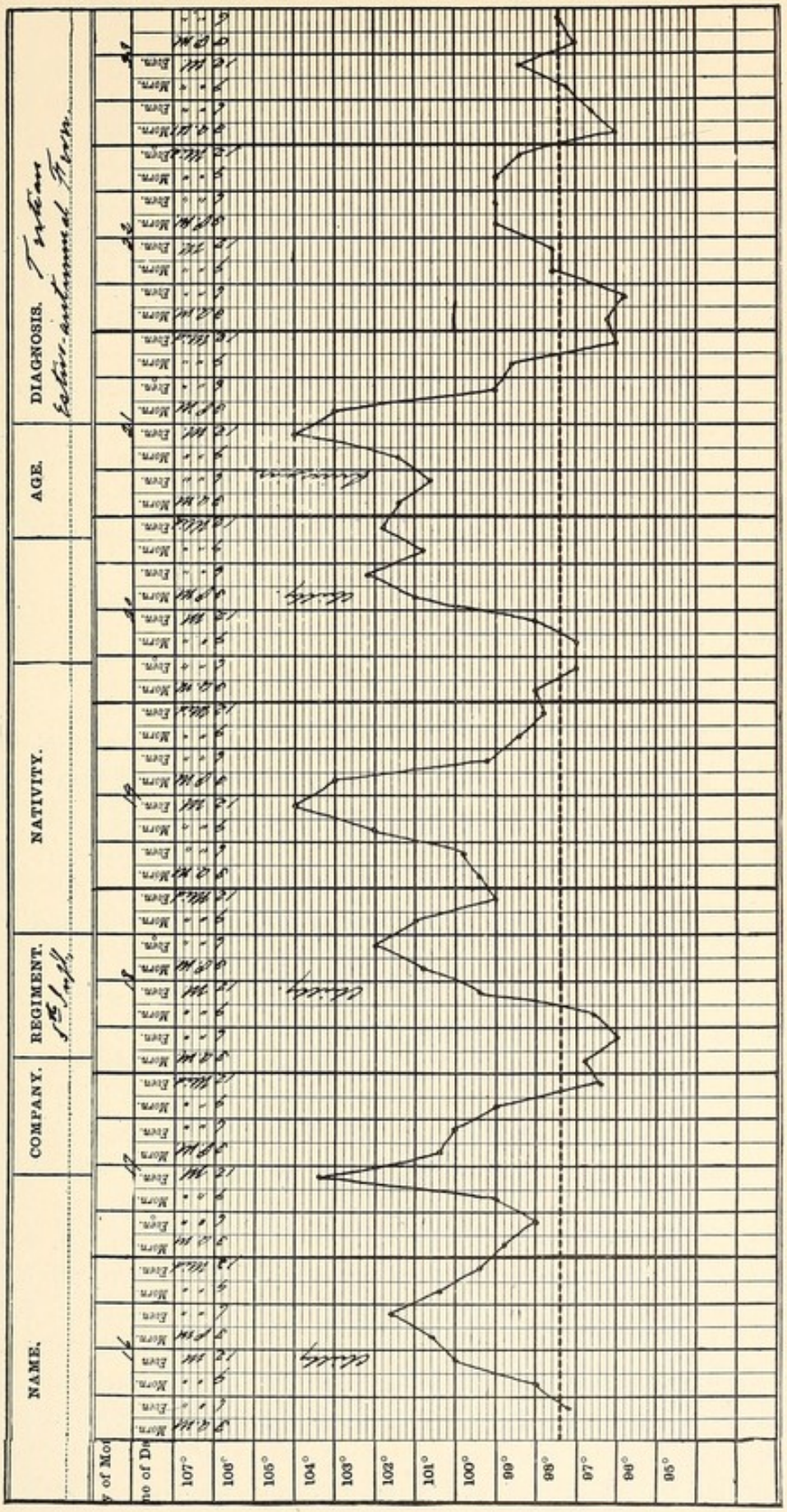

CHART 14.—Tertian Aestivo-autumnal Malarial Fever.

temperature. He had two paroxysms after this, accompanied by fever, intense headache, nausea, general muscular pain, and mental depression.

PHYSICAL EXAMINATION.—Patient anaemic and listless. Skin slightly yellow, tongue slightly coated; heart, lungs, and liver apparently normal. Spleen not appreciably enlarged. Bowels constipated. Pulse full and regular.

EXAMINATION OF THE BLOOD.—Numerous examinations of the blood were made and pigmented and unpigmented forms of the tertian aestivo-autumnal plasmodium were found, and several segmenting forms were observed in the peripheral blood. The pigmented and unpigmented ring-forms have already been described under Case I. The large pigmented parasites were nearly half as large as the infected red corpuscle, and contained numerous fine granules of pigment, generally collected near the center of the organism. The parasites were very sharply defined and very refractive. In some of the pigmented forms the pigment was collected in a solid block at the center of the organism, and faint radial striations could be made out dividing the parasite into several segments.

The segmenting forms observed appeared to be extracorpuscular, and consisted of blocks of pigment with ten or more minute oval spores arranged about them.

TREATMENT.—Quinine, grm. 0.40 every four hours. Recovery.

The temperature chart in this case is interesting in that each of the paroxysms presents a modification of the typical aestivo-autumnal curve. In the first paroyxsm there is no stage of slight remissions, there being a rapid initial rise and almost immediately a pseudocrisis, in which the temperature reached normal; this was immediately succeeded by the precritical rise and followed by the crisis. In the second paroxysm there is also no stage of slight remissions, but the pseudocrisis is more normal and the precritical rise more gradual. The third paroxysm is marked by a well-defined stage of slight remissions, but the pseudocrisis is almost absent.

Such slight modifications as these are very common in the temperature curve of tertian aestivo-autumnal fever, but they do not in the least affect the general character of the curve nor cause a moment's doubt as to the nature of a case showing such a temperature curve as is here presented. Such curves are uniquely characteristic of the tertian aestivo-autumnal infections.

Case V. Chart 15.—C. C. Age 25. Arrived at Santiago, Cuba, in August, 1898. Was there about one month, when he had a sharp chill followed by a high temperature. Chills occurred for a while every other day, but later became irregular. They were always followed by a high temperature. He was admitted to the hospital there five different times, each apparent recovery from the fever being followed by a relapse as soon as he returned to duty. During the paroxysms he suffered from headache, very severe in character; severe muscular pains; nausea and vomiting. He arrived at the Simpson Hospital on December 11, 1898. Had chilly sensations and a headache on the

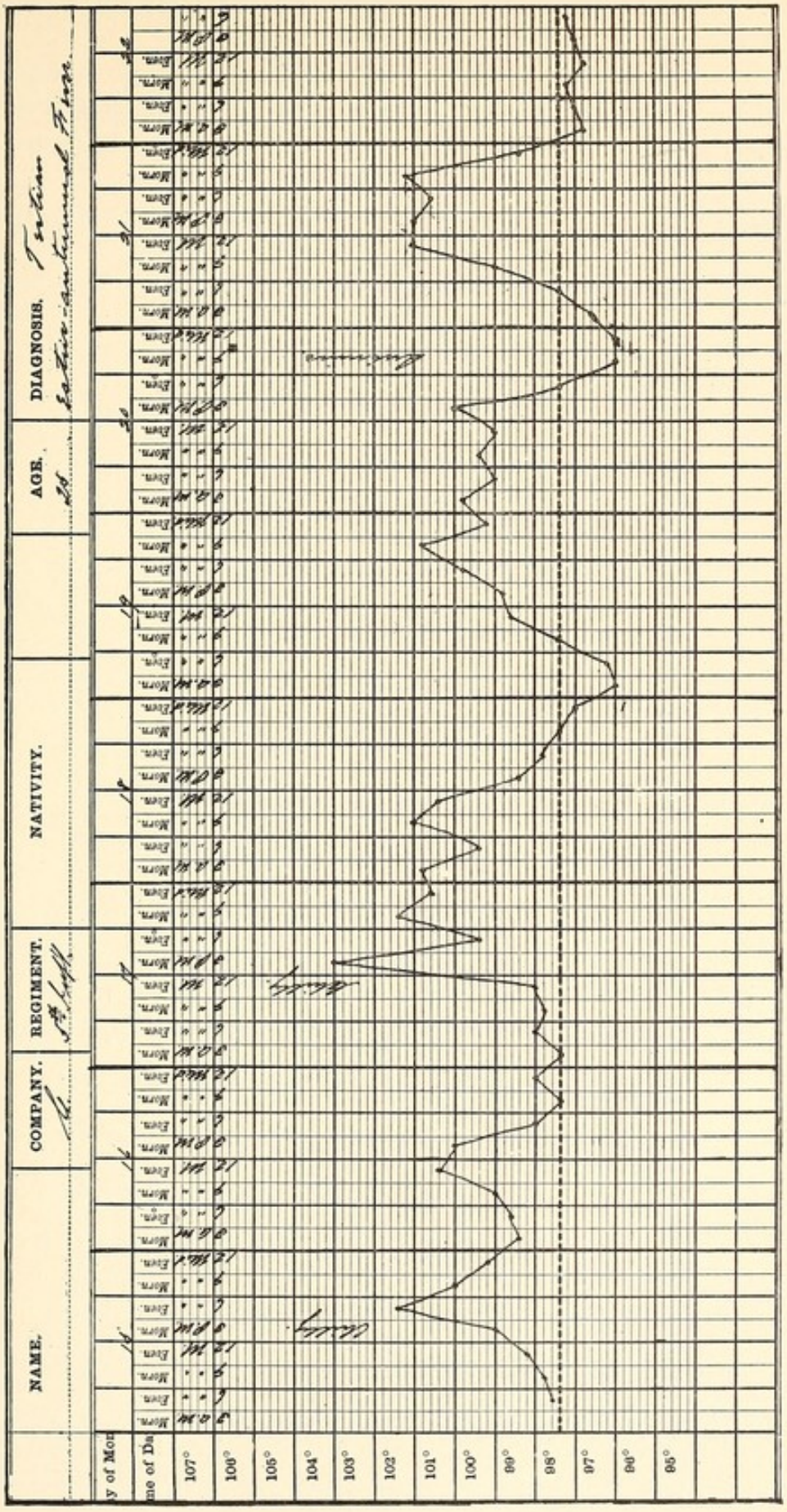

CHART 15.—Tertian Aestivo-autumnal Malarial Fever.

fifteenth, followed by a rise in temperature. He had three slight paroxysms afterward, accompanied by chilly sensations.

PHYSICAL EXAMINATION.—Patient emaciated and anaemic. Skin yellow, tongue flabby and coated. Heart and lungs normal. Spleen greatly enlarged, reaching nearly to the umbilicus. Liver dullness normal. Bowels constipated. Abdomen tender.

EXAMINATION OF THE BLOOD.—The blood in this case showed pigmented "ring-forms" of the aestivo-autumnal plasmodium and numerous *gametes* (crescents). The ring-forms were similar to those described as occurring in Case I. The *gametes*, both male and female, were very much more slender and much larger than those of the quotidian aestivo-autumnal plasmodium, and contained a much greater amount of pigment of a more reddish color. The double outline was less commonly observed, but the protoplasm was much more refractive.

In this case the temperature chart is not as typical as the preceding ones, but it is typical of the more chronic forms of tertian aestivo-autumnal infection. The paroxysms occur every 48 hours, but it is noticeable that the range of temperature is not as high in this case and that there seems to be a tendency toward a spontaneous decline of the infection. The chart is curious in that there seems to be a reversal of the ordinary temperature curve, the highest temperature being reached during the initial rise; but even in this chart the temperature curve is, on the whole, so characteristic that a diagnosis of tertian aestivo-autumnal fever could easily be made from an inspection of it

From the cases of quotidian and tertian aestivo-autumnal malarial fever I have here considered it will be seen that a differentiation of the two types cannot be made from a consideration of the clinical symptoms except that in the quotidian form the chill or chilly sensations occur every 24 hours, while in the tertian form they occur every 48 hours. A consideration of the temperature charts, however, shows such a marked difference in the temperature curves that we must admit that we are dealing with two distinct types of malarial infection. The quotidian aestivo-autumnal type presents a simple intermittent temperature curve, indistinguishable from that of a double tertian infection, while the tertian aestivo-autumnal infections present a most peculiar and characteristic temperature curve, entirely different from that shown in any other type of malarial infection and diagnostic in itself. When to this is added the fact that each form is due to a specific plasmodium, one sporulating in 24 hours, the other in 48 hours, the evidence is complete that there occur two forms of aestivo-autumnal malarial fever, the tertian and quotidian, as first described by Marchiafava and Bignami.

In the study of these infections it is absolutely necessary that the temperature be recorded every three or four hours, as, in many cases, a morning and evening record of the temperature will give but little information regarding the actual range of the fever.

CHAPTER III.

The Pernicious Forms of the Malarial Fevers.

The term "pernicious" as used in the nomenclature of malaria indicates infections in which some one symptom or group of symptoms so preponderate as to color the clinical picture and threaten the life of the patient. Used in this sense, the term is of value in clinical work, but unfortunately some writers have considered the pernicious forms of malaria as disease entities and have used the term to designate certain infections, especially the aestivo-autumnal fevers. With these writers pernicious malarial fevers mean the aestivo-autumnal infections and the use of the term becomes essential in designating this group of fevers. A classification based upon the severity of the symptoms present in any given disease is unscientific and confusing, and is especially so in the malarial infections, which are due to different species of plasmodia. Mannaberg says, regarding the classification of malaria into pernicious and benign forms: "We search pathology in vain for an analogy. As far as I know, there is no other disease, though it runs its course sometimes smoothly and without prognostic danger, again under the severest and most threatening symptoms, for which a division into benign and pernicious had been made. If we were to follow out this division, we should speak of a benign typhoid fever when the disease was mild, of a pernicious typhoid fever when, in its evolution, dangerous symptoms arose. There would be, in addition, an endless series of sub-divisions, depending on whether the dangerous symptoms proceeded from one or another organ." This criticism of Mannaberg's is just, but while the term should not be used to designate disease entities, it is of value as a convenient clinical term in designating malarial infections of great severity and in which certain symptoms arise which serve to distinguish them from the ordinary type of infection. The term cannot be considered accurate, as what shall be considered pernicious symptoms will always depend upon the opinion of the physician, and this will, of course, vary greatly in individual instances.

It should be distinctly understood that there is no species of plasmodium which produces *only* pernicious forms of malaria, but that the same species which causes the mildest infections is also capable of causing rapidly fatal forms. Any of the species of malarial plasmodia may give rise to pernicious symptoms, but the vast majority of fatal cases of malarial fever are due to the tertian aestivo-autumnal plasmodium, the next most frequent parasite being the quotidian aestivo-autumnal plasmodium. As the greater number of fatal cases of malaria occur in patients infected with the aestivo-autumnal plasmodia,

it is very important to remember that there is always an element of danger in these cases, in that they may at any time develop pernicious symptoms which may cause the death of the patient.

The great majority of pernicious attacks of malaria occur in temperate regions in the late summer and in autumn and are rare, while in the tropics they occur throughout the year and are very common. The *frequency* of occurrence of such infections, as given by various authors, varies greatly, depending upon the locality in which the observer was working, the season of the year in which the observations were made, and the number of cases of malarial infection observed. Thus Borius, in Senegal, in 100 cases of aestivo-autumnal malaria, observed 4.1 per cent. of pernicious cases; Laveran, in Algiers, a proportion of 1 pernicious case to 35 others, and A. Plehn, in the Kamerun, a proportion of one pernicious case to eight in which the symptoms were benign. In temperate regions the proportion is *nil* in some localities and very small in almost all regions in which the aestivo-autumnal infections occur but rarely. In my own experience, embracing the study of several thousand cases of malaria contracted in Cuba and the Philippine Islands, the proportion of pernicious cases has not been over 1 to 100, but most of these infections were treated promptly with quinine, which, of course, resulted in a smaller number of pernicious attacks.

As a rule, pernicious symptoms develop only after repeated attacks of the infection, although I have seen more than one instance in which the patient was struck down, as by lightning, with a pernicious attack of malaria, but in which no history of a previous infection could be obtained. However, the great majority of pernicious attacks occur in persons who have suffered repeatedly from malarial paroxysms which have not been properly treated, and the pernicious symptoms often develop, in such cases, during an apparently mild paroxysm.

The Causes of Perniciousness.—Why do certain cases of malarial infection develop pernicious and fatal symptoms? In answer we must admit that our knowledge is, as yet, incomplete, but individual susceptibility to the infection; certain preexisting diseases of the viscera; external conditions, as regards locality, exposure, and poverty; and the species and number of the infecting plasmodia, all undoubtedly help to explain the occurrence of such cases.

Some individuals appear to be very *susceptible* to the malarial poison and always suffer from pernicious attacks, while, on the other hand, an individual but little affected usually may suddenly develop pernicious symptoms. *Alcoholics*, and those *weakened by disease, exposure, and lack of proper food*, are especially apt to suffer from pernicious attacks of malaria. I have repeatedly observed the occurrence of pernicious symptoms in soldiers who have been exposed for too long a time to the tropical sun, and some of the most severe cases of cerebral pernicious malaria that I have observed have developed suddenly in soldiers upon the march in the tropics. Europeans are said to suffer

more frequently from pernicious attacks than natives, and while this is generally true, there are exceptions, as at Camp Stotsenburg, in the Philippines, where pernicious cases were more common among the natives than among our soldiers in the proportion of four to one.

As has been stated, the *species of plasmodium* is of importance, as most pernicious attacks are due to the aestivo-autumnal plasmodia, especially the tertian form. However, we now have the records of many cases of pernicious malaria caused by the simple tertian and the quartan plasmodium, and the statement of Mannaberg that these organisms cannot cause pernicious symptoms can no longer be accepted. In the tropics the aestivo-autumnal infections are more apt to become pernicious than in temperate regions, probably because of the debility and anaemia so common in tropical regions, and the climatic conditions there present.

The *number of plasmodia* present in any given case must have great influence in the production of pernicious symptoms, and it has been definitely proven that in pernicious infections the plasmodia are always more numerous than they are in mild infections. The increased number of plasmodia is not, by any means, manifest in an examination of the peripheral blood, for in the aestivo-autumnal infections, which furnish the majority of pernicious cases, the plasmodia are frequently small in number in the peripheral blood, but occur in immense numbers in the viscera, especially in the brain and the spleen. Thus we can place but little dependence upon the number of plasmodia observed in the peripheral blood as indicating the severity of the infection in many instances, but in such cases a splenic puncture will demonstrate innumerable plasmodia to be present in that organ. I recall a case of fatal aestivo-autumnal infection in which the examination of the peripheral blood resulted in finding only three or four plasmodia after half an hour's search, but at autopsy smears from the brain and the spleen showed so many plasmodia that it was almost impossible to find an uninfected red corpuscle. In the cerebral types of pernicious malaria the capillaries of the brain are always found crowded with plasmodia, although the examination of the peripheral blood may have shown but few plasmodia.

Although we have no reliable data at present concerning the malarial *toxin*, it is but reasonable to suppose that a more powerful toxin is elaborated in the pernicious infections, or better, perhaps, that a greater amount is produced because of the increase in the number of plasmodia.

The *situation* of the plasmodia has certainly something to do with the production of pernicious symptoms. Bastianelli and Bignami have carefully studied this subject, and make the following distinctions as regards distribution of the plasmodia and the symptoms produced by them:

"1. Cases in which the number of parasites is most abundant, yes, enormous, in the brain, while all the organs are less uniformly invaded. These are the commonest forms of pernicious malaria, and are usually accompanied by coma.

"There are some cases in this category in which the number of parasites in the blood of the finger, of the spleen, of the bone-marrow, etc., is enormous, while the number in the brain is scanty. Clinically, the absence of cerebral phenomena is noted.

"2. Cases in which the number of organisms is absolutely and relatively scanty in the bone-marrow, the spleen, and in the liver, while they may be relatively few in the blood of the finger, and yet other organs are crowded with them. Among these the following localizations are to be made out:

"*a.* The brain and the meninges are filled with parasites, either in sporulation or in all their stages of development. Clinically, there are cerebral phenomena.

"*b.* The stomach and intestines are chiefly invaded. In these organs the mature forms of the parasites are usually found; these are the cases of pernicious fever which present clinically intestinal phenomena."

Some authorities have endeavored to prove that the increased *fever* observed in many cases of pernicious malaria is responsible for the occurrence of the pernicious symptoms, but this is disproven by the fact that many cases of pernicious malaria do not prevent any increase in fever as usually observed in malarial infections, and some cases occur in which the fever is so slight as to hardly attract attention.

Classification of Pernicious Fevers.—The pernicious forms of malaria may be classified in three ways, *i.e.*, from the species of plasmodium causing them, as *tertian*, *quartan*, and *aestivo-autumnal* pernicious infections; from the character of the temperature curve, as *tertian*, *quartan*, *remittent* and *larval* infections; and from the most prominent symptoms present. Under the latter classification we may have *comatose*, *delirious*, *tetanic*, *eclamptic*, *hemiplegic*, *dysenteric*, *choleraic*, *algid*, *cardialgic*, *hemorrhagic*, *pneumonic*, *bilious*, and *typhoidal* pernicious fevers.

I shall describe the more important forms, using the terms applied to them because of their most prominent symptoms, but it must be remembered that these forms are not disease entities, and are classified in this manner only for purposes of clinical description.

Comatose Pernicious Form.—This is the most common form of pernicious malarial fever, and occurs in two ways, either as a sudden attack of coma or a gradually developing comatose condition during a paroxysm of fever.

The sudden development of coma is rare and, unless at once recognized and treated, invariably fatal. In this form the patient, who has generally suffered from repeated attacks of malaria and who has not felt well for some time, is suddenly stricken with profound coma, falls to the ground, and in fatal cases does not again regain consciousness. This form is apt to be mistaken for apoplexy or sun-stroke. The face is suffused, the pupils contracted, the pulse at first full and bounding, later soft, rapid, and thready, the respirations hurried and sometimes stertorous. The temperature is irregular, seldom reaching 103° F., and is often subnormal. Death generally occurs within two days.

The most common form of comatose malaria is that in which coma develops more or less gradually during an attack of the fever. The symptomatology of the attack is the same as in the ordinary paroxysm, but the nervous symptoms, such as restlessness and delirium, may be more marked. As a rule, the patient is restless and mentally depressed. Following this there develops a tendency to somnolence, which deepens into stupor and finally coma. Unconsciousness is complete, the patient lying perfectly quiet, or there may be restless movements of the arms and legs. The skin is often somewhat icteric in hue, and hot and dry; the pupils are generally equally contracted, but may be unequal or equally dilated. The icteric hue, which is often present in the conjunctivae, has led to a diagnosis of yellow fever in infected regions. The face may be cyanotic, but in old infections it is generally pale. Slight spasms of the muscles of the face are not infrequent. The tongue is tremulous, dry, and thickly coated, and slight hemorrhages into the skin are sometimes observed. There may be hemiplegia or total paralysis. The patellar reflex may be absent or slightly increased. The respirations are generally slow and quiet, but may be rapid, irregular, or stertorous. The Cheyne-Stokes type of respiration is sometimes observed. The pulse is generally slow, full, and incompressible at first, but becomes rapid and weak as the paroxysm progresses. The faeces and urine are passed involuntarily toward the last, and retention of urine may occur. In cases having a fatal termination, the pulse becomes thready, rapid, and irregular; the respirations intermittent, labored, and shallow; the skin pale and bedewed with a cold perspiration; the features pale, shrunken, apparently emaciated, and death occurs by collapse. In cases which recover, the temperature falls, accompanied by perspiration and the consciousness is slowly regained, but in many of these cases the improvement is only apparent and the patient relapses in the course of a few hours into a second paroxysm, and perhaps into a third, which usually results fatally. Between the paroxysms the mental condition is one of torpor or great mental depression, accompanied by severe headache. The duration of the coma is variable, lasting from a few hours to three or four days, but it generally does not persist longer than 24 to 26 hours.

As regards the course of the temperature in this form of malaria, it may be stated that it is irregular. Some patients have a high fever throughout, between 103° and 104° F., while in others the temperature may remain slightly above normal, or may be subnormal most of the time. In fatal cases the fever, if present, declines, as a rule, some hours before death, but it may ascend. Manson cites temperatures of 110° and 112° F. before death.

As an illustration of how low the temperature may run the following temperature record of a fatal case of quotidian aestivo-autumnal fever, of the comatose type, is of interest. This case was under my personal observation and was in the person of a soldier who had returned from the Philippine Islands infected with malaria.

TEMPERATURE RECORD.

July 15,	A. M.,	98.4° F.;	P. M.,	101° F.
July 16,	A. M.,	99° F.;	P. M.,	99.6° F.
July 17,	A. M.,	98° F.;	P. M.,	97.8° F.
July 18,	A. M.,	96.4° F.;	P. M.,	98° F.
July 19,	A. M.,	100.2° F.;	P. M.,	98° F.
July 20,	A. M.,	103° F.;	P. M.,	Died.

In this case the disease was not recognized by the attending physician until a few hours before death, when a blood examination was asked for, and large numbers of quotidian aestivo-autumnal plasmodia were found.

OTHER PERNICIOUS FORMS OF MALARIA IN WHICH NERVOUS SYMPTOMS PREDOMINATE.—Besides the comatose form of pernicious malaria there are other forms in which nervous symptoms predominate. Among these may be mentioned the *delirious* form, in which the patient has hallucinations, followed by violent excitement; the *eclamptic* form, which is common in children, in which the symptoms are similar to those of cerebrospinal meningitis, there being vomiting, headache, fever, pain in the back of the neck, convulsions, and coma; the *hemiplegic* form, characterized by hemiplegia; the *paraplegic* form, characterized by paraplegia; and the *amaurotic* form, in which, after the comatose symptoms have subsided, complete blindness may result. Among the most infrequent forms of pernicious malaria may be mentioned the *tetanic* form, characterized by trismus, convulsions, opisthotonos, and delirium, and the *ataxic* form, cases of which have been very thoroughly studied by Torti and Angelini.

In all cerebral types of pernicious malaria there may be present slight deviation of the eye-balls and slight convulsions, clonic in character, of the extremities. Epileptiform convulsions occur but rarely in adults, but are not uncommon in children. At Camp Stotsenburg almost every case of pernicious malaria that I observed among the native children was accompanied by epileptiform convulsions.

THE BULBAR FORM OF PERNICIOUS MALARIA.—A rare form of pernicious malaria, associated with symptoms of bulbar paralysis has been studied by Marchiafava, Bignami, and Bastianelli. Marchiafava thus graphically describes the symptomatology of this form of the disease. "The chief symptoms are difficulty in articulation, which may even reach anarthria, a weak and nasal voice, inferior facial paralysis often of one side only, a half-open mouth from which drops the saliva, a pendent lower lip, a dry and only slightly movable tongue, difficult or abolished deglutition. With these symptoms there are sometimes associated disturbances of equilibrium which recall the staggering gait of cerebellar disease. In a case of relapse Bastianelli and Bignami noticed an unsteadiness of gait as in drunkenness, diminution of strength of the left side, right facial paralysis, deviation of the tongue to the left, difficulty in speaking, nasal voice, grave prostration and apathy."

The symptoms in these cases, under proper treatment, do not persist for a longer period than two weeks, as a general rule.

THE PARALYTIC FORMS.—Malarial infections in which either *hemiplegia* or *paraplegia* occur are rare, and I have observed only one case in which hemiplegia was present. Landouzy has added much to our knowledge of such infections, and in his Thesis de Paris, of 1880, has collected 12 cases of hemiplegia occurring during malarial infection, of which eight were accompanied by aphasia. An intermittent form of paralysis has been described occurring with the paroxysms, and remitting afterward, but it is probable that the majority of these cases were hysterical in character.

THE ALGID FORM.—In certain regions of the Southern and Middle States and in other localities there occur pernicious forms of malaria known as algid forms. The symptoms develop after one or more ordinary paroxysms or they may be the primary symptoms. The characteristic condition is one of extreme collapse attended by profuse perspiration, the temperature at the same time being more or less elevated, although in some cases the temperature is subnormal. Patients suffering from this form of malarial infection present a characteristic countenance, the cheeks being drawn and pinched, the eyes sunken, the nostrils dilated and the skin bedewed with perspiration. The entire body is cold, the skin cyanotic and bathed with a cold sweat. The lips and finger-nails are intensely cyanotic. The tongue is tremulous, dry, and coated with a dirty white fur. The pulse is rapid, thready, and easily compressible, and generally more or less intermittent; the heart sounds are muffled and the second sound almost inaudible, and as death approaches the pulse becomes imperceptible; the respirations are irregular, superficial in character, and labored; the muscular weakness is extreme, while the mental condition of the patient is one of apathy to his surroundings and indifference as to his condition. These symptoms rarely last over a few hours, death generally resulting. This is one of the most pernicious types of malarial infection and one which is most resistant to treatment. Such cases have been described by Laveran, Thayer, Marchiafava, Bignami, Osler, and Sternberg. In one case observed by the writer in the person of a soldier who contracted aestivo-autumnal fever in Cuba, algid symptoms developed and death occurred in six hours despite all therapeutic aid. He had suffered from several paroxysms previously, none of which were of great severity and had been easily controlled by quinine. His blood showed numerous tertian aestivo-autumnal plasmodia.

THE CHOLERAIC FORM.—Certain cases of aestivo-autumnal infection present symptoms very closely simulating those of Asiatic cholera. It is not rare to observe cases of malaria accompanied by more or less diarrhoea, but in cases presenting the choleraic symptoms the stools suddenly become watery, very profuse, and numerous; they may be blood- or bile-stained, or almost colorless, and may contain mucus in small flakes, thus resembling the rice-water stool of cholera. The profuse diarrhoea lends to collapse, the face becoming pinched, the eyes sunken, the skin cold and clammy, and cyanotic in appearance. The

pulse and respiration become greatly weakened, and the patient, in a husky or tremulous voice, complains of severe cramps in the abdomen and thighs and intense thirst; he is greatly worried over his condition, and there is great mental depression. Death is the usual result in untreated cases, but where proper therapeutic measures are employed, the majority of the cases will recover. The temperature in the choleraic form is generally elevated. It is rarely that the choleraic symptoms recur, but when they do the result is almost invariably fatal.

This form of pernicious aestivo-autumnal fever simulates cholera so closely that the differentiation is very difficult, especially in countries where cholera is endemic or epidemic. The recognition of such cases is of great importance and can only be assured by the microscopical examination of the blood. Major Chamberlain, of the U. S. Army, has recently reported a most interesting case of choleraic pernicious fever, in which the symptoms were indistinguishable from those of cholera.

THE CARDIALGIC FORM.—This form of pernicious malarial fever is comparatively rare, and is generally associated in classification with the *gastralgic* form. The prominent symptoms are severe, agonizing pain in the epigastrium or over the cardiac region, and the vomiting of matter tinged with blood. Hiccough is often a distressing symptom, and severe hematemesis may occur. These symptoms occur during the febrile paroxysm. The patient presents an anxious countenance, a dry, glazed tongue, brilliant eyes, a retracted abdomen, cold extremities, hurried respiration, and a rapid, weak pulse; he suffers intense pain, and either groans or calls out under the torture which he is enduring. In fatal cases collapse occurs, accompanied by the symptoms of the algid form.

Laveran, Colin, and Haspel have described cases of the cardialgic and gastralgic forms of pernicious malaria. I have seen but one case conforming to this type. The patient was a soldier, 22 years of age, who had suffered from repeated attacks of malaria in the Philippine Islands. During the paroxysm in which I observed him he had most intense pain over the left nipple and the epigastrium, which radiated to the vertebral column and down the thigh; the pain was so intense that screams were forced from him. He repeatedly vomited blood-stained fluid and suffered greatly from hiccough. His temperature reached 103.4° F., his pulse was very rapid and thready, his extremities cold, and he complained of great prostration and was very anxious regarding his condition. Under repeated hypodermics of quinine his condition gradually improved and he eventually recovered.

THE DYSENTERIC FORM.—A considerable proportion of patients suffering from aestivo-autumnal malaria present symptoms of dysentery, consisting in frequent mucoid and bloody stools, tenesmus, colicky pain in the abdomen, and progressive emaciation. Scheube observed such cases in Japan and describes the malarial paroxysms as accompanied by the usual symptoms of acute dysentery. At the U. S. Army General Hospital at the Presidio of San Francisco, Cal., a very large proportion of cases of malaria, chiefly of the aestivo-autumnal

variety, presented dysenteric symptoms. In fact, 65 per cent. of cases of unrecognized malaria (before a blood examination) observed there were diagnosed either as diarrhoea or dysentery. This proves how commonly dysenteric symptoms are produced by malarial infection, and it is undoubtedly the fact that in tropical regions a certain proportion of cases diagnosed as dysentery are in reality the dysenteric form of malarial infection.

There exists a chronic form of malarial infection characterized by the symptoms usually observed in chronic dysentery, the patient suffering from attacks of diarrhoea, pain in the abdomen, muscular weakness, and loss of flesh and strength. This condition I have often observed in soldiers and it is always cure by the persistent use of quinine. The proper administration of this drug in multitudes of cases supposed to be dysenteric nature, until this was disproven by the microscope, has always resulted, in my experience, in the disappearance of the symptoms and a return to health. There is no doubt in my mind that there not only exists an acute, and sometimes fatal form of pernicious malaria, characterized by dysenteric symptoms, but that there is a form of malaria, more chronic in character, which is common in the tropics, which is characterized by repeated attacks of diarrhoea, dysenteric in type, and which is generally diagnosed by the practitioner as a mild form of dysentery.

THE HEMORRHAGIC FORM.—Marchiafava and Laveran have described cases of pernicious malarial fever characterized by severe hemorrhages into the skin and mucous membrane, as well as the occurrence of hematemesis, epistaxis, and hemoptysis. These symptoms may be so severe as to cause death. Another group of cases occurs in which the hemorrhages occur within the viscera, especially the lungs, and some of the pneumonic malarial infections are doubtless explained in this way. The temperature is extreme in most of these cases, which are undoubtedly very rare. Epistaxis even of quite severe character, is not, however, a very rare symptom in attacks of aestivo-autumnal malaria, for I have observed a large number of such cases.

THE PNEUMONIC FORM.—This form of pernicious malaria must be carefully distinguished from pneumonia which occurs as a complication of malaria. To Baccelli we owe the demonstration of a class of pernicious malarial fevers which, in their symptomatology, simulate lobar pneumonia. The chief symptoms are cough, pain in the side, dyspnoea, and the expectoration of blood-stained sputum. The onset does not differ from an ordinary paroxysm, but sometimes during the attack the lung symptoms mentioned develop suddenly, and the case looks clinically like a case of lobar pneumonia. It will be noticed, however, that the temperature curve is intermittent, and that during the afebrile periods the symptoms disappear as a rule. Percussion shows dullness over the affected lung, generally the lower lobe of one or both lungs, and auscultation coarse, sibilant râles. The condition is not a true pneumonia, but is due to the congestion brought about by the localization of the plasmodia in the capillaries of the lungs and the consequent plugging of certain circulatory areas.

I have observed several cases in which the symptoms so closely simulated lobar pneumonia that without the microscope they would have undoubtedly been considered as slightly atypical instances of that disease. The chart which is here given (Chart C) is a good illustration of the temperature in these cases, and is from a case regarded as pneumonia, because of the clinical symptoms, until a microscopical examination of the blood showed numerous tertian aestivo-autumnal plasmodia and the administration of quinine quickly cured the infection.

The following case for which I am indebted to Lt. Col. Charles Richard, Medical Corps, U. S. Army, is an interesting example of this form of malaria. "The patient, a soldier, gave no history of a previous malarial attack. He had suffered for some days from fever, but had no chills. Had much pain in the chest, a cough with expectoration, and some vomiting. The maximum temperature was 104° F., but there was no regularity in the curve. The man looked very sick and was the picture of lobar pneumonia. Physical examination showed a general bronchitis. The spleen could be felt below the ribs. The examination of the blood showed numerous "ring-forms" of the aestivo-autumnal parasites, and treatment with quinine resulted in recovery."

Scheube has observed cases of pneumonic malaria in Japan and has no hesitation in claiming that they are due to the localization of the plasmodia in the lungs, and if we consider the frequency with which these organisms are found localized in other organs, as the brain, and the connection clearly established between such localization and the symptoms produced, we must admit that there is no reason to doubt that the symptoms observed in this type of malaria are due to the plasmodia. Microscopic study of sections of the lung from fatal cases of malaria conclusively prove that, in rare instances, the plasmodia occur in immense numbers in the capillaries of the lung, and that the lesions produced are sufficient to excite symptoms simulating those of lobar pneumonia.

The Bilious Form ("Subcontinua bilosa").—Certain cases of malarial infection present a symptom-complex in which jaundice and the vomiting of bile-stained fluid are most prominent. These cases have long been known under the term of "bilious remittent fever." The attack is generally characterized in the beginning by well-marked malaria paroxysms, but the temperature soon becomes more or less remittent or continuous. Marked jaundice appears and severe vomiting is present, the matter vomited being greatly bile-stained. Epistaxis is common, and hematemesis often occurs. Delirium may be present or there may be a condition of semi-coma or even coma. The patient often complains of severe pain in the epigastrium and hiccough is one of the most common symptoms. The temperature curve in well-marked cases is generally remittent or almost continuous, somewhat resembling that of typhoid fever. If untreated, this form of the disease is almost invariably fatal, but if properly treated recovery is generally the result.

Of the very rare forms of pernicious malaria may be mentioned the *syncopal* form, first described by Sternberg, in which syncope occurs upon exertion dur-

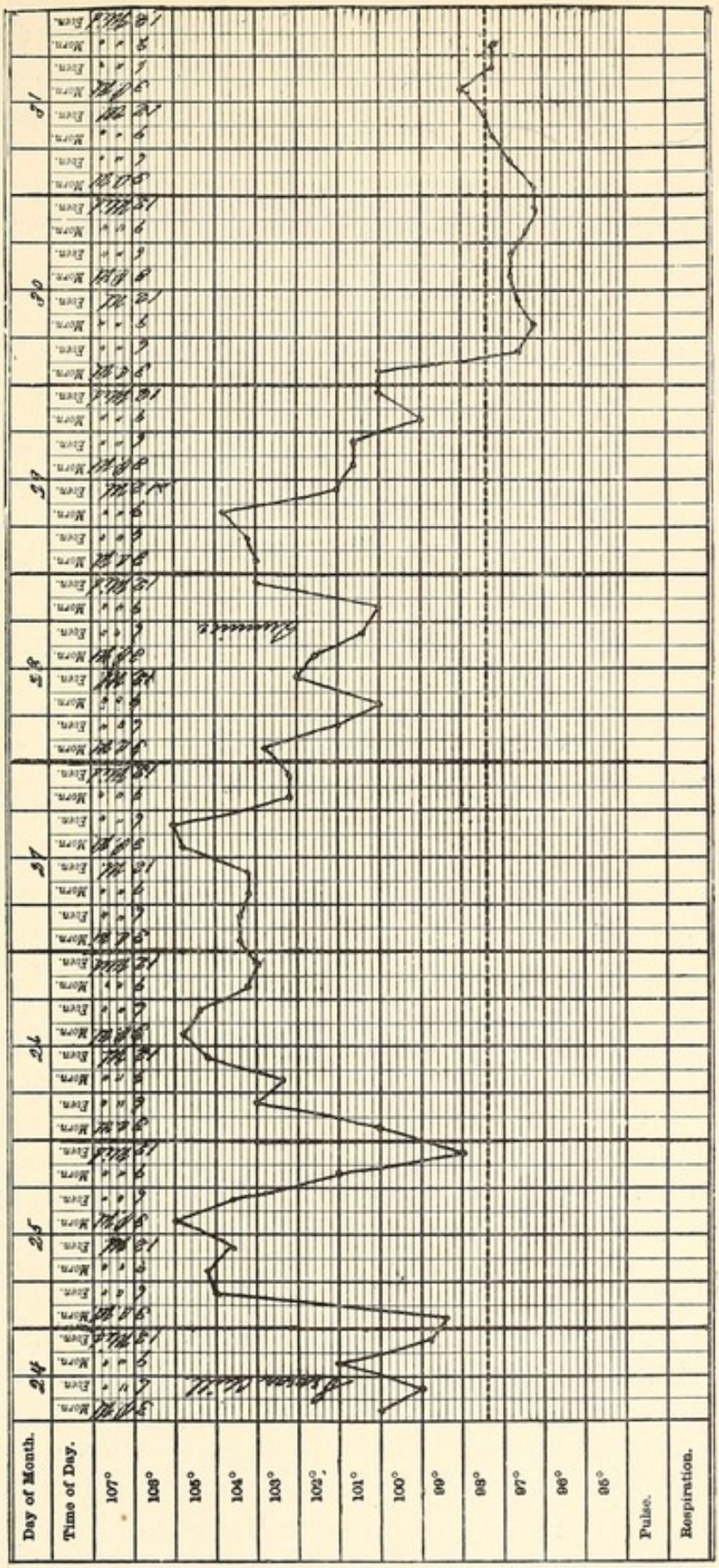

CHART C.—Aestiva-autumnal Malaria. Pneumonic type.

ing the decline of the fever; the *diaphoretic* form, characterized by the occurrence of very profuse sweating, so severe as to produce collapse and death; the *exanthematous* form, characterized by the occurrence of a scarlatiniform rash upon the skin during the paroxysms, followed by desquamation; the *pleuritic* form, in which intermittent attacks of sharp, lancinating pain occur in the side, and, lastly, pernicious infections without fever, which have been described by Pampoukis, who considers such infections much more dangerous than those in which the temperature is high.

Examination of the Blood in Pernicious Malaria.—The examination of the blood during an attack of pernicious malarial fever will almost invariably result in the demonstration of large numbers of malarial plasmodia, whatever species may be concerned in the etiology of the infection. In no other forms of malaria are the plasmodia so numerous in the peripheral blood as in pernicious attacks, and often a single microscopic field will contain from ten to twenty infected corpuscles.

The findings in the blood vary in many cases with the period of time in which the examination is made, but as most pernicious infections are due to multiple group infection, the examination will show the presence of plasmodia undergoing various stages of development. In the case of regularly intermittent aestivo-autumnal pernicious infections, if the blood be examined at the acme of the paroxysm, the plasmodia present will be mostly of the unpigmented variety, while if the blood be examined during the intermission or one or two hours before the beginning of the paroxysm, the pigmented forms of the plasmodium will be found. At whatever time the blood is examined, however, it will be found that the plasmodia are all approximately in the same stage of development.

On the other hand, if the blood of cases suffering from pernicious aestivo-autumnal fever, in which the temperature curve is irregular or almost continuous, be examined, it will be found that both pigmented and unpigmented plasmodia will be present, at whatever period the blood be examined. These remarks apply also to pernicious cases due to the tertian and quartan plasmodia, save that in these two forms of infection the sporulating stage will be found in peripheral blood. As I have shown, the presence of a few organisms in the peripheral blood in aestivo-autumnal infections is not always evidence of a mild infection, as multitudes of plasmodia may be localized in the viscera, and the infection may be of a very deadly nature.

The aestivo-autumnal pernicious fevers present themselves in so many disguises, and exhibit so many atypical symptoms, that even the most acute clinical diagnostician may be entirely deceived regarding these cases. The microscopical examination of the blood should never be neglected in the diagnosis of any form of malarial infection, and certainly not in pernicious cases in which the life of the patient is threatened and every moment is precious. The blood examination consumes but little time, is absolutely conclusive in its results, and may save the life of the patient. The fact should never be forgotten that

the aestivo-autumnal fevers may readily become pernicious, and that the longer a malarial infection remains unrecognized the greater are the chances for the development of pernicious symptoms, and, therefore, the greater the danger of the patient. Ignorance of the use of the microscope is no excuse for an omission which may cost a human life.

In illustration of this I have in mind the case of a soldier believed to be suffering from acute catarrhal jaundice. His symptoms upon entering the hospital were so typical of this condition that the physician in charge delayed the request for a blood examination for several days. The patient finally lapsed into a semi-comatose condition and a blood examination was then requested. The blood was found to be literally loaded with quotidian aestivo-autumnal plasmodia, and, while the most energetic treatment was at once instituted, despite all that could be done the patient died in a few hours. Without doubt this man's life could have been saved had the blood been examined earlier, before the intense malarial intoxication had occurred. In another case the patient lay in coma for three days before a blood examination was requested, upon the supposition that he was suffering from some brain lesion, and here again death occurred because the malarial condition was not determined in time. The only safety against mistakes of this character in regions in which malaria is endemic or in the case of patients coming from malarial localities is a careful microscopical examination of the blood.

CHAPTER IV.

Latent Malaria; Masked Malaria; Recurrent Malaria; Etiology of Latency and Recurrence; Intracorpuscular Conjugation of the Malarial Plasmodia.

Latent Malarial Infection.—In the study of the malarial fevers one is much impressed by the fact that a considerable proportion of patients showing some form of the plasmodia in the blood present no symptoms of the infection, and these cases are of great importance from an epidemiological standpoint. In such patients the infection is *latent*, a latent malarial infection being one in which the plasmodia may be demonstrated to be present in the blood, but in which no clinical symptoms of the disease of sufficient gravity to attract attention are to be observed. The term should not be confined to those instances in which no symptoms of malaria have ever been present, for if the plasmodia be present in the blood during the afebrile period in recurrent cases, the disease is as truly latent during that period as before the initial attack. In many latent infections some complicating disease may be present, and this is almost invariably true of latent malarial infections discovered in hospital practice. It is obvious that all cases of latent malarial infection are a great source of danger to others in localities where the Anophelinae are present.

The material upon which the observations and conclusions detailed in this chapter are based consists of 1,653 cases of malarial infection, 1,267 of which were observed at the U. S. Army General Hospital, Presidio, of San Francisco, in American soldiers returning from service in the Philippine Islands, and 386 cases studied at Camp Stotsenburg, in the Philippine Islands. Of the latter cases 248 occurred in Americans and 138 in Filipinos. Besides the cases mentioned a considerable portion of the data regarding latency and recurrence has been obtained from the observation of malarial infections contracted by American soldiers while in Cuba, and studied at the Simpson U. S. Army General Hospital, Fortress Monroe, and at Camp Columbia, near Havana, Cuba. Of the 1,653 cases of malaria upon which the statistics of this chapter are based, 424, or a little over 25 per cent., were latent infections. Of these 307 were in American soldiers, while 115 occurred in natives of the Philippine Islands.

As regards the species of plasmodium present in the blood, the 424 cases were divided as follows:

Tertian,	110
Quartan,	8
Tertian aestivo-autumnal,	272
Quotidian aestivo-autumnal,	25
Combined tertian and tertian aestivo-autumnal,	7
Combined tertian and quotidian aestivo-autumnal,	2
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In order to understand the significance of the above table it will be necessary to consider the latent infections of Americans and of natives of the Philippines separately.

Latent Infections in Americans.—The latent infections of Americans, as regards the species of plasmodium present, were divided as follows:

Tertian,	81
Quartan,	0
Tertian aestivo-autumnal,	199
Quotidian aestivo-autumnal,	21
Combined tertian and tertian aestivo-autumnal,	4
Combined tertian and quotidian aestivo-autumnal,	2
	307

The 307 latent cases observed in Americans occurred, with but few exceptions, in soldiers invalided home from the Philippines. As is evident, the aestivo-autumnal plasmodia are much more frequently encountered in latent cases than any other species, 220 of the 307 latent infections in Americans being due to either the tertian or quotidian aestivo-autumnal plasmodium. The occurrence of so large a proportion of aestivo-autumnal infections is not due to any peculiarity in the type of plasmodia other than that the aestivo-autumnal organisms are much more resistant to quinine than the other species, and for that reason more latent infections with these plasmodia are found in the class of patients examined, who had probably all taken quinine at one time or another. It is also true that in the Philippines, as in other tropical countries, the aestivo-autumnal fevers are more prevalent than tertian or quartan fevers.

The fact that aestivo-autumnal infections are particularly apt to exist in a latent form is of importance, as the diagnosis of such an infection may prevent a sudden pernicious attack; and it is also important from an epidemiological standpoint, as an individual thus harboring the plasmodia is, or may become, a source of infection to the community in which he is living. It is thus evident that the blood of every individual returning from a malarial region should be examined, both as a safeguard to himself and to the community in which he may be residing.

Frequency of Latent Infection in Americans.—Of the 1,297 cases of malaria studied in Americans, 307 or nearly 24 per cent., were latent infections. It should be remembered that in all of these cases there were absolutely no symptoms of malaria present, and had it not been for the examination of the blood these men might have remained sources of infection for weeks or months.

As showing the frequency of latent malarial infections and the importance of their recognition, I quote the following from a report upon latent and masked infections by the writer, published in American Medicine, in 1904:

In August, 1902, Company H, 16th Infantry, U. S. Army, returned to San Francisco from the Philippines, having served in the Cagayan Valley, a notori-

ously malarial region in those islands. On August 16, 1902, this company, out of a total strength of some 60 men, had 14 men in hospital suffering from malarial infection, all having had chills since arrival in the United States. On account of this large proportion of infected men, I believed that it would be advisable to make a blood examination of the entire company, and accordingly, on August 17, I examined the blood of every man on duty in Company H, with the following results: Of the 47 men who were doing duty, including the officers, I found that 27 presented some form of malarial parasite in their blood. Of these 27 cases, 25 were infected with the aestivo-autumnal plasmodia; 13 showing *gametes* (crescents) of the tertian aestivo-autumnal species; 10 showing crescents and ring-forms of the same species; two showing crescents and ring-forms of the quotidian aestivo-autumnal plasmodium; and two showing nearly full-grown forms of the simple tertian plasmodium. Thus of a total strength of 60 men, 41, which includes those sick in hospital, showed some form of malaria infection, while 27, without presenting any symptoms of malaria, showed parasites in the blood.

A study of the blood findings in this company is of great significance, not only as showing the importance of a blood examination in persons returning from the tropics, but because, in most instances, the *gametes* of the aestivo-autumnal plasmodia, the most dangerous of the malarial parasites, are the forms present. As the *gametes*, or crescents, are the forms which undergo development within the mosquito it is evident that these men could infect mosquitoes of the genus *Anopheles* wherever they might go. In this way localities hitherto free from this dreaded type of malaria might become infected.

Latent Malarial Infection Complicating Other Diseases.—A very large number of latent malarial infections in Americans occur as complications of some other disease process, and it is important that the malarial factor in such cases be recognized and removed. As an illustration of the frequency of this condition I have compiled the following table, giving the original diagnosis in 106 cases in which a latent malarial infection was found to exist. In nearly all of these cases the removal of the malarial complication resulted in improvement of the health of the patient.

Diagonisis	Number of cases
Chronic dysentery	15
Chronic diarrhoea	20
Pulmonary tuberculosis	3
Fractures and wounds	11
Chronic gastritis	8
Amoebic dysentery	15
Chronic indigestion	3
Hernia	3
Otitis media	3

Diagnosis	Number of cases
Acute melancholia	3
Rheumatism	3
Syphilis	2
Insanity	2
Paralysis	2
Acute dementia	2
Convalescent from operation	1
Arthritis formans	1
Retinitis	1
Varicocele	1
Tachycardia	1
Uncinariasis	1
Diabetes mellitus	1
Paraplegia	1
Acute endocarditis	1
Hemorrhoids	1
Adenitis, cervical	1
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A consideration of some of the data given in the above table is of interest.

In 15 cases of chronic dysentery, non-amoebic in type, a latent malarial infection was discovered. All of these patients gave a history of having suffered from malaria in the Philippines, but of not having had any symptoms of the disease since arrival in the United States. The much controverted statement that there exists a form of dysentery due to the localization of the malarial plasmodia in the capillaries of the intestine is of interest in connection with these cases, as treatment of the malarial infection resulted in every case in marked improvement of the dysenteric condition and ultimately in complete recovery, so that it is probable that some of these cases were entirely malarial in character. From personal observation I know that some aestivo-autumnal infections are accompanied by a bloody diarrhoea, and it is my belief that many cases diagnosed as dysentery in tropical countries are due to the invasion of the intestines by the malarial plasmodia or to the action of the malarial poison. The same remarks apply to the 20 cases of chronic diarrhoea in which a latent malarial infection was discovered.

In 15 cases of amoebic dysentery a latent malarial infection was observed. In these cases *Entamoeba histolytica* was present in the faeces and one of the species of plasmodia in the blood.

In nine cases of fractures and two of bolo wounds an examination of the blood showed the presence of malarial plasmodia, although no symptoms of such infection were noticed. This was also true in one case convalescent from operation.

Latent Infection in Natives of the Philippine Islands.—I have already noted the results of various observers in the examination of the blood of native races in tropical countries, and have shown that latent infection is very common in certain localities among the native population. The following observations upon the latent infections of the natives of the Philippines, made at Camp Stotsenburg, are in agreement with those of other observers and prove that the Filipino, like other tropical races, suffers from malarial infections in early childhood, but, unlike some native races, does not establish any marked immunity in adult life.

Frequency of Latent Infection in Filipinos.—During five months in which I was stationed at Camp Stotsenburg I observed 386 cases of malaria in which I was able to demonstrate the parasites in the peripheral blood. Of these, 248 occurred in Americans and 138 in Filipinos. As regards the type of infection, 98 were infected with the tertian plasmodium, of which 63 were Americans and 35 natives; eight with the quartan plasmodium, of which 2 were Americans and 6 natives; and 272 with the aestivo-autumnal plasmodia, 183 being Americans and 89 natives. Of the aestivo-autumnal infections, 258 were due to the tertian aestivo-autumnal plasmodium and 14 to the quotidian variety. All of the latent infections, 115 in number, occurred in Filipinos.

It appeared probable to me in considering the malarial situation at this post that the natives living in the barrios in close proximity were the principal source of infection, as the sanitary conditions in the post proper were such as to prohibit the belief that much malarial infection could originate there, while breeding-places of mosquitoes abounded in the barrios and mosquitoes belonging to the Anophelinae were much more numerous in them than at the post. The barrios were constantly visited by the soldiers, especially at night, and the conditions for the spread of both human and mosquito infection were ideal. In order to determine how large a proportion of the native population of the barrios was infected, I made blood examinations of as many natives as possible, living within two miles of the post. The result proved beyond question that the origin of malarial infection at Camp Stotsenburg was to be found very largely in the natives living in the immediate vicinity, and that any efforts to limit the spread of the disease must take this condition into account. In a considerable number of the cases of latent infection, even in the youngest children, a history of previous attacks of fever could be obtained, but in none of them were any symptoms of malaria present at the time of the examination of the blood. In all, the blood of 225 Filipinos was examined, of which 115, or 51.1 per cent., showed a latent malarial infection.

This percentage of latent malarial infection should not be regarded as typical of all localities in the Philippines, for many localities are free from malaria, while in others the malarial index is low. Routine blood examinations of the natives of a tropical country will give much valuable information as to the malarial endemicity of the locality, and such examinations should be

made before permanent military posts or civilian residences are established in the tropics.

Of the 115 latent infections discovered, the tertian plasmodium was present in 29, the quartan in six, and the aestivo-autumnal in 77; of the latter, 73 were due to the tertian aestivo-autumnal plasmodium, and four to the quotidian aestivo-autumnal plasmodium. There were three combined infections with the tertian and the tertian aestivo-autumnal plasmodia.

Latent Infection in the Adult Natives.—I was able to examine the blood of but 45 adults, of whom 28, or 62.2 per cent. were infected; of these, five infections were due to the tertian plasmodium, and 23 to the tertian aestivo-autumnal plasmodium. It is very probable that a further study of the blood of a greater number of adults would materially reduce this great percentage of infections, but from the results obtained, it is evident that the adult Filipino is more often infected than the negro in Africa or the native of India. It is more than probable that the adult Filipino possesses little or no immunity to malaria, despite the fact that in malarial localities such adults have, from childhood, suffered from repeated attacks of the disease. I have notes upon several adults, who, within two years, were admitted to the hospital from 8 to 16 times with malarial infections. The reason for this lack of immunity of the adult Filipino to malarial infection is difficult to understand, but I believe that there is no question but that it does exist to a marked degree even in the most malarial localities.

Latent Infection in Native Children.—Of the 180 children whose blood I examined, 87 or 48.3 per cent., showed the presence of the malarial plasmodia. Of these latent infections, 34 were due to the tertian plasmodium, six to the quartan, and 44 to the aestivo-autumnal species. Of the latter, 40 were due to the tertian aestivo-autumnal species and four to the quotidian. There were three combined infections with the tertian and tertian aestivo-autumnal plasmodia. The infections in children diminished in number with advancing age. Thus, between the ages of one month and five years, among 40 children, 79 per cent. were infected; between 5 and 10 years, 37 per cent.; and between 10 and 15 years, 24.5 per cent. These results agree with those of Koch, Stephens and Christophers, James, and others, who invariably found that the younger the child, the more susceptible it was to malaria.

The percentage of latent infections in children varies considerably in the different barrios in which the examinations were made. For instance, in the town of Mabalacat, 25 school children between the ages of 5 and 10 years were examined, of whom seven, or 28 per cent., were found infected; while of children between 10 and 15 years of age, 35 were examined; of whom seven, or 20 per cent., were infected. In the town of Dolores, 11 school children between the ages of 5 and 10 years were examined, of whom seven, or 63.6 per cent., were infected; while of 13 children between 10 and 15 years of age, four, or nearly 31 per cent., were infected.

Family Infection.—Not only do the barrios differ in the ratio of malarial

individuals to those in health, but certain portions of the barrios are most malarious, while other portions are almost free from infection. It was also observed that malaria in these barrios was very largely a family disease, certain families suffering severely, while others were free from infection. The following table illustrates the family character of malarial infection, being compiled from the data obtained in one barrio where all of the families resided.

Family	No. members	No. infected	Type of infection
1	4	2	1 aes-autumn. 1 ter.
2	3	2	2 aes-autumn.
3	4	2	1 aes-autumn. 1 ter.
4	5	4	2 aes-autumn. 1 ter. 1 quartan.
5	4	2	2 aes-autumn.
6	3	2	2 aes-autumn.
7	4	3	2 aes-autumn. 1 ter.
8	3	2	1 aes-autumn. 1 ter.
9	3	2	2 tertian.
10	6	4	2 aes-autumn. 2 ter.

In considering this table it should be remembered that all these infections were latent in character, and I have repeatedly observed families in which every member was suffering from a malarial infection, either latent or active. Family No. 4 in the above table is of special interest because, of its five members, one was suffering from a severe attack of tertian malaria at the time I made the examination, while of the other four, two presented aestivo-autumnal, one the quartan, and the other the tertian plasmodium in the blood, so that in this one family all the species of the malarial plasmodium could be studied.

The *pathology* of latent malarial infection has already been considered in the chapter devoted to the special pathology of the malarial infections.

Practical Deductions.—From the facts given above, I believe that it is obvious that latent malarial infections are of much importance from both epidemiological and clinical standpoints; it is certainly true that latent infections are a great source of malarial disease, and in the tropics, the latent infection of the native is undoubtedly the principal source of infection of the white man. The importance of an examination of the blood of the native population of any given locality cannot be overestimated in the fight against malaria. This is especially true in the tropics, for only from the results of such an examination can the endemic areas of malaria be found and guarded against. Only to one who has attempted it, can the almost hopeless task of exterminating mosquitoes in tropical regions be appreciated, and, in fact, in many localities it is impossible of accomplishment. This being so, it is apparent that it is useless

to rid a locality of malaria, if it is impossible to eliminate the mosquito, unless the infection is first stopped in the native, and in the tropics it appears to me that the greatest hope of success is combating malaria lies in the treatment of the latent infections of the natives.

Masked Malarial Fever.—Cases of malarial infection in which the symptoms are masked by those of some other disease or in which the symptoms closely resemble those of other diseases are known as masked infections. In such cases malarial symptoms are present, but they are overshadowed by the symptoms of the complicating disease. Such cases are common and should be carefully distinguished from those instances of latent infection occurring during other disease processes. In the latent cases no symptoms of malaria are present, while symptoms are present in the masked cases. The following table shows the diagnosis in 91 cases of masked malaria in all of which the symptoms of the disease diagnosed masked those of the malarial infection.

Disease	No. cases masked
Chronic dysentery	45
Chronic diarrhoea	5
Pulmonary tuberculosis	18
Amoebic dysentery	4
Acute bronchitis	2
Rheumatism	1
Measles	3
Typhoid fever	2
Pneumonia	2
Abscess of the liver	1
Furunculosis	1
Diabetes mellitus	1
Gonorrhoea	4
Cellulitis	1
Appendicitis	1
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The instances in which the malarial symptoms so closely simulate those of some other disease are also numerous, and it may truly be said that malaria may simulate almost any disease so closely that only a microscopical examination of the blood will enable us to make a diagnosis. As a rule, however, the periodical nature of the attacks will raise a suspicion of their malarial nature. It should also be remembered that in the older literature of malaria many conditions were classed under masked malaria which were not malarial in nature and which would have been correctly diagnosed had the plasmodia been discovered at the time they were described. No case should be considered as one of masked malaria, unless a blood examination has shown the presence of

the malarial plasmodium. Among the most common atypical symptoms of malaria which are often considered as being due to some other disease may be mentioned various neuralgic affections, periodical in type, especially of the fifth nerve, the intercostal nerves, and of the occipital region; convulsions especially common in malarial attacks in children; various nervous conditions, as insomnia, delirium, melancholia, mania, and dizziness; and certain of the infectious diseases may be so closely simulated by malaria as to be almost indistinguishable, especially typhoid, pneumonia, yellow fever, cerebrospinal meningitis, and pulmonary tuberculosis.

The following table of 96 cases of masked malaria in which the diagnosis as made before the malarial nature of the condition was discovered is given, well illustrates how frequently malaria simulates other disease processes, and how valuable a microscopical examination of the blood is in the diagnosis of disease. In all of these cases, the symptoms present were sufficiently typical of the disease diagnosed as to render the diagnosis justifiable, and in all, treatment with quinine caused a rapid disappearance of the symptoms.

Diagnosis	No. of cases
Neuralgia, facial	3
Chronic dysentery	15
Chronic diarrhoea	6
Pulmonary tuberculosis	5
Acute bronchitis	4
Pneumonia, lobar	3
Appendicitis	2
Peritonitis	1
Insolation	6
Syphilis	2
Melancholia	4
Insanity	2
Rheumatism, muscular	4
Typhoid fever	10
Malta fever	6
Anaemia	20
Acute catarrhal jaundice	1
Yellow fever	1
Cerebrospinal meningitis	1
	96

It is not necessary to consider this table in detail, but I would call attention to the fact that in most of these cases the infection was due to the aestivo-autumnal plasmodium, and that most of them had been insufficiently treated with quinine, which, no doubt, had much to do with the atypical nature of the symptoms. The confusion of malarial infection with typhoid, Malta fever,

and tuberculosis is of frequent occurrence and has much to justify it, as the symptoms of malarial fever of aestivo-autumnal type, often very closely simulated those of any one of these diseases.

At first sight it would seem almost impossible that a diagnosis of lobar pneumonia would be made in a case of malarial fever. I have already described the occurrence of cases of malaria so closely simulating lobar pneumonia that without the microscope a differential diagnosis could not be made, and believe that the two following clinical histories amply illustrate how closely the symptoms of a malarial infection may simulate those of lobar pneumonia.

I am indebted for the notes of Case I to Dr. Edmund Barry, formerly of the United States Army.

Case I.—W. D. C. Patient was admitted to the hospital from the Presidio of San Francisco, with a transfer slip diagnosis of lobar pneumonia. On admission the patient was somewhat emaciated; his mental condition was apathetic; tongue coated, and bowels constipated; he complained of chilliness most of the time. The spleen was enlarged considerably and tender. Soon after admission he had a severe chill and became delirious, his temperature reaching 106.2° F. There was marked difficulty in breathing and severe pain in the side. An examination of the lungs showed marked friction sounds over the middle lobe of the right lung, and dullness over the same area. Patient remained slightly delirious for five days and during this time the physical signs of pneumonia increased, marked dullness developing over the lower lobe. Respirations were rapid, exceeding 50, and the pulse very weak. He coughed considerably, but there was no expectoration. At the end of five days the blood was examined and numerous "ring forms" of the tertian æstivo-autumnal plasmodium were found. Immediately upon receipt of the laboratory report, quinine was administered, and in two days the patient was so much better that he was able to sit up and was about within four days.

I personally examined this patient during the period in which he was considered to be suffering from pneumonia, and his symptoms were typical of that disease. His temperature curve was atypical, however, showing marked remissions. (See Chart C.)

Case II.—C. S. The patient was admitted to the hospital with a diagnosis of acute lobar pneumonia of the lower lobe, right lung, and at the time of admission was in a comatose state. After recovery the following history was obtained: The illness began with a soreness in the chest and expectoration, slightly blood-tinged. Just before admission he had a severe chill, accompanied by pain in both sides of the chest, and at this time he spat up considerable blood. The pain was very distressing on deep inspiration. At the time of admission his respirations were 40; pulse 100; and temperature 104° F.

An examination of his lungs showed increased vesicular breathing, almost bronchial in character; increased vocal fremitus; and numerous crepitant râles over the right lung and lower lobe of the left. Both lower lobes were dull upon percussion. The spleen was very much enlarged and there was slight enlargement of the liver. He was admitted to hospital Jan. 20, and a blood examination was made the next day. The blood showed numerous full-grown tertian plas-

modia and a few "ring-forms" of the quotidian aestivo-autumnal plasmodium. Before the blood examination was made the diagnosis of pneumonia was concurred in by the attending surgeon, and treatment for that condition instituted. On receipt of the report from the laboratory, quinine was administered, which was followed by a rapid improvement in the patient's condition, the temperature falling from 104° F. to 96° F. The administration of quinine was continued and rapid recovery ensued.

In this case we have a clear history of the outset of what was apparently true lobar pneumonia, the symptoms agreeing in every way with those usually observed in that disease. There was pain in the side, chill, high temperature expectoration of blood-stained sputum, and the physical signs which are considered so characteristic of lobar pneumonia, yet two days' treatment with quinine brought the temperature to normal, all of the symptoms disappeared, and the patient was up and about within a week. Such cases as these prove that the localization of the malarial plasmodia within the capillaries of the lungs is capable of producing true pneumonic symptoms.

In rare instances a malarial infection will simulate appendicitis or peritonitis so closely as to render the diagnosis impossible clinically. The following case is of special interest, as it demonstrated how closely malarial infection may simulate appendicitis.

The patient was an officer of the U. S. Army who was transferred to the Army General Hospital at San Francisco with a diagnosis of suspected appendicitis, transfer being made with a view to operation if the diagnosis was verified. He gave a history of having had intermittent malarial attacks in the Philippines which did not necessitate admission to sick report. He had not been feeling well for some time, and on the day before admission to the hospital he had an attack of pain in the region of the ascending colon. Upon admission he complained of pain in this region, at times very severe; his tongue was coated; bowels regular; and his pulse and temperature about normal. A blood count was made and a slight leucocytosis was found. Physical examination showed no rigidity of the muscular wall, but he complained of pain in the right iliac region on pressure, and after careful examination, operation the next morning was determined upon. That evening he had a slight chill and his temperature rose to 104° F. An examination of the blood was made and numerous hyaline forms of the tertian aestivo-autumnal plasmodium were found. Quinine was promptly administered, which resulted at once in a fall of temperature, and continued administrations in complete recovery. In this case an operation would undoubtedly have been performed in the morning for a condition essentially malarial in character.

It is obvious that the recognition of these cases of latent and masked malarial fever is of the greatest importance, as in the latent infections we are thus able to cure the disease before any annoying or dangerous symptoms appear, and in the masked cases we are able to remove the malarial element in those cases in which other disease symptoms mask the malaria, or discover and treat the

true cause of disease in those cases in which the malarial symptoms resemble those of other infections.

Duration of Latent and Masked Malarial Infections.—The length of time during which a latent infection may exist is uncertain, but it is probable that in many cases it may be for weeks or months. I recall one case in which the aestivo-autumnal plasmodia were found in the blood for six weeks before a paroxysm occurred, and I have observed many cases in which the plasmodia were demonstrated in the blood for from seven to fourteen days before the appearance of clinical symptoms.

The masked cases may continue for weeks where the infection is not of a pernicious character or death may occur within a few days.

It should always be borne in mind that most latent and masked infections are caused by the aestivo-autumnal plasmodia and that such infections are especially liable to develop pernicious symptoms; that the clinical symptoms in many of these cases are absolutely unreliable, so far as diagnosis goes; and that in all diseases occurring in malarial regions a microscopical examination of the blood should never be omitted.

Recurrent Malarial Infections.

It is probably a fact that with very few exceptions (and these most vigorously treated with quinine) every primary malarial attack is followed by one or more relapses or recurrences. By recurrences I mean the appearance of symptoms due to the same group of parasites causing the original infection, and not to a reinfection by another group. So common are recurrences in malaria that a prevalent belief is that "once a victim of malaria, always a sufferer from the disease"; while this belief is unfounded, recurrences often do persist for months, and sometimes, although very rarely, for years. They are most common and persistent in the aestivo-autumnal infections, as would be expected from the greater resistance of these infections to treatment.

To the clinician the time elapsing between the initial attack and the recurrences is one of the greatest interest, while to the investigator the etiology of recurrences and the *modus operandi* have proven a fruitful field for controversy and, from the very nature of the problem, of theoretical deduction.

