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"THERE are more mistakes made in the diagnosis of malaria with the microscope than perhaps over any other similar study; on the other hand, if properly employed, it may give valuable information, leading perhaps to the saving of life" (Manson).

A PRACTICAL STUDY

OF

MALARIA

BY

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THESE PAGES ARE
AFFECTIONATELY DEDICATED
TO MY MOTHER

PREFACE

WHILE there is a number of good books on malaria, I believe there is a place for a work written by one engaged entirely in private practice largely in country districts, in the home of the severer forms of the disease.

In the endeavor to make the work as practical as possible especial attention has been devoted to that mystic paramalarial syndrome, hemoglobinuric fever, and to the diagnosis and treatment of malaria. Prophylaxis has been considered in the light of Ross' epoch-making discovery.

The parthenogenetic cycle of the parasite, whose significance was first recognized by Schaudinn, and which affords the only rational explanation of latency and relapse, is described for the first time, perhaps, in our language.

While I have not hesitated to draw from the literature for the illustration of practical points, due credit is given in the reference portion. I am especially indebted to the works of Ewing, Dock, Barker, Marchiafava and Bignami, and Kelsch and Kiener for pathologic data.

I am grateful to my wife for copying the manuscript and for assistance in reading the proof, to Mr. W. C. Seckler for the photographic work, and to the W. B. Saunders Co. for courtesies throughout the publication of the book.

W. H. D.

MARIANNA, ARKANSAS, *October*, 1909.

CONTENTS

CHAPTER I

PAGE

INTRODUCTION 17
History of Hemoglobinuric Fever 23

CHAPTER II

GEOGRAPHIC DISTRIBUTION 31
Geographic Distribution of Hemoglobinuric Fever 34

CHAPTER III

ETIOLOGY 38
Dissemination of Malaria by Mosquitoes 69
The Malaria-bearing Mosquitoes 74
Classification of the Mosquitoes of North and Middle America . . 86
The Parasites of Malaria 112
Pathogenesis 129
Etiology of Pernicious Malaria 140
Etiology of Hemoglobinuric Fever 153

CHAPTER IV

PATHOLOGIC ANATOMY 174
Acute Malaria 175
Chronic Malaria 178
Hemoglobinuric Fever 180

CHAPTER V

CLINICAL HISTORY 184
Acute Malaria 184
Pernicious Malaria 203
Hemoglobinuric Fever 216
Complications and Sequelæ 232

CHAPTER VI

DIAGNOSIS 256
Differential Diagnosis 284
Diagnosis of Pernicious Malaria 287
Diagnosis of Hemoglobinuric Fever 289

CHAPTER VII

PAGE

PROGNOSIS 292

CHAPTER VIII

PROPHYLAXIS 302
Measures Directed for the Destruction of Mosquitoes 305
Measures Directed Toward the Destruction of Parasites 315
Measures to Prevent the Access of Mosquitoes 322
Prophylaxis of Hemoglobinuric Fever 332

CHAPTER IX

TREATMENT 334

REFERENCES 388

INDEX 397

A PRACTICAL STUDY
OF
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DEADERICK

A PRACTICAL
STUDY OF MALARIA

CHAPTER I

INTRODUCTION

A CERTAIN dusky tropical queen was wont to say that she did not fear the invasion of the white man, for she had two mighty generals, The Fever and The Forest.

Malaria has been one of civilization's greatest foes, both in time of war and in peace. Where shot and shell have slain their thousands, malaria has slain its tens of thousands. Malaria is the chieftain of the army of disease. Even Napoleon acknowledged its supremacy when he wrote his minister of war on the occasion of the disastrous English Walcheren expedition: "We are rejoiced to see that the English themselves are in the morasses of Zealand. Let them be kept only in check, and the bad air and fevers peculiar to the climate will soon destroy their army." It is said that the French crowed over the expedition "with the force of reason, the bitterness of sarcasm, and the playfulness of ridicule." How accurately Napoleon's prediction was verified is well known.

In the tropics the man who works the soil digs his own grave. Gigantic commercial enterprises have been undertaken and then abandoned on account of the havoc wrought by this scourge. Only recently has it been recognized that the medical man must precede and prepare the way for the engineer and the laborer.

But warring and canal-digging are not the only stages upon which the malarial tragedy is enacted. Within the family, at

home, the disease appears in a varied succession of forms, rapidly fatal, or slowly sapping the vitality, influencing the birth-rate, longevity, and even the intelligence and morality of entire countries.

In highly malarial regions, as the mortality increases the natality diminishes on account of abortions and sterility. Premature senility is frequent and advanced age is not so commonly attained.

Malaria, leaving its subjects anemic and neurotic, is responsible for inertia, loss of will power, intemperance, and general mental and moral degradation. Jones, who maintains that malaria was a potent factor in the decline of Greece and Rome, concludes that "malaria made the Greek weak and inefficient; it turned the sturdy Roman into a bloodthirsty brute." Monfalcon attributes abortion, infanticide, universal libertinism, drunkenness, want of religion, gross superstition, assassination, and other crimes to the direct influence of malaria.

Malaria costs the South incalculable wealth. Besides loss through untilled acres, diminished earning capacity, loss of time, and death, it produces in its victims a disinclination for work whose influence cannot be estimated in money. A conservative computation of the loss to the Southern States through malaria is fifty millions of dollars annually.

The importance to the world at large of the subject of malaria is evidenced by the fact that two of the seven Nobel prizes in medicine which have been awarded have been granted for discoveries in malaria—to Ross in 1902, and to Laveran in 1907.

The history of malaria may be traced to the age of fable. The story of Hercules and the Hydra is a familiar one. This monster dwelt in the morasses in the neighborhood of the Lake of Lerna, where Hercules was dispatched to destroy him. As each of the nine heads was struck off two new ones appeared. With the aid of his faithful servant, Iolaus, who burned each wound caused by the removed head, the beast was finally conquered. Even before the birth of Christ this myth was construed to typify the reclamation of swamp lands, uninhabitable on account of the prevalence of malaria. Antipater wrote,

"Hercules, the greatest subduer of the foggy atmosphere in times past, was placed among the gods for having destroyed the Hydra; in other words, for having reclaimed the marshy desert." The slaying by Apollo of the Python which arose from the fertile ground after the recession of the flood is similarly interpreted.

More than one thousand years before the birth of Christ malarial disease is mentioned in the Orphic poems, and the tertian and quartan types are alluded to. In the *Iliad of Homer* and in the *Wasps of Aristophanes* allusions are made to a fever which was probably malarial. Paludism was probably introduced into Greece from Egypt. According to Groff the word AAT, which is found among the inscriptions of the temple of Denderah, referred to a disease, doubtless malaria, which recurred every year at the same season.

Hippocrates divided malarial fevers into continuous and intermittent, which he subdivided into quotidian, tertian, and quartan. He recognized the etiologic influence of season, rains, and stagnant water, and the dangers of malignancy, dropsy, and affections of the spleen. Plato describes splenic enlargement, and other early Greek writers undoubtedly refer to malaria.

References by Roman writers to malaria are not numerous, the earliest being that of Plautus, who died 184 B. C. Cato speaks of "black bile and swollen spleen," and Cicero, Varro, Celsus, Livy, and others show unmistakable evidence of a knowledge of the disease.

Passing over the development during the middle ages of the knowledge of malaria, the names of Morton, Lancisi, Sydenham, and Torti appear.

Morton, 1697, gave accurate clinic descriptions of the pernicious and simple intermittent fevers, and attributed them to miasmatic effluvia. He was an ardent advocate of cinchona, whose value was at that period being hotly contested.

Sydenham, 1723, accurately described the malarial fevers. The intermittent fevers he divided into spring and autumn fevers. He justly concluded that the intermittent and continuous forms of malaria were due to the same cause. Syden-

ham ably defended cinchona, and, after clinic experiments with its use, formulated useful rules for its administration.

Lancisi, 1717, stated the etiologic relationship between marshy regions and malaria, and was the first to seek for a microscopic organism as the cause of the disease.

Torti, 1753, wrote an exhaustive treatise upon the various forms of malaria. His classification of the pernicious forms has become classical. Numerous quotations from Torti's treatise are to be found even in recent works upon malaria.

Varro, 118-29 B. C., expressed the opinion that malarial fever was caused by animals so minute that they could not be seen by the naked eye, and which enter the body with the air through the nose and mouth. Similar opinions were held by Columella, Palladius, and Vitruvius. Rasori is quoted as saying, "For many years I have held the opinion that the intermittent fevers are produced by parasites, which renew the paroxysm by the act of their reproduction, which occurs more or less rapidly according to the variety of their species." Le Diberder, 1869, maintained that the fever was due to the presence in the blood of animals which preyed upon the blood, and that the paroxysms depended upon reproductive acts between which apyrexia occurred.

Mitchel, 1849, claimed to have found in the sputa of malarial subjects fungous spores in great numbers, which he believed to have been inspired with marsh air and to have caused the disease.

Salisbury, 1866, announced the discovery in the urine and sweat of malarial patients of a species of alga, *palmella,* common on the marshy regions along the Ohio and Mississippi Rivers, which he alleged to be the causative element.

Until the true parasite of malaria was discovered the most widely accepted parasitic theory was that proposed in 1879 by Klebs and Tommasi-Crudeli. These investigators found constantly present in the mud of the Roman marshes a short bacillus. They were able to cultivate it upon fish gelatine, and when injected into rabbits produced a fever similar to malaria. They named it the *bacillus malariæ.*

The malarial parasites were undoubtedly seen and described

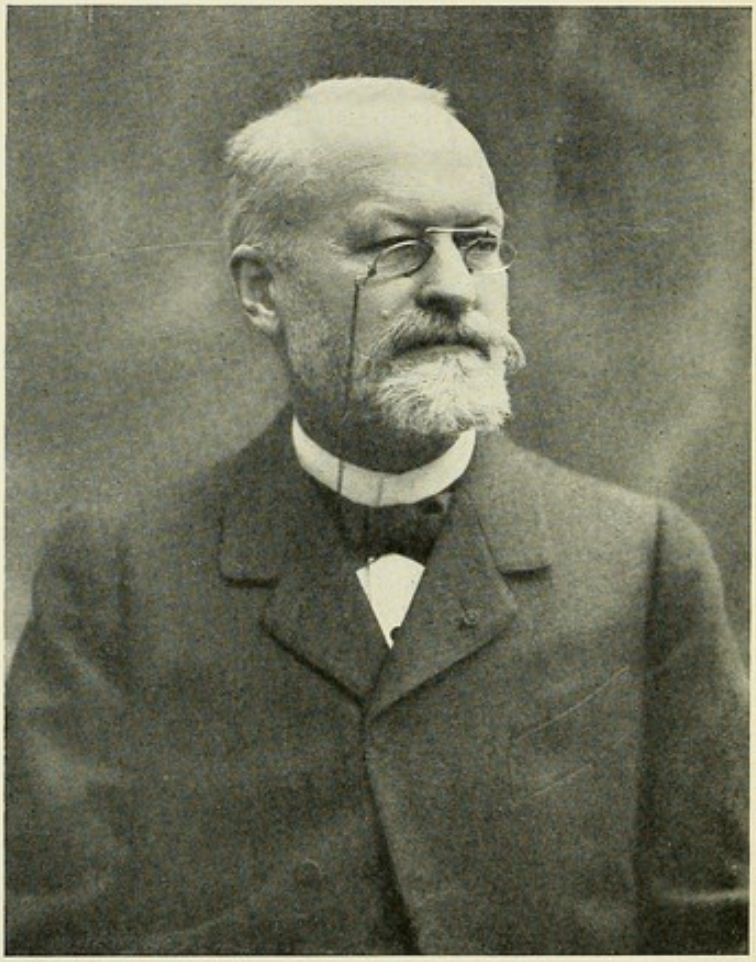


Fig. 1.—Charles Louis Alphonse Laveran, the discoverer of the parasite of malaria.

before Laveran discovered them. In 1847 Meckel, who first discovered malarial pigment, described bodies containing pigment which correspond to the malarial parasites. Virchow, in 1849, in a description of the pigment, depicted cells now known to be parasites, as did also Frerichs in 1866. The pigment was observed also by Dlauhy, Heschl, and Planer. None of these investigators, however, recognized the significance of these bodies, and their parasitic nature was not suspected until 1880 by Laveran, to whom all the more honor is due.

Charles Louis Alphonse Laveran was born at Paris, June 18, 1845. He entered the military service and was assigned to Algeria, where his brilliant discovery was made on November 6, 1880, and announced to the Paris Academy of Medicine November 23, 1880. He was using a one-sixth inch dry lens when examining the blood. He says,[1] "My first researches date from 1878; at this time I was on duty in the hospital of Bône, in Algeria, and a great number of my patients were suffering with malarial fever. I had occasion to perform autopsies upon several subjects of pernicious malaria, and to study melanemia which had already been observed, but was not considered as a constant change in malaria, nor as a specific lesion of that disease. I was struck by the singular appearance of granulations of black pigment, especially in the liver and in the cerebral vessels, and I endeavored to follow, in the blood of patients suffering with malarial fever, the study of the formation of pigment. I found in the blood leucocytes charged with pigment, already seen by other observers, but besides melaniferous leucocytes, spherical bodies, varying in size, pigmented, endowed with amœboid motion, and pigmented crescentic bodies attracted my attention. I supposed at that time that these were parasites.

"In 1880, at the military hospital of Constantine, I discovered, besides the spherical pigmented bodies, in the blood of a malarial subject filiform elements resembling flagella, which writhed with great vivacity and displaced the neighboring corpuscles. From then I had no further doubt as to the parasitic nature of these elements which I had found in the blood."

Laveran's discovery was not accepted by the medical world

until several years later; now it has been confirmed the world over. Among Americans who first corroborated Laveran's views may be mentioned Sternberg, Councilman and Abbott, Osler, James, Dock, Thayer and Hewetson, Barker, Woldert and Welch.

The discoveries of Golgi in 1885 were of great importance with reference to the life history of the parasite. He was able to follow tertian and quartan parasites throughout the endogenous cycle of development, and showed that a close relationship existed between certain phases of parasitic growth and certain stages of the paroxysm. Other Italian investigators proved the same for the estivo-autumnal parasites.

A vague suspicion that malaria and mosquitoes were in some indefinite way connected has been entertained in certain countries for a long period. A definite mosquito theory, however, was born in America. While reference is sometimes made to a paper on the "Mosquital Origin of Malarial Disease," supposed to have been published by Dr. John Crawford in the Baltimore Observer, 1807, no such article has been found, and the reference is probably erroneous.

In 1848 Dr. Josiah Nott,[2] of Mobile, published a paper upon yellow fever, in which he maintained the dissemination of that disease by insects, and suggested that malaria was spread by the "mosquito of the lowlands."

The most complete theory was proposed by King[3] in 1883. His views are supported by nineteen arguments, most of which are incontestable at the present day.

That mosquitoes are agents in the spread of malaria was advanced by Koch in 1884, by Laveran in 1884, by Flügge in 1891, by Manson in 1894, and by Bignami in 1896.

Undertaking the work at Manson's suggestion, and after several years (1895-1898) of toil and discouragement, Ross proved conclusively that certain species of mosquitoes are concerned in the dissemination of malaria. The debt owed him by mankind was acknowledged by the gift of a Nobel prize; his own feelings over the discovery are expressed in these lines, which he wrote:

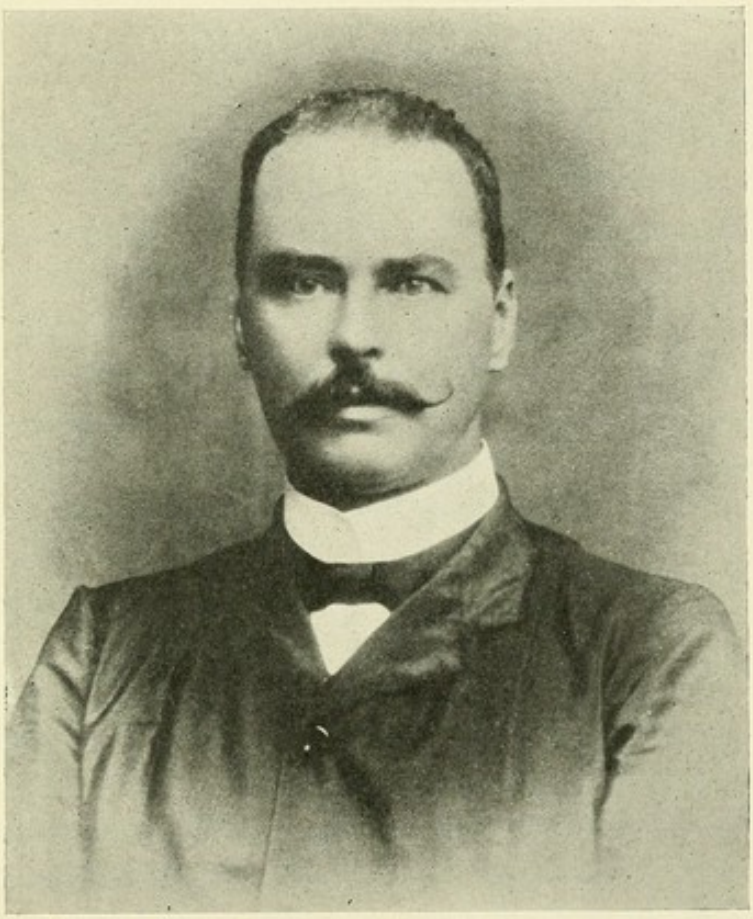


Fig. 2.—Major Ronald Ross, the discoverer of the rôle of the mosquito.

"This day relenting God
Hath placed within my hand
A wondrous thing, and God
Be praised. At his command

"Seeking His secret deeds,
With tears and toiling breath,
I find thy cunning seeds,
Oh million-murdering death.

"I know this little thing
A myriad men will save;
Oh, death, where is thy sting,
Thy victory, oh grave?"

A discovery, secondary in importance only to those of Laveran and of Ross, was made by MacCallum in 1898, who demonstrated that the flagella represent male sexual elements, analogous to spermatozoa.

HISTORY OF HEMOGLOBINURIC FEVER

It is probably unique in historical pathology that a complex of symptoms so striking as hemoglobinuric fever should have such an obscure history. As this obscurity is intimately associated with the etiology and symptomatology of the condition an investigation of some of the factors in its history is not without interest. After a short statement of the history of hemoglobinuric fever we will briefly consider how far it has been influenced by (1) its confusion with bilious remittent fever and yellow fever, (2) the introduction of cinchona bark and its alkaloids into the treatment of malaria, and (3) the advent of Europeans into endemic regions.

In the years from 1850 to 1853 blackwater fever was described by Lebeau, Daullé, and Leroy de Méricourt, physicians of the French navy, who observed it in Madagascar, and especially on the Island of Nossi Bé, off the northwest coast of the former island. They named the condition *icteric pernicious fever.* In 1861 cases observed in the Antilles, Guiana, and Senegal were described by Dutrouleau as *hematuric bilious fever.* In the early sixties Barthèlemy-Bénôit also described *hematuric bilious fever,* and in 1874 appeared the monograph of Bérenger-Feraud on *melanuric bilious fever.* This writer

states that the disease has existed in Goree since 1845, and in St. Louis, in Senegal, according to the hospital records of that city, at least since 1820, shortly after the settling of the Europeans there. The first twenty-three settlers at Gabun, in 1843, were attacked with blackwater fever and almost all of them died. A great increase in frequency has occurred since 1850.

Crosse[4] believes his own case, in 1888, to be the first on record in the Niger Territories, though he states that the disease was said by old coasters to have existed in the Niger Delta since 1882. F. Plehn[5] does not believe the disease to be of recent introduction into West Africa, but attributes its comparatively late recognition to two facts—first, that the susceptible population, who formerly lived as traders on anchored hulks, began to take up their abode on the shore; second, that the disease was formerly confounded with yellow fever. It has been known in Senegambia since 1855,[6] and in the Dutch East Indies since the Atjeh War, 1874-78.[7] Calmette saw a number of cases in Gabun in 1886-87, and Fluit, in San Juan del Sur, has seen numerous cases since 1850.[8] The condition was not described in India until 1855, and Sambon[9] regards this as conclusive of its recent introduction, as "it would be absurd to think that it could have escaped the attention of such men as Annesley, Chevers, Carter, Martin, Fayrer, Morehead, and Maclean had they met with it."

Dr. Elliotson,[10] in 1832, mentioned a case of ague accompanied by a discharge of bloody urine during the cold stage.

Todd,[10] in 1849, asserted that "a state of general cachexia, such as often occurs in scurvy, may bring on hematuria, or such as results from an aguish state brought on by the malaria of marshy districts."

In the United States hemoglobinuric fever was first described by Dr. J. C. Cummings,[11] of Monroe, Louisiana, in 1859. He reported 6 cases, and refers to numerous cases during the previous season. Faget[12] treated the disease as early as 1859, and states that cases with hematuria and hematemesis had frequently been seen in New Orleans and been mistaken for yellow fever. Inasmuch as Faget considered hematemesis a common symptom of hemoglobinuric fever,

it is possible that he himself confounded the two diseases in some instances. In 1867 Dr. T. C. Osborn,[13] of Greensboro, Ala., observed 10 cases, 5 of which ended fatally, some with anuria and uremia. All the patients had been repeatedly attacked with malaria. A few months later his son, Dr. J. D. Osborn,[14] read a paper before the Greensboro Medical Society, from which it is evident that the disease was becoming more prevalent, and that the country people were regarding it as yellow fever. Dr. H. C. Ghent,[15] of Port Sullivan, Texas, in 1866 reported hemoglobinuric fever endemic in parts of Texas. In March, 1869, Dr. R. F. Michel, of Montgomery, Ala., read a paper before the Medical Association of the State of Alabama in which he spoke of the disease as "a malignant malarial fever, following repeated attacks of intermittent, characterized by intense nausea and vomiting, very rapid and complete jaundiced condition of the surface as well as most of the internal organs of the body, an impacted gall-bladder, and hemorrhages from the kidneys. These phenomena presented themselves in an almost uninterrupted link, attended by remissions and exacerbations. It is a fever peculiar to the United States." He recorded the morbid anatomy in one of his fatal cases. In Arkansas hemoglobinuric fever was first recorded by Dr. E. R. Duvall, of Fort Smith, in a paper read before the State Society in 1871. He believed the case he recorded to be the first to occur in the State. This paper is said to be a model of accurate clinic observation. In 1880 Dr. G. B. Malone, in Monroe County, Arkansas, reported 155 cases met in his practice. The affection was first reported in Georgia by Dr. W. A. Greene, of Americus, in 1872, and in North Carolina by Dr. Norcom, of Edenton, in 1874. Norcom asserts that the disease did not, as some claimed, make its first appearance a few years ago, but that it had long been recognized. Dr. McDaniel,[10] of Camden, Alabama, described hemoglobinuric fever in 1874, and says, "In calling up my own reminiscences, I am sure that I have occasionally ever since my boyhood seen isolated cases of what was considered intense bilious fever with the surfaces and under tissues stained deeply yellow and with the urine deep red. They were nearly all fatal, and were

called in older phrase "bilious congestive," and in more recent "pernicious bilious." I have also, but more rarely, known groups of similar cases associated, say 3 or 4 cases occurring on the same premises or in the same family, about the same time. All such cases, in addition to the deep so-called bilious color and the red urine, had jactitation, suspirous breathing, inordinate thirst, and vomiting of various shaded and tinted so-called bilious matters. By diligently inquiring I have ascertained that very many old physicians, some of whom have now retired from practice, are satisfied that they have observed similar cases, sometimes singly and sometimes in groups.

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

The acrimonious dispute of the earliest writers on the subject of what constituted the coloring matter of the urine is parallelled only by that occurring later concerning quinine in the treatment. While Daullé and Bérenger-Féraud stoutly maintained that the dark color was due to the presence of bile in the urine, Dutrouleau, Pellarin, Barthèlemy-Bénôit, Antoniades, and Corre ascribed it to blood. It is remarkable that none of the first American writers attributed the color of the urine to bile, but considered it due to blood. Corre (1881) and Karamitsas (1882) proved that the process was a hemoglobinuria instead of a hematuria.

The credit of first directing attention to the etiologic relation between quinine and hemoglobinuric fever is generally credited to Tomaselli, who published his first observations in 1874, but this is an error. At a meeting of the Greek Medical Society, November 6, 1858, Veretas[15] reported that the majority of physicians practising in the marshy regions of Greece had noticed hematuria following the administration of quinine. He adds, "Among these observers my father has a place, having attentively observed this action of the medicament not

only in several other persons, but in himself also, unfortunately, as he was for a long time tormented with intermittent fever during his long residence at Vonitsa." Konsola[15] is said to have observed similar cases in 1858. During this year, also, Antoniades published an article on "Hemorrhages and Particularly Hematuria in Intermittent Fever," in which he opposes the theory that quinine is a cause. Other Greek physicians whose observations were published before those of Tomaselli are Papavassilou, Rizopoulos, and Karamitsas.

1. The close relationship between malaria and blackwater fever renders it easily understood why the latter might have been confounded with bilious remittent fever. Moreover, the early pyretologists almost completely ignored the condition of the urine in fevers. Hence, in a clinical scene, preceded by or opened with ordinary malarial paroxysms and characterized by dark urine, between the color of which and the bilious urine of bilious remittent fever there are all degrees, it is slight wonder that the two conditions were confounded.

This probably occurred chiefly in India and to a less extent in certain portions of Africa and America. One is struck, on reading accounts of the Indian fevers, with the description of the intense jaundice of the skin and scleræ, out of all proportion to this symptom in the bilious remittent fevers of the present day. In fact, some of these descriptions—for instance, Johnson's[16] of his first case in India—lack only the mention of the characteristic urine, about which the author is altogether silent, to make a fairly complete case of hemoglobinuric fever. Cleghorn[17] graphically depicts what he regards as a form of tertian fever, accompanied with hemorrhages, dark urine, deep jaundice, and other symptoms of hemoglobinuric fever. Since it is reasonably certain that there was no yellow fever in Minorca during the period of Cleghorn's sojourn in the island, namely from 1744 to 1749, it may reasonably be inferred that he saw cases of blackwater fever.

The fact that the early history of hemoglobinuric fever opens with disputes as to whether the coloring matter of the urine was due to blood or to bile is evidence of the confusion by some observers between hemoglobinuric fever and bilious re-

mittent fever, since formerly *bile* and *malaria* were practically synonymous.

It has been mentioned that the first reliable records of the existence of hemoglobinuric fever were, according to Bérenger-Féraud, those of the hospital of St. Louis in Senegal, where it is shown to have existed as early as 1820. It is a singular coincidence that this city afforded, in 1778, the first epidemic of yellow fever occurring in Africa.[18] Later Plehn[5] gave as one of his reasons for believing that hemoglobinuric fever was not a new disease in West Africa, that it had formerly been mistaken for yellow fever. Besides Senegal, two of the other regions where hemoglobinuric fever was first seen, the West Indies and Guiana, were yellow-fever foci. In the United States we have the early statement of Dr. J. D. Osborne that the condition was then regarded as yellow fever.

The similarity of the symptoms and the relative immunity of the black race to both diseases render the mistake somewhat excusable. As recently as 1897 Below[448] maintained the identity of yellow fever and blackwater fever.

2. Cinchona bark was introduced into Europe in 1640 by the Countess del Cinchon, wife of the vice-regent of Peru, in whose honor it has received its name. The efficacy of the bark in malaria was first known to the Indians in the region of Loxa, in the southern portion of Ecuador. The Corregidor of Loxa, hearing of the severe illness of the countess with tertian fever at Lima, in 1638, advised her physician, de Vega, to give the bark a trial, which effected a prompt cure, and in those days was regarded as nothing short of miraculous. When the countess returned to Spain she took a supply of the bark with her. Here it seems first to have been employed chiefly by the Jesuits, who introduced it into Rome in 1649. It was then known as countess' powder, or Jesuits' powder. Its use was antagonized by other religious denominations and by the medical profession. Bark was imported into England in 1671 by Sir Robert Talbot, an English quack, who kept the remedy a secret and sold it for one hundred louis d'or per pound. Louis XIV, who was attacked with a rebellious and severe intermittent in the year 1679, was cured by Talbot with

a concentrated vinous tincture of the bark, purchased and made public the secret remedy, for which he paid £48,000 and a life annuity of £2000.

In India the remedy was employed by Bogue[20] as early as 1657. In these times in Spanish-America, where the bark was indigenous, extraordinary methods were employed to prevent the nature of the drug becoming recognized. But during the eighteenth century cinchona bark was almost universally known. Lind is said to have employed in Lower Senegal, during 1765, over 140 pounds of the bark. In 1714 Ramazzini[21] wrote that should a fever patient die it was considered a crime not to have employed cinchona. In fact, so widespread was the use of large doses of bark that Calmenero (1647), Casati (1661), Daval (1684), Ramazzini (1714), and others wrote vehemently against the abuse of the drug.

Pelletier and Caventou, in 1820, succeeded in isolating quinine from the bark.

The institution of cinchona plantations in Java in 1854 and in Ceylon in 1859 caused a drop in the price of quinine, which had formerly sold for its actual weight in gold, to one-twentieth the original price.

Marchiafava and Bignami[22] seek to explain the seeming late appearance of hemoglobinuric fever by the use of quinine becoming prevalent at the time when the disease was first described. It is probable that this factor has caused an increase in certain localities, but a comparison of the history of the disease with that of the drug shows no very intimate chronologic relations. Further, blackwater fever is on the decrease in some regions where the use of quinine is becoming more general. This is reported to be the case in German East Africa by Meixner,[23] in Cameroon by Ziemann,[23] in Togo by A. Plehn,[24] and by Kohlbrugge[7] in the Malay Archipelago. The large number of cases occurring without the previous use of quinine should also be considered.

3. A consideration of the importance, in the history of hemoglobinuric fever, of the immigration of Europeans into regions where the condition is endemic involves the history of the tropics and subtropics. This factor is manifestly an

essential in countries where the natives are nearly immune, as in parts of Africa. Historic events, which were probably potent in the development of blackwater fever, were the discovery of America, the Portuguese discoveries and settlements on the coast of Africa, the African slave trade and the later efforts to abolish the same, the advent to Africa of missionaries and explorers, especially in the early part of the nineteenth century, and the operations of the East India Company.

The accession of Europeans was influential in the history of hemoglobinuric fever in several ways—by the increase of susceptible population, by the importation of quinine, and by the advent of physicians competent to recognize and to describe the disease.