Time of Recurrence.—Authorities differ somewhat as to the time of recurrence in the different types of malarial infection, and when we consider the difficulty of ruling out reinfections, especially in those who reside in a malarial locality, the slight difference in the time as given by various observers is indeed surprising. In malarious regions it is obviously impossible, in many instances, to be sure that the reappearance of symptoms is not due to reinfection, unless a different species of plasmodium be present than that found during the initial attack. As a basis for the computation of the time of recurrence, Celli reckons "as recurrent every case of fever which repeats itself in the same

individual from the July of one year to the end of June of the following year, or during all the cycle of the same yearly epidemic." While, of course, errors are bound to occur with this method of computing recurrences, Celli believes, and I think justly, that for practical purposes it is as perfect as is possible under the circumstances. I have used this method in compiling the table of recurrences which follows, but have taken the further precausion of selecting only those cases which I am reasonably sure could not have become reinfected.

Borius, an investigator working in Senegal, found that recurrences took place preferably upon the seventh, fourteenth, twenty-first and twenty-eighth day after the initial attack. Of 226 cases, 128 relapsed, and of these 18 relapsed upon the seventh day, 64 on the fourteenth, 31 on the twenty-first, and nine on the twenty-eighth day. Ninety-eight cases relapsed irregularly on the ninth, tenth, sixteenth, and twentieth days. All of the cases took quinine at the time of the attack. Barudel from his observations, concludes that quotidian fever most frequently relapses upon the seventh day, tertian upon the fourteenth, and quartan upon the twentieth.

Mariotti-Bianchi concludes that benign tertian infections relapse between the fifth and eighteenth days after infection, while aestivo-autumnal fevers relapse between five and twenty-one days, but frequently between five and nine days after the initial attack.

Zieman found that in West Africa aestivo-autumnal infections relapsed between nine and twelve days after the primary attack, which, as he points out, is practically the same as the incubation period.

Werlhof, from his experience, decides that tertian infections relapse most frequently in the second, and quartan in the third week, while Duden claims that on the east coast of Africa, quotidian fever relapses almost invariably upon the seventh day.

Authentic recurrences after long intervals of time are rare, but such cases unquestionably occur. Thayer relates an interesting example and Mariotti-Bianchi observed in tertian infections recurrences between three and thirteen months, and in aestivo-autumnal fevers, between four and eight months apart. V. Leyden observed a recurrence of a malarial infection three years after the initial attack, and Schilling has observed recurrences after eight and a half months and after two and a half years. As regards recurrences after such long intervals as two or three years I agree with Mannaberg that the evidence is not sufficient to prove undeniably that the so-called recurrences were not reinfections, and such cases appear to me to be very doubtful.

The following table of recurrences in aestivo-autumnal and tertian malaria are prepared from carefully selected cases in which reinfection was considered at least very improbable, and which, I believe, may be considered as portraying the exact length of time occurring between the relapses in these types of malarial fevers. The patients were all American soldiers observed in hospital and thoroughly treated with quinine during the active symptoms, while most of them received prophylactic doses of quinine once a week, which undoubtedly delayed somewhat the relapses in the men so treated.

Aestivo-autumnal Tertian Recurrences.—Time of the Various Recurrences in 55 cases of Tertian Aestivo-autumnal Malarial Infection.

Case No.	Initial attack	First recurrence	Second recurrence	Third recurrence	Fourth recurrence	Fifth recurrence
1	Oct. 12	10 days	30 days	36 days	.....	.....
2	Nov. 19	12 days	.....	.....	.....	.....
3	Feb. 27	15 days	20 days	30 days	.....	.....
4	Nov. 2	18 days	30 days	30 days	.....	.....
5	Mar. 30	19 days	20 days	.....	.....	.....
6	Dec. 8	19 days	.....	.....	.....	.....
7	Jan. 24	20 days	.....	.....	.....	.....
8	Feb. 12	20 days	60 days	.....	.....	.....
9	Dec. 24	20 days	.....	.....	.....	.....
10	Feb. 6	20 days	20 days	.....	.....	.....
11	Feb. 6	20 days	48 days	.....	.....	.....
12	Dec. 25	21 days	33 days	.....	.....	.....
13	Mar. 1	22 days	.....	.....	.....	.....
14	Nov. 29	22 days	.....	.....	.....	.....
15	Nov. 14	24 days	.....	.....	.....	.....
16	Feb. 4	24 days	20 days	38 days	30 days	.....
17	Oct. 30	24 days	16 days	.....	.....	.....
18	Aug. 29	24 days	26 days	.....	.....	.....
19	Mar. 17	24 days	.....	.....	.....	.....
20	Feb. 4	25 days	16 days	20 days	.....	.....
21	Dec. 30	26 days	36 days	30 days	90 days	30 days
22	Jan. 26	26 days	48 days	90 days	.....	.....
23	Jan. 11	26 days	22 days	.....	.....	.....
24	Oct. 2	27 days	.....	.....	.....	.....
25	Nov. 2	27 days	.....	.....	.....	.....
26	Mar. 2	27 days	52 days	.....	.....	.....
27	Feb. 5	28 days	21 days	20 days	21 days	.....
28	Dec. 12	28 days	28 days	.....	.....	.....
29	Oct. 29	29 days	48 days	15 days	.....	.....
30	Jan. 17	30 days	.....	.....	.....	.....
31	Jan. 1	30 days	30 days	.....	.....	.....
32	Jan. 19	30 days	.....	.....	.....	.....
33	Jan. 20	32 days	.....	.....	.....	.....
34	Oct. 19	33 days	26 days	90 days	.....	.....
35	Jan. 19	34 days	40 days	.....	.....	.....
36	Oct. 18	34 days	50 days	.....	.....	.....
37	Jan. 25	34 days	26 days	17 days	.....	.....
38	Oct. 21	36 days	56 days	.....	.....	.....
39	Feb. 30	36 days	66 days	.....	.....	.....
40	Aug. 13	36 days	35 days	.....	.....	.....
41	Nov. 27	36 days	.....	.....	.....	.....
42	Sept. 1	37 days	49 days	.....	.....	.....
43	Oct. 18	38 days	.....	.....	.....	.....
44	Oct. 17	38 days	.....	.....	.....	.....
45	Aug. 13	38 days	.....	.....	.....	.....
46	Sept. 6	41 days	.....	.....	.....	.....
47	Oct. 31	42 days	20 days	.....	.....	.....

Case No.	Initial attack	First recurrence	Second recurrence	Third recurrence	Fourth recurrence	Fifth recurrence
48	Jan. 1	45 days	30 days	.....	.....	.....
49	Nov. 3	46 days	21 days	.....	.....	.....
50	Dec. 7	49 days	.....	.....	.....	.....
51	Feb. 24	50 days	24 days	41 days	.....	.....
52	Oct. 24	51 days	39 days	.....	.....	.....
53	Jan. 18	61 days	156 days	.....	.....	.....
54	June 14	64 days	66 days	14 days	20 days	20 days
55	Mar. 3	80 days	120 days	96 days	.....	.....

A consideration of this table shows that the first relapse in tertian aestivo-autumnal malaria occurred at periods varying from 10 up to 80 days; in none of the cases did a relapse occur before 10 days after the initial infection, which does not agree with the results obtained by Mariotti-Bianchi and Zieman, who found that this type of malarial infection relapsed most frequently in from 5 to 20, and 9 to 12 days, respectively. The administration of quinine in many of these cases probably delayed the relapse, but even so, it will be noticed that the great majority of the cases did not relapse until after the twenty-fourth day. Taken in periods of ten days, an analysis of the table shows that six cases recurred between the tenth and twentieth days; 23 between the twentieth and thirtieth; 16 between the thirtieth and fortieth; five between the fortieth and fiftieth; and the remainder at periods later than the fiftieth day from the initial attack. The greatest number of relapses occurred between the twentieth and thirtieth days, namely, 23, and almost as many between the thirtieth and fortieth days, namely, 16. Of single days, five cases recurred upon the twentieth day; five upon the twenty-fourth day; four upon the thirty-sixth day; and three upon the twenty-sixth, twenty-seventh, thirtieth, thirty-fourth, and thirty-eighth days after the initial attack.

In most instances secondary relapses occurred at longer intervals than the primary one, although numerous exceptions to this rule will be noticed in the table.

The statement that the longer the infection lasts the longer becomes the interval between relapses is not borne out in this series of cases, if the majority of the cases be taken into account. Thus in Case 16, relapses occurred at periods of 20, 38, and 30 days; in Case 21, at periods of 26, 36, 30, 90, and 30 days; in Case 27, at periods of 28, 21, 20, and 21 days; in Case 37, at periods of 34, 26, and 17 days; in Case 51, at periods of 50, 24, and 41 days; and in Case 54, at periods of 64, 66, 14, 20, and 20 days.

Of the 55 cases, 36 had two relapses; 14, three relapses; 4, four relapses; and 2, five relapses. This well illustrates the persistency of aestivo-autumnal

infections, and their resistance to treatment, unless the treatment be continued for a long period of time.

A most interesting feature of the aestivo-autumnal cases is the fact that 21 of them suffered from at least two relapses when the primary relapse occurred as long as 27 days after the initial attack. In the benign tertian infections not a single secondary relapse occurred after the twenty-sixth day. In the aestivo-autumnal infections it will also be noticed that no security against future recurrences is apparent when the primary relapse occurs after a long period of time from the acute attack, whereas in the benign tertian infections one can almost rest assured that secondary relapses will not occur if the primary relapse occurs a month after the initial attack of fever.

Tertian Recurrences.—The following table gives the data concerning recurrences in 18 cases of benign tertian malaria. The number is small, but while my records contain data covering hundreds of tertian malarial infections, in only 18 cases can I be sure of genuine recurrence. The vast majority of tertian cases, if properly treated, do not recur, and very many of them recover spontaneously, although in such cases recurrence is much more common, and, indeed, may be stated to be the rule.

Table of Recurrences in 18 Cases of Tertian Malarial Infection.

Case No.	Initial attack	First recurrence	Second recurrence	Third recurrence	Fourth recurrence	Fifth recurrence
1	Nov. 2	16 days	21 days	.....	.....	.....
2	Aug. 4	18 days	20 days	.....	.....	.....
3	Aug. 28	19 days	30 days	26 days	46 days	.....
4	Nov. 6	20 days	24 days	.....	.....	.....
5	Jan. 17	20 days	32 days	30 days	24 days	.....
6	Nov. 23	21 days	20 days	26 days	.....	.....
7	Oct. 6	21 days	30 days	.....	.....	.....
8	Sept. 17	21 days	22 days	27 days	.....	.....
9	Aug. 27	22 days	36 days	.....	.....	.....
10	Feb. 12	22 days	18 days	16 days	27 days	.....
11	Jan. 17	27 days	.....	.....	.....	.....
12	July 20	30 days	.....	.....	.....	.....
13	May 3	30 days	.....	.....	.....	.....
14	Nov. 1	30 days	.....	.....	.....	.....
15	Sept. 22	33 days	.....	.....	.....	.....
16	Sept. 1	37 days	.....	.....	.....	.....
17	Dec. 13	38 days	.....	.....	.....	.....
18	Sept. 22	41 days	.....	.....	.....	.....

A consideration of this table shows that tertian relapses occurred at periods of from 16 to 41 days; the shortest period after the initial attack was 16 days,

while Mariotti-Bianchi found that recurrences in benign tertian appeared as early as five days and not later than 18. Of the 18 cases, relapse occurred in 1 in 16 days; in 1 in 18 days; in 1 in 19 days; in 2 in 20 days; in 3 in 21 days; in 2 in 22 days; in 1 in 27 days; in 3 in 30 days; in 1 in 33 days; in 1 in 37 days; in 1 in 38 days, and in 1 in 41 days. Secondary relapses occurred in 10 cases; a third relapse in six cases; a fourth in three cases; and a fifth in one case. No secondary relapse occurred if the primary relapse occurred more than 22 days after the initial attack, and, therefore, in tertian infections we may say that if a relapse does not occur within a month after the initial attack there is practically no danger of future recurrences.

A study of the two tables given enables us to conclude that in aestivo-autumnal tertian infections, relapses occur most frequently between the twentieth and fortieth days after the initial attack, and in benign tertian infections between the fifteenth and twenty-second days; during these periods of relapse as they may be termed, quinine should be given in full therapeutic doses, and increased to the point of cinchonism at the appearance of the first symptoms indicative of a malarial attack. It should be remembered that quinine was given in prophylactic doses, once a week, to nearly all the cases quoted in the tables, and thus the occurrence of the relapses was undoubtedly delayed somewhat, which accounts for the difference in my results and those of others who have studied the subject in cases uninfluenced by quinine.

Etiology of Recurrences and Latency. Intracorpuscular Conjugation.—The etiology of recurrent and that of latent malarial infection should be considered together, as an explanation of the one would necessarily explain the other, since the infection must be latent in the system during the periods between the recurrences. Many investigators have endeavored to explain recurrence in malarial infections, but almost all of our knowledge of these subjects is theoretical and incapable of proof. It is evident that the plasmodia must exist in some form in the body during the intervals in which no symptoms are present, and I have already shown, in considering the pathology of latent infection, that plasmodia may be demonstrated in the spleen of patients who have died from some other disease and in whom no symptoms of malarial infection were ever present; these plasmodia did not differ in appearance from those observed in the peripheral blood in acute malarial attacks, and, furthermore, were undergoing normal *schizogony* within that organ, but in numbers insufficient to produce clinical symptoms. In such cases it may be urged that after a certain period of multiplication the plasmodia become numerous enough to produce symptoms of malarial infection, and thus a relapse may follow. While this is undoubtedly true in some instances, it will hardly account for long-interval relapses, for it is impossible to believe that the plasmodia of malaria continue to grow and multiply for weeks, and even months, within the body of man without becoming numerous enough to produce clinical symptoms.

To overcome this objection, Bignami considers that the plasmodium exists in some latent form, perhaps encapsulated, in the spleen or other inter-

nal organ, which may not be rendered visible with our present staining methods, and which, resting as a spore, is only set free under certain favorable conditions, the nature of which we are ignorant.

Celli, in discussing this subject says, "How are these recurrences explained? It is difficult to say; perhaps they depend on forms resulting from sexual multiplication that remain in some viscera—possibly the bone-marrow—and, from time to time, invading anew the blood, give rise to new generations of the asexual cycle."

Recently Schaudinn, in an excellent study of *Plasmodium vivax*, stated that recurrences are due to parthenogenesis of the *macrogametes* which are not fertilized by the *microgametes*, and remain in the blood of the human host. After a certain period of time these macrogametes liberate *schizonts* which penetrate the erythrocytes, undergo *schizogony*, and thus produce a relapse. This process is completed in from 9 to 12 days, and, according to Zieman and Mariotti-Bianchi, agrees with the period in which relapses are most frequent. Schaudinn's observations have never been confirmed and it is difficult to understand how such a process explains relapses occurring at irregular intervals as shown in the tables given, where it is obvious that no regularity is present in the development of either the primary relapse or of those succeeding it. How can the parthenogenesis of the *macrogamete*, which must occur in a cyclical manner, be the cause of relapses occurring all the way from 16 to 80 days after the initial attack of fever? I cannot confirm Schaudinn's results in this direction, and believe, with Celli, that the cause of relapse in malarial infection is a resistant form of the plasmodium which is capable of remaining unchanged in the human body for considerable periods of time, and which, under favorable conditions, undergoes development, thus giving rise to the symptoms which are the evidence of a recurrence. I have been so fortunate as to be able to devote much study to a form of development of the malarial plasmodia within man, which is evidently asexual in its nature, and which results in the production of a form of the parasite which I believe is the cause of latent and recurrent infections. To this process I have given the name "intracorpuscular conjugation,' as it consists essentially in the conjugation of two malarial plasmodia within the infected red blood-corpuscle.

The Process of Intracorpuscular Conjugation.—In December, 1905, I described a process of conjugation in the malarial plasmodia taking place within the infected red cells. This process had been described previously by Ewing, who considered it of rare occurrence and of comparatively little significance. He noted that the process occurred in only a certain proportion of the cases studied by him and that it occurs in the first generations of the infection. He says: "It seems probable that conjugation occurs in the first generations of infection, and becomes less frequent as the disease progresses, the infection in the human host thereby tending to limit itself." The material for my own studies upon this subject consisted of nearly 300 cases of malaria presenting clinical symptoms, observed at the U. S. Army General Hospital Presidio, of

San Francisco, Cal., together with over 100 cases of latent infection observed at the same place; a series of 75 latent cases in Filipino children studied at Camp Stotsenburg, and 96 cases of acute infection observed at that post and in Manila; together with acute infections observed at Fort Leavenworth, Kansas. As a result of my studies, which cover a period of nearly seven years, I have become convinced that intracorpuscular conjugation is not an accidental occurrence of no essential importance in the life history of the malarial plasmodia, but is a process which is most essential and one that occurs invariably in all acute infections in which quinine has not been given at such a stage as to prevent its occurrence. In this process I believe we have the true explanation of latency and recurrence, and that where it does not occur the malarial infection disappears.

Morphology of Intracorpuscular Conjugation.—This form of conjugation always occurs between two young hayaline ring-forms and is always completed before the formation of pigment begins. The process may be divided for convenience of description into three stages: In the first stage, or *stage of protoplasmic union*, the two young hyaline ring-forms, situated within a red corpuscle, are seen to be in contact, and careful examination demonstrates that at the point of contact there is a direct union of the protoplasm; in stained specimens it will be noted that the nuclear chromatin of the two parasites is separated at this stage and that union begins in the protoplasm of the plasmodia. In this stage the chromatin masses may be situated at any portion of the periphery of the two "rings," but they are very rarely seen in apposition at this time. I have been unable to detect any differences in the appearance of the two conjugating bodies, for while one may occasionally be a little larger than the other, this is not so as a rule, and the chromatin masses are always of the same size.

In the second stage, which may be designated as the *stage of complete protoplasmic union*, the chromatin masses, still distinct, become situated in the protoplasm of one organism, formed by the gradual union of the protoplasm of the two; the chromatin masses may be opposite one another or at any portion of the periphery of the organism, sometimes almost in apposition. The complete union of the protoplasm of the two plasmodia results in a more or less perfect "ring-shaped" organism, slightly larger than either of the original plasmodia, containing two masses of chromatin, surrounded by achromatic substance.

The third stage of the process, or *stage of chromatic union*, is characterized by the union of the two masses of chromatin, one large mass resulting. In many cases a very minute granule of chromatin is extruded from the plasmodium before the chromatin union is complete. In stained specimens the plasmodium resulting from this form of conjugation is larger than other unpigmented plasmodia, and consists of a mass of protoplasm staining a brilliant blue with Wright's stain, enclosing a very large and bright mass of chromatin, surrounded by an unstained area. The resulting organism grows

rapidly, develops much pigment, and when fully grown, entirely fills the red cells containing it, and eventually becomes free in the blood plasma.

Briefly stated, then, intracorpuscular conjugation consists in the complete and permanent union of two unpigmented plasmodia within the red blood-corpuscle. It is absolutely necessary, apparently, to the maintenance of malarial infection in man, and in those instances in which it does not occur, the plasmodia undergo asexual sporulation for a limited time and then perish, thus causing spontaneous recovery. It is present most frequently in those cases in which the clinical symptoms are most severe, and is present in all varieties of malarial infection, whether caused by the tertian, quartan, or aestivo-autumnal plasmodia, although most easily observed in the aestivo-autumnal infections.

The Significance of the Process of Conjugation in the Protozoa in General.—In order to understand the significance of intracorpuscular conjugation as it occurs in the malarial plasmodia, it is necessary to review briefly the significance of this process as it occurs in the Protozoa in general. It may be stated that conjugation has been observed at some stage in the life-history of individuals belonging to all the classes of the Protozoa. In the *Rhizopoda*, the *Flagellata*, the *Sporozoa* and the *Infusoria* organisms are found in which the process of conjugation occurs and in which it has been thoroughly studied. The morphological changes occurring in intracorpuscular conjugation of the malarial plasmodia are similar to those occurring in the conjugation of other protozoan organisms, and it is reasonable to believe that the significance of the process is also similar. We already know that the plasmodia of malaria undergo sexual conjugation during their development within the mosquito and that this is absolutely essential to sporulation or the formation of the *sporozoites*. However, in contradistinction to the form of conjugation just described as intracorpuscular conjugation, the conjugating organisms are sexually differentiated in the *sporogony* of the malarial plasmodia. In the mosquito, as regards the malarial plasmodia, conjugation is a fertilizing process *per se*, while intracorpuscular conjugation simply stimulates the organism to renewed activity and to the formation of a resisting form of the parasite.

The process of conjugation in the Protozoa was first observed and described by O. E. Muller. His work was confirmed by Balbiani, who claimed that certain of the Protozoa not only reproduced by simple division but also by conjugation, the latter being a sexual act leading to the formation of the young parasites. It is to Bütschli that we owe the corrected interpretation of conjugation in the Protozoa. He observed that continued reproduction of many of these organisms by simple division led eventually to the exhaustion of the capability of division, and thus to the death of the organisms. He, therefore, regarded the process of conjugation as intended to bring about rejuvenescence of the nearly exhausted individuals of a generation of organisms. Englemann confirmed the interpretation of Bütschli, and to-day his definition of the process is accepted by all zoologists. Briefly defined, conjugation is a

process intended to bring about a restoration of former reproductive activity in exhausted organisms, this result being secured by a rejuvenescence of the vital activities of the organism.

Calkins, in discussing this subject says: "The various conjugation phenomena seen in the Protozoa seem to show that each cycle starts with a certain potential of vitality which is gradually exhausted in the vegetable activities of the long line of individuals formed by simple division or by spore formation." It is to rescue such generations of organisms that conjugation occurs, but it also leads, in many instances, to the production of resting and resistant forms of the Protozoa. That it is not a reproductive act in many of the Protozoa is shown by the fact that the time consumed in conjugation is sufficient for reproduction by simple division to occur many times; this is well illustrated in those Protozoa in which a resting stage succeeds conjugation.

In reviewing the phenomena of conjugation in the Protozoa we find that in many of them, after the union of the conjugants, a resting or *zygote* stage results, which possesses greater resistance to injurious influences than the original organisms, and in which they remain latent, so to speak, no further development occurring until conditions are favorable for the existence of the original parasites.

The conjugation of a protozoon within its intermediate host is purely sexual in nature and is followed at once by reproduction. Such a type of conjugation should be clearly distinguished from that in which there is a union of two individuals followed by a period of inactivity or a *zygote* stage. The sexual type occurring in an intermediate host is well illustrated in the conjugation of the *micro-* and *macrogametes* of the malarial plasmodia within the mosquito's stomach, while intracorpuscular conjugation of the same organisms is a typical example of asexual conjugation. It is apparent, therefore, that asexual conjugation is not a reproductive act, but one intended to preserve the function of reproduction in a race of organisms threatened with extinction by repeated division, or intended to evolve a resistant form of the organism when conditions are unfavorable for reproduction in the ordinary way.

The Relation of Intracorpuscular Conjugation to Latent and Recurrent Malarial Infections.—Having thus briefly reviewed the significance of conjugation in Protozoa in general, we are in a position to consider the significance of that peculiar form of conjugation in the malarial plasmodia which I have called intracorpuscular conjugation. The conjugation of malarial plasmodia within the infected red blood-corpuscle is asexual, it being impossible to detect any constant difference in the appearance of the two conjugants. It occurs between two hyaline plasmodia and is completed, so far as can be seen, by the permanent union of both protoplasm and nucleus. It occurs whenever the generations of plasmodia are in danger of perishing from repeated sporulation in the usual manner; it is therefore most frequently observed during the latter part of the acute attacks, instead of before the appearance of clinical symptoms. As I have stated, conjugation occurs in many if not almost all organisms, when

unfavorable conditions arise, such as exhaustion from repeated division, insufficient nutriment, or the presence of conditions in the environment that are unfavorable to growth in the usual manner; it has also been shown that under such conditions a resting or *zygote* stage succeeds conjugation, in which the usual vital activities of the organism are wholly or in part suspended until the conditions again become favorable, when the vital activities are resumed and reproduction occurs as before.

If we consider carefully the phenomena of intracorpuscular conjugation as seen in the malarial plasmodia it is evident that they conform to those observed during conjugation in many of the Protozoa, and that, if there is any value in analogy, the conditions leading to the process and its significance are similar. Considered in this way, I believe that intracorpuscular conjugation is easily explained, and that the theory of the etiology of latency and recurrence which follows and which is based upon this process is one that is worthy of careful study and one that is well supported by the known significance of conjugation in other protozoan organisms. Intracorpuscular conjugation in malaria occurs after a series of reproductions by spore-formation, during which time the initial potential energy of the race of plasmodia has gradually declined; during this same period the clinical symptoms of malaria have been present, and the environment of the plasmodia rendered unfavorable, perhaps by the administration of drugs, such as quinine; as a consequence, decreased ability to reproduce by spore-formation leads to intracorpuscular conjugation, and the formation of a resistant form of the plasmodium; the process occurs within the red blood-corpuscle, because only here can nutriment be obtained for further development.

When conjugation is completed by the permanent union of the protoplasm and nucleus of the two conjugants, growth occurs at the expense of the red corpuscle, until finally the entire cell is destroyed, as in *schizogony*, and the spherical pigmented organism is liberated; this form now, in all probability, becomes encysted and enters upon a resting or *zygote* stage, and it is more than probable that it is this stage that was considered by Schaudinn as a *macrogamete* which by parthenogenesis gives rise to recurrences. The large pigmented bodies are found in the peripheral blood in tertian and quartan infections at any time after their formation, but are seldom seen in the peripheral blood in aestivo-autumnal infections, being found in the spleen and bone-marrow. They are difficult to distinguish from the *macrogametes* in tertian and quartan fevers, although they are larger and contain less pigment and a greater amount of chromatin, while in aestivo-autumnal infections they are distinguished from the *gametes* by the absence of the crescentic shape.

This stage is probably more resistant to injurious influences, such as quinine, than other forms of the plasmodia, and may continue unharmed in one of the internal organs, as in the spleen, or the bone-marrow, for long periods of time. When conditions are favorable the cyst (for, as has been stated, the organism is probably encysted) ruptures, and liberates a generation of spores which have developed within it; these young plasmodia penetrate the red

blood-corpuscles and undergo *schizogony* in the usual manner. Latency is thus rendered possible by the resistance of the resting or *zygote* stage, and recurrences are due to the liberation of the young plasmodia which have developed in the resting form, and their subsequent sporulation within the red corpuscles. In cases in which this form of conjugation exists, numerous large pigmented plasmodia are present, both within and external to the red corpuscles, which show no evidence at any time of segmentation or flagellation; in these the pigment is small in amount and distributed throughout the protoplasm in an irregular manner, in the form of very fine granules. In aestivo-autumnal infections these bodies are seen only in the blood obtained by splenic puncture, and they are absent in cases in which this form of conjugation is absent. These bodies probably become encysted and situated in some internal organ or in the bone-marrow. The growth of the conjugating form within the red cell is rapid until the destruction of the cell and the liberation of the organism; it then enters upon the resting stage and the duration of this stage probably varies with conditions present, but I believe lasts for several days at least.

Reasoning from analogy, this stage must continue for some time, for, as has been shown by Bütschli, Maupas, and Hertwig, in the Protozoa, the two conjugating organisms might by simple division give rise to many generations during the time occupied in conjugation, and this is true of every organism in which asexual conjugation occurs, so far as I know. It would, indeed, be strange if the malarial plasmodia were exceptions to so general a rule, and therefore it follows that the resting stage must continue for several days, and that intracorpuscular conjugation, admitting that it produces this form of the plasmodia, is the most probable cause of latency and recurrence. The periods of time between relapses, which vary somewhat, but are remarkably uniform when quinine has not been administered, are explained by the time consumed in the completion of the process of intracorpuscular conjugation, and the development of the young plasmodia within the encysted *zygote* while the marked irregularity in the period between relapses after quinine has been administered, is explained by the liberation of the young plasmodia only when the environment becomes favorable, *i.e.*, when the quinine has been discontinued, the quantity administered decreased, or when absorption of the drug fails to occur. We thus see relapses quickly follow the discontinuance of quinine in all malarial regions, and Celli, in his suggestion that relapses may depend upon forms which remain inert in some viscera, stated what is in all probability the true explanation of recurrences in malaria, the inert sexual bodies of Celli being the *zygote* or resting form of the plasmodia, produced by intracorpuscular conjugation. That such a latent or resting form of the malaria plasmodia is present somewhere in the body in malarial infection, is proven by the fact that the withdrawal of quinine in cases which have been taking it for weeks is often promptly followed by a relapse, and the reappearance of the plasmodia in the peripheral blood; it is impossible to believe that normal *schizogony* has occurred in such instances for weeks, even when quinine has

been administered in large doses, without producing symptoms, and while, as I have already shown, in discussing the pathology of latent infections, *schizogony* does occur within the spleen without symptoms being produced, it should be remembered that in the patients in which this was observed no quinine was being administered, and symptoms would probably have soon appeared had the patients lived. The administration of quinine, even in very moderate doses, has a very marked effect upon intracorpuscular conjugation as observed in the peripheral blood, the conjugating plasmodia disappearing, perhaps collecting in the spleen or bone-marrow, while in those cases in which the process has not appeared it is never observed, if quinine be administered promptly. This fact again is a strong argument in favor of the view that this form of the plasmodia is the cause of recurrences, for it is well known that primary cases of malaria thoroughly and promptly treated with quinine seldom relapse, while those which have been treated improperly or in which the infection has lasted for several days are almost sure to suffer from one or more relapses.

The large pigmented forms which result from conjugation show no morphological changes after the administration of quinine, and it is evident that this drug has no effect upon this form of plasmodia.

It should be remembered that the list of the Protozoa in which the life cycle has been followed through an intermediate host is not very large, and, therefore, our knowledge of the exact details of asexual and sexual conjugation in any single organism, at all stages of its development, is very limited. Among the *Haemoflagellates* recent research has confined the presence of asexual and sexual conjugation in the life cycle of *Trypanosoma lewisi;* asexual conjugation occurring in the blood of the rat has been studied in this organism by Bradford and Plimmer, Doflein, and Stassano; and the researches of Prowazek prove that sexual conjugation occurs in an intermediate host. This observer found that *Trypanosoma lewisi* undergoes a portion of its life cycle within the rat louse, *Haematopinus spinulosum;* after reaching the mid-gut of the louse, reduction occurs in the nucleus, and male and femate *gametocytes* are formed, which can be easily distinguished; sexual conjugation between these forms follows, the *zygote* becomes an *ookinete* and this eventually results in a single trypanosome, which again infects the rat and reproduces as usual.

From the researches of the investigators mentioned, it is evident that in *Trypanosoma lewisi* asexual conjugation occurs in the blood of the rat and sexual conjugation in the mid-gut of the rat louse, and it is probable that further research will demonstrate that asexual conjugation is constantly present in those Protozoa which require an intermediate host for the completion of their life cycle, sexual conjugation occurring within the intermediate host, and asexual conjugation within the definitive host.

CHAPTER V.

Subcontinued or Remittent Malarial Fevers; Mixed Malarial Infection; Chronic Malarial Infection and Malarial Cachexia; Spontaneous Recovery.

Any of the malarial fevers may become irregular or remittent in character as regards the temperature, but the aestivo-autumnal infections are especially prone to present irregularities in the fever, which in many instances are very confusing. A malarial fever may become continuous, irregular, or remittent in various ways, the principal of which are: anticipation or retardation of the paroxysm; infection with more than one group of plasmodia or with more than one species; and insufficient treatment with quinine. In most of these infections, especially those due to the aestivo-autumnal plasmodia, it is very seldom possible to demonstrate the entire *schizogony* in the blood, but in those cases which are caused by mixed infections with more than one species of plasmodium, the species present may be easily demonstrated. It is these forms of malaria which are so often confused with other diseases, such as typhoid fever, in regions where malarial infections are rare.

Subcontinuous Fevers Due to the Tertian Plasmodium (Plasmodium Vivax).—While the great majority of benign tertian fevers are regularly intermittent in type, it is not so very unusual to observe irregular or even subcontinued forms of tertian infection. Thayer and Hewetson describe a case of tertian infection in which the diagnosis of typhoid fever was made and I have seen a few cases in which the temperature curve was slightly remittent and the cases were at first regarded as typhoid fever. Such cases are rare, it being much more common to observe tertian cases in which a double infection is present and in which the paroxysms are prolonged, thus resulting in a very atypical temperature curve. In these cases the temperature curve may show an almost continuous fever or it may resemble very closely that of a tertian aestivo-autumnal infection.

An examination of the blood in cases of irregular or subcontinued tertain fever generally shows numerous plasmodia in various stages of development.

The symptoms of the subcontinued form do not differ in character from those usually observed in tertian infections, except that they are apt to be more severe and in some cases resemble closely those of typhoid fever.

Subcontinuous Fevers Due to the Quartan Plasmodium (Plasmodium Malariae).—Irregular and subcontinued fevers due to the quartan plasmodium are so rare as to be of little practical importance. I have observed but one case of quartan fever in which the fever was of the subcontinued type, and Marchiafava and Bignami state that while they have seen a few cases of ir-

regularly intermittent quartan fever they have never observed one showing a continuous fever, although Antolisei and Feletti describe such cases. In the case observed by myself the blood showed quartan plasmodia in all stages of development and the symptoms were very suggestive of typhoid fever.

Subcontinued Fevers Due to the Aestivo-autumnal Plasmodia (Plasmodium Falciparum and Plasmodium Falciparum Quotidianum).—The vast majority of irregular and subcontinued malarial fevers are caused by the aestivo-autumnal plasmodia, for in this variety of malarial infection the development of the life cycle of the plasmodia is more apt to be atypical, and multiple and mixed infections are observed more frequently I agree with Marchiafava and Bignami in prefering the term "subcontinuous" to the terms "remittent" and "continuous" so frequently used in connection with these fevers. I have already mentioned the various ways in which a malarial infection may become continuous or remittent, but will briefly recapitulate here, as it is in the aestivo-autumnal infections that these causes are most frequently operative:

1. The paroxysms may be prolonged so that they overlap each other, thus causing a more or less continuous temperature curve.

2. The paroxysms may anticipate, one beginning before the preceding one ends.

3. The paroxysms may be duplicated.

4. There may be a mixed infection with the quotidian and tertian aestivo-autumnal plasmodia or with the benign tertian or the quartan plasmodium.

5. Quinine may be administered in such doses as to cause the temperature curve to become atypical without curing the infection.

Subcontinued aestivo-autumnal infections may begin as such, which is frequently the case, or they may gradually develop during a typical attack of either the tertian or quotidian infection. When developing in the latter manner they are generally easy of recognition, but when an aestivo-autumnal infection begins as a subcontinued fever, it is often impossible to recognize it without an examination of the blood, and, if the plasmodia are present in but small numbers, repeated examinations of the blood will have to be made. To depend upon clinical symptoms in the diagnosis of subcontinued aestivo-autumnal malaria is to attempt the impossible in most instances, and if there is one thing in the medical history of this country which should teach the profession the folly of attempting to diagnose the malarial fevers by the symptoms alone it is the experience of our armies in the camps throughout the South in 1898 and the experience of the British army in South Africa during the Boer War.

Symptoms.—The symptoms of the subcontinuous aestivo-autumnal fevers vary considerably in different cases, and various types have been described, as the typhoidal, the pneumonic, and the bilious, but such a classification is loose and unscientific and undeserving of consideration. It is but rarely that a case of subcontinued or remittent aestivo-autumnal fever is observed for a period of time sufficient to gain an adequate idea of its symptoms and course,

as quinine is generally given at the beginning of the attack and the disease arrested. In those cases I have observed the symptoms have varied, but on the whole resembled those of typhoid fever very closely at some time in the course of the disease. The prodromal symptoms are generally weakness and malaise, headache, dull pains in the muscles of the trunk and extremities, and loss of appetite. The attack usually begins with slight chilly sensations, a distinct chill being observed but rarely. The patient's appearance is often very suggestive of early typhoid, the face being flushed, the eyes brilliant, the conjunctivae congested, the mucous membranes hyperaemic, and the skin hot and dry. Severe headache is present and pain in the muscles of the back and legs; the patient is very nervous and restless, sleeping poorly and waking with a start, and there may be slight delirium. The tongue is dry and coated and may resemble very closely the tongue of typhoid, while nausea and vomiting are present and diarrhoea is a frequent symptom. The pulse is rapid and dicrotic in character, while the respirations are hurried and very often superficial. There is often present marked tenderness over the abdomen, and the spleen is enlarged and tender upon pressure.

In those cases which most closely simulate typhoid fever—the so-called "typhoid pernicious malarial fever"—the resemblance is indeed startling—epistaxis, roseolar eruption, gurgling and tenderness in the right iliac fossa, the cerebral symptoms and the headache, all being present in addition to the symptoms enumerated. Before the discovery of the malarial plasmodia such cases caused much confusion, but there is no difficulty in diagnosing them to-day by the aid of the microscope. It is to this class of cases that the term "typho-malarial fever" has been applied by some observers, but the microscope has definitely proven the falsity of this appellation, and we know that there is no such disease entity as typho-malarial fever, although there may be a mixed infection with typhoid and any of the malarial fevers.

The temperature curve in the subcontinued aestivo-autumnal fevers is very variable, but there may usually be traced slight intermissions corresponding to the termination of the paroxysms. In some cases, however, the curve much resembles that of typhoid fever, there being slight daily remissions; this is especially true of the subcontinued fevers due to the quotidian plasmodium. The chart shown is fairly typical of such a fever. (Chart No. 16.)

The duration of the subcontinued or remittent fevers may be several weeks, but usually spontaneous recovery or death occurs within three weeks. If properly treated, the symptoms are easily controlled within a week, although in very rare instances the plasmodia may be very resistant to quinine and persist for eight or ten days. An examination of the blood, if carefully made and repeated, if necessary, will invariably demonstrate one or perhaps both of the aestivo-autumnal stages of development. Very rarely a sporulating organism may be seen in the peripheral blood.

The point of greatest importance to remember regarding subcontinued forms of malaria is that these infections pursue a more or less continuous or

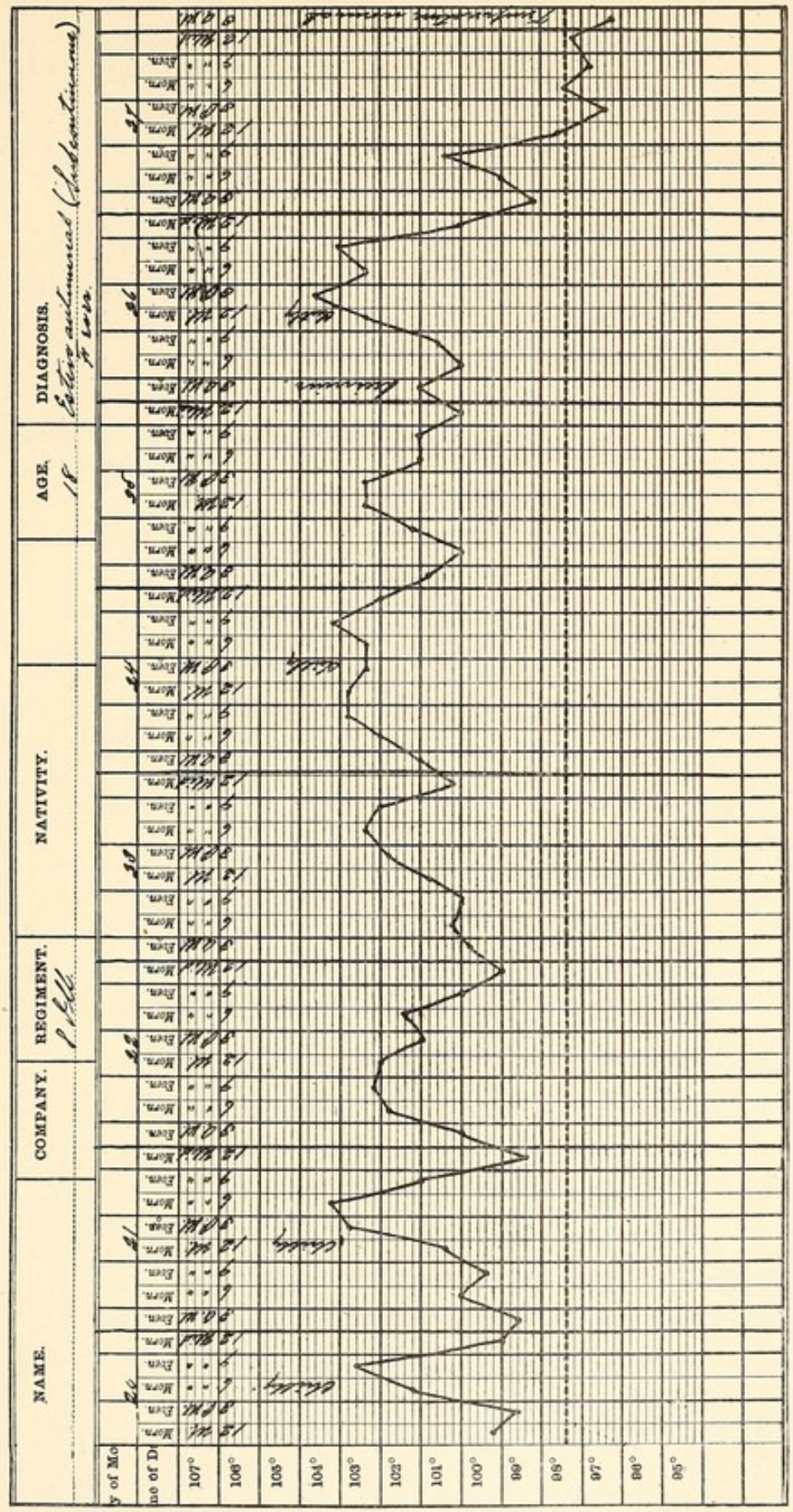

CHART 16.—Subcontinued or Remittent Aestivo-autumnal Fever.

remittent course as regards the temperature, resembling typhoid fever or other febrile processes clinically, and that the only way of quickly diagnosing them is by the microscopical examination of the blood. These fevers are apt to become pernicious at any time, and death may occur suddenly, so that a prompt diagnosis and proper treatment is of the very greatest importance.

Mixed Malarial Infections.—Any of the species of the malarial plasmodia may occur together, thus causing what is known as a mixed or combined infection. Such infections are very common in some localities and are rare in others, as would be expected. In those localities in which more than one type of malaria is common, mixed infections are common, while in those in which only one type of infection occurs, they will be absent or very rarely occur as imported cases.

In 2,803 cases of malaria occurring in soldiers who contracted their infection in Cuba and in the Philippines, I observed but 61 cases of mixed infection, of which 51 were combined tertian and tertian aestivo-autumnal infections; nine combined tertian and quotidian aestivo-autumnal infections; and one a combined tertian and quartan infection. This is a very small percentage of mixed infections, but is explainable by the fact that in most of the localities in which these men had been, the aestivo-autumnal infections were practically the only infections present, and thus the men did not become infected with the other varieties. In mixed infections the temperature chart is apt to be irregular or remittent, but very often one type of plasmodium may so predominate in numbers that the infection will present the characteristic symptoms caused by that organism. Thus we may have combined infection with aestivo-autumnal and tertian plasmodia in which the aestivo-autumnal plasmodia are so much more numerous than the tertian, that the case will present the symptoms of an aestivo-autumnal infection. As would be expected, some very peculiar temperature charts are observed in these mixed infections, and the symptoms are often so anomalous that a diagnosis cannot be made without the aid of the microscope.

Chart No. 17 is a beautiful illustration of a case in which there existed a combined infection with the tertian and the tertian aestivo-autumnal plasmodium and in which the aestivo-autumnal and tertian paroxysms occurred independently of one another. This is the only instance of the kind I have ever observed and I believe that this chart is unique in the literature of the malarial fevers. A blood examination in this case demonstrated the presence of both species of plasmodium, and the life cycle of the tertian plasmodium could be easily followed in the peripheral blood and correpsonded with the chart.

The Symptoms of Chronic Malarial Infection and Malarial Cachexia.—I have already described the pathology of chronic malarial infection and malarial cachexia and have spoken of the changes occurring in the blood in such infections.

In patients who have suffered from repeated attacks of malarial fever, which have not been properly treated, there develops a peculiar condition, the

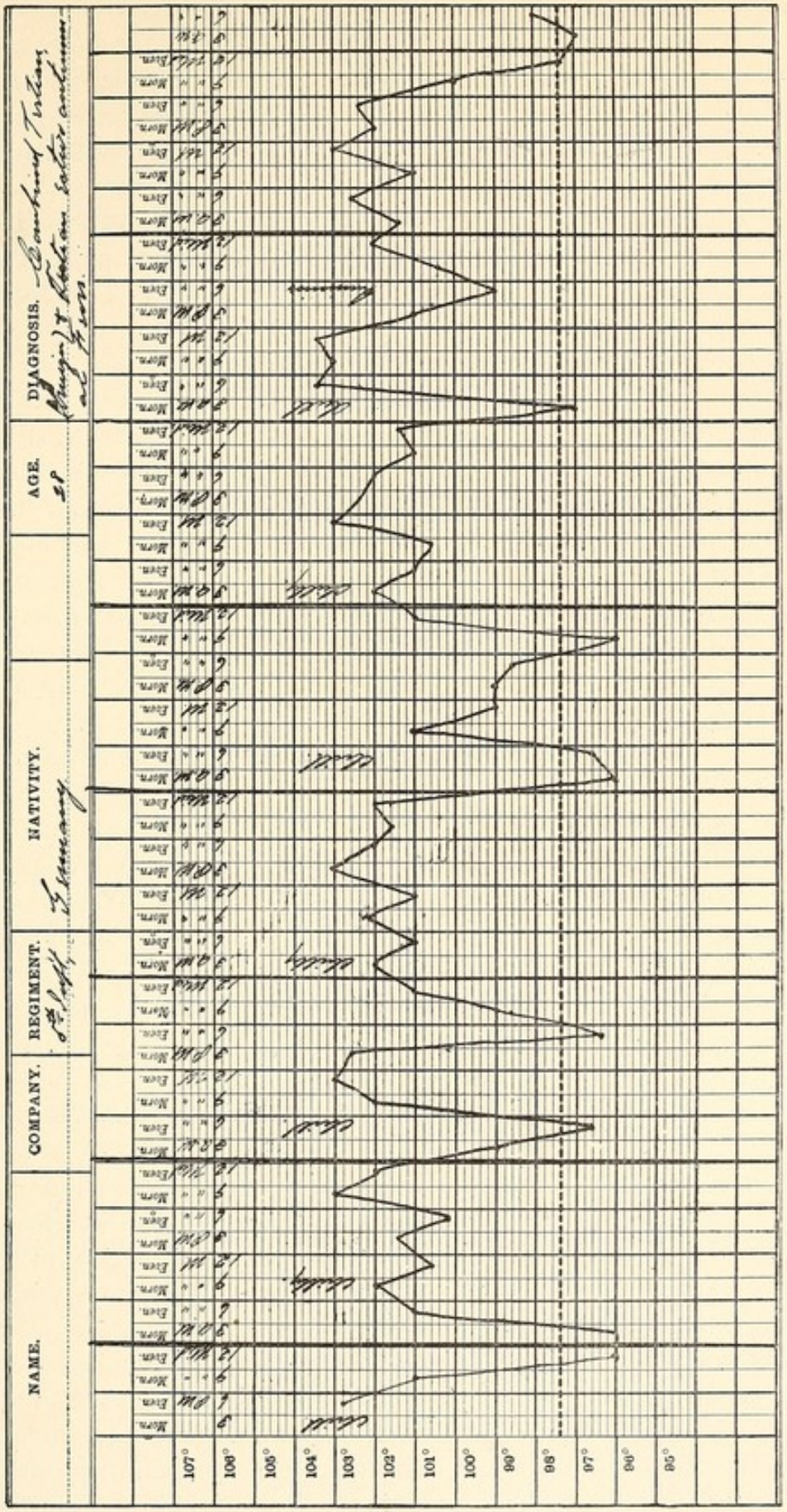

CHART 17.—Combined Benign Tertian and Tertian Aestivo-autumnal Malarial Fevers. The paroxysms occurred independently.

most characteristic symptoms of which are a more or less severe anemia and a greatly enlarged spleen. This so-called malarial cachexia is most frequently observed in tropical regions in which the aestivo-autumnal infections are endemic and least frequently in localities in which only tertian fevers are present. It is especially apt to develop after latent and masked infections, which have gone untreated because unrecognized.

While malarial cachexia is a common condition in natives of tropical regions, and in Europeans who have long resided in such regions, it is by no means as common as many writers would lead us to believe. Since the discovery that kala-azar is a distinct disease, for instance, it has become necessary to revise our conceptions of the pathology and symptomatology of malarial cachexia, for kala-azar was long believed to be a chronic malarial infection and many of our classical descriptions of that condition were based upon the symptoms and pathology of kala-azar. We now know that the enlargement of the spleen, which is used by some authorities as an index of malarial endemicity, can no longer be so used in India, for this is one of the constant and one of the most important symptoms of kala-azar. We should be careful, then, in making a diagnosis of malarial cachexia, remembering that other tropical diseases produce symptoms resembling very closely those present in chronic malarial infection, and that some of our most important symptoms may be due to an unrecognized condition, as was the case with kala-azar.

Chronic malarial infection is characterized, as a rule, by repeated attacks of fever and the gradual development of anaemia and an enlarged spleen. The patients suffering from malarial cachexia present a peculiar yellowish or grayish hue of the skin, or an earthy pallor, while the mucous membranes are very pale, due to the anaemia which is invariably present. There is a loss of appetite, diarrhoea, dyspnoea, emaciation, and a general condition of nervous exhaustion. Between the febrile attacks the temperature may be normal, but generally shows a slight rise toward evening; it seldom reaches 102° F. The condition is especially frequent in children living in tropical localities. It should be remembered that in many instances repeated attacks of malaria do not produce the symptoms of malarial cachexia, and this is well illustrated in our soldiers, hundreds of whom have suffered from numerous attacks of malaria, but who have never developed the symptoms of cachexia, being, between the attacks, in vigorous health and presenting no anaemia of consequence. In many patients suffering from malarial cachexia, epistaxis and hemorrhages into the mucous membranes are common symptoms, due to the hydraemic condition of the blood, while in others albuminuria, oedema, and nephritis are frequently observed.

The anaemia which is present in malarial cachexia partakes of the character of a secondary anaemia, the red cells being reduced to 2,000,000 or less per cubic millimeter, while there is a marked increase in the large mononuclear leucocytes and a corresponding decrease in the haemoglobin. In some instances the blood becomes so impoverished that a recurrent attack of the fever may

prove fatal, if the plasmodia are numerous, because of the added acute destruction of the red corpuscles, and after such an attack a pernicious form of anaemia may develop. In such cases the blood findings differ from those of primary pernicious anaemia in the absence of nucleated red cells and the slight degree of poikilocytosis.

Enlargement of the spleen is a common condition in malarial cachexia, but not an invariable one. I have observed many cases of chronic malarial infection in which the spleen was but little, if any, enlarged. In old cases the organ may be enormously enlarged, reaching as low as the crest of the ilium, but as a rule it does not extend more than 4 to 8 cm. below the border of the ribs. It is firm and not painful upon palpation. The liver is usually enlarged and pain is often complained of over the hypochondria.

Neuralgic affections have long been considered by some observers to be due to malarial poisoning, but I believe that it is only occasionally that malaria is the cause of neuralgia. The long-continued malarial infection renders these patients especially liable to acute infectious diseases and slight injuries are often attended by suppuration, phlegmonous inflammation, or haemorrhage.

Marchiafava and Bignami state that it has never been their experience to observe in patients suffering from malarial cachexia grave infections with many parasites in the blood, but that there are always a few parasites and very little melanaemia. I agree with them in this and would impress upon the student of this subject that malarial cachexia cannot always be determined by a causal examination of the blood, as the plasmodia will not be present in any number except when acute symptoms are present and in many cases melanaemia may be absent.

Spontaneous Recovery.—By spontaneous recovery we mean the disappearance of a malarial infection without the intervention of medicines; in other words, the cure of the infection by the infected individual. In the prequinine days this was the way in which most malarial infections were cured, and, as often happens, the physician received the credit due to Nature. To what, then, when spontaneous recovery occurs, is it due? We are unable to answer this question exactly, but some deductions may be drawn from the examination of the blood in such cases, and the known facts regarding the defensive agencies of the human body.

The examination of the blood in cases which are undergoing spontaneous recovery shows a gradual diminution in the number of the plasmodia present as improvement occurs in the condition of the patient. Together with this diminution, which is progressive, there occur certain degenerative changes in the plasmodia, such as vacuolation and fragmentation, and numerous pigmented leucococytes, macrophages, and much free pigment appears in the blood. Many times, in cases undergoing spontaneous recovery, the entire life cycle of the plasmodium may be observed in the blood, in tertian and quartan fever, but the organisms are so few in number that no symptoms of the infection are observed.

Metchnikoff and his adherents have laid much stress upon the relation of phagocytosis to spontaneous recovery, and although it is doubtless a factor in the production of spontaneous recovery in malaria, there are other factors present which are doubtless of as great importance. It must, I think, be admitted that the phagocytes, by destroying numerous plasmodia, and removing from the blood large quantities of pigment and excrementitious matter, greatly help in producing recovery from the infection, but phagocytosis *per se* is not the sole cause of spontaneous recovery, which is undoubtedly due to several factors, some of which are active in one case and some in another.

According as we are followers of Ehrlich's or of Metchnikoff's theory of immunity, we may explain differently the occurrence of spontaneous recovery in malaria, but I believe that both theories should be applied in this instance, as it is obvious that strict adherence to one does injustice to the other, and that both present valuable evidence helping us to understand the process under discussion. For instance, there can be no question but that in malaria the phenomenon known as phagocytosis is of immense importance in the production of spontaneous recovery, and to entirely ignore it in favor of Ehrlich's views would be both unjust and unscientific. For this reason I have endeavored to view this subject from a somewhat broader standpoint than is usual, and in doing so I have been inevitably led to include both Ehrlich's and Metchnikoff's theories in the explanation of the process.

I believe that spontaneous recovery in malaria may be brought about by the following factors:

1. The presence in the blood serum of antiplasmodial and antitoxic principles, preexistent in the serum or liberated by phagolysis of leucocytes, or both.

2. Absorption of the malarial toxin or toxins by the leucocyte.

3. Formation and excretion of antiplasmodial and antitoxic materials by the leucocytes.

4. Phagocytosis.

5. Inability to produce the "latent phase of the plasmodium" which may depend upon any of the above factors or may be due to other causes.

6. A partial natural immunity, dependent upon the factors discussed in the chapter dealing with Immunity.

In addition to the factors enumerated and which are of prime importance in the production of spontaneous recovery, there are secondary factors which are active in assisting the natural body defenses, such as good nursing, good food, rest and quiet, and the prevention of reinfection.

It is certainly most probable that there are present in the blood serum in malaria certain antiplasmodial and antitoxic substances which serve to overcome the infection, and that other substances of this nature are evolved during the progress of the disease. The degenerative changes observed in the plasmodia during spontaneous recovery are indicative of the existence of such bodies, and while Mannaberg believes that the fever present is detrimental to

the growth of the parasites, this can hardly be so, for often the cases showing the highest temperatures present large numbers of plasmodia, all of them in normal condition; Marchiafava leans to the theory that in malaria, as in bacterial diseases, the parasite gradually loses its virulence, but in opposition to this it may be urged that the cause of malaria is not a bacterium, but belongs to the animal kingdom, and that there is no evidence of such a diminution in virulence, and even in the case of bacteria a diminution in virulence does not cause degenerative changes in the organism. If, then, neither the fever nor diminished virulence can result in degeneration of the plasmodia, it is, I believe, justifiable to conclude that it is due to antiplasmodial substances existing either preformed in the blood serum or produced in reply to the stimulation of the plasmodia. The antiplasmodial bodies which produce degeneration and fragmentation of the plasmodia probably consist of plasmodicidal and plasmodilytic bodies.

In addition to antiplasmodial bodies it is evident that antitoxic bodies are present in many instances and thus are explained those cases in which numerous plasmodia may develop for weeks without the appearance of symptoms and those cases in which repeated infection has resulted in very slight symptoms only, even though many plasmodia are present in the blood. The origin of these antiplasmodial and antitoxic bodies is unknown, but according to Metchnikoff may be the leucocytes or, according to Ehrlich, of indefinite origin, being found only in the serum.

Phagocytosis has already been discussed, but it is evidently of great importance in the production of spontaneous recovery. The malarial plasmodia, whether living or dead, are engulfed by the phagocytic cells and destroyed, and though in many cases there exists an apparent decrease in the leucocytes in the peripheral blood in malaria, we must remember that there is an increase in the large mononuclear leucocyte, and that, after all, the decrease may be only apparent, the greater number of the leucocytes being collected in the internal organs, where they are acting as phagocytes. There is much anatomical evidence in favor of this view, for in sections of the spleen and the bone-marrow, the phagocytic cells are present in immense numbers in cases dying of pernicious malaria.

The process of intracorpuscular conjugation, or, rather, its absence, is of great importance in the production of spontaneous recovery. Unless the resistant form produced by conjugation is present, the malarial infection will disappear in time as the initial potential energy of the race of plasmodia will become exhausted after a series of reproductions. When, therefore, for any reason, intracorpuscular conjugation does not occur during a malarial infection, spontaneous recovery must necessarily follow after a certain period of time.

I have already considered the factors at work in the production of immunity and, where the immunity is only partial, these factors are of importance in the explanation of the cause of spontaneous recovery.

Often, however, spontaneous recovery is thought to have occurred when,

in reality, it has not. The fever may disappear, together with many or all of the clinical symptoms, only to be followed in a week or ten days by a relapse. Often also after spontaneous recovery is thought to have occurred, an examination of the blood will demonstrate the presence of a few plasmodia, and these may persist for weeks without causing any noticeable symptoms. Again, the plasmodia may entirely disappear from the peripheral blood, but may be found in numbers in the blood obtained by splenic puncture. In aestivo-autumnal infections especially we should be very careful to draw a sharp distinction between apparent and real recovery, and I am convinced, after a large experience with these fevers, that it is impossible to say with certainty when a patient is cured, for relapses occur so frequently that a guarded statement concerning cure is always advisable.

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PART IV.

THE SEQUELAE, COMPLICATIONS, AND PROGNOSIS OF THE MALARIAL FEVERS.

CHAPTER I.

The Sequelae of the Malarial Fevers.

If we consider the lesions produced by malarial infections in the blood and viscera in pernicious cases and the extensive changes occurring in the blood in all instances of malarial infection, we can easily understand the reason for the occurrence of many grave sequelae of these infections. Properly speaking, the sequelae of a disease are those affections developing after the disease itself has ceased and which are due to poisons generated during the course of the disease. The toxins elaborated during the development of the malarial plasmodia within man may give rise to certain conditions which develop coincident with or after the malarial infection has ceased, and these must be regarded as sequelae of the disease. It is not always easy to differentiate sequelae from complications, for in many instances a certain morbid process will develop during an attack of malaria and it will be impossible to say whether or not it is the result of the malarial infection or is simply a complication of the disease. In such instances we must depend upon a careful clinical survey of the case and the recorded experience of others in deciding the question.

The sequelae of malaria affect almost every organ and tissue in the body and will be considered under the following headings: Sequelae affecting the Nervous System, the Circulatory System, the Digestive System, the Genito-urinary System, the Glandular System, and the Organs of Special Sense.

1. **Sequelae Observed in the Nervous System.**—Sequelae are not infrequently observed in the nervous system due to the blocking of the brain capillaries by the malarial plasmodia or their products or to certain toxins produced by the plasmodia, and are especially numerous following the aestivo-autumnal infections. In many instances the conditions are evanescent in character, but in others they may persist for months. Such a case I recall, in which a paresis of one side of the face developed during an aestivo-autumnal attack, which persisted for two months after the disease was apparently cured.

Not uncommonly, after severe malarial attacks, the mind appears to be sluggish and inactive, *memory* being very defective, and sometimes an almost stuporous condition may be present. While focal neuroses are uncommon in my experience, they are described by many observers as of frequent occurrence. Thus Mannaberg describes cases of *hemiplegis*, *aphasia*, *paraplegia* and *monoplegias*. Sensation may be diminished or there may be marked *hyperasthesia*. Boinet and Salabert report a case of motor aphasia, which continued a month after the malarial infection was cured, and from which recovery finally ensued. Vincent reports an interesting case in which there was paralysis of the extensors

of the right hand and aphasia following malaria, while Sacchi reports cases of amaurosis and loss of the sense of taste and smell. I have observed two cases in which *aphasia* was present, but both recovered.

Affections of the spinal cord are very rare as sequelae of the malarial fevers. *Paraplegia* is the most common form observed, accompanied by either loss of sensation or hyperasthesia. I have observed one case in which there was a paraplegia, with partial paralysis of the rectum and bladder. Marchiafava and Bignami describe cases in which the symptoms were those of *bulbar paralysis*.

It is probable that some of the cases reported as suffering from sequelae of malaria affecting the spinal cord have been instances of infection with other diseases, as beriberi and syphilis. In tropical regions especially, where both malarial infections and beriberi are present, this mistake is very likely to occur.

A condition almost indistinguishable from multiple sclerosis has been described by Torti, Angelini, Bignami and Bastianelli and Canalis, as occurring after attacks of aestivo-autumnal malaria. In these cases the symptoms disappeared after treatment with quinine, but relapses occurred in some of them. Kahler and Pick describe an ataxic condition, or *pseudotabes*, occurring as a sequela of malaria.

Affections of the peripheral nerves are not uncommon, and many observers have reported cases of neuritis following the malarial fevers. Boinet and Salabert report a case in which there was atrophy of the muscles, diminution of the tendon reflex, and neuritis. *Multiple neuritis* has been described as following aestivo-autumnal malaria by Gowers, Raymond, and Jourdan. Glogner has studied very exhaustively several cases of polyneuritis following malarial fever, the symptoms consisting of severe pain in the lower extremities, increased by pressure; formication; motor weakness in the legs; partial or total loss of the deep reflexes; partial or total loss of response to electrical stimulation, and oedema. His observations have been confirmed by those of Chiarini and Bardellini, in Rome, and there can be no doubt that polyneuritis may be a sequel of the malarial infections.

Bastianelli, Bignami, and Chiarini have described cases in which symptoms similar to those of *electric chorea* or "Dubini's disease" followed aestivo-autumnal malarial infections.

Neuralgia is a common sequelae of malaria infections, although it should be added that it is not as common as is generally supposed. Many cases of so-called" malarial neuralgias" have in reality no connection with malaria, and the name is used as a cloak for ignorance of the etiology of the affection. The regions most frequently affected by true malarial neuralgia are the face and the lumbar region. I have observed one case of severe *intercostal neuralgia* following aestivo-autumnal infection, one case of severe *abdominal neuralgia*, and one case of very severe *sciatica* following a tertian aestivo-autumnal attack. In all of these cases continued treatment with quinine resulted in recovery.

Neurasthenia not infrequently is observed following attacks of malaria, and in our soldiers many instances of this condition were observed during the Philippine insurrection. While it is true that hardship, anxiety, homesickness, and the depressing influences of a tropical climate had a great influence in the production of these cases, it must be admitted that there were numerous instances in which the condition did not develop until after repeated attacks of malaria, and that the continued and vigorous use of quinine resulted in the recovery of most of them.

Melancholia, *mania*, and *delusional insanity* occur as sequelae of the malarial infections. Manson, Segard, and Pasminik, as well as other observers, have described cases of insanity following malaria, uncomplicated by heredity or alcohol. Pasminik in 5,400 cases of malaria observed mental disturbances in 106 cases. Melancholia and delusional insanity are the most common forms occurring as sequelae of malaria, and the duration of the cases varies from less than a week to six months or more. In very many cases the mental depression occurring with and following the paroxysms is very great, and it is a very common occurrence for patients who have suffered from malaria to complain for weeks afterward of suffering from "the blues" or of ill-defined forebodings; an exaggeration of this condition becomes melancholia which I have found to be the most common mental disturbance following malaria. I have observed many cases of slight melancholia in soldiers in the Philippines and returning therefrom, which were undoubtedly due to repeated malarial infection, generally of the aestivo-autumnal type, and it has been remarkable how quickly the condition disappeared under the proper administration of quinine. I have also seen cases of mania and delusional insanity following malaria in which there can be no question that the condition was due to the malarial infection.

Persistent *insomnia* often occurs after malarial infection, especially among Europeans who are residing in the tropics, and it is sometimes very resistant to treatment.

2. **Sequelae Observed in the Circulatory System.**—It may be said with truth that malaria has but little effect upon the heart and blood-vessels. Lancereaux has endeavored, without success, to prove that *acute endocarditis* may be caused by malaria, and he and Huchard claim that *chronic arteritis* is often of malarial origin. Their arguments are illogical and they furnish no convincing proof of the truth of their assertions. It is certainly a fact that no such sequelae have been described by those who have studied malarial infections in tropical regions and it is evident that if such sequelae were present they would have been reported by many different observers. When these diseases occur with malarial infections they are complications and not sequelae.

3. **Sequelae Observed in the Digestive System.**—As a result of the localization of the plasmodia in the mucous membrane of the stomach or intestine, a true *acute or chronic ulcerative enteritis* may result, and, very rarely, the formation of *gastric ulcers*. *Parotitis* has been described by Lancisi, but I have never observed a case. Mannaberg describes haemorrhage from the

bowels in malarial cachexia, and Pensuti reports one case in which there was atrophy of the mucous membrane of the stomach. From the results of a large number of autopsies upon patients dying of chronic dysentery, most of whom had suffered previously from malarial infection, I am very much inclined to doubt the occurrence of such cases as that described by Pensuti, as even in the cases autopsied, which were certainly very liable to such changes, atrophy of the mucous membrane of the stomach was not common.

I have already noted the occurrence of *dysenteric symptoms* in many cases of malarial infection and following such infections. It is my belief that dysenteric symptoms are often due to the localization of the plasmodia in the mucous membrane of the intestine, and that in rare instances *chronic dysentery* may be a sequela of such infections.

4. **Sequelae Observed in the Genito-urinary System.**—*Albuminuria* is of very common occurrence along with and following malarial infections, especially of the aestivo-autumnal type. As a rule, it is a complication of malaria rather than a sequela, but I have seen several cases in which a persistent albuminuria resulted from malarial infection, no other renal symptoms being present. Rem-Picci has contributed much to our knowledge of this subject, and he divides the albuminurias into the febrile, which occur with the malarial paroxysms, or follow them at once, and the postmalarial, which persist after the malarial attack and occur in malarial cachexia.

Nephritis both in an *acute* and *chronic* form may occur as a sequela of malaria, especially after aestivo-autumnal infections. That even chronic nephritis may be induced by repeated malarial attacks has long been believed by such observers as Rosenstein, Bartels, Laveran, Herz, McLean, and Kelsch and Kiener. The latter authorities describe two forms of kidney affections following malarial infection, one characterized by a congested kidney, the other by an atrophic kidney. They describe two forms of nephritis, the glomerular and the granular. The *glomerular* form is divided into acute and chronic, the first developing during or immediately after the acute malarial infection, the second during chronic infection. The clinical symptoms are those of acute and chronic parenchymatous nephritis. The *granular* form is also divided into acute and chronic, the first developing in patients who have suffered from numerous relapses of malaria, the clinical symptoms being those of subacute and chronic interstitial nephritis.

Rem-Picci, in his exhaustive and most valuable study of nephritis following malaria, divides the condition into acute and chronic forms, the first developing either during or after the malarial infection, the second developing insidiously after the malarial attack. The acute form may be severe or slight in character and varies in duration. As a rule, the prognosis is good. He finds that it is most common in aestivo-autumnal infections in autumn or winter, and in young rather than in old people. The chronic form is a true interstitial nephritis, which may develop without a previous acute attack. It is much more rare than is the acute form.

Thayer, in a valuable study of malarial nephritis, states that of 112 cases of acute nephritis observed in the Johns Hopkins Hospital, 21, or 18.7 per cent., were of malarial origin. He observed four cases of chronic nephritis following malarial infection in 1,832 patients suffering from malaria, and in 758 cases of malarial fever treated in the wards of the hospital he found that 17.5 per cent. presented casts of the urinary tubules in the urine. He found that nephritis was much more common in aestivo-autumnal infections than in either tertian or quartan, occurring in 4.7 per cent. of aestivo-autumnal infections as compared with only 2.3 per cent. of all other infections combined.

From personal observation I believe that some form of nephritis follows aestivo-autumnal infection in at least 3 per cent. of all cases, but that it does not follow tertian or quartan infections except in rare instances, not over 0.5 of 1 per cent. of my tertian and quartan cases showing nephritis as a sequela. In all fatal cases of malaria some form of nephritis will invariably be found. Nephritis following malaria may be divided into subacute parenchymatous, chronic parenchymatous, and chronic interstitial forms, and these forms do not differ in their symptomatology from such conditions as observed when occurring alone or as a complication or sequelae of other diseases. The chronic forms may develop insidiously, but the subacute form is always preceded by an acute attack. *Amyloid degeneration* may occur in certain cases of parenchymatous nephritis.

From my own observations I would say that casts of the urinary tubules occur in 25 per cent. of the cases of aestivo-autumnal malaria, and in 5 per cent. of all cases of benign tertian and quartan malaria, but that only a comparatively small number of these cases develop nephritis.

Polyuria is a frequent sequela of the malarial fevers, especially of the aestivo-autumnal variety, transient as a rule, but in some cases very persistent. I have observed a large number of cases of polyuria following malarial infection, and in some instances the condition was very marked. In one case the amount of urine passed during the 24 hours varied from 20,000 to 25,000 cubic centimeters, and this condition existed for several weeks.

Glycosuria is a very rare sequela of aestivo-autumnal infection, so rare that there is good reason to doubt its occurrence. Marchiafava and Bignami report a case in which glycosuria developed during malarial cachexia, but there is no proof that the condition was due to malaria.

5. **Sequelae Observed in the Glandular System.**

THE LIVER.—In cases which have suffered from repeated attacks of malaria, especially the aestivo-autumnal fevers, a condition known as hypertrophic malarial hepatitis develops, characterized by enlargement of the organ, the perilobular tissue being increased, and the capillaries markedly dilated. This condition, however, does not cause much disturbance in the functional activity of the organ, and no clinical symptoms are present which are characteristic.

Typical *atrophic cirrhosis* of the liver is, I believe, very rarely the result of

malarial infection. Many observers differ upon this point, but there is no evidence sufficient to prove that cirrhosis is often the result of such infection. It is, of course, present in some cases, but generally occurs as a complication due to some other cause. That this is so is evidenced by the fact that cirrhosis of the liver is no more common in intensely malarial regions than it is in immune districts.

THE SPLEEN.—I have already mentioned the enlargement of the spleen occurring in patients who have suffered from repeated malarial attacks, and to this enlargement are due certain other interesting sequelae of malarial infection, such as floating spleen and rupture of the organ.

In rare instances the enlarged spleen, by its weight, sinks into the abdominal cavity, the ligaments holding it in place become stretched, and the organ can be felt as a movable mass through the abdominal walls. The condition is known as wandering or floating spleen. The symptoms are pain upon movement, a feeling of weight in the abdomen, and reflex disturbances, such as headache, nausea, and vomiting.

In acute or subacute infections the spleen is generally very soft and friable, and rarely this leads to *rupture* of the organ. This result may be induced by blows, falls, retching in vomiting, or sudden movements of the body. The capsule may be lacerated or there may be a slight tear in one region. Laceration of the capsule only occurs when the rupture is due to violence. The symptoms are sharp, lancinating pain in the left side, and the usual signs of collapse due to hemorrhage. Death may occur almost instantly, or a day or two may pass before the fatal ending, depending entirely upon the extent of the laceration and the consequent hemorrhage. I have observed two cases of rupture of the spleen and one case has been reported to me by Captain Banta, of the Medical Corps of the U. S. Army. The occurrence of *abscess* of the spleen has been reported, following malarial infection, by Laveran and other observers. Fassina has collected seven cases in the literature and saw two himself. Without doubt such abscesses have resulted from bacterial invasion, although the malarial infection may have produced conditions favoring the infection. The symptoms have been pain, swelling, the formation of a tumor, fever, and diarrhoea. Rupture of the abscess may occur.

LYMPHATIC GLANDS.—Martin and Bodnar describe enlargement and subacute inflammation of the lymphatic glands as sequelae of chronic malarial infection, accompanied by intermittent or remittent fever. I have never observed such cases, and believe that they may have been confused with cases of climatic bubo, glandular fever, or syphilis. It should also be remembered that in infected regions, sleeping sickness, in its early stages, and kala-azar might easily be considered as chronic malarial conditions and the enlargement of the glands present in these diseases be regarded as of malarial origin.

Orchitis and *epididymitis* have been described as sequelae of malaria by Berthelon, Martin, Magnin, and others, but a careful examination is sufficient

to prove that many of these cases are based upon untrustworthy evidence, although I believe that a case such as that reported by Zieman, in which no other cause could be demonstrated and the malarial plasmodia were found in the blood, proves that such a condition may very rarely occur. The cases reported in which there is good reason to believe that the cause was really malarial presented a remittent fever, with enlargement of the testicles and the epididymis, and some pain and inflammatory swelling; the symptoms were easily controlled by quinine, but the enlargement lasted in some of the cases for months.

6. **Sequelae Observed in the Organs of Special Sense.**

THE EYE.—Affections of the eye are not uncommon as sequelae of malarial infections, especially in the tropics and following aestivo-autumnal infections. I shall mention briefly the most important.

Amaurosis.—In severe malarial attacks amaurosis sometimes occurs during the attack, but it also occurs as a sequela. One of the first instances of this kind was reported by Jacobi, in 1868, and Chiarini has since reported several cases in which there was optic neuritis. The more chronic condition may be followed by partial or total loss of vision by reason of atrophy of the optic nerve.

Retinochoroiditis has been described by Poncet as occurring in chronic malarial infections, and Guarnieri has given in detail the pathological lesions observed in such cases. He found that the retinal capillaries contained red corpuscles entirely, many of them containing pigmented plasmodia. In the choroid he found the larger vessels filled with pigmented leucocytes and many of the leucocytes contained parasite-infected red corpuscles.

Keratitis.—In 120 cases of malaria observed in the United States, Kipp found keratitis to be present, and Poncet, and Sedan and Levrier have seen similar cases.

Vitreous Humor.—Bull reports 17 cases in which haemorrhage had occurred into the vitreous humor, and Seely and, later, Sulzer, described *serous engorgement* of the vitreous followed by almost total blindness. The lesion consists in a serous infiltration of the vitreous, and is seen as a whitish cloudiness of that body. In one of Seely's cases recovery occurred under quinine.

Suppurative choroiditis is described in one case by Pennoff, terminating in destruction of the eye.

Paralysis of the power of accommodation has been noted by Bull as the result of malarial infection, and spasm of the accommodation by Stilling.

THE EAR.—Certain affections of the ear have been ascribed to malaria, but only a few can be regarded as really due to the malarial infection. *Intermittent otalgia* occurs as an expression of chronic malarial infection and is relieved in such cases by quinine. Frank, Politzer, and De Rossi have recorded cases of this character; intermittent attacks of *deafness* due to lesions of the internal ear or the auditory nerve brought about by malarial infection have been reported by Bar, Wolff, and Ferreri, but there is always, in such cases, the possibility that

the deafness was really due to quinine, although some of the cases described by these observers were undoubtedly due to the malarial infection.

Labyrinthine vertigo occurs as the result of malarial poisoning and has been very carefully studied by Ferreri. In one case the patient, who had suffered from slight symptoms of aural trouble for some time, had an attack of fever and some time afterward an attack of deafness, ringing in the ears, and vertigo of so severe a type that he fell; this was followed by three similar attacks and the examination of his blood showed the presence of aestivo-autumnal plasmodia. Treatment with quinine cured the condition in two months.

The cases of *suppurative otitis media* mentioned by Liel, Hotz, and De Rossi, cannot be considered as due to malarial infection, for the malarial plasmodia are not pyogenic organisms and there is no well authenticated instance upon record of any suppurative process due to these parasites.

The special senses of taste and smell are not affected by malarial infection.

Miscellaneous Sequelae.—*Pigmentation* of the skin is a very common result of malarial infection, and in some instances is so marked as to closely simulate Addison's disease. It is probable that much of the pigmentation of the skin following malaria of Europeans in the tropics is as much due to the tropical sunlight as to the malarial infection, for it is a common experience to observe decided pigmentation of the skin brought about by residence in a tropical country.

Gangrene.—Fischer and Sarda have reported severe cases of dry gangrene following intense malarial infection, but such a condition must be very rare.

The changes observed in the subjects of *malarial cachexia* have already been considered.

Postmalarial Anaemia.—An anaemia, pernicious in character, and presenting the same blood findings as are found in cases of primary pernicious anaemia, occurs very rarely as a sequela of malarial infection. I have observed but one such case, but in this case the findings in the blood were exactly similar to those found in primary pernicious anaemia and I believe that the condition was the direct result of malarial infection.

In the aestivo-autumnal forms of malaria the anaemia produced by repeated attacks may be very severe and very persistent. In the tertian and quartan fevers the regeneration of the blood is very rapid as compared with the aestivo-autumnal fevers, and in the latter the number of red blood-corpuscles may reach a very low level. I remember several cases in which the number of red cells was not over 900,000 per cubic millimeter, and one in which the blood-count showed but 497,000 red corpuscles per cubic millimeter. I have already discussed the anaemia following the malarial infections, especially that of pernicious character, and will not reconsider the subject here.

In reviewing the subject of the sequelae of the malarial fevers I have included only those sequelae which are of importance and which occur with enough frequency to merit description. There are many sequelae which have been reported from time to time, by various authors, which I have not spoken

of, partly because they are of such rare occurrence as to be of no practical interest, and partly because many of them could have had no relation to malarial infection. Because a certain condition develops after an attack of malarial fever, it does not follow that it is due to that infection, and we should be most careful in our conclusions regarding the etiology of clinical symptoms and conditions following the malarial fevers.

CHAPTER II.

The Complications of the Malarial Fevers.

The malarial fevers may be complicated by or associated with many other diseases, and in some instances it would appear that the malarial infection is responsible for certain of the complications, but the old theory, first advocated by Boudin, that all malarial complications were due to the malarial poison, has long since been abandoned. The malarial plasmodia are not the cause of a lobar or bronchopneumonia complicating malaria nor of a typhoid which may be coexistent with it; in each case the complicating disease is due to its specific organism, and though the course and clinical symptoms of either disease may be more or less altered by their association, yet their etiology remains unchanged. In other words, there is no such thing as a typical lobar pneumonia due alone to the malarial plasmodia or a peculiar form of typhoid fever caused by these organisms.

Of the many diseases which may complicate the various forms of malaria, and especially the aestivo-autumnal infections (for these infections, being more severe in character than the tertian and quartan, are more apt to be accompanied by complications), the following may be mentioned:

Complications Observed in the Nervous System.—Coincident with the malarial fevers there may occur attacks of *acute mania*, such cases having been described by Yanarris, but this complication is very rare. *Hysteria* is a common complication in nervous women, and even in men, and, as in hysterical attacks in general, the symptoms vary greatly in character and severity. *Paraplegia* and *hemiplegia* may rarely complicate these fevers, and *neuroses* of various kinds are not uncommon. *Meningitis* may occur as a complication.

Complications Observed in the Respiratory System.—The most common complication observed in the respiratory system is *acute bronchitis*. A mild form of this affection is observed in very many cases of malaria, probably due to the infection *per se*, but not infrequently a severe form of bronchitis will complicate our malarial cases and may persist for weeks after the infection has disappeared.

Both *lobar* and *lobular pneumonia* occur as complications of the malarial fevers, the first being by no means a rare complication. Early observers held that the pneumonia sometimes accompanying malaria was directly due to the malarial plasmodia, but recent investigations have conclusively shown that these organisms are unable to produce a true pneumonitis. The pneumonic symptoms which appear in certain cases are undoubtedly due to the localization of the plasmodia in the lungs, and I have already described the form of pernicious

malaria in which the symptoms are chiefly referred to the lung and are practically identical with those of lobar pneumonia, but a microscopical examination of sections of the lung in such cases shows that the lesions present differ considerably from typical of lobar pneumonia.

Lobar pneumonia may complicate the malarial fevers at any time, and may develop suddenly or insidiously. In some instances the course of the disease is similar to that in a patient in whom no malarial infection is present, while in others, the course of the pneumonia is interrupted by chills and exacerbations of fever due to the malarial infection. The pneumonic symptoms may mask the malaria, or *vice versa*. The prognosis in pneumonia complicating the aestivo-autumnal fevers is very grave, Ascoli placing the mortality as high as 60 to 78 per cent. in patients who have suffered from repeated attacks of malaria. Death may occur from thirty-six to seventy-two hours from the initiation of the pneumonic symptoms.

Broncho-pneumonia or *lobular pneumonia* occurs as a complication less frequently than lobar pneumonia and resembles in its pathology the form produced by the plasmodia more closely than does lobar pneumonia. Clinically, the two conditions (typical lobular pneumonia and the form produced by the plasmodia) cannot be distinguished.

In cases of pneumonia complicating malaria which recover, the convalescence is generally very slow, resolution being greatly delayed. An *empyema* may result in rare instances. Not rarely the affected portions of the lung become fibroid, and a *chronic fibroid pneumonia* results, or *bronchiectasis* may occur.

Pneumonic septicaemia has been described by Bignami, Marchiafava, and Nazari as complicating malaria. This condition appears in patients suffering from long-continued malarial infection who have developed pneumonia, and has only been observed in aestivo-autumnal infections.

In malarial patients in whom pneumonia has occurred as a complication, the latter disease is very apt to terminate in delayed resolution; a typhoid state, followed by death; pneumococcic septicaemia or induration. All of these terminations are frequent in patients who present the symptoms of malarial cachexia.

Pleurisy has been reported by Hertz as a complication of the malarial fevers, but it is a very rare one.

Tuberculosis.—The old belief that tuberculosis and malaria were antagonistic and that they seldom occurred together has been proven false, and we now know that both diseases are very commonly associated and that fatal cases of malaria may occur in patients suffering from tuberculosis. Marchiafava claims that "if the malarial infection attacks organisms affected by tuberculosis, the latter is not arrested, but acquires a tendency to spread, and produces miliary tuberculosis." This statement is interesting and in my experience true, for I have repeatedly observed miliary tuberculosis in malarial subjects, and the number of instances of miliary tuberculosis discovered at autopsy in patients who were also the victims of severe malarial infections, has,

in my experience, been remarkable. I have repeatedly seen cases diagnosed as pulmonary tuberculosis in which there were physical signs of cavity formation and consolidation, and which later developed severe malarial infection. At autopsy, besides the presence of cavities and large areas of consolidation, a severe miliary tuberculosis was found, thus proving, I believe, the truth of Marchiafava's contention, that malarial infection in the subjects of tuberculosis stimulates the formation of miliary tubercles. The same authority claims that, unlike other cachexias, malarial cachexia does not predispose to tuberculosis. In view of the effect of malarial infection upon existing tuberculosis, it is obvious that such infection should be promptly recognized and eliminated.

If quinine be administered to a patient suffering from any of the complications mentioned, it will be followed by the cessation of the malarial symptoms, and the complicating process will run its usual course.

Complications Observed in the Circulatory System.—Any of the *organic* diseases of the heart may complicate a malarial infection, and in severe aestivo-autumnal infections the prognosis may be exceedingly grave. *Acute endocarditis* may occur as a complication, but is never due to malarial infections, as has been claimed by Lancereaux. The *ulcerative* form of endocarditis may occur following a pneumonic complication. A *systolic murmur* is often present in severe malarial infections, and *functional* disorders are very common. A *slow pulse* during convalescence is very frequently observed, sometimes counting but forty beats to the minute.

Complications Observed in the Genito-urinary System.—The most common complication observed in the genito-urinary system is *nephritis*. While *albuminuria* is very common, it can hardly be called a complication, as it is undoubtedly due to the malarial infection and is so common as to constitute a symptom of the disease. Thus Thayer, in 691 cases of malaria, found albuminuria in 321 instances, or 46.4 per cent. In my own experience I have found albuminuria in at least 50 per cent. of all cases. It is most frequently observed in aestivo-autumnal infections; thus Thayer found that in tertian and quartan infections it occurred in 38.6 per cent. of all cases, while in aestivo-autumnal infections it occurred in 58.3 per cent. of all cases. My own figures confirm those of Thayer as regards tertian and quartan infections, but I have found that at least 65 per cent. of aestivo-autumnal infections show albumin in the urine and that the condition is always present in fatal malarial infections.

Some form of *nephritis* occurred as a complication in at least 4 per cent. of the aestivo-autumnal cases I have observed, and in one-half of 1 per cent. of tertian and quartan infections. Very often the nephritis is an acute one, due directly to the malarial infection, as is proven by the disappearance of the condition after the cessation of the malarial attack, but not infrequently a *chronic* or *subacute nephritis*, already existing, complicates the malarial infection, and in such cases the prognosis is often grave. Thayer states that among 1,832 cases of malarial fever observed at the Johns Hopkins Hospital, acute nephritis was present in 26 instances, in all but three instances undoubtedly due to the ma-

larial infection. Of these cases four died, one from the malarial infection, the others as the result of the nephritis. It will thus be seen that this complication is sometimes a fatal one and that in the majority of instances it is caused by the malarial infection. A further discussion of nephritis as a result of malarial infection will be found in the chapter dealing with the sequelae of the malarial fevers.

Orchitis and *epididymitis* may occur as complications of the malarial fevers, but a history of gonorrhoea is usually to be obtained. These complications are especially common among soldiers, and neither condition appears to be aggravated by the malarial plasmodia. In some cases of epididymitis the temperature chart is rendered atypical because of the fever accompanying the genital condition. The cases of orchitis described by Maural, Calmette, Schmidt, and others are open to serious question, as being due to malarial infection, although very rarely such a condition may occur.

Gangrene of the penis, the scrotum, and the labia has been described by Mannaberg as complicating or following malarial infection. These conditions might easily occur as complications, but I believe that it is very doubtful if they occurred as the result of malarial infection.

Complications Observed in the Gastrointestinal Tract.—The most frequent and important disease of the gastrointestinal tract complicating malaria is *dysentery*, either *amoebic* or *specific*, or some form of enteritis. In patients returning to temperate regions from the tropics where either specific or amoebic dysentery is epidemic or endemic, it is very common to observe the coexistence of these diseases with malaria. In the case of soldiers returning from the Philippine Islands, as observed at the U. S. Army General Hospital at San Francisco, over 65 per cent. showing malarial plasmodia were also suffering from either *chronic specific dysentery* or *amoebic dysentery*. Of these cases 25 per cent. were suffering from amoebic dysentery, as shown by the presence of *Entamoeba histolytica* in the faeces. The combination of these two protozoan infections, malaria and amoebic dysentery, is very common in the Philippine Islands, and the malarial infection appears to aggravate the dysenteric condition. When malaria is complicated by dysentery, or *vice versa*, the dysenteric symptoms are aggravated, and the prognosis is much worse than when either disease occurs alone. The symptoms of malaria are often masked by those of dysentery, or the malarial infection may be latent. The administration of quinine in patients suffering from malaria complicated by dysentery, not only removes the malarial infection, but, in the majority of instances, markedly benefits the dysentery condition, and a return to health is more rapid. The explanation of this fact is not hard to find. We know from pathological studies that the mucous membrane of the intestine is generally invaded by the malarial plasmodia, which invasion must necessarily injure the vitality of the tissues; removal of the plasmodia by quinine aids the tissues in regaining their normal vitality, and thus indirectly improves the dysenteric condition.

In a certain proportion of patients suffering from malarial infection in

which dysenteric symptoms are present, the latter symptoms are undoubtedly due to the localization of the plasmodia within the capillaries of the intestine, as I have already shown, and in such patients the administration of quinine is rapidly followed by complete recovery.

Typhoid Fever.—The complication of malarial infection by typhoid fever is a most important and interesting one, which will be fully considered in the following chapter.

Cholera may complicate malaria, and such instances have been described by Bastianelli and Sternberg. I have autopsied several Filipinos who had died of cholera in whom the spleen showed evidence of malarial infection, but I have never observed a case clinically in which cholera and malaria coexisted. There is no reason to doubt, however, that cholera complicates malaria frequently during widespread cholera epidemics.

Acute Infections Complicating Malaria.—Almost all of the acute infectious diseases have been reported as complicating malaria. *Smallpox*, *measles*, *diphtheria*, *Malta fever*, *erysipelas*, *acute articular rheumatism*, and *streptococcic septicaemia* have all been observed during malarial attacks, and it is probable that such cases occur much more frequently than we have supposed in regions in which malaria is prevalent.

Miscellaneous.—To Sternberg and to Kelsch and Kiener we owe the knowledge that *insolation* is a frequent complication of the malarial fevers, and that it often aids in the production of a pernicious attack. Exposure to the sun's rays in a person debilitated by repeated malarial paroxysms is very apt to be followed by sunstroke, and it is well known that such exposure is very efficient in bringing out the symptoms of malaria in cases in which the infection is latent. I have often observed that a drill in the tropics is followed by the admission to the military hospital of many cases suffering from malaria, developing, in those so exposed, during or immediately after the drill, and in my experience more than one pernicious attack of malaria was preceded by prolonged exposure to the rays of the tropical sun. It is now generally admitted that an individual who has suffered from repeated attacks of malaria is much more sensitive to the sun's rays than one who has not, and that insolation is very apt to occur in such cases.

Puerperal women who have suffered from attacks of malaria are more liable to complications, such as *puerperal fever*, *hemorrhages*, and *abortion*, than are those free from such infection, because of the anaemia invariably present, and the lowered vitality of the tissues. *Abortion* complicates malarial infection frequently in regions where the aestivo-autumnal fevers are prevalent, and it has long been known that abortion is much more frequent in malarial countries than in others. Thus Weatherley, who has given this subject careful study, found that in the East Indies as many as 46.6 per cent. of pregnant women aborted, while in England only 3.56 per cent. aborted. Of course these figures are likely to be only approximate, but they demonstrate the fact that in malarial regions abortion occurs much more frequently than in immune localities.

In the tropics the malarial infections may be complicated by infection with any of the animal parasites so commonly found in such regions. A combined infection of malaria and *Anchylostoma duodenalis* or *Necator americanus* is frequently observed, and is always a serious condition, as both parasites produce anaemia. Combined infections of malaria and *filariasis* have been reported several times and are probably of a very common occurrence in regions where filariasis is prevalent. Infections with *Schistosoma haemotobium* and *Paragonimus westermanii* sometimes complicate the malarial fevers and greatly delay recovery from the malarial infection. I have already discussed the frequent association of the malarial plasmodia and *Entamoeba histolytica* and called attention to the importance of recognizing this complication.

Of other diseases which may complicate the malarial fevers may be mentioned *diabetes mellitus*, *sciatica*, *tonsillitis*, *parotitis*, and various *skin diseases*. Any of the chronic diseases affecting the viscera may complicate the malarial fevers and in many instances render the prognosis very grave.

Malaria as a Puerperal and Postoperative Complication.—A malarial paroxysm often follows parturition in women who have become infected, and pernicious symptoms may develop in such cases unless the infection is promptly treated. It is also well known that a latent malarial infection is often made manifest by an operation or by trauma, and in malarial regions many postoperative fevers are malarial even though quinine may have been administered in small doses as a prophylactic. In fevers arising during the puerperium and following wounds and operations it should always be remembered that a microscopical examination of the blood is indicated, especially in malarial regions or in patients who have resided in such localities; such an examination will often remove a load of anxiety from the mind of the obstetrician or surgeon, and frequently result in the saving of the life of the patient.

Literature upon the Sequelae and Complications of the Malarial Fevers.

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CHAPTER III.

Coincident Typhoid and Malarial Infection.

The simultaneous occurrence of typhoid and malarial fever is a subject of much interest to investigators, and one which has given rise to much controversy, and has evoked many varying opinions from eminent authorities. During the war of the Rebellion a great number of cases of fever were observed which did not answer to the typical characteristics of either typhoid fever or the malarial fevers, and Woodward, a Major Surgeon of the Union Army, designated such fevers as "typho-malarial" fever, a classification accepted by the Army authorities. From July 1, 1862, until June 30, 1866, there were reported to the Surgeon-General's office 57,400 cases of typho-malarial fever, with 5,360 deaths. Woodward, in thus designating these fevers, never intended that the name should indicate a disease entity, but a hybrid condition, brought about by the combination of typhoid and malarial infection, and differing clinically from either of these diseases. Thus, in a paper read before the International Medical Congress at Philadelphia, in 1876, he stated:

"I never meant this term (typho-malaria) to represent a specific type of fever, but intended it to designate all the many-faced brood of hybrid forms resulting from the combined influence of the causes of malarial fever and of enteric fever."

Again he says:

"And this brings me at length to answer the question, Is typho-malarial fever a special type of fever? and I reply unhestitatingly that it is not. I, at least, am free from the blame of that error, if anyone has fallen into it."

Unfortunately, many practitioners did fall into the error of regarding typho-malarial fever as a distinct disease and the term soon became of common diagnostic use, and was the cause of great confusion in the study of the continued fevers. Too often it was employed to cover ignorance of the condition present and even to-day a diagnosis of typho-malarial fever is not infrequently made in long-continued fevers in which uncertainty exists as to the exact nature of the infection. For this reason the term should be abandoned, for research has demonstrated that while typhoid fever may be complicated by malaria, and *vice versa*, there is no reason for applying a special name to the combination, and clinically the cases do not present any characteristic group of symptoms.

While a great number of coincident infections with typhoid and malarial fever have been reported in the literature of medicine, very few have been studied scientifically, and since the discovery of the plasmodia of malaria and

the Widal test there have been but a small number of cases reported in which the diagnosis was rendered certain by the use of laboratory methods.

Historical.—Prior to the use of the Widal test in the diagnosis of typhoid fever numerous observers had reported cases in which the malarial plasmodia were found in the blood and in which, after the disappearance of these organisms, the fever persisted and presented the symptoms of typhoid. Laveran was probably the first to mention such cases, describing two, in one of which intermittent fever occurred during convalescence from typhoid, and another in which the malarial fever preceded and followed the typhoid. Kinyoun described several cases in 1899, dividing them into those in which the malarial symptoms predominated and those in which the symptoms of typhoid were most prominent. Other cases have been reported by Thompson, Osler, and Vincent. While most of these cases were undoubtedly instances of coincident typhoid and malarial infection, and the malarial plasmodia were demonstrated in the blood of the patients, in none of them was the Widal test applied, nor were the typhoid bacilli separated from the excreta, so that an element of doubt exists regarding some of the cases.

The only cases in which we can be sure that such a coincident infection occurs are those in which one of the malarial plasmodia can be demonstrated in the blood, and at the same time some substantial proof of the existence of typhoid, as the separation of the bacilli from the blood, rose spots, or excreta, or a positive reaction to the Widal test, can be shown to exist. Applying such tests the number of cases of coincident typhoid and malarial infection which have been reported are surprisingly few, and I believe that while the combination of these diseases is much more common than the number of cases reported would lead us to believe, still the condition is a rare one when we consider the chances of such infections in localities in which both diseases are prevalent.

Frequency of Occurrence.—The researches of Lyons and of Reed, Vaughn, and Shakespeare prove that coincident typhoid and malarial infection is of rare occurrence. Lyons, in 1900, collected all of the cases of coincident typhoid and malaria on record in which the plasmodia were found in the blood and sufficient proof existed that typhoid fever was present, and found that they only numbered 29 in all. In the classical report upon the "Spread of Typhoid Fever in the United States Military Camps during the Spanish War of 1898" by Reed, Vaughn, and Shakespeare, which included data up to 1904, there are collected 95 cases in which these diseases coexisted, but only 12 are reported as occurring during the active stage of the typhoid fever. Curry, who examined the blood of hundreds of cases of typhoid during the same war found only one case in which malaria occurred during the active symptoms of typhoid, and Ewing, at Montauk Point, observed no case in which such infection occurred, although he saw many cases of typhoid develop malaria during convalescence. As the result of his observations he concludes that typhoid and malaria are incompatible, the malarial symptoms apparently being held in abeyance by the coexisting typhoid infection. Da Costa reports three cases of coexistent

typhoid and malaria, Muehleck, five cases, and Witherington, three cases in which the malaria was coincident with the active symptoms of typhoid.

In my own experience, covering the observation of hundreds of cases of typhoid fever, and thousands of malarial infection, I have seen but ten instances of coincident typhoid and malarial infection. It should be understood that I regard as coincident infections only those in which the malarial paroxysms occur during the active symptoms of typhoid and not during convalescence. It is not at all uncommon to observe the occurrence of malarial paroxysms during convalescence from typhoid or preceding that disease, but such instances cannot be considered as true examples of coincident infection.

From the data given it is evident that coincident infections with typhoid and malaria are rare, and that while cases do occur, their number is insignificant when compared to the number of cases of typhoid and malaria observed in the endemic areas of these diseases. There is, I believe, good reason for thinking that there does exist a certain amount of incompatibility between the two infections, for it is frequently observed that when typhoid develops in a patient suffering from malarial fever, the malarial symptoms disappear, as well as the plasmodia from the peripheral blood, and only reappear during convalescence from the typhoid.

Species of Malarial Plasmodium Present.—Any of the species of malarial plasmodia may be present in coincident typhoid and malarial infection, but *Plasmodium vivax* has been most frequently observed. In 44 cases collected by Reed, Vaughn, and Shakespeare, the tertian plasmodium occurred in 22 the aestivo-autumnal in 12, the tertian and aestivo-autumnal in 9, and the quartan in one, a case reported by the writer. In the 10 cases observed by myself, six were infected with the tertian aestivo-autumnal plasmodium, three with the tertian plasmodium, and one with the quartan plasmodium.

Symptomatology.—It may be stated that there are no characteristic symptoms of coincident malarial and typhoid infection, every case differing somewhat in this respect. The occurrence of the malarial complication is generally evidenced by a chill, but in the aestivo-autumnal infections the chill may be absent, the patient complaining only of slight chilly sensations. The fever may show a sudden exacerbation and in some instances every malarial paroxysm may be clearly seen upon the temperature chart, owing to the sudden rise in the temperature curve. This is beautifully illustrated in the chart given of coincident typhoid and quartan malaria and also in that illustrating a coincident typhoid and aestivo-autumnal infection. Paroxysms of chill, fever, and sweating, occurring during an attack of typhoid are very significant of a malarial complication, but such paroxysms occur in typhod from other causes, and we cannot, therefore, base our diagnosis upon them. The abdominal symptoms are generally increased during the malarial infection, and this is also true of the symptoms connected with the nervous system. The headache is very severe and delirium is almost invariable present, even in those cases in which it was absent before the appearance of the malarial paroxysm. In

general, it may be stated that all the symptoms of typhoid are increased in severity and there are added to them the symptoms commonly observed in a malarial paroxysm.

When malaria occurs during convalescence from typhoid it is generally manifested by chills, fever, and sweats, and the temperature curve is characteristic of the type of malaria which may be present. It should be remembered, however, that paroxysms of chill, fever and sweating are sometimes observed at the onset of typhoid and during convalescence from that disease, so that the occurrence of such paroxysms does not always mean the presence of a malarial infection.

The effort which has been made to ascribe to cases of so-called "typho-malarial fever" a more or less definite and characteristic symptomatology has resulted in failure, and the most that we can say as to the symptomatology of these coincident infections is that the symptoms present are those commonly present in both diseases, but in these cases combined, thus giving rise to atypical clinical pictures, in which sometimes the typhoid symptoms predominate and sometimes those of the malarial infection.

Illustrative Cases.—The following cases of coincident typhoid and malarial infection were observed in soldiers of the U. S. Army, and are typical of all similar cases I have studied. In these patients the malarial paroxysms were present during the active symptoms of typhoid fever, and although the symptomatology may have been slightly altered by the administration of quinine, the malarial infection was present for a sufficient length of time to profoundly alter the course of the typhoid, and to give to the temperature chart characteristics of a malarial infection.

Coincident Typhoid and Quartan Malarial Fevers.—The following case was observed at the Sternberg U. S. Army General Hospital, Chickamauga Park, Ga., in 1898, and is, so far as I know, the only case recorded of coincident typhoid and quartan malarial infection. The patient was a Southern physician who had suffered previously from repeated attacks of malarial fever, but had been free from the disease during the time he was at the Park. The clinical history which follows is compiled from my own observation and from information furnished me by Acting Assistant Surgeon Barnhardt, U. S. Army, who was in attendance upon the patient during the latter portion of his illness and until his removal to another hospital.

Clinical History.—D. R. P. had suffered from September 29 to October 5, from general malaise, constipation, and headache, with an evening temperature of from 101° F. to 102° F. Although feeling ill he did not take to his bed until October 5, when he was admitted to the hospital, complaining of severe headache and great nervousness. The previous evening he had had a slight chill. On admission he presented the following clinical symptoms: Gurgling and tenderness in the right iliac fossa; a dry, hot skin; brilliant eyes, with injected conjunctivae; and a typical typhoid tongue. The typhoid symptoms gradually increased, and he developed tympanites, epistaxis, rose spots, extreme restlessness, and a slight bronchitis.

October 12, or about the twelfth day of the fever, his blood was tested for the Widal reaction and found positive, the reaction being marked; he also showed the diazo-reaction in his urine The patient had never had typhoid fever previously.

Upon Obctober 15, the morning temperature had fallen to 100° F.,and his general condition appeared much improved, but later in the day he had a slight chill and the temperature rose to 103.4° F. The attending physician thought little of the chill, as, by evening, the temperature had fallen to 101° F., and for the succeeding two days ranged between 100° F. and 102° F. October 18, however, just 72 hours after the first chill, a second and more severe chill occurred, the temperature rising to 104° F.

At this time I was called upon to examine the blood, and found the quartan malarial plasmodium present in large numbers. The blood examinations are detailed below. At the time of the first blood examination the patient's general condition was markedly altered for the worse, and he suffered from general muscular pains, severe in character, a weak, irregular pulse, and was very weak and tremulous.

From October 18 to October 21 his temperature ranged between 98.8° to 100.6° F. The administration of quinine in small doses (5 grains night and morning) was begun upon October 18. Upon October 21, a third paroxysm occurred, but was delayed somewhat (probably by the quinine), so that it extended into the 22d, the acme of the fever being reached at 4 A. M. of that day. This paroxysm was very severe, the chill lasting thirty minutes, and the temperature rising from 99.2° F. to 104.6° F. A fourth paroxysm occurred upon October 25, the quinine, for some reason, having been stopped upon the 23d. A fifth paroxysm occurred upon October 28, after which quinine in large doses (10 grains every four hours) was given. Upon October 31, a very slight chill occurred, with a rise of temperature to only 102° F.

From this time on the patient had no further paroxysms and his temperature gradually reached normal. The convalescence was very slow. During the malarial complication the patient's condition was that of a desperately sick man, and none of the surgeons who saw him entertained any hopes of his recovery. He became greatly emaciated and very anaemic, and was delirious much of the time. During the entire time his blood showed numerous quartan plasmodia, corresponding in their development with the time of the paroxysms. The blood always gave a marked Widal reaction whenever tested.

The following is a brief summary of the results of the examination of the blood in this case.

The blood was first examined at the time of the second chill, when numerous full-grown and segmenting quartan plasmodia were found. Examinations were made every day, and plasmodia were always demonstrated without difficulty. The last plasmodium observed in the blood was a full-grown quartan organism, upon October 31.

A record of four days, which follows, shows the average findings for that period throughout the course of the malarial fever.

October 18.—Chill. Large numbers of full-grown organisms; a few segment-

ing plasmodia; a few fragmenting bodies; and a few extracellular and hyaline bodies.

October 19.—Numerous hyaline, unpigmented plasmodia; a few pigmented; and one fragmenting body.

October 20.—Many half-grown and nearly three-quarters grown, pigmented quartan plasmodia, a few vacuolated.

October 21.—Many full-grown plasmodia; several segmenting bodies; and fragmenting and extracellular bodies.

A careful study of the clinical chart (Chart No. 17.5) in this case is of great interest. Up to October 15, the twenty-second day of the typhoid, the course of the fever had been typical, and the temperature had begun to decline gradually, as is characteristic of the disease. On the fifteenth, following the chill, the temperature rose, but instead of falling to normal or below, which is characteristic of the decline of ordinary malarial fevers, it fell only to the point previously held by the original disease. From that time a gradual decline took place in the temperature until the second chill, upon October 18, when the fever rose from 99.4° F. to 104° F., but fell in the course of four hours to 99° F. If, now, we discard the rises in temperature due to the malarial infection, we will observe that the course of the temperature is that of a typical declining typhoid, which holds true up to the twenty-fourth, when the temperature between the malarial paroxysms became very irregular. Prior to the twenty-fourth the temperature curve illustrated most instructively how these two diseases, which existed together, influenced the temperature chart. The malarial paroxysms occurred, but did not materially influence the course of the typhoid temperature, which gradually declined just as it does in uncomplicated cases, while the temperature of the malarial paroxysms was also typical of that observed in ordinary quartan infections. This observation conclusively proves that a malarial infection may occur during the active course of typhoid and that each fever preserves its characteristic temperature curve.

The irregularity of the temperature curve after the twenty-fourth may be explained by the development of severe hypostatic congestion, and the extreme state of nervous excitability from which the patient suffered. Naturally of a very nervous disposition, he was passing through a very severe attack of typhoid fever, only to be set back and exhausted by the severe chills and high fever which accompanied the malarial infection; he became extremely nervous and discouraged, and so changed in appearance that one would recognize at a glance the terrific strain under which he was struggling. He came to look forward with the utmost dread to the chills; and this intensely nervous condition, taken with the hypostatic congestion, undoubtedly explains the irregularity of the temperature toward the latter part of his disease. It may be possible that there was a multiple infection with the quartan plasmodia, but the blood findings would appear to preclude this.

It will be observed that the fever was very resistant to small doses of quinine, but that large doses of this drug reduced it very promptly. The

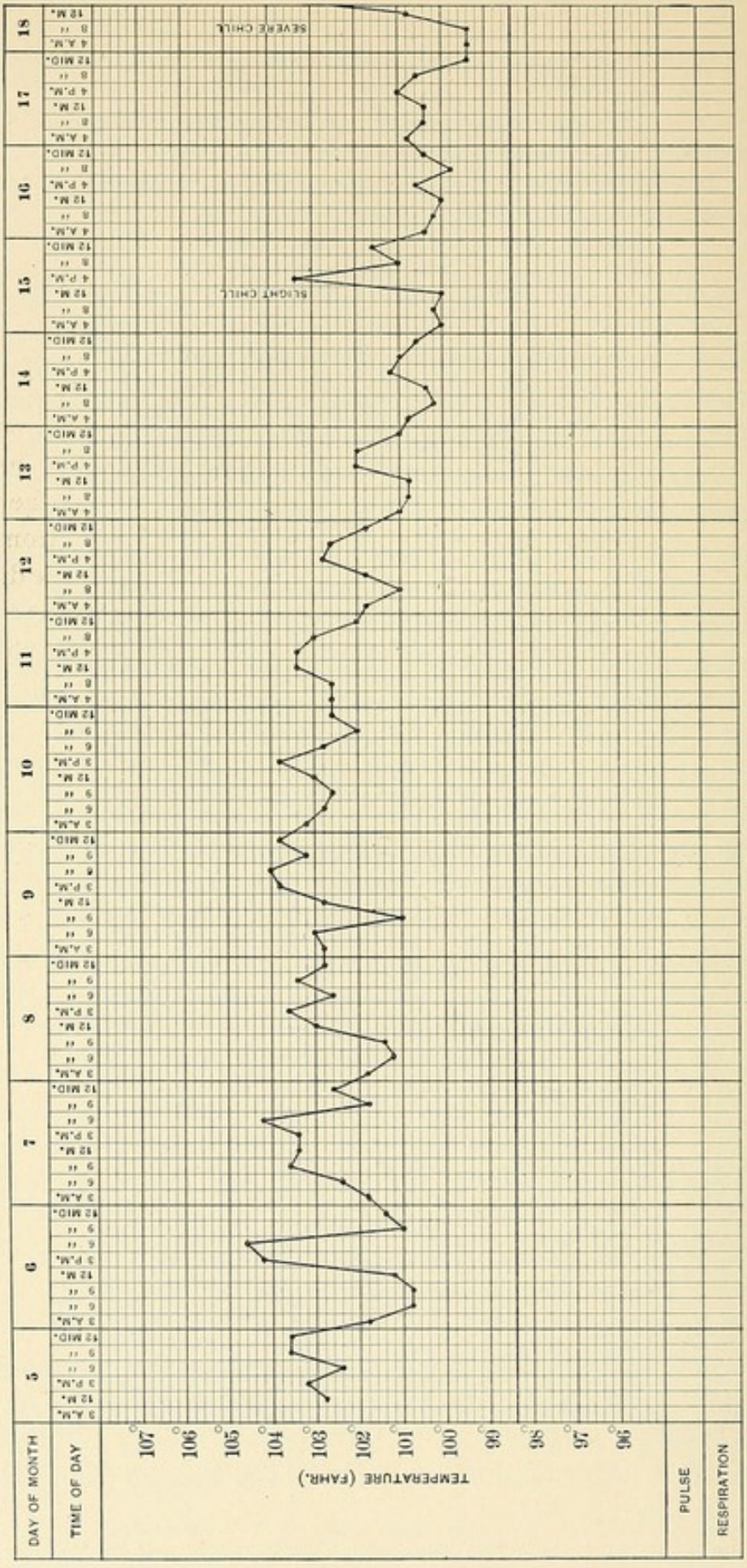
SEVERE CHILL
SLIGHT CHILL
DAY OF MONTH
TIME OF DAY
TEMPERATURE (FAHR.)
PULSE
RESPIRATION
107
106
105
104
103
102
101
100
99
98
97
96

CHART 17½. A.

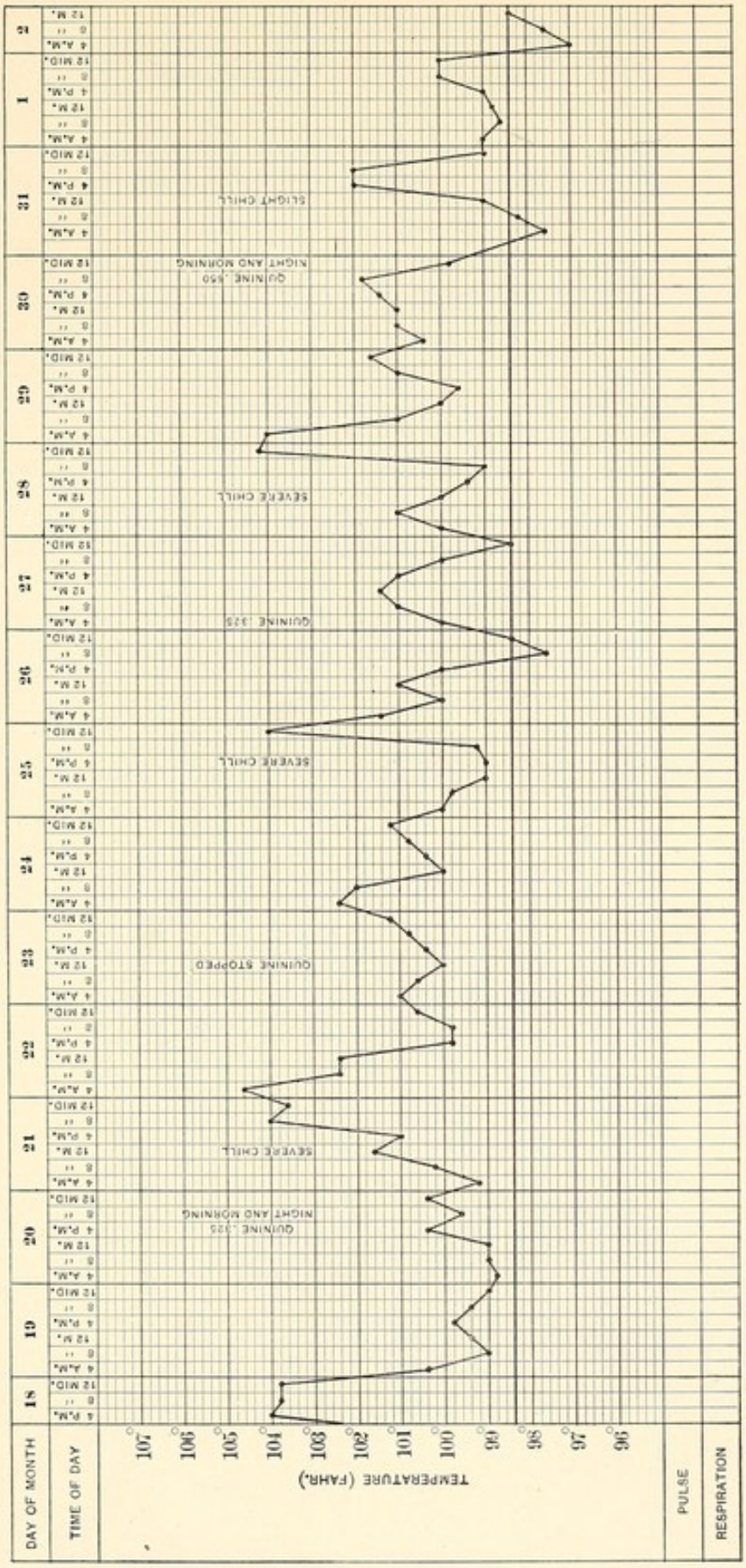

CHART. 17½ B.—Combined Quartan Malarial Fever and Typhoid Fever.

patient was convalescent when I lost sight of him, but I have since learned that he died of pneumonia several weeks later. This case is of especial interest because the type of malaria present was the quartan variety, a form very rare even in malarial localities in the United States.

The two following cases of combined typhoid and aestivo-autumnal malarial fever are fairly typical of such infections and occurred in soldiers of the U. S. Army.

CASE I.—S. J. Colored. Was admitted to the hospital suffering from typhoid fever and presenting the usual signs and symptoms of that disease. Date of admission, March 16, 1899. Had been sick for two weeks before admission, but had had no chills. Upon the seventeenth of March he had a chill and his temperature rose to 104.4° F. He suffered from headache, backache, and nausea. Physical examination showed an enlarged spleen; tender abdomen; hot, dry skin; and suffused and brilliant eyes. An examination was made of his blood and numerous "ring-forms" of the tertian aestivo-autumnal plasmodium were found, every microscopic field showing one or more. Quinine was at once administered, but as the temperature did not decline the Widal test was made and a marked reaction was obtained. All of the typical symptoms of typhoid fever was present, and the course of the disease, after the malarial complication was eliminated by quinine, was that of a gradually declining typhoid.

In this case it will be observed that the malarial complication occurred during the acute stage of the typhoid, and a study of the chart (Chart No. 18) will demonstrate how little the malaria affected the course of the typhoid, and that but for the microscope the diagnosis of the malarial infection could hardly have been made.

CASE II.—This case, observed at the U. S. Army General Hospital, Presidio of San Francisco, Cal., occurred in the practice of Captain Bevans, Medical Corps, and I am indebted to him for the clinical notes upon the case, which are given in his own words.

"Corporal R. M. Co. K, 29th U. S. V. Inft. Aged 21, born in Tennessee, was admitted on October 3, 1899. The man lived in his native State until enlistment in the Fourth Tennessee Volunteer Infantry in the fall of 1898. He then served in Cuba, and during his first service had a few light chills, which continued after his return home and until his reenlistment in August 1899. The chills appeared again at Fort McPherson, where he stayed about a month, and continued irregularly up to the time of his present sickness. En-route to the Presidio, where he arrived October 1, he was confined to his bed with headache, light chills, and general malaise. He had not, previous to that time, been on sick report. After three days in quarters in camp he was sent to the General Hospital. As he was brought into the ward he appeared pale, emaciated, and cold. His temperature was 102.4° F., respiration 22, and pulse 94. His tongue was coated, the abdomen tender, the liver and spleen somewhat enlarged. His mental condition was dazed. By October 7 rose spots had

developed and he was in an active delirium. He had involuntary passages of urine and faeces. Light chills occurred daily after the sixth. On the eleventh the chill was prolonged and severe. Malarial parasites were first found in the blood upon that day. Quinine was then administered in large doses and the last chill was observed two days later. Delirium continued until the twenty-fifth. The temperature curve and symptoms after the thirteenth were those of typhoid fever. The temperature reached normal on the twenty-ninth, and slow convalescence has taken place."

Captain Bevans asked me to examine the blood in this case upon the fourth of October, and also to make a Widal test, but both examinations were negative, and it was not until the eleventh that I was able to demonstrate the plasmodia in the blood and the Widal test was not positive until after the temperature had become normal. The late appearance of the positive reaction to the Widal test is of interest, as in other cases of coincident typhoid and malarial infection the response to the Widal test has always been prompt. Upon the eleventh of October numerous "ring-forms" of the tertian aestivo-autumnal plasmodium were found in the blood, which soon disappeared after the administration of quinine. The chart in this case is not given as it is not typical of anything but an ordinary typhoid with a sudden rise of temperature marking the occurrence of the malarial paroxysm.

From the examples of coincident typhoid and malarial fever which have been given it is evident that Woodward's definition of typho-malarial fever as a hybrid disease presenting certain characteristic symptoms is not borne out, for there was nothing in any of these cases which would differentiate them from ordinary typhoid with the exception of the occurrence of chills, but chills also occur in typhoid uncomplicated with malaria, and where septic infection exists. I think it may be stated with truth that no one of the symptoms described by Woodward as characteristic of typho-malarial fever has been proven by recent research to be so, and Dock, in an excellent discussion of this subject, in which he gives the conclusions of years of study, states that "we find that the belief in a characteristic disease composed of typhoid and malarial elements is not based on sufficient evidence," and with this statement I am fully in accord.

The *prognosis* in cases of coincident typhoid and malarial infection is always grave and it is the concensus of opinion of all who have observed such cases that during the malarial paroxysms the patient appears to lose ground rapidly, and that the occurrence of malarial infection during an attack of typhoid appears to increase the severity of the symptoms of that disease.

The recognition of these cases is of great importance, especially in regions in which the aestivo-autumnal fevers are prevalent, but it should be remembered that such recognition is only possible by the use of the microscope, and quinine should never be administered to a patient suffering from typhoid fever, presenting atypical symptoms, unless the malarial plasmodia can be demonstrated in the blood, for while the administration of this drug is always beneficial

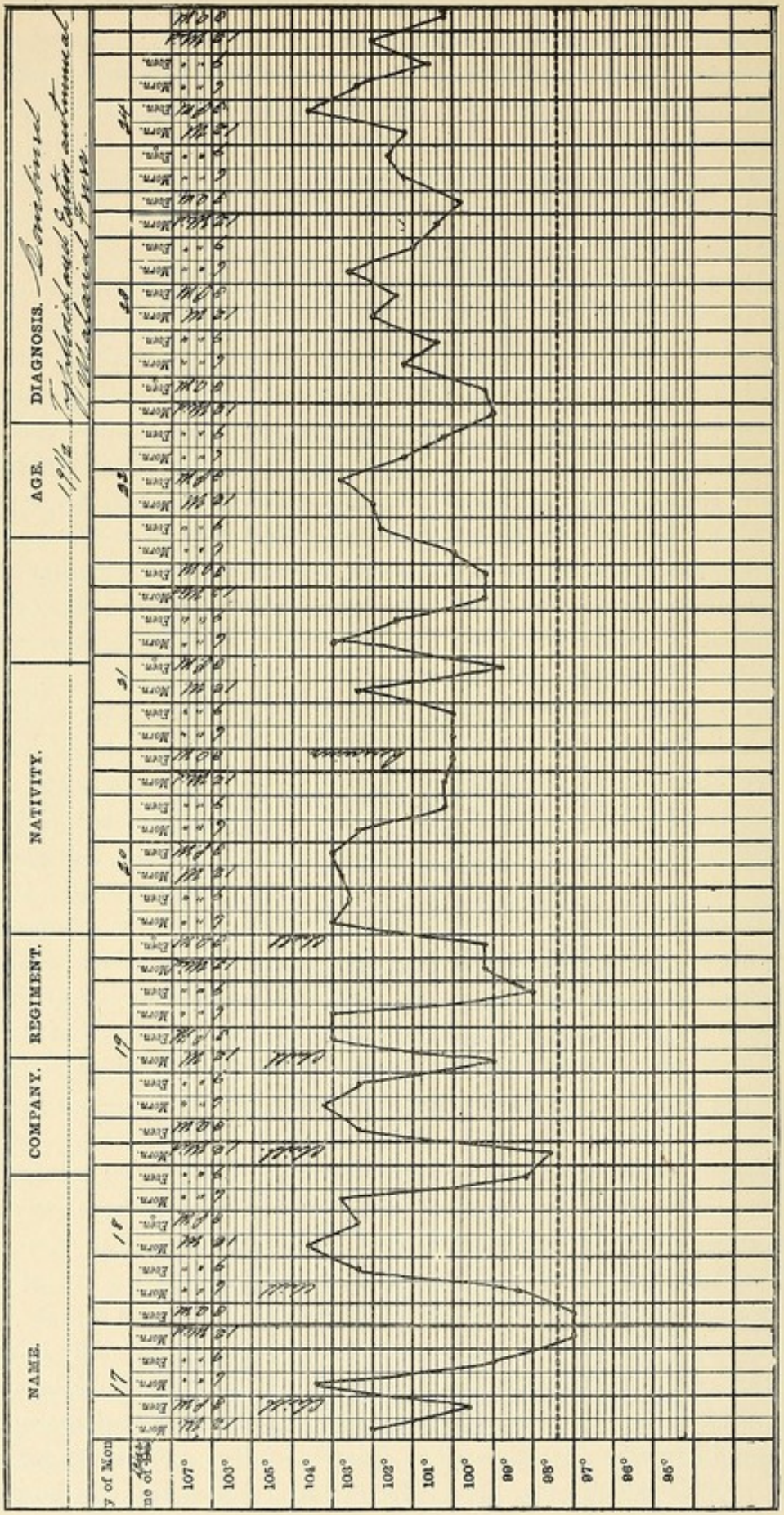
NAME.
COMPANY.
REGIMENT.
NATIVITY.
AGE.
DIAGNOSIS.
Day of Month
Hour of Visit
107°
103°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
95°
Morn.
Even.

CHART 18 A.

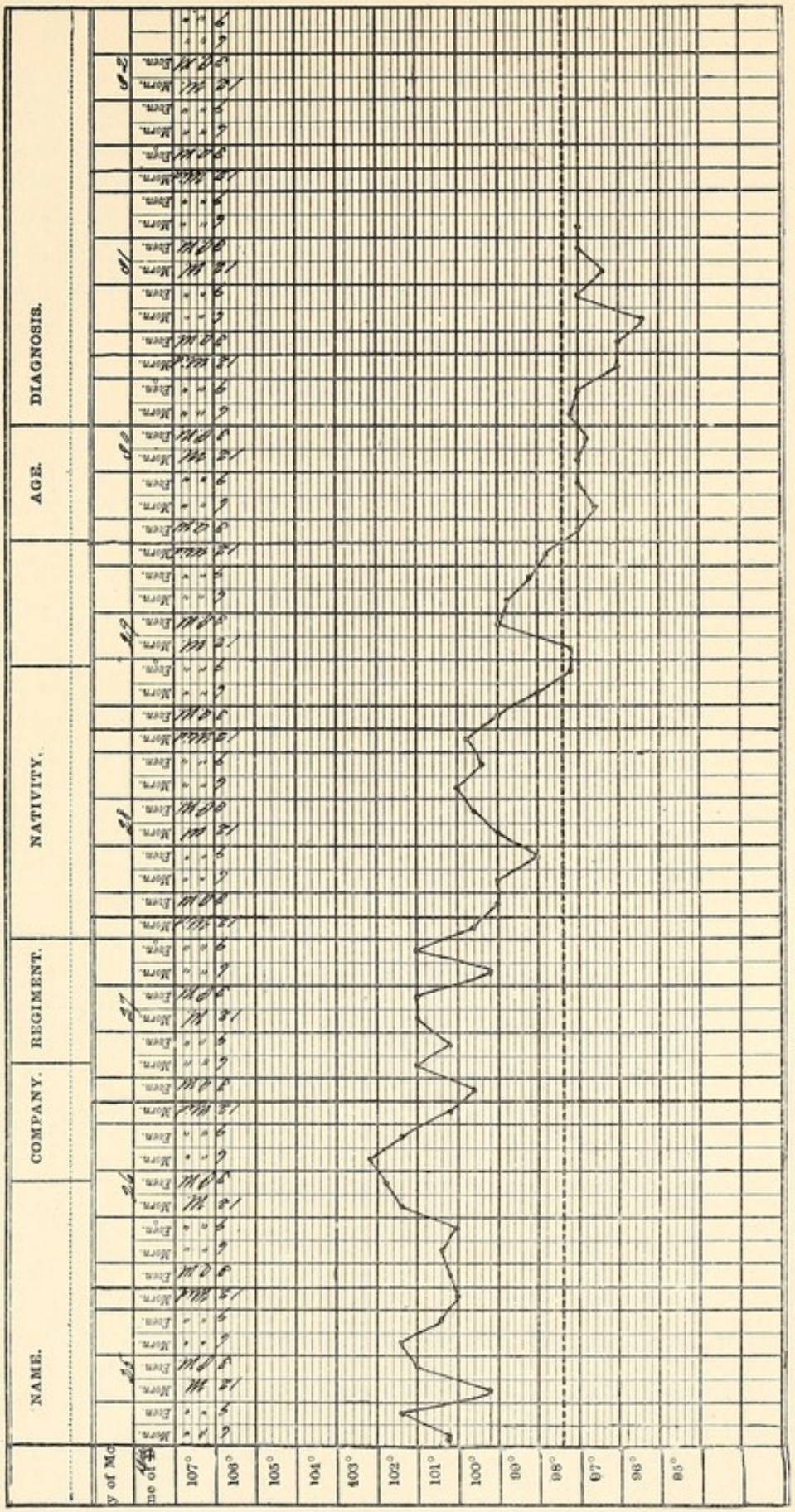

CHART 18 B.—Combined Typhoid and Tertian Aestivo-autumnal Malarial Fevers (two plates).

in malaria, it is always harmful in typhoid. Thayer has very aptly discussed this point as follows:

"The mere use of the term typho-malarial fever has indicated to many the advisability of the administration of quinine, and not infrequently this drug is used for days and for weeks in cases of uncomplicated typhoid fever in doses which cannot but be injurious to the patient. This is a matter of really grave importance. It is one of the positions in which the physician actually has done and does do, to-day, really serious harm to his patient. There is no excuse for cinchonizing an individual with continuous fever who, after three or four days, shows no change in the symptoms, while the blood is free from malarial parasites."

This statement of Thayer's has been borne out in my own experience for I have more than once observed cases in which the attending physician had administered quinine in doses of from 40 to 60 grains, for four weeks, in typical attacks of typhoid fever, under the impression that the disease was really typho-malarial fever or remittent malaria. Such treatment is nothing less than criminal and cannot be too strongly condemned. The use of the term "typho-malaria" should be entirely discarded in medical nomenclature, for its retention will lead inevitably to the extensive use of quinine in atypical cases of typhoid fever.

Osler's dictum, that any continued fever which resists the use of quinine for over five days is not malarial in character, has been proven by every experienced practitioner in malarial localities to be true, and I am convinced that the vast majority of malarial fevers are checked or markedly affected by this drug within three days of its administration, and that it is folly to continue giving quinine in fevers which resist its action for more than five days.

While it is the testimony of all practitioners who have had much to do with the malarial fevers that the above statement is true, it is still all too common to observe the indiscriminate and continued use of this drug in typhoid fever, often to the great injury of the patient. A microscopical examination of the blood would obviate this mistake, and quinine should never be administered in typhoid fever unless such an examination demonstrates the presence of malarial plasmodia.

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CHAPTER IV.

The Prognosis of the Malarial Fevers.

If one were to draw his deductions concerning the prognosis of the malarial fevers from the vital statistics of the cities and towns of the United States, he could not but conclude that the prognosis in these fevers is very bad, for the number of deaths ascribed to malaria in such statistics is very great. In speaking of this Osler calls attention to the fact that while in temperate climates it is well known that the prognosis in malaria is most favorable, still the vital statistics in some of our large cities show a greater death rate for malaria than for typhoid fever. He says:

"In the United States Census Report of 1890, which covers the six preceding years, the deaths from malarial fever in New York and Brooklyn were more numerous than from typhoid fever. In both these cities it is notorious that a death from malarial fever is a great rarity. No more than three or four cases occur each year in the entire hospital practice of the city of New York."

Nothing could illustrate more forcibly the immense importance of a scientific diagnosis of malarial fevers by an examination of the blood than does this quotation, and the condition of ignorance of the true nature of malaria which it portrays is a reproach to American medicine.

General Factors Influencing Prognosis.—Certain general factors should be taken into consideration in estimating the prognosis of the malarial fevers, the chief of which are locality, race, age, occupation, and physical and social condition of the patient.

Locality.—In certain localities the prognosis of malaria is much more grave than it is in others. In the tropics the prognosis of all varieties of malarial fever is more grave than it is in temperate regions, this being true of the aestivo-autumnal infections as well as of the quartan and tertian infections. Again, in certain regions in the tropics the aestivo-autumnal fevers are much more fatal than in others. For instance, these fevers are more fatal in Santiago, Cuba, than they are in Havana, although the climate is practically the same. The prognosis of malaria in the tropics should always be guarded, for here we meet with most of the pernicious types of fever, and the aestivo-autumnal infections occur in most cases, and in them the prognosis is always grave.

Race.—The negro and many native races in the tropics enjoy a relative immunity to the effects of the malarial plasmodia, acquired through repeated attacks during childhood and early youth; but in regions in which only the aestivo-autumnal fevers are present, while an immunity may be present against *them*, exposure in another locality to tertian or quartan infection may result in

severe attacks of these forms and the prognosis in individual cases may be grave. As a general rule, it may be stated that in adult natives, living in infected regions, the prognosis of malaria is good, even severe infections being rapidly recovered from.

Age.—The prognosis is most grave at the extremes of life. In very young infants and in the aged the prognosis of the aestivo-autumnal fevers is always very grave.

Occupation.—Certain occupations, by decreasing the resisting powers of the individual, render the prognosis of malaria very grave, especially if the aestivo-autumnal infections be present. All occupations leading to anaemia, loss of muscular strength, and deficient nutrition, increase the gravity of the prognosis in the malarial fevers.

Physical and Social Condition of the Patient.—It is obvious that the prognosis in patients suffering from organic disease or severe functional disorders will be more grave than in the case of those who have previously been in good health, and in individuals weakened by long-continued disease or by severe attacks of other acute fevers the prognosis, especially in aestivo-autumnal infections, is always grave.

The social condition of the patient has much to do with the severity of a malarial attack and markedly influences prognosis. The prognosis in the well-to-do is always more favorable than in the poor, both because the physical condition of the first class is better, as a rule, than that of the second, and because in the first class the disease is at once treated, while in the second, because of the fear of expense, a physician is not called, and repeated attacks may occur before treatment is instituted. The prognosis in the case of laborers who have been exposed to repeated malarial infection and in soldiers serving in tropical climates is always grave, as has been conclusively proven in the case of laborers upon the Panama Canal and in our soldiers in Cuba and the Philippine Islands. While intelligent treatment has, in the vast majority of cases, prevented a fatal termination of the acute attack, the debility and anaemia occasioned by repeated recurrences have often induced a state of chronic invalidism, and in many cases death has eventually resulted. In considering in detail the prognosis in the malarial fevers, I shall discuss the prognosis in each variety of infection separately, as by doing so we can arrive at a more just conception of the prognosis as it is affected by the occurrence of certain symptoms.

Tertian and Quartan Infections.—The prognosis in cases of uncomplicated tertian and quartan malarial infection is good, but it should be remembered that fatal cases of both these forms of malaria have been reported, and in tropical regions the prognosis in the quartan infections, especially, should be guarded, as very often these infections are resistant to treatment, recur frequently, and may assume pernicious forms at any time.

Quotidian Aestivo-autumnal Malaria.—The prognosis in cases of quotidian aestivo-autumnal fever, provided they are not pernicious in character and treatment is begun promptly, is always favorable so far as im-

mediate danger to life is concerned. If, however, treatment is not persisted in for several weeks after the symptoms have disappeared, relapses almost invariably occur, producing marked anaemia and debility, and in such cases the prognosis should be more guarded. Several times I have observed fatal cases of anaemia following attacks of this form of malarial fever, in one case the red blood-corpuscles falling to 400,000 per cubic millimeter before death.

In cases which are unrecognized or improperly treated the prognosis is grave. Repeated relapses, together with the complications which may arise, render a favorable prognosis as to ultimate cure impossible. When complications, such as pneumonia, nephritis, dysentery, and severe nervous conditions, accompany the paroxysms the prognosis is grave and should be very guarded.

In all infections with the quotidian aestivo-autumnal plasmodium the prognosis given should be influenced by the fact that pernicious symptoms are apt to develop at any time.

Tertian Aestivo-autumnal Malaria.—In uncomplicated cases of tertian aestivo-autumnal fever, properly treated, the prognosis is good. If, however, the patient has suffered from previous attacks and is greatly debilitated by them the prognosis is much more grave, as such infections are often very resistant to treatment. This heightened resistance is probably due to diminished ability to absorb quinine or to a more resistant form of the plasmodium. In cases in which grave complications, such as nephritis and cardiac disease are present, the prognosis should be guarded, and often depends quite largely upon the nature and severity of the complication. In untreated cases of tertian aestivo-autumnal malaria the prognosis is grave, and the liability of this form of infection to develop pernicious symptoms should always be considered in giving a prognosis. While formerly I considered that the prognosis in tertian aestivo-autumnal fever was more favorable than in the quotidian form, further observation has led me to believe that very little difference exists between the two forms as regards prognosis. While a greater number of pernicious cases, in which the result has been fatal, have been found to be infected with the tertian aestivo-autumnal plasmodium, I cannot help but believe that this is largely due to the more frequent occurrence of the tertian infections, and that further investigation will demonstrate that the quotidian plasmodium produces as severe infections as does the tertian species.

The Pernicious Forms of Malarial Fever.—As I have already stated, pernicious forms of malaria may be produced by any of the species of malarial plasmodia, although the vast majority of such forms are due to the aestivo-autumnal plasmodia. Whatever the species concerned in their etiology, the prognosis is practically the same, and depends more upon the character of the symptoms produced than upon the species of plasmodium present.

The prognosis in the pernicious cases varies with the number of paroxysms which have occurred and the clinical character of the attack. If the patient is first seen after having suffered from one or more pernicious paroxysms, the prognosis is very grave although, if treatment be rigorously instituted, not

hopeless. If seen during the first paroxysm, the prognosis is grave, and treatment should be at once instituted. In such cases a fatal paroxysm may follow, even after the most energetic treatment.

The Cerebral Pernicious Forms.—The prognosis is very grave in those forms of pernicious malaria which exhibit cerebral symptoms. This is especially true of the comatose form in which the prognosis is always most grave. A large number of such cases recover with proper treatment, but this form furnishes the greater number of cases of fatal pernicious malarial fever. The forms characterized by delirium and acute maniacal attacks also are of grave prognosis. Untreated, the cerebral forms of pernicious malaria are almost invariably fatal.

The Algid Form.—The prognosis in the algid form is almost as grave as it is in the cerebral forms, and such cases, if untreated, are usually fatal. Prompt treatment will save many, but not a few terminate fatally despite all treatment. The prognosis as to ultimate recovery in the algid form is unfavorable, as convalescence is slow, the patient greatly weakened, and relapses are apt to occur.

The Choleraic Form.—The prognosis in this form is very grave and Marchiafava and Bignami believe that this form ranks next to the cerebral forms in fatality.

The Dysenteric Form.—The prognosis in the dysenteric form of aestivo-autumnal fever is grave, and I have observed several cases which resulted fatally despite all treatment, but only where treatment was delayed for several days after the onset of the symptoms. The prognosis in these cases should depend largely upon the severity of the dysenteric symptoms and the degree of anaemia present. The paroxysms are apt to be hidden by the intestinal phenomena, and the malarial element thus remains long undetected before treatment is instituted. Death is usually the result of exhaustion and anemia in these cases. If treatment be promptly instituted most cases of dysenteric pernicious fever will recover, but an irritable condition of the bowels persists for some time afterward.

The Pneumonic Form.—In the pneumonic form the prognosis is always grave and, if untreated, a large proportion of such cases terminate fatally. This form is so rare that it is difficult to estimate the relative gravity of it and the other forms of pernicious malaria, but I believe that untreated it is a very fatal form of malaria.

Other Pernicious Forms.—The prognosis in the other pernicious forms of malarial fever, as the diaphoretic, cardialgic, haemorrhagic, and the forms characterized by convulsions and paralysis, is always grave, and these cases demand immediate treatment.

Prognosis in Irregular and Sub-continued Fevers.—The prognosis in the irregular and sub-continued malarial fevers differs, of course, with the severity of the symptoms present, but it is always more grave than in the regularly intermittent fevers, but less so than in the pernicious forms. As these infections are very apt to be considered of non-malarial nature, they may have

persisted for some time before treatment is instituted, and this, of course, renders the prognosis more grave than it would otherwise be. Most of these cases, however, recover promptly under the proper administration of quinine.

Prognosis in Complicated Cases of Malaria.—The prognosis in cases of malarial fever attended by important complications is that of the type of malaria present and the added complication. It is always more grave than in uncomplicated cases. Among the complications which render the prognosis very grave may be mentioned pneumonia, the infectious fevers, tuberculosis, sunstroke, and typhoid fever.

Prognosis of the Sequelae of Malaria.—As a general rule, it may be stated that the prognosis of the sequelae of the malarial fevers is good, recovery usually occurring within a few weeks or months. The most important of the sequelae will be considered in detail.

Nervous and Mental Sequelae.—The prognosis in the various nervous and mental sequelae is good and recovery usually occurs within a few weeks, even in cases in which paralysis has followed a malarial attack. Insanity, occurring as a sequela of malaria, does not generally persist for more than six months, although there may be impairment of the mental faculties for a long time afterward. The condition of melancholia, so often observed following severe malarial attacks, especially in our soldiers serving in the Philippines, is quickly recovered from under the persistent use of quinine, and upon a change of station to the United States.

Nephritis.—The majority of cases of nephritis occurring with, or following the malarial fevers are rapidly recovered from and the prognosis is good. A few cases become subacute or chronic, and in rare instances the acute nephritis occurring as a complication terminates fatally.