CHAPTER II

GEOGRAPHIC DISTRIBUTION

North America.—In the United States it is chiefly the southeastern portion in which malaria is most prevalent. Along the Atlantic coast, south of New York and especially the lowlands of Maryland and of Virginia, and in the Carolinas, Georgia, and Florida the disease occurs frequently. Along the Gulf coast and up the Mississippi River and its tributaries malaria is widely prevalent. The portions of the States lying along the Appalachian Range are almost exempt, but the disease appears as the Mississippi River and the Atlantic coast upon either side are approached. West of the Mississippi, Arkansas, Louisiana, and Texas present the most numerous foci of malaria. In portions of Pennsylvania and New York autochthonous cases are not infrequently observed. In the more southern New England States malaria is still encountered, and in some places is even increasing in frequency. In the neighborhood of the Great Lakes malaria is very rare, excepting, possibly, that of Lake Erie and of Lake Michigan. In the Central States malaria has almost or quite disappeared, except in certain low river valleys. Along the Pacific coast the disease is not so frequent as along the Atlantic. In Washington it occurs in the Puget Sound Basin and the Columbia River, Chehalis, and the Yakima valleys. In Oregon malaria is found in the Columbia, Williamette, Rogue, and the Umatilla valleys, and in California in the Sacramento, San Joaquin, Tulare, Kern, and Santa Clara valleys. In certain parts of New Mexico malaria is occasionally met with.

Canada is free from paludism except along the northern shore of Lake Ontario.

In Mexico severe forms of malaria occur, particularly in the low coast regions.

Malaria abounds in Central America along the Atlantic coast and to a less extent upon the Pacific side.

South America.—The eastern coast of South America is more intensely infested with malaria than is the western coast. Venezuela (in the valleys), Guiana, and the greater portion of Brazil are highly malarial. Portions of Paraguay and of Bolivia afford a great many cases, while the disease is much less prevalent in Uruguay and almost absent from the Argentine Republic. On the Pacific border the deep valleys of Peru and of Ecuador are malarial centers.

The entire island of Cuba is malarial to a greater or less extent, as is also Jamaica. Of the Lesser Antilles, St. Vincent, Antigua, and Barbadoes are relatively exempt. Malaria is said to be almost unknown in the Bermudas.

Europe.—Great Britain, once infested, is now free from endemic malaria. In Germany the disease occurs infrequently in the Rhine and Danube valleys and near the mouths of rivers along the coast. Malaria is met in Holland, chiefly upon the island of Zeeland and in North and South Holland. The valley of the Danube, in Austria, affords a considerable number of cases. There are few regions in Hungary in which the disease does not occur, but it is especially along the western half of the southern border that it is prevalent. The marshes along the west coast and in the south of France give rise to a number of cases of malaria. In Spain and Portugal malaria occurs in the coast regions and in the larger river valleys. The disease is practically unknown in Norway, but is occasionally reported from Sweden, as well as from certain of the islands of Denmark. In Russia it is in the southern portion, particularly along the coasts and along the valleys of the rivers flowing southward, that malaria is encountered. Cases are occasionally observed in the southwest of Switzerland. The portions of Bulgaria most highly malarial are the Danube valley, the coast region, and the southern part. Almost the whole of Italy is sorely afflicted with malaria, as are also Sicily and Sardinia. Greece is the most severely scourged country of Europe. It is said that in the plains of Thessaly, Phthiotis,

Acarnania, Boeotia, Elis, Messenia, Argos, and Laconia hardly a single inhabitant escapes the disease.

Asia.—Asia Minor, Arabia, and Persia present foci of malaria, both in the coast neighborhoods and in the interior lowlands. In the swampy regions of Afghanistan and Beloochistan malaria is common and severe. In India portions of the northwest provinces and of the Bengal and Bombay Presidencies are intensely malarial. The foothills of the Himalayas, the Duars, and Terai are famous malarial seats. Both the coast regions and the interior highlands of Ceylon are endemic territory. Burmah, Siam, the Malay Peninsula, and French Indo-China are malarial in portions of their extent, and parts of China are intensely infested. Malaria is found in Japan, Formosa, and the Philippines, and portions of the East Indies are among the most highly malarial regions of the world.

Africa.—On the west coast the territory, between the Senegal and the Congo Rivers, is headquarters for malaria of malignant type. Approaching South Africa the disease diminishes in frequency and in severity. On the east the region from Delagoa Bay to Eritrea is malarial. In the interior of Central Africa, excepting the high elevations, malaria is widespread. Malaria abounds in Madagascar excepting upon the northeast coast and the mountainous interior. Reunion and Mauritius are also malarial. In Egypt it is chiefly the region overflowed by the Nile in which the disease is most prevalent. Malaria abounds about the coasts and marshes of Algeria.

In Australia malaria occurs from Cape York to Brisbane, on the east coast, diminishing toward the south. New Zealand is apparently free from malaria, and the Sandwich Islands and most of the other Pacific islands are remarkably exempt.

The relative frequency of the forms of malarial infection varies greatly. It may be stated as a general proposition that the quartan is the rarest form, the tertian is the form prevailing in temperate regions, and the estivo-autumnal in warm and hot climates. There are regions, however, in which the quartan predominates, as in certain portions of Italy and of India; in other localities it is the only form of malaria present, as upon the island Merite, of the Bismarck Archipelago.

The following table shows the relative frequency of the types of malaria in various regions:

Locality.	Authority.	Tertian.	Quartan.	Estivo-autumnal.
Texas	Moore[25]	23	0	30
Georgia	Curry[26]	34	0	16
Camp Wikoff	Ewing[27]	74	0	261
New Orleans	Charity Hospital Records[28]	373	1	203
Baltimore	Thayer and Hewetson[29]	338	5	188
Panama	Kendall[30]	22	0	291
St. Lucia	Gray and Low[31]	12	2	109
Panama	Gorgas[32]	4,812	8	10,815
Italy	Koch[33]	32	5	78
Italy	Koch[34]	202	15	191
Greece	Cardamatis and Diamessis[35]	87	3	145
Bulgaria	Mollow[36]	99	10	67
Italy	Italian Statistics[37]	32,392	6,846	23,520
British Malaya	Wright[38]	78	56	117
British Malaya	Watson[38]	19	4	28
Philippines	Craig[39]	98	8	272
India	Hope[40]	217	933	547
Cyprus	Williamson[41]	12	8	4
East Indies	Koch[42]	57	119	123
Philippines	Chamberlain[43]	55	3	62
India	Rogers[44]	1,372	71	1,311
India	Buchanan[45]	56	12	118
Assam	Bentley[46]	134	46	74
Japan	Tsuzuki[47]	345	12	107
Togo	Ziemann[48]	1	7	32
German East Africa	Meixner[49]	5	1	102
German East Africa	Grothusen[49]	5	7	68
Senegal	Thiroux and d'Anfreville[50]	7	44	266
German East Africa	Kudicke[51]	3	2	118
German East Africa	Exner[52]	11	4	328
German East Africa	Ollwig[52]	7	0	134
German East Africa	Schörnich[52]	1	2	130

Infections with more than one form of the parasite are not uncommon. Of these a combination of the tertian and the estivo-autumnal is the most frequent, the tertian with the quartan being rare, and the three forms together very rare.

GEOGRAPHIC DISTRIBUTION OF HEMOGLOBINURIC FEVER

In North America hemoglobinuric fever is found in the Southern States, especially parts of Texas, Louisiana, Arkansas, Mississippi, Tennessee, Alabama, Georgia, Florida, North Carolina, South Carolina, and Virginia. It is prevalent in Central America, particularly in Honduras, Nicaragua, and Costa Rica. It is found in the Greater Antilles, but appears to be rare in Hayti. In the Lesser Antilles it is more common

on the islands of Guadeloupe and Martinique. Numerous cases have been reported from Panama.

In South America hemoglobinuric fever prevails more notably on the north and east coasts, in Venezuela, Guiana, and Brazil, at least as far south as Rio de Janeiro.

It is rare in Italy, but rather more common in Sicily, Sardinia, and Greece. Otto[53] has reported an autochthonous case from Krakau. It has appeared in some of the valleys of Spain, and, according to Schoo, was formerly observed in Holland.

The regions in India in which hemoglobinuric fever is endemic are as follows: Between the Ganges River and the Himalayas in Behar Province; between the Godavari and the Mahandi Rivers in the Madras Presidency; a region in the Punjab between Meerut and the Indus River; a region of which Nagpur is the center; certain localities in the region of Bombay; and in Assam and in upper Burmah. It is found in Asia Minor, Cyprus, and Syria (being common in Palestine), the Malay Peninsula, Siam, Cochin-China, Tonking, and other portions of French Indo-China, and in Southern China. In the East Indies it appears in Sumatra, Java, Celebes, and more commonly in New Guinea and the Bismarck Archipelago. It has been reported from Formosa, but is comparatively rare in the Philippines.

Tropical Africa is the home of blackwater fever. Here, between the parallels of 15° N. and 15° S., it has been one of the deadliest foes to civilization. On the West Coast it occurs from Senegal to Damara Land, especially in Sierra Leone, Gold Coast, Nigeria, Cameroon, and the Congo region. On the east it prevails from Somali Land to Delagoa Bay, particularly in British and German East Africa and the Congo Free State, and is met with in the Bahr-el-Ghazal region and in Sudan. In Algeria, Laveran,[11] during a residence of five years, did not observe a single case and Brault[54] saw only one. However, Coste[52] has recently published his observations of 25 cases treated during 1904-05 in the region of Arzew. It rages in parts of Madagascar and Reunion, and is known in Mauritius and the Comora Islands, notably Mayotte. The mountainous islands of the Gulf of Guinea afford a few cases.

Thus it is seen that, while the peculiar geographic distribution of hemoglobinuria is embraced by that of malaria, it is not coextensive with the latter. And here the relation ceases. While all localities in which blackwater fever exists endemically are highly malarial, there are very extensive regions in which the severest forms of tropical malaria are rampant where hemoglobinuric fever is unknown.

It has been attempted to explain the distribution by saying that the frequency of hemoglobinuria in a given locality is in direct ratio to the endemic index of that locality—that is, the percentage of native-born children whose blood harbors malarial parasites—but this explanation also presents difficulties, as the disease is not present in all localities whose endemic index is high.

Wellman[56] maintains a close relationship between the geographical distribution of *Myzomyia funesta* in Angola and that of blackwater fever. Daniels[57] believes that if the disease is due to one or all of several varieties of mosquitoes which he mentions, *M. funestus* must be one of those implicated. F. Plehn[58] suggested a possible relation between the geographic range of hemoglobinuric fever and that of certain mosquitoes.

In certain localities the disease seems to be on the increase. Crosse[4] says that it is increasing in certain parts of West Africa. Manson[59] refers to the belief of competent observers that it is yearly becoming more common in Africa. Johnson[60] and F. Plehn[61] assert that it is undoubtedly becoming more prevalent on the west coast of Africa, and A. Plehn[62] believes that it is increasing in frequency in New Guinea. The inhabitants of the region of Jalpaiguri, in India, are recently said to be alarmed at its increase in that section.[63]

On the other hand, there are places in which it is becoming less frequent. The medical report from German East Africa for the year 1903-04 shows a decrease from the preceding year. The report from Duala shows a steady annual decrease from 1901 to 1904 inclusive.[49] Kohlbrugge[7] declares that it is becoming rarer in the Malay Archipelago. A. Plehn,[24] after mentioning the decrease in certain sections of West Africa, prophesied that in half a century this scourge of tropical Africa

would become, if not a historic reminiscence, at least an insignificant rarity. It is probably becoming less frequent in some of the Southern States.

Epidemics of hemoglobinuric fever have been described. Masterman[64] states that in 1893 there was a regular epidemic of malaria in and around Jaffa, and among the fatal cases were a great many of hemoglobinuria. Says Plehn,[61] "Not infrequently the disease appears in epidemic form, as was the case several years ago in Goree, Quittah, and Bonny." Sambon[9] mentions several epidemics, as follows: "The disease broke out among the laborers employed in making the canal through the Isthmus of Corinth; it attacked the Chinese laborers on the Congo Railway; and in 1885, according to Dr. Wenyon, of Fatshan, China, it ravaged, like a plague, the Chinese army on the Tonquin border of Kwangsi. In collective dwellings—such as barracks, hospitals, schools—it may attack several persons at the same time. In 1885 it broke out in a prison in Castiades, Sardinia, attacking 24 out of 800 convicts."

CHAPTER III

ETIOLOGY

DEPENDING as it does for its existence upon the life histories of three species of animals, malaria is of rather complex etiology. While within the blood of man the parasite is not subject to great variations of environment, no matter what the season or the latitude, nevertheless exposure to cold, wet or heat, dietary or other excesses, will have the effect of awakening latent malaria.

But it is the influence of external factors upon the life history of the mosquito that determines the greatest variations in the prevalence of malaria according to climate, season, temperature, rainfall, altitude, etc.

Climate.—It may be said, as a general rule, that the frequency and virulence of malaria increase as we approach the equator. The conditions of warmth and moisture are more propitious for the development of parasites within the bodies of mosquitoes in tropic than in colder climates; this is especially true of the estivo-autumnal form of the malarial parasite. Exposure to the heat of the tropical sun predisposes to the cerebral forms of pernicious malaria, and undue exposure to the sun's rays is ofttimes sufficient to stimulate sporulation of the parasites of latent malaria.

With respect to latitude Hirsch[18] reached the following conclusions as to the northern boundary of malaria in the northern hemisphere. The line starts from 55° N. on the western side of North America, sinks to 45° on its eastern side, rises to 63° or 64° on the western side of the old world (Sweden and Finland), and runs across Northern Asia in about the latitude of 55°.

Long before the discovery of the rôle of the mosquito in malaria it was known that the disease was not endemic unless the summer temperature maintained a certain average. During the middle of the last century Drake[65] assumed that an

average summer temperature of sixty degrees is necessary to the existence of malaria, and that it will not prevail as an epidemic where the average temperature falls below sixty-five; also that the fever will occur in winter at all places where that season has a mean temperature of sixty degrees or upward. Hirsch maintained that the summer isobar of 59°-60.8° F. marks the limit of the occurrence of malarial fever, and that those regions where the mean summer temperature does not reach that height are exempt from the disease. Curiously enough, it has been recently repeatedly demonstrated that this is the lowest temperature at which the parasite will develop in the body of the mosquito.

Season.—While relapses may occur at any season, and in certain tropic regions fresh infections may occur during any period of the year, in all temperate and most tropic regions there are seasons during which the disease is especially prevalent. This is commonly known as the *malarial season,* and varies according to latitude, temperature, rainfall, soil, etc.

The season of primary attacks depends entirely upon the life history of the malaria-bearing mosquitoes. This season usually begins a few weeks after the first brood of anophelines appears, which is at the height of summer, and continues, in temperate climates, until after the nights become cool. In each individual locality the beginning of the season is rather definite, the disease recurring at a certain period each year with more or less exactitude. In most of the regions of the Southern States the malarial season begins in the earlier half of July. In the latitude of Baltimore the most notable increase in cases begins during August. The malarial season in California is from August to October.

The following seasonal distribution of malaria in Panama is compiled from the "Reports of the Department of Sanitation of the Isthmian Canal Commission," and is the aggregate of the three years, 1906-1908:

January	4,301	July	6,399
February	3,624	August	6,319
March	3,591	September	5,384
April	2,400	October	5,276
May	2,127	November	3,814
June	3,900	December	3,647

In Italy a large number of cases from various sources[37] are distributed as follows:

January	8,567	July	41,855
February	6,811	August	61,335
March	8,124	September	52,525
April	9,302	October	35,640
May	11,101	November	23,298
June	15,106	December	12,670

In Guiana the season of greatest prevalence is said to be from October to December inclusive; in St. Lucia, W. I., from January to March; in Germany, from the end of July to the middle of September; Holland, from the middle of May to middle of September; France, from July to November; Bulgaria, May to October; Italy, from the end of June to November; Greece, from May to November; in Tonkin, from April to November; Calcutta, from October to December; Cyprus,

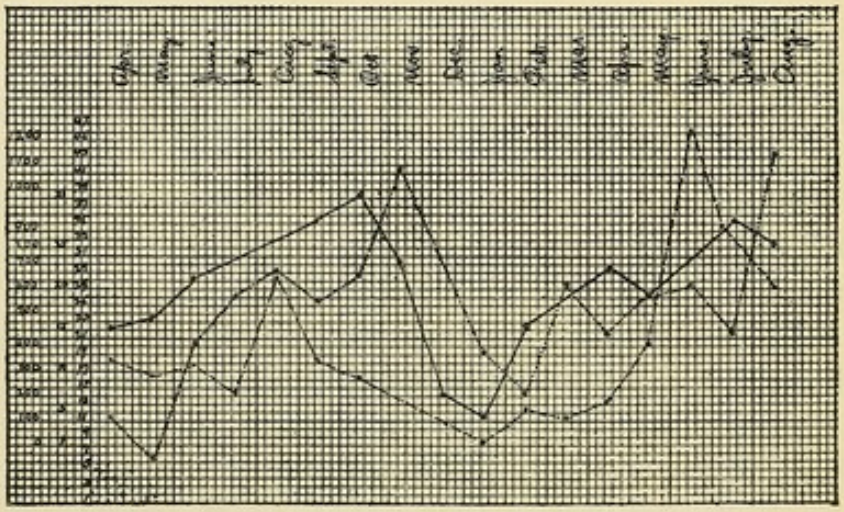


Fig. 3.—Diagram showing relation between rainfall and malaria (Plehn).
..... Malaria morbidity.
.—.—.—.—. Rainfall.
_____ Rainy days.

from July to October; Singapore, April to July; German New Guinea, from November to June; Northern Africa, from the middle of June to November; and in German East Africa, from April to July.

Where both tertian and estivo-autumnal malaria are endemic the malarial season is usually ushered in by cases of the former, the estivo-autumnal variety appearing at the height of

the season. The pernicious forms of malaria occur with greatest frequence at the height of estivo-autumnal prevalence. In Italy quartan malaria begins late in the summer and continues late in the fall. In America this variety is too infrequent to justify any definite conclusions. Mixed and multiple infections occur more frequently late in the season than early.

Rainfall.—The influence of rainfall upon the extent of malaria is very decided. Breeding places for mosquitoes are

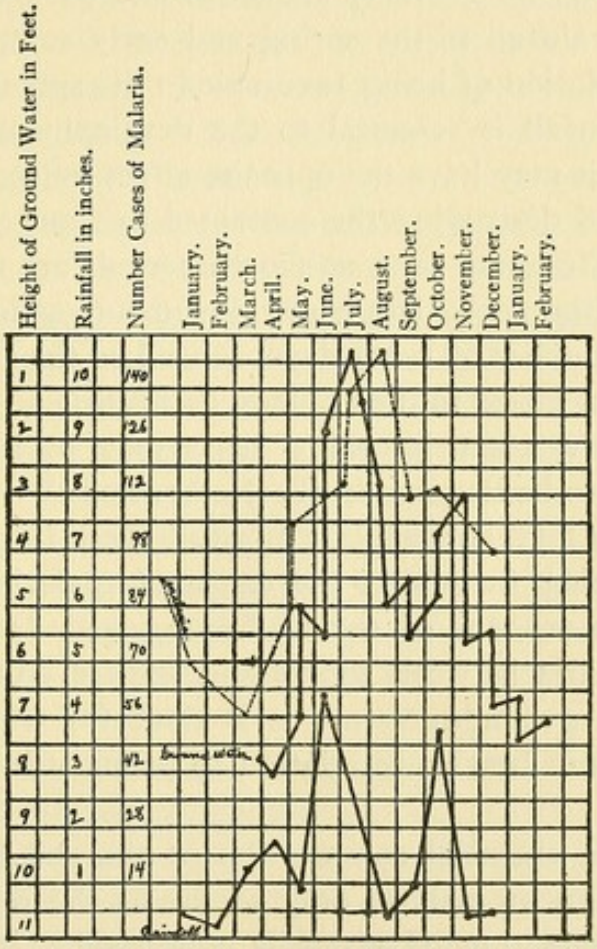


Fig. 4.—Relation between rainfall, ground water, and malaria (Ziemann).

essential in the etiology of malaria, and limited pools, such as result from a fall of rain, are well suited to the taste of the malarial mosquitoes.

Rain has a twofold effect upon the prevalence of malaria. First, exposure to wet is not infrequently followed by a recrudescence of a former infection. This effect is usually immediate. Second, rainfall produces breeding pools for the dis-

seminators of malaria. The effect of fresh breeding places is not shown immediately. Allowing twenty days for the aquatic stages of the mosquito, ten days for the mosquito cycle of the parasite, and a like period for the incubative stage in man, it would be, obviously, several weeks before an increase in malaria could be expected from such a source. This is well exemplified in the tropics, where so much depends upon rainfall. Here the height of the malaria curve is attained toward the end of the rainy season or shortly after.

A heavy rainfall in the spring and early summer has long had the reputation of being favorable to the spread of malaria.

While rainfall is essential to the development of malaria, if excessive it may have the opposite effect by scouring breeding pools and destroying the contained ova and young of the mosquito. Moderate rains at short intervals are more productive of breeding pools than heavy downpours at long intervals. Hence, the number of rainy days, as well as the actual rainfall in inches, is a factor in the etiology of malaria.

In very low countries rainy years may be healthy years. This is said to be the case in the Netherlands.[66]

Dew and a high atmospheric moisture were formerly accredited with being factors in the cause of malaria. This was doubtless on account of the well-recognized danger of contracting malaria between sunset and sunrise. Other than as an index of ground-moisture it is doubtful whether atmospheric moisture bears any relation to primary infections with malaria.

Soil.—The chemical composition of the soil has an effect upon the reign of malaria only so far as the relation of the soil to the retention of water is concerned. More depends upon the physical conformation than upon the geologic characteristics of the soil. As a rule, clay soils retain moisture better than the sandy, though there are exceptions. Rocky regions are less apt to harbor breeding pools because of good drainage, but pools upon a rock-bed are very persistent. The soil must be of such a character as to retain surface water sufficiently long for the aquatic stages of mosquito life to be completed.

More depends upon the nature of the subsoil than that of the surface soil. Even where the surface soil is very porous, an impervious subsoil favors the accumulation of surface water by preventing further percolation. Thus the height of the ground water during the malarial season bears a close relation to the volume of the malarial endemic. Proximity to collections of water, by raising the height of the ground water, favors the development of malaria.

Topography.—In countries designated malarial, regions entirely free from the disease are not uncommon. In a region within a short distance of a severely scourged locality malaria may be entirely absent. The difference in the prevalence of malaria within limited areas is dependent, in great measure, upon the physical characteristics of the surface of the land.

It has been known for centuries that malaria is partial to low marshy places, swamps, lakesides, low coast levels, and river valleys, and especially the deltas of large rivers. The cleaner the banks and the swifter the current of the streams at all stages the less apt they are to be malarious. Streams with sluggish or no currents, and with weedy banks which foster eddies, are breeding places for mosquitoes.

Nearly two hundred years ago Lancisi[67] described noxious and harmless swamps. His description of the former depicts well the favorite breeding places of the malaria-bearing mosquitoes.

Drake[65] well describes the topography of the malarial region of the United States as follows:

"In the maritime parts of Florida, Alabama, Mississippi, Louisiana, and Texas surface water is abundant, for one side of each rests on the Gulf, which has many inlets and little bays, the banks of which are inhabited. The rivers, moreover, are numerous, and as they approach the Gulf expand into broad estuaries or deltas. The delta of the Mississippi abounds in lakes, lagoons, and bayous. As we ascend this and the smaller rivers wide cypress and liquid-amber swamps, annually replenished, skirt both sides. The intervening plains are cut up by smaller streams, which have wide alluvions, often subjected to inundations, and the country between them

abounds in swamps, from which even the sandy pine-plateaus are not entirely free. This continues to be their condition till we reach the flanks of the Cumberland Mountains on the east and those of the Ozark Hills to the west. As we ascend the Mississippi to the mouth of the Missouri we find its annual floods leaving small lakes, ponds, swamps, and lagoons, which in the aggregate are of great extent and but partially drained or dried up before the next inundation. Now, as we have seen, the whole of this region is infested with autumnal fever beyond any other portion of the valley.

"In North Alabama, Tennessee, and Kentucky swamps are almost unknown, except along the few rivers which have wide bottom lands, most of which, moreover, are exempt from inundation. The rivers, however, are sinuous, and in summer sluggish and pondy, and it is in their vicinity chiefly that autumnal fever prevails. In the States of Illinois, Indiana, and Ohio the rivers generally flow through wide valleys, many of which are liable to be overflowed. Small lakes, ponds, and swamps are also frequent in certain portions of these States, and it is precisely these localities which are most infested. To the east of all the States mentioned, as we climb the mountains, the surface water is no longer found in basins, and the streams generally have a rapid current, down narrow and rocky channels, and here autumnal fever nearly disappears, or when present is confined to the valley of some stagnating stream. Everywhere west of the States of Arkansas, Missouri, and Iowa surface water is scarce, the declivity of the plain which stretches from the Rocky Mountains favoring its escape, while the subjacent sand almost absorbs even considerable rivers. Thus, as we advance into that desert, we come at the same time to the limits of the surface water and of autumnal fever. In the North there is no deficiency, for the whole country is essentially lacustrine, and up to a certain latitude the fever prevails. Thus the shores of Lake Ontario and Lake Erie, with those of the southern extremity of Huron and Michigan, are infested, and suffer far more than the dry lands which surround them. But beyond these limits, on the shores of the two latter lakes and on those of Lake Superior,

the fever, as we have seen, is never epidemic, although water is abundant; and still further North, where small lakes and their connecting streams exist in countless numbers, the disease is unknown, showing that, while water is essential to the production of this fever, other causes must coöperate to give it power."

Canals, dams, stock, and other ponds, railroad and levée borrow pits and other collections of water, particularly when stagnant, often breed anopheline larvæ, hence favoring the development of paludism.

It is generally believed that salt marshes are never malarious, and that *anopheles* larvæ cannot develop in sea-water. This is, however, not strictly true. DeVogel[68] has recently shown that *anopheles* larvæ may develop in sea-water evaporated to half its initial volume, and a number of other observers have found larvæ in salt water. But marshes of pure sea-water are not nearly so noxious as those of brackish water, a mixture of salt and fresh water, which are famous *anopheles* breeders. It appears that in some instances where salt water is inimical to the development of the aquatic stages of mosquitoes they may gradually become accustomed to the environment.

Altitude.—Malaria is essentially a disease of the low lands, high altitude being relatively exempt. This is partially accounted for by the better drainage of elevated altitudes and fewer pools in which malarial mosquitoes may breed. The lower temperature of high altitudes is also a factor in maintaining a low malarial morbidity in these regions.

It is known that anopheline mosquitoes do not fly to great heights. Hence sleeping in an upper story or in a building situated high above the ground gives a measure of protection from malaria. Laborers employed in highly malarial sections, and who sleep in the surrounding hills, even of moderate altitude, often remain entirely free from infection.

A few hundred feet in altitude may show a more marked difference in the prevalence of malaria than as many miles in latitude.

The general rule that malaria is a disease of low countries

has some exceptions. This is especially true in the tropics, where the disease may be encountered at very high altitudes. It may be said that the altitude at which malaria may occur varies in inverse ratio to latitude.

Malaria has been found on Lake Nyssa at an altitude of 1,560 metres; at Colico, 2,500 metres; in the Himalaya Mountains, at 2,000 metres; in the Andes, at 2,500 metres; at Blantyre, at 3,000 feet; German East Africa, at 1,550 metres; at points in Central Africa, at heights of over 5,000 feet; and in some of the high-lying valleys of Syria, at altitudes of 1,200 metres.

Some of the cases in high altitudes reported as malaria may be mistakes in diagnosis; other cases may be malaria contracted in the lowlands. Thus Tosari, at an elevation of 1,777 metres, had been cited as a place where malaria prevailed without the presence of mosquitoes, and this was used as an argument against the "mosquito theory." Koch,[69] investigating the place in 1899, examined the blood of eighty-two children; in none was the parasite of malaria detected. The only case of malaria found was in a man who, twelve days before the beginning of his illness, had spent the night in a highly malarial place upon the coast.

However, malaria is endemic in certain places of high altitude. Such are Eritrea, in altitudes of 1,750 metres; Upper Tonkin, at 1,000 metres; parts of Madagascar, at 1,100 metres; parts of Reunion Island, 1,200 metres; in Java, at 1,000 metres; and in the Philippines it is said that, while certain valleys are almost free from malaria, the hills in the vicinity are notoriously infected.[70] Wright,[38] in British Malaya, found *anopheles* larvæ in pools at an elevation of 2,300 feet.

Earthquakes and **volcanic eruptions** have been followed by a great development of malaria. Examples are cited of Rome in 1703, in Reggio in 1783, and Palermo in 1828. Remarkable instances have occurred in Peru also. The most recent illustration is that of Amboina, in the East Indies, which had until 1835 been remarkably free from malaria. In that year a severe earthquake occurred, and since then the malaria has increased both in extent and intensity.[18]

Such results can be explained only by an increase of stagnant water following these violent disturbances, probably through the interruption of the flow of ground-water.

Inundations.—Since very early times overflows have been recognized as a prolific cause of epidemics of malaria. Tacitus, Suetonious, Livy, Dionysius, Cassio, and Strabo mention such results from inundations of the Tiber. This stream experienced an overflow in 1695, which was described by Lancisi. The water covered a broad area of country, filling ditches, sewers, and canals. The following June, July, and August were extremely hot. An epidemic of malignant malarial fever ensued and, spreading far and wide, occasioned a great mortality.

In giving a description of a trip up the Tigris River, Lind[71] gives the following account of a curious strategem: "Here we were informed that the Arabs had broken down the banks of the river near Bassora, with a design to cover with water the deserts in its neighborhood. This, it seems, is the usual method of revenge taken by the Arabs for any injury done them by the Turks in Bassora, and it was represented to us as an act of the most shocking barbarity, since a general consuming sickness would undoubtedly be the consequence. This was the case fifteen years before, when the Arabs, by demolishing the banks of this river, laid the environs of Bassora under water. The stagnating and putrid water in the adjacent country and the great quantity of dead and corrupted fish at that time lying upon the shore polluted the whole atmosphere and produced a putrid and mortal fever. Of this fever between 12,000 and 14,000 of the inhabitants died; at the same time not above two or three of the Europeans who were settled there escaped with life."

Epidemics of malaria following overflows of the Nile, Ganges, Indus, Euphrates, Niger, Senegal, Volga, Danube, Saone, Rhone, Loire, Mississippi, and other rivers have been described.

The immediate effect of an inundation is to check the development of malaria. This is a result of a destructive effect of the flood upon the breeding pools of mosquitoes. It is only

after the waters have subsided and pools and marshes are left that the epidemic develops.

Trees and Vegetation.—It was formerly believed that, while decaying vegetation was the cause of malaria, living plant life greatly retarded its development. Whole volumes have been devoted to this subject. It was supposed that vegetation filtered the miasm from the air. It was argued that if air vitiated by respiration be confined in a bottle containing a living plant and exposed to the rays of the sun, the carbonic-acid gas will be absorbed and the air restored to its original condition, plant life consuming carbon dioxide and exhaling oxygen. So firm was this belief that in the days of ancient Rome trees were protected by law.