Postmalarial Anaemia.—The various types of anaemia occurring as sequelae of the malarial fevers have already been described, and it may be said that the prognosis depends entirely upon the character of the anaemia. In simple anaemia following malaria the prognosis is generally good, the blood regaining the normal number of red corpuscles after a period of days, weeks, or, in the more severe secondary forms, months. This recovery often occurs in cases in which the red corpuscles have been very seriously reduced in number, and I have observed cases in which, after repeated attacks of aestivo-autumnal fever, the red blood count was less than 1,000,000 per cubic millimeter, but in which a return to normal was observed within a month. As a rule, in the more severe cases of secondary anaemia the red cells increase in number rapidly until they reach 2,000,000 per cubic millimeter, after which the increase is very slow, and it may be months before the normal number of red cells is attained.

The prognosis in those cases in which the anaemia following malaria assumes the pernicious type is always most grave, death usually resulting within a few months.

Malarial Cachexia.—In cases of malarial cachexia in which a change of climate is possible, the prognosis, under suitable treatment is excellent, but in

those cases which are unable to leave the locality in which they have contracted their infection the prognosis is always grave as to ultimate recovery, and such patients usually succumb to some intercurrent disease to which they are rendered less resistant because of the weakened condition brought about by the long-continued malarial poisoning.

In estimating the prognosis in the malarial fevers it is usually possible, in all but the pernicious forms, to give a favorable prognosis as to immediate recovery from the malarial attack, but the physician should always give a guarded prognosis as to ultimate cure, unless he can be satisfied that the patient will pursue faithfully an extended treatment with quinine. Relapses are sure to occur, especially in the aestivo-autumnal infections, unless quinine is given for weeks after the first paroxysm, and very often a change of climate is found necessary before the infection can be overcome. One of the most discouraging features of the aestivo-autumnal fevers is the extreme tenacity of these infections, and it is a great mistake for the physician to assure the patient that he is cured because the administration of quinine has resulted in the cessation of the symptoms of an acute attack. The physician who does not insist upon his malarial patients persisting in the use of quinine for weeks after the disappearance of the acute symptoms fails in his duty to the patient and to himself.

In the prognosis of the malarial fevers the following axiom should never be forgotten: The prognosis in *all* cases of aestivo-autumnal malaria is grave, because pernicious symptoms may arise at any time during their course.

PART V.

THE DIAGNOSIS, PROPHYLAXIS, AND TREATMENT OF THE MALARIAL FEVERS.

CHAPTER I.

The Laboratory Diagnosis of the Malarial Fevers; Staining Methods; Examination of the Blood; Examination of Malarial Mosquitoes.

The diagnosis of the malarial fevers may be considered from two standpoints: the diagnosis by laboratory methods and the diagnosis from the clinical character of the fevers. As I have tried to make plain, it is only in the most typical cases of malarial fever that we are able to arrive at a diagnosis from the clinical symptoms alone, and therefore that the diagnosis of malaria, and especially of the type of malaria, should always rest upon the results of a blood examination.

The importance of the use of laboratory methods in the diagnosis of the malarial fevers cannot be too strongly emphasized, and when we remember that the technic is not difficult, requires but a few moments of time, and but a very small amount of laboratory apparatus, it is evident that there is no excuse for the neglect of this method of diagnosis. The plea, so often urged by the busy practitioner, that he has not the time, can be seldom urged truthfully, and when true is no excuse, as it is possible, in most regions, to secure the services of some one who is familiar with methods of blood examination and who *has* the time to devote a few moments to the study of the blood of a suspected case. I have seen so much misery result from the neglect of blood examinations in fever cases, even the death of the patient in some instances, that I feel that I cannot urge too strongly the vital importance of such examinations in all cases of fever. I believe that the time will come when it will be considered malpractice to neglect the blood examination in fever cases, and that he who loses a patient from malaria and has not recognized the disease because of the neglect of a blood examination will be amenable to the law.

The examination of the blood is the quickest and most reliable method of diagnosing any of the varieties of malarial fever, and in those cases, which are numerous, in which the clinical symptoms are atypical, the diagnosis must rest upon the result of a blood examination. The therapeutic test by the administration of quinine, urged by some writers, is unsatisfactory, for while the fever, if malarial, will succumb to the drug, there is no surety that malaria was the disease present, for every fever which declines after the administration of this drug is not malarial in nature. Our vital statistics are burdened with hundreds of cases of fevers diagnosed as malarial because quinine reduced them or they disappeared spontaneously, and it is evident that we can never be sure of the variety of malaria present when we employ quinine as a diagnostic aid to the exclusion of the blood examination. Again, the continued use of quinine is

often injurious to the patient, as has been noted in the discussion of typho-malarial fever, and to keep a typhoid patient cinchonized for weeks, under the impression that the fever is due to malaria, when a few moments' examination of the blood would definitely decide the question, is hardly less than criminal.

As a rule, one examination of the blood, if carefully made, will be found sufficient; but if a negative result is obtained in a suspected case, repeated examinations should be made at intervals, for in some cases so few plasmodia are present in the blood that such repeated examinations are necessary in order to demonstrate them. The statement so often made that cases of malaria occur in which it is impossible to demonstrate plasmodia in the blood, while it may be true, has not proven so in my experience. From personal observation, I believe that such cases must be very, very rare and so mild in character that it would be impossible to recognize them clinically. I have yet to observe a case of malarial fever severe enough to cause clinical symptoms in which it was impossible to demonstrate plasmodia in the peripheral blood, if repeated examinations were made. On the other hand, I have records of hundreds of cases of very mild and latent infections, in which plasmodia were found in the peripheral blood.

The *general* factors to be considered in arriving at a suppositional diagnosis of malaria are the following: The season of the year; the locality, as to whether it is malarious; the location of the dwelling of the patient; the history of previous attacks of fever; the presence of Anophelinae; the periodicity of the fever; the chances of infection; the age of the patient, if we are dealing with natives of the tropics; the presence of the signs of malaria cachexia or of anaemia; and the occurrence of similar fevers in other members of the household.

The microscopical diagnosis of the malarial fevers depends upon the finding of the plasmodia in the blood or the presence in the same fluid of pigmented leucocytes. The finding of free pigment is also conclusive of malarial infection, past or present, but it is often impossible to distinguish such pigment from extraneous substances, and a diagnosis based upon the presence of free pigment alone is always open to question. The endeavor to diagnose malaria by a differential blood count has not resulted in success, as a similar differential count is found in other acute fevers.

The Examination of the Blood.

The blood may be examined in the fresh condition or various staining methods may be employed which render the plasmodia easier of detection than they are in fresh preparations. Where it is desired to study the movements and vital phenomena of the plasmodia the use of fresh preparations is necessary, but since the development of the Romanowsky staining method and its modifications, the examination of stained specimens is far better in diagnosis, both because the plasmodia are more easily seen and because there is less chance of mistaking

other objects for them. The use of one of the chromatin stains is also necessary when we desire to study the exact structure of the malarial plasmodia.

Apparatus.—The apparatus necessary in making a blood examination for malaria is very simple and can easily be transported to the bedside of the patient, if that be necessary. A good compound microscope, with a 1/12 inch oil immersion lens; microscopic cover-glasses and slides; two or three medicine droppers; a bottle of staining solution, and a bottle of distilled water are all that is necessary to enable us to make the most exact examination of the blood for malaria. The 1/12 oil immersion lens is absolutely essential, for while the larger forms of the tertian and quartan plasmodia, and the *gametes*, or crescents, of the aestivo-autumnal fevers may be seen with a lens as low as a 1/6 inch, the small hyaline ring-forms can only be well seen when the 1/12 lens is used. It is a great mistake to undertake the microscopic diagnosis of malaria without a 1/12 inch oil immersion lens. An Abbe condenser is, of course, an essential portion of the microscope, and, if possible, the microscope should be equipped with a mechanical stage, for the use of such a stage increases the chance of finding the plasmodia very greatly, and this fact, together with the infinitely greater ease of manipulation, and the satisfaction of knowing that the same portion of the specimen has not been looked over twice, is worth far more to the observer than the slight additional cost of such a stage.

Objects Which may be Mistaken for Plasmodia.—There is no one thing more essential to success in recognizing the malarial plasmodia in the blood than a practical knowledge of the microscopical appearance of both fresh and stained specimens of normal and pathological blood. He who supposes that he has only to look into his microscope at a specimen of blood in order to find the plasmodia, without having had previous experience in blood examinations, will invariably be disappointed, and will either give up the search in disgust or mistake some artefact or other object for the malarial plasmodium. Success might possibly attend the search of such a tyro in the case of the large, fully developed forms of the quartan or tertian plasmodium, but never when the hyaline "ring-forms" of the aestivo-autumnal plasmodia are alone present. The use of a good chromatin stain has done much to enable the less experienced observer to recognize these organisms, and for this reason the use of stained specimens in diagnosis is preferable to the examination of the fresh blood.

In *fresh* specimens of blood the following objects may be mistaken for malarial plasmodia:

Crenations.—These occur if the blood be exposed long to the air in making the specimen or if the slide or cover-glass be not clean, and are confusing to an inexperienced observer if they be looked down upon directly, as they thus appear as round, rather haline bodies within the red corpuscles, but they have no ring-like outline, and when focussed upon appear alternately as light and dark areas.

Retraction of the haemoglobin from the edge of the red cell is often

observed at some point on the periphery of the cell, giving rise to small areas devoid of haemoglobin, but they have no amoeboid motion, and when focussed upon often present a reddish refraction about the edge. Cracks in the haemoglobin are similar in appearance and are generally easily differentiated from plasmodia.

Vacuoles.—There is no more deceiving object in the blood than a small vacuole within the red corpuscle. Sometimes, especially if the border of the vacuole alters in shape, the resemblance to the hyaline disk-form of the aestivo-autumnal plasmodia is well-nigh perfect. I have time and again had such vacuoles shown to me for plasmodia by experienced microscopists who had had but little practice with malarial blood. The greater refraction of the vacuole, its less opaque character, and the fact that vacuoles "open out" or grow larger and smaller as focussed upon, should distinguish them from any of the stages of growth of the malarial plasmodia.

Areas devoid of haemoglobin or "eye spots" as they have been termed by some observers, occur within the red cells frequently in diseases, such as typhoid fever, tuberculosis, pneumonia, and the acute infectious diseases, and are also observed in normal blood. They may be situated at any portion of the corpuscle, and may be round, spindle-shaped, oval, or ring-shaped, and hyaline in appearance. Many of them, especially the oval and spindle-shaped areas contain a darker dot at the center, which resembles pigment. These bodies have been several times described as new parasites and sometimes their superficial resemblance to the ring-forms of the malarial plasmodia is striking, but the absence of ameboid movements, and the much greater degree of refraction should serve to differentiate them from the plasmodia.

Platelets.—Occasionally a blood platelet, if superimposed upon a red blood-corpuscle, will resemble slightly a malarial plasmodium, but upon focussing it will be observed that there is a great difference in the level of the two objects and that the platelet is less opaque and less refractive than the malarial plasmodia.

Haemokonien or blood-dust may sometimes be mistaken for plasmodia, especially when the small active granules lodge upon a red cell, but a little practice will soon suffice to differentiate these bodies.

Granules derived from broken-down leucocytes sometimes resemble small plasmodia when they rest upon the red corpuscles, but their size, the absence of amoeboid motion and their less hyaline appearance easily serve to distinguish them.

Other objects which may cause trouble to the beginner are grains of dirt which may be mistaken for pigment; the normal lighter colored center of the red corpuscles, especially marked in persons suffering from anaemia; cocci or bacteria in the blood; and flaws or dirt upon the slide or cover-glass.

In *stained* specimens the objects most apt to be mistaken for plasmodia are the blood plates, especially when, as often occurs, they are observed with the red corpuscles. They may be distinguished by their smaller size (as a rule)

and the minuteness of their chromatin granules, as well as the absence of the distinct blue protoplasm observed in the malarial plasmodia.

Bacteria upon the red cells; *Yeasts*, and extraneous matter, which may be stained, are all sometimes mistaken for plasmodia, but a very little experience in the examination of stained specimens of blood will render such mistakes impossible. Flaws upon the slide, in which the stain may settle, sometimes resemble extracellular plasmodia, but careful examination will demonstrate their nature.

The flagellated plasmodia are simulated by certain erythrocytes undergoing degeneration, in which long, slender, active protoplasmic pseudopodia are observed projecting from the periphery of the misshapen red cell. These bodies may be distinguished from the flagellated plasmodia by the greenish color due to the haemoglobin of the red cell and by the absence of pigment.

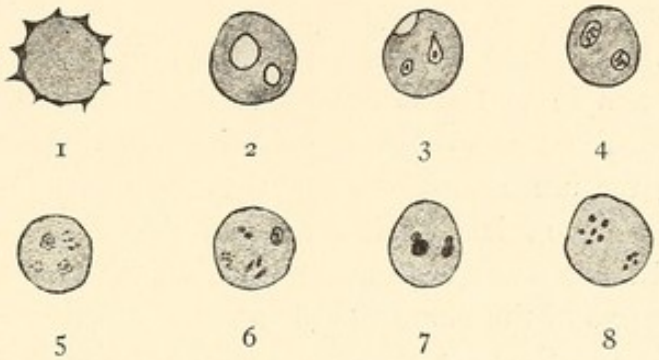

FIG. 23.—Appearances in the Red Blood-corpuscles which have been mistaken for Plasmodia 1, Crenations; 2, Vacuoles; 3, Areas devoid of haemoglobin; 4, Blood plates; 5, Blood dust; 6, Bacteria of various kinds; 7, Yeast cells; 8, Free pigment granules.

The crescents or *gametes* of the aestivo-autumnal plasmodia are frequently confused with folded red cells, which have a crescentic outline, but such cells may be easily differentiated from the plasmodia by their green color and the absence of pigment.

Preparation of Blood Specimens.—The following procedure is recommended if it be desired to procure *fresh* specimens of blood for examination. The patient's ear lobe, or the tip of the finger, is carefully cleaned with alcohol, dried thoroughly, a slight puncture made with a lancet or needle, and the first drop or two of blood allowed to flow away. A small drop is then taken upon a slide which has been carefully cleaned and a cover-glass dropped gently upon it. If the cover-glass is thin, and the drop of blood on the slide small, the blood will spread evenly and quickly, but if it does not, very slight pressure upon the cover-glass will suffice to spread the blood and will do no harm. If upon examination it is found that the blood-cells are in clumps or rouleaux, the preparation should be discarded and one obtained in which the red cells are spread singly and evenly over the field. The preparation of the specimen should take as little time as possible, as exposure of the blood to the air crenates the red cells and thus renders it difficult to find the plasmodia. A little practice will enable

one to secure suitable specimens very quickly. The specimens should be examined as soon as possible, but if carefully wrapped in tissue-paper can be carried in the pocket for several hours without much danger of changes occurring which will obscure the plasmodia, and if the specimens be ringed with vaseline they will keep well for as long as twelve hours. The ear is preferable to the finger for obtaining the blood, especially in children, as there is less pain, and the patient cannot watch the operator during the procedure. At least half an hour should be spent upon the examination of the specimen before it is considered negative, and more than one specimen should be examined when a negative result is obtained. For the examination of certain phenomena in the life cycle of the malarial plasmodia, such as exflagellation, the use of fresh specimens of blood is essential, but with our improved methods of staining, better results in diagnosis will be arrived at, by the majority of physicians, if stained specimens be used, provided some practice has been had in distinguishing these organisms in such preparations.

Preparation of Stained Specimens.—The preparation of blood smears for staining is so simple that it is remarkable to read in many of our works upon diagnosis the elaborate methods advocated for making blood smears, some of them involving the use of special apparatus. All that is necessary in the way of apparatus are two microscopic slides and a needle with which to make the puncture in the ear or finger. After washing the ear as described and allowing a drop or two of the blood to flow away, a small drop is caught upon the end of one slide and the edge of the other slide applied to it, when the blood will spread along the applied edge. As soon as this occurs, draw the edge of the slide gently along the surface of the slide upon which is the drop of blood, and a thin even smear will result. This is allowed to dry and is then ready for staining. Good smears may be obtained by spreading the blood over the slide with the needle, but the smears so obtained are apt to be thicker than when the edge of the slide is used.

Staining Methods.—Many methods have been devised for staining the plasmodia of malaria, but prior to the description in 1890, by Romanowsky, of his staining method, the results obtained were unsatisfactory from a diagnostic standpoint as well as from a morphological one. In Romanowsky's method, however, the staining reactions of the plasmodia were so distinctive that they could hardly be mistaken for other objects, and thus the method was generally adopted in the diagnosis of the parasites of malaria. Various modifications of the method have been evolved, many of them superior to the original and easier of application. The success of the Romanowsky stain and all of its modifications depends upon the fact that when a solution of methylene blue is acted upon by sodium carbonate or some other alkaline reagent, methylene azure and methylene violet result, being formed in the solution. When these bodies are in turn acted upon by a solution of eosin, certain bodies result which have the power of staining the nuclear chromatin an intense red, hence the name "chromatin stains" applied to these staining methods. In old poly-

chrome methylene blue solutions these staining bodies are present, but they can be quickly produced in fresh solutions if certain procedures are followed. I shall describe here only those staining methods which I have personally found satisfactory, merely mentioning those which have been used by various observers, but which have not proven generally useful.

Wright's Stain.—In my own work I have found Wright's stain, as modified by Oliver, most satisfactory, and at the present time I use this stain to the exclusion of all others. In over 10 years' experience I have always found this stain reliable when properly made and when the right ingredients were used. It should be remembered that this stain depends for its efficiency upon chemically pure ingredients and the substitution of others will always result in disappointment.

Chemicals Used in Preparation of Wright's Stain.—The following chemicals are used in preparing Wright's stain: 1. Methylene blue (Grubler's). 2. Eosin. Yellow. Water soluble (Grubler's). 3. Methylic alcohol (Merck's reagent).

Method of Preparation.—The stain I use is prepared as follows: Add 0.5 gm. of sodium bicarbonate to 100 c.c. of distilled water, dissolve thoroughly, and add 1 gm. of methylene blue (Grubler); heat the mixture for one hour in an Arnold sterilizer or other steam sterilizer, after the steam is up. After heating allow the solution to cool. Make a 1 to 1,000 solution of yellow aqueous eosin (Grubler) and add this, while stirring, to the cooled mythylene blue solution, in about the proportion of 500 c.c. of the eosin solution to 75 c.c. of the methylene blue solution. This should be done in a white dish of some kind, in order that the precipitate that forms as the eosin solution is added may be easily seen. The proportion of eosin solution added to the methylene blue solution will vary in different batches of the stain, but the eosin solution should always be added until a well-marked precipitate follows after stirring. A marked metallic scum will appear upon the surface of the mixture at the time the eosin solution is in sufficient quantity and this may be used as an indicator, but if no precipitate is present when the metallic scum appears the eosin solution should be added until it appears. The mixture should then be allowed to stand for fifteen or twenty minutes, and then filtered through one small filter-paper, the precipitate saved, dried in a hot-air oven, removed from the filter-paper, and used in making the staining solution. The precipitate, which is a fine powder, greenish in color, will keep well and can be used as stock material for months.

The staining solution is prepared as follows: Take 0.3 gm. of the powdered precipitate and add it to 100 c.c. of pure methylic alcohol (Merck's reagent), filter, and to 80 c.c. of the filtrate add 20 c.c. of the methylic alcohol, or if more than 80 c.c. be left after filtration, enough to bring the entire amount up to 100 c c. The staining solution is now ready for use and will keep unimpaired for weeks.

Method of Use.—To stain, add a few drops of the staining solution to the blood smear prepared in the manner directed, and let stand for from two to four

minutes. This fixes the specimen. Then add enough distilled water to cause a slight metallic scum to form upon the surface of the preparation; let stand for from three to five minutes, wash in running distilled water, and examine when dry. The washing in distilled water is important, as by it the precipitate formed during the staining process is removed, and it should be continued until the specimen is a delicate shade of pink or pinkish-brown. If it is desired to preserve the specimen, do not mount in Canada balsam, but preserve the slide without the addition of a cover-glass.

Prepared and used in the manner described, it will be found that Wright's stain is always reliable and can be depended upon to give the most beautiful pictures of stained malarial plasmodia. I have had but little success with this stain as prepared by manufacturing chemists, and would strongly advise that the stain be made by the one using it, and that only the ingredients mentioned be used in its manufacture. None of the other modifications of Romanowsky's stain, such as Leishman's, Nocht's or Jenner's can compare with this stain, in my opinion, as regards ease of manipulation and the results obtained.

The Staining Reactions of the Blood With Wright's Stain.—In specimens of blood properly stained with Wright's stain, the red blood-corpuscles are stained a brownish-pink or a light pink, while the various leucocytes are stained as follows: the polynuclear leucocytes present a light red nucleus with unstained protoplasm except for light pink granules which are generally present within the protoplasm; the mononuclears and lymphocytes have a dark ruby-red or violet nucleus, very sharply defined, while the protoplasm is stained a light blue; the eosinophiles have a deep violet nucleus and the granules are stained a pale red, in the coarsely granular variety, a brilliant red; the mast cells have dark purplish-black granules, and a dark red nucleus; the blood plates stain a bright ruby-red, with, in most instances, a well marked, pale lilac margin.

The staining reactions of the malarial plasmodia when Wright's stain is used have already been thoroughly described in the section dealing with the morphology of the plasmodia. It may be repeated here, however, that the protoplasm of the plasmodia stains a robin's egg-blue, the vesicular portion of the nucleus remains unstained, while the chromatin of the nucleus stains a beautiful ruby-red.

Other Methods of Staining the Malarial Plasmodia.—Among the other methods in use for staining the malarial plasmodia the following are the most important and useful:

Romanowsky's Method.—Two solutions are used: Sol. 1. Methylene blue (Grubler), 1 part. Sodium carbonate, 1.5 part. Water, 100 parts. Sol. 2. Eosin, yellow aqueous (Grubler) 1 part. Water, 1000 parts. Solution 1 should be mixed and kept in an incubator for several days or in the sun-light, until a distinct purple tinge develops, and solution 2 should be kept in the dark.

The staining solution is made by mixing 5 c.c. of each solution with 95 c.c. of water and then adding the methylene blue solution to the eosin solution in the proportion of one part of the former to two parts of the latter. The stain

should be allowed to act for at least fifteen minutes and the best specimens are obtained after from one to two hours. After staining, the smears should be thoroughly washed in running distilled water. The staining reactions are similar to those obtained with the Wright stain.

Leishman's Method.—This method is a favorite one in England, but I have not secured as good results with it as with Wright's method, although it is an excellent stain for the plasmodia. The method of preparing this stain is as follows.

1. Make a 1 per cent. solution of Grubler's medicinal blue in distilled water made alkalein by the addition of 0.5 per cent. of sodium carbonate. Heat for 12 hours at 65° C. in an oven and allow to stand for 10 days at room temperature before using.

2. Prepare a 1 to 1000 solution of eosin (Grubler's extra B. A.).

3. Equal volumes of these two solutions are mixed in an open dish and allowed to stand for from 6 to 12 hours, during which time the mixture should be stirred at intervals.

4. Collect the precipitate that results upon one small filter-paper and wash with distilled water until the washings are colorless or a pale blue; the precipitate is then dried and powdered.

5. To make the staining fluid, dissolve 0.15 gm. of the powder in 1,000 c.c. of Merck's methylic alcohol (reagent).

The method of using the staining solution is similar to that of Wright's, a little of the stain being added to the smear, allowed to remain for two to three minutes, when distilled water is added until a slight metallic scum appears upon the surface; the specimen is then stained for five more minutes, and washed in running distilled water. After washing, Leishman recommends that the stained smears be allowed to soak in distilled water for one minute, claiming that this intensifies the chromatin stain, removes deposits, and changes the color of the red blood-corpuscles to a delicate pink. If this be done the smears will be free from any precipitate. The staining reactions are the same as with Wright's stain.

Nocht's Method.—The following method, advocated by Nocht, is said by Ewing to be excellent for staining the malarial plasmodia, but I have not found it as satisfactory as Wright's stain. The following solutions are used:

1. To 30 c.c. of polychrome methylene blue (Grubler) add five drops of a 3 per cent. solution of acetic acid (U. S. P., 33 per cent.).

2. Make a saturated solution of methylene blue (Grubler) dissolving the powder by gentle heat in water. This solution should be kept for at least a week before it is used.

3. Make a 1 per cent. solution in water of yellow aqueous eosin (Grubler).

The staining solution is prepared as follows:

To 10 c.c. of water add four drops of the eosin solution, six drops of the polychrome methylene blue, and 2 drops of the 1 per cent. methylene blue solution, mixing well.

The stain is used as follows:

The blood smears are fixed by absolute alcohol for five minutes or by heat, stained for two hours or more with the staining solution, in a moist chamber, washed in distilled water, and examined. The best result is obtained after six or more hours' staining.

According to Nocht, the two methylene blue solutions may be replaced by a 1 per cent. solution of Ehrlich's rectified methylene blue to which has been added a few drops of a half of 1 per cent. solution of sodium hydrate, the mixture having been heated for a few days in an incubator at 50° C. When this solution is used the method of staining consists in adding two or three drops of the eosin solution to 2 c.c. of water, and to this adding, drop by drop, the methylene blue solution, until the red color of the eosin solution had nearly disappeared. The results are not as good as when the original method is used. With this stain the staining reactions are similar to those obtained by Wright's stain.

Plehn's Method.—The following method, advocated by Plehn, is sometimes useful, but the chromatin staining is uncertain.

The following solution is used:

Concentrated aqueous solution of methylene blue (Grubler),	60 parts.
One-half per cent. sol. of eosin in 75 per cent. alcohol,	20 parts.
Distilled water,	40 parts.
Twenty per cent. solution of sodium hydrate,	12 drops.

The blood smears are fixed in absolute alcohol for five minutes, stained in the above solution for from five to ten minutes, washed in water, and examined.

Marino's Stain.—This stain, somewhat more complicated in technic than Wright's, but which gives excellent results when carefully prepared and used, is as follows:

Sol. I.	Methylene blue (Grubler's),	0.5 gm.
	Azure blue,	0.5 gm.
	Water,	100.0 c.c.
	Sodium bicarbonate, 0.5 per cent. sol.,	10.0 c.c.

This solution is kept in the incubator at 73° C. for from two to four days, or heated to 60° C. for six hours.

Sol. II. A 0.2 per cent. solution of aqueous eosin (Grubler's). The eosin solution is added to the methylene blue solution until a well-marked precipitate occurs, which is collected by filtration, dried, and used as stock material.

The staining solution is made by adding 0.4 gm. of the methylene-azure powder, obtained by filtration, to 20 c.c. of pure methylic alcohol, and is used as follows:

The blood smears are covered with the staining solution, the number of drops required to do so being recorded. After the stain has been allowed

to act for three or four minutes, double the number of drops of an aqueous solution of eosin, containing 0.05 gm. of eosin to 1,000 c.c. of water are added, and left on for from two to three minutes. The smears are then thoroughly washed in distilled water and examined at once.

Giemsa's Stain.—This stain, so useful in staining *Treponema pallidum* and *Treponema pertenuis*, is also a valuable stain for the plasmodia of malaria, but its method of preparation is so complicated and requires so much care that, while the results obtained by it are reliable, it is not as available for general use as is the more simple Wright's method. It is also very prone to overstain and to undergo changes with age which render it useless for the staining of the malarial parasites. The stain is prepared as follows:

In preparing the stain and using it the utmost care should be taken that everything is chemically clean and that none of the dishes or implements used are moist, and that they are absolutely free from acid. The dishes should all be sterilized before using and thus rendered free from bacterial contamination.

Preparation of Stock Staining Solution.—Weigh out the following:

Azure II-eosin,	3.0 grams.
Azure II,	0.8 gram.

Dissolve these, with constant shaking, in chemically pure glycerine (250 c.c.) at a temperature of 60° C. After solution is complete add 250 c.c. of absolute methyl alcohol (Kaulbaum I) previously heated to 60° C. This mixture is shaken well, allowed to stand at room temperature for 24 hours, and then filtered into a chemically clean, sterilized air-tight stock bottle. During the filtration the funnel must be covered with an inverted watch-glass to protect the hydroscopic fluid from moisture.

The stain should always be protected from the sunlight.

The method of using this stain is as follows:

For structures such as spirochaetes, the Treponema, and the malarial plasmodia proceed as follows:

1. Make thin, even smears of the material to be examined upon fat-free cover-slips or slides.
2. Dry in the air and fix for twenty minutes in absolute ethyl alcohol.
3. Blot off the alcohol with smooth, closely woven, white filter-paper.
4. Stain with the following solution:

Stock solution,	10 drops
Distilled water,	10 c.c.

One per cent. sol. potass. carb. 1 or 2 drops to each 10 c.c. of the mixture of distilled water and stock solution.

If the malarial plasmodia are to be stained, the staining solution should be allowed to act for from 5 to 10 minutes, but if the treponema is to be stained it should be at least an hour before the stain is removed.

5. Wash the stained smears in running distilled water, air dry, and examine

at once. With this stain the protoplasm of the plasmodium colors a very dark blue, the vesicular part of the nucleus remains unstained, and the chromatin takes a very dark red, almost black color.

Staining of Flagellated Parasites.—The flagellated forms of the malarial plasmodia may be stained by any of the methods mentioned, Wright's stain being especially serviceable. A patient should be selected in which *gametes* are numerous, and the blood should be exposed a short time to the air after securing it on the slide, or the slide may be breathed upon to hasten exflagellation. The smear should be thick and should be allowed to dry slowly. The technic of staining is the same as for the other forms of plasmodia, but it is well to allow the stain to act longer after the water has been added.

Bodies in Stained Specimens Which may be Mistaken for Plasmodia.—To one who has had much experience in the examination of stained specimens of malarial blood, where any of the chromatin stains have been used, the mistake of confusing any stage of growth of the plasmodia with artefacts, granules of dirt, or other objects, is impossible, for the staining reactions of the plasmodia are very distinctive, and a comparatively little practice will enable one to recognize the stained organisms without any difficulty. Certain objects may be mistaken in stained specimens for plasmodia by those unused to studying such preparations, the most important of which are the following:

1. *Flaws* in the slide in which a portion of the stain may collect. If these be situated beneath a red blood-corpuscle they may resemble a poorly stained plasmodium, but upon focussing it will be observed that they are situated at a different level than the red cell and thus they may be easily distinguished.

2. *Blood platelets*, especially if lying upon the red blood-corpuscles, as frequently happens, are commonly mistaken for plasmodia by those unaccustomed to stained preparations. They are differentiated by the lack of a blue-stained protoplasm and the bright ruby-red mass of chromatin, the chromatin of the blood plate being darker in color, irregular in outline, and more granular in appearance. Most blood plates are surrounded by a well-marked bluish limiting membrane, especially well observed when the plate is lying free in the plasma. Sometimes the blood plates are collected in crescentic masses and might be mistaken for crescents, but a little study should served to obviate such mistakes.

3. *Vacuoles*, in which some of the stain has been retained, may occur in the red blood-cells, but may be easily distinguished from the plasmodia by the absence of the blue protoplasm and the red chromatin.

4. *Leucocytes* have been mistaken for stained malarial plasmodia, but such a mistake could only be made by the merest tyro in blood examinations. Among other objects which might be confused with the plasmodia in stained specimens may be mentioned particles of dirt of extraneous origin, yeast cells and other micro-organisms, degenerated leucocytes, neucleated red cells, and basophilia of the red corpuscle. It is obvious that an acquaintance with the appearance of both normal and diseased blood in stained specimens will make

such mistakes impossible, and, as I have stated, a knowledge of the microscopic appearance of normal blood, in both fresh and stained preparations, is absolutely essential to one who expects to study the malarial plasmodia or to make microscopic examinations of blood for diagnostic purposes.

The Microscopic Diagnosis of the Species of Malarial Plasmodia.—The species of malarial plasmodia may be differentiated in both fresh and stained specimens of blood, and in making such a differentiation two factors should be borne in mind, *i.e.*, the character of the infected red corpuscle and the character of the parasite infecting it. I have already described in detail the characteristics of the various species of plasmodia and the changes occurring in the infected red cell in the chapter dealing with the morphology of the plasmodia, but for convenience I shall here give a brief summary of the distinctive features of the plasmodia which may be used in diagnosing the species present in any given case.

Tertian Plasmodium.—The red cell infected with *Plasmodium vivax* is invariably enlarged, even during the earliest stage of growth of the parasite, and after the occurrence of pigment the red cell is markedly larger than the uninfected cells and is lighter green in color. The occurrence of Schuffner's dots is characteristic of tertian infection. The youngest "ring-forms" are larger, more veil-like in appearance, and more noticeably amoeboid than are the "ring-forms" of any other species. The pigment when developed is in finer, lighter brown granules than in the other species, and is much more actively motile. The organism after the development of pigment and until within a few hours of segmentation is actively amoeboid, thus leading to an irregularity in shape that is characteristic. When fully developed the organism fills the entire red cell, which is greatly enlarged, often twice to three times the size of a normal red cell.

In stained specimens the youngest tertian "rings" are with difficulty distinguished from those of other species, but with the development of pigment, the larger size of the red cell and the irregular shape of the organism serves to distinguish it from the other species. At all stages it is larger than any of the other plasmodia at a corresponding stage, and the pigment is distributed throughout the protoplasm instead of collected in clumps as in the other species.

Quartan Plasmodium.—The infected red cell in quartan infection, or infection with *Plasmodium malariae*, is unchanged or slightly smaller than normal and slightly more greenish in color. The young "rings" are smaller than the tertian "rings," more refractive, regular in shape, and generally contain a little pigment. The larger forms are more refractive, regular in shape, being oval or spherical, and the pigment is in larger, darker brown granules than in the tertian plasmodium, and is collected about the periphery of the organism. The segments number from 8 to 12, while in the tertian form the segments number from 12 to 24. At no stage of development is the infected cell enlarged.

In stained specimens this species is distinguished by the non-enlargement of the red cell, the fact that when fully developed the organism fills the entire

cell; the character of the pigment; the more deeply staining chromatin, which is present in larger amount; and the number of the segments. The absence of Schuffner's dots is also a distinguishing point.

THE AESTIVO-AUTUMNAL PLASMODIA.—The red cells infected with *Plasmodium falciparum* and *Plasmodium falciparum quotidianum* are always smaller than the uninfected red cells, and much darker green in color. In infections with these plasmodia the so-called "brassy corpuscles" occur, and only in such infections. At every stage of development of the plasmodia the infected red cell is smaller than normal, and is generally somewhat irregular in shape. In these infections only the "ring-forms" and the young pigmented bodies are found in the peripheral blood in the vast majority of cases. The red cell is never entirely filled by either of these plasmodia, generally not more than one-half of the cell being occupied when the parasites are fully developed. The occurrence of crescents is diagnostic of aestivo-autumnal infections. A diagnosis of aestivo-autumnal infection may be made when repeated examinations of the blood never show any but hyaline "ring-forms" and small pigmented forms to be present, for in tertian and quartan infections the larger developmental forms will be present as well as sporulating bodies.

The terian aestivo-autumnal plasmodium is differentiated from the quotidian by its larger size, the occurrence of several granules of lighter brown pigment; its less refractive outline; greater amoeboid motion; and by the fact that the tertian crescents are more slender, both male and female, than are the quotidian, and contain a greater amount of pigment. They are also smaller.

For a more extended discussion of the differential features of the malarial plasmodia the reader is referred to the chapter treating of the morphology of the plasmodia (Chapter II).

Demonstration of Plasmodia in Sections of Tissue.—It is often desirable to demonstrate the plasmodia in the organs of fatal cases of malaria, and this may be done by taking smears of the organic pulp, and staining as with blood smears, or by sectioning the invaded organs and then staining. In most instances, where it is desired to simply prove or disprove the existence of a malarial infection, all that is necessary is to make a few smears of the splenic pulp by simply drawing the microscopic slide across the cut surface of the organ and then staining with Wright's stain. Where it is desired, however, to demonstrate the exact situation of the plasmodia in the tissues, it is necessary to section the invaded organs, and to stain the section with some suitable solution. The following method I have found satisfactory:

The tissue is cut into small blocks not over 3 mm. in diameter, and then passed through 50, 65, 75, and 90 per cent. alcohol, and finally absolute alcohol, allowing about three hours in each alcohol. The tissue should then be washed and left for two hours in chloroform, after which it is embedded in paraffin at a temperature which will just keep the paraffin in a fluid state. The tissue should remain in the paraffin bath for about six hours, and then the paraffin allowed to harden around it, after which sections may be cut with any good

microtome, the sections to be as thin as possible, as only in very thin sections will the plasmodia show to advantage when stained.

For staining Delafield's haematoxylin is very useful, as is methylene blue and Giemsa's stain. It is difficult to secure good results with any of the modifications of the Romanowsky method, although I have seen fairly good staining with the Wright stain.

The technic of staining the sections is as follows:

The section is removed from the microtome and placed upon a slide which has smeared upon its surface a little egg-albumin water. The section is then successively washed in xylol to remove the paraffin in 95 per cent. and absolute alcohol and water; and stained with haematoxylin and eosin, thionin, or Wright's stain. The stain should be allowed to remain for from ten minutes to an hour, then washed off with alcohol, and the sections cleared in oil of clove. They are then mounted in balsam, and are ready for examination. Care should be taken in dehydrating with alcohol that all the water is removed, and if it is found that in order to do this too much stain is removed, the alcohol should be blotted off and the section covered with oil of clove, which will complete the dehydration without removing so much of the stain. Care should be taken that during no stage of the staining the sections become dry. In sections of tissue properly stained the plasmodia show well, but appear much smaller than in stained smears or in fresh blood specimens, owing to the shrinkage brought about by the hardening and embedding processes. In sections the chromatin staining is very seldom well defined, and the infected corpuscles do not show distinctly, the plasmodia appearing to lie free within the capillaries. The parasites are most numerous in the smaller capillaries and are scarce in the large vessels. In the smaller vessels the plasmodia occur chiefly along the walls of the vessel, very few being observed toward the center, but in the minute capillaries the plasmodia occur in masses which often occlude them. The plasmodia are often at different stages of development or they may be practically all in one stage of their life cycle. In aestivo-autumnal infections it is common to find the capillaries of the brain and of the spleen filled with spherical pigmented plasmodia of the same size and appearance. In all cases of pernicious malaria or cases suspected to be such smears of the brain and of the spleen, as well as of the bone-marrow, should be stained and examined, and in addition sections of the brain and spleen should be made.

The Diagnostic Value of Free Pigment and Pigmented Leucocytes.—The presence of *free pigment* in the blood is characteristic of malarial infection, but, unfortunately, is of little diagnostic value, as such pigment is so easily simulated by particles of dirt, artefacts, and other matter that it is generally impossible to be sure of the diagnosis of malarial pigment. It is, therefore, unjustifiable to make a diagnosis of malaria, because material resembling malarial pigment is observed free in the blood plasma. When, however, the pigment is observed enclosed in mono- or polynuclear leucocytes; when it is of a characteristic golden-brown or blackish color; and when several pigmented

leucocytes are observed in two or more smears, carefully prepared, we are justified in making a diagnosis of malarial infection, either past or present; but under such circumstances it is impossible to diagnose the variety of malarial infection present. The pigment is generally observed in the large mononuclear leucocytes, but in my experience it has not been rare to observe pigment in the polynuclear leucocytes. To one who has had experience in the examination of malarial blood the pigmented leucocyte is easy of recognition and is always indicative of a malarial infection.

The Diagnostic Significance of Blood Counts.—I have already mentioned the increase of large mononuclears in chronic malarial infections and in infections in which several relapses have occurred. This mononuclear increase is believed by Rodgers to be of diagnostic importance, but I am unable to agree with him that such an increase is diagnostic of malarial infection. A similar increase is observed in other acute fevers as well as in chronic infections. Thus in dengue one of the most characteristic blood pictures is a mononuclear increase, while in kala-azar the same condition occurs. I consider it very unsafe to base a diagnosis of malaria upon the differential blood count, and I believe that further research will show that a mononuclear increase is observed in most infections due to the Protozoa.

Agglutination Test in Diagnosis.—It has been demonstrated by La Monaco and Panichi that the blood serum of patients suffering from malarial fever possesses agglutinative power over the blood of healthy individuals, while Stephens and Christophers have noted the agglutination of malarial *sporozoites* by malarial blood. This subject is of great scientific interest, as it would indicate the presence of specific precipitins or agglutinins in malarial blood, but the agglutination test is of no practical value at present in the diagnosis of malarial infection.

The laboratory diagnosis of malarial infection rests upon the finding of the plasmodia or of pigmented leucocytes in either fresh or stained specimens of blood or in smears or sections of tissue from a suspected case. The best time for the examination of the blood in tertian and quartan cases is a few hours before the chill or at the time of the chill, while in aestivo-autumnal infections the best time for blood examination is a few hours before the expected paroxysm. In the latter class of cases it is not unusual to find that the time of onset of the paroxysm cannot be foretold, and in such instances the blood should be repeatedly examined, at hourly intervals, until several smears have been looked over, and thus a negative result assured, as not infrequently the plasmodia are very few in number in the peripheral blood and only by repeated examinations will their presence be demonstrated.

Puncture of Spleen.—I have never found puncture of the spleen necessary from a diagnostic standpoint, and I would earnestly advise against this procedure for such a purpose. The operation is always dangerous where the spleen is enlarged and softened, and it should only be undertaken by one skilled in the technic and under the most careful precautions as regards asepsis and guard-

ing against haemorrhage. The spleen should never be punctured unless it reaches well below the border of the ribs, as otherwise there is great danger that the capsule will be torn by the needle coming in contact with the ribs during inspiration, for it is almost impossible to guard against more or less movement of the organ during the pain of the puncture.

The Examination of the Malarial Mosquitoes.

It is essential to the student of malaria that he be able to recognize the malarial mosquitoes, and that he possess enough knowledge of their habits to be able to rear them and thus be enabled to procure specimens for experimental purposes. In this section I shall give briefly the most important diagnostic features which serve to distinguish the Anophelinae from other mosquitoes, features which are easily learned and a knowledge of which will enable any one, who cares to take the time, to recognize the presence of malarial mosquitoes; general directions will also be given concerning the rearing of these insects and the methods of using them in experimental work.

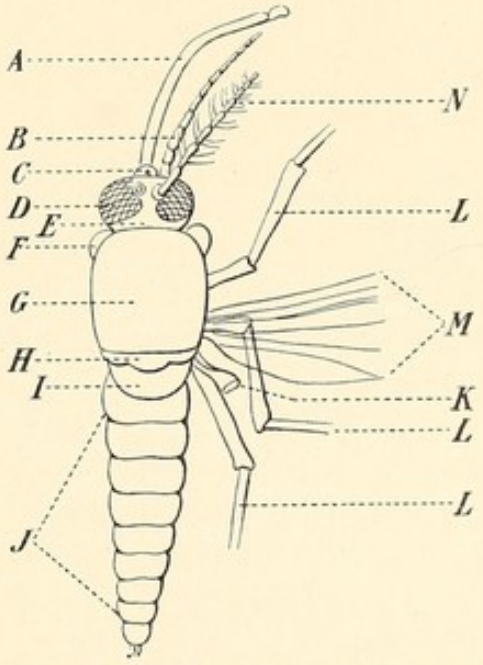

FIG. 24.—Diagram of Typical Anophelina.

A, Proboscis; B, palpi; C, Cylpeus; D, eye; E, occiput; F, prothoracic lobe; G, mesothorax; H, scutellum; I, metathorax; J, abdominal segments; K, halter; L, legs; M, wing; N, antenna. (Modified from Theobald.)

Diagnosis of Malarial Mosquitoes.—The Anophelinae, or malarial mosquitoes, are easily differentiated from other mosquitoes by certain well marked characteristics of the adult insect, which may be summarized as follows:

1. THE RELATIVE LENGTH OF THE PALPI AND THE PROBOSCIS.—In the Anophelinae the palpi of the female are as long as the proboscis, while in the female Culicinae the palpi are short, stubby structures. An examination of the palpi and proboscis of any mosquito will, therefore, enable one to say

whether it belongs to the Anophelinae or the Culicinae. In the males of both the Anophelinae and the Culicinae the palpi are long and plumose, being covered with delicate hairs, giving a plume-like appearance.

2. The Angle of the Proboscis with the Body.—In the Anophelinae the proboscis does not form an angle with the rest of the body, but continues in a direct line with it, thus differing from *Culex*, *Stegomyia*, and *Taeniorhynchus*, in which the proboscis forms a distinct angle with the rest of the body. This characteristic gives mosquitoes belonging to the Anophelinae a peculiar "business-like" appearance, the entire insect resembling a boring instrument.

3. The Attitude when Resting Upon a Surface.—Mosquitoes belonging to the Anophelinae, when resting upon a flat surface, such as a wall, form a distinct angle with the surface, the insect resting upon the first two pairs of legs, the last pair floating in the air or held out straight behind it. In many instances the angle maintained by the insect is almost a right angle, and the body is always on a line with the probosis. The position assumed by other mosquitoes, as *Culex*, is well described as "hunch-backed," the tail approaching the resting surface, while the thorax is distinctly higher than any other portion of the body, thus giving the "hunched" appearance. Certain mosquitoes rest with the body parallel to the resting surface, but the Anophelinae alone form a distanct angle with it. One species belonging to the Anophelinae, *Myzomyia culicifacies* Giles, rests with its body parallel to the resting surface, thus resembling a *Culex*, but this is the only exception so far discovered to the general rule noted (see Fig. 20).

4. Most of the Anophelinae have Spotted Wings, but this is also true of at least a few other mosquitoes. However, for practical purposes, mosquitoes having distinctly spotted wings may be classed as Anophelinae. For species determination the reader is referred to the generic table given, and to Theobald's classic work upon these insects.

The *ova* of the Anophelinae may be distinguished by the fact that they lie separately upon the water, or, at most, are only connected by the ends, while the ova of *Culex* occur in boat-shaped masses. The ova of the Anophelinae are also provided with lateral air-cells or "floats," which are characteristic. The *larvae* of all Anophelines are easily distinguished from those of *Culex* by the absence of a respiratory siphon, so that when they are at the surface of the water they are obliged to lie nearly parallel to it, while *Culex* hangs head downward at an acute angle with the surface of the water. The larvae of the Anophelinae have smaller heads in proportion to the body than other mosquito larvae, and they move in a much more jerky manner when rising to the surface of the water (see Fig. 18).

The Collection of Ova, Larvae, and Adult Mosquitoes.—The *ova* of the Anophelinae may be collected along the edges of small natural pools, but they are detected with difficulty, and a much more satisfactory method of obtaining them is to catch a number of the mature insects, confine them in jars containing water, and collect the ova from the surface of the water for examination.

The *larvae* of the Anophelinae may be collected from the edges of small puddles, shallow pools, and slowly running streams, by muddying the water, when the larvae, if present, may be clearly distinguished by reason of their grayish color, and can be easily removed by aid of a small dipper. The *adult insects* may be captured at night by placing a lamp so that a portion of a wall is but slightly lighted, upon which the mosquitoes will gather, and from which they may be captured by aid of a test-tube having a large mouth, or of small straight glass cylinders, closed at one end. Cotton should be used to close the open end of the cylinder or tube. If it is desired to kill the mosquitoes as they are collected, a cyanide bottle may be used, or a little cotton saturated with chloroform may be placed at the bottom of the test tube or cylinder. When it is desired to collect mosquitoes for rearing or for experimental work the test-tube or cylinder should be gently placed over the insect, as it rests upon the wall, and then gently moved across the surface of the wall, when the insect will fly to the closed end, and the tube may then be sealed with the cotton stopper. The best places to search for the adult *Anopheles* is in the dark corners of rooms; under surfaces of tables and sinks; in closets; and about the base-boards of rooms not exposed to sunlight. In regions in which these insects are common a search of such localities will always result in finding many specimens.

To Kill and Mount Mosquitoes.—Mosquitoes may be killed by exposing them to tobacco smoke, the fumes of chloroform, or by using a cyanide bottle in their capture. If chloroform is used be careful not to wet the insect, as by so doing the scales are removed from the wings and thus a distinguishing feature, useful in the differentiation of species, is lost. In order to properly mount mosquitoes for purposes of preservation the following apparatus is necessary: Cardboard, preferably white; entomological pins and forceps, the pins being large and small (No 20); and glass specimen tubes and corks.

A disk, slightly smaller than the diameter of the specimen tube, is cut from the cardboard, and a fine entomological pin is pushed through the center of the disk for about two-thirds its length. The mosquito is placed upon its back upon a piece of white paper, and transfixed with the fine entomological pin which has attached to it the paper disk, the pin entering the insect at the center of the under surface of the thorax, and emerging as close to the center of the dorsum of the thorax as possible, where it should extend for about a millimeter. The entire specimen is now mounted by transfixing the edge of the paper disk with a coarse entomological pin or a common pin in a direction opposite that of the fine pin, for three-quarters of its length, the point being pushed into the cork of the specimen tube upon its inner side (see Fig. 25).

To Dissect Mosquitoes.—In order to make good dissections of the Anophelinae for the purpose of detecting malarial infection or for studying the development of the plasmodia within these insects the following apparatus is necessary: Microscopic slides and cover-glasses; fine dissecting needles, mounted in handles; a good dissecting microscope, and some normal salt solution. A compound microscope with high-power lenses is, of course, necessary for studying the

development of the plasmodia. The portions of the mosquito of greatest interest to the student of malaria are the salivary glands and the mid-gut or stomach.

To Dissect the Salivary Glands.—While in most works upon mosquitoes it is said to be a simple procedure to dissect out the salivary glands, it will be found in practice that it is indeed a very difficult task to secure perfect specimens of these glands, although it is comparatively easy to secure portions of the glands sufficiently perfect to allow of demonstrating the *sporozoites*. The glands are situated within the thorax, lying ventrally, commencing at the posterior portion of the neck and ending at the level of the first pair of legs. The simplest way of securing them for study is to cover the insect with salt solution and place it so that the head is toward the dissecting hand. While the needle of the left hand steadies the thorax, the needle of the right hand makes traction upon the head, separating it gently from the body. If the operation has been successful it will be observed that a little white bit of tissue has been extracted from the thorax with the head, and upon examination with the microscope it will be observed that in this bit of tissue lie the salivary glands, which may now be separated from the head and carefully studied. The glands may also be isolated by making an antero-posterior cut in the ventral portion of the thorax and a connecting cut at right angles with it, and then separating the glands from the portion of thorax removed by teasing gently in salt solution, but this method almost always results in mutilation of the glands.

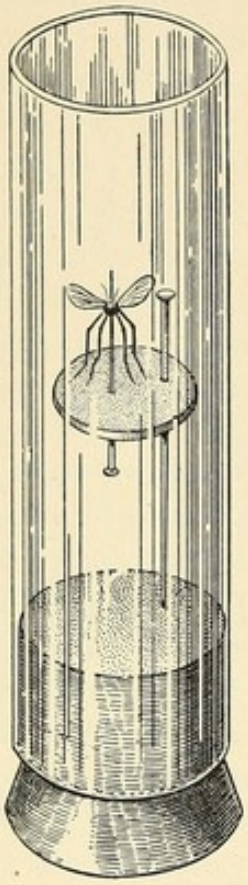

Fig. 25.—Method of Mounting and Preserving Mosquitoes.

In order to determine the presence of malarial *sporozoites* the glands are pressed, upon firmly enough to rupture them, when the *sporozoites*, if present, will be liberated in the salt solution. A one-sixth lens should be used for the examination and as little light as possible. The *sporozoites* appear as fine, hyaline, curved rods, having more or less active motion in some instances, lying free in the salt solution or in large numbers within the cells of the salivary glands. They measure about 14μ in length, and about 2μ in width. They may be permanently preserved by making thin films of the salt solution containing them upon glass slides, and drying and staining with Wright's stain, as described for blood films. For the study of the morphological structure of the *sporozoites* a one-twelfth lens is essential. In stained specimens the *sporozoites* are fusiform in shape, consisting of blue stained protoplasm having a mass of red chromatin at the center or distributed along it in the form of a narrow ribbon or thread.

To Dissect the Mid-intestine or Stomach.—The dissection of the mid-intestine of the mosquito is essential if we are to study the development

of the malarial plasmodia within this insect, and with a little practice it is easily accomplished. The insect, from which the wings and legs have been removed by dissecting forceps, is moistened with a little alcohol and then immersed in the salt solution upon a glass slide, a dark background being employed to facilitate the dissection. Placing the insect upon its back, the left-hand needle is used to steady it, while with the right a nick is made in the chitin on either side as near the posterior end as is possible; the left-hand needle is now placed firmly upon the thorax, and the right upon the end of the abdomen and gentle traction exerted, when between the separating abdominal segments a white mass of viscera will be observed; the traction is continued until it is possible to separate easily the anterior end of the mid-gut, which consists of an anterior tubular portion and a posterior saccular portion, lying at the level of the fifth and sixth abdominal segments, and which is the portion in which *zygotes* will be found if the mosquito is infected. If it is found that this portion of the mid-gut contains blood, the specimen should be discarded, unless it be desired to study exflagellation, as the *zygotes* cannot be distinguished easily in the mid-gut when undigested blood is present. In examining mosquitoes for malarial infection it should be remembered that only a comparatively few of the insects collected will prove to be infected and therefore several insects should be examined before a negative report is of value.

Demonstration of Zygotes.—The specimen of the mid-gut or stomach should be examined with both a one-sixth and a one-twelfth lens, the larger *zygotes* being easily visible with a one-sixth lens, while for the detection of the earlier stages a one-twelfth lens is necessary. Any granule resembling malarial pigment should be carefully inspected, as by so doing the *zygotes* are most quickly discovered, even in the earliest stage of development. The earliest stage is an oval or spherical body, about 8μ in diameter, containing pigment, the character of which varies with the species of the plasmodium, the aestivo-autumnal *zygotes* having black pigment collected in a clump; the tertian, yellowish or brown pigment collected in delicate strands; and the quartan, coarse dark brown pigment collected in a large clump. As development advances, the species of the *zygote* becomes indistinguishable, and each organism is surrounded by a well-developed cyst wall, within which the *sporoblasts* are developed. At a later period of development the *sporozoites* may be observed packing the cysts, which have become so large as to be visible with a two-thirds inch lens, while the *sporozoites* are easily seen with a one-sixth lens. The pigment disappears in many of the *zygotes* as development proceeds, but many contain black clumps of material, which probably represents residual pigment, or parasitic infection.

To Section Mosquitoes.—The following method, advocated by Stephens and Christophers and given in their own words, is an excellent one when it is desired to section infected mosquitoes for purposes of study and demonstration.

1. Select *Anophelines* free from blood and kill by chloroform vapor.

2. Fix in (a) acetic alcohol for 5 or 10 minutes (glacial acetic acid one part, absolute alcohol, six parts, chloroform, three parts); wash in absolute alcohol till free from acid (it is often advisable, especially with thick flies, to nick the chitin at some unessential part in order to allow penetration of the fixative), or (b) sublimate alcohol, or (c) absolute alcohol, 15 minutes.

3. Place in 1 per cent. celloidin for a day and in 3 per cent. celloidin for another day. These times may with advantage be increased, but sometimes a few hours only suffice. (The solution of celloidin is made by dissolving dry chips in 50 per cent. alcohol and then in a day or so adding 50 c.c. of ether.

4. Transfer to cedar-wood oil, and when the mosquito sinks transfer to

5. Paraffin for half to one hour, and then section and strain.

To Rear Mosquitoes.—Many species of *Anopheles* are reared with great difficulty under artificial conditions, but others breed well in confinement. The more nearly we imitate nature in the surroundings of our rearing cages for mosquitoes, the greater will be our success in rearing these insects. Cages built of light wood and covered with fine wire gauze are suitable and each should contain a vessel of water. Glass jars containing water and vegetable material make good breeding-places , and pieces of large bambo sawed off some distance from the joints have been used with great success by many investigators. When jars or other open-mouthed receptacles are used the open end should be covered with gauze.

A goodly number of mosquitoes should be captured, both males and females, and liberated in the breeding receptacle, which should be placed in a shaded part of the room or in a closet. The males soon die, but the females will, many of them, lay their eggs, and in due time the larvae will appear. The insects may be fed by placing small pieces of banana within the cages or by laying slices of banana upon the gauze covering the jar or other breeding place. Dead insects should be removed each morning, and, with care, adult insects may be kept for many days in this manner. If it is desired to breed out the larvae they should be removed from the cage and placed in a jar of water exposed to light but not to excessive heat. The insects live longer in glass jars than in gauze cages, as a general rule.

Feeding Experiments.—When mosquitoes are required for feeding experiments they should be removed from the breeding jar and transferred to a glass jar having a wide neck covered with cotton gauze, where they should be kept for at least three days without food. It is better to use mosquitoes bred out from the larvae in such experiments, as they are sure to be free from infection, and will bite readily 48 hours after birth. At least 25 mosquitoes should be used in each feedng experiment, in two jars. A patient is selected whose blood contains *gametes*, and, after dark, allowed to place his arm over the gauze covered neck of the jars. Biting is hastened by washing the arm in warm water just before the experiment. The insects usually bite within half an hour, but it will be found that some of them require a longer time to bite and that some will not bite. It is well to wait for an hour before ceasing the ex-

periment, thus allowing the insects plenty of time. The jar should be labeled with the time and date of biting, and the insects dissected at various intervals after the first twenty-four hours if it is desired to follow the development of the plasmodia, or kept for twelve days before allowing them to bite if we desire to transmit malaria experimentally.

The Diagnosis of Malarial Regions.—Before establishing residences or permanent military camps or posts in the tropics or in regions in which mosquitoes capable of transmitting malaria abound, it is of the greatest importance that the presence or absence of the malarial fevers be determined and in the examination of the blood of the natives, and the mosquitoes, as to the presence of malarial infection, we possess methods which enable us to make a malarial survey of any locality.

A map of the locality should be obtained and there should be marked upon it the location of the breeding-places of mosquitoes and the species found in each breedery, also whether any of the insects examined were found to be infected with plasmodia; the dwellings of any individuals found infected with malaria during the blood examination of the natives should be indicated upon the map, and thus the relation of the breeding-places of the mosquitoes to such infections will be clearly shown. The map should also show the ratio of infected individuals and of infected mosquitoes, and the most dangerously infected localities. The work of a few days in the examination of the blood of the natives, the dissection of mosquitoes, and the search for the breeding-places of these insects will result in a most valuable mass of data enabling one to judge of the advisability of locating in the region examined. Such a preliminary survey of the malarial endemicity of localities is of the very greatest sanitary importance in the selection of camp sites of a permanent nature or sites for permanent military posts in the tropics and in the malarial regions of the temperate zones.

CHAPTER II.

The Clinical Diagnosis of the Malarial Fevers; The Differential Diagnosis of the Malarial Fevers.

As I have stated the diagnosis of malarial infection, without the aid of laboratory assistance, is often impossible, and still more frequently is it impossible to diagnose the variety of infection present. In uncomplicated and single tertian and quartan infections a diagnosis may be reached by the study of the temperature chart, the regularly recurring paroxysms of fever being sufficient to establish the type of infection present, but in many cases of both tertian and quartan malaria the temperature chart is misleading, the paroxysms occurring at irregular intervals, thus causing an irregular temperature curve. It is in the aestivo-autumnal infections, however, that we most frequently find it impossible to arrive at a diagnosis without the aid of the microscope, for these infections occur in so many atypical forms that the diagnosis from clinical symptoms alone is seldom easy and very frequently impossible. The microscopical examination of the blood is the only infallible method of arriving at a diagnosis and should never be neglected. The therapeutic test by quinine, *i.e.*, the administration of the drug in suspected cases, has been lauded as a means of diagnosis, but the malarial fevers are not the only fevers that are influenced by this drug, and it is illogical to regard every fever that declines after the administration of quinine as malarial. Added to the worthlessness of the quinine test as a *diagnostic* test of malaria, it is dangerous to rely upon this drug in diagnosis, for it is usually given by the mouth in such instances and it is well known that many pernicious infections are very resistant to quinine when so administered. In this way the diagnosis may be delayed until the patient is in grave danger or even moribund. While it is undoubtedly true, as stated by Osler, that any fever which resists the action of quinine properly administered for over four or five days is not malarial in character, it is foolish to wait so long to establish our diagnosis when a few moments' examination of the blood will enable us to reach the same conclusion.

Certain factors are of value in arriving at a suppositional diagnosis of malarial fever, among the most important of which may be mentioned the time of occurrence of the disease; the character of the locality in which the patient is resident or from which he has come; the location of the dwelling-house in relation to water and thus to possible breeding-places of mosquitoes; the history of previous attacks; the periodicity of the attacks; the species of mosquitoes present; and the occurrence of similar fevers in other members of the family.

Diagnosis of the Various Forms of Malarial Fever.—A differential

diagnosis of the various types of malarial infection is most quickly and scientifically made by an examination of the blood. In this way the entire life cycle of the tertian and quartan plasmodium may be studied, and the aestivo-autumnal plasmodia easily differentiated. Where, however, an examination of the blood is impracticable, clinical symptoms have to be relied upon to determine the type of infection and in a limited proportion of cases such symptoms are sufficient.

Tertian Infection.—The temperature range in uncomplicated cases of tertian infection is so typical that a temperature chart is often all that is needed to enable us to make the diagnosis. The occurrence of a definite paroxysm, accompanied by chill, fever, and sweating, every 48 hours, is generally sufficient to prove the type of malaria present, but certain cases are indistinguishable clinically from mild tertian aestivo-autumnal infections, while if double tertian infections be present or small doses of quinine have been administered, it becomes impossible to distinguish the type of infection present without the aid of the microscope.

Quartan Infection.—In uncomplicated cases of quartan infection the temperature chart is absolutely characteristic. The occurrence of a paroxysm of chill, fever, and sweating every seventy-two hours is absolutely characteristic of quartan malarial infection and we may safely make a diagnosis of such infection under such conditions, but double and triple infections occur in which the temperature chart is untrustworthy, and in these we have to depend upon the microscope in diagnosing the type of malaria present.

Quotidian Aestivo-atumnal Infection.—When an aestivo-autumnal infection is known to be present, the diagnosis of the quotidian form from the tertian is comparatively easily made, because of the usual occurrence of a distinct chill in the quotidian form and the character of the temperature curve. The differential diagnosis of this type from a double tertian or triple quartan infection is, however, impossible without the aid of the microscope.

Tertian Aestivo-autumnal Infection.—While the diagnosis of the tertian type of aestivo-autumnal fever from the clinical symptoms alone is very often impossible, there not infrequently occur cases in which this form of malarial infection may be diagnosed from the temperature chart alone. I have already described the peculiar range of the temperature in tertian aestivo-autumnal infection when uncomplicated, and a chart showing this peculiar curve, which is not found in any other fever, is absolutely diagnostic, provided the temperature be taken at least every four hours. It is obviously illogical, however, to wait several days until such a typical chart is obtained, when an examination of the blood upon the very first day will clear up the diagnosis. In tertian aestivo-autumnal fever the chill is, as a rule, either absent or very slight, and the general symptoms of no value in making a differential diagnosis, aside from the temperature.

Pernicious Infections.—These infections, usually due to the aestivo-autumnal plasmodia, are easily diagnosed from the benign fevers by the

character and severity of the symptoms, which have already been described. From other disease processes they can very seldom be diagnosed without the aid of the microscope, and it is safe to say that hundreds of lives have been sacrificed to malaria which could have been saved had an examination of the blood been made in the endeavor to arrive at a diagnosis. In all cases in which a suspicion of malaria exists, and especially in those cases presenting pernicious symptoms, the first thought of the diagnostician should be the microscopical examination of the blood.

I have noted the most important differential features of the various types of malaria, but I would impress upon the reader the vital importance of an examination of the blood in the diagnosis of malaria. The data we possess regarding the occurrence of malarial fevers in various localities, and the type of infection present, are almost worthless, because the cases have been diagnosed upon clinical symptoms, the examination of the blood being neglected, and the obsolete classification of the malarial fevers, so often observed in the vital statistics of the public services, is directly due to the constant endeavor to diagnose malaria by clinical symptoms instead of by the examination of the blood. The absurdity, for instance, of a classification of malarial fevers based upon the intermittency or remittency of the temperature curve is evident at once to one who has had even a limited experience with these fevers, and such classifications are a reproach to scientific medicine. Aside, however, from this aspect of the subject, the life of many patients depends upon the quick recognition of the malarial infection, and this is only possible through the microscopical examination of the blood.

The Differential Diagnosis of the Malarial Fevers.

The differential diagnosis of the malarial fevers from other diseases is only possible, in many instances, by an examination of the blood, and this should never be neglected when we are called to see a fever in malarial localities or in an individual returning from such a locality. The difficulty of a differential diagnosis by aid of clinical symptoms alone is especially great in the case of the aestivo-autumnal infections in which the occurrence of atypical symptoms are common and in which pernicious symptoms occur which simulate those present in other specific diseases. The following diseases not infrequently have to be differentiated from malarial fever, and most of them are sometimes so closely simulated by malaria that the differential diagnosis has to be made by the microscope.

Typhoid Fever.—Perhaps no other disease has been so often mistaken for malaria as has typhoid, and if there is anything in the history of medicine which proves the futility of attempting to diagnose the malarial fevers by clinical symptoms alone, it is the experience of our surgeons in the war with Spain. When one has seen, as the writer has, hundreds of cases of severe typhoid diagnosed as remittent malaria and treated accordingly, one is inevitably

forced to the conclusion that the diagnosis of the malarial fevers by means of clinical symptoms alone is, to say the least, attended with great difficulty, and places the patient in peril of his life in many instances. At least three-fourths of the fevers occurring in our Southern camps during 1898 and diagnosed as "remittent malarial fever" were, in reality, typhoid, as shown by the examination of the blood and the Widal test. Clinically, the confusion of these two diseases has much to justify it. It is probable that a typical tertian or quartan malaria is never suspected to be typhoid, or *vice versa*, but in the more irregular aestivo-autumnal infections this mistake has often been made. This is so because many cases of aestivo-autumnal malaria present the same symptomatology, at least in part, as typhoid, and without an examination of the blood it is impossible to arrive at a diagnosis. The mistake, however, of considering a typhoid infection as one of malaria after the administration of quinine for over five days without result is, it appears to me, inexcusable, yet I have observed scores of cases of typhoid given large doses of quinine for weeks under the impression that they were suffering from malarial infection, and in supposedly malarial regions almost every typhoid patient is drenched with quinine simply because of the neglect of the blood examination.

The differential diagnosis depends upon the microscopical examination of the blood, the Widal test, and the therapeutic test by quinine. If the plasmodia are present in the blood and the Widal test is negative, the diagnosis is at once established; if the Widal be positive and there is no history of a previous attack of typhoid, we are dealing with a combined infection, but it should be remembered that such infections are very rare, and a careful inquiry should be made concerning the previous occurrence of a continued fever; if the Widal test be positive and no plasmodia are present, after repeated examinations, the case is one of typhoid; while if neither the plasmodia be present nor a positive Widal can be secured after repeated trials, the fever must be due to some other infection. If a blood examination is impossible and a Widal test cannot be made, the administration of quinine for three or four days will clear up the diagnosis, as if the case is malarial the quinine will reduce the temperature within five days, if properly administered. During the defervescence of the fever in typhoid the temperature may become intermittent, the curve resembling that of a double tertian or quotidian aestivo-autumnal infection. (Chart No. 19.) Chills may also occur at this time, during the onset, or at any time during the course of the disease; thus further increasing the resemblance to malaria, and in such cases a diagnosis is often made of "typho-malarial" fever. Any diagnosis of malarial fever under such circumstances is utterly worthless unless confirmed by a blood examination. With the Widal test, and the improved methods we possess of staining the malarial plasmodia it is inexcusable to-day to fail in differentiating the malarial fevers from typhoid fever.

Yellow Fever.—In regions in which both malaria and yellow fever are endemic the differentiation of these diseases is often exceedingly difficult without a blood examination, and pernicious cases of aestivo-autumnal fever are not

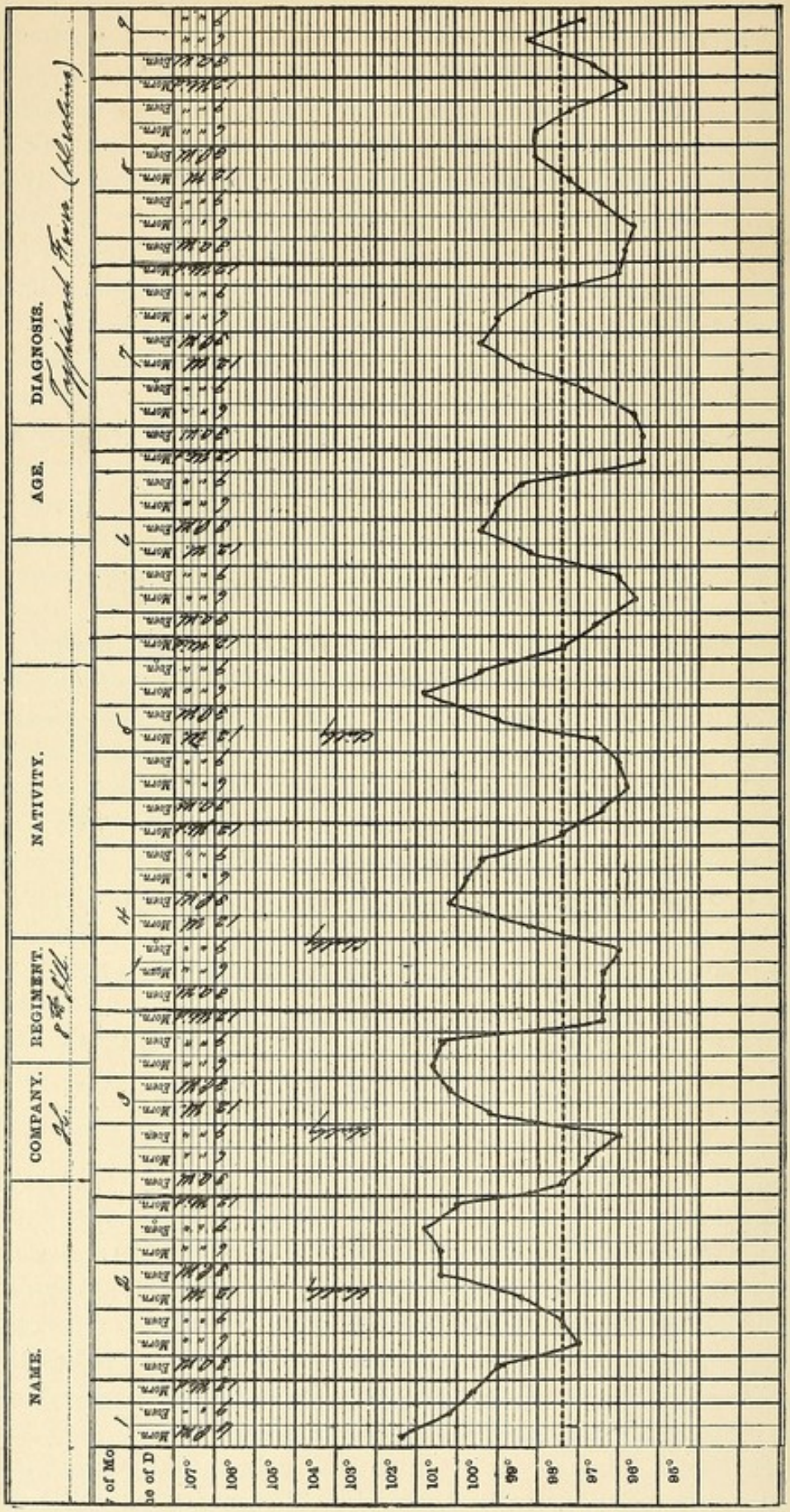

CHART 19.—Typhoid Fever. Decline.

infrequently mistaken for yellow fever. This is especially true of the so-called bilious remittent and haemorrhagic forms of pernicious malaria, in which the yellow tint of the skin, the congested eyes, the flushed cheeks, the severe vomiting, often of black fluid resembling the dreaded "black vomit," the high temperature, and the not infrequent occurrence of albumin in the urine, form a clinical picture closely resembling that of yellow fever. A patient presenting such a picture in a yellow fever region is almost always thought to be suffering from that disease, and in such cases the examination of the blood is of the very greatest importance.

Kala-Azar.—The differentiation of kala-azar and the malarial fevers is of interest and importance, as kala-azar was for years considered a chronic form of malarial infection, and only with the discovery of the *Leishmania-donavani* was the distinction recognized and the differentiation of the two diseases made possible. In kala-azar we have an enlarged spleen, anaemia, an irregular temperature curve similar to that of many cases of aestivo-autumnal malaria; and an examination of the blood will alone enable us to be sure of our diagnosis.

Dengue.—The malarial fevers may be confused with dengue fever, but in the latter disease the more severe character of the muscular pains and the occurrence of an eruption will, in most cases, serve to distinguish the two. An examination of the blood is often necessary, however, and should never be neglected.

Malta Fever.—In regions in which Malta fever occurs there is often much difficulty in differentiation between this disease and the more atypical forms of the aestivo-autumnal fevers. An examination of the blood will at once demonstrate the plasmodia if malarial infection be present, and a positive reaction will be obtained from the blood with the agglutination test with *Micrococcus melitensis*, if Malta fever be present.

Other Fevers.—Among the numerous other febrile processes often mistaken for malaria may be mentioned *puerperal fever*, which has already been discussed; *septicaemia* and *pyaemia*, in which the chills, occurring at regular intervals, followed by fever and sweating, often produce a picture very suggestive of malarial fever; *pyelitis* attended by chills and fever; the early stages of the *eruptive* fevers; *relapsing fever*, in which the demonstration of the spirochaetae in the blood is sufficient to establish the diagnosis, and *trypanosomiasis*, which depends for its diagnosis upon the demonstration in the blood of *Trypanosoma gambiense*. All of these conditions may be easily differentiated from the malarial fevers by a careful microscopical examination of the blood.

Tuberculosis.—Many cases of tuberculosis, especially if complicated by a streptococcus infection, exhibit a temperature curve closely resembling that of a double tertian or a quotidian aestivo-autumnal infection, and there may also be daily chills or chilly sensations, while the patient presents the anaemia and the facies so often observed in long-continued malarial infections. There is no enlargement of the spleen, however, and an examination of the chest will show

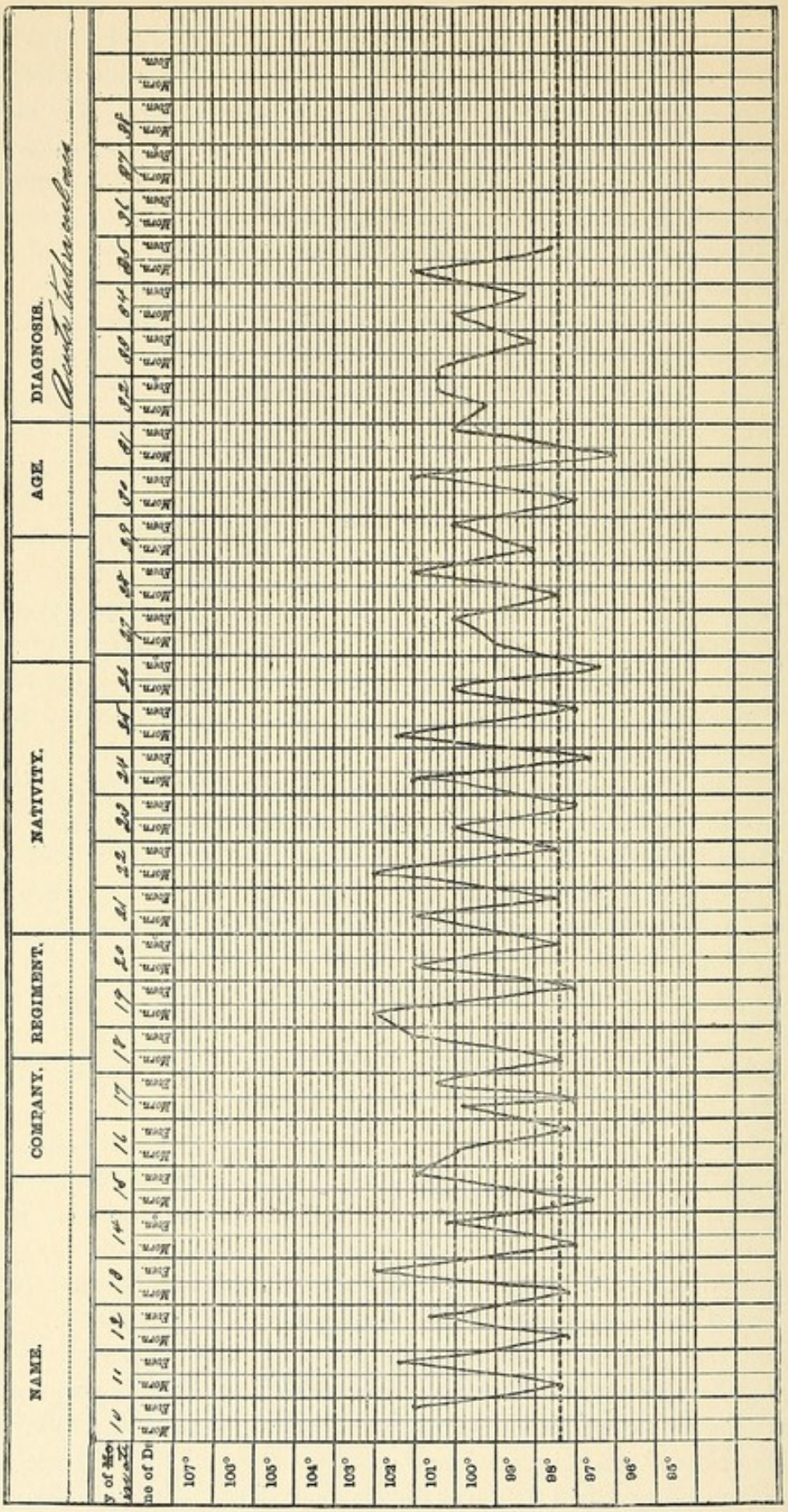

CHART 20.—Acute Tuberculosis of Lungs.

lesions not found in malaria. The examination of the blood for the malarial plasmodia and of the sputum for *Bacillus tuberculosis* will definitely establish the diagnosis. Not very rarely cases of tuberculosis are complicated by some form of malarial infection, and thus an examination of the blood is of great importance, as the discovery of the malarial infection and its removal will greatly benefit the patient. Such cases are usually stumbled upon accidentally while examining the blood of tubercular patients for leucocytosis, but it should be a routine practice, in malarial regions, to examine the blood of all tubercular patients, presenting chills and a temperature above 100° F., for the malarial plasmodia. (Chart No. 20.)

Hepatic Abscess.—In regions where amoebic dysentery is endemic, certain patients suffering from hepatic abscess due to the amoebae may present symptoms which closely simulate those of malarial fever; thus, there may be chills occurring at daily intervals, and a temperature curve, which, while that of sepsis, very closely simulates that of some of the forms of aestivo-autumnal malaria. The chief clinical points in favor of hepatic abscess are enlargement of the liver and tenderness over the hepatic region, while the spleen is not enlarged; the occurrence of very profuse perspiration, independently of the decline of the fever, and the history of dysentery. An examination of the blood will establish the diagnosis of malaria by the finding of the plasmodia, while in those cases in which the symptoms are suggestive of a chronic malarial infection, the absence of plasmodia or pigmented leucocytes and the presence of a leucocytosis would point to the presence of hepatic abscess. I have observed more than one case in which autopsy showed the presence of multiple abscesses in the liver of patients diagnosed and treated for malaria, so that this mistake is one that is frequently made and one that should be carefully guarded against.

Ulcerative Endocarditis.—The temperature curve in ulcerative endocarditis often resembles that of a quotidian malaria, while there may be present paroxysms of chill, fever, and sweating. Dock has published a very interesting case of this kind, the chart of which is here reproduced. (Chart No. 21.) Examination of the heart will generally suffice to determine the nature of such cases, and if not, an examination of the blood will generally settle the question at once.

Dysentery.—As has been shown, malarial infection may occur with dysentery, and the removal of the malarial element in a large proportion of such cases results in a rapid improvement in the dysenteric symptoms and their final disappearance. In view of this fact, *i.e.*, that malarial infection is capable of producing the clinical symptoms of dysentery, it is important that we be able to differentiate between these cases and true cases of dysentery, either amoebic or specific. The examination of the blood and of the faeces should quickly enable us to differentiate dysentery and the malarial fevers, and such an examination is most useful also in that it will often result in demonstrating a combination of the two diseases.

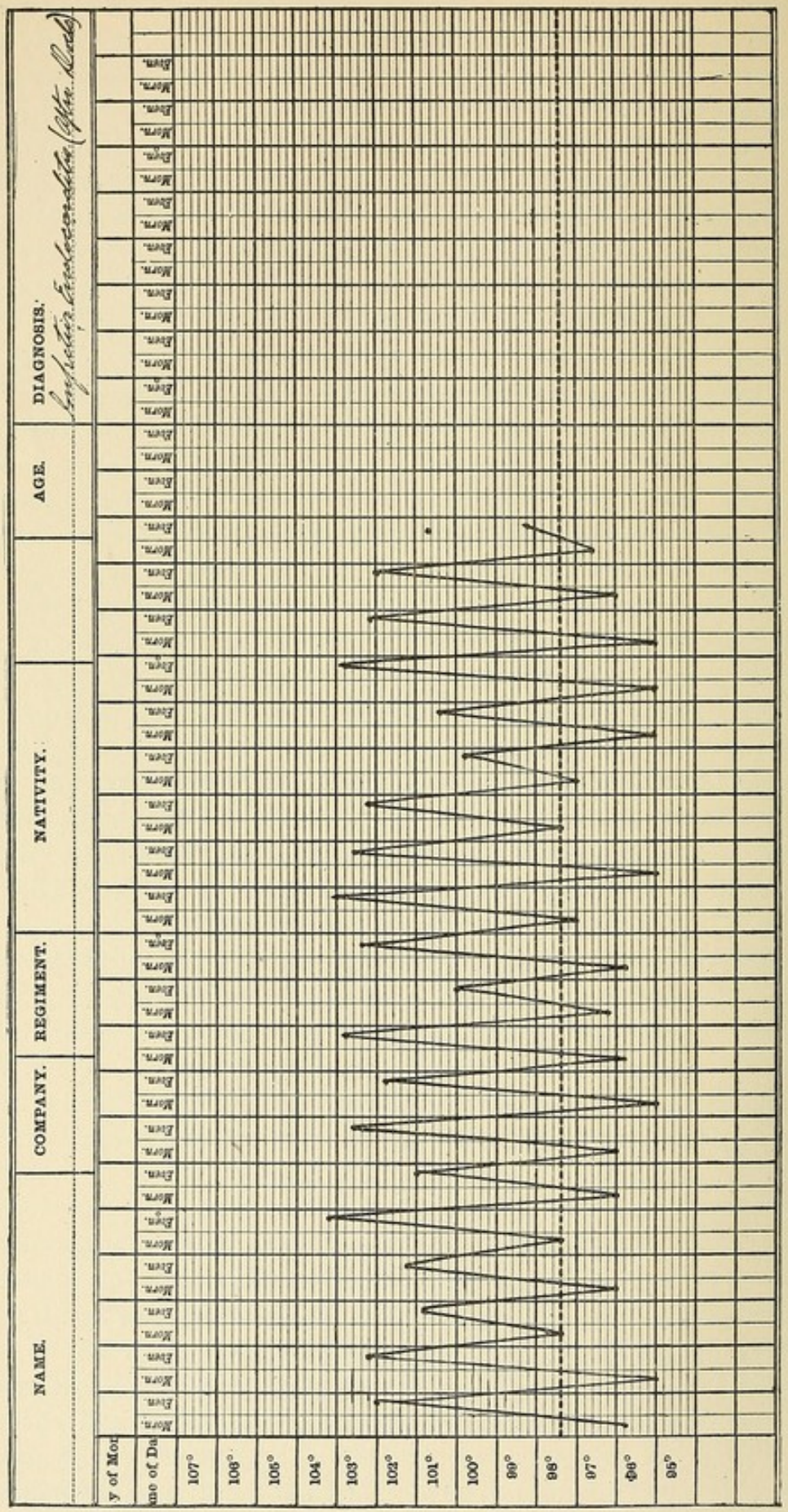

CHART 21.—Infective Endocarditis. (Dock.)

Cerebral Apoplexy.—The differential diagnosis between cerebral apoplexy and some forms of pernicious malaria, such as the comatose form, is often extremely difficult without a blood examination. Cerebral pernicious malaria is often manifested by coma, stertorous breathing, loss of reflexes, and other symptoms which so closely simulate apoplexy that a clinical diagnosis is almost impossible. The main clinical points to be relied upon in differentiating the two are the high fever in malaria, although this is not constant; the age of the patient, and the presence of splenic enlargement if the cause be malarial. An examination of the blood should be made at once in all cases of sudden loss of consciousness in malarial regions.

Sunstroke.—In tropical or subtropical regions certain cases of pernicious malaria very closely simulate sunstroke. I have already described such cases and have spoken of the fact that heat very often aggravates or brings on severe malarial paroxysms. It is therefore necessary that we be sure that an apparent case of sunstroke is not in reality a case of pernicious malarial fever, and a microscopic examination of the blood is our only means of assuring ourselves of this fact. I can recall three instances in which men were brought to the hospital supposed to be suffering from sunstroke, whose blood, when examined, was found to be teeming with malarial plasmodia. The history of no previous attacks of malaria; the lack of anaemia; and the absence of splenic enlargement will aid us in arriving at a diagnosis of sunstroke, but an examination of the blood should never be neglected.

Among other disease processes which may be confused with malaria may be mentioned *cholera*, in which the diagnosis rests upon a blood examination; disease of the *gall-bladder* and *bile-ducts*, if suppurative; *lobar* and *lobular pneumonia; Weil's disease; purpura haemorrhagica*, and *uraemia*. A microscopical examination of the blood will suffice to differentiate the malarial fevers from any of these conditions.

Leukaemia.—In very rare instances the malarial fevers may be confused with leukaemia, as in the latter disease chills and fever frequently occur, and more or less anaemia is present. Very rarely leukaemia is complicated by malaria and a microscopical examination of the blood will result in a diagnosis of both diseases. I have records of a most interesting case of this kind in the person of a young soldier who entered the hospital for the first time, suffering from a chill and a temperature of 103° F. The blood was sent to the laboratory for examination for malaria, and was found to present the typical picture of myeloid leukaemia, but upon a hasty examination no malarial plasmodia were found. However, a blood count showing 1,520,000 leucocytes per cu. mm. and only 410,000 red cells per cu. mm. indicated a more careful examination of the blood, which resulted in finding numerous tertian plasmodia, thus proving that the symptoms present were indeed malarial in character, and that the patient was in addition suffering from leukaemia, which had not been suspected. The spleen in this case reached to the umbilicus, but had never occasioned the man any trouble. The very great reduction in the red corpuscles is of interest, being

produced by the combined action of the leukaemia and the plasmodia. The elimination of the malarial infection resulted in a rise of the red blood count to over 2,000,000 cells per cu. mm.

It is from the study of such cases as this that we realize the importance of a blood examination in every febrile condition, and with the improvement in our microscopical methods, the reduction in the cost of microscopes, and the opportunities given every physician to master the technic of blood examinations, it may be truly said that he who to-day loses a patient from malarial fever because of inability to recognize the disease, bears upon his shoulders a heavy weight of responsibility which no regret will lessen.

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CHAPTER III.

The Prophylaxis of the Malarial Fevers.

The subject of prophylaxis in the malarial fevers is of the very greatest importance, for these fevers are preventable, and since the discovery of the plasmodia and the method of the transmission of these parasites by the mosquito, we are in a position to control the spread of fevers of malarial origin. Until recently we were ignorant of the source of the infection in malaria and could do but little toward prevention, but we now know the etiological factors concerned in the production of the malarial fevers and their method of transmission, and we also know that proper methods of prophylaxis have already resulted in the disappearance of the infection from numerous localities. It is not too much to believe that, in time, the malarial fevers will be as rare as are now some of the acute infectious fevers, provided we maintain and extend the present prophylactic methods in use against this class of fevers.

Man and mosquitoes are, so far as we know, the only sources of malarial infection, and the mosquitoes have to become infected from man; it therefore follows that if it were possible to destroy all mosquitoes capable of transmitting malaria or to destroy all plasmodia infecting man, we would be able to cause the disappearance of these fevers, but as this is impossible, we must depend in prophylaxis on methods directed both toward the destruction of the mosquito and the destruction of the plasmodia, remembering that while it will be given us in many instances practically to rid certain localities of malaria, in many others the most that we can hope for, because of local conditions, is a distinct reduction in the number of cases. The success of malarial prophylaxis is very largely a question of local conditions and the assistance given by the local and governmental authorities.

The prophylactic methods at present in use against malaria consist in:

1. The prevention of the development of the plasmodia in man and the destruction of the plasmodia in infected individuals. Both these aims are accomplished by the administration of quinine, *i. e.*, quinine prophylaxis.
2. Destruction of the mosquitoes transmitting malaria.
3. Protection of man from the bites of mosquitoes.
4. Education of the public regarding malarial prophylaxis.

In order to be most successful all of the methods mentioned should be employed in prophylaxis, although in certain localities it may be found possible to achieve success by attention only to mosquito destruction or to quinine prophylaxis, while in others we may have to rely chiefly upon quinine prophylaxis because of the manifest impossibility of destroying the breeding-

places of mosquitoes. If possible, however, we should employ all of the methods of prophylaxis mentioned, as by so doing we will more quickly attain a successful result.

1. **The Destruction of the Plasmodia.**—It is obvious that if we can destroy the plasmodia in infected individuals or prevent their development we will be successful in preventing malaria, as it will be impossible for mosquitoes biting such individuals to become infected. This fact is the basis of quinine propyhlaxis, which consists in the administration of the drug to all individuals harboring the plasmodia and to all individuals exposed to the bites of mosquitoes belonging to the Anophelina. We know that quinine is capable of destroying the malarial plasmodia in the blood of man and that it is most effective in the younger stages of development of these parasites, but that in all stages, with the exception of the *gametes*, it is capable of interfering with the life cycle in the human body and eventually destroying it. The fact that quinine has, so far as we know, no effect upon the crescentic *gametes* of the aestivo-autumnal infections, and probably none upon the *gametes* of tertian and quartan infections, renders quinine prophylaxis uncertain and makes it essential that we also direct our methods toward the destruction of the mosquito.

The advocates of quinine prophylaxis, such as Koch, have claimed that by this method *alone* it is possible to rid a community of malaria, but practically this can only be true in very exceptional localities, where the universal use of the drug can be enforced. That such enforcement would eventually render the occurrence of malaria impossible is undoubtedly true, as the development of the *sporozoites* inoculated by mosquitoes would be rendered impossible by the prophylactic dose of quinine, and no new mosquitoes could become infected. In addition, those already infected would be harmless. As a matter of fact, however, such results could only be obtained by the administration of quinine for a long period of time to every individual in the infected locality, and the prophylactic use of the drug would have to be continued indefinitely, for as long as *Anopheles* mosquitoes are present so long is there danger of the spread of malarial infection from imported cases of the disease. While it is unwise, as has been shown by experience, to depend wholly upon quinine prophylaxis, it is a fact that the use of the drug in this manner is of the greatest value and should never be neglected. This method has now been tried for years and the data on hand concerning its efficiency prove conclusively that it is of prime importance in the prevention of the malarial fevers.

The authorities differ as to the dose of quinine to be administered in prophylaxis and the best time for its administration. Koch believes in using 1 gm. (15 grains) administered upon every eighth and ninth day; Laveran, 0.4 to 0.6 gm. every 12 days; A. Plehn, 1 gm.once a week; Laborde, 0.1 to 0.3 gm. daily; and Zieman advocates 1 gm. given upon every fourth day. The method recommended by Koch has been adopted by many observers. He claims to have secured better results by it than by any other method, and at Stephensort, New Guinea, he claims that he was able to entirely rid the place of malaria by

this method alone. Frosch, in Istria, found that whereas 16 per cent. of the inhabitants were infected before the use of Koch's method (407 infections), one year after the initiation of the method there were only 17 new infections, and a year after that there were none. Gosio, in Toskano, Italy, reports a decrease in the malarial morbidity from 47 per cent. to 12 per cent. with this method alone after two years' trial. In South Africa, Vagedes began Koch's method in the summer, the fever-free season. As a result he found a great decrease in the number of cases of malaria during the next malarial season. Thus, in Tutara, where the previous year, before the use of Koch's method, there had been a morbidity of 75 per cent., this season there was a morbidity of only 7 per cent.; in Kanas, previous year a morbidity of 30 per cent., this year none; in Franzfontain, previous year a morbidity of 75 per cent., this year only 9 per cent.

Other authorities have not secured as good results with this method as with the daily administration of quinine in smaller doses or administered in larger doses at more frequent intervals. Ollwig has shown that in uncivilized communities, such as Dutch East Africa, such a method as Koch's is impracticable as it is impossible to administer quinine to all of the inhabitants, or even to all who harbor the malarial plasmodia. Zieman considers the method useful but not to be depended upon alone, and this opinion is also held by Manson and A. Plehn. In considering the results attained by those who advocate the method of Koch, it should be remembered that the percentage of malarial infections varies very greatly, even in badly infected regions, from year to year, and also that the success of the method depends upon how many of the inhabitants of a given locality have the resistant *gametes* in their blood, and the number and species of the Anophelinae present.

Zieman recommends the administration of quinine as a prophylactic in doses of 1 gram every fourth day, and if quinine be disagreeable in its effects that euquinine in doses of 1 gram be substituted. He has shown that by the use of this method not only is the number of new infections greatly reduced, but that haemoglobinuria is not so apt to occur in those taking the quinine as it is in those who have not taken the drug. Zieman does not believe that in regions where pernicious forms of malaria occur Koch's method is sufficient, as he claims that the dose of quinine is too small if given only upon the eighth and ninth days.

Duncan, from his experience in the prophylactic use of quinine in large military commands, concludes that quinine, in daily doses of 0.2 grm. to 0.6 grm., reduces the admissions to hospital from malaria over one-half, and in regions where only tertian and quartan infections are found, I have demonstrated that daily doses of 0.15 grm. of quinine are sufficient to prevent malarial infection in the vast majority of instances. At Camp Stotsenburg, in the Philippine Islands, where nearly 36 per cent. of the command, a regiment of cavalry, entered the hospital with malaria during the malarial season, I recommended the prophylactic use of quinine, the drug being administered every seventh day in doses of 1 grm. This method was used for several months and resulted in a

diminution of over two-thirds in the malarial infections entering the hospital. At this post every other prophylactic method was used previously to the use of the quinine, such as destruction of mosquitoes, use of mosquito bars, etc., but only when to these methods was added the prophylactic use of quinine did we secure the fullest measure of success in combating malaria. Since using the method of quinine porphylaxis I have found that the best results are secured by administering the drug in doses of 0.6 grm. (10 grains) upon retiring, every third, sixth, and ninth days for two weeks, and then the same amount upon every fifth day thereafter. The object of giving the drug more frequently for a period of two weeks is to destroy any plasmodia that might have been present at the time the quinine prophylaxis is instituted.

The most important contribution to the subject of quinine prophylaxis has been given us by Celli, as the result of the work of the Italian Society for the Study of Malaria. He states that in Italy it has been found practically impossible to prevent recurrences in all malarial infections, and that, therefore, it is necessary to prevent the malarial infection itself. In order to do this he relies mostly upon quinine prophylaxis, although all the other methods of prophylaxis are used faithfully by the society. As the result of their experience he believes in the daily administration of quinine as a prophylactic, in average doses—0.4 gm. of the bisulphate, hydrochlorate, or bihydrochlorate to adults; 0.2 gm. of the same salts for children, or 0.3 gm. of the tannate of quinine, in all cases compounded with sweet chocolate, thus disguising the bitter nauseating taste. Where the malarial infections are of very severe character he recommends the daily administration of 0.5 to 0.6 gm. Celli says: "He who takes quinine every day, and therefore has always a supply of quinine in the blood stream, can undergo with impunity inoculations of blood full of malarial parasites, and can expose himself with little or no danger to the bites of infected mosquitoes."

He also says: "The unanimous agreement of both the doctors and patients during these last years have convinced us more and more that this daily quinine treatment diminishes notably the recurrences, causes the perniciousness to disappear, prevents cachexia, and very frequently the primary infections, and at least renders the fevers milder and more readily curable by simply increasing the quinine for a few days to the therapeutic dose and then returning to the prophylactic dose."

"Hence it is that from the Agro Romano, where we made our first experiments, *the daily use of quinine, which is as necessary as daily bread in the districts and months of malaria*, has to-day extended to every malarious province of Italy, and it is extending more and more among the rural populations, the State employes living along the railways, and in the army. Thus in Italy (where we have employed it from 1899), Algeria, and Russia it has been proved to be the most suitable method for guaranteeing health and the power of work to man even in the most desolate malarious regions."

These eloquent words of Celli speak conclusively of the value of quinine

prophylaxis in malaria, but it is only because the Government supported the Italian Society by the state issue and sale of quinine that such results have been possible. Thus in Italy the state sells quinine to those who can afford to pay for it, at the minimum price; workers of every kind have quinine issued to them gratuitously for the treatment of malaria, at the expense of their employers; workers of every kind have quinine issued to them gratuitously for prophylaxis, at the expense of the State; and, finally, the poor have quinine given them gratuitously. As Celli says, these laws conflicted with many private interests, but were, nevertheless, enforced, and to-day Italy has the honor of pointing out to the world the proper legislative control of a disease that has made her lands barren in the past and has destroyed countless thousands of her inhabitants.

The following table, given by Celli, illustrates the results obtained by quinine prophylaxis in Italy, and also demonstrates that the state has profited not only by the saving of the lives of thousands of its citizens, but also financially. It should be stated that the profit made by the state from the sale of quinine is expended in the prevention of malaria in other ways, as in drainage works, etc.

STATE QUININE AND MORTALITY FROM MALARIA.

Consumption of state quinine		Mortality from malaria		Net profit of administration of state quinine in lire
Financial year	Kilograms sold	Solar year	Deaths	
1895	0	1895	16464	0
1896	0	1896	14071	0
1897	0	1897	11947	0
1898	0	1898	11378	0
1899	0	1899	10811	0
1900	0	1900	15865	0
1901	0	1901	13861	0
1902–3	2242	1902	9908	34270
1903–4	7234	1903	8513	183039
1904–5	14071	1904	8501	183382
1905–6	18712	1905	7838	293395
1906–7	20723	1906	4871	462290

The above table shows that while from 1895 to 1902 an average of 13,000 individuals died annually in Italy from the malarial fevers, since the introduction of quinine prophylaxis in 1902 the mortality has steadily declined until in 1906 it was less than 5,000 per annum. Who can doubt the efficacy of this method of prophylaxis when such evidence as this is presented and how small any pecuniary out-lay would be, placed beside the thousands of lives which

have been saved by the free distribution of quinine in Italy. It is, however, cheering to observe that the state has profited financially through the sale of the drug to those able to buy, and that in reality thousands of lives have been saved at actually no expense to the state. The experience of Italy well illustrates the fact that no state can stand to lose financially by caring for the health of its inhabitants.

Celli claims that the issue of quinine in 1905 saved no less than 7,500 lives, and he states that of 59,340 persons taking daily doses of four centigrams of quinine, only 5.8 per cent. developed malaria, including both initial infections and relapses. In the south of Italy, where malaria is most severe, the percentage of infections has been reduced from 80 per cent. to 18 per cent.

Bettinetti, in the commune of Milan, used daily doses in 3,453 cases, of whom only 4 per cent. developed malaria, and Brignoni and Algona found that by using as small a daily dose as 20 centigrams they were able to prevent infection in most of those experimented upon. Thus of 80 persons who took this daily dose none developed malaria, while of 175 who took the same dose at irregular intervals, 13 developed the fever. Of 50 individuals who did not take any quinine, 31 developed malarial infections. From the evidence adduced I believe that it is impossible to deny that quinine prophylaxis in malaria is of the greatest value, but it should be remembered that we cannot depend upon this method *alone*, except in very exceptional instances, and even those who have used it most extensively have also used the other prophylactic methods known to be of service, such as destruction of the mosquitoes, protection from mosquito bites by screening, isolation of malarial cases, and avoidance of notoriously infected regions. It is not too much to say, however, that unless quinine prophylaxis is used we will not be successful in our efforts at prophylaxis in most localities, and therefore this method should never be neglected.

2. **Destruction of Mosquitoes.**—One of the most valuable prophylactic measures we possess against malaria is the destruction of the insect which transmits the disease, *i.e.*, the mosquito, and in suitable localities this measure may in itself be sufficient to rid the locality of malarial infection. Generally, however, it will be found that it is practically impossible to entirely rid a locality of mosquitoes, and while we should do our utmost in this direction, we will have to depend also upon other prophylactic measures if we expect to achieve success in our endeavors. Only to one who has attempted it can the almost hopeless task of exterminating mosquitoes in many regions, especially in the tropics, be appreciated, and in many localities it is impossible of accomplishment. This being so, it is evidently useless to expect to rid a locality of malaria from which the mosquitoes cannot be eliminated, unless the infection is first stopped among the inhabitants; and it appears to me that the greatest hope of success in combating malaria in such localities lies in the distribution of quinine to the inhabitants. On the other hand, it has been proven in a few instances that the destruction of the mosquito alone was sufficient to cause a practical disappearance of malaria.

The success of mosquito extermination depends entirely upon local conditions as regards terrain, the size of the infected territory, and climatic changes.

As examples of the success attending the destruction of mosquitoes in the prophylaxis of malaria may be mentioned the following:

At Ismailia, a town of 6000 inhabitants, upon the Suez Canal, the prophylaxis of malaria was undertaken in 1902, by the destruction of mosquitoes. In 1900 there had been over 2,000 cases of malaria in Ismailia and the results attending mosquito destruction are seen from the following figures:

Years,	1900	1901	1902	1903	1904	1905
Cases,	2250	1990	1548	214	90	37

At the beginning of 1906 Ismailia was declared to be free from malarial infection, and Pressat, who has reported these results, claims that he was able to effect the greater part of the work, as regards destruction of the mosquitoes, by a mosquito brigade of only four men. Quinine prophylaxia was used also at Ismailia.

The effects of mosquito destruction upon malaria is brilliantly illustrated by the campaign against these insects carried on at Klang and Port Swettenham, in the Federated Malay States, by Watson and Travers, and reported by them and by Ronald Ross. The following figures show the diminution in malaria after mosquito prophylaxis was instituted.

Years,	1901	1902	1903	1904	1905
Cases,	610	199	69	32	23

The mosquito campaign was commenced in 1902.

The results achieved by Col. Gorgas, of the U. S. Army, in exterminating the mosquitoes of Havana will always stand as a monument to the efficiency of this method of prophylaxis against yellow fever and malaria, as is shown by the following figures, the mosquito campaign commencing in 1900:

Years,	1895	1896	1987	1898	1899	1900	1901	1902	1903
Yellow Fever,	552	1385	745	128	122	302	5	0	0
Malaria,	206	450	811	1907	909	325	151	77	51

The results secured upon the Isthmus of Panama will be discussed later.

Mosquitoes may be destroyed in the larval and the adult stage, and by *chemical*, *physical*, and *biological* methods.

Chemical methods are efficient in all stages of development of the insect, and many substances have been experimented with in the hope of obtaining one which would prove efficacious, being at the same time cheap and easily obtained. Howard, in 1892, published the result of his work upon the destruction of mosquito larvae by sprinkling a thin layer of kerosene upon the surface of the water in which they breed. This method acts mechanically by preventing the larvae from reaching the air when they attempt to breathe, but it also is capable of killing the adult mosquito when in the act of depositing her eggs. It is

especially applicable to collections of water which cannot be drained and which are not of great extent. The quantity of kerosene used is approximately one ounce (30 gms.) to every 15 square feet of surface, but enough should be used to entirely cover the surface of the water. The application does not need to be renewed more than once a month in most instances, although I believe that it would be better to renew the application at least every three weeks. This method has been very extensively used in all parts of the words with very great success, and it is invaluable in rendering artificial collections of water harmless, as well as water in fire buckets and other receptacles which would prove to be breeding places for mosquitoes.

Many other chemical substances are capable of killing the larvae, such as sulphurous oxide, permanganate of potassium, hydrochloric acid, sulphate of iron or copper, corrosive sublimate, formalin, cresol, certain aniline dyes, and coal tar. Celli has experimented very extensively with various chemical agents and has found that larvicide and gallol, two aniline dyes, are very efficient, the first killing the larvae in 24 hours if added to the water in the proportion of 0.00015 parts per mille, the second in the same time in the proportion of 0.0125 parts per mille. These dyes are not poisonous to man or to animals, and if added to the water in larger amount will kill the larvae in twelve hours. He believes that these substances are superior to kerosene and that they deserve a more extended use.

The powder of the unexpanded flowers of the chrysanthemum, or pyrethrum powder, is a very efficient larvicidal substance and is easily soluble in water.

Of all the chemical agents mentioned the only ones of practical interest are pyrethrum powder, the aniline dyes, larvicide and gallol, and petroleum. Of these the most widely used has been petroleum and it is also the cheapest and probably the most generally practical, although I believe that the aniline dyes should be given a more extended trial. It is of great importance to inspect the pools which have been treated with petroleum at least every week, and see that the film of oil remains constant, as it is very apt to become displaced by currents created by winds and by the movements of aquatic animals. It will not infrequently be found impossible, in tropical regions especially, to make a very extended use of petroleum in the destruction of mosquito larvae, and in such regions, because of the luxuriant jungle growth, it is often impossible to even locate the breeding-places of the mosquitoes which abound. The experience of James, at Mian Mir, in India, where despite the most careful oiling and drainage, the *Anopheles* still continued to breed, is an example of the ill success which will attend our efforts in not a few localities.

The destruction of the *adult* mosquito is possible by means of many chemical substances, such as the fumes of burning pyrethrum powder, tobacco smoke, sulphur dioxide, eucalyptus, larvicide, and pitch, or by odors such as those from the essential oil of turpentine, camphor, musk, menthol, and nutmeg. These substances are many of them useful in houses at night, being burned or

exposed when the mosquitoes begin to appear. Thus pyrethrum powder or tobacco may be burned early in the evening in the living-rooms and bed-rooms and thus the insects present many be destroyed and many prevented from entering by the odor of these substances. The most powerful of the fumes are those from tobacco, which kill mosquitoes instantly, while pyrethrum powder produces death in five minutes. Sulphur dioxide is the most powerful of the gases, producing death instantly, and is easily generated by burning sulphur; it is much used for the destruction of mosquitoes in the holds of ships and in buildings which can be closed tightly and kept so for a sufficient period to allow thorough disinfection as regards mosquitoes. This agent is not a suitable one for household use because of the irritating character of the gas. Celli has experimented, in company with Casigrandi, upon a large number of chemical substances which may be used in the destruction of the adult mosquito, and the following table is compiled from their report.

ACTION OF CULICIDAL SUBSTANCES ON ADULT MOSQUITOES OF THE GENUS ANOPHELES.

Substances used	Time in which death occurred	
	Apparent	Real
I. Gases.		
Sulphur dioxide	Instantly	1 m.
Hydrogen sulphide	Instantly	1 m.
Ammonia	1 m.	2 m.
Illuminating gas	1 m.	2 m.
Formaldehyde	2 m.	10 m.–15 m.
II. Fumes.		
Of tobacco	Instantly	1 m.–3 m.
Of larvicide	Instantly	5 m.
Of pyrethrum powder	5 m.	1 hr.
Of valerian root	5 m.	2 hr.
Of fresh leaves of eucalyptus	3 m.–5 m.	3 hr.
III. Odors.		
Of oil of turpentine	1 m.	1 m.
Of iodoform	10 m.	40 m.
Of menthol	10 m.	45 m.
Of nutmeg	10 m.	2 hr
Of musk	30 m.	3 hr.
Of camphor	4 m.–5 m.	4 hr.–5 hr.

The great objection to the use of any of these substances is the fact that in order to be efficient the air of the room has to be saturated and only a few of them are available for habitual use on this account, as most of them are too

disagreeable to enable one with any comfort to remain in a room in which the air is saturated. Celli found a powder composed of larvicide, the unexpanded flowers of the chrysanthemum, and valerian root to be less disagreeable and more efficient than any other chemical substance for the destruction of the adult insect, one to two tablespoonfuls burned in the room in the evening stupefying the mosquitoes until morning.

The *biological* means available for the destruction of mosquitoes consist in the use of fish which will devour the larvae, the use of insects which will devour the adult mosquito, and the introduction into the breeding-places of vegetable organisms capable of destroying the larvae and nymphae. All of these methods have been used, but it must be said with but little success. The introduction of fish into certain reservoirs from which the water was used for drinking purposes, but which abounded with mosquito larvae, has been tried with partial success, the fish used being the German carp or the common little stickle-backs. The rearing of dragon flies, which destroy the mosquito in both the larval and adult stage, in ponds filled with larvae, has been suggested and tried, but with very little success. Galli-Valerio and de Jongh, in their experiments upon animals or plants that kill or impede the development of mosquitoes, found that *Triton cristatus* was very efficient in destroying the larvae, and that cultures of *Aspergillus niger* and *Aspergillus glaucus* when added to water containing the larvae quickly destroyed them. They tried the latter method with success upon natural collections of water, and it would appear that this method merits attention and experiment.

The *physical* means available for the destruction of mosquitoes and their larvae consist in the destruction of the breeding-places by drainiage, filling in of low land, and removal of shelter for the insects. The most important of all methods of destroying the mosquito larvae is that by *drainage* of the breeding-places, and this is a method which can be applied over very large areas of country in which malaria is endemic, and which has been proven to be of the greatest service in the fight against these fevers. To secure results, however, in the drainage of malarial localities we must have the support of the local and often also of the state authorities, for this method of prophylaxis calls for the expenditure of large sums of money in many instances, and to secure them the consent of the state is essential. In many regions in which malaria is endemic in its most virulent form, drainage is feasible and can be carried out with but little trouble, although the expense involved is often apparently prohibitory, but as Celli says, "such methods for the destruction of the mosquitoes, while experimentally soluble, will only be practically so when economic interests demand it." Where drainage is impossible the breeding-places of mosquitoes may be filled in with sand or loam, and it is always important in malarious localities to fill up all areas of depression in the surface of the land that cannot be adequately drained. Swampy areas, if not too large, may thus be filled in and one of the greatest sources of mosquitoes eliminated. The success that has attended the campaign against the mosquito upon the Isthmus of Panama is

due very largely to drainage and the filling in of depressions which would serve as breeding-places for the insects.

Another most important method of destroying mosquitoes is the removal, so far as possible, of all shelter such as is afforded them by jungles, long grass, luxuriant vegetation, and decaying vegetable matter along the edges of streams. The clearing of tropical jungles for a distance of at least a mile from inhabited districts; the removal of high grass from about residences; the clearing of the water of small streams are all of importance in the prophylaxis of malaria. At Camp Stotsenburg, P. I., it was invariably noted that mosquitoes increased greatly in number whenever the grass about the post was allowed to grow to any length, and that a coincident increase occurred in the number of malarial infections. The cutting of the grass was followed at once by a marked diminution in the number of mosquitoes and in the cases of malaria. At one time, on account of the lack of facilities, the grass was allowed to grow for weeks and the mosquitoes became so numerous as to be almost unbearable while the number of cases of malaria admitted to the hospital became alarming. The change brought about by the mowing of the grass was remarkable and proved conclusively the great danger of affording shelter to the mosquito.

Besides the methods mentioned the formation of mosquito brigades, as suggested by Ross, is of the greatest service in limiting malarial infection. The brigades consist of a certain number of men, the number varying with the ground to be covered, whose business it is to inspect the premises of every individual in a locality and destroy the larvae in the small breeding-places which harbor the *Anopheles*, such as domestic water receptacles, water butts, and tanks; the removal of small puddles in streets and yards as well as empty tins, jars, broken bottles, or anything in which water may collect and in which mosquitoes may breed. In the formation of such brigades the area to be covered such as a town or city, is divided into districts, to each district being assigned an overseer and a number of men, whose entire time is occupied in searching for, and destroying the breeding-places of mosquitoes. Methods similar to this were employed in Havana by Colonel Gorgas, and resulted in the almost total disappearance of the yellow fever mosquito from that city.

Garden wells and water barrels and tanks, being prolific sources of mosquitoes, should be covered with wire netting, thus preventing the laying of the eggs and the development of the larvae. If this is not practicable the surface of the water, if not used for drinking purposes, should be covered with petroleum.

The results obtained by Colonel Gorgas, of the Medical Corps of the U. S. Army, in the prevention of yellow fever and malaria upon the Isthmus of Panama by the use of the physical methods of destroying mosquitoes just mentioned, prove conclusively the value of such methods in the prophylaxis of malaria. As is well known, the Isthmus of Panama has for centuries been notorious for the prevalence of yellow fever and the most pernicious forms of malaria, and during the days of the French control of the Isthmian canal, work was rendered difficult, and many times impossible, by reason of the great

mortality of the laborers employed in digging the canal. How different has been the history of the American "occupation" of the Isthmus of Panama. To-day the canal is being built, and it is being built with a smaller sick rate than the normal one of many European and American cities, and this great difference is due entirely to the destruction of mosquitoes and modern sanitation. No greater object lesson exists to-day of the beneficent results of sanitary science than the Panama Canal. The following data illustrates what has been accomplished in the prevention of yellow fever and malaria upon the Isthmus of Panama.

As regards yellow fever the cities of Panama and Colon, once hot-beds of this disease, have been entirely free from this fever for years, and this is true also of the Canal Zone. As regards the malarial fevers, the following table, given by Colonel Gorgas, illustrates the decrease in these fevers:

Year.	Force Employed.	No. Cases Admitted.	No. Cases per Thousand.	No. Deaths.	No. Deaths per Thousand.
1905	16511	8496	514	92	5·57
1906	26705	21938	821	199	7·45
1907	39344	16709	424	138	3·51
1908	43890	12372	282	59	1·34

From this table it will be seen that despite the fact that the force employed upon the Isthmus is constantly increasing the number of cases of malaria is steadily decreasing. These results have been achieved by screening, destroying the breeding places of mosquitoes, the prophylactic use of quinine, and oiling where drainage was impracticable.

3. **Protection of Man from the Bites of Mosquitoes.**—One of the most valuable methods of malarial prophylaxis is the protection of individuals from the bites of *Anopheles*. This protection applies not only to uninfected persons, but is especially important in the case of those suffering from these fevers. Such protection may be secured by the use of screening about houses, head nets, mosquito bars, certain substances placed upon the skin, the isolation of patients suffering from malaria, and, of course, by the methods of mosquito destruction which I have already described.

Isolation of Malarial Patients in screened rooms is of the greatest importance from a prophylactic standpoint, and yet how seldom we see this precaution taken even in regions in which the malarial fevers are endemic and severe. We have seen that the mosquito is necessary as an intermediate host in the life history of the malarial plasmodia and that the mosquito becomes infected by biting an individual suffering from malarial disease. From this it is obvious that if we can place the infected individual in a position where the mosquitoes cannot gain access to him the transmission of the infection will

be impossible. Theoretically, if every individual infected with malaria could be screened from mosquitoes for a sufficient period of time these fevers would disappear, but practically the infection is of such a nature that even when no symptoms are present the plasmodia may be present in the blood and thus the mosquitoes may become infected. In aestivo-autumnal infections the crescentic form of the plasmodia (*gamete*), the very form intended to undergo its life cycle in the mosquito is very frequently present in the blood when no symptoms of malaria are noticeable, so that it is obvious that we cannot in this way entirely prevent malaria, but in the light of our present knowledge the malarial fevers should be regarded as infectious and the patient strictly isolated in a screened room, and he who neglects to thus protect the uninfected is guilty of gross negligence. Not only is this isolation of importance to those surrounding the patient, but also to himself, for if he his not protected from mosquitoes he is constantly exposed to reinfection by the bites of these insects. This form of prophylaxis should never be neglected in any locality, but is especially important in regions were the pernicious forms of malaria are prevalent.

In addition to isolation of the malarial patient, *segregation of the natives* in tropical regions has been suggested by Ross and Stephens as a measure of great value in the prevention of malarial infection among the foreign European population. I have already shown how frequent is latent malarial infection in natives of malarial localities and how often the disease is masked by other symptoms. By segregation of the natives we at once remove a common source of infection in the person of the natives suffering from a latent infection, and also protect the European from the effects of the filthy habits of the native population. The suggestion of Ross and Stephens that the European quarter should not be placed, as is common, in the midst of the native village or city in malarious localities, but should be situated at some distance, is an excellent one, for it is often impossible to secure proper hygienic conditions if we be forced to live among a native population. Unfortunately, for business reasons, it is generally impossible to do much in the way of segregation of the native, although the method is applicable in the establishment of military posts and camps.

The *screening* of all dwelling-houses in malarial regions is a measure which has resulted in infinite good as regards the prophylaxis of malaria, and one that should be insisted upon by every sanitarian. The screening used should be of copper wire if possible, containing 11 wires to 2 cm. of surface. The use of wire screening other than copper is more expensive in the end, as such screening quickly rusts and becomes useless. If other screens be used the netting should be covered with two coats of good paint. The experiments of Sambon and Low, repeated by many others, prove conclusively that even in the most malarious regions the infection may be escaped by living in properly screened houses. Sbacchi has shown that, in the case of the employee's of the Sicula Occidentale Railway in Italy, those protected by living in mosquito-proof houses suffered but little from malaria, while those not so protected developed

the disease in almost every case. Of 641 persons living in screened habitations, only 4.8 per cent. developed malaria, which corresponds to the results obtained by quinine prophylaxis, and it is probable that had both methods been used the malarial percentage would have been almost nil. The barracks of troops serving in malarial localities should be carefully screened, for this will not only protect them from malaria, but also from yellow fever and dengue. The latter disease has been proved by Graham and Ashburn and myself to be transmitted by *Culex fatigans*, and our work has been confirmed by Phelan and Nichols, so that screening of the barracks of troops or dwelling-houses in infected localities offers a large measure of protection against the malarial fevers, yellow fever, dengue, and filiariasis. Probably no one sanitary measure which can be accomplished at so little cost is productive of so much good and protects against so many diseases as does the screening of buildings against mosquitoes.

In conjunction with the screening of houses and barracks the use of the mosquito bar for the bed, and the head net and gloves for wear when obliged to be out at night, are very valuable prophylactic measures. In houses or barracks which are not screened, the use of the mosquito bar for the bed should never be neglected, and it is also well to provide a small mosquito-proof compartment, either in a room or upon the porch, for use in the late afternoon and evening. The use of the mosquito bar has very greatly reduced the number of cases of malaria in our posts in the Philippines and Cuba, but strict attention must be paid to the enforcement of the use of this bar in military commands, as the soldier generally dislikes to sleep under it on account of the heat. An inspection of the barracks at night after the men have retired will generally demonstrate that many of the men are not using the bar or that it is improperly used, and such inspections are necessary if we are to secure good results from this method of prophylaxis. When mosquito bars are used they should be large enough to be suspended several feet above the bed, and should be placed in position and tucked beneath the mattress early in the evening, and examined before retiring in order to see that mosquitoes have not gained an entrance. The mosquito bar for protection of the bed is an absolute necessity in malarial regions, and should always be carried by the traveler in such regions. To neglect its use is to invite infection.

By the use of the methods mentioned for the protection of man from the bites of the Anophelinae, especially by the screening of barracks, Procaccini, in Sardinia, reduced the number of cases of malaria among the troops from 70 per cent. to 57 per cent., in one season, and later the percentage was reduced to less than 20 per cent. In Formosa, Tzuzuki protected 115 soldiers by screening their barracks from Sept. 21 to Dec. 8, and not a case of malaria developed, while in the same time among 717 soldiers not so protected there developed 251 malarial infections. Head nets were used during the day and the men were confined to the barracks after dark.

This experiment of Tzuzuki's shows what may be accomplished by a rigid enforcement of the use of screens in the prophylaxis of malaria, but it

is doubtful if our soldiers would consent to being confined to their barracks as did the Japanese. Nevertheless, great good may be accomplished by as rigid an enforcement as possible of the use of the mosquito bar, and in the tropics and in all malarial localities our military barracks should be thoroughly screened.

The use of punkas and of electric fans is of service in keeping mosquitoes away by keeping the air in motion, while the burning of pyrethrum powder or larvicide is efficient in small rooms, stupefying the insects so that they are unable to bite. Everyone who has lived in malarial regions is aware of the protection afforded one when smoking a cigar or pipe, a protection which really constitutes the strongest argument for the use of tobacco in the tropics.

A limited amount of protection is afforded against mosquito bites by applications to the skin of such substances as oil of citronella, oil of eucalyptus, camphor, and petroleum, or covering the skin with bland ointments, which prevent the mosquito from biting by reason of mechanical interference. Mense recommends a solution of quinine and glycerine, 1–1000 rubbed upon the skin, as an efficient protective. All of these substances are more or less unpleasant and the protection afforded is evanescent, so that they are really of but little practical value in the prophylaxis of malaria.

4. **Education of the Public Regarding Malarial Prophylaxis.**—As so many of our best methods of prophylaxis against malaria are dependent upon the public support, because of their financial and social aspects, it is essential that for their success, the public be informed as to their nature and what is expected to be accomplished by their use. In Italy this has been accomplished by the Society for the Study of Malaria to such an extent that there is probably no one so ignorant in that country as to doubt the efficiency of the methods already instituted for the suppression of malaria, or who does not know why they were instituted, and how they are proving successful. The example of Italy may well be followed by every state in which malaria is endemic, for only by educating the public can we hope to fight a winning battle against these infections. Thus the education of the public is a powerful means of prophylaxis against malaria, for upon the response of the public, both financially and socially, must we depend for the sinews of war.

Besides the more important prophylactic measures which have been mentioned, there are certain measures which may be taken by the individual which will assist in protecting him from malaria. Fatigue, exposure to rain and to the sun, excessive indulgence in alcoholics, and excesses of every kind should be avoided in malarial regions, for these all deplete the natural resisting powers of the individual and render him more liable to infection. In traveling, the season of the year in which the malarial fevers are most prevalent should not be selected, if possible, and the journeys should be made in the daytime. In the selection of camp sites and sites for building, high, well-drained land should be chosen, and the vicinity of swamps and collections of water carefully avoided. The drinking-water should always be boiled, for, while malaria is not transmitted

by water, this measure may prevent other diseases which would so weaken the individual as to render him an easy prey to infection. The prophylactic use of quinine and the use of a mosquito net at night should never be neglected by the traveler in malarial regions.

General Summary.—The methods which have been found serviceable in the prophylaxis of malaria may be briefly summarized as follows:

1. The prophylactic use of quinine, in daily doses of from 0.12 to 0.30 gm. (2 to 5 grains), according to the severity of the malarial infection in the locality in which this method of prophylaxis is practiced. The administration of quinine to all natives, both infected and uninfected, is a most valuable measure, but requires governmental control, which, in many places, we are unable to secure.

2. The destruction of the breeding-places of mosquitoes by drainage and filling in, and the destruction of the insects by other methods which have been described.

3. Protection of man from the bite of mosquitoes, secured by screening all buildings in which he lives or works; the use of mosquito bars; head nets, and gloves; and of various fumes and applications to the skin.

4. The avoidance of all excesses and of exposure of the person to rains, the tropical sun, and to physical hardships.

5. The education of the public to the importance of the prevention of the malarial fevers.

6. The segregation of the natives in malarial regions; a simple and very efficient measure, but one that can be carried out only in rare instances because of political, business, and social reasons.

The method of prophylaxis suggested by Kuhn, which consists in producing immunity to malaria by the injection of horse serum from horses immunized to "horse pest" is, at the present time, of no practical importance. While he claims that the injection of such serum kills the plasmodia and produces immunity, his results have not been confirmed, and it is very problematical if they will be in the future.

The Existence of the Plasmodia Outside Man and the Mosquito.—As to whether the plasmodia of malaria may exist in any form outside of man and the mosquito our knowledge is very limited, but such as it is it would appear to prove that the parasites cannot so exist. Schaudinn has demonstrated that the *sporozoites* are very delicate, degenerating when placed in water, or in blood serum removed from the human body, and his experiments would appear to prove that malaria cannot be transmitted by water containing mosquitoes infected with the malarial plasmodia. More work should be done along this line, however, before we can be sure that malaria is not transmitted save by the mosquito.

So far as we know, the plasmodia of malaria do not occur in any of the lower animals, although plasmodia have been found in bats and monkeys which very closely resemble the human parasites in morphology. Dionisi has de-

scribed three species occurring in bats, but they may be easily differentiated from those occurring in man. Koch found a plasmodium in monkeys which resembles somewhat *Plasmodium vivax* of man, but this organism could not be transmitted to man nor could human malaria be transmitted to monkeys. Richard, Di Mattei, Fischer, and Koch have all endeavored to transmit the malaria of man to monkeys, but without success. Koch has demonstrated that it is impossible even in the case of the anthropomorphic apes; he experimented upon three orang-outangs and three *Hylobates agilis*, injecting both the blood of patients suffering from tertian and from aestivo-autumnal malaria, but without being able to produce the slightest symptom of infection, while the blood of these animals remained free of the plasmodia. It would appear, therefore, that the conclusion is justified that the plasmodia of human malaria are found only in the blood of man and in mosquitoes belonging to the Anophelinae. The success attending the methods of prophylaxis which have been described is additional proof that in our fight against malaria we have only to deal with man and the mosquito.

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CHAPTER IV.

The Treatment of the Malarial Fevers.

For the treatment of the malarial fevers medicine possesses one of its few true specifics, *i.e.*, quinine, and by quinine is meant all of the derivatives of cinchona bark. This bark was introduced into Europe in 1640 by the Countess del Cinchon, who had been treated with it in South America, where it had been used for many years in the treatment of malarial fevers by the natives. In 1820, Pelletier and Caventou discovered the alkaloids quinine and cinchonine in the bark, and in 1852, quinidine was isolated. When properly administered quinine will invariably destroy the malarial plasmodia, and Osler has well said that "the physician who at this day cannot treat malarial fever successfully with quinine, should abandon the practice of medicine."

While there are rare instances in which the drug appears to be powerless to limit the course of a malarial infection, a careful study of such cases will invariably show that it has been administered improperly. For instance: Certain individuals are unable apparently to absorb quinine through the intestinal tract, but in such indivduals the hypodermic use of the drug will result in a cure of the infection. *The successful treatment of malaria by quinine depends wholly upon the proper administration of the drug.*

Historical.—The history of the discovery of the efficiency of cinchona bark in malaria and its introduction into Europe is of much interest and is well told by Markham, in his book entitled "A Memoir of the Lady Ana de Osorio, Countess of Cinchon," published in London in 1874. Regarding the discovery of the value of the drug, Markham, says: "In 1638 the Countess of Cinchon, the wife of the Viceroy of Peru, lay very ill with tertian fever at Lima, the capitol city. The news was carried to Canizares, then Corregidor of Loxa, a town among the Andes, in the present Ecuador. Though the natives of Peru were unacquainted with the curative power of the bark, those of the more northern-lying countries appreciated its worth, and from them Canizares obtained the secret. He therefore sent a parcel of it to the vice-queen. Her physician, de Vega, agreed to its employment, and she recovered in a short time. In 1640 the Countess returned to Spain and carried with her a large quantity of the precious bark, which she distributed about her native place in the vicinity of Madrid. De Vega followed and brought likewise a large amount of the bark to Spain, which he sold at Madrid for a hundred orrales a pound. The Countess employed the bark so extensively that for a long time it bore the name 'Countess's Powder' (Pulvis comitissae)."

Although the value of the bark was proven beyond doubt, it was many years before it was used in general practice. The bigotry of the learned of the day refused audience to a remedy discovered by savages, and those using it were even subjected to religious persecution. About the latter half of the seventh century the bark was adopted by the Jesuits and was used by them in the treatment of fevers, being known at that time as Jesuits' bark, but "it had still to encounter the sneers of the learned and the hate of bigots, and it was not until an English quack succeeded in curing by its means men of high rank that fashion broke down the prejudices which reason could not remove."[1]

Medicinal Treatment.—It is essential that every case of malarial fever be thoroughly treated with the specific, quinine, both from a therapeutic and prophylactic standpoint. The mild intermittent malarial infections, such as the tertian and quartan, tend toward spontaneous recovery, but while this is true in many instances, it should be remembered that even these infections may become malignant, and even if they do not, the occurrence of repeated paroxysms results in a diminution of the vitality of the patient, as is evidenced by the anaemia which invariably accompanies such repeated attacks. Added to this we have the important fact that every malarial patient is a source of infection to others unless the plasmodia be rendered harmless, so that we must admit that every malarial infection, no matter how mild in character, should be treated medicinally and not be left for nature to cure.

In considering this portion of our subject it may, for convenience, be divided as follows:

1. The action of quinine upon the malarial plasmodia.
2. Choice of preparation.
3. Time of administration.
4. Methods of administration.
5. The amount to be administered.
6. Contraindications and substitutes.

1. **The Action of Quinine upon the Malarial Plasmodia.**—That quinine is a specific in the malarial fevers is proven by its action upon the malarial plasmodia. The drug exerts its beneficial action upon malarial infections by directly destroying the plasmodia, a fact first proven by Binz in the case of some other protozoa, and repeatedly confirmed by other investigators as regards the malarial plasmodia.

Although a considerable amount of research has been devoted to the action of quinine upon the plasmodia of malaria, reference to the reports of the various investigators who have been so engaged reveals the fact that much confusion still exists regarding the exact effect of this drug upon the plasmodia, and, therefore, the best time for its administration in the treatment of the malarial fevers. This is well illustrated in the following quotation from Manson[2] who, in speaking of the action of the drug, says:

[1] National Dispensatory, 5th Ed., p. 1352.
[2] Tropical Diseases, 4th Ed., p. 124.

"In what way quinine acts has not yet been satisfactorily explained. Some, reasoning from the toxic influence this drug exerts on many kinds of free amoebae, say that it acts in malaria in the same way; that is, as a direct poison to the parasite. They support this view by pointing to the degenerative changes, as evidenced by imperfect staining reaction, exhibited by such parasites as persist in the blood after administration of quinine has been commenced. Others maintain that it acts in stimulating the phagocytes, the natural enemies of the parasite. Some experimentalists, allege, on the other hand, that it paralyses the white corpuscles. It is said by some to be most effective against the free spores and the very young intracorpuscular forms, but inoperative against the more mature parasites; hence they advocate giving it early in the parasitic cycle. Others, on the contrary, maintain that it is operative only on the large intracorpuscular forms, and therefore advocate its use at a late stage of the cycle."

Much confusion which exists regarding the action of the drug upon the plasmodia is due, I believe, to the staining methods employed by various observers, many of which were imperfect, and to the interpretations arrived at from them. In my own work I have used the modified Wright's stain already described, by which method the chromatin of the nucleus of the parasite stains a brilliant red, the protoplasm a robin's-egg blue, while the vesicular portion of the nucleus remains unstained. The method is uniform in its results and in the great number of specimens examined the morphology of the plasmodia after the administration of quinine was always the same for the various periods in the life cycle of the organisms.

While stationed at Camp Stotsenburg, P. I., in 1905, where all varieties of the malarial fevers were prevalent, I spent several weeks in studying the effect of quinine upon the malarial plasmodia, in order to determine, if possible, the actual effect of the drug upon the various species of plasmodia, and therefore the best time to administer quinine in treating the malarial fevers. The conclusions arrived at are the result of the examinations of a very large number of both fresh and stained specimens of blood after the administration of quinine was begun, and they represent, I believe, the exact action of the drug upon the various species of malarial plasmodia in all stages of their human life cycle.

Historical.—Before considering the results of my studies, the following historical summary is of interest: Binz, in 1867, was the first to interpret the curative action of quinine in malaria as being due to its effect directly upon the cause of the disease, which he concluded to be some low form of animal life. In support of his position he instanced the effect of solutions of the drug upon many species of infusoria. In 1881 Laveran demonstrated that a 1–1000 solution of quinine caused the immediate cessation of the movements of the plasmodia when added to a preparation of malarial blood under the microscope and asserted that "it is because it destroys the parasite that quinine causes the disappearance of the manifestations of paludism."

The Tertian Plasmodium.—Golgi claimed that the action of quinine was most marked upon the tertian plasmodium, even the adult forms being affected by it. His studies were made upon fresh blood and the changes produced by the drug, as described by him, consisted in a shrinkage of the parasites, while the protoplasm became coarsely granular and opaque. The segmenting parasites

were shrunken and contained numerous pigment masses and a smaller number of spores.

Romanowsky, using his admirable staining method, found that in the young intracellular tertian parasites the drug caused a disappearance of the vesicular portion of the nucleus, while the chromatin stained less intensely. The adult parasites showed more marked changes, becoming round in shape, while the pigment was distributed throughout the organisms or else collected about the periphery; the protoplasm stained uniformly; the chromatin was reduced in amount, stained less intensely and the vesicular portion of the nucleus had disappeared. He found that in the sporulating bodies the segments stained uniformly, the nucleus slightly, while the unstained area was absent.

Mannaberg studied both fresh and stained specimens of blood. In the former he found that amoeboid motion became lessened, and that several hours after the administration of the drug fragmentation occurred. In the full-grown forms the pigment became immotile, while the protoplasm became more refractive and homogeneous. In stained preparations he claimed that quinine causes the chromatin to lose its power of staining and in the segmenting forms most of the segments contained no chromatin. Zieman found that when quinine is administered during apyrexia, the parasites become fragmented, but the chromatin remains normal in appearance, while if the drug be given at the time of fission this process is not hindered, even the chromatin dividing as usual.

The Quartan Plasmodium.—Antolisei, from his observations, concludes that the adult quartan plasmodium is not affected by quinine, development and sporulation occurring as usual; but in the attack following the administration of the drug, the young intracellular forms occur in much smaller numbers.

Golgi agrees with Antolisei, but found that the effect of the drug upon the young parasites varies, many being killed, while others were hindered in their development, which produced irregularities in the type of fever. He claims that the drug does not affect the adult quartan parasite.

Mannaberg found that the changes observed in the quartan plasmodia after the administration of quinine were the same as those observed in the tertian plasmodium.

The Aestivo-autumnal Plasmodia.—Baccelli observed that in aestivo-autumnal infections quinine produced an increase in the amoeboid movements, and that the plasmodia disappeared from the blood without any degenerative changes being apparent.

Marchiafava and Bignami, after a careful study of this subject, determined that quinine caused the young plasmodia to leave the infected corpuscle, and that staining showed no evidence of morphological change after the administration of the drug. They state that development is hindered, however, as shown by the non-development of pigment, thus proving that nourishment is hindered. These authors believe that quinine not only acts directly upon the plasmodia, but also modifies the erythrocyte in such a way that it becomes impossible for the plasmodium to develop within it. In conclusion they say: "Quinine acts upon the malarial parasites in that phase of their life history in which they are nourished and develop."

La Monaco and Panichi claim that the resistance of the plasmodia to quinine is greatest during the apyrexial period, and least at the approach of and during the pyrexial. In their experiments they found that the effect of the quinine varies with the strength of the solution employed, weak solutions causing swelling of the parasites and stimulating amoeboid motion; medium solutions greatly stimulating movement, resulting in the extrusion of the plasmodium from the erythrocytes; while strong solutions caused contraction and death.

Cappogrossi concludes that the exit of the plasmodium from the erythrocyte is not the result of the specific action of quinine, but is purely physical, being due to the hypotonicity of the quinine solution. He claims that quinine in an isotonic solution of sodium chloride does not cause the plasmodia to leave the erythrocytes, but results in loss of motility, while the protoplasm becomes more opaque and tinted with haemoglobin.

Personal Observations.—In considering the action of quinine upon the malarial plasmodia I shall describe the changes occurring in each species, in both fresh and stained specimens of blood.

Plasmodium Vivax (Tertian Plasmodium).—The action of quinine upon the tertian plasmodium is evident in fresh blood specimens during every stage of the life cycle in man except immediately before sporulation. The changes produced by the drug consist chiefly in a granular degeneration of the protoplasm and fragmentation, the latter being most common in the nearly full-grown parasites. To these changes should be added a great diminution in the amount of pigment in the developing forms, thus showing a marked disturbance in the nutritive functions of the organisms.

The effect of the drug varies with the time of administration and the dose, but it is effective upon all but the segmenting bodies, and therefore is curative whenever given, whether in one large dose just before sporulation or in divided doses.

If quinine is administered when the young intracorpuscular plasmodia are present the changes produced by it are an increase in amoeboid motion, followed in an hour by a decrease and finally by complete cessation; an increase in the refractive quality of the protoplasm; and finally granular degeneration of this portion of the plasmodium. During the stage of stimulation, the amoeboid motion may become very active, the pseudopodia being projected so swiftly that it becomes almost impossible to follow the process. After the cessation of motion the young plasmodia become "ring-shaped" or spherical, and much more sharply outlined than is the normal tertian plasmodium. At this stage of growth no shrinkage of the organisms was observed as described by Golgi.

If now the blood be examined at regular intervals, the quinine being continued, it will be found that the plasmodia diminished greatly in number up to the time of sporulation, proving that at every stage of their growth quinine is capable of destroying them. Although this is so, a considerable number succeed in developing and finally reproduce by sporulation, but, as will be shown in studying stained specimens, even these more fortunate organisms develop atypically, as the majority of the spores are sterile and incapable of further development.

In those plasmodia which perish prior to sporulation, quinine causes fragmentation, and eventually complete degeneration. Such fragmented parasites are very numerous in specimens of blood from tertian infections after the administration of quinine, and in those instances in which the drug has been given after pigment formation, fragmentation is the most common form of

degeneration, but is always preceded by increased motility and by an increased refractive index. Numerous erthrocytes are observed containing plasmodia which are fragmented, the fragments containing pigment in most instances. The pigment may be motile or immotile, and is collected in the form of rather large blocks or masses. The protoplasm of the fragmented organism is always more refractive than that of the normal tertian plasmodium, and generally appears coarsely or finely granular. In many instances the fragmented parasites are extruded in whole or in part from the red blood-corpuscles and thus become free in the plasma, from which they quickly disappear, and in tertian infections after the administration of quinine it is very common to find many free degenerated plasmodia in the blood. Fragmentation of the tertian plasmodium due to quinine occurs at every stage in the human life cycle of the organism up to the sporulating form, but in the latter bodies I have never observed any evidence of this process.