It is needless to say that the protective power of living plants was as much overestimated as the faculty of decaying vegetation to cause malaria. Their power of absorbing moisture from the soil is more than outweighed by the shade they afford the ground.

While the clearing of land of trees and vegetation may be followed by an outbreak of malaria, this may be due to the overturning of the soil, which usually goes hand in hand with opening land, and to the hardships attending such labor. The ultimate effect of clearing trees from the land is to diminish malaria by permitting the sun to dry the soil.

If trees have any protective virtue whatever it is probably through affording shelter and food for mosquitoes. The culture of eucalyptus trees is now known to have no prophylactic effect upon malaria.

Weeds and other vegetation growing in the water favor the development of mosquito larvæ by protecting the surface of the water from agitation by the wind.

Vegetable decomposition bears no relation to the etiology of malaria other than as an index to heat and moisture.

Wind.—The wind was formerly held responsible for transmitting malaria long distances. It was believed that the malaria of Edinburgh was imported by the winds from Holland, and that Italy became malarious through the agency of the African sirocco. The land breezes, especially if they blew

over marshy areas, were regarded as more highly noxious than the sea breezes.

As a matter of fact, the wind has little or no power to transmit malaria for distances of any consequence. While it is theoretically possible for infected mosquitoes to be borne by the wind, in reality these insects, especially the anopheles, being weak fliers, seek shelter while a breeze is blowing. The immunity from mosquito bites afforded by the Indian punkah, or a common fan, is evidence of this.

Furthermore, the disturbing effect of the wind upon the surface of the water interferes with oviposition of the adults and with respiration of larvæ and pupæ.

Exposure to cold winds may have the effect of arousing latent malaria. An incident related by Watson[72] is a striking illustration. Thirty ladies and gentlemen had sailed to the mouth of the Tiber on an excursion of pleasure. Suddenly the breeze shifted to the south and began to blow over a marshy tract of land situated to windward of them. Twenty-nine of the thirty were immediately after attacked with tertian ague.

The occurrence of malaria upon shipboard has been cited as an argument that malaria is an air-borne disease. Bilge water in the holds of vessels has also been accredited with producing malaria at sea. The dangers of malaria from cargoes of sugar and fruits were recognized by old writers.

Malaria occurring upon ships may be accounted for in several ways. These cases may be manifestations of malaria contracted upon shore. Even cases occurring long after embarking may be explosions of latent malaria. If vessels anchor too close inshore in malarial regions infected mosquitoes may easily gain access to the crew—a half mile from shore is probably a safe distance. It has been proven that mosquitoes may be carried for considerable periods in the holds and sleeping apartments of ships.

Commercial vessels are more apt to carry mosquitoes than are warships, through loading and unloading of cargoes.

There are many places where, notwithstanding apparently favorable topographic and meteorologic conditions, malaria is

entirely absent. This is due to the absence of either malaria-bearing mosquitoes, or malarial parasites, or of both. Among a number of such places may be mentioned the city of Rome and other portions of Italy, Madeira, portions of Cameroon, Chole Island, Comoro Island, Rodriquez Island, the Seychelles Islands, portions of India and of Borneo, the French Islands, Ponape, Saipan, Samoa, New Caledonia, Tahiti, Barbadoes, and portions of Brazil and of the Argentine Republic. The majority of such localities are islands and in the southern hemisphere.

Race; Immunity.—Certain protozoan diseases among lower animals confer immunity. In the Texas fever of cattle an attack, if recovered from, is followed by immunity. There are said to be breeds of cattle naturally immune to the disease. In the large game animals of Africa one infection with *trypanosoma brucei* confers immunity. Koch found that birds that had been infected with *proteosoma grassii* could not be reinfected.

From analogy it might therefore be expected that immunity to malaria might exist with some individuals or races. This is true, however, in only a limited sense.

While the various races of mankind vary somewhat in susceptibility to malaria none can be said to possess absolute immunity.

Caucasians residing in non-malarial countries are, when exposed, most liable to contract malaria. Negroes bred in highly malarial regions are, as long as they remain upon the native soil, least susceptible to paludal infection.

Immunity within the race increases generally as we go toward the equator. Thus the negroes of the Southern States display less immunity than the negroes of the West Indies or of tropic Africa. Likewise it may be said that immunity is much more marked in countries with a high than in those with a low, endemic index.

The immunity of the negro race has been variously estimated, some observers maintaining that they are absolutely proof against malarial invasion, while others hold that they are as susceptible as the whites. The truth lies between these

two extremes. Adult negroes reared in malarial regions are much less liable to paludism, as long as they remain indigenous, than are the whites. The negro race does not, however, enjoy an absolute but only a relative immunity from malaria.

According to Sternberg,[73] there were in the Department of Texas of the United States Army during the year ending June 30, 1883, among the white soldiers 21.36 per cent.; colored, 6.27 per cent., of periodic fevers to all kinds of fevers.

In 1845 most of the Europeans aboard the steamer L'Eclair, stationed upon the coast of Africa, died of malarial fever, while none of the forty Kroo negroes who were members of the crew were attacked.

In the hospitals of St. Louis and of Goree, among 100 European patients 36 have malaria, while of 100 black patients only 9 have malaria.[1]

The medical statistics of the French colonial troops for the year 1903 give the following figures for French West Africa: European troops, malarial morbidity, 690; mortality, 7.5 per thousand of effective force; negro troops, malarial morbidity, 12.45; mortality, 0.3 per thousand.

The following table from La Roche[74] will show the comparative ratio of mortality from the disease per thousand of mean strength in various commands of the British Army:

	Whites.	Blacks.
Windward and Leeward Islands	36.9	4.6
Jamaica	101.9	8.2
Bahamas	159.1	5.6
Honduras	81.0	4.4
Sierra Leone	410.2	2.4
Mauritius	1.7	0.0
Ceylon	25.7	1.1

Sternberg[73] gives the ratio per thousand of mortality from malarial diseases in the United States Army thus:

	1868.	1869.	1870.
White	94.20	140.67	72.99
Colored	74.62	15.62	38.46

From a compilation of the mortality statistics for the years 1852-1866 in Guiana, Maurel[75] gives the following results:

	Number of Deaths.	Ratio.
Europeans	12,819	12.00
Arabs	1,112	8.54
Negroes	1,172	5.75

According to Hirsch,[18] there died of malarial fevers per thousand of population in Ceylon:

Negroes	1.1
Indians	4.5
Malays	6.7
Singalese	7.0
English	24.6

During the Civil War both the morbidity and mortality from malaria in the negro race were greater than in the white race. However, the negro soldiers are said to have been more exposed to malaria than the whites, having been aggregated in malarial localities.[76]

With the better hygienic surroundings and more limited exposure of the whites the negroes would probably be attacked less often than they are. Whether the color, thickness, or other qualities of the skin of this race have anything to do with their relative immunity is not known.

The Chinese are said to be very susceptible to malarial infection. The Arabians and the Siamese are almost as frequently and as gravely attacked as the Europeans.

Laveran[1] states that it is difficult to estimate exactly the relative frequence of malarial fevers in the Europeans and in the Algerians, since the latter often escape observation, but he believes the natives have a degree of resistance and of tolerance not possessed by the Europeans.

The disease is said to be relatively rare in the natives of Madagascar. Adult Filipinos are more frequently attacked than the African negroes. The Abyssinians are often infected. The Malays, Javanese, and Tamils are much less susceptible than the Caucasians.

At Stephansort Koch[42] found various races infected in the following proportions:

	Number of Persons Examined.	Number infected with Malaria.	Per Cent.
Europeans	21	12	57.1
Chinese	240	63	26.3
Malays	209	53	25.3
Melanesians	264	29	10.9
Total	734	157	21.4

Immunity from malaria is probably an acquired immunity in the great majority of instances, though the contrary opinion

is held by some competent authorities upon the subject. The reasons for believing that this immunity is acquired by repeated infection, especially in childhood, and by prolonged residence in a malarial region, a sort of acclimatization, are that immunity is much more prevalent in adults than in children; that immunity is often diminished by a change of residence, or may be entirely lost by a temporary residence in a non-malarial climate; and that immunity in an individual may exist toward one form of malaria and not toward others.

That immunity is much more manifest in adults than in children is evident from the consideration of the endemic index of a malarial region, particularly of countries where the latter is high. During the first years of life many individuals examined show evidence of malarial infection, older children in a less proportion, and adults evince a relative immunity. This would hardly be the case if the immunity were racial and congenital.

The effect of a change of residence upon malarial immunity is a well-known fact. Plehn[5] says that the Soudan negroes, relatively immune at home, are often afflicted with malaria when going as soldiers to other parts of the continent. Smith[77] states that, while the native negroes of Sierra Leone are infrequently attacked, and only with mild degrees of malaria, in the West Indies regiment of negroes stationed in Sierra Leone the fever is of a very severe and often fatal character.

Individuals once immune to malaria may become susceptible on returning home from a temporary residence in a malaria-free country. Plehn[5] mentions three Cameroon negroes who, shortly after returning from a several years' sojourn in Europe, were attacked with severe remittent fever.

Repeated infection and consequent immunity to one form of malaria does not usually protect the individual from the other forms. Koch[78] found certain islands among the Bismarck Archipelago where quartan fever alone was endemic. Laborers from these islands sickened readily with tertian and estivo-autumnal malaria in Stephensort. Elting[79] has shown that persons who could not be artificially inoculated with a certain variety of the parasite could be with another.

In the South there is little difference between the races as regards susceptibility to the various forms of malarial infection—tertian, quartan, and estivo-autumnal. Clinically, however, pernicious cases, cachexia and hemoglobinuric fever, are rarer in the negro.

Instances of cachexia followed by immunity have been observed, especially by the Italian school. In these cases, after recession of the spleen and liver, and restoration of the blood elements, a stable immunity resulted. Subjects of existing cachexia, even though free from clinic evidences of acute malaria for years, can hardly be regarded as immune.

Rarely are persons encountered in highly malarial localities who have never been attacked with malaria. Such persons are supposed to possess *congenital immunity*. Celli[80] obtained precise histories of four persons living in the Pontine Marshes who were absolutely immune, having never had malaria, though they took no prophylactic precautions; their color was good, and their livers and spleens normal. In persons claiming never to have had malaria allowances must be made for the possibility of unrecognized attacks, especially in early childhood, which might give rise to an acquired immunity.

In conclusion, the resistance of the black race to malaria is due to repeated attacks in early childhood, and not to any great extent to heredity. While in a sense natural selection is a factor, it is largely an individual struggle, the selection of the fittest occurring in infancy, and but little being derived from progenitors.

Sex.—As a general rule, females are less often attacked with malaria than males, though in childhood the proportion is about even.

That women are less frequently infected is not due to a higher degree of resistance, but to the fact that they are less often exposed and are more temperate in their habits. It is probable that if they were equally exposed with males they would be even more often infected than the latter, on account of the greater delicacy of the skin and the manner of dress.

In certain localities women are not less frequently attacked than men. In Panama there is said to be very little, if any,

difference between the sexes in this respect.[80] In the Dutch East Indies European women are more susceptible than men.[81] Davidson[66] says that from 1871-75 the death rate of soldiers' wives in India was 4.20 per thousand, as compared with 2.81 for the men; and that in Bombay, 1885-86, the female death rate was 10.14; that of males, 7.56.

The following are some figures showing the sex distribution in a few localities:

	Males.	Females.
Stephansort[42]	32	21
Alabama[74]	585	451
Italy[82]	312	327
Italy[83]	311	236
Bulgaria[56]	1,742	995
Italy[84]	268	147
Greece[68]	1,202	972
Baltimore[29]	493	121
Total	4,945	3,270

In an institution in Alabama Simms and Warwick[85] found among deaf mutes 1.05 per cent. of the males and 6 per cent. of the females infected; among blind, 6 per cent. of the males and 3 per cent. of the females.

Pregnant women are probably less often infected because, on account of their condition, they are less often exposed; when exposed they are very susceptible. The puerperium predisposes to malaria.

Age.—Children are more frequently and more severely afflicted with malaria than adults. This is probably due to their more delicate skin, their manner of dress, sounder and more prolonged sleep, and inability to defend themselves against mosquito bites. The fact that cases of malaria in children more often escape correct diagnosis may account somewhat for the greater frequency, especially of relapses.

The subjoined figures show the distribution of malaria according to age:

Age	0-10	10-20	20-30	30-40	40-50	50-60	60-70	70-80	80-90
Thayer and Hewetson[29]	18	146	204	130	65	36	11	3	1
Rogers[86]	2	13	10	3	...	...	...	...	...
Cardamatis[68]	729	499	398	230	144	100	55	15	3
Conti[82]	245	146	83	61	63	...	...	...	...
Total	994	804	695	424	272	136	66	18	4

Of 2,073 malarial subjects observed by De Brun[86] at Beirut 1,065 were children and under eight years of age.

Of 1,784 cases recorded by Hope,[40] 862 were in children under fifteen and 922 in persons of fifteen or over.

Malaria causes a greater number of deaths in children than among adults. Strachan[87] tabulates 2,377 deaths from malaria, of which 1,428 occurred in children under one year of age, 275 from one to five years of age, 157 from five to twenty, and 517 from twenty to seventy-five years of age.

The following figures show the percentage mortality of malaria, according to age, compiled from the table of Savas[68] in Greece:

0-5 Years.	5-10 Years.	10-20 Years.	20-40 Years.	40-60 Years.	60-80 Years.
54	10	8	11	9	8

Endemic Index.—The percentage of children infected in a given locality is the index to the prevalence of malaria in that region (Fig. 5). As Ross[88] expresses it, "There is probably

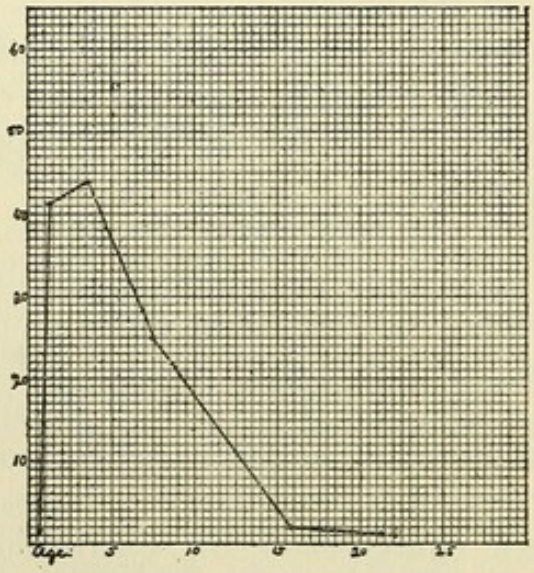


Fig. 6.—Spleen rate in British Central Africa (after Daniels).

only one really accurate method by which we can determine the degree of malaria in a given locality, and that is by ascertaining the average time in which a newcomer becomes infected. The shorter this period the greater, evidently, the



Fig. 5.—This group shows a high *Index endemicus.*

malaria potential of the locality. Native children constitute the class of newcomers most accessible for making the estimate."

The most accurate method of determining the *index endemicus* of an area is to make a large number of blood examinations of native children at various ages. This requires a great deal of time. It has been repeatedly shown that in regions where malaria prevails extensively a large per cent. of young children harbor the parasites without manifesting any symptoms of the disease, the index decreasing as the age increases. For this reason young natives with latent malaria are the source of the greatest danger to the community.

Koch[78] records the following indices:

At Bogadjim:	Per Cent. Infected.
Children under two years	80.0
Children from two to five years	41.6
Persons over five years	...

At Bongu:	Per Cent. Infected.
Children under two years	100.0
Children from two to five years	46.1
Children from five to ten years	23.5
Persons over ten years	...

Panse's[89] observations at Tanga may be tabulated thus:

	Per Cent. Infected.
Children under one year	48.0
Children from one to three years	87.6
Children from four to seven years	65.1
Older children and youths	39.4
Adults	15.3

Similar results were noted by Schaudinn[90] in San Michele di Leme:

1901.	Per Cent. Infected.
Children under five years	100.0
Children from five to ten years	83.0
Children from ten to fifteen years	100.0
Persons from fifteen to sixty years	...

1902.	Per Cent. Infected.
Children under five years	100.0
Children from five to ten years	100.0
Children from ten to fifteen years	83.0
Persons from fifteen to sixty years	7.7

Annett, Dutton and Elliott,[91] in Nigeria, obtained the results recorded in the following tabulation:

Age.	Per Cent. Infected.
Under one year	27.3
From one to two years	63.0
From two to three years	63.0
From three to four years	51.0
From four to five years	48.8
From five to six years	38.8
From six to seven years	6.6
From seven to eight years	27.5
From eight to nine years	25.0
From nine to ten years	14.0
Ten years and over	10.0

Craig[91] reports the endemic index about Camp Stotsenburg as follows:

	Per Cent.
From one to five years	72.5
From five to ten years	37.0
From ten to fifteen years	24.5

In calculating the endemic index a sufficiently large number of persons should be examined in order to eliminate error. It has been estimated that if fifty persons be examined and the blood of twenty-five found to contain parasites, the margin of error being 20 per cent., the index would not be 50 per cent., but between 30 and 70 per cent. Furthermore, while a high index indicates widespread malaria, an index of zero must not be construed to indicate an entire absence of the disease, since experience has shown that it may exist where the index, estimated in this manner, is zero.

In comparing the indices of two localities the figures should be taken at corresponding seasons, since the index of a given locality varies according to season. Thus Rogers[44] observed in the tea gardens of Assam that the endemic index reached 80 per cent. in October, but was only 30 per cent. in the same place early in April. Laveran[1] states that, while the endemic index of a certain portion of Java was 57.5 per cent. in January, it fell to 32 per cent. in May.

The prevalence of splenic enlargement has been employed to calculate the extent of paludism, this method requiring much less time than the examination of the blood. Among unhealthy villages of Borneo, Nieuwenhuis[86] found the spleen enlarged in 80 per cent. of the children examined. Schellong[92] found the spleen index at Finschhafen to be 84 per cent. An

examination of the school children held at Marathon in October, 1906, showed that enlargement of the spleen was to be found in every pupil.[93]

The spleen rate and the endemic index, estimated by a microscopic examination of the blood, do not usually correspond even approximately. In Algeria the Sergents[86] found the spleen rate in children from one to five years old to be 63.58 per cent., while the parasite rate was only 18.18 per cent. Stephens and Christophers[94] have prepared the following table to illustrate the relation between the spleen rate and the parasite rate:

Locality.	Spleen Rate.	Endemic Index.
Calcutta	0.0	0.0
Jalpaiguri—		
Bustee children	27.0	16.1
School children	14.7	0.0
Babu children	14.2	0.0
Mainaguri	74.0	25.0
Rungamutty	83.0	43.6
Sam Sing	7.1	16.0
Kurseong I	0.0	0.0
Kurseong II	0.2	0.0

These investigators draw the following conclusions:

1. A high endemic index may exist without any appreciable spleen rate (Africa).

2. A high spleen rate may exist in adults without a corresponding parasite infection.

3. In India (Bengal) among children a high spleen rate is a fair indication of the parasite infection.

4. The spleen rate, unlike the parasite rate, increases up to a certain age limit and may be considerable when the parasite rate is *nil.*

The writer does not believe that the spleen rate would disclose the true endemic index of regions in the Southern States.

Length of Residence.—In highly malarial regions, especially in the tropics, newcomers are usually infected during the first year. Craig[70] says that of the hundreds of cases of malaria occurring in our soldiers in Cuba almost 95 per cent. gave a history of being there from two to six weeks before the onset of the disease, and that one month was the period most commonly given.

In the Southern States the period before infection varies greatly according to circumstances. Newcomers who live in hygienic surroundings, and who observe ordinary precautions, may go for years without developing the disease. On the other hand, persons coming South who take no precautions, and who expose themselves carelessly, are liable to be attacked early. Thus, it is said that when the Beaumont oil fields were opened up people flocked there from nearly every section of the country, and nearly every newcomer was struck down within a few weeks with malarial fever in some form.

Residence, even prolonged, in a malarial locality does not confer absolute immunity to malaria.

Change of Residence.—The effect of a change of residence upon the immunity in the negro race has been referred to.

It is a common observation that moving to another locality "brings the malaria out of the system." This malaria is usually latent—always so, of course, if the new residence is in a non-malarial region. It is not uncommon for persons who have never had recognizable paroxysms to suffer an outbreak upon leaving the endemic region.

Occupation.—This is a factor in the etiology of malaria in two respects: first, by reason of certain occupations exposing the person to the bites of mosquitoes; second, by reason of the exposure and exertion attending certain occupations awakening latent malaria.

Rural avocations more commonly expose to malaria than urban. Occupations which necessitate residence at highly malarious spots are especially dangerous, as well as those that require being out of doors at night.

Overturning the soil, as in gardening, farming, ditching, railroad, levée, and canal construction, predisposes to malarial infection. Fishermen, soldiers, night-watchmen, engineers, and timber-workers are often exposed.

Rice culture, requiring as it does the retention of water from the surface of the ground, is not an unalloyed boon as an innovation into many of our Southern States. The dangers to the community from the growth of rice were recognized many decades ago near Savannah and Charleston. Malaria



Fig. 7.—Exposure to the sun is one of the predisposing causes of malaria.

is said to have almost disappeared from the regions of Parma and Vincenza when rice culture was discontinued.

Social Condition. Civilization.—Formerly malaria attacked all classes. Many noted persons were frequently infected, and James I and Cromwell died of the disease. Moats and lakes near castles and country estates were doubtless to blame.

Now malaria is chiefly a disease of the poor and ignorant classes. The man in the well-constructed and properly-screened residence is much less liable to become infected than the one in the loosely built and unprotected hut. The occupations and food of the poorer classes are also factors in the greater prevalence among them.

Persons living in cities and towns are much less apt to be exposed to infection than those in villages and in the country. Many towns and cities in the heart of malarial areas are relatively free from the disease. Suburbs are more highly malarious than the more dense populated sections, for the reason that the mosquito has more opportunity to breed in the former.

Other Factors.—There are certain factors of the utmost importance in the etiology of malaria, and before the truth was known were looked upon as causing the disease. These are overwork, fatigue, exposure to sun, rain, and cold, excesses in Bacchus and in Venus, psychic emotions, loss of sleep, traumatism, surgical intervention, overeating, hunger, thirst, digestive disorders, menstruation, parturition, intercurrent affections, and the administration of certain medicaments.

Watermelons, muscadines, cucumbers, and other articles have yet the reputation in parts of the South of causing chills.

The administration of tuberculin and of potassium iodide are said to be followed not infrequently by outbursts of malaria.

It is obvious that the influence of these factors is upon latent malaria, or the parthenogenetic cycle of the parasite's life history.

Insufficient and improper food both lowers the resistance to new infections and kindles latent malaria into activity.

The effect of deficient nourishment upon malaria mortality is well illustrated by the following table, compiled by Roux from statistics in India, where rice is the staple food of the lower classes:

Year.	Price of Rice.	Deaths from Malaria.
1874	2 rupees 4	891
1875	2 rupees 9	842
1876	2 rupees 12	902
1877	3 rupees 12	991
1878	4 rupees 8	1,002

While the major portion of many older works on malaria was devoted to the rôle of drinking water in the contagion of malaria, it is now known that it is of minor importance.

Celli[67] had several healthy individuals, in the San Spirito Hospital of Rome, to drink for a number of days water obtained from the Pontine marshes and from stagnant pools. The results were uniformly negative.

Zeri[67] conducted three series of experiments with water from malarious localities: 1. He had nine individuals drink from 1½ to 3 litres of water daily from five to twenty days, each person consuming from 10 to 60 litres of the water. 2. In sixteen individuals the mucous membranes of the respiratory tract were sprayed with marsh water by means of a compressed-air atomizer. 3. In five persons water from malarial places was injected into the rectum. The results of all these experiments were negative.

It has been maintained that water in which mosquitoes harboring parasites have died is capable of producing malaria. This is based upon the single experiment of Ross, who had an Indian native drink a small quantity of water in which there were dead mosquitoes which had fed upon malarial blood. Eleven days later the native developed fever which terminated spontaneously after three days without relapsing. In the blood were found ring forms of the estivo-autumnal parasite. This experiment was repeated, but the result could not be confirmed, so must be regarded as co-incidental.

In regard to the immunity to malaria enjoyed by opium-eaters, Russell[95] states that the observations of several sur-

geons of extensive experience in opium-eating regions confirm the popular belief that the opium-eater, in the early stages of the habit, while as yet not constitutionally broken by its long continuance, does, as a matter of fact, enjoy considerable immunity from malarial affections. This writer concludes that this power of opium is partially responsible for its prevalence in some of the eastern countries. Moore[15] testifies also that opium-smokers are more resistant to malaria.

Epidemics.—Malaria, known as an endemic disease, occasionally prevails so intensely as to acquire the dignity of an epidemic. Becoming more frequent and fatal in its native haunts, it may spread to regions ordinarily immune, and may even assume the extent of a pandemic.

The first pandemic of which we have any knowledge occurred in 1557 to 1558, and is said to have overspread all of Europe. The next appeared from 1678 to 1682, and was nearly as extensive as the former. Similar epidemics arose during 1718-1722, 1748-1750, 1770-1772, and 1779-1783. During the past century an epidemic occurred from 1806 to 1812, and one from 1823 to 1827 is said by Hirsch[18] to have been one of the most extensive, severe, and persistent of pandemics, of which reports were received from almost all parts of the world. Between 1845 and 1849 and 1855 and 1860 malaria assumed epidemic form, and the great pandemic of 1866 to 1872 marked the invasion of Mauritius and Reunion, where malaria was previously unknown.

Quite recently epidemics of malaria have been reported in Algiers, Greece, and elsewhere.

What may be called house epidemics or domestic epidemics are common in the experience of many observers.

It is well known that the residents of certain houses suffer much from malaria, and that certain houses are seldom free from the disease during the malarial season. For this local conditions are responsible.

The writer has more than once seen as many as half a dozen cases in one family at the same time, and in many families every member is successively attacked during the season.

Modes of Infection.—The only known modes of transmis-

sion of malaria necessary to consider are: 1, congenital; 2, artificial inoculation, and 3, inoculation through the bites of certain species of mosquitoes.

Congenital Malaria.—It was formerly believed that malaria was not infrequently transferred from mother to fetus. Ducheck[96] published a case, in 1858, of a child whose mother suffered from malarial paroxysms during pregnancy. The child dying three hours after birth, at autopsy the liver and spleen were found to be enlarged, and the spleen and blood of the portal vein contained considerable pigment.

Two cases are reported by Felkin.[97] In the first case the diagnosis was based upon intrauterine quivering of the fetus, enlarged spleen at birth, and fever later, the date of which is not recorded. In the second case the mother had never had malaria, having never been outside of Edinburgh, but the infection is attributed to the father, who had contracted malaria in Africa several years previously and, as Felkin believes, had transmitted the disease to no less than three infants.

Watson[72] cites the case of a woman who was suffering with tertian ague. On alternate days when she missed the paroxysms she could feel the child shiver with chills. Bark was prescribed and the paroxysms of the fetus were first interrupted, then those of the mother.

However, of numerous cases recorded by a score or more of early writers, all are open to two objections: First, the diagnosis was not certainly established; secondly, postnatal infection was not excluded.

Marchiafava and Bignami[22] mention four cases in which the blood of the fetuses of malarial mothers was entirely negative.

Thayer[98] records a case of a negress who had had malaria at least five months and whose blood contained three groups of the quartan parasites when she gave birth, during a paroxysm, to a child whose blood, upon repeated examination, was found free from parasites and pigment. While both parasites and pigment were found upon the maternal side of the placenta, none was found upon the fetal side.

Sereni,[86] who examined the blood of four infants born of

malarial mothers, was unable to find evidences of malaria in any case.

Ziemann,[48] likewise, in four cases of new-born children of malarial infected mothers, had uniformly negative results.

The writer has upon several occasions obtained blood from infants, immediately after birth, whose mothers harbored malarial parasites, and in no case have parasites been detected. Similar results have been obtained by Bastianelli,[22] Caccini,[22] Borne,[90] Schoo,[90] F. Plehn,[5] Terburgh,[79] A. Plehn,[99] Wellman,[68] and others.

Pezopoulos and Cardamatis[100] based the following conclusions upon six cases, five full-term labors and one abortion, which they studied.

1. In the blood of the six mothers there were parasites, more or less abundant.

2. In the blood of the new-born and of the aborted fœtus, examined a few hours after expulsion, there were no parasites.

3. In the blood of the liver and spleen, as well as in sections of these organs of the two fetuses which were examined postmortem, no parasites were found.

4. In the blood taken from the maternal surface of the placentæ of the five new-born children there were parasites in abundance, while in the blood taken from the fetal surface there were no parasites, or at most a very few.

5. In blood taken from the umbilical cord no parasites were found.

6. In the blood of the placenta of the aborted fetus no parasites could be detected.

Bein and Kohlstock[101] are said to have found malarial parasites in the blood of a four-months-old child born sometime after the arrival of the mother in a region free from malaria.

Winslow[102] records a case which he believes to be congenital, though the parasites were not detected until the child was eleven weeks old.

A case of malarial fever in infancy thought to be maternal in origin is reported by Peters.[103] The examination of the blood on the second and third days after birth was negative, though parasites were found on the fifty-first day.

Moffatt[104] observed a case supposed to be congenital malaria, though the parasites were not detected before the seventh week.

Bouzian,[105] in Algeria, detected parasites in the blood of an infant only twelve days old.

Hitte[106] collected from the literature 21 cases of malaria considered congenital. In 13 of these the blood was not examined; in 1 parasites were detected four months after birth, and in 5 cases parasites were found from several weeks to two months after birth. The remaining 2 cases were observed by Hitte personally, who claims to have found parasites in the blood obtained from the umbilical cords. The mothers of both children were suffering with malaria.

Parasites were found by Simms and Warwick[85] in the blood of three babies between three and seven days old; the mothers had previously had malarial paroxysms.

Holt[107] mentions a case in which he states there seems little doubt that the disease was contracted *in utero*. The mother had been suffering with tertian intermittent. Eighteen hours after birth the child showed evidences of a malarial paroxysm. The next day malarial organisms were found in the blood.

Economous[108] reports 6 cases with almost conclusive evidence of congenital origin. In each of these cases the blood, examined from eight to forty-eight hours after birth, contained malarial parasites. The mothers had, previous to delivery, suffered with malaria.

Bel[109] mentions a female patient who died of pernicious malaria. The parasite was found in the blood, pericardium, meninges, and spleen, as well as in a seven-months fetus.

As may be inferred, properly proven cases of congenital malaria are rare. This reluctance of the parasites to pass through the placenta is in keeping with their aversion to leave the blood-vessels. It has been pointed out that no parasites are found in the hemorrhages and perivascular exudates in cases of pernicious malaria, though they may exist in hordes within the vessels. Congenital malaria is probably to be explained in the majority of cases through placental lesions permitting direct mingling of maternal and fetal blood during parturition.