While fragmentation of the plasmodia is very often the result of the action of quinine upon these parasites, it does not invariably occur, for many of the plasmodia present certain changes which do not eventuate in fragmentation. These changes consist in a marked shrinkage in the size of the organism, loss of motility of the pigment, and increase in the refractive index, together with granular degeneration of the protoplasm.

Upon the fully developed tertian plasmodium prior to the beginning of sporulation, quinine exerts a marked action, causing a shrinkage of the organism, and a markedly granular appearance of the protoplasm, while the pigment becomes immotile, and is collected in large clumps throughout the protoplasm or is distributed about the periphery in small masses. Fragmentation may occur, but it is not as common as in the younger pigmented forms.

When quinine is administered just at the beginning of sporulation it produces no morphologic changes in the plasmodia, but if it has been present during the period of growth of the plasmodia it will be found that the sporulating bodies, which have evidently partially resisted the action of the drug, are smaller, appear more refractive than normal, while the number of spores is reduced.

There can be no doubt that quinine is very fatal to the young spores resulting from segmentation, while they are yet free in the blood plasma, but it is not fatal to all of them, for in every case careful examination will demonstrate that some escape, penetrate the erythrocytes, and undergo more or less complete development. This can be demonstrated even in those cases of tertian malaria which do not present clinical symptoms of the infection, *i.e.*, the latent cases.

From the changes which have been described it is evident that if quinine is administered when the blood contains the young intracellular plasmodia of tertian malaria it produces death in a certain number, while others are able to develop more or less perfectly, but are undoubtedly injured during every stage of their growth if the drug be given at regular intervals. This injury may result in death at a later period of development or by atypical development. If sporulation occurs, the spores are reduced in number, and, as will be shown in

the description of the stained specimens, most of them are sterile. Upon al forms of the pigmented tertian plasmodium until the beginning of sporulation quinine has a marked action, causing either fragmentation, shrinkage in size, or granular degeneration of the organism. The effect of the quinine upon all stages of growth of the plasmodium is most marked when it is administered in divided doses at regular intervals of time, thus keeping the blood supplied with it. If given just prior to the expected chill, in one large dose, the majority of the young plasmodia are destroyed while free in the blood plasma, but those which escape and develop present but little evidence of the action of the drug, as would be expected, for the blood is free from quinine for several hours before the administration of the next dose.

In *stained* specimens of blood containing the tertian plasmodium the action of quinine is very clearly demonstrated. The modification of Wright's method already described was used invariably, and invariably the same morphological changes were observed after the administration of this drug. From my observations I have been able to confirm many of Romanowsky's published results, but I have been unable to demonstrate that the chromatin of any of the species of plasmodia loses its staining properties, but, rather, I have found that this important portion of the nucleus stains even more intensely than normal, but that the brilliant red color is replaced by a very dark violet or almost black. While this is true it was invariably observed that the unstained portion of the nucleus had disappeared, and in those plasmodia which continued the developmental cycle, the chromatin had either failed to divide or divided imperfectly, many of the spores showing no chromatin, as described by Mannaberg. The statement of Zieman that the chromatin remains normal in appearance and divides as usual can only be true of those cases in which the quinine is administered just before sporulation, for if this drug be given during the formation of pigment the vast majority of the plasmodia which live to sporulate present either no evidence of division of the chromatin or division is imperfect, only a few of the spores showing any chromatin.

In order to study the morphologic changes occurring in the tertian plasmodia as the result of the administration of quinine it is necessary that the drug be given in divided doses to single tertian infections, the first dose just before sporulation; specimens of blood should then be taken at intervals of three hours and immediately stained. Given just before sporulation and repeated at intervals of every three hours, the quinine acts upon the plasmodia not only while free in the plasma, but also upon every stage of their life cycle in man, and it is thus possible to study the morphologic changes produced by quinine in every stage of the development of these organisms.

The young, unpigmented "ring-forms" stain very intensely after the administration of quinine, the protoplasm a much darker blue than normal, while the chromatin stains a very dark crimson, often almost black. Besides the increase in the intensity of the stain, the loss of the unstained area about the chromatin (the vesicular portion of the nucleus) is very noticeable, and con-

stitutes a most important evidence of the injurious action of the drug upon these parasites.

In tertian plasmodia a little further advanced in development, the staining reactions are the same as for the "ring-forms," but the increased motility of the plasmodia is shown in the great number and "bizarre" arrangement of the pseudopodia. Fragmentation is observed even before the formation of pigment, some of the unpigmented plasmodia being broken up into deeply stained portions, the chromatin lying in one of these portions or free near the periphery of the red cell.

After the formation of pigment, and especially after the plasmodia are from one-half to three-quarters grown, the evidence of fragmentation and extrusion of the chromatin becomes more marked. Many of the erythrocytes contained deep blue portions of protoplasm, the chromatin lying free within the red corpuscle. The latter is frequently situated at the extreme periphery of the red cell or even partly outside of it. At this stage numerous extracellular plasmodia are observed, either undergoing fragmentation or other forms of degeneration. Many of the fragments are entirely devoid of pigment, staining a deep uniform blue throughout, while some may be almost filled with blocks and granules of pigment. The vesicular portion of the nucleus is always absent, nor is there any evidence of an increase in the amount of chromatin which is so noticeable in the normal plasmodium when at this stage of development. If fragmentation be absent, the protoplasm of the plasmodium stains a very dark blue and the chromatin a dark violet or almost black. The pigment is generally collected about the periphery of the plasmodium. In many instances the chromatin is situated at the extreme periphery of the parasite or may lie partly or wholly outside of it within the erythrocyte, proving that quinine possesses the power of causing extrusion of the chromatin, thus rendering the plasmodium sterile.

Together with absence of the vesicular portion of the nucleus there is seldom any evidence of increase in the amount of chromatin and of division of the latter.

In fully developed tertian plasmodia fragmentation frequently occurs, many of the fragmented parasites being free from chromatin, but the characteristic change at this period of development in those plasmodia in which fragmentation is absent, as shown by stained specimens, lies in the fact that although the chromatin may be present and stains an intense violet, it has increased but little or not at all in amount, and division is either absent or imperfect, only two or three small masses being present, which lie close together near the periphery of the organism. In tertian plasmodia which have not been acted upon by quinine, and have reached this stage of development, the chromatin has always greatly increased in amount and is found divided into numerous masses which are scattered throughout the protoplasm. The morphology of the plasmodia at this stage of their growth indicates clearly that quinine prevents an increase in amount of chromatin and either hinders division or prevents it altogether.

At this stage the protoplasm of the plasmodium stains a deep blue and the

pigment is collected about the periphery in blocks or granules, or more rarely, distributed throughout the protoplasm in the form of fine granules or small clumps. The vasicular portion of the nucleus is always absent.

Those plasmodia which sporulate after having been exposed to the action of quinine throughout their entire cycle of development present very marked morphological evidences of the injurious action of the drug, in stained preparations. While sporulation may not be entirely prevented the majority of the spores are devoid of chromatin, and are undoubtedly sterile. The spores are also greatly decreased in number and may be distorted in shape, while in those which show the presence of chromatin the latter is in the form of minute irregular masses, very distinct from the compact spherical mass observed in normal parasites. Very often sporulating bodies are observed in which only two or three of the spores possess chromatin; in such spores the protoplasm stains a deep blue, the chromatin almost black, and there is no evidence of the vesicular portion of the nucleus. Associated with the chromatin containing spores are from six to eight, or perhaps more, deeply stained spores devoid of chromatin. In the sporulating plasmodia, the pigment, instead of being collected in a dense compact mass, as is the rule in the normal tertian plasmodium, is reduced in amount, and scattered in small clumps or granules between the spores.

From the changes demonstrated in stained specimens of tertian plasmodia after the administration of quinine it is evident that this drug, administered in divided doses, exercises a markedly injurious effect upon every stage in the human life cycle of this organism, either causing the death of the parasite at some period of its development or preventing normal sporulation by restraining the production and division of the chromatin prior to segmentation. The death of the organism is evidenced by fragmentation or extrusion of the chromatin, while the effect upon sporulation is shown by the lessened production of this substance, the limited division of the chromatin present, and the number of spores which are devoid of this essential portion of the nucleus. The loss of the vesicular portion of the nucleus is probably responsible for the changes which are observed.

If quinine is administered in one large dose just prior to segmentation and the dose is not repeated, the changes produced are the same in kind as those described, but a very large number of the plasmodia escape entirely or are but little injured. When given in this way segmentation occurs as usual, and both the sporulating bodies and the individual spores appear normal.

Plasmodium Malariae (the Quartan Plasmodium).—The changes produced by quinine in the quartan plasmodium, as shown by both fresh and stained preparations of blood, are practically the same as those described for the tertian plasmodium, and I cannot agree with Antolisei and Golgi that upon the adult quartan plasmodium quinine has no effect. In the young intracellular forms development is hindered or stopped, there being the same initial stimulation of amoeboid movement, while in the older forms fragmentation and degen-

eration occur as frequently as in the tertian plasmodium. I have not been able to observe any difference, so far as morphologic evidence goes, in the effect of quinine upon the tertian and quartan plasmodia, although it is undoubtedly true that because of greater resistance to the drug, a larger number of quartan plasmodia escape destruction at the time of sporulation. As in the tertian infections, the effect of the drug is most apparent when it is administered in divided doses at regular intervals.

Plasmodium Falciparum. Plasmodium Falciparum Quotidianum (The Tertian and Quotidian Aestivo-autumnal Plasmodia).—As the effect of quinine is the same upon both species of aestivo-autumnal plasmodia, I shall consider them together. As stated in the historical summary, Marchiafava and Bignami found that in fresh specimens, after the administration of quinine, the plasmodia assumed a discoid form and left the erythrocytes, while the motility was normal or increased. While I have been able to confirm the occurrence of the discoid shape, I have not been able to confirm their observations regarding the exit of the plasmodia from the red cells. The following observations are based upon the study of the action of quinine upon both fresh and stained specimens of blood containing the aestivo-autumnal plasmodia, including every form of the organisms except the fully developed pigmented bodies and the sporulating bodies.

In *fresh* specimens, a few hours after the administration of quinine in divided doses, the time varying with the rate of absorption of the drug, the hyaline "ring-forms" become much more refractive and sharply cut than normal while the amoeboid motion is always greatly stimulated. In most instances, the "ring-forms," owing to the great increase in the activity of the amoeboid motion, lose their distinctive form, becoming discoid or assuming irregular shapes, and not infrequently change their position in the red corpuscle very rapidly, occupying the same portion of the cell only a few seconds at a time, but I have never observed their exit from the red corpuscle.

Upon the larger pigmented forms, and pigmented "rings" quinine appears to have less effect, the only change observed in fresh specimens being an increase in the refractive index, while the outline of the plasmodia becomes more sharply defined. I have not observed degeneration by fragmentation in the aestivo-autumnal plasmodia, although it is so common in the tertian and quartan parasites.

In *stained* specimens the results of my observations are opposed to those of Marchiafava and Bignami, who claim that no morphologic changes occur in these plasmodia after the administration of quinine, and that the unpigmented parasites do not become pigmented after its administration. I have repeatedly observed pigmented forms of both the tertian and quotidian aestivo-autumnal plasmodia develop after quinine had been administered for as long as three days, while the morphologic changes produced, though not so marked, are similar to those observed in the tertian and quartan plasmodia.

In the "ring-forms," which are most easily studied, the staining capacity

of both the protoplasm and the chromatin is increased, but the unstained area surrounding the chromatin disappears. A large number of the "ring-forms" may appear normal, but careful examination will demonstrate that most of them show the loss of the vesicular portion of the nucleus and that the "rings" are distorted in shape owing to the increased amoeboid motion. In a few instances I have observed the separation of the chromatin from the body of the plasmodia, thus proving that extrusion had occurred. I have never observed fragmentation of the "ring-forms."

The changes produced in the young pigmented forms of the aestivo-autumnal plasmodia, as shown in stained preparations, are similar in every respect to those occurring in the tertian and quartan plasmodia, consisting in fragmentation, loss of the vesicular portion of the nucleus and extrusion of the chromatin.

Effect of Quinine upon Gametes and upon Intracorpuscular Conjugation.—No morphological changes occur in the *gametes* (crescents) of the aestivo-autumnal plasmodia so far as can be observed in both fresh and stained preparations, and Marchiafava, Gualdi, and Martirano have proven that the crescents are not destroyed by quinine and that they are still capable of undergoing development within the mosquito, after quinine has been administered, for long periods of time. Crescents, however, do not appear if quinine be thoroughly given during the first attack of an aestivo-autumnal infection, a fact well known to every student of the aestivo-autumnal fevers.

As regards the effect of quinine upon the *tertian gametes*, Schoo, in Holland, has demonstrated that quinine prevents the development of the tertian *gamete* in the mosquito; his experiments follow:

A case of tertian fever was bitten by a large number of *Anopheles*, all becoming infected. One gm. of quinine was then administered for three days, and 16 *Anopheles* allowed to bite, none becoming infected.

A case of tertian malaria was bitten by 10 *Anopheles* during the afebrile period, of which eight became infected. Four hours before the chill he was given 1 gm. of quinine, and six hours afterward was bitten by nine *Anopheles*, of which none became infected.

Upon the *quartan gametes* we possess no evidence showing that quinine is capable of preventing their development in the mosquito.

In both tertian and quartan infection the prompt administration of quinine during the first attack of fever will prevent the development of the *gametes*.

Upon *intracorpuscular conjugation* quinine has a fatal influence, for, after the administration of this drug, conjugating plasmodia entirely disappear from the peripheral blood and do not reappear unless the administration has been stopped, and then only after an interval of days or even weeks. Even in those instances in which the drug is given in such small doses as to injure but slightly the developing plasmodia, the conjugating organisms quickly disappear, and as the process of conjugation is undoubtedly intended to assist in maintaining malarial infection, the marked action of quinine upon it offers another explana-

tion of the efficiency of the drug in curing these fevers if it be properly given during the initial attack.

From the evidence submitted I believe that it is an incontrovertible fact that quinine is a true specific for the malarial fevers, acting directly upon the plasmodia causing these fevers, during every stage of their human life cycle, except the presegmenting stage, and that its persistent administration will invariably result in the cure of any malarial infection, provided the drug be properly administered.

2. **Choice of Preparation.**—Of the eighteen or more salts of quinine which have been used in the treatment of the malarial fevers, but a very limited number are deserving of attention, in that they are of practical use. The most useful are the sulphate and the bihydrochloride or bimuriate of quinine. Of these two salts the bihydrochloride is the more soluble, being dissolved in the proportion of 1 part to .96 parts of water, while the sulphate is only soluble in 1 to 800 parts of water. Of the two salts the sulphate is the more used, as it is much cheaper and can be procured more easily. The following table of the chief salts of quinine and their solubility will prove useful to the therapeutist, but practically it will be found that the sulphate is most useful in the vast majority of our cases of malarial fever.

Salt	Alkaloid in salt	Solubility in cold water
Sulphate	73.5 %	In 800 parts.
Hydrochloride	81.8 %	In 40 parts.
Bihydrochloride	72.0 %	In .96 parts.
Hydrobromide	76.6 %	In 45 parts.
Bihydrobromide	60.0 %	In 7 parts.
Bisulphate	59.1 %	In 11 parts.
Phosphate	76.2 %	In 420 parts.
Valerianate	73.0 %	In 120 parts.
Lactate	78.2 %	In 10 parts.
Salicylate	70.1 %	In 225 parts.
Arseniate	69.4 %	Very slightly soluble.
Tannate	20.0 %	Very slightly soluble.

For hypodermic use the bihydrochloride or bimuriate of quinine is most commonly employed, but the bihydrobromide, the lactate, and the bichloride of quinine and urea may also be used for hypodermic injection.

3. **Time of Administration.**—The time of administration of quinine in malarial infections has been the subject of much discussion, but from what we know of the action of the drug upon the malarial plasmodia it is difficult to see why this should be so. As I have shown, the drug acts upon every stage in the development of all the species of plasmodia except the presegmenting

stage and therefore it is evident that if the blood constantly contains the drug the best effects will be secured. Those who advocate the administration of quinine in one large dose just before the expected paroxysm, trusting that all of the newly developed spores will thus be killed, lose sight of this fact, and also of the fact that many of the spores escape when the drug is thus administered. While in tertian and quartan infections, in which the paroxysms occur at regular intervals, good results may be obtained by giving the quinine in one large dose during the decline in the temperature, in aestivo-autumnal infections and in irregular tertian and quartan infections the best results are obtained when the drug is given in divided doses at regular intervals, and I have found from personal experience that the latter method of administration is preferable in *all* cases of malarial infection.

It is not necessary to discuss here the many contributions to the literature of malaria dealing with this subject, but those interested should consult the valuable paper of Dock which contains a summary of the opinions of various writers upon the administration of quinine in malaria. From the studies of the action of this drug upon the plasmodia it is evident that in order to secure the best therapeutic results the drug should be present in the blood continually, and therefore it should be administered in divided doses at regular intervals of time. Given in divided doses at regular intervals the blood constantly contains a sufficient quantity to practically stop the development of the plasmodia which have succeeded in escaping it while free in the blood plasma, and recovery is thereby hastened.

The practice of giving quinine in the manner mentioned is not only justified by the morphologic changes observed in the plasmodia, but its value is proven by practical experience. Manson recommends the administration of quinine in divided doses, and many tropical practitioners have found that this is the most successful method of administration. I have at present the records of over 2,000 malarial cases (mostly in the person of soldiers of our army, returning from the Philippines and serving in the Philippines), including tertian, quartan, and aestivo-autumnal infections, in which quinine was administered in doses of 0.50 gm. every three hours until from 1.50 to 2.00 gms. were taken, and in all of these cases recovery was prompt and occurred more quickly than in similar cases in which one large dose of the drug was administered prior to sporulation. In the tertian cases it was very rarely that a second chill occurred after the beginning of the administration of the drug, although in about 20 per cent. of the cases a rise of a temperature was noted upon the day of the expected paroxysm. In the quartan cases a second paroxysm never occurred after the beginning of the administration of quinine in this way; while in the aestivo-autumnal cases, which comprised nearly two-thirds of the total number of cases, the temperature, except in two pernicious cases, reached normal in from two to three days and recovery followed. It is in the latter type of malarial infection that the administration of quinine in divided doses is especially efficient, for in this type it is generally impossible to tell the

exact time of the ensuing paroxysm, and thus it is impossible to attack the plasmodia while they are free in the blood plasma by the administration of one large dose of the drug. In these infections it is *necessary* to give quinine in divided doses of from 0.30 to 0.60 gm. (5 to 10 grains) at intervals of four to six hours until the temperature reaches normal, and to increase the number of doses if experience shows that the quantity advised is insufficient. When the temperature reaches normal the quinine should be administered in one large dose at bedtime or in smaller divided doses during the twenty-four hours. In pernicious and irregular forms of the malarial fevers, especially if due to the aestivo-autumnal plasmodia, the administration of the drug should not be delayed, but it should be given hypodermically in doses of 1 gm. (15 grains), repeated in three hours if necessary.

In tertian and quartain infections the drug should preferably be given in divided doses, but nearly as good results will be secured if it be administered in one large dose during the decline in the temperature or at the end of pyrexia. Given in this way the next paroxysm will be prevented in the majority of the cases as the drug has thus been brought in contact with the free spores upon which it acts most vigorously. In all such cases the sulphate administered in solution or in capsules will be found the cheapest and most efficient preparation. Quinine should not be discontinued, even in the mildest cases of malaria, after apparent recovery, but should be given in doses of from 0.30 to 0.60 gm. (5 to 10 grains) daily for at least a week and once a week in doses of 0.60 gm. (10 grains) for at least two months afterward. Unless some such plan is adopted recurrences are bound to occur and may lead to chronic malarial cachexia.

4. **Methods of Administration.**—Quinine may be administered by the mouth, by the rectum, intravenously, and hypodermically. Inunctions through the skin have been practised in rare instances, but are of little practical importance. In the vast majority of cases of malarial infection the administration of quinine by the mouth will be found the most practicable method of using the drug.

Administration by the Mouth.—There are comparatively few cases in which quinine cannot be administered by the mouth. In pernicious cases, in patients who appear to be unable to absorb the drug from the stomach, and in those very rare instances in which the drug so deranges the stomach as to produce grave symptoms of poisoning, quinine will have to be administered in some other way, but in the vast majority of our cases of malaria the drug may be given by the mouth. When administered in this way quinine may be given in the form of pills, tablets, wafers, capsules, and solutions. The drug should never be given in pill or tablet form unless we can be sure that these are readily soluble, and in most instances it will be found that the pills and tablets of quinine ordinarily found in drug houses are very insoluble, and therefore the use of the drug in these forms should be avoided if possible. The best form in which to administer quinine is in solution, but on account of the intensely

bitter taste this method is often inapplicable, and then we should administer it in capsules or in wafers. I have found from experience that to secure good results in the treatment of malaria quinine should *never* be administered in the form of pills or tablets, and that the best results are secured when it is administered in solution.

When solutions are used, the sulphate is most frequently employed, a drop of dilute hydrochloric or sulphuric acid being added for every 0.065 (grain) of the drug. The bitter taste of the solution may be partially disguised by the addition of yerba santa, or a chocolate syrup, to the solution. For children and for those who are very easily nauseated by the bitter taste of quinine, the administration of the drug in the form of chocolate troches containing the tannate of quinine is indicated, and in Italy the combination of chocolate with quinine has been adopted by the Government as the most palatable method of dispensing the drug to children and is the form in which the quinine issued by the Government is always dispensed.

Administration by the Rectum.—The administration of quinine through the rectum has been advocated by some authorities, but will be found most unsatisfactory in practice. This method is recommended in children, but is much more disagreeable to them than the administration of the drug by the mouth in the form of a cholcolate syrup containing it or chocolate troches containing the tannate. By the rectum absorption is very slow, a much larger dose of the drug has to be given, and rectal irritability and pain is almost certain to occur. When the drug is given in this way the dose should be one-half again as much as when given by the mouth, and should be prepared in the form of a rectal suppository. If given in solution by the rectum an enema of 150 to 250 c.c. of sterile salt solution should be given containing the dose of the drug, with from five to ten drops of tincture of opium added.

Cutaneous Inunctions.—Feuchtwanger and Rasch have advocated cutaneous inunctions of quinine in children, but this method is only mentioned to be condemned, as the absorption of the drug is so slow that but little can be expected from this form of administration in well marked cases of malaria, and we possess so many other and better methods of administration in this class of patients that cutaneous inunctions are undeserving of consideration. The chocolate tablets containing tannate of quinine will be found the easiest method of administering this drug to children, but it should be remembered that the tannate is very slowly absorbed and that the dose should be twice that of the sulphate.

Administration by the Hypodermic Syringe Subcutaneously.—In the *pernicious* forms of the malarial fevers and in those cases in which, for any reason, the drug cannot be administered by the mouth, the hypodermic injection subcutaneously of the more soluble salts of quinine, such as the bihydrochloride, the bihydrobromide, and the bichloride of quinine and urea is indicated. When these cannot be secured the bisulphate, which is soluble in 11 parts of water, may be employed for hypodermic injection. The following

solution I have found most useful in treating malaria by the hypodermic injection of quinine:

Bihydrochloride of quinine, 5 gm. (gr. lxxv)
Distilled water, add 10 gm. (℥iiss)

In this solution 1 c.c. (15 m.) contains 0.5 gm. (grs. viiss) of quinine.

In giving hypodermic injections of quinine the utmost care should be taken that everything used in the operation, as well as the skin of the patient is sterile, as abscesses and extensive necrosis of the skin is apt to occur, and even tetanus may develop after the use of a dirty syringe or a septic solution. The syringe used should be, if possible, constructed entirely of glass, with the exception, of course, of the needle, and should be boiled for 15 minutes before use. The quinine should be placed in sealed glass tubes and sterilized in a hot-air chamber. The skin over the region to be injected, preferably the back or buttock, is thoroughly cleaned with soap and water, then scrubbed with ether, and finally with alcohol, and the injection should be made deep into the subcutaneous tissues, as otherwise necrosis of the skin is of frequent occurrence. The *intramuscular* method of injection is best. If the materials used in the operation are sterile, abscess formation will not occur, but despite our greatest care there is generally much discomfort and pain following the injections and a considerable amount of induration frequently occurs about the site of the injection.

Owing to the possibility of abscess formation and the pain and discomfort arising from the injections, this method of administration of quinine should not be used save in cases in which it is essential to secure the effect of the drug rapidly, as when pernicious symptoms develop and where, for any reason, such as unconsciousness or inability to retain the quinine, it is impossible to give the drug by the mouth. The tendency of many practitioners in late years to administer quinine hypodermically in most of their cases of malaria is to be deplored, for it is but rarely that the drug cannot be administered with good results by the mouth.

After injecting the quinine solution the wound made by the syringe needle should be carefully washed with alcohol and sealed with a collodion dressing. The dose of the drug hypodermically is 0.5 gm. (gr. viiss), repeated every four hours if necessary.

Intramuscular Injection.—Koch advocates the intramuscular injection of quinine in cases of recurrent malaria and in severe cases of aestivo-autumnal infection, even though pernicious symptoms be absent. He states that the dose required is less than one-half that by the mouth and that the infection is cured more quickly and recurrences are less apt to occur.

The gluteal muscles are used for intramuscular injections, and the solution used is the same as for hypodermic injection, the same precautions being used as regards the prevention of injection. Maurer and Schüffer use the bimuriate of quinine in equal parts of water and glycerine for intramuscular injection, and claim that with this solution there is but little danger of abscess formation.

Intravenous Injection of Quinine.—To Baccelli we owe this method of administering quinine. It is indicated whenever we desire the most prompt effect of the drug, as in comatose cases; pernicious cases after one pernicious paroxysm has been succeeded by another; when the patient's strength is rapidly failing; or when other treatment has proved unavailing. Marchiafava and Bignami urge the value of this method especially in the algid forms of pernicious malaria. The following solution will be found most uesful when it is desired to give the drug intravenously:

Bihydrochloride of quinine,	1 gm. (grs. xv)
Chloride of Sodium,	0.075 (grs. iss)
Distilled water,	10 gm. (℥iiss)

This solution should be perfectly clear and the entire amount is to be injected, the fluid being luke-warm. In injecting, the veins of the forearm are made prominent by a circular tourniquet and one of the most prominent selected for the injection. The same precautions are observed regarding asepsis as described already, and the needle is introduced from below upward into the lumen of the vein. The injection is made slowly and when the entire amount is injected the site of puncture is sealed with collodion. Extreme care must be taken that no air is introduced into the vein, and that the needle is sterile, as well as the solution. The dose may be repeated if necessary. By this method the mortality of the pernicious malarial fevers has been markedly reduced and it should always be adopted in those cases which have resisted other forms of treatment or which require the immediate effect of quinine. Baccelli states that whereas before the use of intravenous injections of quinine the mortality in those cases of pernicious malaria treated by the hypodermic method of administration was 17 per cent., with his method the mortality has been reduced to less than 6 per cent., and his conclusions are confirmed by those of many other observers.

5. **The Amount of Quinine to be Administered.**—There is no doubt that we err more often upon the side of excess in the administration of quinine than *vice versa*, and in most cases of malaria too much of the drug is usually given. It is not uncommon to observe the use of from 5 to 6 grammes of the drug during the 24 hours, even in the mildest cases of tertian and quartan fever, and a general impression appears to prevail in the profession that the malarial fevers require massive doses of quinine in their treatment. The employment of the large amount mentioned above is entirely unnecessary and simply makes the patient more miserable while undergoing treatment. It should be remembered that it is as much the manner in which the quinine is administered as it is the dose, which counts in the treatment of malaria, and that the use of over 40 grains of quinine in the 24 hours is *never* necessary, even in the treatment of the most severe infection. From personal experience I believe that 2 grammes (30 grains) of quinine, administered in divided doses each 24 hours, is amply sufficient to cure any ordinary case of aestivo-autumnal infection, while in tertian and quartan infections a single dose of

1 gramme (15 grains) will prevent the next paroxysm, and the same amount, administered in divided doses during the 24 hours, will eventually cure the infection. In my experience with the aestivo-autumnal infections I have yet to see a single case in which treatment was begun in time that did not recover in a few days when treated with 2 grammes of quinine during the 24 hours, and I have seen scores recover rapidly when but 1.3 grammes (xx grains) of the drug was administered during the 24 hours.

When the drug is used hypodermically a dose of 0.5 gm., or 7 1/2 grains, should be administered and repeated, if necessary, until about 1.5 gm. (grs. 24) have been injected. Some very severe cases may require more than this amount, but they will be rare, and in such instances the intravenous methods of administration should be adopted.

As soon as the active symptoms of the paroxysm have subsided the dose of quinine may be gradually diminished, but the drug should be used for several weeks thereafter, as otherwise recurrences are bound to occur in the majority of cases. I have found the following doses of quinine efficient in curing most of the malarial infections with which I have come in contact, and it is rarely that the doses as given will need to be increased.

In *tertian* and *quartan* infections, in which the paroxysms occur at regular intervals, namely, in single infections, the attack may be promptly cured by the administration of 1 to 2 gms. (15 to 30 grains) of quinine by the mouth during the decline of the temperature, and the dose repeated upon the following day, or (and I have found this method preferable) the same amount of quinine is given in 0.32 gm. (5 grains) doses every four hours until 1 to 2 gms. are given and the active symptoms disappear. For a period of at least one month the drug should be given in gradually decreasing doses, thus preventing a recurrence. In cases of *tertian* and *quartan* infection in which, because of double or mixed infections, it is impossible to foretell the time of the paroxysm, quinine should be administered as in aestivo-autumnal infections.

In aestivo-autumnal infections quinine should be given by the mouth in doses of 0.32 gm. (grs. 5) every four hours until the active symptoms disappear and every five or six hours afterward for a period of three days. During the next week the drug should be administered in doses of 1 gm. (15 grains) at bedtime on every other day, and for at least two months thereafter upon the evening of every sixth day. If the drug be thus administered a definite cure of the vast majority of the aestivo-autumnal infections may be predicted. In cases showing pernicious symptoms quinine should always be given hypodermically.

One of the most serious mistakes made in the treatment of the malarial fevers is the abandonment of quinine after the disappearance of the active symptoms, and this mistake is responsible for recurrences and the continuation of malarial infection in many localities. The malarial infections are resistant to treatment, especially the aestivo-autumnal fevers, and while a few days' treatment with quinine will cause the disappearance of the symptoms, a limited

number of the plasmodia may escape, and multiplying gradually, will cause a recurrence of the infection. In all malarial infections, and especially in the aestivo-autumnal fevers, quinine should be administered in the manner suggested for several weeks after all evidence of the infection has disappeared, and only by so doing can we be sure that recurrences will not occur. This is a lesson which the physician in malarial localities seems to have hardly appreciated as yet, and it is most important, both from a therapeutic and prophylactic standpoint.

In view of the researches of Ehrlich and Browning upon the production of strains of trypanosomes resistant to certain drugs which are usually curative, this resistance being produced by insufficient dosage of the drug, and followed by relapses of the injection, it would appear that a similar resistance to quinine may be acquired by the malarial plasmodia, and this may explain the cases of malarial infection characterized by numerous relapses and resistance to this drug. Reasoning from analogy it is reasonable to believe that the malarial plasmodia, like the trypanosomes, may become resistant to certain chemicals which ordinarily are fatal to them.

Quinine should never be administered during the height of a malarial paroxysm, except in pernicious cases, as the drug will greatly increase the discomfort of the patient, and can be as well given during the decline in the temperature, when it will prove practically as effectual, as if given during the height of the fever. This is a point of some importance in the treatment of malaria in children and in nervous individuals, in whom I have observed violent maniacal delirium follow the administration of large doses of quinine at the height of the paroxysm. In the treatment of malaria in children under one year of age 0.032 to 0.065 gm. (grs. iss to i) for a dose is sufficient, the dose to be repeated as in the adult. In older children the drug is better borne and should be used, without hesitation, in large doses in pernicious attacks.

6. **Contradictions to, and Substitutes for Quinine.**—In rare instances the administration of quinine is contraindicated in malarial fever because the drug produces such dangerous symptoms that it cannot safely be used. It has been the experience of most physicians that many patients suffering from these fevers protest against the use of the drug, claiming that they are unable to take it because of the dangerous symptoms produced in their case. In most instances it will be found that these patients *can* take quinine, and that the belief that they cannot is founded upon nothing more than a vivid imagination. If the physician be firm in insisting upon the use of the drug most of these patients will be found able to take large doses with no more than the usual disagreeable effects. Idiosyncrasy to quinine, however, does exist in certain individuals, and therefore some substitute for the drug must be administered.

In nearly all individuals the use of moderately large doses of quinine produce unpleasant symptoms, such as tinnitus aurium, vertigo, confusion of thought, slight deafness, or congestion of the cerebral blood-vessels and headache. In very susceptible persons these symptoms may be produced by very small doses of the drug, and I have observed one case, a delicate girl of 18 years of

age, in which 1/4 of a grain of sulphate of quinine produced the above symptoms. Such symptoms, however, do not contraindicate the use of quinine, but when amaurosis, total deafness, syncope, dyspnoea, alarming irregularily of the heart, haematuria, and severe bleeding from the bowels and mucous membrane occur, the quinine should be discontinued and one of the substitutes to be mentioned should be administered. The question of the production of haemoglobinuria by quinine will be fully discussed in the section upon haemoglobinuric fever, but it may be stated here that very rarely quinine does produce haemoglobinuria and that in cases in which there is a history of such a condition following its administration, the drug should not be used.

Certain eruptions of the skin sometimes follow the use of quinine, even in small doses, the most common of which are *erythema* and *urticaria*, the latter, in some instances, being very severe. Extensive desquamation of the epidermis is rarely observed, one case coming to my attention peeling so extensively that practically the entire epidermis of the body was replaced. Almost perfect casts of the hands and feet, composed of epidermis, were obtained in this case, and in several other cases I have observed considerable desquamation following the use of this drug.

F. Plehn has described a condition which he has called "quinine fever" occurring in those who have taken the drug for long periods of time, and he believes that it is due to the destruction of the red blood-corpuscles by the drug and the consequent absorption of toxic substances. While such a form of fever may occur in certain localities, and among certain races, it must be very rare, as in thousands of cases of malaria observed in the United States, Cuba, and the Philippine Islands, I have never observed the occurrence of this form of fever.

The use of quinine in the treatment of malaria during *pregnancy* deserves attention. It is an undoubted fact that in women who abort easily this drug is capable, in considerable doses, of producing miscarriage, but it is also true that repeated malarial paroxysms will lead to the same result, and I believe that miscarriage is more apt to occur if the malarial infection remains untreated. In pregnant women the drug should be carefully administered in the smallest efficient dose, but it *should* be administered if a malarial infection be present. In the event of pernicious symptoms developing the treatment should be the same as in any pernicious case of malaria, for the prospective mother's life is endangered, and we are justified in disregarding that of the child.

Substitutes for Quinine.—The substitutes for quinine which have been recommended from time to time comprise preparations of the drug which are less toxic than the ordinary salts, and other drugs which have been found to be beneficial in the treatment of malaria. It may be stated with truth that none of them are as efficient as the salts of quinine and on account of their cost, in many instances, are of very limited use in practice. The following are the more important substitutes, but I have never found it absolutely necessary to employ any of them.

Among the other derivatives of *cinchona* bark may be mentioned *chincho-*

nine, *chinchonidine*, *quinidin*, and *quinoidia*, all of which have been used in the treatment of the malarial fevers, but as the symptoms attending their use are similar to those produced by quinine and as they are very much less efficacious, they have never enjoyed the confidence of the profession in the treatment of malaria.

Euchinin, an ethyl carbonate of quinine, is a tasteless preparation, and has been extensively used in malaria by Nikastro, Celli, di Mattei, and Sylvain. It has to be given in larger doses than quinine and is apt to produce deafness and derangement of vision. St. George Gray and Mori consider it a very valuable addition to our therapeutic resources in the treatment of malaria. The dose is a little less than twice that of quinine. Personally, I have had no experience with this preparation, and it is too costly for general use.

Salochinin, or salicylate of quinine, has been recommended by some writers, and Kunst commends very highly a preparation known as *Aristochin* which is administered in doses one-half as large again as quinine.

Methylene blue has been used quite extensively in the treatment of malaria, and was first advocated by Guttman and Ehrlich, whose attention was drawn to it by the observations of Celli and Guarnieri, who proved that the malarial plasmodia could be stained by this agent while still in the circulation. I have used this drug but seldom and have found it unreliable. In rare instances it will effect a cure, but it is not to be compared to the salts of quinine in efficiency. Marchiafava and Bignami believe that this drug is worse than useless, as it may produce strangury, albuminuria, and diarrhoea. When administered, only the medicinal methylene blue should be used, and it may be given in capsules in doses of 0.13 gm. to 0.2 gm. (grs. ii–iii) every four hours. It is well to add a little powdered nutmeg to the dose given as this tends to prevent strangury, and warning should always be given that the urine will be colored blue by the drug. This drug has been found efficient in tertian infections by Thayer, Kunst and Ivanoff, but in quartan, and especially in the astivo-autumnal infections it has not proven of much value. It is always less efficient than the salts of quinine.

Phenocoll.—The hydrochlorate of phenocoll, a derivative of phenacetin, has been investigated by numerous observers, notably Albertoni, Pucci, Novi, Anconi, and F. Plehn. The general concensus of opinion is that, while this drug is sometimes useful in the mildest tertian and quartan fevers, it cannot be depended upon in the treatment of the aestivo-autumnal infections, and that it is not free from injurious effects, as symptoms of collapse have followed its use in therapeutic doses. The dose is from 1 to 3 grams (grs. xvi to lv) during the 24 hours.

Various arsenical preparations have been recommended as substitutes for quinine in the treatment of acute malaria, but I have never observed that arsenic had any effect whatever upon the course of a malarial infection, and I agree with Manson that "the place for arsenic is not as a substitute for quinine during fever, but as a blood restorer after fever."

From the summary given of the substitutes for quinine it will be observed that they are comparatively few in number and that all of them have been found to be less efficient in the treatment of malaria. In very rare instances it may be found necessary to employ one of them, but I have found that practically all cases of malarial infection may be treated by quinine, provided it is properly administered, and I have yet to see a single case in which quinine, if given early enough, did not succeed in curing the infection.

General Treatment and Treatment of Special Conditions.

General Treatment.—All malarial patients should be confined to the bed during the active symptoms of the disease, and after the active symptoms have subsided in the aestivo-autumnal cases it is well to insist upon the patient remaining in bed for two or three days. The bowels should be thoroughly evacuated, preferably by a cathartic dose of calomel or of magnesium sulphate. During the acute stages symptomatic treatment should be adopted; thus in the *cold* stage, warm drinks, with the application of external heat in some form, are indicated; while in the *warm* stage, baths of tepid or cold water or an alcohol sponge will be found very beneficial. The ice-pack or bath should always be used in hyperpyrexia. Antipyretics, such as acetanilide or phenacetine, should never be used during a paroxysm of malarial fever, as they never do any good and may do much harm. If vomiting be exhausting, the nervous symptoms pronounced, or pain be excessive, a hypodermic of morphia is allowable, but this drug should not be used if it is possible to avoid it. Subnormal temperature is best combated by hot baths, strong coffee, and massage, while severe headache is often greatly relieved by the ice-cap. Should cardiac weakness be present, suitable stimulants should be administered, the most useful being strychnine, atropine, and brandy; if the weakness is extreme these should be administered hypodermically. While the treatment of special symptoms arising during the malarial paroxysm is of great importance, it should be remembered that all other treatment is useless unless quinine be administered, so far as curing the infection is concerned, and that the prompt and proper administration of this drug will alone, in many instances, cause the disappearance of all alarming symptoms. It should always be our aim to administer quinine at once in every patient known to have malarial fever.

During the attack the *food* should be liquid in character, consisting largely of milk, broths, and thin gruels. The *drink* should be water or lemonade, the latter especially being greatly relished by most patients, and Tomassi-Crudelli has observed a marked improvement in cases in which the juice of the lemon was administered during the attack and convalescence. As the active symptoms abate the regular diet may be gradually resumed, and during convalescence a nutritious diet is necessary.

Convalescence.—The convalescence from malarial infections which have been properly treated is usually rapid, except in the severe aestivo-autumnal

infections, when convalescence may be very slow. During convalescence besides the administration of quinine in the manner already described, the use of some form of iron and of arsenic is advisable, on account of the anaemia invariably present. Blaud's pill and Fowler's solution are excellent, or other well-tried preparations of these drugs may be used. The *diet* should be generous and nutritious, sufficient outdoor *exercise* should be insisted upon, and precautions taken to avoid reinfection. In all cases, where it is possible, a change of climate to a high, dry region, known to be non-malarious, should be urged, as this will do more for the patient than any other therapeutic measure. Bitter tonics are often very useful in stimulating appetite and digestion, and the use of some good mineral water, laxative in action, is indicated, especially in female patients.

Treatment of Special Conditions.

Pernicious Fevers.—In all malarial infections presenting pernicious symptoms our *first* thought must be to get a sufficient dose of quinine into contact with the plasmodia *at once*, and for this reason the drug should be administered by the hypodermic syringe in the dosage already mentioned. After this has been done the case should be treated symptomatically, but a thorough action of the bowels should be secured by the use of calomel. If the case be one of the bilious remittent type the vomiting may be stopped or allayed by an emetic dose of ipecac or mustard water followed by large doses of subgallate or subnitrate of bismuth; mustard plasters over the epigastrium, the sucking of cracked ice, and the hypodermic injection of small doses of morphia are often efficient in allaying the vomiting. Symptoms of collapse should be treated as already described. In *choleraic* cases opium is indicated and the intravenous injection of normal salt solution. If *coma* be present, the bladder and intestine should be thoroughly emptied and quinine administered intravenously. Where there is intense congestion of the cerebral vessels and acute delirium, bleeding may be performed with advantage in robust subjects, but this is contraindicated when marked anaemia is present. *Hyperpyrexia* should be promptly treated by immersion in the cold bath until the temperature is reduced. It is well to give always the cold bath if the temperature by the mouth reaches 106° F., and to remove the patient from the bath when the temperature has been reduced to 102° F. or 102.5° F. If the temperature begins to rise again the bath should be repeated if it reaches 104° F. In *algid* forms of pernicious malaria injection of salt solution, external heat applied by means of hot-water bottles and warm blankets, and the free use of alcoholic stimulants is indicated.

Malarial Cachexia (Chronic Malarial Infection).—The treatment of chronic malarial poisoning or malarial cachexia consists in the use of those drugs which build up the blood, the employment of hygienic measures, and the use of quinine in proper doses at regular intervals. It may be stated with truth that the treatment of this condition is generally unsatisfactory if the

patient remain in the locality in which he contracted his infection, or if he live in a locality in which he is continually exposed to reinfection. While various remedial measures may be pursued under such conditions, it will often be found that little result will follow unless a change in climate be secured, and thus we should always, in such cases, counsel a change to a high and dry, non-malarial region, and in the case of patients living in the tropics, a change to a temperate region. The chief drugs used in the treatment of this condition are arsenic, iron, and quinine.

Arsenic is best used in the form of Fowler's solution, commencing with 4 drops after each meal, and increasing 1 drop every three days, until from 12 to 15 drops are taken three times a day. If symptoms occur at any time indicating that the physiological limit to the use of the drug has been exceeded, the treatment should be interrupted for a few days, and resumed with the same dose which was being taken just prior to the occurrence of the unfavorable symptoms. There can be no doubt that arsenic has some effect upon the plasmodia of malaria, as Gautier has shown that it produces fragmentation of the protoplasm of the *gametocytes* and Durham claims that this form of the plasmodia is destroyed by the drug. From this it would appear that arsenic might be of great value in the prophylaxis of malaria, although we have no data which indicate that it is of much value in this direction.

Iron in some form, such as Basham's mixture or the Blaud pill, is of undoubted value in the treatment of malarial cachexia, stimulating the blood-forming organs and thus repairing the damage done to the blood by the plasmodia.

Grassi has recommended a combination of quinine, arsenic, and iron, known as *esanophele* in the treatment of both acute and chronic malaria and in malarial prophylaxis, claiming that better results are obtained with this mixture than with any of the drugs when used alone. The preparation is made in the form of pills or in solution. Schaudinn used this combination in chronic malaria showing recurrences and in latent infections with good results, but in aestivo-autumnal infections and in the malarial infections of the tropics, better results are obtained in the treatment of *acute* malarial attacks by the use of solutions of quinine alone. In malarial cachexia the *esanophele* pills are very useful, especially in the treatment of children. The formulae of the *esanophele* pill is as follows:

Quinine bimuriaticum,	0.1 grm.
Acid arsenosum,	0.001 grm.
Ferrum citricum,	0.3 grm.
Ext. amara,	0.15 grm.

Each pill to contain the above.

Dosage: Children, 3 to 6 years, 1 pill at 6 A. M. and 1 pill at 6 P. M.
7 to 14 years, 2 pills at 6 A. M. and 1 pill at 6 P. M.
Adults, 2 pills at 5 A. M., 2 at 8 A. M. and 1 at 6 P. M.

In children from 1 to two years of age the following solution, known as Esanophele Solution No 1 is given:

Each teaspoonful contains, Quin. bimuriate, 0.12 gm.; Arsenous acid 0.0003 gm.; Ferrum citricum, 0.03 gm.; and Ext. amara, 0.1. A teaspoonful, or 5 c.c., is given at 6 A. M., 9 A. M. and 12 noon for 15 days.

In children from 7 to 12 months of age, Esanophele Solution No. 2 is recommended, each teaspoonful containing; Quin. bimuriate, 0.1 gm.; Arsenous acid, 0.0002 gm.; Ferrum citricum, 0.013 gm.; and Ext. amara, 0.1 g. A teaspoonful is given at 7 A. M. and at 10 A. M. for 15 days. I have had no experience with this mixture, but it would appear from the evidence of those who have used it that it is valuable in the treatment of malarial cachexia and in latent malaria in the inhabitants of malarial localities.

WARBURG'S TINCTURE has been used very extensively in the treatment of chronic malaria, but I have never seen much benefit follow its use in the few cases in which I have employed it, although many practitioners in the tropics consider it an invaluable mixture in the treatment of malaria. I believe that where it does do good it is entirely due to the quinine which it contains, and it is a well-known fact that the formula of the original Warburg's tincture has been lost and that the preparations in the market are filled with inert drugs, possessing, so far as we know, no therapeutic use whatever. Some authors claim that they have seen this preparation succeed in curing malaria where quinine alone has failed, but it is very doubtful if a careful study of such instances would establish the truth of this statement. I have, from personal experience, arrived at the conclusion that Warburg's tincture is of little use in the treatment of acute malarial infections, but that it may have a place in the treatment of chronic infections where active symptoms are not present and in the mild latent infections so common among the inhabitants of malarial localities.

Patients suffering from chronic malarial infection should be clothed warmly, should avoid exposure to either cold or heat, should live quietly, and eat plenty of nourishing food. The great importance of a change of climate has already been mentioned, but such patients should be very careful about exposing themselves to cold winds or to dampness, as much exposure is very apt to be followed by a recurrence of active symptoms. In patients going from the tropics to a temperate locality it is especially important that chilling be avoided and that quinine be taken during the sea voyage or land journey and for weeks after arriving at their destination. There is nothing more commonly observed than acute attacks of malaria occurring after arrival in a temperate climate in those who have suffered from malaria in the tropics Such attacks could be avoided by the daily administration of quinine.

Treatment with the Roentgen Rays—The effect of the *X*-rays upon certain protozoa has been thoroughly studied by Schaudinn and his results offer no hope that the treatment of malaria by this means will ever result in practical benefit, as the exposures are so long as to endanger the patient. That prolonged exposure to the *X*-ray will ultimately destroy, or at least so injure the

plasmodia as to render them harmless, has been proven, but the method is not at present capable of practical application.

Serum Therapy.—That the serum therapy of malaria will ever be of practical utility is open to very serious question, and the results so far obtained are of more interest to the bacteriologist and protozoologist than they are to the physician. A curative serum would hardly become popular, as we possess in quinine a specific for the malarial fevers, but a prophylactic serum would certainly be a great boon to mankind. Up to the present, however, such a serum has not been obtained, and it is very doubtful if it ever will be. Several investigators have studied this phase of malarial therapy, and some of their results are deserving of mention. Kuhn, for instance, has endeavored to use the serum of horses immunized to the South African horse sickness in the treatment of malaria. This disease, according to Laveran, is due to a protozoon, *Babesia equi*, and Kuhn considers that the horse sickness is similar to human malaria, is produced by a similar parasite, and that the serum of an immunized horse should, therefore, prove specific in the treatment of human malaria. He and Hovorka tried this method of treatment in 13 cases of tertian malaria, 16 cases of quartan, and 14 cases of pernicious malaria; in the quartan cases it was useless, but in the tertian and pernicious cases it appeared to have a very feeble curative action. These results have not been confirmed and there are so many objections that might be raised to the technic of the method practised and the interpretation of the results that we are forced to conclude that Kuhn's method is of no value in the treatment or prophylaxis of malaria.

The investigations of Major J. H. Ford, of the Medical Corps of the U. S. Army, are of interest in that they suggest that further study of this subject may result in a specific serum therapy for the malarial fevers. He endeavored to secure an antitoxic serum by inoculating rabbits, monkeys, and goats with blood containing the plasmodia of human malaria. His conclusions regarding his work with *Plasmodium vivax* are as follows:

"From the cases recorded it would appear that the successive inoculations of monkeys or goats with blood containing *Plasmodium vivax* gives rise in those animals to an antitoxin which, when injected in adequate dosage into human beings, may be followed by disappearance of the parasites from the circulation and disappearance of the symptoms of malaria. This agent has no apparent influence on infections caused by a variety of the malarial parasite other than that from which it was developed."

In a personal letter to the writer Ford states that his further work upon this subject appears to indicate that an immunity to the various species of plasmodia cannot be produced by the use of serum from the animals experimented with, but suggests that the serum may prove of value in the differentiation of species. While of some value in the treatment of malaria, according to Ford, the serum is not as efficient as quinine, and therefore is of no practical value in the treatment of these fevers. Ford's work yet awaits confirmation, and it would appear that further research in this direction is needed before the theory can be accepted as proven that immunity to any of the species of human

plasmodia can be obtained by using the serum of animals which have been inoculated with them or that in such animals an antitoxin develops which can be used in the treatment of human malaria. .

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PART VI.

HAEMOGLOBINURIC FEVER.

HAEMOGLOBINURIC FEVER.

Synonyms.—Black-water fever; Bilious remittent fever; Bilious haematuric fever; Melanuric fever; Haematuric fever; Malarial haematuria; Haemoglobinuria. GERMAN: Schwarzwasser fieber. FRENCH: Fièvre bilieuse haemoglobinurique; Fièvre haematurique; Fièvre malanurique. ITALIAN: Febbre emoglobinurica.

Definition.—An acute febrile disease, occurring in tropical and subtropical regions, and characterized by fever, bilious vomiting, jaundice, and haemoglobinuria.

Believing as I do that haemoglobinuric fever has no etiological connection with the malarial fevers, it would seem somewhat out of place to consider this condition in a work devoted to the malarial fevers and to the protozoa of the blood, but as the disease most frequently occurs in malarial regions, and very often in the subjects of malarial infection, I have thought it wise to give a concise description of haemoglobinuric fever, including the most recent views regarding its etiology.

Like kala-azar, this disease has long been considered as due to malarial infection, but the more we inquire into its etiology, its distribution, symptomatology, and pathology, the more must we become convinced that the malarial nature of the condition is far from certain, and that the evidence points to its being a separate disease entity, in all probability caused by a hitherto undiscovered organism. At the present time the question as to the etiology of this fever is still undecided, but I believe that it is wise to abandon the malarial hypothesis and endeavor to study the disease without being biased by preconceived ideas as to its malarial nature. There is no more important problem awaiting solution in tropical medicine than the etiology of haemoglobinuric fever.

Historical.—We owe our first knowledge of haemoglobinuric fever to the French naval surgeons, Dutrouleau, Bèrenger-Féraud, Corre, and le Roy de Méricourt, who studied it in the natives of Madagascar and the surrounding islands, as well as in Guinea and the West Indies. Their descriptions were published during the latter portion of the nineteenth century, and since then a voluminous literature has accumulated dealing with this subject. The researches of Marchiafava and Bignami, Mannaberg, Koch, Stephens and Christophers, Thayer, Manson, the brothers Plehn, and Cardamantis have added greatly to our knowledge within recent years, and the disease is now being studied by numerous investigators in all parts of the world. The first cases reported in this country were those of Cummings, in Louisiana, in 1859.

Geographical Distribution.—The geographical distribution of haemo-

globinuric fever is very wide, and it is an important fact, as regards etiology, that this fever, while most common in malarial localities, also occurs in regions which are free from malaria, while in many of the most severely infected malarial regions the disease does not occur except in the form of imported cases.

In NORTH AMERICA haemoglobinuric fever occurs in almost all of the Southern States, having been reported from Virginia, North Carolina, South Carolina, Georgia, Florida, Louisiana, Texas, Arkansas, Mississippi, Alabama, and Tennessee. It is commonly observed in some localities in most of these States. but has been investigated but little as to its frequency and mortality.

In CENTRAL AMERICA the fever occurs upon the Isthmus of Panama, in Honduras, Nicaragua, Costa Rica, and along the entire coast-line.

In SOUTH AMERICA the disease occurs in Venezuela, Guiana, the Argentine Republic, and Brazil, always along the coast-line and in swampy areas.

In the WEST INDIES, black-water fever occurs in Cuba, Martinique, Guadeloupe, Trinidad and some of the smaller islands belonging to this group.

In EUROPE and ASIA MINOR the disease is most prevalent in Sardinia, Sicily, and Greece, but it is also found in Italy, Russia, Turkey, in the Caucasus, and along the banks of the Danube. In Palestine it occurs in limited localities.

In INDIA there is good evidence for the belief that the disease is of recent importation, for it is only since 1885, according to Manson, that it has been described as occurring in Hindustan or the East. At present it has been observed in the Madras Presidency, in the Punjab, along the Ganges, around Bombay, and in Assam and Burmah. The Malay Peninsula, Cochin-China, Siam, and Southern China are all infected with haemoglobinuric fever.

In the EAST INDIES, haemoglobinuric fever has been reported from Sumatra Java, the Celebes, the Bismarck Archipelago, and New Guinea. It is very rare in the Philippine Islands, only a few cases having been reported, and it is probable that these were imported or were suffering from a haemoglobinuria induced by other causes.

In AFRICA this disease has been most thoroughly studied and there it is most prevalent. From the earliest explorations of that continent black-water fever has been one of the most dreaded foes of the white man and one of the greatest obstacles to the opening up of the country. It is not found in all parts of Africa, but is especially deadly along the West Coast and along the Congo and the deltas of the Niger and Gambia rivers. In Sierra Leone, Cameroon, Nigeria, and along the Gold Coast black-water fever is a veritable curse. It occurs also along the East Coast, in British, German, and Portuguese East Africa and in the Congo Free State. It occurs in British Central Africa, in Uganda, the Soudan, and Algeria. Egypt is free from this disease. It occurs also in Madagascar and in Mauritius, Reunion, Bourbon, and the Comoro Islands. Cases have been reported from Formosa.

From this summary of the geographical distribution of haemoglobinuric fever it is evident that while the disease does occur in many regions in which the malarial fevers are endemic, it also occurs in others in which malaria is rare or

absent, and that it does not occur in many regions which are intensely malarial. Thus certain parts of Japan are badly infected with malaria, but black-water fever has never been reported as occurring there. In the Philippines, where I served in a most intensely infected region as regards malaria, I never observed a single case of haemoglobinuria, and it may be stated as a fact that haemoglobinuric fever is so rare in these islands as to be a medical curiosity, despite the fact that all forms of malaria are extremely common throughout the islands, many of them being of pernicious character. There is good reason to doubt, indeed, if a single case of genuine haemoglobinuric fever has ever been observed in the Philippine Islands.

Some authorities endeavor to explain the absence of haemoglobinuric fever in malarial regions by claiming that it is frequent only where there is a large amount of latent infection, but there are many observations upon record which negative such a contention. Thus, at Camp Stotsenburg, in the Philippines, the ratio of latent infection (or children and adults showing plasmodia in the blood without symptoms) was very high, yet a case of haemoglobinuric fever has never been observed in that locality.

The disease is limited, as regards its endemicity, to low-lying coast-lines, and swampy regions situated near the coast. This, of course, suggests the transmission of the disease by mosquitoes, and also its relation to malaria.

As regards *seasonal prevalence*, it may be stated that in the United States the disease is most prevalent in the late summer and in autumn, while in tropical regions it is most prevalent following the end of the rainy season.

Epidemics of black-water fever have been reported by Masterman, Wenyon, and Plehn, but such epidemics are very rare, and occur only when unsanitary conditions, such as overcrowding and exposure, are present.

Frequency of Occurrence.—On account of the lack of sufficient data it is very difficult to arrive at a true conception of the frequency of the occurrence of haemoglobinuric fever, but it is an undoubted fact that it is a rare disease when compared to the malarial fevers, which, by many, are considered to stand in etiological relationship to it, for in many regions in which the malarial fevers are very numerous, black-water fever is unknown or is so rare as to occasion surprise when a case occurs. The following table, compiled from Deaderick's excellent résumé of this fever, will serve to illustrate the frequency of this disease as observed by various authors:

Observer	Place	Time	No. of cases
Brown	British Honduras	1 year	3
Gorgas	Panama	8 months	20
Moscato	Porto Empedoclo	12 years	17
Seal	India	7 years	6
Doering	Cameroon	9 months	40

As regards the relative frequency of the malarial fevers and haemoglobinuric fever in localities where both occur, the following data is of interest: Pampoukis, in Greece, observed 34,937 cases of malaria, of which 0.7 per cent. presented haemoglobinuria; Burot and Lagrand, five out of 599 fatal cases of malaria; Ipscher, in Cameroon, observed 285 cases of malaria in one year, and 20 cases of haemoglobinuric fever; Sims saw over a hundred cases of haemoglobinuria in 20 years' practice in the Congo region, but during that time saw thousands of cases of malaria. Burot and Legrand saw 31 fatal cases of haemoglobinuric fever in Senegal and the Soudan and 155 deaths from the malarial fevers, while Davidson states that in Nossi Be the proportion of black-water cases to malaria was as 1 is to 14.

The statistics given above apply only to those regions in which haemoglobinuric fever is most prevalent, but if we take those localities in which the malarial fevers are prevalent and in which black-water fever is rare, the relative proportion will be very greatly reduced. In my own experience, covering 10 years' observation of the malarial fevers, during which time I have studied nearly six thousand cases of malaria, I have observed haemoglobinuria but once, and then the condition was not at all typical of haemoglobinuric fever. All of these cases were observed in Cuba or in the Philippines, or in the United States in the persons of soldiers returning from those countries. When we take into consideration that most of the patients were white men, susceptible to haemoglobinuric fever and all suffering from malaria, I regard it as evident that haemoglobinuric fever is not due to the malarial plasmodia, but to some other cause.

Predisposing Causes.—All ages and both sexes are susceptible to this disease, but it is said to be most frequently observed in the middle aged, and in those debilitated by preexisting disease. A previous attack of malaria is said by many authorities to be absolutely necessary in order that haemoglobinuric fever develop, and some have gone so far as to claim that there is no case upon record of the occurrence of this disease in an individual who had never suffered from a malarial infection. As a matter of fact, there are numerous instances of persons who had never had malaria developing haemoglobinuric fever, and Manson[1] says: black-water fever frequently attacks people who previously had never had a single paroxysm of intermittent fever." It is but natural that the two diseases should occur in the same individual frequently, in regions in which both are endemic.

Length of residence appears to have an important influence upon the liability to haemoglobinuric fever in many instances, but that a long residence in the infected locality is unnecessary is shown by the experience of such observers as Plehn, Ritchie, Cardamantis, Daniels, and Lynch and Scott, who all report instances of perfectly healthy individuals being attacked within two to three months after reaching the infected territory, and before there was any evidence

[1] Tropical Diseases, 4th Ed., London.

of a malarial infection. Manson states that he has been frequently informed by officers of the African colonial service that they were suddenly attacked by black-water fever while in perfect health, and Daniels states that a malarial history is denied by a goodly proportion of the sufferers from black water unless they have resided for over a year in the infected region.

As regards *race*, haemoglobinuric fever chiefly attacks the whites, but the negro is not immune as a race. In localities in which the fever is endemic the negro, if present, undoubtedly develops an immunity against the disease, but numerous observers have seen instances of infection in negroes. F. Plehn reports an epidemic occurring among the negroes in the Cameroon, and it has been repeatedly observed that negroes introduced into an infected region from an uninfected one, are susceptible to the disease. Chinese are said to be almost as susceptible as the white man, but Daniels claims that the native of India is only one-fourth as susceptible as is the European.

Change of Residence is often followed by a recurrence of haemoglobinuria in those who have suffered from the disease, or may be the exciting cause of the primary attack, especially if the change be an abrupt one as regards climate or altitude. *Recurrences* are frequently observed and are generally brought about by exposure, change of climate, or removal from a low to a high altitude. Patients returning from the tropics to England or America sometimes develop haemoglobinuria after arrival.

Among the other predisposing causes of an attack of haemoglobinuric fever may be mentioned exposure and fatigue, traumatism, excessive venery, and alcoholic excesses. Haig believes that the uric acid diathesis strongly predisposes to haemoglobinuria, but there is no experimental evidence favoring his view.

Etiology.—The cause of haemoglobinuric fever is unknown, but there are three chief hypotheses regarding its etiology, each supported by some evidence of value, and each ardently believed in by its advocates. These are: that it is due to malarial infection; that it is due to quinine; and that it is a specific disease. All of these theories have been investigated, and the advocates of all are able to point to evidence favoring their claims, but I believe that a careful study of this vexed question by an unprejudiced observer must result in the conviction that the *specific* theory of the etiology of the disease is correct, and that haemoglobinuric fever is a disease *sui generis*, caused by a hitherto undiscovered organism, probably of protozoal nature.

The Malarial Theory.—This theory of the causation of the fever is supported by many eminent students of malaria, notably by Stephens, Plehn, and Mannaberg. The advocates of this theory claim that the distribution of the disease; the presence in a large proportion of the cases of malarial plasmodia; the fact that in most cases a previous history of malarial infection can be obtained; the blood findings apart from the plasmodia, and the fact that the disease affects those who have resided for some time in the infected region, all point to its malarial origin. It is well to consider each of these points separately and by

so doing I believe that the conclusion will be that not one of them can be considered as proving that black-water fever is malarial in origin.

The *distribution* of the disease I have already referred to and have shown that in many malarial regions haemoglobinuric fever is unknown, although these regions are badly infected with the most severe forms of malaria, such as the aestivo-autumnal. In the Philippines, where pernicious cases of malaria are not uncommon and where the mortality from malaria in 1902, according to the census of the Philippines Islands, was 26.8 per cent. of all deaths, there being during that year 118,476, deaths from these fevers, or 17 per thousand, not a single death is reported from haemoglobinuric fever, and this is true of many other malarial localities. The fact that black-water fever has been reported from regions in which malaria is unknown also serves to show how little we can depend upon the distribution of a disease in considering its etiology. Many other acute infectious diseases are most common in regions infected with malaria, but because this is so we do not at once conclude that they must therefore be due to malarial poisoning.

The *presence of malarial plasmodia* in the blood of a large proportion of patients suffering from haemoglobinuric fever is considered by many as proving its malarial origin, but many other conditions occur in malarial regions which no one would consider for a moment as being due to malaria, but in which malarial plasmodia are found in the blood.

It is but natural that, in an intensely malarial district, patients suffering from haemoglobinuric fever should present plasmodia in their blood, and the fact that the latter fever is most prevalent in malarial districts does not prove that it is due to malaria, but that it depends for its spread upon factors which also favor the transmission of the malarial fevers. As regards the frequency of the occurrence of malarial plasmodia in the peripheral blood of black-water fever patients, I have collected 273 cases reported in the literature, of which 109, or nearly 40 per cent. showed malarial plasmodia in the blood. Stephens and Christophers and Mannaberg have shown that the number of plasmodia in the blood varies with the time of examination, 95 per cent. of patients showing them the day before the attack, 60 to 70 per cent. showing them the day of the attack, and 17 to 20 per cent. showing them the day after the attack. This fact has been used in the endeavor to discount the proofs of the absence of plasmodia in haemoglobinuric 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?

It appears to me most illogical to claim, that because a large proportion of patients suffering from haemoglobinuric fever show malarial plasmodia in their blood, the disease must necessarily be due to them. Take, for example, infection with ankylostoma. This parasite is most common also in malarial

regions, because such regions are most favorable to its development. It also will be found present in a vast majority of patients suffering from malaria in such regions, yet we do not for a moment believe that ankylostomiasis must therefore be due to malaria, for in this instance we have demonstrated that it is due to a definite parasite. In haemoglobinuric fever, unfortunately, the parasite has not been discovered, and so it is easier to consider it of malarial origin, because the two diseases frequently coexist. In India for years kala-azar was considered of malarial origin, and it was not until the discovery of *Leishmania-donovani* that this notion was abandoned. Such an experience should serve as a warning to us in our conceptions of the etiology of haemoglobinuric fever.

A *previous history of malarial infection* is undoubtedly to be obtained in most of our cases of haemoglobinuric fever, but here again the reason is not far to seek. The occurrence of the disease most frequently in malarial localities makes it inevitable that most patients suffering from it should have previously suffered from malaria or may be suffering from that infection at the time they develop haemoglobinuria. From what we know of black-water fever it is evident that, compared with malaria, it is a rare disease, and it therefore happens that most patients residing long enough in a locality to develop black-water fever have already suffered from malaria. It has been asserted by the most ardent advocates of the malarial origin of haemoglobinuric fever that not a single case is on record of the outbreak of this disease in a patient who had not previously suffered from malaria, but such an assertion can only be made by one who is little acquainted with the literature, for numerous cases are reported in which haemoglobinuric fever developed in perfectly healthy individuals within two or three months after reaching the infected locality and in whom there had never been any symptoms of malaria. Such cases have been reported by Manson, Cardamantis, Plehn, Ritchie, Daniels, and many other observers.

The *blood examination* in cases of haemoglobinuric fever generally demonstrates an increase in the large mononuclear leucocytes, and frequently the presence of pigmented mononuclear cells. This fact has been used as a weighty argument by the believers in the malarial origin of the fever, as similar results are found in malaria. However, it is of little real value as an argument, for a large mononuclear increase is observed in several other diseases due to the protozoa, as kala-azar and trypanosomiasis, while the pigmented leucocytes are present in patients who have suffered from malaria, even after symptoms of infection have been absent for weeks. While the presence of pigmented leucocytes may indicate that at some time the patient has suffered from malarial infection, it certainly is very poor proof that an attack of haemoglobinuric fever is due to malaria.

The relation of *long residence* in an infected locality to the malarial origin of the fever has already been mentioned. It is sufficient to repeat that while most cases occur only after the first twelve months of residence, many have been reported in which the disease appeared within two to three months after enter-

ing the infected territory and in perfectly healthy individuals, thus proving that long residence is not essential to the development of the disease. That most of the cases develop after a residence of a year or more would appear to indicate that the disease is one of long incubation or, and this is more probable, due to an organism which is seldom met with or which requires certain peculiar conditions favorable for its development before infection occurs. Recently a number of authors have claimed that while the plasmodia of malaria have no direct etiological relationship to haemoglobinuric fever, malarial infection is, nevertheless, a necessary predisposing cause, bringing about certain conditions in the blood and tissues necessary for the existence of the parasite causing the fever. While these theories are interesting, they simply beg the question, and I believe are of little value as working hypotheses, for, as shown, haemoglobinuric fever does occur where there has been no malarial infection, and, therefore, we are justified in believing that it is not caused by the malarial plasmodia or dependent upon the changes produced in man by infection with these parasites.

The Quinine Theory.—Many observers, while denying that malaria is responsible for the appearance of haemoglobinuria, believe that this fever is produced in certain susceptible individuals by the administration of quinine. In 1858, Veratas, a Greek physician, suggested this explanation of the occurrence of haemoglobinuria, and in 1874, Tomaselli, of Italy, reported in favor of this theory, and it has since been accepted by many practitioners in malarial localities. When Koch gave it the support of his great authority, the scientific world believed that at last the etiology of the disease was explained, but even Koch does not state that quinine is the sole cause of the fever. As a matter of fact, many cases of black-water fever have been reported in which no quinine had been taken previously to the attack, and Cardamantis has reported no less than 32 cases in Europeans who had never taken a dose of quinine. It is true, however, that very rarely the administration of quinine has been followed by the appearance of haemoglobinuria, but it is very doubtful if the symptoms, beyond the occurrence of blood in the urine, were those of black-water fever. I have seen two cases in which quinine caused haemoglobinuria, even when given in small doses, but there were no symptoms in the least suggestive of haemoglobinuric fever. That quinine has been administered in most cases of haemoglobinuric fever prior to the outbreak of the disease is due to the fact that as the disease occurs so frequently in malarial localities the drug has been given to combat malarial infection. It is certainly illogical to claim, because quinine has been administered to a patient suffering from malaria and who afterward develops haemoglobinuric fever, that the drug is the cause of the disease. In many regions quinine is given as a prophylactic to practically the whole population, but because this is so must we believe that the cases of black-water fever which may occur are due to this drug? How can we explain upon such a hypothesis the absence of haemoglobinuric fever in regions such as the Philippine Islands, where malaria is common and quinine is given very extensively?