Inoculation.—Even before the parasite of malaria was discovered Gerhardt[110] succeeded, employing the blood of malarial subjects, in inoculating healthy persons with malaria.

Since then many similar experiments have been performed. Tertian malaria has been transmitted by inoculation by Bein, Bacelli, Antolisei and Angelini, Mannaberg, Elting, and others; quartan by Gualdi and Antolisei, Di Mattei, Calandruccio, Bacelli, and Celli and Santori; estivo-autumnal by Gualdi and Antolisei, Di Mattei, Celli and Santori, Bastianelli and Bignami, and Elting.

The injection of blood containing only crescents gave negative results in the experiments of Thayer, Bastianelli, Bignami, and Elting. Di Mattei and Calandruccio, however, observed an irregular form of fever to follow such an injection. This can be explained only by parthenogenesis.

The injection of blood containing a certain species of parasites is followed by fever characteristic of that species, and these parasites are to be found in the blood of the person inoculated.

There are only two experiments which, at first sight, seem to contradict this specificity of the different parasites. These were performed by Gualdi and Antolisei. Blood from two patients suffering with quartan malaria was inoculated into two healthy persons. In one case the injection was followed in ten days by irregular fever and estivo-autumnal parasites were detected in the blood. In the other case after twelve days an irregular fever began and estivo-autumnal and a few quartan parasites were found in the blood. It was later discovered that the patients from whom the blood was taken had recently suffered with quotidian, tertian, quartan, and irregular fever, hence it is evident that a pure culture of quartan parasites was not obtained. These same observers, in subsequent experiments, found that the injection of one species of parasite was followed by the characteristic fever and the appearance of the same species of parasites in the blood of the person inoculated.

There are those who cannot be successfully inoculated with one species of parasite but can with another. It has been

shown also that one species of parasite often disappears from the blood upon inoculation with a different species. Di Mattei found that the inoculation with estivo-autumnal parasites of a patient already infected with quartan malaria caused a disappearance of the quartan and a development of the estivo-autumnal parasites, and that the inoculation with quartan parasites of a patient already infected with estivo-autumnal caused a disappearance of the latter and a development of the quartan parasites.

The degree of development of the parasites apparently has no effect upon the result, since the disease develops as readily after the injection of blood containing adult organisms as after that containing young parasites. It is immaterial also whether the blood be injected intravenously or subcutaneously. A very small amount of blood, even less than one drop, is often sufficient for inoculation.

The injection of defibrinated blood, of centrifugalized corpuscles, and of blood diluted with an equal quantity of distilled water and inoculated immediately have given positive results. The injection of dissolved dried blood, and blood diluted with an equal quantity of distilled water and allowed to stand an hour, have proven negative.

Jeffries[111] reports the case of a New York surgeon who had never had malaria supposed to have contracted the disease by pricking his finger several times during an operation upon a woman infected with malaria. Sixteen days after the operation the surgeon had the first chill and had several subsequently. The blood contained many estivo-autumnal parasites.

Dochmann[86] attempted to inoculate malaria from man to man by means of the serum from a herpetic vesicle. While he claims to have succeeded, the results of his experiments have never been confirmed.

Efforts to inoculate the lower animals with human malaria have been fruitless. Such attempts have been made upon horses, mules, dogs, monkeys, rabbits, mice, guinea-pigs, hedge-hogs, bats, wolves, cats, pigeons, doves, magpies, screech-owls, turtles, frogs, and lizards.

DISSEMINATION OF MALARIA BY MOSQUITOES

The discovery by Ross of the rôle of the mosquito in the dissemination of malaria is the most startling achievement of modern medical science.

Mosquitoes do not cause malaria; they carry it from infected to healthy persons. The parasites, sucked with blood from a malarial individual, undergo a cycle of development within the body of the mosquito, and are then inoculated into healthy persons. Man is merely the intermediate host of the parasite, the mosquito is the definitive host, and it has been said that man gives malaria to the mosquito, and not the mosquito to man.

Not all species of mosquitoes can serve as hosts for the malarial parasite. It is only certain members of the subfamily *Anophelinæ* that have been found to act in this capacity. Of this subfamily the following have been determined, with more or less certainty, to be malaria carriers:

Anopheles annulipes.
Anopheles bifurcatus.
Anopheles cohacsus.
Anopheles crucians.
Anopheles farauti.
Anopheles fluvialis.
Anopheles formosæensis.
Anopheles maculipennis.
Anopheles martini.
Anopheles punctipennis.
Anopheles pursati.
Anopheles vagus.
Anopheles vincenti.
Cellia albipes.
Cellia argyrotarsus.
Cellia pharœnsis.
Myzomyia Christophersi.
Myzomyia culicifacies.
Myzomyia funesta.
Myzomyia Hispaniola.
Myzomyia Listoni.
Myzomyia Ludlowii.
Myzomyia Lutzii.
Myzomyia picta.
Myzomyia Rossii.
Myzomyia Turkhudi.
Myzorhynchus barbirostris.
Myzorhynchus Coustani.
Myzorhynchus paludis.
Myzorhynchus sinensis.
Myzorhynchus Ziemanni.
Nyssorhynchus fuliginosus.
Nyssorhynchus Jamesii.
Nyssorhynchus maculatus.
Nyssorhynchus maculipalpis.
Nyssorhynchus Stephensii.
Nyssorhynchus Theobaldi.
Pyretophorus Chaudoyei.
Pyretophorus costalis.
Pyretophorus jeypurensis.
Pyretophorus superpictus.

Not all of these mosquitoes serve equally well as hosts of the malarial parasites. *Myzomyia Rossii* is a very poor carrier of malaria, while the *Christophersi* is a very efficient carrier.

As yet very little is known of the relation between the species of mosquitoes and species of malarial parasites. *Pyretophorus costalis* is known to transmit tertian, quartan, and estivo-autumnal malaria, while *Myzorhynchus sinensis* carries tertian and quartan, but not estivo-autumnal malaria.

It is possible that some mosquitoes acquire a sort of immunity to malaria which may account for their incompetence as malaria disseminators. There are certain regions where, in spite of members of a malaria-bearing species of mosquito and the immigration of infected persons, malaria does not spread, though temperature and other conditions are apparently favorable.

The food of mosquitoes has much to do with their susceptibility to infection. Experiments have shown that *Anopheles maculipennis* fed upon fruits and sweets are not readily infected from feeding upon malarial blood, but if allowed only water for several days before and after feeding on malarial blood they are almost always infected.

One feeding upon blood containing parasites does not always suffice to infect the mosquito. Daniels,[112] investigating this subject, examined fifty-seven mosquitoes which had fed once or oftener at intervals of two days.

	Per Cent.
Nineteen fed only once, and five had zygotes	26.0
Thirteen fed twice, and six had zygotes	46.0
Sixteen fed three times, and ten had zygotes	62.0
Nine fed four times, and six had zygotes	66.6

Of these 57 anopheles 27, or 47.5 per cent., were infected.

The effect of fertilization upon the power of mosquitoes to transmit malaria is not definitely settled, but it is thought by some that fertilized females are the most desirable, if not indeed the sole, hosts of the parasite.

In order that anopheline mosquitoes may be infected from malarial blood it is necessary that the sexual forms of the

parasite be present in sufficient numbers, of proper maturity, and suitable proportion of sexes.

How is the existence of the malarial parasite perpetuated; why does not the disease become extinct over winter when there are apparently no mosquitoes to further the life history of the organism?

The subject of latent or chronic malaria furnishes the solution. The parasites here lie dormant or undergo parthenogenesis at longer or shorter intervals, and are ready the following season for the sexual cycle in the body of the definitive host, the mosquito.

It is possible that in a few instances the parasites persist in the bodies of hibernating mosquitoes. While some investigations have led to a different conclusion, Martirano has found in the neighborhood of Rome as late as the middle of March that from 1 to 5 per cent. of anophelines were infected, and Stephens and Christophers observed at Freetown, during the dry season that from 5 to 20 per cent. were infected.[90]

From analogy with the transference of Texas fever hematozoa by the tick to its progeny, it has been sought to establish such an inheritance of malarial parasites by mosquitoes. While Schaudinn found in the ovaries of an anopheline mosquito forms which he considered malarial organisms, no other investigators have been able to confirm this observation, and it must be considered as yet unproven that infected mosquitoes can communicate the infection to their offspring. It was also believed that infected mosquitoes dying in the water after oviposition and being eaten by larvæ might thus communicate the parasites to these larvæ. This has, however, not been determined.

The relation of the mosquito to malaria explains the prevalence of the latter with reference to season, temperature, and rainfall. It explains malaria as a disease chiefly of low altitudes and marshy regions; a disease of the country rather than of the city. House epidemics of malaria are thus rendered clear and the relation of ship malaria and proximity to the shore becomes obvious. The bearing of age, sex, and occupation upon the endemic is in thorough harmony with the

theory. That malaria is more easily contracted at night is understood from the feeding habits of the malarial mosquitoes. That all measures directed toward the prevention of mosquito bites are followed by a commensurate reduction of the prevalence of malaria is one of the strongest arguments. The analogy with filiariasis, Texas fever, hematozoan infection of birds, and similar diseases strengthens the theory. Numerous and accurate experiments have absolutely proven the dissemination of malaria by certain mosquitoes. One of the earliest of these was that of Dr. Patrick Manson. Mosquitoes fed on tertian malarial blood in Rome under the supervision of Bastianelli were sent in suitable cages to London. There they were permitted to bite Dr. Thurburn Manson and Mr. George Warren, neither of whom had ever been previously exposed to malaria. In due time both developed malaria, and tertian parasites were found in the blood at this time and later during several relapses.

The sexual cycle of the parasite within the mosquito has been followed many times.

An objection that has been frequently urged against the "mosquito theory" is that there are numerous localities in which mosquitoes abound and from which malaria is entirely absent; indeed, mosquitoes are said to be well nigh intolerable in portions of the arctic regions. It must be remembered, however, that only a certain subfamily of mosquitoes can serve as hosts for the parasite. Furthermore, the surrounding temperature must be suitable for the sexual development of the parasites within the definitive host. But it cannot be denied that there are areas, even in the midst of a malarial country, in which anophelines are present, the temperature is favorable, and other conditions apparently suitable, but autochthonous malaria does not appear. Among such localities reported may be mentioned Singapore, Penang, Malacca, Soekaboemie, and portions of Brazil, of Italy, and of Lower Egypt. This has not as yet been satisfactorily explained, but may be due to an acquired immunity on the part of the mosquito, or to the influence of their food on the development of the parasite.

It was formerly maintained that there were highly malarial

regions in which there were no mosquitoes, and a number of such places have been reported. But in each case where investigated by a competent observer anopheline mosquitoes have been found where malaria is endemic. Koch[69] mentions that at Tosari, elevated 1,777 metres, while there was some malaria, there were no anopheles. The malaria occurred, however, in those who were employed in the neighboring lowlands and not in the children who remained in the town.

The habits of the anopheline mosquitoes are such that they may be easily overlooked except by an expert. Retiring to dark recesses during the day, biting only at night, and not singing a great deal, their presence may not be felt, especially by persons in whom the bites do not cause much irritation.

It may therefore be stated confidently that there is no endemic malaria without mosquitoes.

The misproportion between the number of infected anophelines and the number of cases of malaria has been cited to overthrow the mosquito doctrine. In Algiers Sergent[90] found 4 per cent. of the anopheles and 100 per cent. of the children infected. A. Plehn[79] found in one of the most malarial localities, Cameroon, among 860 anopheles only 2.2 per cent. infected. Stephens and Christophers[113] believe that about 5 per cent. of all the anopheles of tropic Africa are infected. At Aro they found the sporozoit rate in anopheles caught in native huts to be 50 per cent.

It should be borne in mind that one infected anopheline mosquito is capable of infecting a number of persons. Also the sporozoit rate varies according to season and according to the kind of mosquito, since it has been shown that some species are better malaria carriers than others.

The fact that malaria is decreasing in, or has disappeared from, regions formerly highly malarial, but in which malaria-bearing mosquitoes are yet found, is another argument which has been proposed against the relation of the mosquito to malaria. With reference to Great Britain, Nuttall, Cobbett and Strangeways-Pigg[114] concluded that:

1. The disappearance of ague from Great Britain does not depend upon the extinction of mosquitoes capable of harboring the parasites of malaria.

2. Three species of anopheles (*A. maculipennis, A. bifurcatus, A. nigripes*) are to be found in Great Britain in all districts which were formerly malarious, but also in places concerning which there is no record of the former prevalence of ague.

3. The anopheles to-day are most numerous in low-lying land containing many ditches, ponds, and slowly-flowing water, suitable for their habitat, and corresponding to the districts where ague was formerly prevalent.

4. Since the disappearance of ague does not depend upon the extinction of anopheles, it is probably due to several causes operating together:

(*a*) A reduction in the number of these insects consequent upon drainage of the land; this being in accord with all the older authors, who attributed the disappearance of ague largely to this cause.

(*b*) Reduction of the population in infected districts as the result of emigration about the time when ague disappeared from England. This would naturally reduce the number of infected individuals and thus lessen the chance of the anopheles becoming infected.

(*c*) It is possible that the use of quinine has reduced the chances of infecting the anopheles through checking the development of the parasites in the blood of subjects affected with ague.

Finally, it has been maintained that persons who have never had malaria have contracted it in uninhabited wildernesses, where, obviously, only uninfected anophelines would be found, since man is the only intermediate host of the parasite.

To this it may be answered that no such instance has been so accurately reported as to prove conclusively that infection has ever occurred under these circumstances.

THE MALARIA-BEARING MOSQUITOES

The genus *Anopheles* was established in 1818 by Johann Meigen. The bestowal of the name appears prescient, since *anopheles* signifies *troublesome* or *hurtful.*

Of the fifty or more species and subspecies of anophelines

now known seven occur in the United States: *A. maculipennis, A. punctipennis, A. crucians, A. franciscanus, A. barberi, C. argyrotarsus,* and *C. albipes.*

Breeding Places.—The different species of anophelines vary a great deal in the choice of a breeding place. Furthermore, with each species there may be said to be places of choice and places of necessity.

Contrary to the usual custom of culex, the anopheles usually selects water more or less pure in which to deposit her ova. Ground water appearing at the surface is especially suitable. Pools of at least some degree of permanence are preferred to those which might dry before the aquatic stage of the insect is completed. Natural accumulations of water more often contain anopheles larvæ than do artificial collections. Pools, ponds, swamps, inlets of lakes, and of small, slowly-flowing streams, ditches along roadsides, canals, borrow pits along railroads and levées, and rice fields are common breeding places. Water contained in the tracks of animals may harbor larvæ.

When water is scarce, as during the dry season, anopheline larvæ may be found in tubs, barrels, boats, buckets, bottles, cisterns, mollusc and cocoanut shells; in water retained by the leaves and stalks of tropic plants, or even within vases in dwellings, though these locations are to be regarded as places of necessity and not of choice.

While, as said, clean water is usually chosen by these mosquitoes, at least one species, *M. Rossii,* is known to breed in very foul pools. Another species, *M. Listoni,* is said to breed in swiftly-flowing streams, which is contrary to the usual habit of this subfamily.

In regard to salt water as a medium for anopheline larvæ many opinions are held. It seems that the species indigenous to the United States do not breed in salt water, and this was the experience of Celli and other Italian investigators. However, Centanni and Orta[115] found anopheles larvæ in water containing 8.77 per 1,000 of sodium chloride. Ficalbi and others[115] found them in water containing 40 to 50 grams of sodium chloride per litre. In Algiers and the Dutch Indies

anophelines are found breeding in concentrated sea-water, and Banks[116] found *M. Ludlowii* breeding in sea-water in the Philippines. Bancroft in Queensland found a species of anopheles breeding in sea-water, and at Accra, on the west coast of Africa, Stephens and Christophers[117] obtained numerous anopheline larvæ from water containing 6 per cent. of salt. De Vogel[68] at Semarang found certain kinds of anopheles breeding not only in sea-water, but in that which had been condensed to half its volume.

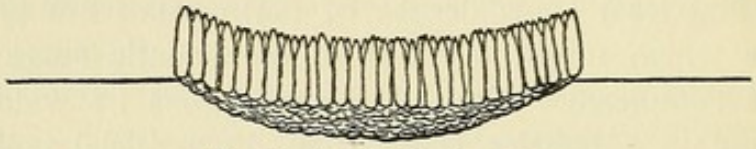


Fig. 8.—A raft of culex ova.

Ova of Anophelines.—These mosquitoes do not deposit their eggs in a raft-like mass, as do the culex (Fig. 8). They are laid in irregular piles, but soon become scattered, lie horizontally, and may form attractive patterns (Fig. 9) upon the surface of the water. In captivity the eggs may be laid upon some floating object.

The ova are from .7 to 1.0 mm. in length by about .16 mm. in breadth. They are fusiform in shape and somewhat broader

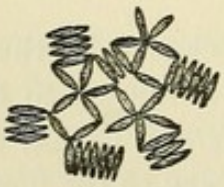


Fig. 9.—Patterns assumed by anopheles ova.

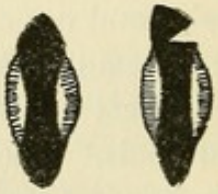


Fig. 10.—Anopheles ova.

at one end than at the other. The lower surface is convex, the upper nearly flat. From the middle third of each side protrudes a transversely corrugated membrane which acts as a float, somewhat after the manner of the air chambers of a lifeboat. These floats are said to be absent only in the ova of *M. turkhudi.* Around the margin of the upper surface of the ovum is a frill, usually transversely corrugated. When first laid the eggs are whitish, but soon become almost black.



Fig. 11.—A young anopheles larva. Magnified.

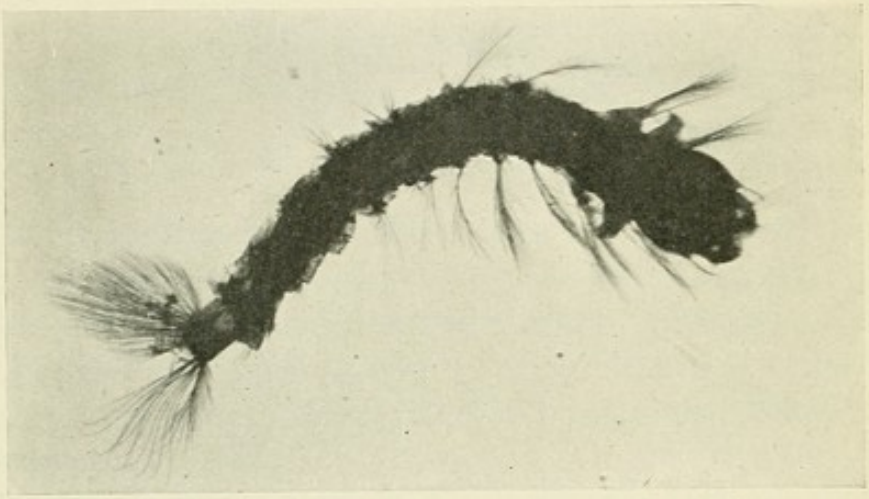


Fig. 12.—Half-grown anopheles larva. Magnified.

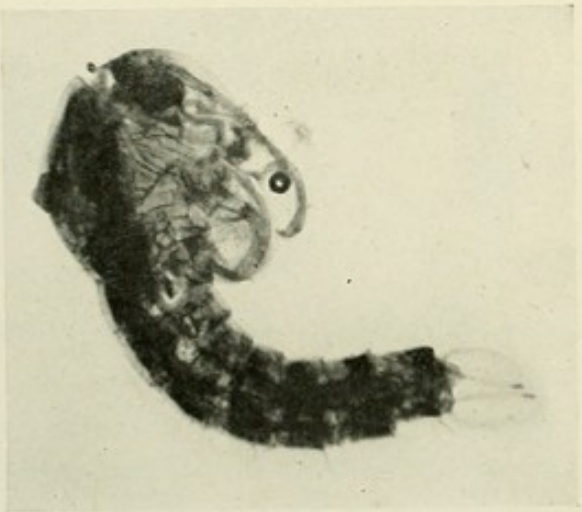


Fig. 14.—Anopheles pupa. Magnified.

The head of the larva lies in the broad end of the egg and escapes by loosening a circular cap from this end. It is said that if an ovum is partially removed from the water the broad end always hangs downward in order that the larva may be born into the water instead of into the air.

The duration of the egg stage varies with the temperature, but is generally from two to four days.

Stephens and Christophers[118] did not succeed in hatching the ova after dessication for two or three days, but Grassi[116] is said to have hatched them after keeping them dry for twelve days.

The Larva.—The head of the anopheles larva (Fig. 13) is more or less globular; the eyes are situated laterally at the

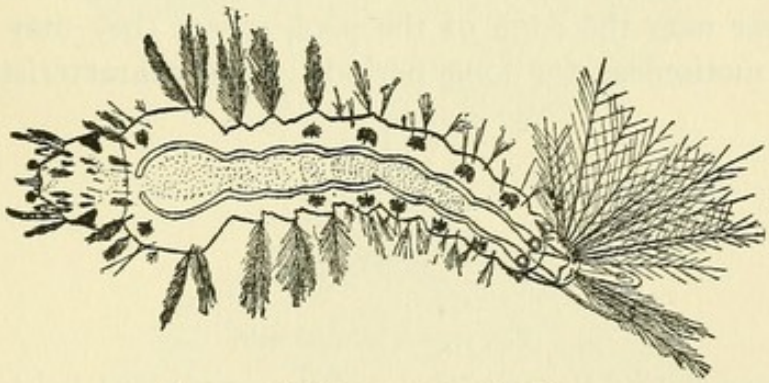


Fig. 13.—Full-grown anopheles larva.

broadest part of the head. The antennæ are rod-shaped and unjointed; at the end are two leaflets, between which arises a branched hair. The mouth parts consist of the feeding brushes or whorl-organs, the maxillary palps, the mandibles, the under lip, and the clypeus.

The neck is very narrow in the full-grown larva.

In the young larva (Fig. 11) the thorax is little, if any, wider than the head, but in older specimens it is much wider.

There are nine post-thoracic segments. The first three segments bear branched lateral hairs. The third to the seventh segments have upon the dorsum a pair of fan-shaped structures, known as the palmate hairs (Fig. 17).

The eighth segment contains the two openings of the respiratory system, which ends abruptly at the dorsum of this seg-

ment without the prolonged breathing tube of the other subfamilies.

The ninth or caudal segment bears four flaps containing respiratory branchiæ. This segment is armed with two large tufts of hair.

The color of the larva varies greatly, according to food and environment, and may be grayish, green, almost black, reddish, or mottled with black or white.

The full-grown larva is about 8 mm. in length.

Anopheline larvæ are omnivorous. Their diet consists of the spores of algæ, diatoms, animalcules, bacilli, other larvæ, moulted skins, mosquitoes, and other small insects. In captivity they eat dry rice greedily.

The customary location of these larvæ is at the surface of the water near the edge of the pool, where they may remain almost motionless for long periods. The characteristic posi-

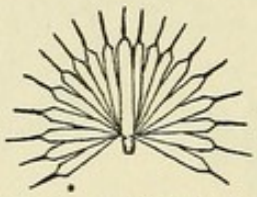


Fig. 17.—A palmate hair.

tion is parallel with the surface of the water and so close to it that a portion of the dorsum appears to rise above the surface, which, however, is not the case. When feeding the constant motion of the mouth parts creates a flow of water toward the mouth, bringing in small particles of food. The head is often rotated suddenly, so that it turns through an arc of 180 degrees, the lower surface looking uppermost. On taking hold of something too large to swallow the larva will often shake the head vigorously and may bend the body to steady the particles against the last segments of the body. In captivity they often rest with the tail against the sides of the container and the head toward the center, when numerous forming a fringe around the circumference. Locomotion is very jerky and irregular. When disturbed they not infrequently feign death. From the behavior of the anopheline larvæ it does not appear that the sense of sight is very acute.

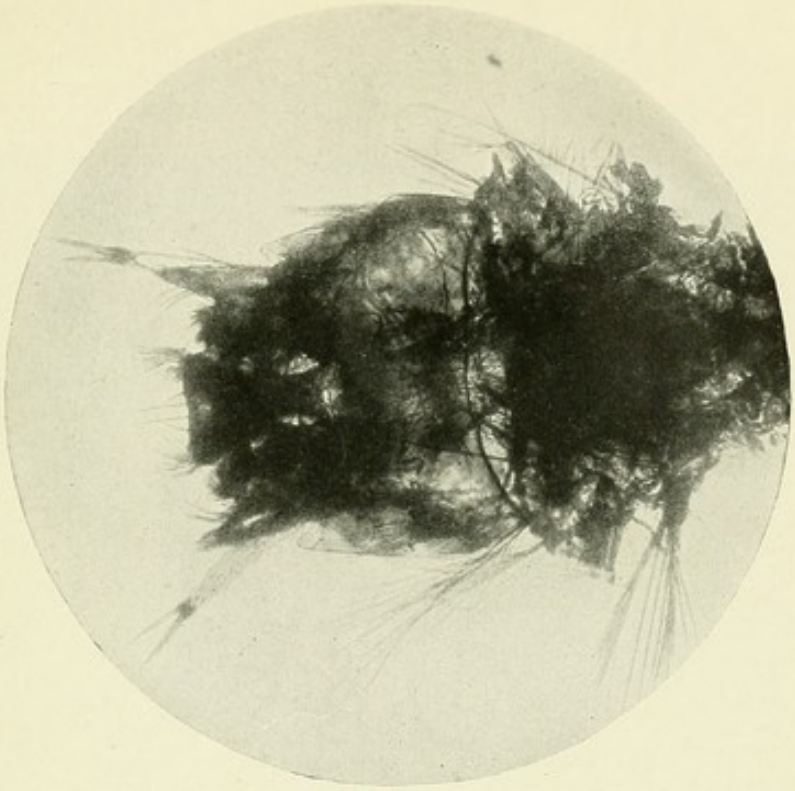


Fig. 15.—Head of anopheles. Magnified.

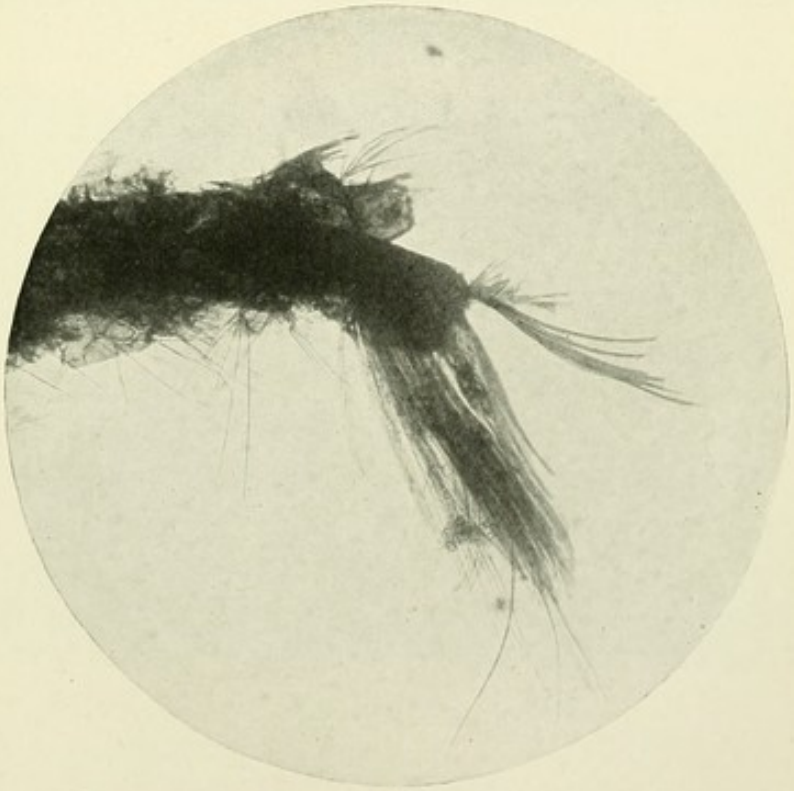


Fig. 16.—Tail of anopheles larva. Magnified.

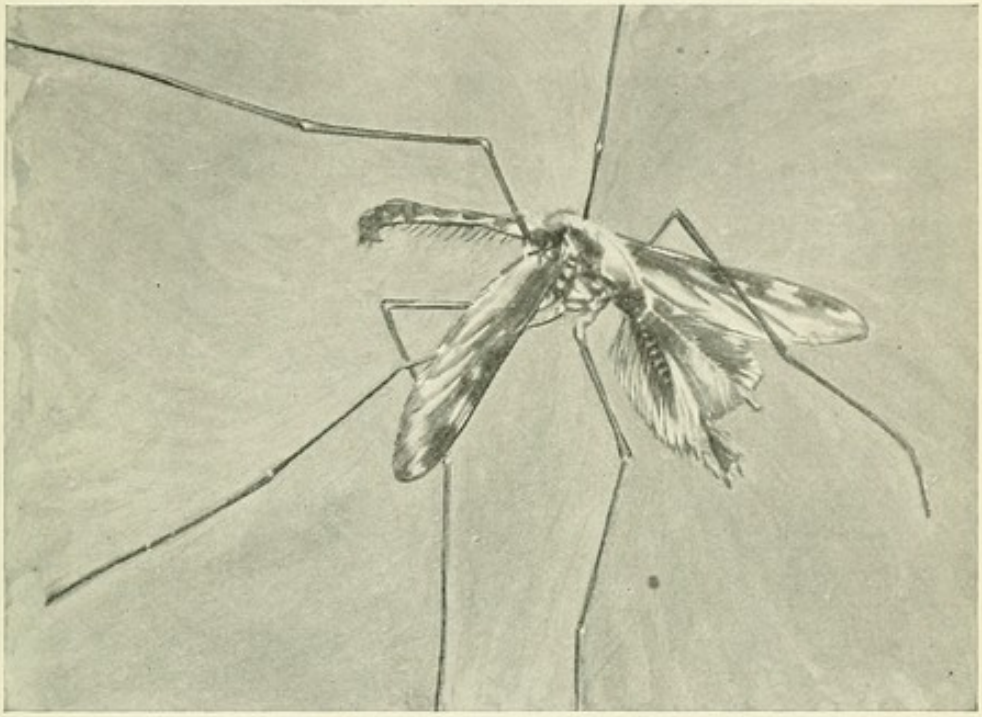


Fig. 20.—Male anopheles.