If we take into consideration also that quinine is given in many other infections without producing haemoglobinuric fever; that it is used with good results in the treatment of the disease itself, when a malarial complication is present; that there exists no relation between the amount of the quinine given and the severity of the disease; and that even in those who have suffered from an attack of the fever apparently produced by quinine, the use of the drug afterward is harmless; I believe that we must admit that quinine is not the cause of black-water fever.

The Specific Theory.—Recently the theory that haemoglobinuric fever is a distinct disease, produced by a specific parasite, probably protozoal in nature, has been gaining ground, and I believe that ultimately this theory will be found correct. The most ardent advocates of the specific nature of the disease are Manson, Sambon, Rho, and Blanchard, while numerous other investigators believe that only by admitting the specific nature of the disease can we explain the apparent contradictions inherent in the other theories. Manson[1] says: "I have long entertained the idea that too much has been taken for granted in relegating black-water fever to malaria, and thereby ignoring its possible individuality as a separate disease; an individuality strongly suggested not only by the symptomatology, but also by epidemiology and analogy." The resemblance of the disease to paroxysmal haemoglobinuria and the occurrence of a somewhat similar disease in cattle, known as Texas fever, forcibly suggests that haemoglobinuric fever is a distinct disease, and that it may be due to a protozoon closely allied to the parasite of Texas fever, *Babesia bigemina*. The discovery of other parasites in animals belonging to this genus, some of them very small, is of importance in the consideration of this disease, for it is not at all improbable that black-water fever may be due to a babesia or allied organism so small as to escape our present microscopic lenses, or it may prove to be actually ultramicroscopic in size. Certain it is that the distribution of the disease, its epidemiology and symptomatology, and its resemblance to other protozoal diseases, would appear to justify us in regarding it as probably due to a protozoon, and in view of the fact that neither the malarial theory nor the theory that the disease is due to quinine has been proven, that it is wise to consider the etiology of this disease as still unsolved.

Pathology.—The pathology of haemoglobinuric fever is but little characteristic, if we do not take into consideration the condition of the urine. The principal changes are found in the kidneys, blood and urine, the other organs, save for the changes brought about by preexistent or existing malarial infection, showing little change of importance.

The Kidneys.—The kidneys are always congested and present the evidences of acute venous congestion or acute nephritis. The capsule is not adherent, the cortex is thickened, the intertubular capillaries much congested, and the general appearance of the section that of an acute tubular nephritis. Microscopical examination shows marked epithelial desquamation in the

[1] *Ibid.*

tubules, congested Malpighian tufts, and congested capillaries. If the patient dies after three or four weeks the kidneys present the lesions of a subacute parenchymatous nephritis. In instances where a malarial infection complicates the haemoglobinuria, the sections of the kidneys may show melanin within the capillaries or enclosed within the cells. In almost every instance the cells within the tubules contain a considerable amount of yellow pigment, derived from the broken-down red corpuscles.

The Spleen.—Except in patients who have suffered from malarial infection few pathological lesions are observed in the spleen in fatal cases, beyond enlargement, congestion, and decrease in consistency. In fact the spleen is that usually observed in acute infectious fevers, and does not contain malarial pigment unless preexistent malarial infection has occurred. A large amount of yellow pigment is generally present, due to the destruction of the red cells.

The Liver.—The liver is enlarged, decreased in consistence, and usually of a yellowish color. Sections show albuminoid degeneration of the liver cells, and haemosiderin is common in the degenerated cells. There may be marked congestion of the capillaries, and it is not uncommon to observe areas of focal necrosis in the region of the intralobular vein. Melanin is not present except in patients suffering from coincident malarial infection.

The Brain.—The brain shows no pathological lesions which are characteristic, and only in patients having a coincident malarial infection is pigment or parasites observed in this organ. The total absence of pigment in the brain in many fatal cases of black-water fever is very suggestive of the lack of relation of malaria to this fever, for in almost every fatal case of malaria it is not difficult to demonstrate plasmodia, and especially pigment, in the capillaries of the brain.

Bone-Marrow.—No changes of importance occur in the bone-marrow. If malarial infection is present or the patient has suffered from repeated attacks of malaria, the changes are those observed in that disease which have already been described.

The Blood.—The blood looks yellowish or yellowish-red in color, and is less viscid than normal. Haemoglobinaemia or cholaemia may be present, but in many cases haemoglobinaemia is not present. Microscopically the blood-cells appear normal in size and shape, but are generally paler than normal. The presence of malarial plasmodia in the blood of haemoglobinuric fever has already been discussed, and it may be stated that in many cases they are not present at any time during the disease or preceding it, and that when they are present it simply means a coincident malarial infection. Neither is melanin present in the blood in uncomplicated cases of haemoglobinuric fever. During the early symptoms of the fever there may be a marked leucocytosis, but later in the disease the polynuclear cells are decreased, and there is a marked increase in the large mononuclear leucocytes, a fact on which great stress is laid by the advocates of the malarial nature of the disease. As we have shown,

this mononuclear increase is present in other protozoal diseases, and therefore cannot be considered as characteristic of black-water fever.

The Urine.—The color of the urine is usually a dark cherry red, but it is sometimes necessary to use the spectroscope to detect the presence of haemoglobin; in such instances the color is a light brownish-yellow. The reaction is alkaline, the specific gravity low, and there is generally a large amount of sediment, which, upon being examined, is found to consist of yellowish granular matter, numerous hyaline and haemoglobin casts, and a very few red blood-corpuscles. The granular material is evidently composed mostly of the detritus of degenerated red blood-corpuscles, and as haematuria is not a characteristic of the disease, this explains the very few red corpuscles which are present in the urine. Crystals of haemotoidin occur in sparse numbers in the sediment. The bile-pigments, may be present; but are not commonly observed. Albumin is always present in large amount, mostly in the form of serum-globulin, which is derived from the blood. The spectroscopic examination of the urine shows the characteristic spectrum of oxyhaemoglobin and, in some instances, of methaemoglobin.

Period of Incubation.—The period of incubation in haemoglobinuric fever is unknown. From the observations of Scott, in Africa, it would appear that the fever may occur after a period of eight days from exposure in the infected territory, but it is probable that the period of incubation is a very variable one, for we know that recurrences take place at long intervals, even of months. Manson mentions cases in which the disease appeared for the first time in Europeans who had been absent from the infected localities for months, so that it would appear that, as in the malarial fevers, black-water fever has a very uncertain period of incubation.

Symptomatology.—In almost every case the disease begins suddenly with a chill, after which the temperature rises rapidly to 103° F. or higher. The chill is generally severe, but may be so slight as to be hardly noticeable. The usual symptoms of fever are present, such as malaise, pain in the muscles and articulations, loss of appetite, and mental depression. Later in the attack the pain is more severe in the lumbar region and over the liver and spleen, while in many instances severe bladder pain is complained of. After the symptoms are well pronounced there is marked desire to pass the urine which presents the characteristic brownish-red color of "black-water." The fever may be intermittent, remittent, or almost continuous in type, and jaundice slowly develops in many instances. Tympanites is a common symptom and pain over the stomach is often elicited upon pressure. In favorable attacks there is bilious vomiting, but it is not so excessive and so long continued as it is in cases which go on to a fatal termination. In not a few instances bilious vomiting is absent, so that this symptom cannot be said to be characteristic of haemoglobinuric fever. The termination of the attack in patients who recover is usually by crisis, the temperature receding, accompanied by profuse perspiration, while the haemoglobinuria disappears. Great prostration is often observed

after an attack of haemoglobinuric fever, and convalescence may be much delayed by recurrences of the haemoglobinuria and fever or by the recurrence of the fever alone. The haemoglobinuria may last only for an hour or two in mild cases or may persist at intervals for weeks. As the haemoglobinuria disappears, the urine, which may have been greatly decreased in quantity at the height of the attack, becomes lighter in color, greater in quantity, and is passed with less discomfort to the patient. The acute attack may last only a day or may be prolonged over several days. Diarrhoea is common, but constipation is frequently observed.

In fatal cases the temperature may go to 104° F. or higher; there is severe and prolonged bilious vomiting; bilious diarrhoea; great pain in the loins and the epigastric region; and a gradually developing somnolence which deepens into a fatal coma. In some instances the symptoms are those of uraemia, due to total suppression of the urine or to the development of nephritis, while in others the fatal symptoms are those of severe haemorrhage, or death may occur from hyperpyrexia or the typhoid state may develop. A marked decrease in the total quantity of urine passed in twenty-four hours is always an unfavorable symptom.

The following clinical facts are of importance in the symptomatology of haemoglobinuric fever; the temperature is not in any way characteristic of the disease; haemoglobinuria is constant, but unless accompanied by the other symptoms, such as fever, vomiting, and jaundice, cannot be considered as peculiar to this disease; the vomiting of bile-stained material is so commonly observed as to be an important confirmatory symptom, but alone is of no value; the microscopic character of the sediment in haemoglobinuric fever is not characteristic, as the same elements are found in haemoglobinuria due to other causes; the development and persistence of jaundice is very characteristic when accompanied by other symptoms.

The physical signs during an attack of haemoglobinuric fever consist in an enlargement of the spleen and liver and a jaundiced condition of the sclerae and skin. A systolic murmur is not infrequently heard, haemic in character, and not transmitted. A bronchitis may be present or there may be evidence of congestion and oedema of the lungs. Anaemia is generally marked when the blood count is made during the attack, but counts made after the symptoms have disappeared do not show as severe a degree of anaemia as one would expect from the obvious destruction of the red cells.

In malarial localities an attack of haemoglobinuric fever is often complicated by a coincident attack of malaria, and it is certain that many of the symptoms of black-water fever, which have become almost classic in our text-books upon the subject, were in reality those of malaria, and it is very probable that a more careful study of our cases will result in proving that haemoglobinuric fever has a definite and characteristic symptomatology which will enable us to recognize it as having no connection with the malarial fevers and peculiar unto itself. At the present time the subject, both from an aetiological and clinical

standpoint, is in a far from satisfactory condition and is one of the most important of all tropical problems in medicine.

Complications and Sequelae.—These are few in number, nephritis being the most common of the sequelae, and malaria of the complications. Anaemia is a frequent sequela, but is rapidly recovered from under proper treatment. Parotitis, neuraligia, pleurisy, endocarditis, and severe chronic enteritis have been reported as sequelae of the fever.

Prognosis.—The prognosis is always grave, the mortality varying from 10 to 30 per cent. The mortality varies in different localities and in different years, being sometimes very low and sometimes appalling, even as high as 95 per cent., but there is good reason to believe that the disease has often been confused with yellow fever, and that thus the mortality has been overestimated, especially in our Southern States. Some attacks are so mild as hardly to be recognized, but in the majority of cases the prognosis should be guarded. Unfavorable prognostic signs are decrease in the quantity of urine, excessive vomiting, continued hiccough, and somnolence. Plehn has reported cases in which sudden death has occurred from thrombus formation in the large vessels or the heart.

Diagnosis.—Of the diseases which may be confused with haemoglobinuric fever may be mentioned yellow fever, paroxysmal haemoglobinuria, pernicious malaria of bilious remittent type, and Weil's disease.

Yellow fever may easily be confused with haemoglobinuric fever by one who has had little acquaintance with either disease, but if it is remembered that in yellow fever the icterus does not begin until the third or fourth day; that haemoglobinuria is absent; that albuminuria occurs from the second to the fourth day; and that the temperature is characteristic, it is not difficult to make a differential diagnosis. The diagnosis from paroxysmal haemoglobinuria in a region where both diseases occur is most difficult, and may be impossible, but in the majority of cases the greater severity of the symptoms in haemoglobinuric fever will serve to distinguish it. Pernicious malarial fever, of the bilious remittent type, may be confused with haemoglobinuric fever, but the presence of the plasmodia until quinine is administered, the prompt subsidence of the infection under quinine treatment, and the absence of haemoglobinuria, should serve to enable us to diagnose the malarial nature of the malady. Weil's disease might be mistaken for haemoglobinuric fever, but haemoglobinuria is not present; the urine, if affected, containing multitudes of erythrocytes.

I have mentioned the rare occurrence of haemoglobinuria following the administration of quinine in malarial patients. This condition may be easily differentiated from haemoglobinuric fever by the absence of acute symptoms, the occurrence of the condition in localities known to be free from "black water" and in patients who have never been exposed to the latter disease, and the prompt disappearance of the haemoglobinuria upon ceasing the administration of quinine.

Prophylaxis.—It is difficult to lay down rules regarding the prophylaxis

of a disease when we are unacquainted with its cause and the method of its transmission, but we have good reason to believe that the measures taken for the prophylaxis of malaria are also quite efficient in the prophylaxis of this disease. This fact has been used as an argument in favor of the malarial origin of black-water fever, but it is simply an argument in favor of the insect transmission of the disease and of its protozoal nature. That the methods adopted in the prophylaxis of malaria are also efficient in the prophylaxis of haemoglobinuric fever is merely a coincidence, just as protection from the mosquito is efficient in the prophylaxis of filariasis and dengue as well as in malaria.

A. Plehn, in Cameroon, has found that the prophylaxis of malaria there has not only resulted in a reduction in the number of malarial infections, but also in the number of cases of haemoglobinuric fever, the morbidity of malaria being lowered one-half, while that of black-water fever was reduced one-fourth, and Moffatt has reported similar results. It is therefore recommended that in regions infected with haemoglobinuric fever the utmost precautions be taken regarding protection from the bites of insects and that prophylactic doses of quinine be administered.

Treatment.—The treatment of haemoglobinuric fever is at the present time most unsatisfactory because of the divergent opinions held by observers regarding the use of quinine in this disease. It would be unprofitable here to review *in extenso* the arguments for and against the use of this drug in haemoglobinuric fever, for the question is still far from settled, and statistics are quoted by both parties favorable to their contentions. The association of haemoglobinuria with malaria and the fact that haemoglobinuria may be produced by quinine is responsible for the difference in opinion regarding the use of the drug in treatment. As I have shown, haemoglobinuric fever occurs without coexisting or preexisting malaria and in patients who have never taken a dose of quinine, so that it appears that the question is simply as to whether quinine is beneficial in haemoglobinuric fever or whether it is of no value. I believe that there is little evidence that indicates that quinine, in uncomplicated cases of haemoglobinuric fever, is of any value, and it may well be that the use of this drug in large doses renders the blood more susceptible to the action of the parasite causing haemoglobinuria. When, however, the haemoglobinuric fever is complicated by a malarial infection, as shown by the presence of the plasmodia in the blood, quinine should be given in doses sufficient to cure the malarial complication, but it should not be given unless the plasmodia can be found. As showing the very slight difference between the mortality when quinine is administered and when it is not, the following data, collected by Deaderick are of interest. Of 328 cases treated with quinine, 56 died, a mortality of 17 per cent., while of 374 cases treated without quinine, 57 died, a mortality of 15.2 per cent. Unfortunately, we are ignorant as to how many of these cases were positive for the malarial plasmodia, but I believe that the results as given indicate that it makes but little difference in the mortality of haemoglobinuric fever whether quinine be administered or not,

and as in rare instances quinine is capable of producing haemoglobinuria, it is better to abstain from the use of the drug unless the malarial plasmodia are found in the blood, when, of course, it is indicated not as a therapeutic agent in the treatment of haemoglobinuric fever, but as a specific against the coincident malarial infection.

The following rules governing the administration of quinine in haemoglobinuric fever will be found valuable as a guide to the use of the drug in this disease:

1. In all cases showing the plasmodia of malaria in the blood, quinine should be administered in doses sufficient to cure the existing malarial complication.

2. In all cases which do not show the presence of the malarial plasmodia during the first day of the attack, quinine should be withheld, as most of these cases are uncomplicated, and there is no reason to believe that quinine is of any value in the treatment of uncomplicated haemoglobinuric fever.

3. In cases of haemoglobinuria arising during the administration of quinine in proven malarial infections, the administration of the drug should be discontinued for a day or two, and entirely if malarial plasmodia do not again appear in the blood.

4. If haemoglobinuric fever develop during an attack of malaria which is already being treated by quinine, but in which the plasmodia can still be demonstrated in the blood, quinine should be administered until the plasmodia disappear.

From the above recommendations it is evident that the administration of quinine in haemoglobinuric fever depends entirely upon the presence of the malarial plasmodia, and the drug should never be administered in this disease unless these organisms be present. Quinine is of no use whatever in the treatment of haemoglobinuric fever *per se*, and a very careful examination of the blood should be made for the plasmodia before it is administered. I regard it as conclusively proven that quinine is harmful in haemoglobinuric fever unless the disease is complicated by malarial infection, and this would appear to be a strong proof of the lack of relationship between the two diseases.

General Treatment.—The patient suffering from haemoglobinuric fever should be confined to bed in even the mildest infections, the body should be kept warm, and warm drinks will be found most useful in maintaining the bodily heat. The bowels should be opened by a dose of calomel or by magnesium sulphate, and if there be evidence of suppression of urine, diuretics, such as potassium citrate, should be freely administered, hot fomentations applied over the region of the kidneys, and an exclusive milk diet enforced. If vomiting be slight, liquid nourishment may be given at short intervals, but in cases in which the vomiting is severe nutrient enemeta should be given, and enemata of salt solution should be administered at intervals of four hours. If the enemata are not retained, the salt solution should be injected into the subcutaneous tissue of the breast or of the loins. The use of morphine in this disease requires

great caution and the drug should never be administered when it can be avoided.

The use of stimulants is indicated in most cases, but no form of alcohol should be employed in the treatment of haemoglobinuric fever. Strychnine, digitalis, strophanthus and the aromatic spirits of ammonia are all useful, and the inhalation of oxygen is warmly advocated by Plehn.

The treatment by chloroform, advised by Quennec, has proven of value in some instances, but as it was combined with quinine it is impossible to say how efficacious it really is in uncomplicated cases of haemoglobinuric fever. He uses the following mixture: Chloroform, 6 gms.; gum arabic, 8 gms.; simple syrup, 250 gms. The entire quantity is taken every 24 hours, a sip being taken every 10 or 15 minutes. He claims for the treatment that it controls vomiting, diminishes albuminuria, and increases the quantity of the urine. The Sternberg treatment of yellow fever, by a mixture of bichloride of mercury and sodium bicarbonate, has been used by some practitioners with good results. The method of Vincent, who uses calcium chloride, a well-known antihemolysin, is deserving of consideration in the treatment of this disease, as it is founded upon sound scientific principles. The drug is given in doses of from 4 to 6 grammes per day by the mouth, or from 1 to 2 grammes hypodermically, during the acute symptoms, and in every case in which it has been administered the results have been such as to indicate that it is more nearly a specific than any remedy so far used in the treatment of this disease.

The fever seldom requires treatment, as the temperature is not excessive and does not last many days, but in cases in which there is hyperpyrexia sponging with tepid water and alcohol is generally sufficient; vomiting, often most distressing, may be benefited by mustard plasters over the epigastrium, the sucking of cracked ice, the drinking of carbonated beverages, and, as a last resource, the hypodermic injection of morphine. Champagne is permissible in cases in which the vomiting is severe, the strength exhausted, and no food can be retained by the stomach. It should be given in small quantities, frequently repeated. During convalescence the diet should be light but nutritious, the patient should be warned against overexertion and the use of alcoholics, and every measure should be taken to avoid mental worry and nervous excitement. If possible, the patient should leave the infected locality and never return to it, for longer residence will very often result in recurrences of the haemoglobinuric attack.

From what has been said of the treatment of haemoglobinuric fever it is evident that as yet we have discovered no specific for the disease, and that the treatment is wholly empirical, due to our ignorance of the exact etiological factor. If, as is held by many, haemoglobinuric fever is due to the malarial plasmodia, why is it that treatment with quinine is not successful, and if, as others hold, it is due to quinine, how is it that the continuation of the use of this drug in treatment does not lead to a fatal result in the majority of cases? The truth is that quinine is beneficial in haemoglobinuric fever just so long as

malarial plasmodia are found in the blood, thus proving that the malaria infection is merely a coincidence, for the drug is absolutely useless in those cases of haemoglobinuric fever in which no malarial plasmodia can be demonstrated. The only conclusion possible to an unprejudiced student after carefully considering the epidemiology, symptomatology, and therapeutics of haemoglobinuric fever is that neither malaria nor quinine have anything to do with its etiology, but that it is caused by some parasite, hitherto undiscovered, in all probability belonging to the Protozoa.

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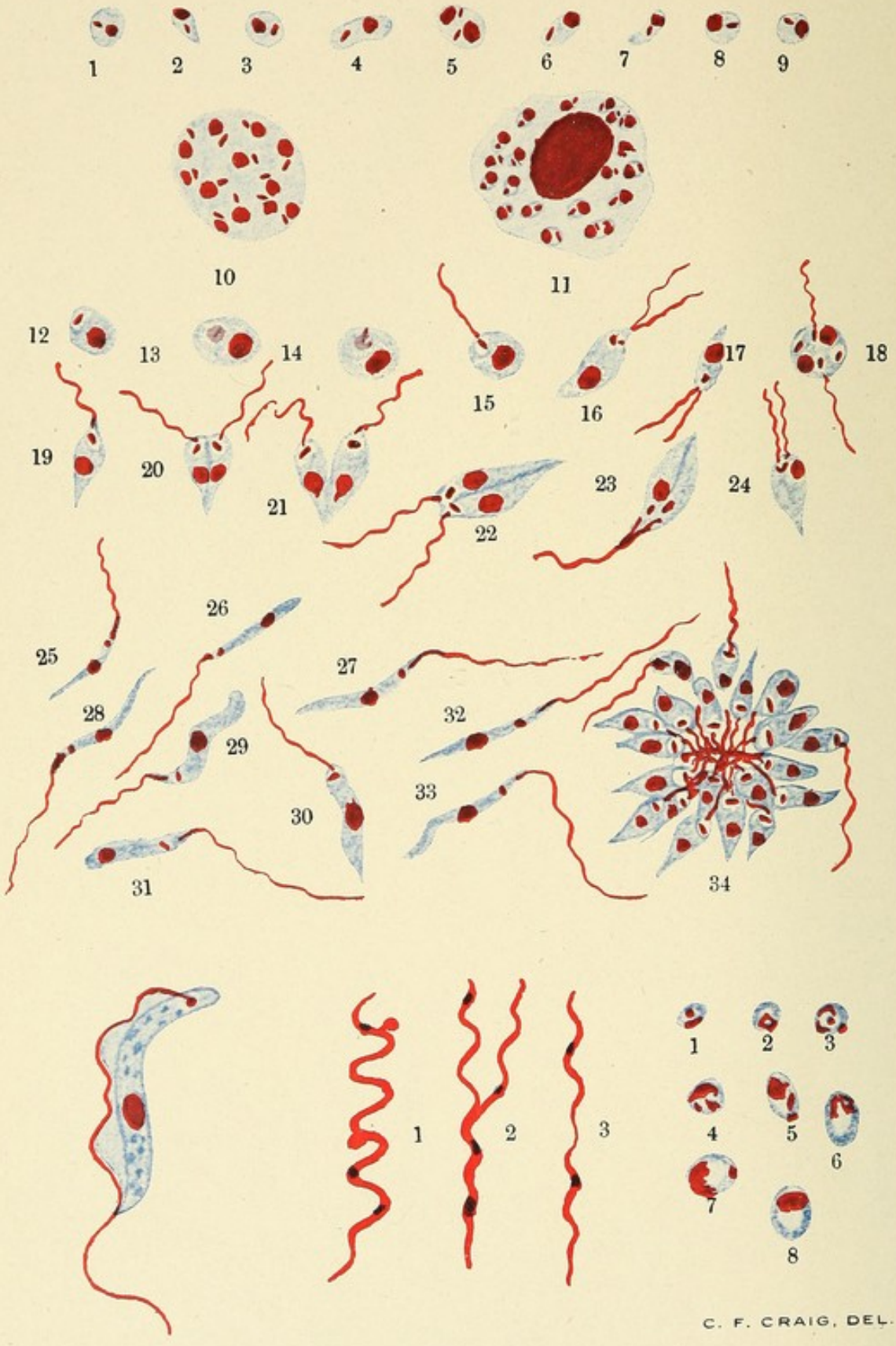
See also the treatises upon "Malaria" by Kelsch and Kiener, Laveran, Mannaberg, and Celli.

PART VII.

THE BLOOD PROTOZOA OF MAN.

Plate IV.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C. F. CRAIG, DEL.

EXPLANATION OF PLATE IV.

Leishmania donovani. Leishman-Donovan Bodies. Stained with Wright's Stain.

1 to 10. Various forms of *Leishmania donovani*, the protoplasm stained blue, the chromatin, red.

10. Matrix containing several *Leishmania donovani.*

11. Large endothelial cell containing many *Leishmania donovani.*

12 to 34. Various cultural forms of *Leishmania donovani.* Many of these forms show division into two parasites.

34. A so-called "rosette" formed by cultural forms of *Leishmania donovani.*

Fig. A. *Trypanosoma gambiense*, stained with Wright's stain.

Fig. B. *Spirochæta duttoni*, stained with Wright's stain.

1. Spirochæta showing peculiar out-growths along its course, containing chromatin.

2. Spirochæta undergoing longitudinal division.

3. Spirochæta undergoing transverse division.

Fig. C. Various forms of *Histoplasma capsulatum.* (After Darling.)

In all of these figures the red equals chromatin and the blue, protoplasm.

CHAPTER I.

The Leishman-Donovan Bodies. Leishmania-donovani.

Since their discovery, the Leishman-Donovan bodies, or *Leishmania-donovani*, have proven of the greatest interest to students of protozoology and tropical medicine, and have been accepted as the cause of a form of tropical splenomegaly, commonly known as kala-azar or "dum-dum fever." Wright's discovery of a similar organism in tropical ulcer (Delhi boil) and the discovery of Pianese and Nicolle in infantile splenic anaemia of a parasite indistinguishable morphologically from these organisms has awakened renewed interest in the subject, and would appear to indicate that parasites belonging to the genus *Leishmania* are more widely distributed than we had supposed and that they constitute a most important factor in the etiology of disease.

While it is far more common to find *Leishmania-donovani* in the liver and spleen than in the blood, it is true that they may be demonstrated in the peripheral blood, and, therefore, have to be considered in any discussion of the protozoa of the blood.

Historical.—The form of tropical splenomegaly known as kala-azar has long been studied in India, where it was first described, and is a unique illustration of the fallibility of medical opinion and deduction. Clarke first called the attention of medical men to kala-azar in 1882, when he studied it in Assam, and states that the disease was recognized in 1869. For many years it was regarded as a persistent form of malaria, or malarial cachexia, and it was not until the discovery of the *Leishmania-donovani* that the theory of the malarial nature of this malady was abandoned, although many other theories had developed regarding its etiology. Thus, Giles, after careful study, announced in 1889 that malaria had nothing to do with the etiology of kala-azar, but that the disease was due to *Anchylostoma duodenale*, as most of the patients suffering from the disease showed ova of this worm in their faeces. Bentley, in 1903, regarded kala-azar as a severe form of Malta fever; while in 1896, Leonard Rogers, and in 1898, Ronald Ross, considered the disease as malarial in nature, Rogers claiming that it was a fatal form of malarial fever, while Ross considered it as malarial fever complicated by some secondary infection. Manson was one of the first to suggest that kala-azar was a disease entity, due to some undiscovered parasite, probably a trypanosoma, and it is interesting to observe how closely this careful investigator guessed at the truth.

To Leishman belongs the credit of first observing and describing, in a soldier of the English Army, the true parasite of kala-azar. In 1900 he had observed in the splenic pulp obtained at autopsy from a soldier who had died of

kala-azar small round or oval bodies, possessing a large and small chromatin mass; at that time he did not call attention to them, but later, having found similar bodies in the blood of a rat infected with the parasite of nagana, he published a paper (in 1903) calling attention to the matter, and suggesting that the bodies observed by him in the splenic pulp of the soldier might be degenerative forms of a trypanosoma. In the same year Donovan found the same parasite in splenic smears obtained at autopsy and in blood from the spleen obtained during life, and their presence was quickly confirmed by Marchand and Manson in patients suffering from kala-azar. The results obtained by the investigators mentioned awakened great interest in the subject and during the next few years the fact was definitely demonstrated that patients suffering from this disease invariably present within their viscera, and often in the peripheral blood, the parasite described by Leishman and Donovan, and at the present time this parasite is accepted as the cause of the disease. That it is the cause has not been absolutely proven, but the fact that it is found always and only in patients afflicted with this fever is, I believe, sufficient to prove that it stands in etiological relationship to kala-azar.

Geographical Distribution.—For years it was thought that kala-azar was a disease peculiar to India, but after the discovery of the parasite it was found that the disease was widely distributed throughout the Orient and every year the geographical distribution of this organism is added to by investigators. At first localized in certain regions in India, it has gradually spread until at the present time it is a veritable scourge in various regions of that country and is said to be still spreading.

It is common in Ceylon and Burma, and has been found in China, in Arabia, Egypt, the Soudan, Algeria, Tunis, and in other parts of Africa. Although it has been carefully searched for in the Philippine Islands, it has not as yet been demonstrated there. The occurrence, however, of a form of tropical splenomegaly in these islands is suggestive, and further research may show that *Leishmania-donovani* is the etiological factor in some of these cases. While serving on the U. S. Army Board for the Study of Tropical Diseases in the Philippine Islands, Ashburn and I repeatedly examined the splenic pulp from a native suffering from splenomegaly accompanied by attacks of fever, but were not able to find the Leishman-Donovan bodies, although hours were spent in the search and many splenic punctures were performed. While in this case the condition was obviously not due to *Leishmania-donovani*, it is possible that it may be the etiological factor in some of the cases of enlarged spleen not infrequently observed, and the subject should be given careful study.

Biological Position.—The biological position of the Leishman-Donovan parasite has occasioned much controversy, and it is impossible to classify this organism permanently until we know every point regarding its morphology and life history. At the present time a provisional classification has been agreed upon, in which the Leishman-Donovan body is placed in the genus *Leishmania*

and species *donovani*, the proper name for the organism being *Leishmania-donovani*.

Leishman considered the organisms as degenerated forms of a trypanosoma, but later investigations have shown that trypanosoma forms are never found in the human body, and while the development of flagellated forms in cultures might appear to confirm Leishman's theory, the flagellated forms are distinct morphologically from any known trypanosoma. Laveran, Mesnil, and Donovan regard the parasite as a *Piroplasma*, as they have seen forms which they have interpreted to be intracellular in the red blood-corpuscle, and Laveran named it "*Piroplasma-donovani*." The existence of forms occurring within the red blood-corpuscles is very doubtful and the further fact that the organism possesses two clumps of chromatin and that, in cultures, flagellate forms develop, definitely place it in some other genus. Rodgers places it in the genus *Herpetomonas* and Birt thinks that it may be the gregariniform stage of a Herpetomonas because of its resemblance to the small ovoid forms of *Crithidia fasciculata*. Ross, who considers it a distinct form of protozoa, suggested placing it in a new genus, *Leishmania*, and named it *Leishmania-donovani*, and until we know more of its life history it is considered wise by most protozoologists to adopt the classification suggested by Ross.

The discovery by Wright, of Boston, of a similar parasite in tropical ulcer, and by Pianese and Nicolle in infantile splenic anaemia, has added two more members to the genus *Leishmania;* the organism associated with tropical ulcer being called *Leishmania tropica*, while that associated with infantile splenic anaemia is known as *Leishmania infantum*.

The Morphology of Leishmania-donovani.—The morphology of *Leishmania-donovani* in the human body and in cultures varies so widely that it is necessary to consider each separately. The flagellate forms observed in cultures have never been observed in the peripheral blood or in smears from any of the organs of the body, so that it is evident that the flagellate stage of growth is extracorporeal, and probably occurs within some insect, as will be shown later in considering the very interesting work of Patton.

Morphology in Man.—The parasite consists essentially of a small mass of protoplasm surrounded by a limiting membrane, and enclosing two chromatin clumps, one considerably larger than the other. The organisms vary somewhat in size, measuring from 2 to 4 microns in length by 1.5 to 2 microns in breadth.

In shape the Leishman-Donovan bodies are generally oval, but may be elongated slightly or perfectly spherical. Pyriform organisms are observed and led to the classification of the organism as a pyroplasma, but it is probable that most, if not all, of the organisms presenting a pyriform shape are so distorted in the process of making the smear. In the fresh preparations the organism is never observed to change its shape, thus indicating that it does not possess amoeboid motility.

The limiting membrane is well defined in the fresh specimen, but in stained

preparations it is commonly dim or may appear absent, although in deeply stained specimens it may be very well defined as a bluish, clearly cut membrane surrounding the almost unstained and vacuolated protoplasm. It does not contain any trace of chromatin.

The protoplasm, in fresh specimens, appears homogeneous and refractive. It does not stain well and appears vacuolated in stained specimens, the chromatin masses appearing to lie in a large vacuole surrounded by the limiting membrane. The protoplasm, when stained by any of the modifications of the Romanowsky stain, appears faintly bluish in color in well-stained specimens, the color being most marked around the periphery of the organism just within the limiting membrane.

The two chromatin masses lie within the cytoplasm, one, the larger, being situated at the center or near the periphery, while the smaller mass is situated opposite the larger, near the periphery of the parasite. In rare instances these two masses of chromatin are joined together by a bluish-stained portion of cytoplasm. The larger chromatin mass, or nucleus, is generally oval in shape, although not infrequently it is perfectly spherical, and stains a dull red or pink, much less intense in color than the staining of the smaller mass. Manson and others believe that the nucleus, prior to division, moves toward the periphery, and becomes elongated, and it is certain that when the nucleus is situated at the center of the parasite it is always oval or spherical in shape, and that the elongated forms are only observed at the periphery. The smaller chromatin mass (centrosome or blepharoplast) is generally rod-shaped, and stains a very intense scarlet with the Romanowsky stains, sometimes appearing almost black. It is situated opposite the nucleus, and the rod may point toward the latter or lie at any angle to it; this body exhibits no distinct structure, staining evenly throughout and appearing like a bacillus. Christophers and James have observed a tail-like prolongation of the chromatic substance of the blepharoplast, extending from it at right angles to its long axis, the significance of which has not yet been determined.

In smears from the liver and spleen the parasites may occur free, lying singly or in groups, or they are observed within the endothelial cells in large numbers, or lying in masses in a granular faintly stained matrix, the remains of the degenerated cell. In man *Leishmania-donovani* are intracellular organisms, invading the endothelial cells of the organs and only appearing free in the blood plasma or the juices of the organs after they have been liberated by the destruction of the host cell. The parasite invades the protoplasm of the host cell and apparently multiplies within it, causing great enlargement and ultimate destruction of the nucleus and degeneration of the entire cell. In the peripheral blood and in smears of the various organs, multitudes of these parasites may be observed within phagocytes, which undoubtedly play a very important part in their destruction within man. In the irregular masses of granular substance already mentioned the parasites may occur in very large numbers, and I have counted in one such matrix over three hundred parasites.

It is not uncommon to observe atypical parasites in these granular masses, in which either the nucleus or blepharoplast is missing and the limiting membrane remains unstained.

Manson and Low, who have contributed valuable studies upon the morphology of the Leishman-Donovan body, distinguish several types of the organism in stained films, and as their description applies to what is usually observed in smears made from the liver or spleen, I give it in their own words:

"In the stained films we recognize the following:

"1. Oat-shaped, oval, and circular bodies, clearly defined in outline, stained a faint blue, and having a rather large and deeply stained, usually spherical nucleus, lying against the capsule about the middle of the parasite, and a still more deeply stained, short, bacillus-like body on the opposite side of the capsule, but directed, as a rule, but not invariably, toward the nucleus at various angles. In a few instances this bacillus-like centrosome, if so we may call it, is represented by a point."

2. "Similar and generally rather larger bodies with the nucleus larger and less deeply stained or with the nucleus spread out as a deeply stained layer on the inside of the capsule, and in the usual position, that is, *vis-a-vis* to the centrosome. In the latter type of parasite, with the exception of the nucleus and centrosome, the contents of the capsule are very faintly stained."

3. "The foregoing bodies in association with a faintly staining and slightly granular substance, which may be either regularly disposed around them or attached to one side of them as a roundish or flocculent irregular mass."

4. "Two of the oval bodies closely applied to each other, one of the bodies being smaller than the other. Occasionally in these twin bodies their respective nuclei and centrosomes are disposed symmetrically."

The last named form of parasite is a dividing form or one in which division is complete. The arrangement of the centrosome as a single small dot of chromatin is not uncommon in the large collections of parasites within a granular matrix, and very often, in such instances, it is impossible to distinguish all of the morphological features which have been described as characteristic of the Leishman-Donovan body.

The morphology of the forms undergoing division will be considered in speaking of the methods of multiplication of these parasites. (See Plate IV.)

Morphology in Cultures.—In 1904, Leonard Rogers, of the Indian Medical Service, first succeeded in cultivating the Leishman-Donovan bodies, and proved that in such cultures true flagellated bodies developed which, on account of their resemblance to the trypanosomatidae, were described by him as trypanosomes, and so regarded until further culture experiments definitely proved that they were not morphologically identical with any known form of trypanosoma.

The first morphological change observed in the parasite in cultures is a considerable enlargement of the nucleus (macronucleus), the chromatin at the same time becoming less compact and staining less intensely; coincidently with

the enlargement of the nucleus the protoplasm apparently increases in amount and the entire organism becomes larger; the centrosome (micronucleus) does not enlarge, and remains unchanged throughout the entire process of flagellation. After the changes described the organism undergoes division by simple fission at least twice, the resulting bodies being round or oval in shape and possessing the same morphology as when observed in man.

After this preliminary division has been completed there appears in the protoplasm a vacuole which contains an eosin staining substance, called by Rogers the "eosin-spot," which is always situated near the blepharoplast (micronucleus). The parasite now becomes elongated and ovoid in shape, one end being more narrow than the other, and the blephoroplast and eosin containing vacuole become situated at one end of the body of the organism, generally the more pointed extremity. After attaining this position the eosin vacuole enlarges and finally reaches the surface of the body, where it appears to liberate a fringe-like structure which eventually becomes a flagellum. This, when fully developed, is seen to arise from the blepharoplast (micronucleus) as in the trypanosomes. No undulating membrane ever develops, nor is there any approximation of the blepharoplast and nucleus at any stage in the process of flagellar formation. After the liberation and development of the flagellum the entire organism elongates, the extremity furthest away from the blepharoplast becoming narrow and pointed, while that from which the flagellum arises is more rounded in appearance; the nucleus is situated toward the non-flagellated extremity in some instances but is central in the majority of the parasites.

The flagellated forms, the development of which has just been described, divide into spirillar-like forms, division being preceded by the appearance of chromatin granules, which are arranged in pairs throughout the protoplasm. The division of the flagellate forms occurs longitudinally and, according to Leishman, more than two spirillar-like organisms result from such division, but Rogers describes an equal division of the organism into two spirillar-like forms. According to Rogers, the blepharoplast (micronucleus) and flagellum first divide, followed by the division of the nucleus, and the longitudinal splitting of the body into two equal portions, each of which repeats the process of division within a short time. This rapid division results in the formation of rosettes in which the flagella point toward the center of the rosette. It will be observed that, according to Roger's description, the flagellum of each organism is already formed when division is complete, while, according to Leishman, the flagellum is developed after division, which has resulted in the formation of several individuals. Minchin also states that the process of division would appear to be "a process of markedly unequal longitudinal fission." As a matter of fact, both forms of division occur, equal longitudinal division being most commonly observed; but not infrequently an organism may be observed in which the splitting off of the minute spirillar-like forms described by Leishman is occurring. The latter forms are at first devoid of a flagellum, but one is developed rapidly and the organism becomes very actively motile.

The forms resulting from equal longitudinal division are at first pear-shaped and broad, but soon elongate and become actively motile, much more so than were the parent bodies at the time of division; the blepharoplast, from which arises the flagellum, is situated anteriorly, while the nucleus is at or near the center of the body. After the formation of the flagellated forms no further development occurs in cultures, and the organisms soon perish. The flagellated forms of the Leishman-Donovan body appear in cultures between the third and sixth day after inoculating the culture media.

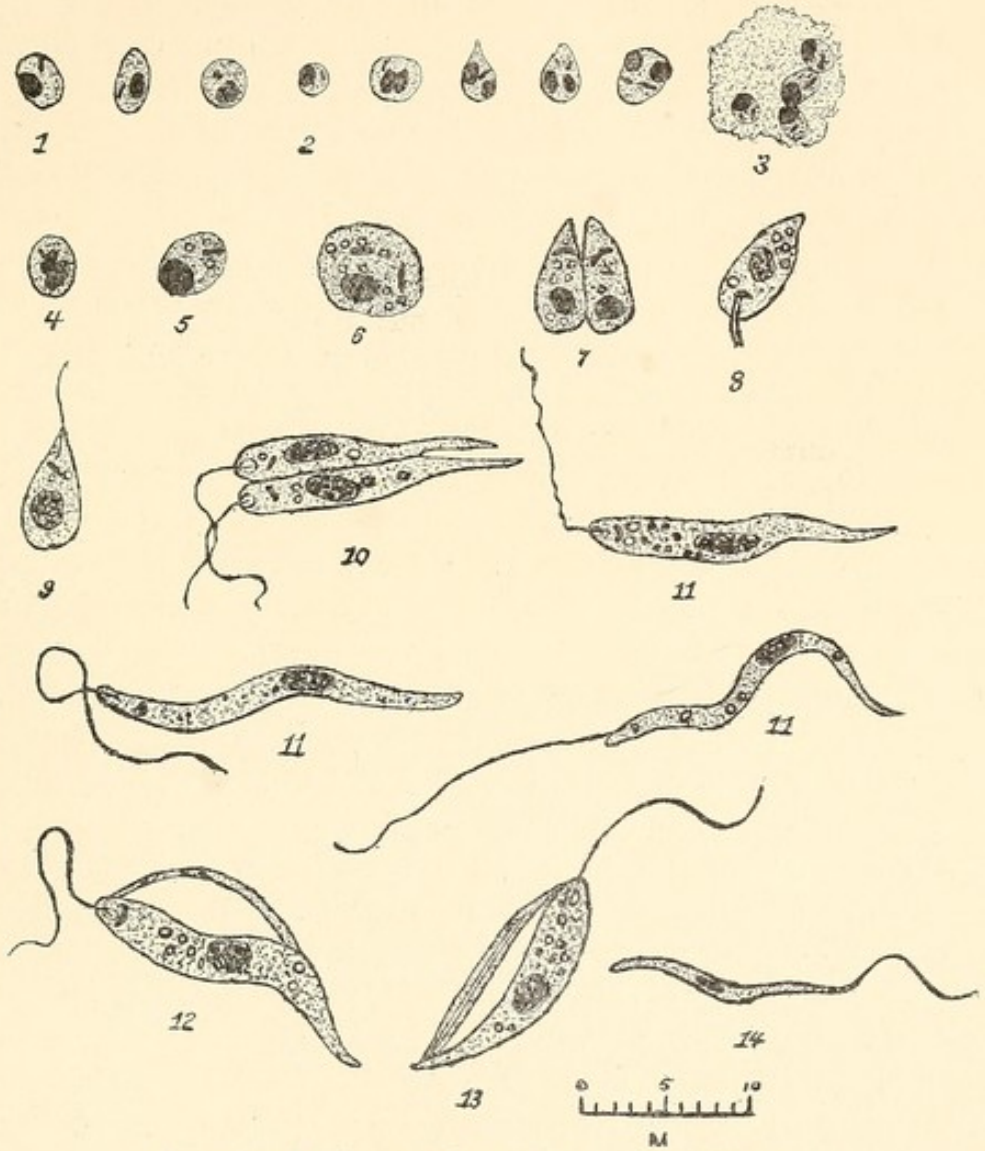

FIG. 26.—Leishmania donovani. (After Leishman.)
1–3, Kala-azar parasites as observed in man. At 3 is seen a large mononuclear cell containing four parasites; 4–14, *Leishmania donovani* as observed in cultures (cultural forms). At 12 and 13 are seen parasites dividing into the spirochæte forms described by Leishman.

Multiplication.—In man, *Leishmania-donovani* multiplies in two ways: by simple fission, binary in character, and by multiple fission. In the former the nucleus first divides into two, quickly followed by the division of the blepharoplast (micronucleus) into two portions, after which the body of the parasite divides longitudinally into two equal portions, each of which contains a nucleus

and a blepharoplast. When multiple fission occurs, the parasite becomes nearly twice as large as normal, the nucleus and blepharoplast divide into three, four or more equal portions, and the protoplasm shows lines of cleavage surrounding each pair of chromatin masses, the nucleus and blepharoplast. In this way the multiplying organism resembles somewhat a malarial rosette, but may be easily distinguished by observing that each segment consists of a mass of protoplasm, and two chromatin masses, one larger than the other, and placed opposite one another, the smaller being rod-shaped. The organisms resulting from this mode of multiplication are much smaller than the parent organism and are sometimes so minute as to require very careful examination in order to demonstrate them.

The multiplication of the parasites in cultures has already been described, and, as will be shown, Patton has demonstrated a similar method of multiplication in the stomach of a certain species of bed-bug.

Cultivation.—Until 1904 nothing was known regarding the extracorporeal existence of the Leishman-Donovan body, but in that year Rodgers was successful in demonstrating that this organism can be cultivated outside of man and that its developmental cycle comprised not only the forms observed in the infected patient, but that it also possessed a flagellate stage which only developed when the organism was removed from the blood or organs of its host. The further researches of Patton, which would appear to prove that the same forms occur in the stomach of the bed-bug, indicate that this insect is the transmitting agent of the disease, and that the flagellate forms, as in malaria, only develop within an intermediate host. Rogers' cultivation experiments were promptly repeated and confirmed by other investigators, notably Christophers, Leishman, Chatterjee, Statham and Patton. I have already described the development of the Leishman-Dononan bodies in cultures and will here discuss briefly the method most successful in cultivation.

Rogers first endeavored to grow the parasites by adding to blood obtained by splenic puncture from kala-azar patients, about 1 c.c. of sterile salt solution containing 5 to 10 per cent. of sodium citrate, and incubating at blood temperature, but he found that by this method the parasites were quickly destroyed and that no development occurred. Using the same method, and incubating at 27° C., he found that the parasites lived for several days and that evidences of division occurred, but no flagellate bodies appeared. However, upon incubation at 22° C. he found that the parasites multiplied very rapidly and that the characteristic flagellate forms developed within from three to six days.

The following procedure will be found to result in success if carefully carried out: Prepare some normal salt solution and to it add about 8 per cent. of sodium citrate, dissolving thoroughly; if the resulting solution is not acid in reaction it should be made very slightly so by the addition of citric acid, after which it is sterilized. Several test-tubes of small caliber should be sterilized after stopping them with cotton wool, and a reliable glass syringe, to

be used in securing the blood, should be sterilized along with the other materials. A patient suffering from kala-azar, in whom numbers of the parasites have been demonstrated by microscopic examination of smears from the liver, is selected, and the liver punctured, using the sterile syringe and observing the most careful precautions regarding the sterilization of the skin and of the hands of the operator. About 1 c.c. of blood, or more if the blood flow freely, is withdrawn and about half placed in one culture tube, the remainder in another, and to each tube about 1 c.c. of the citrate solution is added. If the organisms are not very numerous it is preferable to add all of the blood to 1 c.c. of the citrate solution in one tube. After gently shaking together the blood and the citrate solution the tubes are placed in an incubator at 22° C. (in most countries where kala-azar occurs an ice incubator will be necessary) and the preparation examined daily, care being taken not to infect the tubes, as such infection inevitably results in the destruction of the Leishman-Donovan bodies.

Rogers calls attention to the following important points which should be most carefully regarded if we are to expect success with the culture of *Leishmania-donovani:* 1. The *temperature* used for incubation should be from 20° to 22° C., as very marked development never occurs above 25° C. According to him, an exposure for even a short time to a temperature above 25° C. results in the destruction of the parasites in the culture. The minimum temperature at which the organisms can develop is about 17 ° C.

2. The mixture of blood and citrate solution must be *sterile* except for the *Leishmania-donovani*, for he found that whenever the cultures became contaminated with other organisms the parasites quickly degenerated and disappeared. All bacteria are inimical to successful cultivation, but Rodgers found that the staphylococci especially were most fatal to the Leishman-Donovan bodies in cultures.

3. The medium should have a slightly *acid reaction*, the acidity being secured by the addition to the infected citrated blood solution of a drop or two of a weak citric acid solution. Rogers found that after thus modifying the culture media the flagellated forms appeared more rapidly and in far greater numbers, and that the development was much more uniform, the flagellates appearing about the third day.

On account of the danger attending splenic puncture, it is preferable to puncture the liver in order to obtain material for culture.

Transmission and Pathogenicity.—Aside from the forms observed by Patton in a species of bed-bug, no phases in the development, under natural conditions, of *Leishmania-donovani* outside the human body have been observed, nor have we any direct experimental evidence that this parasite will produce kala-azar upon being inoculated in man. It is very probable that certain forms of the organisms occur in natural conditions which have not as yet been observed, and that the infective stage may be so different in its morphology from the known developmental stages as to render its recognition impossible. The observations of Patton, of the Indian Medical Service, would

appear to indicate that the parasite is transmitted by the bed-bug, and while his observations have not been confirmed, I believe that he has shown that the parasite can undergo development within an insect and that this method of transmission is the most probable one in every respect.

The development in cultures of flagellated forms; the fact that development occurred best in cultures at a temperature between 20° C. and 22° C., and that the medium should be acid in reaction, as well as certain well-known epidemiological peculiarities, suggested to Rogers and his co-workers that the parasite of kala-azar was transmitted to man by a biting tick or insect. Rogers endeavored to discover the organism in the bodies of bed-bugs, examining no less than 200 bugs, but was unsuccessful. Christophers obtained negative results from his examinations of mosquitoes and ticks, and the work of a few other investigators was equally unsuccessful in demonstrating the parasite within the body of the insects. In 1907, Patton published a preliminary note describing the results obtained by him in infecting a species of bed-bug with *Leishmania-donovani* by feeding experiments, in which he claimed that in the stomach of the infected bugs there occurred forms similar to those observed in cultures. Patton has continued his researches in this direction and has, I believe, proven that in bed-bugs allowed to suck the blood of kala-azar patients and kept at a temperature of 22° C. or thereabouts, flagellated forms develop like those observed in cultures, and that the entire process of development has been observed in blood within the stomach of the insect. In a postscript to his original paper Patton states "Since writing the above I have found in the bed-bug (*Cimex macrocephalus*) all the intermediate stages of development and numerous fully developed flagellates similar to those seen in cultures of splenic blood," and in a letter to Rogers, quoted by the latter in his work, "Fevers in the Tropics," he says: "There is no shadow of doubt that the bed-bug transmits the disease." The bed-bug in which Patton was successful in following the development of the flagellated stage of *Leishmania-donovani* is *Cimex rotundatus* Signoret (*Cimex macrocephalatus* Fieber).

While further observation will probably confirm Patton's work, it should be noted that much still remains to be done before we possess a clear understanding of the exact method of transmission of this disease, and it is especially important that the question of the hereditary transmission of the infection to bed-bugs be determined.

Distribution of the Leishman-Donovan Bodies in Man.—These parasites may be found in almost every organ of the body, but are most numerous in the spleen, bone-marrow, and liver. The pathology of kala-azar and the distribution of the parasites in the body has been thoroughly worked out by Leishman, Marchand, Statham, Christophers, Ledingham, and Manson, and the occurrence of the parasites in the blood has been studied especially by Laveran, Statham, Christophers, Rogers, Donovan, and James. From the observations of these investigators it has been proven that *Leishmania-donovani* is generally found within the cytoplasm of mononuclear cells, very

seldom being observed free in the tissues or in the blood. The occurrence of numerous parasites within the mononuclear cells appears to have no injurious action until the entire cytoplasm is filled with them, when the nucleus is pushed to one side and the cell eventually ruptures; that the cell itself has no injurious action upon the parasite is evidenced by the fact that fission occurs, as is shown by the presence in most of the cells of divisional forms in all stages of division. The nature of the mononuclear cells and their origin has been shown by the studies of Christophers, who has proven that they are endothelial in character, and originate from the walls of the capillaries and lymphatics. In other words, they are the same cells which act as "macrophages" in malaria, but in the case of the kala-azar parasite the macrophage is unable to destroy the organism, as it does in malaria. Christophers has shown that these cells, crowded with *Leishmania-donovani*, are most common in the spleen and in the bone-marrow, but they have also been found in the liver, mesenteric glands, intestinal ulcers, lungs, kidneys, in the lymphatic glands, in the arachnoid, and in ulcerations of the skin and skin eruptions in kala-azar patients. In fact, the parasite may be said to invade the endothelial cells of the capillaries and the lymphatics in almost every portion of the body, but especially in the spleen, bone-marrow, and liver.

Leishman considers that the parasite, after invading the body, is taken up by the endothelial cells, as these cells are well known as active phagocytes, but it would appear more probable that the parasites themselves invade the endothelial cells, as it would seem that they multiply in man only within these cells. However this may be, it is proven that the Leishman-Donovan body is an intracellular parasite whose host cell is the endothelial cell of the blood-vessels and lymphatics.

After multiplication of the parasite has progressed for a certain time the cytoplasm of the cell becomes filled with young organisms, which distend the host cell and eventually cause its separation from the wall of the blood-vessel or lymphatic. The infected cell then ruptures or degenerates and the young parasites are again taken up by endothelial cells or actually invade them, when the process of division, detachment of the endothelial cell, and liberation of the parasites is repeated. The infection is spread through the body by the presence in the blood and lymph of free parasites and infected leucocytes, the larger of which lodge in the capillaries of various organs; the granular matrix in which hundreds of the parasites are commonly observed embedded is undoubtedly the degenerated cytoplasm of the endothelial cell invaded by the organism.

In the *spleen*, which is greatly enlarged, a microscopical examination shows the sinuses filled with multitudes of mononuclear cells containing *Leishmania-donovani;* the infected cells vary in size and are much more numerous in some portions of the sections than in others, while the Malpighian corpuscles are generally free from the infection. In the *liver* the entire process of infection of the endothelial cell and its subsequent detachment from the wall of the capillary may be easily studied, the walls of the portal capillaries being covered with cells

containing parasites, the cells being in various stages of detachment from the vessel wall. The hepatic capillaries also contain many large mononuclear cells filled with parasites. In the *bone-marrow* there occur multitudes of infected mononuclears, showing parasites in all stages of division. In the *kidney* the endothelial cells showing infection are those of the smallest capillaries, especially those of the glomerular tufts, and the parasites have never been demonstrated in the epithelial cells of the tubules. The parasites have never been found in the urine.

The Blood in Kala-azar.—The observations of Donovan, Christophers, James, Laveran, and others show conclusively that the Leishman-Donovan bodies occur in the peripheral blood and that in many cases it is possible to find

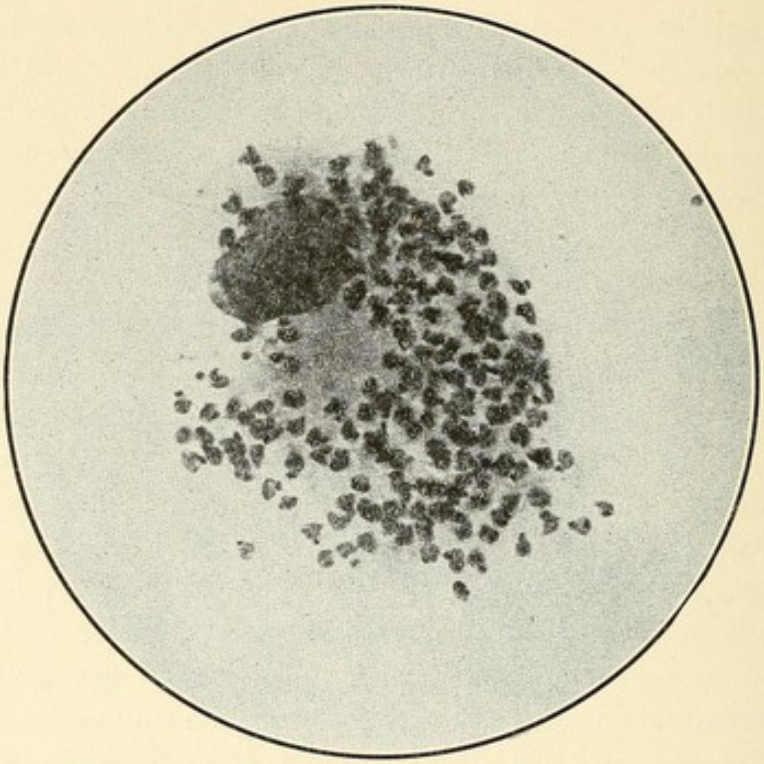

FIG. 27.—*Leishmania donovani* contained within a large endothelial cell. (Note the large number of the parasites.) Photomicrograph from a splenic smear of a patient suffering from kala-azar, kindly sent the author by Dr. Leishman, × 1000.

them in this fluid. Donovan has reported finding the parasites in 75 per cent. of his cases in the peripheral blood while, according to Rogers, Patton was able to find them by a blood examination in even a larger proportion of advanced cases. In the peripheral blood the parasites occur within the leucocytes, chiefly the polynuclears and large mononuclears. Laveran and Mesnil and Donovan have reported the occurrence of the parasite within the red blood-corpuscles, but their observations have not been confirmed, and it is probable that parasites lying *upon* but not *within* the red corpuscles were really observed by these investigators, as numerous workers have reported instances of this character. It has been found that the parasites appear in the blood most frequently during the latter stages of the disease and that repeated examinations of the blood in

new infections almost invariably result negatively so far as the presence of the parasite is concerned.

Certain changes are produced in the blood by *Leishmania-donovani* which are of interest and importance from a diagnostic standpoint. In advanced cases there is marked anaemia, the red blood count being reduced to from 2,500,000 to 2,000,000 per cu. mm. the haemoglobin being reduced in proportion, while there is a marked leucopenia, the white cells numbering from 1,000 to 5,000 per cu. mm. The most characteristic change observed, aside from the very marked leucopenia, is a reduction in the number of the polynuclears and eosinophiles, and a large increase in the relative proportions of the large mononuclears and lymphocytes. The increase in large mononuclears is of greatest importance from a diagnostic standpoint, according to Rogers, but it should be remembered that an increase occurs in these cells in malaria, trypanosomiasis, and other diseases, so that it cannot be considered peculiar to kala-azar.

Elimination of the Parasites.—It may be said that nothing is known with certainty regarding the elimination of *Leishmania-donovani* from the body. They have never been demonstrated in any of the excretions, and the situation of the parasites in the endothelial cells of the capillaries in the kidneys, and their absence from the renal epithelium or the cells of the tubules is almost certain proof that they are not eliminated through the kidneys. The occurrence of the parasites in the intestinal ulcers and in eruptions and ulcerations of the skin suggest that they may be eliminated in the faeces or through the skin, but they have never been found in the faeces, and as the ulcerations of the skin are not of constant occurrence it is not probable that the parasites are naturally eliminated in this manner. When haemorrhages occur, which are not infrequently observed in this disease, the parasites may be found in the blood, and it may be that this is one method of elimination. The bites of insects furnish the most probable method by which the parasites leave man, and the observations of Patton, already referred to, would appear to indicate that the bed-bug is the intermediate host of *Leishmania-donovani*.

Demonstration of Leishmania-donovani.—As the diagnosis of kala-azar rests upon the recognition of *Leishmania-donovani* in the blood or tissues, the methods available for its demonstration require careful consideration. The parasite is most easily recognized in stained specimens, and for staining the method of Wright, of Leishman, and the Giemsa stain, described in the section upon malaria, are suitable. Wright's stain is very satisfactory and I believe will be found most useful, but Leishman's method is excellent and is the one which has been most frequently employed for the demonstration of this organism. The Giemsa stain gives good results, but is more complicated and requires greater care in order to secure good specimens.

The organisms may be demonstrated in stained smears secured from the spleen or liver by puncture or in smears of the peripheral blood. On account of the danger of splenic puncture, the specimen should be preferably obtained from the liver, the utmost precautions being exercised as regards asepsis of the

skin, the instrument used, and the hands of the operator. The abdomen should be tightly supported by a bandage and the patient cautioned against jumping when he feels the sting of the needle; the latter should be a long hypodermic needle having a very sharp point and not too fine a caliber. It should be remembered that it is not necessary to secure much of the material for examination and that if we secure only blood the examination will probably result negatively, as it is the pulp of the liver or spleen which will give the best results in examination.

The examination of the peripheral blood should be made in every suspected case, but it is only in those showing high fever or in advanced cases that we can expect to find the parasite. A one-twelfth inch immersion lens should be used and every leucocyte carefully examined, and several hundred should be inspected before the result is recorded as negative. The examination of the peripheral blood will generally result in the demonstration of the parasite in advanced cases when there is high temperature, but little can be expected from it in the early stages of the disease, and thus it cannot be relied upon as a method of diagnosis in such cases. To facilitate the finding of the parasites in the peripheral blood, from 1 to 5 c.c. of blood may be taken from a vein, added to a centrifuge tube containing a little sodium citrate solution to prevent clotting, and thoroughly centrifuged, after which specimens are prepared from the upper portion of the layer of cells. Leishman recommends this method, but Rogers states that he has not been able to demonstrate the organism by its use. It deserves a more extended trial. The presence in leucocytes or mononuclear (endothelial) cells of bodies possessing a capsule, a spherical or oval mass of chromatin, and a rod-like, much smaller, chromatin mass, the entire organism being about the size of a blood platelet, is conclusive as to the presence of *Leishmania donovani*, when such cells are obtained from the organs or peripheral blood of patients suffering from fever.

Leishmania tropica and Leishmania infantum.—Because of their morphological resemblance to *Leishmania-donovani*, it is necessary to mention briefly two other organisms occurring in man belonging to the genus *Leishmania; i.e.*, *Leishmania tropica*, discovered by Wright in the granulation tissue cells of oriental sore (tropical ulcer) and *Leishmania infantum*, discovered in infants suffering from splenic anaemia by Pianese and Nicolle. Morphologically, these organisms are indistinguishable from the Leishman-Donovan body, but that they are distinct species is proven by the pathological lesions produced by them.

Nicolle, in 1908, produced splenic anaemia in dogs by inoculating them with tissue from cases of splenic anaemia, and cultivated the organisms from the experimental animals on blood-agar, flagellate forms developing in the cultures like those of the Leishman-Donovan body. He was not able to reproduce the disease by inoculation of these cultures, but Novy in the same year was successful in producing the disease in a dog by the inoculation of cultures containing numerous flagellate forms obtained from Nicolle. The results

obtained by Novy prove beyond question that the flagellate forms of *Leishmania infantum*, when inoculated into dogs, produce a disease identical with infantile splenic anaemia, and that the forms found in the dog's tissues are morphologically indistinguishable from the forms of *Leishmania-donovani* observed in man. His results also prove that the flagellate forms revert to forms usually observed in man, and that these forms, when cultivated, develop typical flagella, as he was able to show that in cultures of the infected dog's blood made from the spleen, liver and bone-marrow there developed "enormously rich cultures of the typical flagellate forms." The importance of the work of Novy in its relation to the life history of *Leishmania donovani* cannot be over-estimated, and it will indeed be surprising if, with the light which his studies have thrown upon the subject, we are unable to solve the problem of the transmission of tropical spleno-megaly or kala-azar.

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CHAPTER II.

Trypanosoma Gambiense (Trypanosoma Ugandense).

Trypanosoma gambiense is a protozoan parasite of the blood, occurring in Africa, and causing the peculiar disease known as "sleeping sickness." In the early stages of the disease the parasite is found in the blood and lymphatic glands, and, after the development of typical symptoms, in the cerebrospinal fluid as well as in the blood and the lymphatic glands.

Trypanosomes are probably the most widely distributed of all protozoan parasites, being found in mammals, birds, reptiles, batrachians, fishes, and insects. To Valentin, of Berne, belongs the credit of the discovery of the trypanosomes, a species of which he found in the blood of trout, but it was not until Dutton's discovery of a trypanosome in the blood of man in 1901 and the subsequent work of Castellani, Bruce, and Nabarro, proving this organism to be the cause of sleeping sickness, that the trypanosomes were considered of importance in human pathology.

Historical.—In 1841, Valentin discovered and described the first trypanosome, a parasite of the trout (*Salmo fario*), and his discovery was followed by papers relating to similar organisms, found in the blood of the frog, by Grube and Gluge (1842–1843), the former author first applying the generic term "trypanosoma" to these organisms. In 1845, Gros found a trypanosome in the blood of the field mouse and mole, and in 1850, Chaussat, and in 1871, Ray Lankester, discovered trypanosomes in the blood of batrachians. Interest in these organisms was renewed in 1871, by Lewis, who found that a trypanosome was a common parasite of the blood of rats in India, and his observations were very soon confirmed by workers in other parts of the world, All of the trypanosomes discovered up to and including Lewis's trypanosome, were non-pathogenic, but in 1880, Evans discovered a trypanosome in the blood of horses suffering from "surra," which he proved experimentally to be the cause of that disease. The discovery of Evans was followed in 1894 by that of Rouget, who found another trypanosome in the blood of a horse suffering from dourine (*mal du coit*); of Bruce, of the trypanosoma of nagana; of Elmassion, of the trypanosome of *mal de caderas;* and of Theiler, of the trypanosoma of *galziekte* or gall-sickness of cattle in the Transvaal.

Until 1902, the date of the discovery of the trypanosome of Theiler, it was supposed that the trypanosomes were parasites of the lower animals only, but the observations of Dutton and Todd and of Castellani, Bruce and Nabarro, in 1902 and 1903, conclusively proved that there occurred in man a pathogenic

trypanosome of the greatest importance because of the fatal disease of which it was the etiological factor.

The trypanosome of man is the cause of sleeping sickness, a disease first described by Winterbottom in 1803 as occurring among the negroes along the West Coast of Africa. On account of its peculiar symptoms this disease has always attracted a great deal of attention, and many efforts were made to determine its etiological organism, many bacteria having been described as concerned in its production. Marchoux, Bettencourt, and Castellani were among the most earnest students of the disease and all described some bacterium as the causative factor. Manson for a long time considered that sleeping sickness was due to *Filaria perstans*, because this organism was met with so often in the blood of those suffering from the disease, but the fact that *Filaria perstans* occurs in many regions where sleeping sickness is unknown and that many victims of sleeping sickness are not infected with this parasite, conclusively proved that the filaria had no relation to the disease.

In 1901, Forde observed, in the blood of a European in the hospital at Bathurst, Gambia, minute, actively motile, worm-like bodies, the nature of which he was unable to determine, but Dutton, who examined the blood of the same patient in December, 1901, recognized the bodies as trypanosomes, and gave the name *Trypanosoma gambiense* to the organism. The occurrence of this organism in the blood of certain patients suffering from fever was confirmed by Dutton and Todd, Manson, Broden, Brumpt, and Baker in 1903, and Maxwell-Adams in the same year suggested that the organism might be the cause of sleeping sickness.

In 1903, Castellani, while engaged in examining the cerebrospinal fluid of negroes suffering from sleeping sickness, discovered that a large proportion of them showed a trypanosome in this fluid, which he considered a different species from *Trypanosoma gambiense*, and which he called *Trypanosoma ugandense*, a name afterward amended to *Trypanosoma castellani*, by Kruse. The discovery of Castellani was confirmed by Bruce and Nabarro at once; they found the parasite in the cerebro-spinal fluid, in every one of thirty-eight cases examined and in twelve of them in the peripheral blood. These authors concluded that the trypanosome was the cause of the disease, and their researches were confirmed by Greig, Brumpt, Dutton, Todd, Broden, and Christy.

For some time the trypanosome found in sleeping sickness and that found in patients suffering from irregular fever (*Trypanosoma gambiense* and *Trypanosoma ugandense*) were thought to be different species, and Castellani stated that well-marked morphological differences existed between them, but the observations of Bruce, Nabarro, Greig, Dutton, Todd, and Christy proved that, without doubt, the trypansoma found in sleeping sickness, and discovered by Castellani, was identical with that found in fever cases, and discovered by Dutton and Forde. The later observations of Thomas and Linton, Laveran, Thomas and Breinl, and Gray and Tulloch upon the pathogenic lesions caused in animals by these organisms confirm the observations based upon

morphology, and it is now generally accepted that *Trypanosoma gambiense* and *Trypanosoma ugandense* are identical and that the organism should be known as *Trypanosoma gambiense.*

The earliest symptoms of sleeping sickness are not those of lethargy, but are characterized by fever, swelling of the lymphatic glands, and skin eruptions, and it is during this stage that the trypanosomes are found in the peripheral blood and in the gland juices, while they are found in the cerebrospinal fluid only after the onset of the symptoms typical of sleeping sickness: languor, gradually developing sleepiness, tremor, and coma. In other words, sleeping sickness is merely the termination of trypanosoma infection or trypanosomiasis.