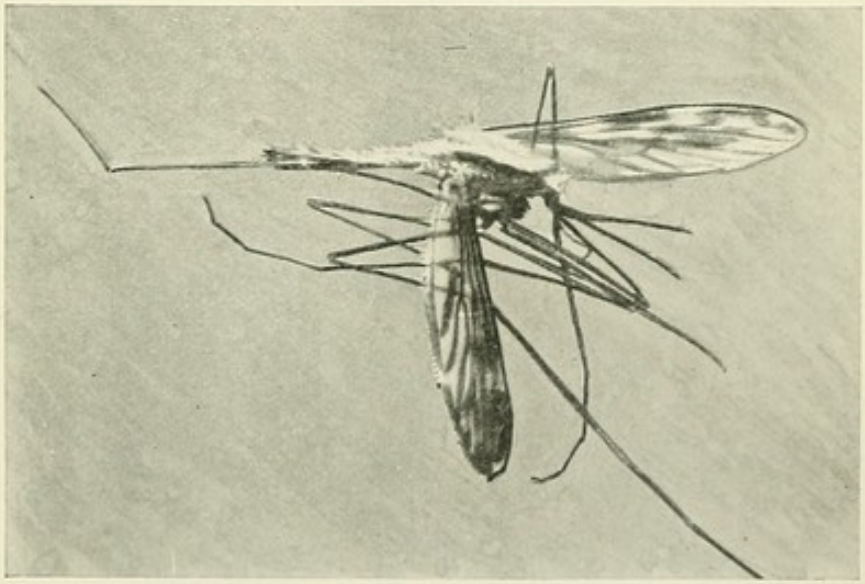


Fig. 21.—Female anopheles.

Culex larvæ have been thawed out of ice in which they were imbedded and have proceeded to develop into insects, but so far as the writer is aware this has not been done with anopheles. The latter have, however, been found in water

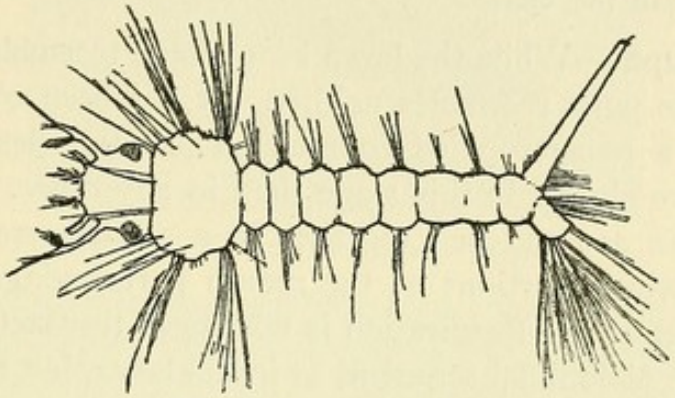


Fig. 18.—Adult culex larva.

under a frozen surface. They may exist for a few hours to a few days upon moist mud.

The duration of the larval stage varies according to temperature, food, and possibly other conditions. The limits may be placed at from ten to twenty-six days. In warm cli-

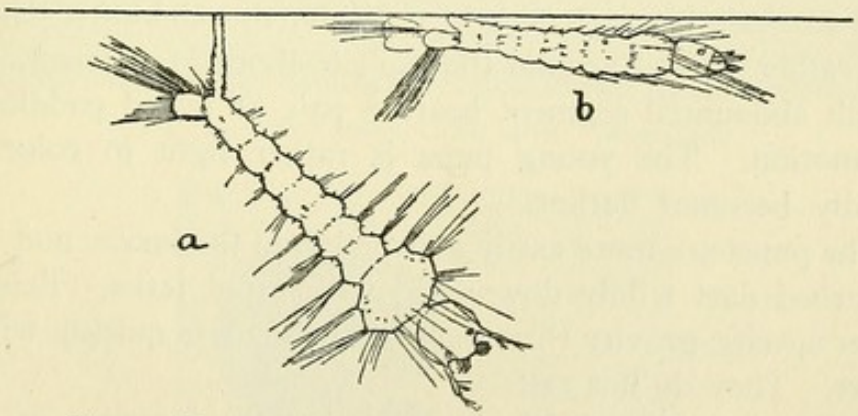


Fig. 19.—Resting positions of larvæ : *a*, Culex ; *b*, anopheles.

mates when suitable food is abundant the duration is ordinarily twelve or fourteen days. In cooler climates and seasons the duration is longer.

Anopheles and *culex* larvæ may be differentiated by the following gross characteristics:

Anopheles.	*Culex.*
Habitually at the surface of the water.	At the surface to breathe only.
Position parallel with the surface.	Hangs at an agle of 50 to 60 degrees to the surface.
No respiratory tube.	Large respiratory tube.
In full-grown larvæ the head is smaller than the thorax.	Relatively larger head.

The Pupa.—While the larva bears some resemblance to the imago, the pupa resembles neither. It has been compared in shape to a hypertrophied comma. The anopheles resembles culex more closely in this stage than in any other. The head and thorax are enclosed together in a semitransparent shell, through which portions of the mouth parts, wings, and legs may be detected. Respiration is no longer transacted through the eighth abdominal segment, as in the larva, but through the trumpet-shaped spiracles or syphons of the thorax (Fig. 27).

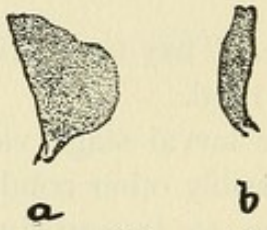


Fig. 27.—Breathing syphons of (*a*) anopheles and (*b*) culex pupæ.

This necessitates a change in position, the abdomen hanging and rather curved around the cephalo-thoracic segment. The eighth abdominal segment bears a pair of broad paddles for locomotion. The young pupa is rather light in color, but rapidly becomes darker.

The pupæ are more easily alarmed than the larvæ, and when disturbed dart wildly downward with rapid jerks. Being of lower specific gravity than the water, they rise quickly without effort. They do not eat.

Italian investigators[115] observed that the nymphæ of some mosquitoes resisted freezing and dessication to a remarkable degree. Enclosed for several hours in ice, they were yet able to develop, and kept in dry soil for two or three days they developed when placed in water.

The duration of the pupal stage is ordinarily from two to five days.

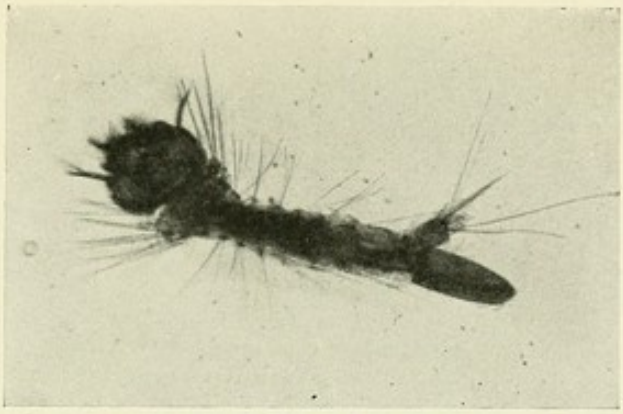


Fig. 22.—Young culex larva. Magnified.

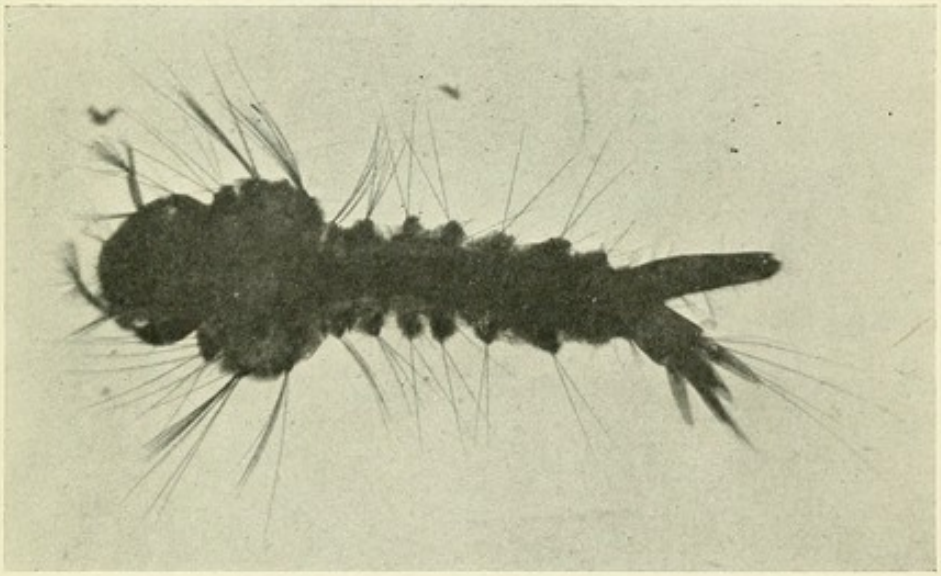


Fig. 23.—Half-grown culex larva. Magnified.

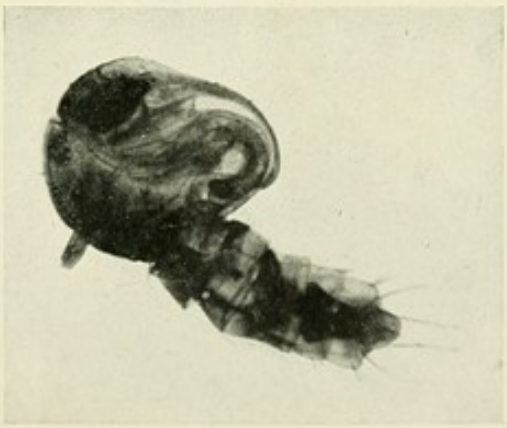


Fig. 24.—Culex pupa. Magnified.

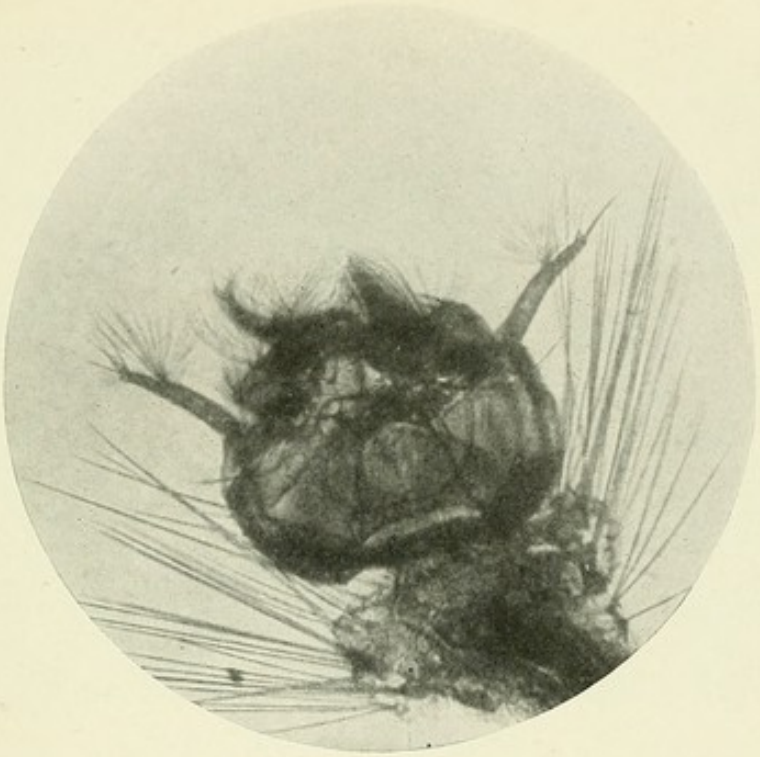


Fig. 25.—Head of culex larva. Magnified.

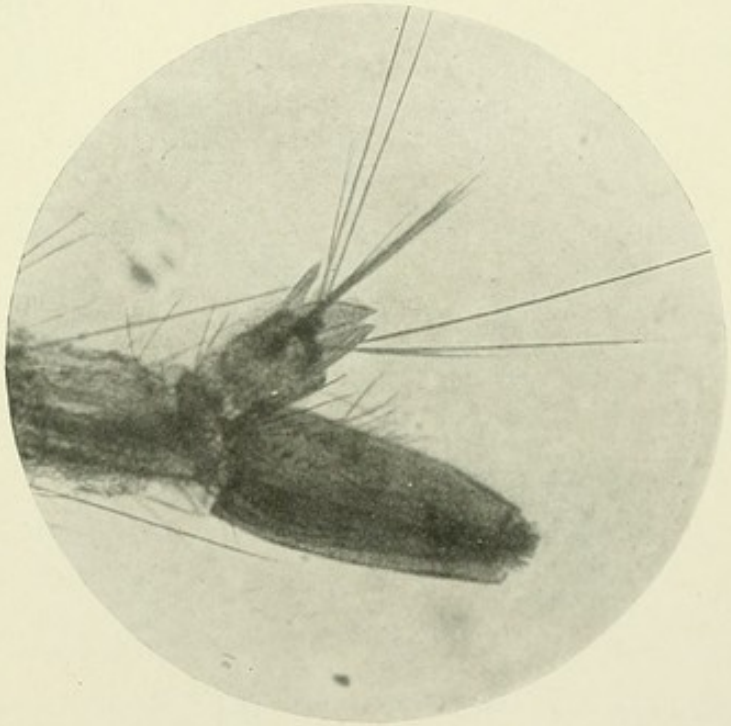


Fig. 26.—Tail of culex larva. Magnified.

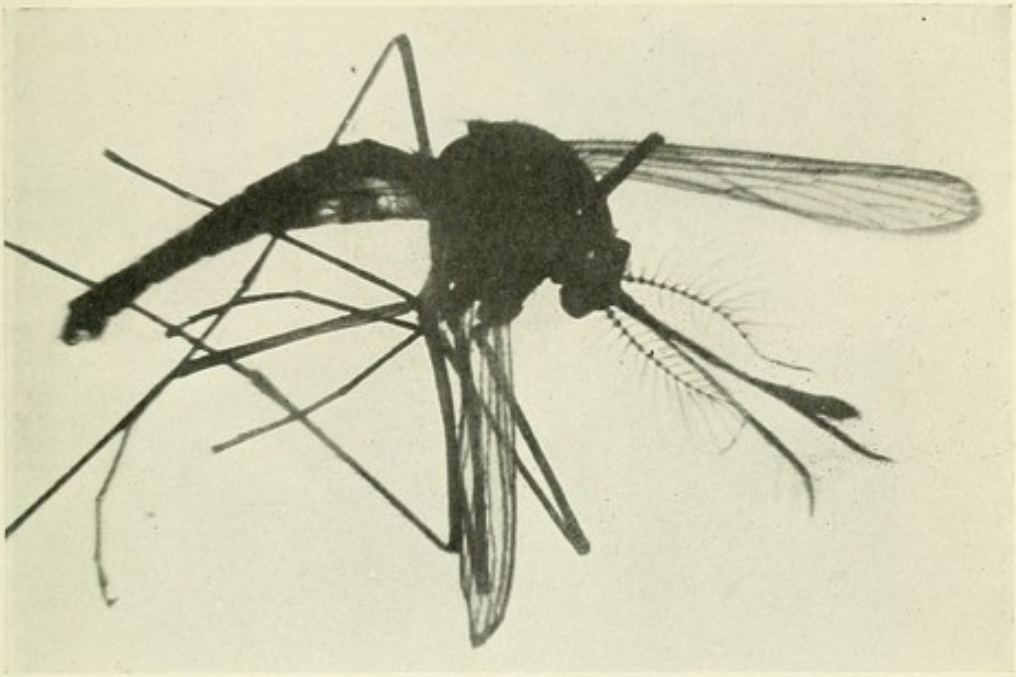


Fig. 28.—Male culex.

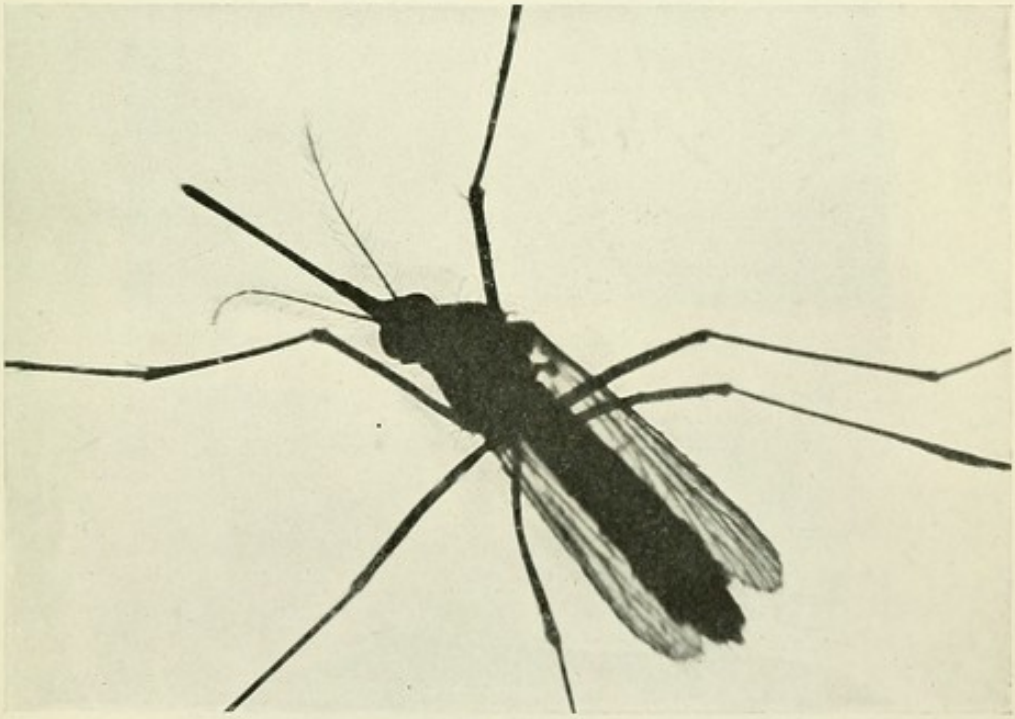


Fig. 29.—Female culex.

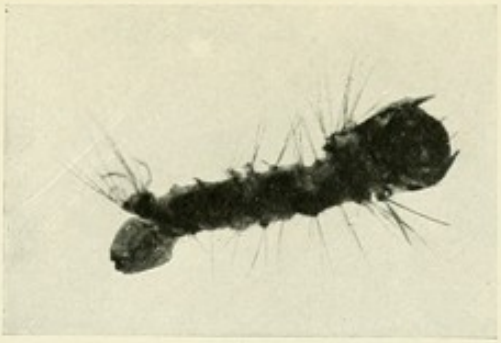


Fig. 30.—Young stegomyia larva. Magnified.

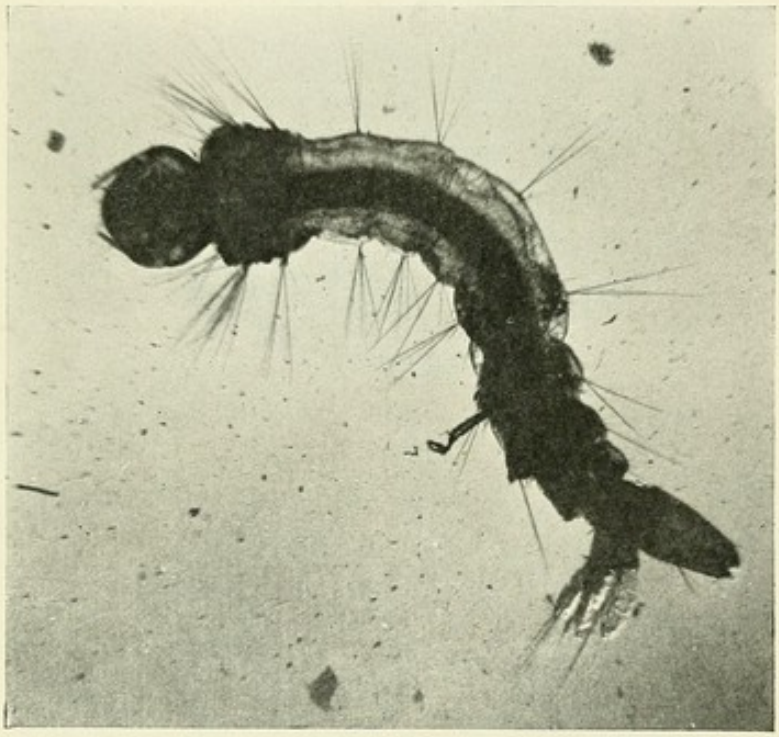


Fig. 31.—Grown stegomyia larva. Magnified.

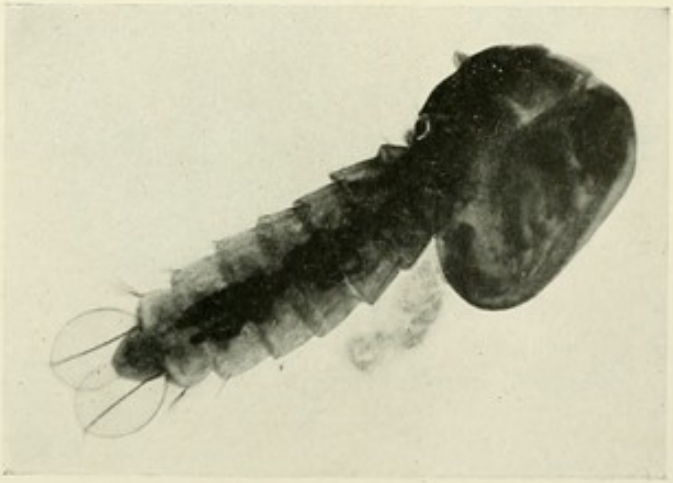


Fig. 32.—Stegomyia pupa. Magnified.



Fig. 33.—Head of stegomyia larva. Magnified.

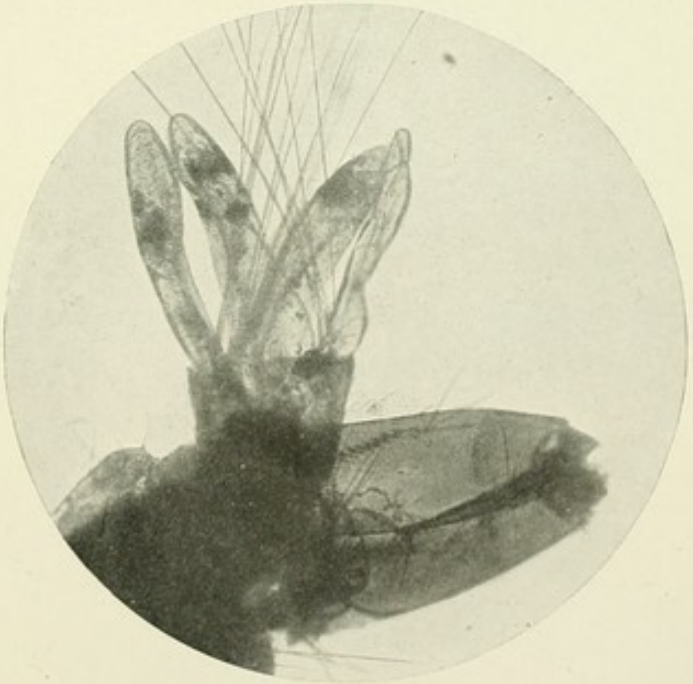


Fig. 34.—Tail of stegomyia larva. Magnified.

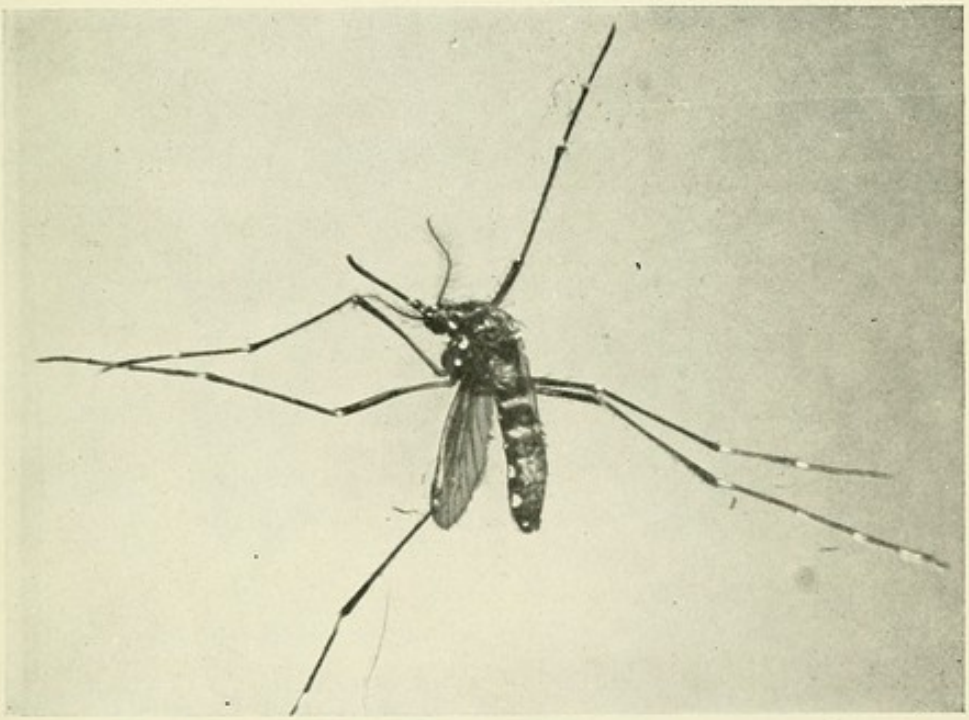


Fig. 35.—Female stegomyia.

The following points may serve to distinguish *anopheles* and *culex* pupæ.

Anopheles.	*Culex.*
Position in water more horizontal.	Position more vertical.
Syphons short, square truncated ends, attached to middle of thorax.	Syphons long and narrow, slit-like opening, attached to posterior part of thorax.
Longer anteroposteriorly, narrower laterally.	Shorter and broader.

When approaching the emergence of the imago the pupa becomes motionless at the surface of the water; the abdomen is extended parallel with the surface; minute air bubbles are seen under the membrane, which then splits along the dorsal line of the thorax. The imago emerges head first, then the thorax and wings, then the legs. At this stage the insect is very liable to be drowned by a breeze or by a ripple in the water.

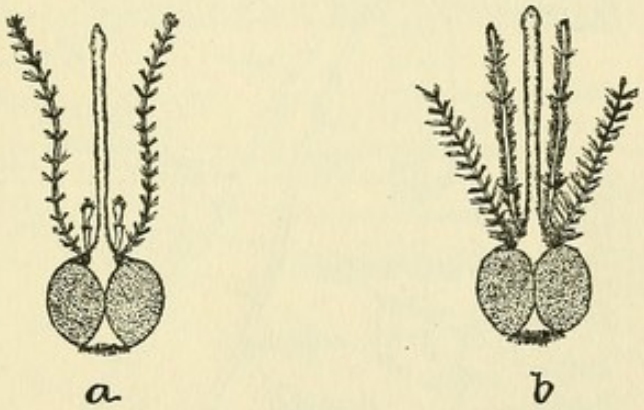


Fig. 36.—Heads of (*a*) culex and (*b*) anopheles females.

The Imago.—The head is subglobular and broader than long. The compound eyes occupy most of the front and lateral portions of the head.

The antennæ, composed of from fourteen to sixteen joints, arise from papillæ immediately in front of the eyes, scantily haired in females, beautifully plumose in males.

The proboscis projects from the middle of the anterior margin of the head at its lowest plane. The proboscis is highly complex. It is composed of a labrum and epipharynx, a hypopharynx, two mandibles, two maxillæ, and a labium which forms a sheath for the other parts. The maxillæ and mandibles serve for piercing the skin. The epipharynx conducts the

blood or other food to the alimentary canal. Through the hypopharynx saliva, containing sporozoits in infected mosquitoes, is injected.

The palpi or feelers lie to either side and somewhat above the proboscis. In anophelines the palpi in both sexes are nearly as long as the proboscis, and are clavate in the male.

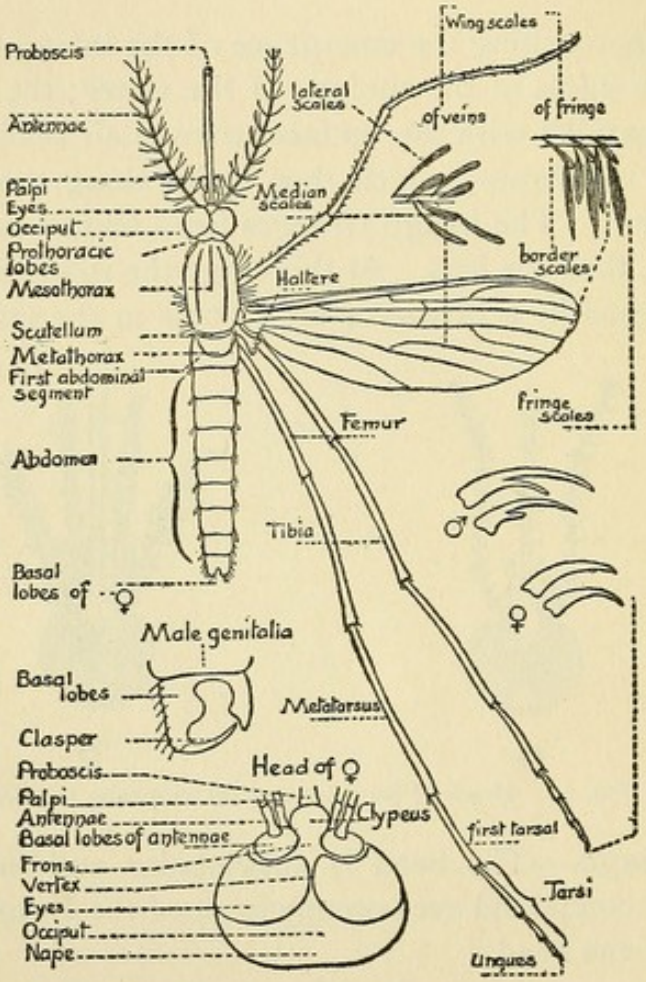


Fig. 37.—Diagram of mosquito (after Theobald).

The thorax is little broader than the head, but is more than twice as deep. It is divided somewhat arbitrarily into three portions, the prothorax, the mesothorax, and the metathorax, though the three segments are fused together into one. From each of these segments arises a pair of legs. But little of the prothorax is visible from above, a small lobe projecting from each shoulder. The mesothorax, comprising the bulk of the

thorax, is covered by the scutum. Behind the scutum and the origin of the wings is the transverse scutellum, behind which is the metathorax or postscutellum.

The abdomen is larger than the thorax, depressed being broader than deep, and is composed of nine segments. The upper and under surfaces of each segment are somewhat rigid; laterally the membrane is softer and contains the openings of ten respiratory tubes or stigmata. The anus opens ventrally upon the eighth segment. The ninth segment bears the external organs of generation.

The legs, six in number, very long and slender, comprise the following joints: The coxa and trochanter, the femur, the tibia, and the five-jointed tarsus, the distal joint of which bears the claws.