Geographical Distribution.—*Trypanosoma gambiense* is confined, as regards its geographical distribution, to certain parts of Equatorial Africa. It is found most frequently along the West Coast, in Gambia, Uganda, the Congo basin, Sierra Leone, Liberia, Upper Guinea, the Ivory Coast, and Yatenga. It is also found in South Angola (Wellman), the Upper Niger, Lagos, Togo, the Cameroon (Ziemann), Angola, Portuguese West Africa, French Congo, the Congo Free State, German East Africa (Ahlbory), and in the Nile Valley. The parasite is found along the banks of lakes and rivers, and the extension of commerce and means of travel in Africa has resulted in the introduction of the parasite into many localities where, until quite recently, it was unknown. The rapid extension of sleeping sickness throughout the river valleys of Africa has become of the greatest economical importance, as the disease is invariably fatal and has already caused the death of hundreds of thousands of the natives of the infected regions. It is estimated that in Uganda alone more than 100,000 deaths have occurred from infection with this parasite during the six years from 1901 to 1907.

Biological Position.—There is no doubt regardng the biological position of *Trypanosoma gambiense.* In 1843, Grube established the genus *Trypanosoma,* in which he placed the trypanosome of the frog, and in which all organisms possessing the morphology of a typical trypanosome must be placed. As regards its generic position, therefore, *Trypansoma gambiense* is a member of the genus *Trypanosoma.* As regards its relation to the Protozoa, in a wider sense, it belongs to the Mastigophora, sub-class Flagellata, and family Trypanosomatidae.

General Morphology of Trypanosomes.—It is necessary, in order to understand thoroughly the structure of *Trypanosoma gambiense,* to consider in detail the morphology of trypanosomes in general and their biological peculiarities. Laveran and Mesnil, in their classical work upon the trypanosomes, state that "Several mammalian trypanosomes resemble one another so closely that it is impossible to distinguish them by their morphological characters alone. This applies to the trypanosomes of nagana, surra, dourine, and sleeping sickness." It will thus be seen that a study of the morphology of the trypanosomes, as a class, is of importance in the study of any one species of trypanosome, as in this way only can we interpret many structural phenomena observed

in isolated organisms or understand the significance of certain biological processes which may only rarely be observed in the organism under consideration.

All typical trypanosomes are spindle-shaped, and possess a nucleus, a centrosome or blepharoplast, and an undulating membrane which ends in a flagellum. Among zoologists there is considerable discussion as to which end of the trypanosome the flagellum arises from, the anterior or posterior. Laveran and Mesnil consider the extremity from which the flagellum arises as the anterior extremity, and this interpretation is accepted by most authorities, but Woodcock, Sambon, Manson, and others, regard the flagellated extremity as posterior. In order to avoid confusion it is better, as suggested by Minchin, to distinguish the two extremities of the body of the trypanosome as the *flagellar* and *antiflagellar* extremities, respectively.

A trypanosome presents for description a body, a nucleus, a blepharoplast, an undulating membrane, and a flagellum.

The *body* is more or less spindle-shaped in all but cultural forms, some of which may be almost spherical. As, however, no one has yet succeeded in cultivating *Trypanosoma gambiense*, the morphology of cultural forms will not be considered in this summary of the general morphology of the trypanosomes. Considerable variation exists as regards the shape of the organism, even in individuals of the same species, and short, blunt-ended forms occur together with slender, pointed organisms, in the same specimen of blood. The shape of the organism may also differ according to the species of animal which is infected.

The *flagellar* extremity of a trypanosome is generally longer and narrower than the *antiflagellar* extremity, and may be pointed or slightly rounded. A careful examination will demonstrate that in nearly every case it is continued for a little distance along the flagellum, which thus does not start abruptly from the body, but gradually, as a continuation of the undulating membrane and the protoplasm of the body.

The *antiflagellar* extremity varies extremely in shape in various species, in individuals of the same species, and in the blood of the same animal. Thus it may be elongated and pointed, short and blunt, or hemispherical in shape, and in *Trypanosoma gambiense* the variation is often very marked.

The *protoplasm* of trypanosomes stains a deep blue when Wright's method is used and is composed apparently of fine granules; arranged in more or less irregular masses. This arrangement of the granules causes an irregular staining of the protoplasm, some areas appearing a deep blue, while others are almost unstained. Chromatic granules are present in some organisms, staining a deep violet, and irregularly distributed in the protoplasm. These granules may be of some service in determining species, but cannot be greatly relied upon for this purpose. The body is not surrounded by a definite membrane, so far as we have been able to determine. The protoplasm surrounds the nucleus and the blepharoplast, and may contain one or more vacuoles, especially in degenerating organisms.

The *nucleus*, which stains a bright crimson or violet, with Wright's stain, or any modification of the Romanowsky method, is known also as the *macronucleus* or *trophonucleus;* it is much larger than the blepharoplast, is round or oval in shape, and situated at or near the center of the body of the organism. In *T. lewisi* it is situated in the flagellar end, and is of diagnostic importance. The nucleus is composed of chromatin granules arranged compactly (the granules varying in size), and connected by a dimly staining nuclear substance. The nucleus divides amitotically.

The *blepharoplast*, also known as the *micronucleus*, *centrosome*, or *kinetonucleus*, is very much smaller than the nucleus, and in most species of trypanosomes is situated near the antiflagellar extremity. In trypanosomes undergoing division the blepharoplast may be near the center of the organism, in close relation to the nucleus, and in some species it is *always* situated in this region. It generally consists of a small, compact mass of chromatin granules, staining a deeper purple or red than the nucleus; spherical in shape; and surrounded by a clear, unstained area, oval in shape, which resembles in appearance a vacuole. It measures from 0.5 to 1 micron in diameter, and generally stains so intensely that the separate granules of chromatin composing it are invisible. As it usually lies near the antiflagellar or narrow extremity of the parasite, it often appears to extend the entire width of the organism, but careful examination will demonstrate that a narrow rim of protoplasm surrounds it, if the vacuole mentioned be absent. The blepharoplast divides by simple fission.

The *undulating membrane* is a beautifully curved and delicate membrane extending as a crest or ridge for a variable length along the body of the trypanosome. It varies in length with the situation of the blepharoplast and, as in most of the trypanosomes, this is near the antiflagellar extremity the undulating membrane extends along the greater portion of the body. The structure of this membrane appears similar to that of the protoplasm of the body, but its border is thickened owing to the flagellum which forms it, together with the protoplasm of the membrane. This membrane always arises opposite the blepharoplast on the lateral surface of the body, and extends toward the flagellar extremity, forming, in most instances, along with the flagellum, the flagellar extremity of the trypanosome. The number of curves varies with the species of trypanosome and in some species the undulating membrane is thin and almost straight. The presence of striations in the undulating membrane of some trypanosomes has been reported by Prowazek and others, but most mammalian trypanosomes do not present any very definite structure of the membrane.

The *flagellum* arises from the blepharoplast, is continued along the border of the undulating membrane, and in most trypanosomes extends for some distance beyond the extremity of the body, or undulating membrane, as a free flagellum. In organisms which show a vacuole lying in contact with the blepharoplast the flagellum appears to arise from the border of this vacuole, but in organisms showing no vacuole the flagellum is observed to arise directly

from the blepharoplast. Laveran and Mesnil divide the flagellum into three portions: the root, that portion extending from the blepharoplast to the commencement of the undulating membrane; the intermediate portion, running along the edge of the undulating membrane; and the free portion, forming the free flagellum of the trypanosome. The thickness of the flagellum varies somewhat, it being thickest along the border of the undulating membrane and thinnest at its origin and its free extremity. With any modification of the Romanowsky stain it takes a dark red or purple color, exactly similar to that of the blepharoplast, thus proving that the flagellum is composed of chromatin. Longitudinal division of the flagellum occurs during multiplication of the parasite in most species of trypanosomes, the blepharoplast first dividing, followed by the division of the flagellum along its entire length. In some species only the blepharoplast divides and the root of the flagellum.

Morphology of Trypanosoma gambiense.—In fresh blood *Trypanosoma gambiense* may be easily found with a 1/6 inch objective, appearing as an active, spindle-shaped, colorless body, forcing its way among the corpuscles or moving in a jerky manner across the field of the microscope. Its morphology cannot be satisfactorily studied in fresh specimens, and for this purpose stained preparations, using some modification of the Romanowsky stain, should be employed.

Trypanosoma gambiense varies considerably in length, measuring from 16 to 30 microns long by 1.5 to 2.5 microns wide, the longest forms being those which are undergoing division. The *flagellum* originates in the blepharoplast, forms the edge of the undulating membrane, and is continued as a free flagellum which forms from one-quarter to nearly one-half the total length of the organism. In rare instances there is no free flagellum, the protoplasm of the body and of the undulating membrane extending and blending with the flagellum for its entire length.

The *nucleus* is oval in shape, comparatively large, and situated near the center of the body or slightly toward the antiflagellar extremity; it stains deeply with the chromatin stains.

The *blepharoplast* is situated at the antiflagellar extremity, stains a deep purple, and is composed apparently of a single large dot of chromatin. An unstained area generally surrounds the blepharoplast but according to Laveran and Mesnil, this appearance is due to faulty technic in preparing the specimen, and it is undoubtedly true that many of the trypanosomes do not present this vacuole. The flagellum, in well stained specimens, is seen to arise from the blepharoplast, being intimately connected with it at its origin.

The antiflagellar extremity of the trypanosome varies in shape, being narrow and pointed sometimes, and sometimes rounded and broad. It is evident that the organism possesses the power of altering the shape of this extremity, and that many of the appearances presented in stained preparations are caused by agonal movements of the parasite.

The flagellar extremity is generally pointed, the body being attenuated

gradually until it becomes blended with the undulating membrane and the flagellum.

The *protoplasm* stains a delicate blue and contains chromatic granules, which vary in shape, size, and number in individual organisms.

The description given applies to the average of parasites observed, but it should be remembered that great variations occur in the morphology of this trypanosome, as observed in stained specimens, some of them due to errors in technic, and others representing stages in the development of the parasite, with which, at present, we are unfamiliar. Thus we often observe long, slender organisms and short, blunt ones in the same specimen; some that stain well and others that stain with difficulty; some in which the nucleus is near the center and others in which it is near the flagellar or antiflagellar extremity; some in which the blepharoplast lies within a vacuole, and others in which the vacuole is absent. Forms also occur without a free flagellum, and others in which the undulating membrane is rudimentary or even absent, while the nucleus and blepharoplast are situated in a nearly spherical body, in close contact with one another. In some chromatic granules are absent while in others they are present in great numbers and are of large size. Many trypanosomes are observed undergoing degenerative changes, the protoplasm being filled with vacuoles while the nucleus and blepharoplast either stain very faintly or not at all, the free flagellum also being absent, and the portion forming the border of the undulating membrane staining so faintly as to be almost invisible.

In most instances two distinct forms of *Trypanosoma gambiense* may be distinguished in the blood: one, slender, and having a free flagellum of considerable length; the other, short and broad, and having a short free flagellum. According to the researches of Prowazek, Luhe, Zieman and Nocht, it is probable that the long slender forms are males and the short, broad forms females, while the forms which are intermediate are the so-called "indifferent forms" which are not sexual in nature.

Multiplication.—In the blood of man *Trypanosoma gambiense* multiplies by binary division, the blepharoplast first dividing into two, followed by the nucleus, the flagellum, and the protoplasm of the body, so that eventually two trypanosomes result. As it has been proven that some trypanosomes undergo a sexual cycle of development in an intermediate host (a blood-sucking invertebrate in all the species so far investigated), it is probable that *Trypanosoma gambiense* also has an intermediate host and that sexual multiplication occurs in that host, but at the present time we are ignorant of the changes occurring during such a cycle, although we know that the parasite is transmitted by *Glossina palpalis* and others species belonging to the same genus.

It is not necessary to call attention here to the work of Prowazek on the changes occurring in *Tr. lewisi* in the stomach of the rat louse (*Haematopinus spinulosis*) beyond stating that he was able not only to demonstrate various stages of development of this trypanosome in the louse, but also to prove beyond question that this louse is, in fact, the intermediate host of the trypanosome,

sexual forms being developed in the gut of the louse. However, while the intermediate host of *Tr. lewisi* is undoubtedly the rat louse, we have no conclusive evidence that *Glossina palpalis* is the intermediate host of *Trypanosoma gambiense*.

The observations of Koch and Gray and Tulloch appeared for a while to indicate that this trypanosome underwent sexual development in the stomach of *Gl. palpalis*, but the careful work of Novy upon the trypanosomes of tsetse flies proved beyond question that the trypanosomes studied by the investigators mentioned were peculiar to tsetse flies and had no relation whatever to *Trypanosoma gambiense*. In a later paper by Minchin, Gray, and Tulloch, these authors say, "We are, therefore, now convinced from the results of these numerous experiments that the trypanosomes found in the freshly caught flies have nothing to do with sleeping sickness and are not developmental stages of *Tr. gambiense*." These authors also found that flies infected with this trypanosome were not infective after 48 hours, and while they describe sexual forms in the fly they are the same that occur in blood films from man. At the present

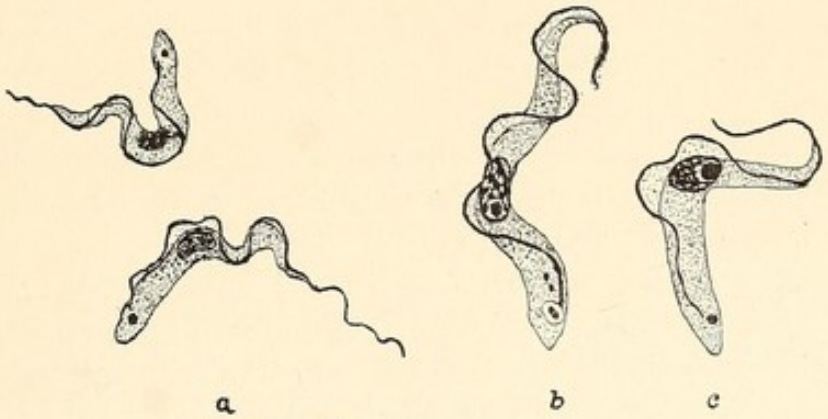

FIG. 28.—*Trypanosoma gambiense*.

A, Trypanosoma gambiense, after Dutton. B, Trypanosoma gambiense, after Lühe. C, Trypanosoma gambiense, after Lühe.

time, therefore, there is no evidence that the tsetse-fly is the intermediate host of *Trypanosoma gambiense*, but that this insect transmits the infection directly, no sexual cycle being necessary before the trypanosome becomes infective. This does not, however, preclude the existence of a true intermediate host for this trypanosome. The observations of Salvin-Moore and Breinl regarding a resistant form of *Trypanosoma gambiense* which they observed in infected rats, have not as yet been confirmed, but are worthy of further investigation. In rats infected with *Trypanosoma gambiense* they observed in the lungs, bone-marrow, and spleen, small round bodies, consisting of protoplasm and nucleus, which they claim are derived from the trypanosomes. Under favorable conditions typical trypanosomes develop from these bodies and multiply as usual. The resistant forms only develop when the trypanosomes begin to disappear from the peripheral blood of the rats. These observations are very suggestive and may explain the persistence of trypanosome infection after treatment has resulted in causing the disappearance of the parasites from the blood.

Cultivation.—Although Novy and MacNeal have succeeded in cultivating certain trypanosomes upon artificial media, and their work has been confirmed by numerous other investigators, the attempts at cultivation of *Trypanosoma gambiense*, with the exception of the partial success of Gray and Tullock, have met with failure. Novy and MacNeal have succeeded in cultivating *Tr. lewisi*, *Tr. brucei*, and *Tr. evansi*, as well as other trypanosomes of less importance, and it was hoped that by following their methods it would be possible to cultivate the parasite of sleeping sickness, but little success has attended the efforts of these who have endeavored to do so, for while it has been possible to keep the parasite alive upon the artificial media used, multiplication occurred in but one experiment, and subcultures could not be obtained. Thomas and Breinl used chicken and veal infusion in their experiments, to which was added 1 to 2 per cent. salt, 2.5 to 3.5 per cent. agar, and 1 to 1.5 per cent. peptone. This medium was prepared and added in the proportion of two to one, or three to two, to rabbit's or sheep's blood, the rabbit's blood being preferable. In this medium the trypanosomes lived for from 10 to 40 days, and in one instance living trypanosomes were found after 50 days, but there was no multiplication of the organisms, and sub-cultures could not be obtained.

The experiments of Gray and Tulloch were more successful in that multiplication did occur in their tubes, but they also were unable to obtain subcultures. They used the media of Novy and MacNeal (agar), adding to it three times the volume of defibrinated blood from the dog.

In their culture tubes, inoculated from the blood of a white rat, which contained many trypanosomes, there were found on the fifteenth day numerous organisms, occurring singly and in groups, many of which were undergoing division. The trypanosomes were longer and broader than those observed in the blood of the rat and of man, and the blepharoplast was placed much closer to the nucleus. After the twentieth day the trypanosomes disappeared from the cultures, which became greatly contaminated by bacteria of various kinds.

Laveran and Mesnil found that when *Trypanosoma gambiense* is placed in horse serum or salt solution it remains alive for from five to six days and for some time longer in blood agar. Tubes of rabbit's blood agar inoculated with blood containing this organism showed living trypanosomes for 28 days after inoculation when kept at a temperature of 22° C. They also observed that division occurred upon such culture media and that the trypanosomes were much larger than those observed in the blood of man. They were not able to secure subcultures.

Biological Phenomena.—*Trypanosoma gambiense*, like all other organisms of this class, shows no nutritive vacuoles, and therefore must nourish itself by a process of osmosis. They do not feed upon the red blood-corpuscles nor enter them, but haemoglobin appears to be essential to their growth upon culture media, as proven by Novy and MacNeal's experiments.

They possess active motility, which varies in rapidity under certain

conditions. Cold evidently decreases motility very decidedly, and exposure of the blood containing them to the air also lessens activity. The motility is chiefly due to the undulating membrane and the flagellum, but the protoplasm possesses contractility, which causes marked contraction of the body as well as a form of amoeboid motion. The organism progresses either with the flagellum forward or backward, but generally with the flagellum forward. The flagellum possesses a lashing movement which is easily made out in the more sluggish organisms, while the movement of the undulating membrane consists in undulations in various directions. In the blood of man the trypanosome often moves so rapidly that it is impossible to detect either the movement of the flagellum or the undulating membrane.

Pathogenicity of Trypanosoma gambiense.—This trypanosome is pathogenic for a large number of animals besides man. Its pathogenicity varies considerably, due, as in all pathogenic trypanosomes, to conditions which have not yet been thoroughly demonstrated. Its virulence depends upon the race and species of animals inoculated, upon the orgin of the trypanosoma inoculated, and upon successive passage through certain species of animals.

In *monkeys*, of which the *Macacus* and *Cercopithecus* are most susceptible, the inoculation of blood containing *Trypanosoma gambiense* is followed sometimes by slight fever and the symptoms of a typical attack of sleeping sickness, but more often the only symptoms noted are emaciation, anaemia, lowering of the temperature, and a tendency to slumber. The trypanosomes may be demonstrated in the blood and in the cerebrospinal fluid in those cases which present marked cerebral symptoms. It is very probable that infection with this trypanosome in the monkey is always fatal. The higher apes appear to be more resistant to infection than the lower, but typical trypanosomiasis has been produced in baboons by Thomas and Linton, Gray and Tulloch, and Thomas and Breinl. Bruce, Nabarro, and Greig have observed typical lethargy in the monkey weeks before death occurred. The period of incubation in monkeys varies from 9 to 40 days, the average being 18 days. The duration of the disease was usually seven months, but the animals may live over a year after infection.

In *dogs* this organism, when inoculated, produces a chronic infection varying in duration from two to nine months, as a rule. The period of incubation and the duration of the disease in the dog is very variously given by different investigators, thus proving that they worked with trypanosomes varying greatly in virulence. The Uganda Commission found the incubation period to be from two to five weeks in dogs, while Brump and Wurtz give the incubation period as 17 days; these authors state that the duration of the disease is 36 days, while Thomas and Linton give the duration as from three weeks to nine months.

The symptoms are emaciation, anaemia, and a subnormal temperature before death, although during the infection the temperature may be higher than normal at intervals. The trypanosomes may be found in the blood in

small numbers. Gray and Tulloch found that around Lake Albert the dogs were naturally infected with *Trypanosoma gambiense*.

This trypanosome is also infective to the jackal (Nabarro), cats, rabbits, guinea-pigs, white rats, mice, jerboas (Laveran), marmots, goats, sheep, and horses. Cattle are very resistant, but may be infected. In all of these animals the infection runs a chronic course, and does not result fatally in the larger mammals, as the sheep, horses, and cattle. In goats the infection may be a very fatal one, as shown by the experiments of Thomas and Breinl.

Methods of Transmission.—It has been determined that *Trypanosoma gambiense* is transmitted to man through the agency of biting flies belonging to the genus *Glassina*. To Bruce and Nabarro we owe the first demonstration that *Glossina palpalis* is the chief agent in the transmission of the trypanosome of sleeping sickness, for in August, 1903, these investigators reported a successful infection of a *Cercopithecus* monkey by the bites of numerous flies of this genus. A later report gives the results these authors obtained, in conjunction with Greig (1903, November), in the experimental infection of monkeys by the bites of infected *Glosinna palpalis*. These flies were allowed to suck the blood of infected negroes and were then placed upon the monkeys, and after an incubation period of about two months the trypanosomes were demonstrated in the blood of the animals. They also proved that the flies were able to infect monkeys 24 to 48 hours after biting the infected negro, but, as has been stated, no developmental stages of the trypanosomes, indicating a sexual cycle, have been found in the stomachs of the flies. The discovery of the etiological relationship of this fly to sleeping sickness at once explained the occurrence of the disease only in certain localities, for further investigation has shown that sleeping sickness is found only where flies belonging to the genus *Glossina* abound.

The discovery by Wellman, of a new species of *Glossina*, *Gl. palpalis wellmani* Austen, in South Angola, and by Massey, in the Upper Congo, where sleeping sickness occurs, indicates that this fly, as well as *palpalis*, is capable of transmitting the trypanosome, and Nabarro and Greig have apparently proven that *Gl. pallidipes*, *Gl. fusca*, and *Gl. longipennis* are able to convey *Trypanosoma gambiense* from sick to healthy animals.

So far as we know, the infection is carried from the sick to the well by the proboscis of the fly, as no evidence exists that the trypanosomes undergo any development within the insect, and the fly is not infective after 48 hours. As so many of the lower animals are susceptible to infection with this trypanosome, which produces in most of them a chronic disease in which the organisms are present in the blood for weeks or months, it is easy to understand how the disease is maintained in localities where it is endemic, and how difficult it has proven to rid a locality of the infection.

Distribution in Man.—In man *Trypanosoma gambiense* is found in the blood, in the lymphatic glands, the cerebrospinal fluid, and in the various organs, within the capillaries. The organism occurs in small numbers in the

blood, in larger numbers within the lymph glands, and in large numbers in the cerebrospinal fluid in well-marked cases of sleeping sickness, after the development of cerebral and spinal symptoms. In sections of the organs of patients dying from this disease the trypanosomes are seldom found, but they have been demonstrated in the spleen, the liver, the bone-marrow, and the lungs. The pathological changes produced by infection with this parasite comprise hypertrophy of the lymphatic glands, lesions in the meninges resembling those of cerebrospinal meningitis, chronic inflammatory lesions of the lymphatics of the central nervous system, and degeneration of the spinal cord. The pathognomonic lesion, according to Mott, to whom we owe our most exact knowledge of the pathology of sleeping sickness, consists in "the universal perivascular cell-infiltration of the central nervous system." He also states that the changes observed in the nervous system are almost identical with those observed in syphilis with the exception that in this disease the proliferative endarteritis leading to thrombosis is absent, whereas it is common in syphilis.

Demonstration of Trypanosoma Gambiense.—The diagnosis of sleeping sickness can be made by an examination of the blood, the cerebrospinal fluid, and juice from the enlarged lymphatic glands. In all of these fluids the trypanosomes occur, but they are said to be most easily demonstrated in the juice obtained from the enlarged lymphatic glands of the cervical region. For staining the modification of Wright's method which I use in staining malarial blood is most useful, but any of the modifications of the Romanowsky stain, such as Leishman's, Jenner's, or the Giemsa stain, may be used.

Examination of the Blood.—The blood may be examined either fresh or stained. As the trypanosomes occur but in small numbers in the blood it is better to make several smears for staining, as in this way more time can be given to the examination, and a greater number of specimens examined at leisure. It is generally better to use some method of centrifuging the blood as the parasites are so few in number that many smears prepared in the ordinary way will have to be examined before a trypanosome is encountered.

The method of examination recommended by Bruce and Nabarro is an excellent one and is as follows: About 10 c.c. of blood is removed from a vein and placed in a centrifuge tube containing a small amount of sodium citrate solution and centrifuged for 10 minutes. The supernatant serum, the leucocyte layer, and the upper portion of the red layer is pipetted off and again centrifuged for ten minutes, after which the upper layer is pipetted off and centrifuged for the same time. A small drop of the supernatant liquid so obtained is placed upon a slide and examined as a fresh preparation, and if the trypanosomes are not present in this a portion of the sediment should be examined, in which they will surely be found if the case is one of sleeping sickness. An examination should be made of each specimen before it is recentrifuged as the trypanosomes may be found after once centrifuging only. Smears may be prepared from the sediment and stained.

Examination of the Cerebrospinal Fluid.—In order to obtain the

cerebrospinal fluid for examination it is necessary to perform lumbar puncture. The following method of performing this operation is that recommended by Tuffier (L'Analgesie chirurgicale par voie rachidienne, Paris, 1901) as given in Laveran and Mesnil's classical work upon "Trypanosomes and Trypanosomiases," translated by Nabarro.

"Use a platinum-iridium needle (which can be sterilized easily) 8 centimeters (about 3 1/2 inches) long, fitted to a hypodermic syringe. The external diameter of the needle should be 1 millimeter, and the internal diameter 0.6 millimeter; the point should be bevelled off very little. It is unnecessary to use a general anaesthetic. The patient should sit up with the arms held in front. The lumbar region is thoroughly washed and rendered aseptic. The iliac crests are used as a guide, the transverse line joining their highest points crossing the spine at the level of the fourth lumbar vertebra (spinous process).

"The left index finger being placed on this spinous process, the patient is told to bend the head well forward. This serves to separate the laminae of the vertebrae between which the needle has to pass. At the moment of inserting the needle the patient must be warned that he is going to be pricked, and that he must remain perfectly still and on no account straighten the back by sitting upright. The needle of the syringe, properly sterilized, is introduced at a point 1 centimeter (about 1/2 an inch) from the middle line close up against the edge of the index finger, which is kept on the spinous process. The point of the needle is directed slightly toward the middle line and upward, and when it enters the subdural space it is distinctly felt that there is no longer any resistance. A clear liquid immediately wells up into the needle and can be collected in a tube, or a syringe can be fitted to the needle."

Nabarro recommends slight aspiration if the needle becomes clogged and states than in sleeping sickness the cerebrospinal fluid, on account of the increased pressure in the spinal canal, often spurts out of the needle in a steady stream and as much as 50 c.c. may be collected at one time. The administration of a general anaesthetic should, in most cases, be insisted upon, as the operation is much easier when the anaesthetic is given, and both Nabarro and Christy recommend chloroform.

In the cerebrospinal fluid the trypanosomes are generally few in number and it is necessary to centrifuge the fluid for ten minutes and the sediment should be examined fresh or stained preparations made, using one of the chromatin stains. Nabarro states that in a few instances the trypanosomes were so numerous that they were detected in the fluid before it was centrifuged, but he also states that in other cases it was necessary to perform lumbar puncture as many as four times before the parasite was discovered. It is probable that the trypanosome is always present in the cerebrospinal fluid in every case of sleeping sickness, but repeated examinations may have to be made in order to demonstrate it. A certain periodicity appears to be present as regards the occurrence of the trypanosomes in the cerebrospinal fluid, and they are never found there in the earlier stages of trypanosomiasis, only appearing when the symptoms characteristic of sleeping sickness appear.

In stained smears made from the cerebrospinal fluid the trypanosomes do

not appear well stained, and for this reason it is not advisable to stain such organisms, but to examine them in the fresh fluid.

Examination of the Gland Juice.—The discovery by Greig and Gray that the juice of the lymphatic glands in human trypanosomiasis contained the trypanosomes in comparatively large numbers has proven of the greatest service in diagnosis. These investigators, following a suggestion made by Mott, examined the contents of the lymphatic glands in 15 cases of sleeping sickness and found the trypanosomes in all of them, and that the organisms were much more numerous than in either the blood or the cerebrospinal fluid. They also found the organisms in the lymphatic glands of patients suffering from trypanosomiasis in whom the symptoms of sleeping sickness had not appeared. At first they excised the glands, but later found that this was not necessary, one of the enlarged glands being punctured with the needle of a hypodermic syringe and some of the juice of the gland aspirated into the syringe, placed upon microscopic slides and examined at once or stained. The cervical glands were found to contain the organisms in greatest numbers, but they were also demonstrated in the enlarged femoral and inguinal glands.

Nabarro gives the following directions regarding the technic of gland puncture:

> "Gland puncture is quite a simple operation, but it is necessary to attend to a few details of technic. The syringe must be boiled before use, then washed with a sterile salt solution, *every trace* of which should be got rid of before using the syringe. After obtaining the drop of gland juice, the piston should be allowed to return almost as far as it will, and then fixed with the finger, otherwise much of the fluid aspirated would be lost in the body of the syringe. The drop of fluid in the syringe must be pushed out by one sharp push of the piston rather than by two or three movements, so as to avoid getting air bubbles in the preparation. The drop is quickly covered with a cover-glass (care being taken to avoid the minute piece of skin punched out by the needle) ringed with vaseline, and examined at once (Todd)."

The observations of Greig and Gray have been confirmed by Dutton and Todd, as well as many other investigators, and it is generally acknowledged to-day that gland puncture is the best method of demonstrating *Trypanosoma gambiense* in early cases of trypanosomiasis and also in those cases in which the symptoms of sleeping sickness have already developed. It is especially in the early cases of infection that this method is valuable, as in such patients the trypanosomes are very scanty in the blood and absent from the cerebrospinal fluid, but are often numerous in the gland juice. The posterior cervical glands have given the best results, according to Nabarro (95 per cent.), the axillary, the femoral, and the epitrochlear following in order. The trypanosomes obtained in glandular juice stain better than those from the cerebrospinal fluid, but not as well, in most instances, as those obtained from the blood. The trypanosomes have also been found in pleural, peritoneal, and pericardial exudates and in hydrocele fluid.

Staining.—For diagnostic purposes staining is not necessary if gland juice or cerebrospinal fluid is to be examined, as the trypanosomes are easily recognized by their active, wriggling movements and their peculiar spindle shape. Examination of these fluids should be made with a 1/6 inch objective and several specimens should be examined before a negative result is recorded. The cerebrospinal fluid should be centrifuged if an examination of the uncentrifuged fluid is negative. In staining with Wright's or Leishman's stain the stain should first be allowed to fix the preparation of blood or other substance for five minutes, the water then added, and the stain allowed to act for from ten to twenty minutes longer, the time being judged by the staining reactions as observed after experimentation with several specimens. In well stained preparations the protoplasm of *Trypanosoma gambiense* should be colored a well-marked blue, the nucleus a crimson or dark red, the blepharoplast a darker red or brilliant violet, and the flagellum, from its origin at the blepharoplast, along the edge of the undulating membrane and throughout its free portion a dark red or violet, the undulating membrane being blue in color. Good specimens can be secured only after a certain amount of experimentation, and the beginner should not be discouraged if the first few specimens stained by him do not show perfectly the morphology of the trypanosome.

Other Mammalian Trypanosomes.—For convenience in reference the following list of the trypanosomes of most interest which infect mammals is appended.

Trypanosoma lewisi. KENT. 1879. A parasite of rats, generally non-pathogenic, but sometimes pathogenic. Discovered by Chaussat in 1850.

Trypanosoma evansi. STEEL. 1885. A parasite of horses, mules, elephants, camels, carabao (the Philippines) buffaloes and dogs. Produces in horses and mules the disease known as "surra." Discovered by Evans in 1880.

Trypanosoma brucei. PLIMMER AND BRADFORD. 1899. A parasite of horses and most of the game animals of Africa. Causes the disease known as "nagana" in horses. Transmitted by the Glossinæ. Discovered by Bruce in 1895.

Trypanosoma equiperdum. DOFLEIN. 1901. A parasite of horses and donkeys, transmitted by coitus. It causes in these animals the disease known as dourine, or "malady du coit." Discovered by Rouget in 1894.

Trypanosoma equinum. VOGES. 1901. A parasite of horses, causing the disease known as "mal de caderas." Discovered by Elmassian, in 1901.

Trypanosoma theileri. LAVERAN. Bruce. 1902. A parasite of cattle. Produces in these animals the disease known as galziekte (gall sickness). Discovered by Theiler in the Transvaal.

Trypanosoma dimorphon. DUTTON AND TODD. 1904. A parasite of the horse and probably of sheep, cattle, antelopes, dogs, and pigs. Causes in horses the disease known as Gambian horse disease. Discovered by Dutton and Todd in 1902.

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CHAPTER III.

The Spirochaetes;[1] Spirochaeta Recurrentis; Spirochaeta Duttoni; Spirochaeta Carteri; Spirochaeta Novyi (Spiroschaudinnia).

The spirochaetae are parasites of the blood causing a group of relapsing fevers endemic in certain localities. It was supposed for a long time that only one spirochaeta, *Spirochaeta recurrentis* (*Spirillum obermeieri*) caused relapsing fever, but the recent investigations of Novy and Knapp, Breinl and Todd, Dutton, Prowazek, Carter, and others have definitely proven that there are at least four species, each causing a peculiar form of relapsing fever, and each apparently limited in geographical distribution.

Historical.—Relapsing fever has been known since the time of Hippocrates but nothing was known of its etiological factor until Obermeier, in 1873, described an organism occurring in the blood of patients suffering from the disease, to which Cohn gave the name *Spirillum obermeieri*, but which had been previously named *Spirochaeta recurrentis* by Lebert in 1874. Obermeier and others proved that this organism produced the symptoms of relapsing fever in animals, and observation has since demonstrated that the organism is invariably present in the blood of cases of relapsing fever occurring in certain parts of Europe, notably Russia and the Balkans. The occurrence of relapsing fever in India, Africa, and in America, associated with similar organisms, led to the belief that all cases of relapsing fever were due to this spirochaeta, but Manson, Sambon, and Koch, in 1904 and 1905, suggested that on account of geographical distribution, and clinical differences, there might be a group of relapsing fevers due to specific organisms, and to Novy and Knapp we owe the first definite demonstration that distinct morphological differences existed between the spirochaetae. In a paper published in 1906 these authors, as the result of their study of spirochaetae from Europe and Africa, concluded that the spirochaeta of relapsing or tick fever of Africa is a distinct species, and named it *Spirillum duttoni*, while they also state that the organism found in the blood of relapsing fever in India is probably a distinct species. As will be seen later, Novy and Knapp regarded all spirochaetae occurring in relapsing fever in man as bacteria, belonging to the spirilli. The observations regarding the African spirochaeta were soon confirmed and it is now generally admitted that it is a distinct species. The investigations of Norris, Flournoy, Pappenheimer,

[1] I have included these organisms among the blood protozoa provisionally, as their exact biological position has not yet been definitely settled and because they are blood parasites. Until it is proven that they are bacterial in nature I believe that they should be regarded as belonging to the Protozoa.

and Novy and Knapp upon a spirochaeta found in the blood of relapsing fever cases occurring in the United States resulted in showing that this organism was probably a distinct species, and Uhlenhuth and Haendel proved by means of agglutination reactions that the American spirochaeta is different from others, and this organism is now known as *Spirochaeta novyi*. Further investigations of the spirochaeta of Indian relapsing fever confirmed the belief of Novy and Knapp that this also was a distinct species, and to it Mackie has given the name "Spirochaeta carteri." As the result of these various studies of the spirochaetae occurring in relapsing fever, we recognize at the present time the four following species:

Spirochaeta recurrentis. LEBERT. 1874. Causing European relapsing fever.

Spirochaeta duttoni. NOVY AND KNAPP. 1906. Causing African relapsing fever.

Spirochaeta novyi. SCHELLACH. 1907. Causing American relapsing fever.

Spirochaeta carteri. MACKIE. 1908. Causing Indian relapsing fever.

Geographical Distribution.—The geographical distribution of the spirochaetae is apparently limited as regards the different species, each species being peculiar to the country in which it is found. The relapsing fever of Africa, better known as "tick fever" is caused by *Spirochaeta duttoni*, and the geographical distribution of this organism is confined to the continent of Africa; the same is true of the other species, *Spirochaeta recurrentis* being peculiar to Europe, *Spirochaeta novyi* to America, and *Spirochaeta carteri* to Asia.

Biological Position.—The biological position of these organisms has not been definitely determined, scientists being divided into two schools regarding this question, one believing that they are protozoa, the other that they are bacteria. It is actually impossible to state at the present writing which school has the better of the argument, but the occurrence of longitudinal division, which I believe has been demonstrated beyond question in these parasites, would appear to prove their protozoal nature. It must be admitted, however, that the evidence regarding their bacterial nature is very strong and that further research may demonstrate that, in reality, they possess features common to both the protozoa and the bacteria, forming, as it were, a connecting link between animal and vegetable organisms.

For those who believe in the bacterial nature of these organisms they must be regarded as spirilli, while for those who believe in their protozoan origin they are placed in the genus "Spirochaetae." Recently some zoologists, as Sambon and Ward, have created a new genus to include the parasites of the relapsing fevers, the Spiroschaudinniae, but this classification has not been generally adopted.

Until the publication of Schaudinn's paper upon *Spirochaeta ziemanni*, the cause of relapsing fever, commonly known as *Spirillum obermeieri*, was regarded as a bacterium, but his statement that in all probability all spirochaetes would be found to be developmental stages of trypanosomes (which has proven

not to be the case) and the demonstration of chromatin and an undulating membrane in some of the spirochaetae, caused investigators to study anew the organisms concerned in the etiology of relapsing fever, with the result that their bacterial nature was disputed. The type species of the spirochaetae, *Spirochaeta plicatilis*, possesses a distinct undulating membrane and is devoid of a flagellum, but many other members of the genus differ considerably in morphology from this typical spirochaeta. The organisms concerned in the etiology of relapsing fevers differ so markedly from a typical spirochaeta, as described by Schaudinn, that I believe that they should be taken from that genus and placed in a new one, that already adopted by Ward (Spiroschaudinnia) being available.

Novy and Knapp, who are ardent advocates of the bacterial nature of the spirochaetes of relapsing fevers, believe that the following evidence is sufficient to prove that they belong to the bacteria: transverse division; multiple flagella; absence of a nucleus, undulating membrane and blepharoplast; resistance to plasmolytic changes and to heat; and, finally, that active immunity is easily obtained, which is not true of protozoal infections.

The evidence that these organisms are protozoal in nature, as believed by Schaudinn, Prowazek, and other zoologists, consists in the occurrence of longitudinal as well as transverse division; the presence of chromatin; the fact that many organisms are twice as thick as others, these being the forms which undergo longitudinal division; the method of natural transmission by an insect, and through the egg of an insect; the reaction of the organisms to solutions of sodium chloride and to solutions of saponin and the bile salts, and the demonstration of a minute mass of chromatin projecting from some portion of the organism. It is evident that further research is needed before a definite conclusion can be reached regarding the exact biological position of these parasites, but until this is possible I believe that it is wise to regard them as belonging to the Protozoa.

Morphology of the Spirochaetae of the Relapsing Fevers.—In describing the morphology of the spirochaetae causing the relapsing fevers of man I shall describe each separately, concluding with a discussion of the differential features of the various species.

Spirochaeta Recurrentis (Spirillum Obermeieri).—This parasite varies in length from 19μ to 29μ and in breadth from 0.3μ to 0.5 μ, the number of curves varying from four to eighteen, the organism being typically spiral in shape, the curves marked and regular. The ends are pointed and, according to Koch and Karlinsky, one or more flagella are present at each end, while Manson states that the flagellum is present at only one of the extremities. The observation of Fraenkel that the organism possesses numerous peritrichous flagella is disputed by Prowazek and Schellach, who insist that the flagella seen by Fraenkel were artefacts produced by the method of staining employed. In specimens stained by any modification of the Romanowsky stain but little structure can be distinguished, but in rare instances an irregular staining is noticed, the body of the parasite containing minute, irregularly distributed

masses of substance taking the chromatin stain. An undulating membrane has been described by Schaudinn and Leishman, but their observations concerning this have not been confirmed. With Giesma's stain the organism presents numerous deeply stained granules throughout its entire length, with the exception of the flagellum. Both transverse and longitudinal division occurs, transverse division being the most frequent method of reproduction, but the occurrence of Y-shaped organisms, which can only be regarded as forms undergoing longitudinal division, prove that this method of reproduction, typical of the Protozoa, occurs in this parasite. The presence of a terminal flagellum at one extremity of the organism is evident in well-stained specimens.

In fresh specimens of blood this organism is very actively motile, passing across the microscopic field so rapidly as to be hardly distinguishable, and this rapid motility may be retained for days and even weeks after the blood has been removed from the body, but sooner or later, the motion becomes more sluggish and it is possible to study its characteristics. The active motion is due to corkscrew-like movements of the parasite which enable it to progress rapidly, but as the organisms become less motile this form of motion is succeeded by undulatory movements of the body, the resulting motion being slowly progressive. In organisms which have been kept outside of the body for weeks, progressive motion is lost, being succeeded by a swaying motion from side to side and slight twitching movements of the body. Careful observation will demonstrate that the extremities of the body possess the power of bending to almost an acute angle, and organisms are observed in which the extremities are apparently united, a perfect circle thus being formed.

Spirochaeta Duttoni (Spirillum Duttoni).—The disease due to this parasite, or tick fever, was first described by Livingstone, but it was not until the discovery of a spirochaeta in the blood of patients suffering from it, by Ross and Milne, in 1904, and almost simultaneously by Dutton and Todd, that the etiology of the disease was placed upon a scientific basis. It is probable that this spirochaeta has been more thoroughly studied than any of this class of organisms and yet the biological position of the organism is undetermined and the morphological data variously interpreted by different observers.

In length *Spirochaeta duttoni* varies from 13μ to 45μ and in width from 0.2μ to 0.4μ. Different authorities give very different measurements, Novy and Knapp stating the length as 16μ; Dutton and Todd as 13μ to 43μ; Ross as 45μ, and Schellach as 24μ. It is probable that some of the longer measurements were obtained by measuring two organisms attached end to end, as they so frequently are. The morphology is similar to that of *Spirochaeta recurrentis*, a flagellum being present at one end and the staining being irregular when Giesma's stain is employed. Transverse and longitudinal division occurs, transverse division being the usual method of reproduction. The motility of this species is greater than that of any other species of spirochaetae found in man.

The observations of Dutton and Todd upon the morphology of this organism and those of Schellach are especially important and demand atten-

tion. Dutton and Todd state that the organism is ribbon-shaped on transverse section, and that it is composed of a central core staining a deep red, the chromatin, and of a delicate periplastic sheath, staining light pink. Both extremites are pointed, but one may be extended through the sheath as a flagellum, which contains no chromatin. The chromatin may not stain as a solid core, but may lie in irregular masses surrounded by unstained areas. Peritrichial flagella were never observed. Many of the spirochaetae presented deeply stained knobs or swellings, either situated at one end or laterally, some of them being separated from the parent organism, but still attached by a very delicate pink-staining thread. Most of these swellings stain uniformly red, but in some the protoplasm is stained blue and contains deep red dots of chromatin.

Some of the organisms are thicker at one extremity than at the other and these forms the authors believe to indicate a stage preceding longitudinal division. The usual method of reproduction was found to be by transverse division, but longitudinal division was frequently observed, being most common toward the termination of the attack. Longitudinal division is preceded by thickening of the organism which then splits, beginning at one end, thus producing the Y-shaped forms frequently observed. In smears made from the spleen, bone-marrow, and liver, the spirochaetae were frequently observed coiled up into spherical masses, which become larger and irregular in shape as the crisis approaches. Interesting changes were observed in some of these organisms, consisting in encystment followed by disintegration of the body of the parasite, the cyst being filled with granules showing the chromatin staining reaction. They note the occurrence of minute, blue-stained bodies, containing chromatin granules, and measuring from 1μ to 3μ in diameter, in the blood and organs of infected animals, but are uncertain of the nature of such bodies. These authors agree with Leishman that *Spirochaeta duttoni* possesses an undulating membrane, stating that they have observed, both in the blood of men and animals, and in blood from the alimentary canal of the tick, an unmistakable undulating membrane. To demonstrate it they recommend the use of the highest powers and a very careful scrutiny of every organism. This membrane extends the entire length of the body and some of the unstained areas in the latter are due to the undulating membrane crossing the body.

Schellach observed the spirochaeta in the living state. He gives the length as 24μ at the most, the width as 0.45μ. The number of undulations as 8 to 12. A terminal flagellum was demonstrated, but while he obtained peritrichial flagella by Zettnow's method, he regards them as artefacts. Deep-staining granules were noted in the protoplasm when Giemsa's method of staining was employed. He also described appearances suggesting longitudinal division, but considers that the method of reproduction is always by transverse division. While Dutton and Todd claim that the organism may occur both within red and white blood-corpuscles, Schellach believes that the organisms are not intracellular at any stage of development and that phagocytosis does not occur.

Breinl, Kinghorn, and Garrett could not demonstrate an undulating membrane or a flagellum, but they describe refractile dots in the protoplasm.

The motility of *Spirochaeta duttoni* is similar in character to that of *Spirochaeta recurrentis*, consisting in cork-screw motions, undulations, and a swaying motion, but it is much more active than any of the other spirochaetae of man.

Spirochaeta novyi (Spirillum novyi).—This spirochaeta resembles in its general morphological characters the organisms already described, but it is shorter and more slender than the other spirochaetae of man. The organism has been thoroughly studied by Norris, Novy, and Knapp and more recently by Schellach.

According to Novy and Knapp, single cells of this organism measure from 7μ to 9μ while Schellach gives the length as from 17μ to 20μ with 6 to 8 undulations. The same author gives the width as 0.31μ. A terminal flagellum has been demonstrated by Novy, Knapp, and Schellach, and while peritrichial flagella have been described by Fraenkel and Zettnow, it is generally conceded that these were artefacts produced by the method of staining. The organism is actively motile, the same varieties of motion being observed as in the preceding spirochaetae. Reproduction occurs by transverse division, but longitudinal division occurs at certain intervals, typical dividing forms having been observed.

Spirochaeta carteri (Spirillum carteri).—As described by Mackie, *Spirochaeta carteri* measures from 12μ to 16μ in length, by 00.3μ to 0.5μ in breadth, but forms are observed measuring from 7μ to 8μ, while in infected lice the spirochaetae may measure only 2μ to 3μ in length. Only in degenerative forms has any trace of structure been discovered, the appearance of chromatin dots being coincident with degeneration of the cytoplasm. A terminal flagellum is demonstrable, but Mackie interprets this as the empty portion of the sheath which surrounds the organism. Transverse division is the common method of reproduction, but Mackie has observed organisms in the stomach of the louse which were probably undergoing longitudinal division and conjugation. An undulating membrane has not been demonstrated. The organism is motile, the movements being similar in character to those described in the other spirochaetae of man.

From the descriptions of the spirochaetae given it will be observed that their differentiation upon morphological grounds alone rests upon the size, the number of undulations or curves, and the character of the curves. The following table illustrates the variations in these particulars in the four species of spirochaetae which infect man:

	Sp. recurrentis	Sp. duttoni	Sp. novyi	Sp. carteri
Length Max.	19μ to 29μ	12μ to 24μ	17μ to 20μ	16μ
Width	0.39μ	0.45μ	0.31μ	0.50μ
No. of Curves	8 to 10	8 to 12	6 to 8	(?)
Shape of Curves	spiral	open flexures	typical spirals	open flexures

Mackie considers that *Sp. Carteri* can be easily distinguished upon morphological grounds from *Sp. novyi*, the latter being shorter, staining less intensely, and thinner and more delicate in contour; the American organism being typically spiral in shape, the Asiatic having very shallow undulations, more open in character.

Fortunately, we do not have to depend upon morphology in order to differentiate the spirochaetae, for we possess in their reactions to immune sera and to inoculation into various animals, a certain and easy method of distinguishing them.

Cultivation of Spirochaetae.—Spirochaeta novyi is the only spirochaete which has, at the present writing, been cultivated upon artificial media outside of the human body. Novy and Knapp succeeded in cultivating the organisms in collodiun sacs placed in the peritoneal cavity of white rats, and in this manner they were able to carry the parasites through successive generations, multiplication being abundant. Their method was as follows: "Collodium sacs were filled with uncoagulated rat's blood and after inoculation were placed at once in the peritoneal cavity of a white rat. Three days later, on removal, the sacs were found to contain active spirilla and in increased numbers. From the sacs transplants were made to new ones and the result was equally satisfactory." They transplanted their cultures every three or four days, using sacs containing from 2.5 to 3 c.c., and it was found that if the sacs were left in the peritoneal cavity for seven days or over the spirochaetae decreased in number or disappeared.

The spirochaetae of all of the relapsing fevers may be kept alive for days and weeks in citrated blood at room temperature, but there is no evidence that multiplication occurs, and transplants cannot be obtained.

The morphology of the spirochaetes in the collodium sacs did not differ from that of the organisms in the blood, and, according to Novy and Knapp, there was no evidence of a developmental cycle in their cultures similar to that demonstrated in some of the protozoa.

Butler has recently shown that in citrated blood, kept in an ice-box at a temperature of 15° C., *Spirochaeta duttoni* develops oval or round enlargements, situated either at the extremities or laterally, which contain granules of chromatin. The parent body degenerates after from two to three months, but the enlargements retain the stain and become free in the plasma. Butler found the same bodies upon spirochaetes in blood obtained from the stomach of fleas allowed to feed upon infected rats. These bodies are the same as those previously described by Dutton and Todd as occurring upon *Spirochaeta duttoni* observed in the blood of infected rats. In our work upon *Treponema pertenue* and *Treponema pallidum*, Ashburn and myself observed similar bodies attached to both these organisms, and the fact that they are observed so frequently is very suggestive that they have something to do with the reproduction of both spirochaeta and treponema.

Pathogenicity.—The group of fevers caused by the spirochaetes described

are characterized by attacks of fever alternating with periods of normal temperature. At the time of pyrexia the organisms are found in the peripheral blood, but become less numerous during the decline in the fever, and after the crisis they entirely disappear from the peripheral blood, although, as shown by Breinl and Kinghorn, in the case of *Spirochaeta duttoni*, the blood is still infective to susceptible animals. These parasites are pathogenic for some of the lower animals, and the reaction of these animals to the inoculation of the different species and the reaction of the organisms to immune sera form our most efficient methods of differentiating the various species.

Spirochaeta recurrentis is pathogenic for man, monkeys, white rats, tame rats, and mice. In monkeys the injection of blood containing this organism is followed by severe fever, accompanied by relapses, and the parasite is easily demonstrated in large numbers in the peripheral blood. White rats and mice can only be infected by the inoculation of organisms which have first been passed through the monkey, and antibodies are formed in the blood of infected animals. To Uhlenhuth and Haendel and Fulleborn and Meyer we owe much of our knowledge of the pathogenic properties of this spirochaeta.

Spirochaeta duttoni is pathogenic for man, monkeys, white rats, common rats, mice, guinea-pigs, rabbits, dogs, sheep, horses, and goats, while cats, pigeons, and chickens are not susceptible. The researches of Breinl and Kinghorn upon the pathogenicity of this organism are most valuable. They found that the white rat is more susceptible to infection than is the monkey, and that the parasite passes through the placenta, thus infecting the foetus. They also determined that it passes through a Berkefeld filter fine enough to retain B. *prodigiosus*. In their work the period of incubation varies from a few hours in white rats to seven days in monkeys, and relapses occurred in most of their experimental animals. (The occurrence of relapses at regular intervals following infection with the spirochaetae is very significant of their protozoal nature, as they indicate that the organism passes through a definite cycle of development.) The disease in monkeys is not generally fatal, but in white rats and guinea-pigs a fatal result is frequent. These observers also demonstrated that the peripheral blood is infective during apyrexia, although the spirochaeta cannot be found in it, which would appear to prove that during apyrexia the parasite is present in the blood in some form which has not yet been recognized.

Spirochaeta novyi is pathogenic for man, monkeys, white rats and mice, and tame and wild rats. Novy and Knapp found that white mice were very susceptible, and that the organisms occurred in their blood in immense numbers. These observers found that rabbits and guinea-pigs could not be infected.

Spirochaeta carteri has been found by Mackie to be pathogenic for white rats and mice, white rabbits, black rats, brown rats, and guinea-pigs. Goats, dogs, cats, and pigeons are not susceptible. As with the other spirochaetes, this organism is pathogenic to man and monkeys. The disease, in laboratory animals, except the monkey, is of slight character, and the organisms

occur in the blood in small numbers. Mackie found that the monkey could be infected by scarification of the skin followed by the rubbing in of infected blood; by feeding with blood containing the organisms, and by puncture of the skin with a grooved needle containing the virtus.

Immunity.—From a diagnostic and therapeutic standpoint the question of acquired immunity to infection with the various species of spirochaetae is of great importance, but as yet an immune serum which can be used for the treatment of human infections has not been produced, although Novy and Knapp have cured infections in rats by the injection of immune blood. It is a fact of prime importance in the differential diagnosis of the species of spirochaetae that an animal which has suffered from an infection with one species is immune to that species but not to the others, so that a differential diagnosis is easily made by the use of immune animals. The occurrence of any of the varieties of relapsing fever in man is followed by a period of immunity, and this is also true of experimental infections in the lower animals, but the duration of the immune period is not known and varies with the species of animal and the species of spirochaeta producing the infection.

The immunity produced by *Spirochaeta recurrentis* is slight and transient in character. Immune substances are produced in the blood of animals suffering from the infection, and blood serum containing them causes paralysis of movement in this spirochaeta, but has no effect upon the other spirochaetae. Metchnikoff's theory that the disappearance of the spirochaetae from the blood was due to phagocytosis occurring principally in the spleen has been disproven by Tictin, Lamb, and Breinl and Kinghorn.

Breinl and Kinghorn, working with *Spirochaeta duttoni*, were unable to produce immunity by immune serum or to cure the infection in animals by the use of such serum. Their conclusions are of great value and are given practically *verbatim:*

1. "Immune serum, whether derived from horses, monkeys, or rats, has no appreciable value either in preventing the occurrence of the attacks in susceptible animals or in curing the disease once contracted. The incubation period may be prolonged to a greater or less extent, but the inoculation of infected blood is always followed by infection.

2. "Hyperimmune serum has no pronounced value in the treatment of the disease in monkeys, does not prevent infection, but given in large doses markedly lengthens the incubation period, and mitigates the course of the disease.

3. "In animals which have recovered from the infection there is a relatively active immunity of comparatively long duration.

4. "We have been unable to produce passive immunity through the use of immune serum.

5. "In animals from which the spleen has been removed, the spirochaetes disappear from the peripheral circulation after the attack as promptly as in normal animals, and relapses occur in the ordinary way."

These authors also proved that animals rendered immune to infection

with *Spirochaeta duttoni*, because of having recovered from such infection, were not immune to *Spirochaeta recurrentis*, and that ticks fed upon infected animals were able to transmit the infection immediately.

The immunity produced by infection with *Spirochaeta novyi* has been carefully studied by Novy and Knapp, whose conclusions are here reproduced in part:

1. "A powerful specific germicidal body is present in the decline and in recovered blood, notably in blood of hyperimmunized rats. An immunizing body is also present and is probably distinct from the germicidal agent.

2. "Pfeiffer's phenomenon can be demonstrated *in vitro* and *in vivo*."

3. "Active immunity follows recovery from the infection. By successive injections of spirillar blood this immunity can be increased to a remarkable degree."

4. "Passive immunity can be imparted by injections of recovered or hyperimmunized blood."

5. "Preventive inoculations can be successfully made in rats, mice, and monkeys."

6. "Infected rats, mice, and monkeys can be promptly cured by injection of hyperimmunized blood."

7. "Agglutination of spirilla occurs *in vitro* and *in vivo* under the influence of recovered or hyperimmunized blood."

8. "The agglutination, germicidal, and immunizing properties of recovered blood can be used in the sero-diagnosis of relapsing fever. Also for the identification of spirilla."

From the results obtained by Novy and Knapp it is evident that this organism differs very greatly from *Spirochaeta duttoni* in its effect upon animals, for, as shown by Breinl and Kinghorn, the latter produces no immune serum capable of preventing or curing an infection, while a very active immunizing and curative serum is produced after infection with *Spirochaeta novyi*.

According to Mackie, the injection of blood from man and monkeys containing *Spirochaeta carteri* into monkeys and goats is followed by a certain degree of immunity, and the blood serum from these animals killed the spirochaetes within fifteen seconds in a dilution of 1 in 20.

Methods of Transmission.—It is now generally believed that all the species of spirochaetae producing relapsing fever in man are transmitted through the agency of insects, and, in the instance of the relapsing fever of Africa, or "tick fever," this method of transmission has been definitely proven.

Spirochaeta recurrentis is believed to be transmitted by an insect, but we possess no definite knowledge as to what insect is concerned, although the bed-bug (*Cimex lectularius*) has been regarded by some observers as the transmitting agent. As long ago as 1897, Tictin concluded, as the result of his experiments, that this bug transmitted the disease. He allowed bed-bugs to suck the blood from patients suffering from relapsing fever, then rubbed them up in a mortar and inoculated them into monkeys, which afterward developed fever. His

experiments were obviously imperfect as regards technic and the more recent negative experiments of Breinl and Kinghorn with these bugs and both *Spirochaeta recurrentis* and *Spirochaeta duttoni* prove that the bed-bug does not transmit these parasites to man.

The method of transmission of *Spirochaeta duttoni* has been definitely ascertained. Dutton and Todd, working in the Congo valley, proved that African tick fever is due to the organism that we now know as *Spirochaeta duttoni*, and that it is transmitted to man by the bite of a tick, *Ornithodorus moubata*, which had sucked the blood of infected individuals. These observers also proved that the infection in the tick is hereditary, as the larvae hatched out of the eggs of infected ticks were also capable of causing the disease. Their observations were at once confirmed by Ross and Milne, and later by Breinl and Kinghorn, and there can be no doubt but that this organism is conveyed to man by the bites of infected ticks or their progeny.

Dutton and Todd have studied very carefully the morphological changes occurring in *Spirochaeta duttoni* in the tick, *Ornithodorus moubata*. Many degenerating forms are observed in the blood in the stomach of the tick after it has bitten an infected animal, as well as all of the forms described as occurring in the peripheral blood. In blood from the receptaculum, obtained 24 hours after ingestion, they observed two distinct types of organism, one slender and the other stout, while a third form was seen rarely, which was twice the usual length and three times the usual breadth. The organisms were also observed coiled up within erythrocytes, leucocytes, and within the cells lining the receptaculum, while encysted forms were very common. Fragmentation of the chromatin was very marked and only a single granule is found in the encysted form. At a later stage of development the granules are double, the parasite consisting of a blue-stained mass of protoplasm containing many pairs of deep red granules. They were not able to follow the further development of these bodies, but suggest that they rupture, setting free the chromatin pairs, which eventually develop into minute spirochaetes. In stained specimens they believe that they have been able to trace the development of a single granule into a comma-shaped clump of chromatin from which a small spirochaete developed. These observations have not been confirmed.

Koch studied the organisms in the stomach of the tick and was unable to trace any cycle of development. He found that the spirochaetae disappeared from the stomach in a few days and could then be found upon the surface of the ovary, where multiplication occurred. Carter describes longitudinal division as occurring in spirochaetes of this species in the eggs of ticks, but this observation still awaits confirmation. We do not know anything as yet regarding the method of transmission to man of *Spirochaeta novyi*.

Mackie has endeavored to demonstrate the method of transmission of *Spirochaeta carteri*, and his results would appear to indicate that the common body louse (*Pediculus corporis*) is capable of transmitting this parasite to man. He found that 14 per cent. of lice taken from a badly infected boy's ward, 2

per cent. from a slightly infected girl's ward, and 13 per cent of lice fed upon infected patients, showed spirochaetes in the stomach blood and in the ovaries, multiplication of the organisms having occurred in both stomach and ovaries. He states that: "A fluid rich in active spirilla (spirochaetes) could be obtained by gentle pressure on the heads of infected lice." Mackie also examined the organs of *Cimex rotundatus* and found the spirochaetes present in the stomach until the sixth day after feeding, but there was no evidence that they underwent multiplication. He allowed bugs of this species, after biting infected monkeys, to bite 10 healthy monkeys, but the disease appeared in only one of these animals, and the infection in this case may have been due to other factors.

Distribution in Man.—The spirochaetes causing the relapsing fevers are blood parasites and are found only in the blood plasma, as they are not intracellular organisms. The observations of Dutton and Todd, which would indicate that these organisms occur within the red blood-corpuscles and the leucocytes, have not been confirmed, and their occurrence in these cells is probably accidental. The organisms are also found in the capillaries of the various viscera after death, but only in a few instances have they been reported as occurring in the endothelial cells and the cells of the tissues.

The examination of the blood in relapsing fever is generally useless (so far as demonstrating the parasite is concerned) during apyrexia, and even when fever is present several stained preparations should be examined before the result is regarded as negative.

Spirochaeta recurrentis is found only in the blood stream during the febrile paroxysm, rapidly disappearing as the crisis approaches, and being entirely absent from the peripheral circulation after the crisis occurs.

Spirochaeta duttoni also occurs only in the blood stream, but in smaller numbers than the preceding parasite, and, according to Ross, they can only be found during the relapse, being absent from the peripheral blood during the primary attack. Dutton and Todd describe this parasite as occurring within the erythrocytes but their occurrence in this situation is accidental.

Spirochaeta novyi and *Spirochaeta carteri* also occur only within the blood, and in both infections the organisms can be easily demonstrated in the peripheral blood during the febrile attack. In the internal organs the parasites occur within the capillaries but not within the tissue cells.

While the parasites cannot be demonstrated in the peripheral blood during the afebrile period, Dutton and Todd have shown, in the case of *Spirochaeta duttoni*, that the apyrexial blood is infective, and Mackie has shown that the apyrexial blood from monkeys infected with *Spirochaeta carteri*, produces infection in other monkeys, so that it is more than probable that the spirochaetes exist in the blood during apyrexia in some unrecognized form, as the examination of scores of blood films at this time always results negatively. We possess no evidence sufficient to prove that any of the spirochaetes causing relapsing fever in man are intracellular organisms, all of the observations pointing to their being true parasites of the blood plasma. In this they differ

from *Treponema pallidum* and *Treponema pertenue*, closely related organisms, which are true tissue parasites.

Demonstration of Spirochaetae.—*Spirochaeta recurrentis*, *Spirochaeta novyi*, and *Spirochaeta carteri* may be easily demonstrated in fresh blood preparations from patients suffering from relapsing fever, provided the blood be obtained during the febrile period, but after the crisis the parasites disappear, and it is then useless to examine the blood. *Spirochaeta duttoni* may also be demonstrated in the fresh blood specimens during the febrile period, but this organism occurs in such small numbers that it is better to make blood smears and stain them by some modification of the Romanowsky method. In fact, in suspected cases of infection with any of the spirochaetes of relapsing fever better results will be obtained by the examination of stained blood smears. If it is desired to examine fresh blood the ear or finger should be pricked with a sterilized needle and a rather large drop of blood be placed upon the microscopic slide and immediately covered with a cover-glass. It is necessary that the blood film be rather thick, as otherwise the organisms, being comparatively few in number, might be overlooked. If it is desired to examine stained smears of blood they should be made rather thick, and should be fixed and stained as recommended in the section of this work dealing with the staining of the malarial plasmodia. Any modification of the Romanowsky stain may be employed, but the Wright stain, used as recommended for the plasmodia, gives the best results. In infections with *Spirochaeta duttoni*, and in other infections in which the spirochaetes are few in number, it is often necessary to centrifuge the blood and examine the sediment, either as a fresh preparation or stained in the same manner as blood smears. The method of centrifugation is the same as recommended for the demonstration of *Trypanosoma gambiense*. In both fresh and stained specimens the spirochaetae are easily recognized, as no other object occurs in the blood which in the least resembles them, with the exception of the free flagella of the malarial plasmodia, and to one who has had any experience in the study of malarial blood, it is easy to differentiate the flagella from the spirochaetes.

In order to differentiate the species of spirochaetae we must depend upon their morphology, their action upon animals, and their reaction to immune sera. I have already spoken of the differences in the morphology of the four species described in man and have also noted for each species the animals to which it is pathogenic. The most practical method of distinguishing species is by the use of immune blood sera, for it has been found that the serum of an animal which has suffered from infection with any one of the species has no effect upon the other species when it is added to blood containing them, but that it agglutinates the species to which the animal has been rendered partially immune. Therefore, if we possess blood serum from animals which have been infected with the four species, we are able to distinguish by the use of these sera any doubtful species with which we are dealing. For instance: A spirochaeta is found in the blood, but we are unable to distinguish the species from morphology

alone. The blood serum of animals infected with each of the four species of spirochaetae is added to blood from the patient containing the spirochaeta, and the preparation in which agglutination occurs contains the serum of the animal immunized to the spirochaeta from the patient. Thus, if the spirochaeta in the patient be *Spirochaeta duttoni* the preparation containing serum from an animal which has passed through an infection with this species will be the only one which will show agglutination of the patient's spirochaetes. In this way it is possible to demonstrate with which species we have to deal in cases in which morphology cannot be depended upon for such differentiation.

It is probable that further research will result in simpler methods of differentiating species, for it must be confessed that the methods in which it is necessary to use animals are too cumbersome and difficult of application to be of much use to the general practitioner in the diagnosis of the relapsing fevers.

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CHAPTER IV.

Histoplasma Capsulatum.

In December, 1905, Darling discovered a protozoan organism in the endothelial cells of the lung, spleen, liver, and bone-marrow to which he gave the name *Histoplasma capsulatum*. While this parasite has not been found in the peripheral blood, and while it is not, strictly speaking, a parasite of the blood, the fact that it closely resembles in its morphology the Leishman-Donovan bodies (*Leishmania donovani*) and that it is found within the endothelial cells in smears from the liver, spleen, and bone-marrow is sufficient excuse for a brief consideration of this interesting organism in any discussion of the blood protozoa. The parasite has only been observed in three patients at autopsy and has never been demonstrated in living individuals. All of the cases have been observed by Darling upon the Isthmus of Panama, the most important clinical symptoms being an irregular remittent temperature, splenomegaly, emaciation, and a marked leucopenia. The parasites were found in the endothelial cells of the lymph and blood-vessels, and in necrotic areas and granuloma-like growths in the intestine, the lymph nodes, the bone-marrow, and the liver, spleen, and lungs. It has never been found free in the blood plasma. A similar organism has been found by Darling in mucus from the colon of a rat, but it is doubtful if the two are identical.

The following description of the parasite is given by Darling in his article upon "Histoplasmosis" in "The Archives of Internal Medicine" for September, 1908.

"The bodies are round and oval. There is among the larger forms a tendency toward an oval outline. An average-sized spherical body is 3 microns in diameter. The longer diameter of an oval body is 3.75 microns. The bodies are always surrounded by a clear, refractile, achromatic zone or capsule, giving the impression at once of an encysted protozoon. The body does not stain homogeneously, but very irregularly, hardly any two parasites looking exactly alike. The body consists of a deeply staining substance or chromatin, a faintly staining substance staining light blue with polychrome stains, and achromatic spaces. The deeply staining substance, or chromatin, is practically always heaped up along one side or end of the body; sometimes it consists of a single mass or several small masses of chromatin; sometimes it is ring-shaped or occasionally extending along half of the periphery of the body, being crescent-shaped. Occasionally a chromatin dot or very rarely a chromatin rod will be seen near the larger chromatin body. This chromatin dot or chromatin rod may sometimes be at the opposite end or side of the body.

There may be several such dots of chromatin. When there are several of good size the bodies appear to be in a presegmenting stage. The faintly staining blue substance takes up the rest of the space, excepting where there may be one or two small achromatic zones, resembling the vacuoles of protozoa. These vacuoles are irregularly disposed, being sometimes in the center and at other times near the periphery of the body. The most striking thing about the parasite is the extremely irregular way in which the staining substance (chromatin) is disposed. This is in striking contrast with the appearance of the Leishman-Donovan body."

From the above description it is evident that the parasite discovered by Darling is a protozoon, and that it does not answer in morphology to any of the known protozoa, thus justifying him in placing it in a new genus. Flagellated forms were observed in smears from the lung in one case, three organisms being noticed, each having a single, short, thick flagellum. As many as 300 of the parasites were observed in an alveolar epithelial cell of the lung, and many cells contained from 10 to 100 parasites. The red blood-corpuscles were never invaded.

The parasite is evidently very rare in Panama as only three cases of infection with it have been observed out of 33,000 admissions to the hospital at Ancon in the Canal Zone. Nothing is known as to its method of transmission, its endemic range or factors predisposing to infection.

The pathological lesions peculiar to infection with *Histoplasma capsulatum* were disseminated hyaline pseudo-granulomata in the lungs; necrotic areas in the liver, infiltrated by the parasites; enlargement of the spleen; and ulceration of the ileum, jejunum, and colon. The ulceration in the intestine appeared to be preceded by the formation of a circular, raised granuloma, which became pigmented, and finally ulcerated, the ulcer measuring about 8 mm. in diameter. It is significant that ulceration also occurs in the intestine in infection with *Leishmania donovani*, and that both infections are accompanied by an irregular fever and an enlarged spleen.

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