The wings originate from the posterior portion of the mesothorax. The wing venation is best understood by referring to

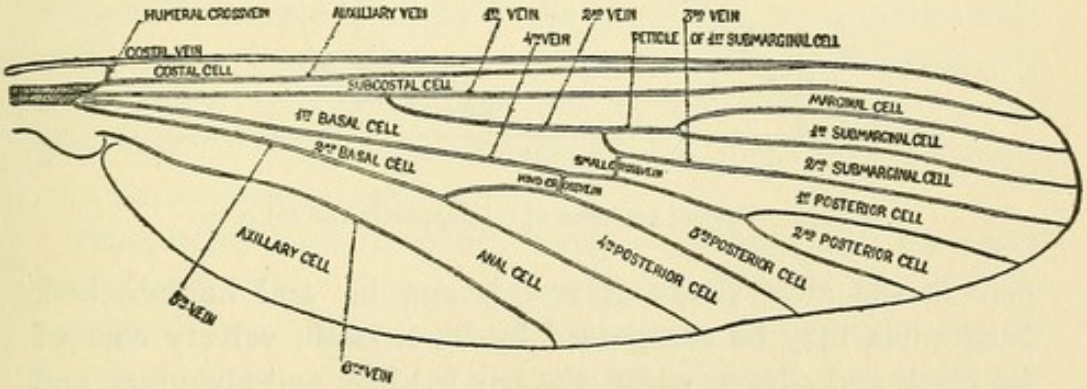


Fig. 38.—Diagram of the wing of a mosquito (*Culex pipiens*), with names of veins, cells, etc. (Coquillett).

the illustration (Fig. 38). The wing scales are of importance in classification.

From the metathorax arises the pair of halteres or balancers, club-shaped organs, rudiments of a second pair of wings. Supplied with one of the largest nerves of the body, they are regarded as sense organs.

Anopheles is distinguished from culex especially by the palpi, which in the former is in both sexes almost as long as the proboscis, in the latter the palpi of the female being very short. Anopheles is more slender, the head is smaller, and the legs

more delicate. The palpi of the female being thickly scaled and lying close to the proboscis give the impression of a thick beak, which contrasts strongly with the short palpi and slender proboscis of the culex. The wings of the anopheles are speckled, which is not the case with any of the common species of culex.

The sitting position of anopheles is characteristic. The body of the insect is at an angle with the surface upon which it rests, the proboscis pointing toward the surface, sometimes even touching it. This angle varies in different anopheline species, in some being almost a right angle, when the insect appears almost like standing upon its head. The proboscis, head, thorax, and abdomen are in the same line. The mosquito at rest has been compared to a brad-awl stuck into the wall. It often rests upon the first two pairs of legs, waving the last

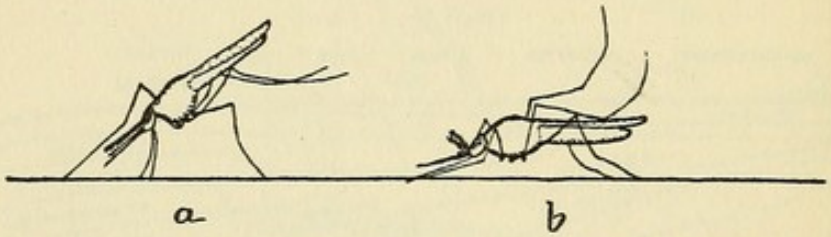


Fig. 39.—Resting positions of (*a*) anopheles and (*b*) culex.

pair in the air. Culex at rest is angular and humpbacked. Stegomyia may be recognized by its smooth, velvety coat of jet black and silvery white, the banded legs and abdomen, and the lyre-shaped ornamentation of the thorax.

The three commonest species of anophelines of the United States are thus described by Giles:[119]

Anopheles Maculipennis (Meigen).—"Wings with four tufted spots on the wing-field, the costa being uniformly dark except at the apex, where its color fades to form a fairly distinct spot; tarsi unbanded, but with an apical yellowish spot to the first joints. Thorax with four broad ferruginous stripes formed of golden hairs, between which the darker ground color is left bare, with a tuft of large golden scales on the anterior border. Abdominal segments brown with yellowish basal markings; anterior femora not thickened at the base.

"*Female.*—Head with two patches of creamy scales divided by a central line, the rest of the head with black scales, a small tuft of white hairs in front; borders of the eyes white; eyes deep purplish-black; antennæ dark brown with pale bands and with ferruginous basal joint, pale pubescence, and brown hairs; proboscis brown; palpi yellowish-brown with dense, dark scales at the base, which is swollen, shorter than the proboscis. Legs with pale coxæ; femora and tibiæ yellowish-brown below, covered with dark-brown scales above; knee spot yellow, apex of the tibiæ paler; tarsi slightly darker than the rest of the leg.

"*Male.*—Antennæ banded, plume hairs brown, last joint darker; proboscis black to dark brown; palpi dark brown; the last two joints, which are clubbed, have a number of short golden hairs internally and are yellow in color, clothed with thick black scales, through which the yellow underground shows; the last joint is truncated. Length 4 to 7.5 mm. male, to 8 or 10 mm. female. This species varies greatly in size, the wings shown me in Italy by Professor Grassi being quite small, while some Canadian specimens in the British Museum are huge gnats, and to illustrate this I have superposed on the plate the drawing of one of Grassi's specimens on the outline of a Canadian specimen."

Anopheles Punctipennis (Say.).—"Wings with the costa black, interrupted by a single large ferruginous spot a little outside the transverse veins, and involving the first and second longitudinal veins. There is also a small apical spot, and some yellow spots near the tips of the long veins, but otherwise the wing is very dark and has no interruptions of the fringe. Legs and tarsi uniformly nearly black. Thorax and abdomen deep brown, nude but for some yellowish-brown hairs. Wings much longer than abdomen.

"Head black with scanty whitish frontal tuft. Palpi and proboscis dark yellowish-brown, unbanded but rather lighter at the tips. Halteres brown. This is not likely to be confused with any other species than my *An. gigas,* but may be distinguished by the base of the wing internal to the large spot being uniformly black instead of spotted with yellow, as in *gigas,* as well as its being altogether a darker species. There appears

to be a triangular swelling at the base of the abdominal segments. It may be distinguished from *An. crucians* by the costa of the latter being uniformly dark and by its having two instead of three dark spots on the sixth longitudinal vein. The middle spot extends much further across the wing than in the *Sinensis* group, and the tarsi are unbanded. Length 5 to 7 mm."

Anopheles Crucians (Wied.).—"Wings with white spots here and there on the brown veins, uniform along the costa; tarsi unbanded, dusky brown; abdomen uniformly brown with grey hairs. Thorax red-brown with linear markings.

"Description from Wied., A. Z. I., p. 12: 'Tawny; the thorax with three deeper-tinted lines; the abdomen covered with grey hairs; the wings with dusky spots and costa. Length 2½ lines (German).'

"Coquillett, in his recent synoptic table of North American *Culicidæ*, states that 'the scales of the last veins are white, marked with three black spots; palpi marked with white at the bases of the last four joints,' and without any spot on the costa, as seen in *A. punctipennis*.

"Professor Nuttall sent Mr. Theobald two females from America in spirit, which, although much damaged, show the two features mentioned by Coquillett very clearly, readily distinguishing the species from the *C. punctipennis* of Say."

The following key to the mosquitoes of North and Middle America is that of Mr. Coquillett,[120] of the Department of Agriculture, by whose kind permission it is here reproduced:

A CLASSIFICATION OF THE MOSQUITOES OF NORTH AND MIDDLE AMERICA

Table of the Subfamilies

A. Scutellum convex behind, never distinctly three-lobed; posterior end of the thorax bare; small cross-vein usually situated considerably before the root of the third vein and connected with it by a stump of a vein; claws of the female simple.

B. Proboscis straight or almost so; back of the head devoid of broad appressed scales, but with many narrow outstanding ones; body never with metalescent scales; first submarginal cell longer than its petiole; claws simple in both sexes.

1. ANOPHELINÆ

BB. Proboscis strongly decurved; back of the head wholly covered with broad appressed scales, but devoid of narrow, outstanding ones; body covered with broad appressed metalscent scales; first submarginal cell less than half as long as its petiole; some of the claws of the male toothed.

2. MEGARHININÆ

AA. Scutellum distinctly three-lobed; small cross-vein usually situated beyond the root of the third vein.

C. Posterior end of the thorax bare.

D. First submarginal cell at least nearly as long as its petiole; some of the claws of the male toothed; thorax never with metallic bluish scales arranged in lines or spots.

E. Second joint of the antennæ less than eight times as long as wide in both sexes, with many long hairs, longer and more numerous in the male.

F. Femora bearing many outstanding scales; wing scales narrow.

3. PSOROPHORINÆ

FF. Femora devoid of outstanding scales.[1]

4. CULICINÆ

EE. Second joint of the antennæ unusually long, in both sexes over fourteen times as long as wide; antennæ in both sexes with a few short hairs only.

5. DEINOCERITINÆ

DD. First submarginal cell less than half as long as its petiole; claws simple in both sexes; thorax with metallic bluish scales which form lines or spots.

6. URANOTÆNIINÆ

CC. Posterior end of the thorax behind the scutellum bearing several bristles and sometimes with a few scales; claws simple in both sexes; antennæ similar in the two sexes, bearing many long hairs.

7. TRICHOPROSOPONINÆ

1. Subfamily ANOPHELINÆ Theobald

TABLE OF THE GENERA

1. Abdomen with clusters of broad, outstanding scales along the sides; outstanding scales on the veins of the wings chiefly rather broad... 4
   Abdomen never with such clusters of scales..... 2
2. Outstanding scales on the veins of the wings lanceolate, or broader, strongly tapering to their bases..... 3
   Outstanding scales very narrow, linear, very slightly, if at all, tapering to their bases; feet with white bands. (Middle America)..*Myzomyia*
3. Veins of the wings having the outstanding scales rather narrow, lanceolate; feet wholly black .....*Anopheles*
   Veins of the wings with many broad, obovate, outstanding scales; feet with narrow, indistinct white bands at the bases of some of the joints. (Middle America).....*Cycloleppteron*

[1]Except in the genus *Aëdeomyia*, which has broad wing scales.

4. Upper side of thorax and scutellum bearing many appressed lanceolate scales; outstanding scales on the veins of the wings rather narrow, lanceolate. (Florida and southward) ..... *Cellia*
Upper side of thorax and scutellum with hairs only; many rather broad, obovate outstanding scales on the veins of the wings. (Middle America) ..... *Nototricha* n. gen.

Genus MYZOMYIA Blanchard

(Synonym: *Grassia* Theobald)

Wings black-scaled and with several white-scaled patches; feet black, banded with white; thorax gray and with four black stripes. (West Indies) ..... *lutzii* Theob.

Genus ANOPHELES Meigen

(*a*) Table of the Species

1. Wings marked with spots of dark or light-colored scales 2
Wings unspotted; length of the head and body about 3 mm. *barberi* Coq.
2. Front margin of the wings with a patch of whitish scales at a point about three-fourths of the way from base to apex of the wing 5
Front margin of the wings wholly black-scaled 3
3. Sixth, or last, vein of the wings wholly black-scaled 4
Sixth vein white-scaled and with three patches of black scales. *crucians* Wied.
4. Hind tibiæ yellowish-white-scaled on the apical fourth; first vein of the wings with a patch of yellow scales before its middle and another on the apex. (Central America) ..... *eiseni* Coq.
Hind tibiæ narrowly yellowish-white scaled at the extreme apex only, first and other veins with black scales only ..... *maculipennis* Meig.
5. Scales of the last vein of the wings white, those at its apex black; third vein white-scaled and with two patches of black scales 6
Scales of the last vein white, those at each end black; third vein black-scaled, the extreme apex white-scaled ..... *punctipennis* Say.
6. Fourth vein of the wings black-scaled, the apices of the forks and usually also a patch at the cross veins white-scaled. *franciscanus* McC.
Fourth vein white-scaled, the forks (except their apices) and on either side of the cross veins black-scaled ..... *pseudopunctipennis* Theob.

(*b*) List of the Species and Synonyms

barberi Coq.
crucians Wied.
eiseni Coq.
franciscanus McCracken.
maculipennis Meig.
  annulimanus van der Wulp.[1]
  bifurcatus Meigen (1804; not of Linné, 1758).
  quadrimaculatus Say.
pseudopunctipennis Theob.
punctipennis Say.
  hyemalis Fitch.

(*c*) Unrecognized Species

bifurcatus Linné, *nigripes* Stæger, and *walkeri* Theobald. These species are said to have unspotted wings, like *barberi*, but are larger, have yellow scales on the thorax, etc.

pictus Loew. This species, described from Asia Minor, was also recorded from North America by its author, but he evidently mistook some

[1]At my request Dr. C. Ritsema Cz compared specimens of *maculipennis* with the type of *annulimanus* in the Leyden Museum, and informed me that they are identical.

other species for it. No specimen of his species has been reported from this country since the time he published the statement.

quinquefasciatus Say (*ferruginosus* Wied.). This is a synonym of *Culex pipiens* L.

Genus CYCLOLEPPTERON Theobald

Thorax with a velvety black dot near the middle of either side; feet almost unicolorous, not distinctly banded; wing scales chiefly brown or black, a patch of yellow ones at a point about two-thirds the length of the front margin and four smaller ones at the apex of the wing ..... *grabhami* Theob.

(*C. mediopunctatus* Theob. belongs to the following genus.)

Genus NOTOTRICHA, New Genus

Thorax with a velvety black dot near the middle of either side and a larger spot in front of and extending upon the scutellum; legs brown-scaled and with many dots and narrow bands of light-colored scales ..... *mediopunctata* Theob.

Genus CELLIA Theobald

(Synonym: *Arribalzagia* Theobald)

(*a*) Table of the Species

1. Hind feet from the middle of the second joint largely or wholly snow-white 2

   Hind feet black, mottled with whitish and with bands of the same color at the sutures of the joints..... *maculipes* Theob.

2. With a black band at the base of the last joint of each hind foot. *albimanus* Wied.

   Without such a band..... *argyritarsis* Desv.

(*b*) List of the Species and Synonyms

albimanus Wied.
  albipes Theob.
  cuber sis Agramonte.
  tarsimaculatus Goeldi.

argyritarsis Desv.
  albitarsis Arrib.

maculipes Theob.

2. Subfamily MEGARHININÆ Theobald

(Synonym: *Lynchiellina* Lahille)

Genus MEGARHNINUS Desvoidy
(Synonym: *Lynchiella* Lahille)

(*a*) Table of the Species

1. Feet with a white band, at least on the hind ones; middle joint of the male palpi with many yellow scales on the outer side; hairs of the male antennæ long and dense..... 2

   Feet wholly black on at least their upperside; palpi wholly purple-scaled; hairs of the male antennæ rather short and sparse. (West Indies.) *violaceus* Wied.

2. Middle and front feet wholly black..... *portoricensis* Roeder

   Middle and usually the front feet with a white band on each. *rutilus* Coq.

(*b*) List of the Species and Synonyms

portoricensis Roeder.
  ferox Walker (not of Wiedemann).
rutilus Coq.

violaceus Wied.
  purpureus Theob.

(*c*) Unrecognized Species

grandiosus Will., *hæmorrhoidalis* Fab., and *longipes* Theob. These three species have been reported from Mexico.

3. Subfamily PSOROPHORINÆ Mitchell

Genus PSOROPHORA Desvoidy

(Synonym: *Chrysoconops* Goeldi)

(*a*) Table of the Species

1. Abdomen yellow or brownish, its scales yellowish..... 3
   Abdomen black, its scales chiefly purple; upper side of the thorax polished black, usually white-scaled toward the sides..... 2
2. Front and middle femora black, their scales purple except at the narrow apex of each femur, where they are white. (Middle America.) *cilipes* Fab.
   Front and other femora yellow, yellow-scaled, their broad apices black-scaled ..... *howardii* Coq.
3. Veins in the front half of the wings, except toward their apices, deep yellow, their scales of the same color, scales on the front half of the thorax golden yellow. (West Indies)..... *fulva* Wied.
   Veins and scales of the wings wholly brown, scales in the middle of the upper side of the thorax golden yellow, those toward the sides white. *ciliata* Fab.

(*b*) List of the Species and Synonyms

ciliata Fab.
- *conterrens* Walk.
- *molestus* Wied.
- *perterrens* Walk.
- *rubidus* Desv.

cilipes Fab.

fulva Wied.
- *flavicosta* Walk.
- *ochripes* Macq.

howardii Coq.

(*c*) Unrecognized Species

scintillans Walk. This species has been recorded from the West Indies.

4. Subfamily CULICINÆ Theobald

(Synonyms: *Aëdeomyinæ* Theobald, *Hæmagoginæ* Lutz)

Table of the Genera

1. Claws of the female toothed on at least the front and middle feet; some of the claws of the male also toothed..... 4
   Claws of the female simple 2
2. Palpi of the male at least three-fourths as long as the proboscis.... 10
   Palpi of the male at most only one-half as long as the proboscis. (Middle America)..... 3
3. Head posteriorly with very narrow scales and with a patch of broad ones on each side..... 18
   Head sparsely or densely covered with broad scales posteriorly.... 21
4. Scales along the sides of the upper surface of the thorax narrow, almost linear, legs never with outstanding scales..... 6
   Scales along the sides of the upper surface of the thorax chiefly rather broad, obovate, hind part of the head with many similar scales scattered about..... 5
5. Legs devoid of outstanding scales..... *Lepidosia*
   Legs bearing many outstanding scales, at least on the hind feet, all feet black, the hind ones alone partly white..... *Janthinosoma*

6. Back part of the head densely covered with broad, appressed scales except sometimes a narrow stripe in the middle..... 7
Back part of the head sparsely covered with narrow, almost linear scales and with a patch of broad ones on each side..... 8
7. Clypeus bearing several scales or hairs, scutellum with broad scales only .....*Stegomyia*
Clypeus bare, scutellum with narrow scales only. (Middle America.) *Verrallina*
8. Wing veins having the outstanding scales narrow, lanceolate, only slightly tapering to the base..... 9
Wing veins having many very broad outstanding scales which taper strongly to their bases; several of the scales are hollowed out at their apices.....*Lepidoplatys*
9. Palpi of the male less than one-fourth as long as the proboscis..*Aedes*
Palpi of the male about as long as the proboscis.....*Ochlerotatus*
10. Head densely covered behind with broad, appressed scales, except a narrow stripe in the middle, or else the thorax has six lines of silvery scales..... 23
Head bearing narrow, almost linear appressed scales behind and with a patch of broad ones on each side; thorax never with lines of silvery scales..... 11
11. Outstanding scales on the veins behind the first one narrow and of nearly a uniform width..... 12
Outstanding scales on at least the apical half of the wings broad, considerably narrowed at their bases..... 17
12. Feet white at each end of some of the joints or else wholly black, in which case the abdomen is wholly black-scaled, or else it has cross-bands of light-colored scales..... 13
Feet white at the bases only of some of the joints, or else wholly black, in which case the abdomen is black-scaled and with the front corners of some of the segments white-scaled.....*Grabhamia*
13. Costa of the wings not spotted..... 14
Costa black-scaled and with three large spots of pale yellow scales. (Middle America).....*Lutzia*
14. Thorax with two distinct bare stripes near the middle of the upper side; hind cross-vein at least its own length from the small cross vein .....*Culicella*
Thorax without bare stripes..... 15
15. Scales of the wings collected into spots; hind cross-vein much less than its length from the small cross-vein.....*Theobaldia*
Scales of the wings uniformly distributed..... 16
16. Hind cross-vein much less than its own length from the small cross-vein .....*Culiseta*
Hind cross-vein situated at least nearly its own length from the small cross-vein .....*Culex*
17. Basal half of the wings having the outstanding scales of the veins narrow and almost linear; proboscis wholly black.....*Melanoconion*
Basal half of the wings having many broad, outstanding scales on the veins 20
18. Wing veins having the outstanding scales narrow, almost linear.... 19
Wing veins having the outstanding scales rather broad, oblanceolate; palpi of the male almost one-half, those of the female less than one-fifth, as long as the proboscis.....*Tinolestes*
19. Palpi in both sexes about one-third as long as the proboscis..*Micraëdes*
Palpi in both sexes less than one-fifth as long as the proboscis. *Isostomyia* n. gen.
20. The outstanding scales on the veins of the wings only moderately broad, over twice as long as broad, their apices rounded; proboscis and feet usually with light-colored bands.....*Coquillettidia*
The outstanding scales chiefly unusually broad, their apices flat or hollowed out.....*Tæniorhynchus*

21. Outstanding scales on the wing veins unusually broad; femora toward their apices bearing several elongate, outstanding scales; body devoid of blue scales .....*Aëdeomyia*
Outstanding scales on the wing veins narrow, almost linear, legs devoid of outstanding scales, head and body chiefly blue scaled..... 22
22. Base of the first submarginal cell nearer to the base of the wing than is that of the second posterior cell; palpi of the male less than one-fifth as long as the proboscis, the abdomen bearing only a few hairs on the under side of the penultimate segment.....*Hæmagogus*
Base of the first submarginal cell noticeably nearer to the apex of the wing than is the base of the second posterior cell; palpi of the male about one-half as long as the proboscis; abdomen of the male with a large cluster of outstanding, blunt spines on the under side of the penultimate segment.....*Cacomyia* n. gen.
23. Scutellum bearing both broad and narrow scales; head behind covered with broad appressed scales except a median stripe of rather narrow ones; outstanding scales on the wing veins narrow. (Middle America) .....*Gymnometopa*
Scutellum with narrow scales only..... 24
24. Back of the head covered with broad appressed scales except a median stripe of rather narrow ones; outstanding scales on the wing veins narrow. (Middle America) .....*Howardina*
Back of the head with narrow scales only; many rather broad, outstanding scales on the wing veins.....*Pneumaculex*

Genus LEPIDOSIA Coquillett

Our two species have the scales of the abdomen deep blue, except those of the first segment and a broad, usually interrupted band on the apices of the other segments, which are pale yellow or whitish.
Hind feet wholly black.....*cyanescens* Coq.
Hind feet black, the last joint white.....*mexicana* Bell.

Genus JANTHINOSOMA Arribalzaga

(Synonym: *Conchyliastes* Theobald)

(*a*) Table of the Species

1. Last two joints of the feet wholly white..... 3
Last joint largely or wholly black, the preceding joint chiefly white.. 2
2. Scales on the upper side of the thorax yellow.....*varipes* Coq.
Scales brown, those toward the sides yellow.....*discrucians* Walk.
3. Upper side of the thorax yellow-scaled and with a broad stripe of brown scales in the middle.....*lutzii* Theob.
Upper side of the thorax wholly yellow-scaled.....*posticata* Wied.

(*b*) List of the Species and Synonyms.

discrucians Walker (not of Giles and Theobald).[1]
arribalzagæ Giles.
lutzii Theob.
albitarsis Neveu-Lemaire (not of Theobald).
discrucians Giles and Theobald (not of Walker).
posticata Wiedemann (not of Theobald).
musica Say.
varipes Coq.
johnstonii Grabham.

[1] The form referred to this species by these two authors has the entire apex of the hind feet wholly white, whereas in his original description Walker expressly states, both in the Latin diagnosis and in the English description, that there is only a subapical white band in *discrucians,* the remainder of the feet being purple.

(*c*) Unrecognized Species

terminalis Coquillett (*posticata* Theobald, not of Wiedemann), was described from St. Lucia, W. Ind., and differs from all of the other species in that the last joint only of the hind feet is white.

Genus STEGOMYIA Theobald

(*a*) Table of the Species

Thorax marked with a pair of curved silvery stripes forming a figure which somewhat resembles a lyre; proboscis unicolorous black, feet black and with white bands at the bases of some of the joints. *calopus* Meig.

(*b*) List of the Species and Synonyms

calopus Meig.
annulitarsis Macq.
bancroftii Skuse.
elegans Ficalbi.
exagitans Walk.
excitans Walk.
fasciata Fab.
formosa Walk
frater Desv.
impatibilis Walk.
inexorabilis Walk.
calopus Meig—Continued.
konoupi Brullé.
luciensis Theob.
mosquito Desv.
queenslandensis Theob.
rossii Giles.
tæniatus Wied.
toxorhynchus Macq.
viridifrons Walk.
zonatipes Walk.

(*S. sexlineata* Theob. belongs to the genus *Gymnometopa.*)

Genus VERRALLINA Theobald

Upper side of the thorax black-scaled, the sides in front of the wings white-scaled ..... *insolita* Coq.
Upper side of the thorax wholly whitish-scaled..... *laternaria* Coq.

Genus LEPIDOPLATYS Coquillett

(*a*) Table of the Species

Scales of the wings mixed brown and white; feet with broad white bands at the bases of some of the joints, tibiæ not distinctly banded. *squamiger* Coq.

(*b*) List of the Species and Synonyms

squamiger Coq.
deniedmannii Ludlow.

Genus AEDES Wiedemann[1]

Upper side of the thorax golden-yellow scaled; abdomen black-scaled and with a band of yellow scales at the bases of the segments; feet unicolorous black..... *fuscus* O. S.
(*A. smithii* belongs to *Wyeomyia.*)

Genus OCHLEROTATUS Arribalzaga

(Synonyms: *Culicada* Felt, *Culicelsa* Felt, *Ecculex* Felt, *Protoculex* Felt, *Pseudoculex* Dyar.)

[1]This genus has commonly been credited to Meigen, but he expressly states that he had not seen a specimen and that both the name and description had been furnished to him by Wiedemann.

(*a*) Table of the Species

1. Ground color of the thorax bright yellow; the scales and bristles of the head and thorax wholly yellow 2
   Ground color of the thorax brown or black..... 3
2. With an ovate black spot above the insertion of each wing; feet not distinctly two-colored, claws of the hind ones simple.
   bimaculatus Coq.
   Without such a spot; feet dark colored and with white bands at the bases of some of the joints. (Middle America).....*knabi* Coq.
3. Feet dark colored and with white bands..... 19
   Feet not distinctly banded, proboscis unbanded..... 4
4. Scales of the abdomen black, sometimes a crossband or pair of spots of light-colored scales on some or all of the segments..... 5
   Scales of the abdomen yellow, except a pair of spots of black ones on some of the segments; claws toothed on all of the feet in the female .....*spenceri* Theob.
5. Light-colored scales of the abdomen forming crossbands situated at the bases of the segments..... 6
   Light-colored scales, when present, forming spots on the sides of some of the segments 14
6. Upper side of the thorax yellow-scaled and with three stripes of brown scales; scales of the wings wholly brown; all the claws of the female toothed .....*trivittatus* Coq.
   Upper side of the thorax not marked like this..... 7
7. Thorax with a brown-scaled stripe along the sides and with a wider space of white scales in the middle; scales of the wings wholly brown; all of the claws toothed in the female.....*dupreei* Coq.
   Thorax not marked in this manner..... 8
8. Sides broadly and the front end of the thorax whitish-scaled; back part of the head also whitish-scaled; all claws toothed in the female 9
   Sides and front end of the thorax yellow or brown scaled..... 10
9. Middle of the thorax with a broad stripe of brown scales.
   pretans Grossb.
   Middle of the thorax having the scales yellow and whitish.
   cinereoborealis Felt.
10. The scales in the middle of the thorax as dark as, or darker than, those along the side 11
    The scales in the middle of the thorax yellow, those along the broad sides brown; claws of the hind feet simple in the female.
    bracteatus Coq.
11. Bristles of the scutellum yellow 12
    Bristles of the scutellum chiefly black; upper side of the thorax golden-yellow-scaled and devoid of stripes of darker scales, although two darker stripes sometimes appear where the scales are very sparse, each stripe being scarcely one-half as wide as the yellow-scaled space between it and the other stripe.....*pullatus* Coq.
12. In the middle of the thorax the scales are wholly yellow..... 13
    In the middle of the thorax is a pair of brown-scaled stripes, each stripe being slightly wider than the yellow-scaled space between it and the other stripe.....*lazarensis* F. & Y.
13. Claspers of the male with a long, stout spine near the base of the inner side .....*impiger* Walk.
    Claspers without such a spine.....*abserratus* Felt.
14. With a median stripe of scales on the thorax of a different color from those along the sides 15
    Without such a stripe; abdomen black-scaled and with the front angles of some of the segments white-scaled; claws on all of the feet of female toothed. (Middle America) .....*nubilus* Theob.

15. Scales in the middle of the thorax, at least on its anterior half, white, the remainder brown; claws on all of the feet of the female toothed 16
Scales in the middle of the thorax black, the remainder yellow or whitish 18
16. Stripe of white scales in the middle of the thorax extending entirely across the latter 17
Stripe of white scales confined to the anterior two-thirds of the thorax .....*confirmatus* Arrib.
17. White-scaled stripe of the thorax much narrower than the brown-scaled portion on each side of it.....*serratus* Theob.
White-scaled stripe wider than the brown-scaled portion on each side of it.....*dupreei* Coq.
18. Upper surface of the thorax white-scaled toward the sides; claws on the hind feet of the female simple.....*triseriatus* Say.
Upper surface of the thorax golden-yellow-scaled toward the sides; claws on the hind feet of the female toothed.....*aurifer* Coq.
19. Proboscis blackish and with a white band near the middle; white bands of the feet confined to the bases of the joints, except on the hind feet, the last joint of which is sometimes wholly white..... 20
Proboscis blackish, not distinctly banded near the middle..... 22
20. Abdomen black-scaled, each segment with a basal band and median longitudinal stripe of yellowish scales, and with a white-scaled spot in the middle of each side..... 21
Abdomen black-scaled, each segment with a band at the base and a spot in the middle of each side white-scaled, wing scales wholly black.....*tæniorhynchus* Wied.
21. Wing scales mixed black and yellowish; light colored scales of the legs yellow, usually a whitish band in the middle of the first joint of the feet.....*solicitans* Walk.
Wing scales wholly black; light colored scales of the legs pure white, first joint of the feet never with a light colored band in the middle.
mitchellæ Dyar.
22. Joints of the feet having the white bands situated at both ends of some of them, last joint of the hind feet white..... 23
Joints of the feet having the white bands situated at the bases only of some of them, last joint of the hind feet black except sometimes its extreme base 28
23. Black scales mixed with white ones on the wings; abdomen whitish or yellow-scaled and with a pair of black-scaled spots on some of the segments 24
Black scales only on the wings, abdomen black-scaled, sometimes with a band of white scales at the bases of the segments..... 25
24. Stripe of scales in the middle of the thorax deep golden brown, covering more than one-fifth of the width of the thorax, its borders well defined. (Salt water species).....*lativittatus* Coq.
Stripe pale brown, covering less than one-ninth of the width of the thorax, its borders not strongly marked, usually a narrow stripe of brown scales on each side of it separated by yellowish white scales. (Fresh water species) .....*curriei* Coq.
25. Upper side of the thorax light-yellow-scaled and with a broad stripe of black scales in the middle; palpi wholly black-scaled in both sexes; abdomen black-scaled and with a band of white scales at the base of each segment .....*atropalpus* Coq.
Upper side of the thorax not marked as above; palpi with whitish scales at the apices in the female and with bands of them in the male 26
26. Segments of the abdomen with distinct whitish bands at their bases; scales of the upper side of the thorax brown and light yellowish.
varipalpus Coq.
Segments of the abdomen never with distinct whitish bands; scales of the upper side of the thorax wholly yellow..... 27

27. Hind feet almost wholly white-scaled.....*nivitarsis* Coq.
Hind feet largely black-scaled.....*canadensis* Theob.
28. Dorsum of the abdomen black-scaled and with a band of light-colored scales at the base of each segment..... 30
Dorsum of the abdomen not marked as above..... 29
29. Abdomen wholly light-yellow-scaled.....*fletcheri* Coq.
Abdomen black-scaled and with white spots on the sides; thorax black-scaled and with four lines of yellow scales. (Middle America.)
quadrivittatus Coq.
30. White band at the base of the second joint of the hind feet covering at least one-third of the length of the joint; claws of the hind feet toothed in the female 32
White band covering less than one-fourth of the length of the second joint of the hind feet 31
31. Seventh segment of the abdomen almost wholly yellow-scaled, many yellow scales in the central portion of the preceding segment; claws of the hind feet of the female simple.....*cantator* Coq.
Seventh and preceding segment chiefly black-scaled; claws of the hind feet of the female toothed.....*sylvestris* Theob.
32. Claspers of the male having, near the base of the inner side, a large process thickly covered with hairs.....*fitchii* Felt.
Claspers without such a process.
subcantans Felt, *abfitchii* Felt, *vittata* Theob.

(*b*) List of the Species and Synonyms

abfitchii Felt.
  siphonalis Grossb.
abserratus F. & Y.
atropalpus Coq.
aurifer Coq.
bimaculatus Coq.
bracteatus Coq.
cantator Coq.
canadensis Theob.
cinereoborealis F. & Y.[1]
  trichurus Dyar.
confirmatus Arrib.
curriei Coq.
dupreei Coq.
fitchii F. & Y.
fletcheri Coq.
impiger Walk.
  implacabilis Walk.
knabi Coq.
lativittatus Coq.
lazarensis F. & Y.
mitchellæ Dyar.
nivitarsis Coq.
nubilus Theob.
pretans Grossb.
pullatus Coq.
quadrivittatus Coq.
serratus Theob.
  mathisi Neveu-Lem.
sollicitans Walk.
spenceri Theob.
  idahoensis Theob.
subcantans Felt.
sylvestris Theob.
tæniorhynchus Wied.
  damnosus Say.
triseriatus Say.
  nigra Ludlow (*Finlaya*).
trivittatus Coq.
varipalpus Coq.
  sierrensis Ludlow.

(*c*) Unrecognized Species

aestivalis Dyar, *auroides* Felt, *excrucians* Walker, *hirsuteron* Theob., *inconspicuus* Grossb., *nemorosus* Meigen, *onondagensis* Felt, *pallidohirta* Grossb., *portoricensis* Ludlow, *provocans* Walker, *punctor* Kirby, *reptans* Meigen, *stimulans* Walker, *testaceus* van der Wulp, and *tortilis* Theobald.

[1]The writer's copy of Science containing the original description of this species was received September 2, 1904, and the National Museum copy is stamped as having been received on the same date. The writer's copy of the Journal of the New York Entomological Society which contains the original description of *trichurus* was received September 6, 1904; the National Museum copy and that of the U. S. Department of Agriculture are stamped with the same date—September 6, 1904.

Genus GRABHAMIA Theobald

(Synonym: *Feltidia* Dyar)

(*a*) Table of the Species

1. Feet unicolorous brown, wing scales wholly brown. (West Indies).. 2
   Feet brown and with bands of white scales at bases of some of the joints 3
2. With an ovate, velvety-black spot above the insertion of each wing; abdomen black-scaled, unmarked.....*ocellatus* Theob.
   Without such a spot; abdomen black-scaled and with a white-scaled spot in the front angles of the posterior segments.
   scholasticus Theob.
3. Proboscis black-scaled and with a light-colored band near the middle; a white band before the apex of each hind femur..... 4
   Proboscis wholly black; abdomen black-scaled and with a white band at the bases of the segments; no white band before the apex of the hind femora. (West Indies).....*imitator* Theob.
4. Wing scales black and whitish..... 5
   Wing scales wholly black; abdomen black-scaled and with a narrow white, usually interrupted, band at apex of each segment. (West Indies) .....*confinis* Arrib.
5. Last vein with many black scales on the basal portion..... 6
   Last vein wholly white-scaled on the basal two-thirds; light and dark scales of the wings collected into spots, costa mixed black and whitish scaled and with a long whitish spot beyond the apex of the auxiliary vein .....*discolor* Coq.
6. Costa and veins bearing mixed black and whitish scales, the latter not forming distinct spots..... 7
   Costa black and whitish scaled, the apical half with four long spots of whitish scales alternating with three long spots of black ones.
   signipennis Coq.
7. First joint of the hind feet light colored in the middle, a small but distinct black-scaled spot at the base of the third vein.
   jamaicensis Theob.
   First joint of the hind feet black in the middle, no distinct black spot at the base of the third vein.....*pygmæus* Theob.

(*b*) List of the Species and Synonyms

confinis Arrib.
discolor Coq.
imitator Theob.
jamaicensis Theob.
  confinis auct. (all references to its occurrence in the United States).
ocellatus Theob.
pygmæus Theob.
  antiquæ Giles.
  nanus Coq.
scholasticus Theob.
signipennis Coq.

(*G. deniedmannii* Ludlow belongs to *Lepidoplatys.*)

Genus LUTZIA Theobald

Joints of the feet white at each end, abdomen black-scaled and with a large apical spot of white scales on each segment.....*bigotii* Bell.

Genus CULICELLA Felt

(*a*) Table of the Species

Feet narrowly white at the bases of some of the joints, proboscis without a lighter band near the middle, abdomen black-scaled and with a broad band of yellow scales at the base of each segment...*dyari* Coq.

(*b*) List of the Species and Synonymy

dyari Coq.
brittoni Felt.

Genus THEOBALDIA Neveu-Lemaire

(*a*) Table of the Species

Front side of the hind tibiæ chiefly black-scaled, the apices very broadly whitish-scaled, white bands of the feet narrow, the dark spots on the wings large.....*incidens* Thom.
Front side of the hind tibiæ with many yellow scales, the apices narrowly and indistinctly whitish-scaled; the dark spots on the wings small.
annulata Schrank.

(*b*) List of the Species and Synonyms

annulata Schrank.
affinis Stephens.
variegata Schrank.
incidens Thom.
particeps Adams.

Genus CULISETA Felt

(*a*) Table of the Species

Wing scales wholly brown, abdomen brown-scaled and with bands of light-colored scales at the bases of the segments in both sexes.
absobrinus Felt.
Wing scales mixed brown and yellowish in the female, abdomen brown-scaled and with bands of light-colored scales in the female, unbanded in the male.....*consobrinus* Desv.

(*b*) List of the Species and Synonyms

absobrinus Felt.
consobrinus Desv.
impatiens Walk.
inornatus Will.
magnipennis Felt.
pinguis Walk.

Genus CULEX Linné

(Synonyms: *Heteronycha* Arribalzaga, *Neoculex* Dyar)

(*a*) Table of the Species

1. Feet black, both ends of some of the joints white.
janitor Theob., *pleuristriatus* Theob., *secutor* Theob., *tarsalis* Coq.
Feet uniformly blackish..... 2
2. Light-colored bands of scales on the abdomen situated at the bases of the segments 3
Light-colored bands located at the apices of the segments, sometimes almost wanting .....*territans* Walk.
3. Upper side of the thorax dark-yellow-scaled, and usually with a small round dot of light-yellow scales on each side of the center; light-colored bands of the abdomen broad and distinct; feet with very narrow, indistinct bands of light-colored scales at the sutures of the joints .....*restuans* Theob.
Upper side of the thorax devoid of such dots..... 4
4. Crossbands of light-colored scales indistinct on the anterior half of the abdomen, almost wanting on the second segment.....*salinarius* Coq.
Crossbands distinct 5
5. Species from the West Indies.....*palus* Theob.; *similis* Theob.
Species almost cosmopolitan.....*pipiens* Linné.

(*b*) List of the Species and Synonyms

janitor Theob.
palus Theob.
pipiens Linne.
boscii Desv.
cubensis Bigot.
fatigans auct.[1] (North American references).
ferruginosus Wied. (*Anopheles.*)
pungens Wied.
quinquefasciatus Say.
pleuristriatus Theob.
restuans Theob.
salinarius Coq.
nigritulus auct. (North American references).
secutor Theob.
similis Theob.
tarsalis Coq.
affinis Adams (not of Stephens).
kelloggii Theob.
peus Speiser.
willistoni Giles.
territans Walk.
apicalis Adams.

(*c*) Unrecognized Species

flavipes Macquart, *biocellatus* Theobald, *inflictus* Theob., *microsquamosus* Theob., *nigripalpus* Theob., and *saxatilis* Grossbeck.
(*C. penafieli* Williston has never been described.)

Genus MELANOCONION Theobald

1. Hind and other feet wholly black..... 2
Hind feet white-scaled on the broad base of the fourth joint; abdomen black-scaled, a row of violet-scaled spots along the sides. (Middle America) .....*urichii* Coq.
2. Thorax on the anterior half golden-yellow-scaled and with a pair of black-scaled spots, the posterior half black-scaled and with two stripes of yellow scales. (Middle America).....*spissipes* Theob.
Thorax wholly golden-brown-scaled..... 3
3. Abdomen with bands of yellowish scales at the bases of the segments. (Middle America) .....*humilis* Theob.
Abdomen unbanded 4
4. Front angles of the segments of the abdomen yellowish-scaled.
atratus Theob.
Front angles and whole of the abdominal segments black-scaled.
indecorabilis Theob., *melanurus* Coq.

Genus TINOLESTES Coquillett

Feet unicolorous black; scales of the upper side of the body black and with light-colored ones in the front angles of some of the segments of the abdomen.....*latisquama* Coq.

Genus MICRAËDES Coquillett

Proboscis and feet unicolorous black; scales of the abdomen purple-black and with light-colored ones in the front angles of some of the segments .....*bisulcatus* Coq.

Genus ISOSTOMYIA Coquillett

Proboscis, feet, and abdomen wholly black-scaled.....*perturbans* Will.
(*Aëdes nigricorpus* Theobald may also belong to this genus.)

[1]In response to my request, Major A. Alcock, superintendent of the natural history section of the Indian Museum at Calcutta, India, sent me specimens of this species in all the stages. The larvæ have been examined by Dr. H. G. Dyar and Mr. F. Knab, who report having discovered differences between them and the corresponding stage of the North American specimens of *pipiens*.

Genus COQUILLETTIDIA Dyar

(*a*) Table of the Species

1. Scales of the wings mixed black and light colored, those of the costa not forming distinct spots; scales of the feet black and with white ones at the bases of some of the joints..... 2
   Scales of the wings wholly black. (Middle America)..... 3
2. Abdomen black-scaled and with a white band at the base of each segment; hind tibiæ with a broad light-colored band before the apex. *perturbans* Walk.
   Abdomen golden-yellow-scaled and with several black scales on the first three segments; hind tibiæ devoid of a distinct light-colored band. (Middle America) .....*flaveolus* Coq.
3. Feet black-scaled and with white bands at the sutures of some of the joints, femora with a whitish spot or band at a point near three-fourths of their length 4
   Feet wholly black except at the base of the first joint, femora devoid of a distinct white mark near three-fourths of their length; abdomen black-scaled and with a white band or median spot at the base of each of the last four segments and a white spot in the front angles of each segment .....*palliatus* Coq.
4. Scales on the upper side of the abdomen black and with spots of white ones along the sides 5
   Scales on the abdomen wholly black, on the thorax wholly brown. *arribalzagæ* Theob.
5. White spots on the sides of the abdomen situated in the front angles of the segments; scales in the middle of the thorax yellow, those toward the sides chiefly black.....*nigricans* Coq.
   White spots on the sides of the abdomen situated near the middle of the segments; scales of the thorax brown and with several lines of light yellow ones.....*fasciolatus* Arrib.

(*b*) Unrecognized Species

niger Giles, described from Antigua, West Indies.
richardi Ficalbi, a European species reported from Canada by Theobald.

(*c*) Species Wrongly Referred to this Genus

antiquæ Giles and *confinis* Arribalzaga belong to *Grabhamia; fulvus* Wiedemann belongs to *Psorophora; sierrensis* Ludlow belongs to *Ochlerotatus.*

Genus TÆNIORRHYNCHUS Arribalzaga

(Synonyms: *Mansonia, Panoplites* Theobald)

(*a*) Table of the Species

Third joint of the feet black-scaled, the base narrowly white-scaled, scales of the tibiæ not forming distinct spots or bands.....*titillans* Walk.
Third joint of the hind feet wholly white-scaled, black and yellowish scales of the tibiæ collected into distinct bands and spots.....*fascipes* Coq.

(*b*) List of the Species and Synonymy

fascipes Coq.

titillans Walk.
tæniorhynchus Arrib. (not of Wiedemann).

Genus AËDEOMYIA Theobald

Proboscis with a white ring near the middle; joints of the feet white at at their bases; scales of the wings brown, yellow, and white. *squamipennis* Arrib.

Genus HÆMAGOGUS Williston

(*a*) Table of the Species

Scales of the abdomen bluish and with a row of silvery spots along each side, sometimes a small median spot of white scales on some of the segments ..... *cyaneus* Fab.

(*b*) List of the Species and Synonymy

cyaneus Fab.
splendens Will.
(The following two species were originally described under *Hæmagogus.*)

Genus CACOMYIA, new genus

Abdomen having white scales in the middle of the last two segments only. *albomaculatus* Theob.

Abdomen having white scales in the middle of some of the other segments ..... *equinus* Theob.

Genus GYMNOMETOPA Coquillett

1. Upper side of the thorax brown-scaled and with six narrow lines of pale yellow scales extending the entire length of the thorax; last two joints of the hind feet black..... *sexlineata* Theob.
   Upper side of the thorax not marked like this..... 2
2. Last two joints of the hind feet and all the tibiæ black..... 3
   Last two joints of the hind feet chiefly white; a spot or band of white scales on the base of at least the first two joints on all of the feet; tibiæ with a silvery mark at a point about one-fourth of their length ..... *mediovittata* Coq.
3. With a dot of silvery scales in the middle of the front end of the thorax; first two joints of the front feet white-scaled at their bases. *albonotata* Coq.
   Without such a dot; front feet wholly black-scaled..... *busckii* Coq.

Genus HOWARDINA Theobald

Feet black-scaled, the base of the first three joints of the hind ones white-scaled; upper side of the thorax white-scaled along the sides, the median portion black-scaled and with four narrow lines of pale yellow scales, the two middle lines united into a single line posteriorly, the outer two lines situated on the posterior half of the thorax. *walkeri* Theob.

Genus PNEUMACULEX Dyar

Thorax on the upper side velvety-brown-scaled and with six narrow lines of silvery scales..... *signifer* Coq.

5. Subfamily DEINOCERITINÆ Mitchell

Genus DEINOCERITES Theobald

(Synonym: *Brachiomyia* Theobald)

(*a*) Table of the Species

Proboscis and feet unicolorous blackish; scales of the upper side of the body also blackish ..... *cancer* Theob.

(*b*) List of the Species and Synonymy

cancer Theob.
magna Theob.

6. Subfamily URANOTÆNIINÆ Lahille

Genus URANOTÆNIA Arribalzaga

(*a*) TABLE OF THE SPECIES

1. Thorax with a median line of bluish scales; feet wholly black..... 2
   Thorax without a median line; hind feet white on at least the last two joints and broad apex of the third..... 3
2. Bluish median line of the thorax prolonged to the scutellum. *sapphirina* O. S.
   Bluish line obliterated before reaching the scutellum....*socialis* Theob.
3. Scutellum with blue scales; a patch of blue scales on the thorax a considerable distance in front of the scutellum; feet white at the sutures of many of the joints. (Middle America).....*geometrica* Theob.
   Scutellum without blue scales; no patch of blue scales on the thorax in front of it; feet wholly black except the last two joints and apex of the third in the hind ones.....*lowii* Theob.

(*b*) UNRECOGNIZED SPECIES

apicalis Theobald and *pulcherrima* Arribalzaga. Both of these have been reported from the West Indies.

7. Subfamily TRICHOPROSOPONINÆ Theobald

(Synonyms: *Hyloconopinæ* Lutz, *Dendromyinæ* Lutz, *Sabettinæ* Blanchard)

TABLE OF THE GENERA

1. Male palpi at least one-half as long as the proboscis; clypeus hairy. (Middle America) .....*Trichoprosopon*
   Male palpi less than one-fourth as long as the probiscis; clypeus bare.. 2
2. Veins of the wings having the outstanding scales narrow and nearly linear; hind cross-vein situated at least its own length before the small cross-vein; legs never fringed with scales.....*Wyeomyia*
   Veins having many rather broad outstanding scales. (Middle America) 3
3. Hind cross-vein slightly before, opposite, or beyond the small cross-vein, each foot bearing two claws..... 7
   Hind cross-vein at least twice its own length before the small cross-vein; legs never fringed with scales..... 4
4. With two claws on each hind foot; no scales on the posterior end of the thorax below the scutellum 5
   With only one claw on each hind foot in both sexes; posterior end of the thorax below the scutellum bearing several broad scales in addition to the bristles 6
5. Proboscis shorter than the body; thickened before its apex..*Dendromyia*
   Proboscis longer than the body, not thickened toward its apex. *Phoniomyia*
6. Male proboscis strongly curved in the outer half and with a cluster of scales at each end of the curved portion.....*Limatus*
7. Legs not fringed.....*Sabethoides*
   Legs fringed in places with outstanding scales in both sexes....*Sabethes*

Genus TRICHOPROSOPON Theobald

(Synonym: *Joblotia* Blanchard)

Feet wholly black.....*lunata* Theob.
Feet black, the last four joints of the middle feet and the last two of the hind ones white.....*nivipes* Theob.

Genus WYEOMYIA Theobald

Proboscis and upper side of the abdomen wholly black-scaled.
grayi Theob., *pertinans* Will., *smithii* Coq.

Genus DENDROMYIA Theobald

Abdomen wholly black-scaled on the upper side; humeri black-scaled; first joint of the hind feet shorter than their tibiæ...*luteoventralis* Theob.

Genus PHONIOMYIA Theobald

(*a*) Table of the Species

Abdomen black-scaled, the front angles of the segments white-scaled.
longirostris Theob.

(*b*) List of the Species and Synonymy

longirostris Theob.
trinidadensis Theob.

Genus LIMATUS Theobald

(Synonym: *Simondella* Laveran)

Thorax golden-yellow-scaled, a median, Y-shaped spot, with the prongs nearest the head, and a large spot above each wing violet-blue-scaled .....*durhamii* Theob.

Genus SABETHOIDES Theobald

Abdomen black-scaled, the under side and front angles of the segments whitish-scaled, the white-scaled front angles prolonged so as to form a crossband which is interrupted except sometimes on the last three segments.....*confusus* Theob.
Abdomen black-scaled, the under side whitish-scaled, and encroaching on the sides of the dorsum, the border of the two colors strongly undulating .....*undosus* Coq.

Genus SABETHES Desvoidy

(*a*) Table of the Species

1. Front and hind legs not fringed 2
Front and other legs fringed in places with outstanding scales; middle legs white-scaled before and beyond the fringed portion; the broad apices of the hind feet chiefly white-scaled.....*longipes* Fab.
2. Legs black-scaled, the apical part of the fringe on the middle legs white. *nitidus* Theob.
Legs wholly black-scaled.....*locuples* Desv.

(*b*) List of the Species and Synonymy

locuples Desv.
remipes Wied.
longipes Fab.
nitidus Theob.

The hatching of the first brood of anophelines bears an intimate relation to the seasonal occurrences of malaria. The seasonal variations of different species are probably dependent upon the presence or absence of breeding pools suitable to particular species. Temperature also exerts an influence, the hibernating females of some species leaving winter quarters

earlier than others, and hibernating larvæ mature at different temperatures.

While the anophelines are mosquitoes of low altitudes, they may be found at considerable elevations. Thus in the Alps they are found at an altitude of 1,145 metres; in the Appenines at 1,283 metres; in Java at 1,000 metres; at Harrar at 2,000 metres; in Africa at 1,900 metres, and in the high plateaus of Mexico at 2,000 metres.[115]

It is the rule among mosquitoes that only the females are blood suckers, hence it is this sex alone that is concerned in the propagation of malaria. The female insects suck not only the blood of man, but of other mammals, birds, occasionally of cold-blooded animals, and even other insects. Blood is necessary for both the procreation of mosquitoes and the development of the sexual cycle of the malarial organism. While both sexes have the blood-sucking apparatus, the puncturing portion of the proboscis of the male is much weaker than that of the female.

There are a few exceptions to the rule that males do not bite. While males do not infrequently light upon the skin and probe around with the proboscis, they usually fly away without partaking of blood. But the male *Stegomyia fasciata* has been known to bite. Doctor Stiles[114] is said to have been bitten by a male *Culex nemoralis,* and the male of *Culex elegans* is said by Sambon[121] to be quite as bloodthirsty as the female. The habitual diet of male mosquitoes, however, is vegetarian. They are very fond of fruits, as bananas, dates, pears, apples, melons, and of the nectar of flowers, wine, and beer. In captivity mosquitoes may be kept alive for some days upon a diet merely of sweetened water.

Anopheline mosquitoes rarely suck blood except during the night. After feeding they usually retire to remote and dark corners or to breeding places to oviposit. Persons may be bitten during sleep without being disturbed, since these insects are not noisy and their bite is not particularly painful. During the day their reserved habits make them difficult of detection. They will ordinarily feed in a few hours after hatching; in captivity, however, it may be difficult to induce them to feed

upon blood. The meal is repeated, as a rule, once every day or every few days. Blood is essential for the maturation of fertile ova, one feeding being sufficient for one oviposition. The act of biting (Fig. 40) has been described as follows: "When the female anopheles bites the proboscis is pointed downwards and the labellæ are pressed against the skin of the victim. The labrum, the hypopharynx, the mandibles, and the maxillæ are pressed together into one solid boring instrument, like the parts of a trocar. Their common tip is forced down at the angle between the spread labellæ, which serve to hold and direct these clustered parts. Whilst the piercing organs pass into the tissues the labium bends backwards at about a third from its base, and its angle, pointing towards the breast of the insect, becomes more and more acute with the deepening of the

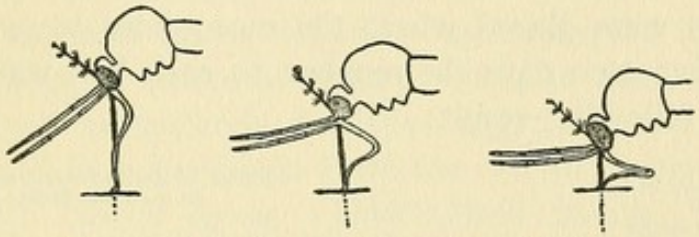


Fig. 40.—A female mosquito in the act of biting.

mouth parts. The palpi, which usually lie parallel with the proboscis, are raised and diverged during puncture."[121]

The buzzing note of the mosquito is produced by the vibrations of the chitinous shreds within the large tracheæ and not by the wings, as commonly supposed. As Howard[122] states, there is quite a difference between the note of *Anopheles maculipennis* and that of the common species of *culex*, the note of the latter being high in pitch, that of the former being several tones lower.

A point of great practical interest is the length of flight of the mosquito and the extent to which it may be borne by the wind. It is a general rule that mosquitoes do not migrate far from their native pools or from dwellings where nourishment may be obtained.

It is very unusual for anophelines to fly farther than a few hundred yards, and half a mile may be regarded as the maxi-

mum limit of flight. They are poorer flyers than most other species. For this reason they are less often borne by the wind, since they seek shelter when a breeze arises. While the wind is not so generally a vehicle for the dissemination of mosquitoes as commonly believed, certain species, especially of salt water breeders, are borne by the wind for several miles. The greater prevalence of mosquitoes in dwellings after a wind may often be due to their retiring thither for protection. Mosquitoes may be carried in wagons loaded with straw, hay, or fruit, and upon railroad cars. Many localities formerly free from the pests date their affliction with mosquitoes from the introduction of railroads. Vessels may not only transport the insects for great distances, but may even afford breeding places.

The preference of anophelines for certain colors has been demonstrated by Nuttall.[123]. Boxes lined with cloth of different colors were placed where the mosquitoes were plentiful, and on seventeen days the number on each box was counted, with the following result:

Color of box.	Number of *Anopheles malculipennis* counted in each box during seventeen days.
Navy blue	108
Dark red	90
Brown, reddish	81
Black	49
Scarlet	59
Slate gray	31
Dark green (olive)	24
Violet	18
Leaf green	17
Blue	14
Pearl gray	9
Pale green	4
Light blue	3
Ochre	2
White	2
Orange	1
Yellow	..
	512

Galli-Valerio and De Jongh[124] counted 119 anophelines resting upon dark colors and 33 upon bright colors, and 349 culex upon dark colors and 120 upon bright.

Mosquitoes are fond of the odor of leather and are usually plentiful upon harness hanging in stables. They are said to prefer the odor of the negro to that of the white man.

Anophelines, like other malefactors, prefer darkness rather than light, and seek the sequestered nooks during the day.

A meal of blood is a prerequisite to fertilization. Females confined with males, then isolated and fed, do not deposit fertile eggs, but must be fed first. A single fertilization is sufficient for several batches of eggs. These are usually deposited between dusk and dawn. Still water is necessary, since the female may be drowned if the surface is agitated. The female sits upon the water or upon the edge of floating leaves or debris. The ova of anophelines are deposited upon the water in clumps, but soon separate and lie horizontally. A batch of ova usually numbers from 100 to 150. Pressat[125] has calculated, on a basis of 150 ova for each female, hatching 50 per cent. females, that a single female in one season produces about five billion mosquitoes.

Parthenogenesis has occasionally been observed in mosquitoes. Kellogg[114] reared a female mosquito from the pupa which almost immediately deposited eggs; she had not been fertilized. Larvæ developed from the ova and nearly reached full growth before dying. Unfertilized female *Stegomyia fasciata* and *Culex pipiens* have also been known to deposit ova, which, however, were not fertile.

It is impossible to determine the length of life of mosquitoes in nature, though even in captivity they have been kept for weeks. Anophelines have been kept alive five days without food or water, and for about two months fed upon bananas. The males are not so long lived as the females. Mitchell[126] has kept *Stegomyia fasciata* sixty-one days. It is well known that mosquitoes survive long droughts, as well as hibernate.

Stephens and Christophers[118] say there is evidence that the ova can survive for some months in moist earth and exposed to frost. Eysell[127] and Galli-Valerio and De Jongh[124] state that the ova of most species of mosquitoes of the northern temperate and frigid zones may hibernate.

Mosquitoes hibernate in the larval stage also. Smith[114] found, in New Jersey, larvæ of *Culex pungens* in ice contained in pitcher plants, and believes that larval hibernation must be

extremely common. Mitchell[126] found anopheles larvæ in tanks and barrels in the Botanical Gardens of Washington, D. C., during winter, and Woldert[128] found these larvæ in December at Tyler, Texas.

Mitchell[126] believes it probable that mosquitoes do not hibernate in the pupal stage, though Galli-Valerio and De Jongh[124] maintain the opposite opinion.

It is chiefly in the winged stage that mosquitoes hibernate. In the late fall the males die, the fecundated females seeking shelter in dwellings, cellars, stable, barns, cisterns, hollow trees, or under bridges. Annett and Dutton[129] thus describe the hibernation of *Anopheles maculipennis* in England:

1. The attitude is peculiar, the insect lying quite flat upon the surface with its legs spread out. In this position the under surface of the thorax touches, or nearly touches, the wall.

2. Only females are found, and these are always fertilized, and have the spermatheca filled with spermatozoa.

3. The insects are difficult to arouse and very sluggish in any movements they make.

4. They do not feed unless the temperature is raised. If kept at a low temperature (provided the air is moist) they remain for weeks without feeding.

5. If aroused by raising the temperature they feed readily and the ovaries rapidly develop. Eggs are laid, and in most cases the female dies after their deposition.

Study of Mosquitoes.—To obtain adult mosquitoes they may be either captured or bred from larvæ. Mosquitoes are best captured by placing very carefully the mouth of a test tube or bottle over the insects while resting. They are killed preferably by the cyanide bottle, by chloroform, or by tobacco smoke. The cyanide bottle is prepared by placing in the bottom of a wide-mouthed bottle a number of small pieces of potassium cyanide and covering with liquid plaster of Paris. When the plaster has hardened the bottle is ready for use, and should then be kept tightly corked, as the fumes are poisonous. Mosquitoes should not be killed immediately after hatching, as the exoskeleton is then soft and marked shrivelling occurs. A net should not be used for capturing adult mosquitoes, for

the delicate scales are thereby worn off and the specimen spoiled.

Mosquitoes should be mounted as soon as killed, since the legs soon lose their pliability and are apt to be broken off. The materials needed for mounting are fine entomological pins, No. 00; ordinary black or mourning pins, and cardboard slips. These latter may be cut oblong, one-half by 1 inch, or circular, using a 16 or 20-gauge wad-cutter. One of the fine pins is run for two-thirds of its length through one of the cardboard slips. The mosquito, lying upon its back upon a piece of cork, is transfixed by the point of this pin through the center of origin of the legs. One of the larger pins is now run through the cardboard in an opposite direction, and when stuck into the cork lining of the cabinet serves as a support.

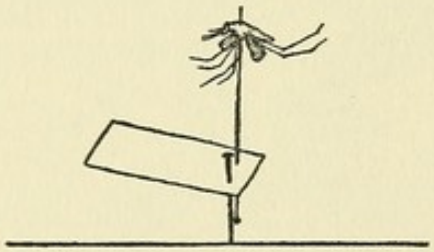


Fig. 41.—A pinned specimen.

Naphthaline or camphor should be placed in the cabinet to exclude mites.

Parts of mosquitoes, the wings, legs, antennæ, scales, etc., may be mounted upon slides. A ring of varnish should be made upon a slide and the object placed in the center of this ring, the cover-glass pressed down gently and its edge ringed, preferably with Damar.

Ova, larvæ, and pupæ may be mounted in concave slides or upon slides having a cell made by ringing with varnish. In this cell the object is mounted with Farrant's medium or with 10 per cent. solution of formalin, and the edge of the cover-glass ringed.

In order to catch larvæ the only implements required are a white enamelled dipper, a spoon, and a container for the wrigglers when captured. To "breed out" larvæ they should be placed in wide-mouthed jars half filled with water and a

layer of sand in the bottom, and covered with gauze held in place by means of a rubber band. The larvæ in each jar should be near the same size, otherwise the larger will devour the smaller ones, and they should not be too numerous. A few grains of dry rice should be dropped in for food.

Adults also should be kept in such jars, which should, however, contain only a small quantity of water, upon which should float a thin sheet of cork, and each jar should contain a slanting strip upon which the insects may rest. A bent hairpin makes a good hook upon which to suspend a piece of fruit from the edge of the jar.

In order to infect mosquitoes with malaria they must, of course, be fed upon blood containing parasites. They may be fed by holding the moistened forearm against the gauze covering of the jar or they may be placed in cages covered

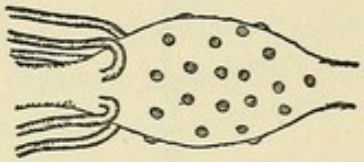


Fig. 42.—Stomach of infected mosquito.

with wire netting, one end of which has an opening protected by a sleeve through which the arm may be introduced. The mosquitoes should be fed in twenty-four to forty-eight hours after hatching and thereafter every day for several days.

In investigating the mosquito cycle of the parasite of malaria the sexual forms must be sought for in the midgut or stomach, and the sporozoits in the salivary glands.

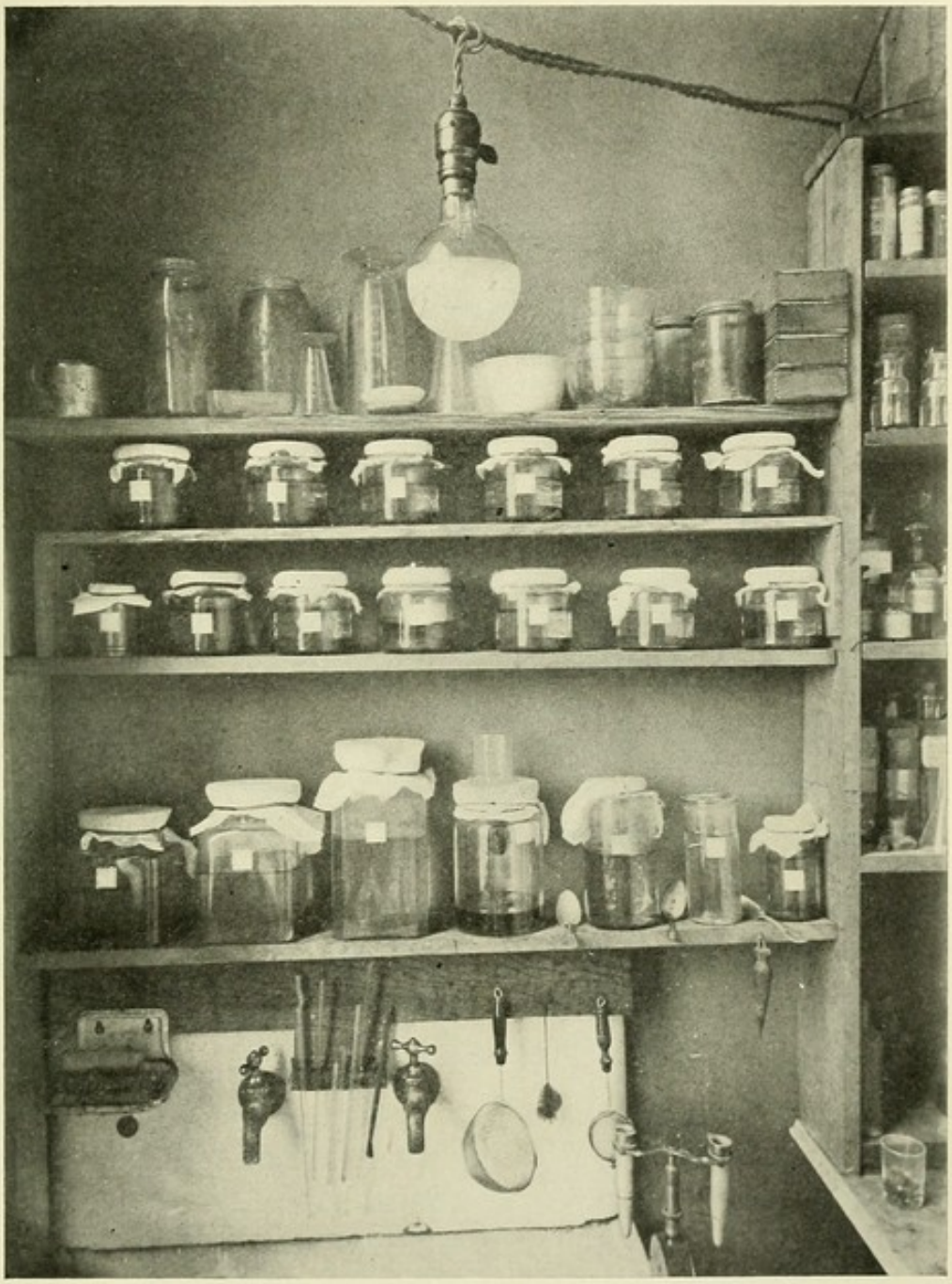
In the dissection of the midgut proceed as follows:

Do not dissect the mosquito until the blood from the last feeding is digested, which may be ascertained by the disappearance of the dark color on the lower surface of the abdomen.

Kill the mosquito by means of cyanide fumes, chloroform, ether, or tobacco smoke.

Pull off the wings and legs and remove the scales with a small camel's-hair brush.

PLATE I



A miniature mosquito farm.

Place, with the ventral aspect up, in a drop of normal salt solution upon a glass slide.

Transfix the center of the thorax with a dissecting needle.

Flatten the abdomen by gentle pressure of the other needle, and nick the intersegmental membrane on each side between the second and third last segments.

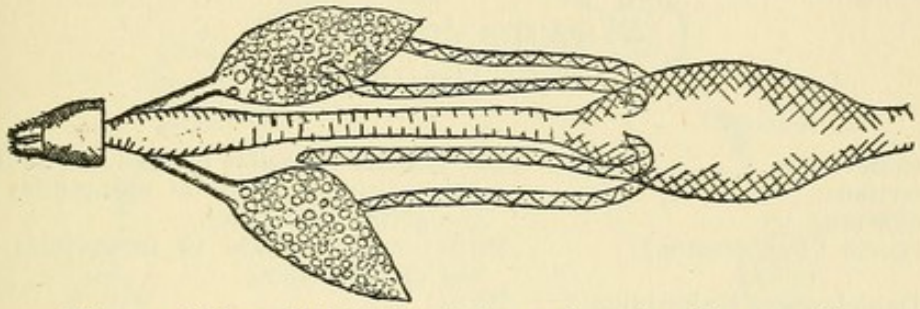


Fig. 43.—Midgut, Malpighian tubules, and ovaries of the mosquito.

With the needle upon the last segment, pull gently until the segments separate and the viscera are drawn out.

Separate the stomach from the esophagus in front and from the hind-gut and Malpighian tubules behind, and remove these organs.

Add more salt solution if necessary and apply a cover-glass

The salivary glands (Fig. 44) lie immediately above the origin of the first pair of legs. One method of removing them



Fig. 44.—Dissection of the salivary glands (after Daniels).

is to transfix the posterior portion of the thorax with one needle and with the other pull off the head, when the salivary glands and a tag of the esophagus are dragged out. Another method is, after removing the wings and legs, to cut off the head and to make an incision parallel to the anterior border of the thorax and on a level with the middle pair of legs. The glands are teased out of this segment after first cutting the exoskeleton in several places. They are recognized as translucent glistening bodies.

THE PARASITES OF MALARIA

Zoological Relations.—The parasites of malaria belong to the animal kingdom, to the division of protozoa, to the class of sporozoa, and to the order of hemosporidia. The hemocytozoa are not peculiar to man, but are found in other classes of vertebrates, and are distributed by Manson[59] into three genera, as follows:

HÆMOCYTOZOA

1. Genus Hæmamœba

Names.	*Hosts.*
H. subtertiana.	The malaria parasites of man, the sexual phase being evolved in mosquitoes of the genus Anopheles.
H. tertiana.	
H. quartana.	
H. relicta (Proteosoma).	Birds; sexual phase in mosquitoes of the genus Culex.
H. Danielewski (Halteridium).	Birds.
H. Kochi.	Several species of monkeys.
H. melaniphera.	Bat (Miniopterus Shreibersii).
H. Metchnikovi.	Trionyx indicus.

2. Genus Piroplasma

P. bigeminum.	Bovines; transmitted by the cattle tick (Boöphilus bovis).
P. canis.	Dogs.
P. ovis.	Sheep.
P. equi.	Horse.
P. hominis.	Man.

3. Genus Hæmogregarina

H. ranarum (Drepanidium).	Frog (Rana esculenta).
H. splendens.	Frog (Rana esculenta).
H. magna.	Frog (Rana esculenta).
H. lacertarum.	Lizard (Lacerta muralis).

About twenty additional but less readily procured species.

There are three sharply defined species of parasites of malaria, the parasite of tertian malaria, the parasite of quartan malaria, and the parasite of estivo-autumnal malaria. The latter is divided by most observers into three, or at least two, varieties, the tertian and the quotidian, of which latter variety a pigmented form and an unpigmented form are described. The writer's opinion is that there are two varieties of the estivo-autumnal parasite, the tertian and the quotidian, and that the pigmented and the unpigmented quotidians are merely forms of one variety.

A number of students of malaria, with Laveran at their head, maintaining the unity of the malarial parasites, hold that the several species are only forms of one species which may be mutually transformed. The arguments upon which

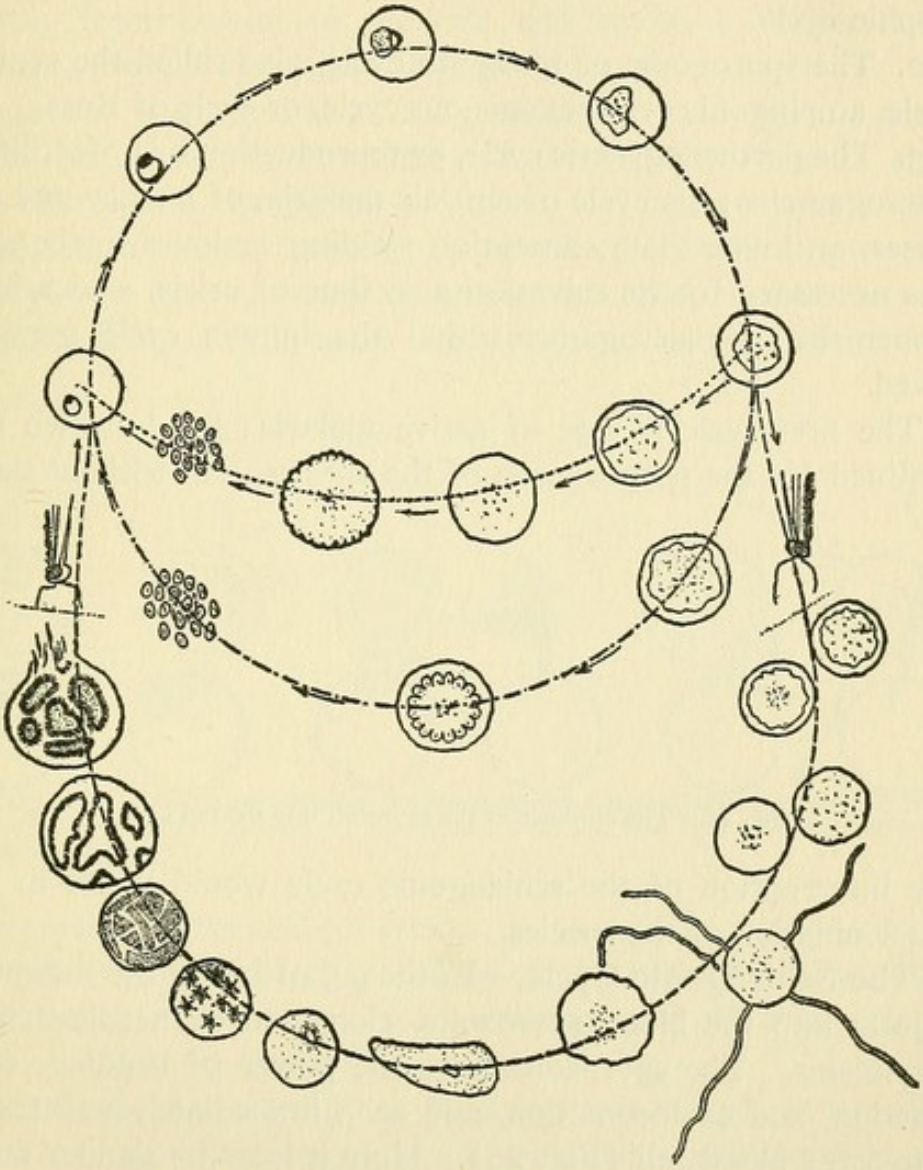


Fig. 45.—Diagram illustrating the cycles of the parasite.
—.—.—.—. Schizogonic cycle.
– – – – – – – – – Sporogonic cycle.
..... Parthenogenetic cycle.

their theory is based are so unsound in the light of our present knowledge that it is unnecessary to review them.

Biology.—The life history of the parasites of malaria is somewhat complicated, inasmuch as man, the mosquito, and

the parasite are involved, and as there are three species of parasites and each species has three biologic cycles. These three cycles are:

1. The schizogonic, or human cycle, also called the asexual cycle, monogonic cycle, endogenous cycle, cycle of Golgi, or trophic cycle.

2. The sporogonic or mosquito cycle, also called the sexual cycle, amphigonic cycle, exogenous cycle, or cycle of Ross.

3. The parthenogenetic cycle, or reproduction by unfertilized macrogametes; the cycle of chronic malaria, of latency and relapses, an immaculate conception yielding saviours to the species necessary for its salvation at a time of crisis, a vicarious atonement of macrogametes that the human cycle may be saved.

The first cycle is that of active malaria; the last two are destined for the perpetuation of the species, and without them

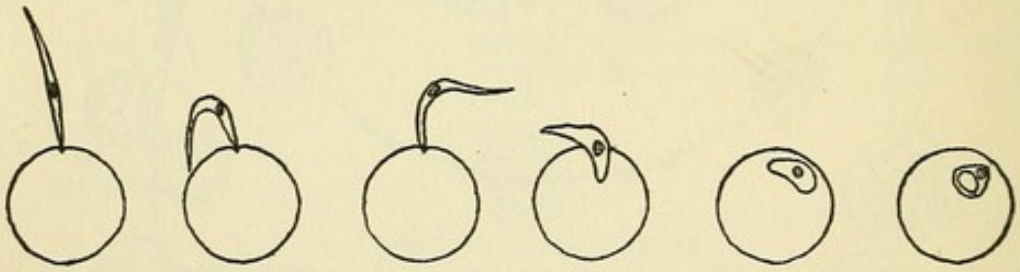


Fig. 46.—The entrance of the sporozoit into the red cell.

the interruption of the schizogonic cycle would result in the extermination of the species.

The Schizogonic Cycle.—In the act of biting the mosquito injects into the blood sporozoits, elongated or needle-shaped organisms. The sporozoits have the power of bending, contraction, and of locomotion, and each immediately penetrates into a red blood-cell (Fig. 46). Here it loses its slender form and appears as a mere dot of protoplasm, whose index of refraction varies but little from that of the red cell. The size of the young parasite varies in different species, but is about 1 or 2 microns in diameter. Ameboid motion is more or less active, pseudopodia being protruded and retracted, the parasite even changing its position within the cell, and has no constant form. There is usually only one parasite in each infected cell,

but there may be several. As the parasite grows it acquires pigment, a few grains at first, gradually increasing in amount with the growth of the parasite. This pigment is from the hemoglobin of the infected cell, and occurs in the form of grains, rods, or clumps. The adult parasite occupies a relatively large portion of the cell, and ameboid motion is less active, though the pigment may be in violent motion. The organism is composed of cell protoplasm, nucleus, and nucleolus, but appears structureless in fresh, unstained blood. Prior to sporulation the pigment becomes concentrated and fused, and fission occurs, dividing the parasite more or less symmetrically into spores, constituting the so-called rosette or marguerite forms, each spore containing a fragment of nucleus.

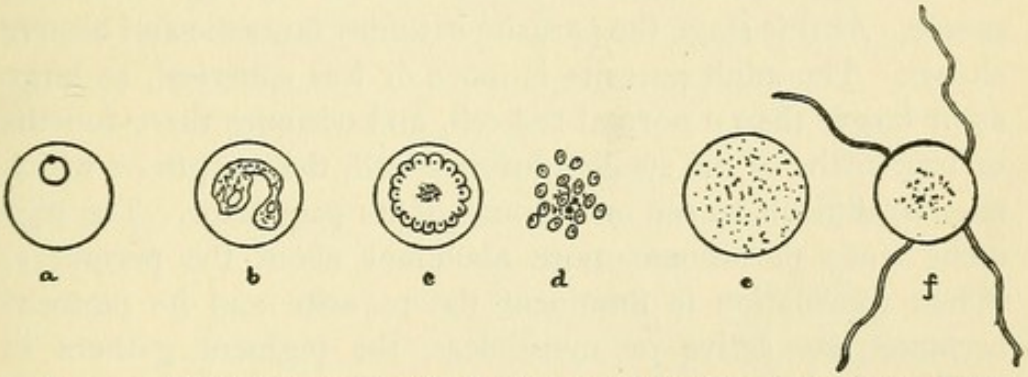


Fig. 47.—Diagram representing the development of the malarial parasite : *a*, Young form ; *b*, half-grown parasite ; *c*, sporulating body ; *d*, free spores ; *e*, macrogamete ; *f*, microgametocyte.

The cell ruptures and the spores, or merozoites, escape into the blood current, where they rapidly enter the blood-cells to repeat the cycle. The corpuscular remnants and the pigment are rapidly taken up by the phagocytes.

Instead of proceeding to sporulation some of the parasites develop into sexual forms, or gametes, large parasites of round, ovoid, spindle, or crescentic shape. It is these bodies which are taken up by the mosquito, undergo a sexual cycle in its midgut, develop into sporozoits, which are injected into man, where they pass through the schizogonic cycle above outlined.

The Tertian Parasite (*Hæmamœba vivax, H. tertianæ, Plasmodium vivax*).—The duration of the asexual cycle of the simple tertian parasite is forty-eight hours. The young

parasites are about one-fifth the size of the red blood corpuscles and unpigmented. They are difficult to distinguish from the young parasites of the other species. They are actively ameboid, protruding and retracting short pseudopodia with rapidity; Y-shapes, T-shapes, and crosses are common forms. The index of refraction of the parasites is low, so that their contours are not clearly distinguished from the substance of the red blood-cells. As the parasite increases in size pigment gradually appears. The pigment of the tertian parasite is fine, rod-shaped, rather light in color, and in active motion. This motion of the pigment has been compared to the bubbling of boiling water and to the swarming of insects. The infected red cell becomes enlarged, swollen, and pale. The half-grown parasite fills about half or two-thirds of the red blood corpuscle. At this stage the parasite assumes fantastic and bizarre shapes. The adult parasite is more or less spherical, as large as or larger than a normal red cell, and occupies three-fourths or four-fifths of the swollen infected cell, the margin of which may be difficult to see on account of its pale color. The pigment tends to become more abundant about the periphery. When sporulation is imminent the parasite and its pigment becomes less active or motionless, the pigment gathers in clumps at the center, and radial striations appear from the periphery toward the center. Usually the sporulating tertian parasite is not so symmetrical as the corresponding stage of the quartan, resembling, rather, a bunch of grapes or a mulberry. Less often there are two concentric rows of spores. The spores are small and oval and vary in number from twelve or fourteen to twenty-six, oftenest sixteen, and more often an even than an uneven number. Sporulation takes place especially in the circulation of certain viscera, but sporulating tertian parasites are much more frequently encountered in the peripheral circulation than in the case of estivo-autumnal infections.

The parasites develop with remarkable uniformity, nearly all appearing to be of the same age. Even in infections with two groups of tertian parasites, which is very common, it is unusual to find a parasite which does not belong to one brood.

DESCRIPTION OF PLATES II AND III

Various forms of malarial parasites: Figs. 1 to 10 inclusive, tertian parasites; Figs. 11 to 19 inclusive, quartan parasites; Figs. 20 to 26 inclusive, estivo-autumnal parasites.

1.—Normal red blood cell. 2.—Young tertian ring. 3.—Large tertian ring. 4.—Half-grown tertian parasite. 5.—Infected cell showing Schüffner's dots. 6.—Adult tertian parasite. 7.—Beginning sporulation. 8.—Sporulation completed. 9.—Tertian microgametocyte. 10.—Tertian macrogamete. 11.—Young quartan ring. 12.—Older quartan ring. 13.—Quartan band. 14.—Older quartan band. 15.—Full-grown quartan parasite. 16.—Mature parasite with divided chromatin. 17.—Sporulation completed. 18.—Quartan microgametocyte. 19.—Quartan macrocyte. 20.—Young estivo-autumnal ring. 21.—Large estivo-autumnal ring. 22.—Mature parasite. 23.—Sporulation completed. 24.—Estivo-autumnal microgametocyte. 25.—Estivo-autumnal macrogamete. 26.—Estivo-autumnal ovoid.

PLATE II



1 2 3

4 5 6

7 8 9

10 11 12

DEADERICK DEL.

PLATE III



13



14



15



16



17



18



19



20



21



22



23



24



25



26

DEADERICK DEL.

The early development of the gametes is not well understood. Half-grown gametes are hard to differentiate from schizonts, but small parasites, without ameboid motion, with much pigment, and with large nucleus may be regarded as gametes. The adult gamete resembles the full-grown schizont. In shape it is more or less spherical and may be twice as large as a red blood corpuscle. Ameboid movement is very slight, the pigment is profuse, fine, reddish, or blackish, and actively motile. The vesicular appearing nucleus is commonly situated near the periphery, and is visible in fresh preparations.

An interesting phenomenon which occurs in the case of the microgametocytes, or male sexual forms, is exflagellation. This takes place from ten to thirty minutes after the blood has been withdrawn, and is favored by exposing the blood for a few minutes to the air, by the addition of a minute quantity of water, and exposure to moisture, as breathing upon the slide before applying the cover-glass. Before exflagellation the pigment is observed to undergo violent and tumultuous motion, then to collect toward the center. Undulations at the periphery are then noted, as if something within were trying to escape. Suddenly the flagella break forth from different points of the margin. These are from four to eight in number and in length are two and a half to three times the diameter of the red blood corpuscle. They may show ovoid swellings at the end or in their continuity. Lashing madly to and fro, the red cells are displaced and a flagellum may be seen to break off from the microgametocyte and dart in a serpentine manner among the cells. The flagella are known as microgametes, and have been shown by McCallum to be spermatozoa. Their function is to fertilize the macrogametes, or female forms, in the midgut of the mosquito.

Tertian gametes may be distinguished from adult schizonts by the former being of larger size, less ameboid motion, their pigment appearing earlier, being more abundant and in more active motion.

The following may serve to differentiate tertian male and female gametes:

Microgametocytes.	*Macrogametes.*
Plasma hyaline.	Plasma granular.
Pigment abundant, in thick rods, brownish yellow.	Pigment in fine rods and granules, brownish black.
Not larger than a red blood-cell.	Larger than a red cell.
Chromatin profuse.	Chromatin less abundant.
Little ameboid motion.	More or less ameboid motion.
Nucleus toward center.	Nucleus toward periphery.

In stained films the early stage of the tertian parasite is seen as a ring. Often the ring is not of the same thickness throughout its circumference, but is composed of a thin segment, and a thicker segment, the chromatin, being upon the thin segment. Usually the chromatin dot is immediately within the ring, but may lie outside, and is surrounded by a pale zone. The achromatic zone may be regarded as the nucleus and the chromatin as the nucleolus. As the parasite develops one arc becomes much thickened, giving the appearance of the signet ring. The forms of the half-grown parasite are varied and peculiar. Pigment appears first and most abundantly in the peripheral region, and does not invade the clear zone. The red cell is enlarged and does not stain deeply. A peculiar stippling of the infected red cells is shown in films containing tertian parasites and stained with the Romanowsky stain or one of its modifications. When the parasite fills one-third of the cell a number of fine, red-stained points, Schüffner's dots, appear, which increase in size but not in number as the parasite grows. In the process of sporulation the chromatin becomes subdivided and surrounded by a clear zone and encircled by the blue cytoplasm, constituting the spore.

The Quartan Parasite (*Hæmamœba malariæ, H. quartanæ, Plasmodium malariæ, Laverania malariæ*).—The duration of the schizogonic cycle of the quartan parasite is seventy-two hours. The young forms of the parasite appear as small, hyaline, unpigmented bits of protoplasm. They are highly refractive and the contour is much more sharply defined than the tertian parasite. Ameboid motion is sluggish and the organism may be watched some time until motion is detected. Pigment appears within twenty-four hours. It is in larger quantities than in the tertian parasite, in coarser grains or rods, and dark brown or black in color. The pigment is accumu-

lated around the margin, and its motion is very slow. In the half-grown parasites the peculiar forms observed in the tertian organisms are not seen, and ameboid movements become more sluggish or cease altogether. The red blood-cell infested with the quartan parasite does not enlarge and decolorize as in tertian infections, but, if there is any deviation from normal, becomes smaller and darker, perhaps greenish and brassy. The adult parasites are almost as large as the red cells. Prior to sporulation the pigment collects toward the center, often in a radial arrangement. Sporulation proceeds after the manner of the tertian parasite, but is slower. The sporulating forms are beautifully symmetrical, and are typical rosettes. The spores are round or oval, relatively large and six to twelve in number, oftenest eight. Sporulating quartan parasites are much more commonly observed in the peripheral blood than are the corresponding forms of the other species.

Quartan gametes are but rarely encountered. The macrogametes are spherical in shape, and as long as they remain intracorpuscular are smaller than tertian gametes, but are equally as large when they become extracorpuscular. Exflagellated microgametocytes have been observed; they are somewhat smaller than the tertian forms, but no less active.

The staining reactions of the quartan parasite are similar to those of the tertian. The young form is a ring and so closely resembles the tertian that it cannot be distinguished with certainty. After twelve to twenty-four hours the parasite becomes disc or band shaped. The latter forms are characteristic. The parasite extends across the center of the infested cell as a more or less broad band, often rather quadrilateral, the pigment being arranged more profusely along the margin of the band. The chromatin body of the quartan species stains less intensely and splits earlier than in the tertian. The adult usually fills the corpuscle, which may be no longer apparent. The sexes of the gametes are differentiated by the same characters as in the tertian.

The Estivo-autumnal Parasite (*Hæmamœba præcox, Plasmodium præcox, Hæmamœba immaculata, Laverania præcox, Hæmomenas præcox, Plasmodium immaculatum, Hæma-*

mœba parva, Hæmatozoön falciform, Plasmodium falciparum). —The young forms of the estivo-autumnal parasites are similar to those of the other species, but are smaller, being from one-fifth to one-sixth the size of the infested corpuscle. Ameboid motion is rather active, stars, crosses, and irregular shapes occurring in succession. At rest the parasites appear annular or discoid. More than one parasite in a single cell is relatively more common than in tertian and quartan infections. Advanced stages of development are rarely seen in peripheral blood. The infested red cells often become shrivelled, crenated, darker, and of a brassy hue. The adult parasites do not attain the size of the red blood corpuscles. Sporulation proceeds in a manner similar to that of the simple tertian parasite. The spores number from five to twenty-five or even thirty. Sporulation is not so uniform as in the other infections; sporulating forms may be associated with young or half-grown parasites.

Estivo-autumnal gametes occur in the form of crescents, and of fusiform, ovoid, and spherical bodies. The crescent is characteristic, being found in this form of malaria alone. They are cylindrical, tapering slightly at each extremity, and slightly curved upon themselves. They are longer than the diameter of the red cell and about a third as broad as long. The changes from crescent to ovoid and round bodies may be easily observed under the microscope. The gametes appear only after the infection has persisted for about a week. The crescent may lie within the cell or may have the appearance of the red cell being attached to the concave side; in some instances there is no evidence left of the infested blood-cell. The cell may be stretched across the concavity of the crescent, and is usually almost decolorized. The crescents have given evidence of a double outline. They possess no ameboid movement, and the pigment in the form of rods or granules is motionless. Before exflagellation the crescent assumes the spherical form, smaller than the tertian, and similar to the quartan.

The staining reactions of the estivo-autumnal schizonts are similar to those of the tertian and quartan. The young para-

DESCRIPTION OF PLATES IV AND V[1]

The drawings were made with the assistan of the camera lucida from specimens of fresh blood. A Winckel microscope, objective ¼ (oil immersion), ocular 4, was used. Figures 4, 13, 23, 24, and 42 of Plate IV were drawn from fresh blood, without the camera lucida.

PLATE IV

The Parasite of Tertian Fever.

1.—Normal red corpuscle.
2, 3, 4.—Young hyaline forms. In 4, a corpuscle contains three distinct parasites.
5, 21.—Beginning of pigmentation. The parasite was observed to form a true ring by the confluence of two pseudopodia. During observation the body burst from the corpuscle, which became decolorized and disappeared from view. The parasite became, almost immediately, deformed and motionless, as shown in Fig. 21.
6, 7, 8.—Partly developed pigmented forms.
9.—Full-grown body.
10–14.—Segmenting bodies.
15.—Form simulating a segmenting body. The significance of these forms, several of which have been observed, was not clear to Drs. Thayer and Hewetson, who had never met with similar bodies in stained specimens so as to be able to study the structure of the individual segments.
16, 17.—Precocious segmentation.
18, 19, 20.—Large swollen and fragmenting extracellular bodies.
22.—Flagellate body.
23, 24.—Vacuolization.

The Parasite of Quartan Fever.

25.—Normal red corpuscle.
26.—Young hyaline form.
27–34.—Gradual development of the intracorpuscular bodies.
35.—Full-grown body. The substance of the red corpuscle is no more visible in the fresh specimen.
36–39.—Segmenting bodies.
40.—Large swollen extracellular form.
41.—Flagellate body.
42.—Vacuolization.

PLATE V

The Parasite of Æstivo-autumnal Fever.

1, 2.—Small refractive ring-like bodies.
3–6.—Larger disk-like and ameboid forms.
7.—Ring-like body with a few pigment-granules in a brassy, shrunken corpuscle.
8, 9, 10, 12.—Similar pigmented bodies.
11.—Ameboid body with pigment.
13.—Body with a central clump of pigment in a corpuscle, showing a retraction of the hemoglobin-containing substance about the parasite.
14–20.—Larger bodies with central pigment clumps or blocks.
21–24.—Segmenting bodies from the spleen. Figs. 21–23 represent one body where the entire process of segmentation was observed. The segments, eighteen in number, were accurately counted before separation, as in Fig. 23. The sudden separation of the segments, occurring as though some retaining membrane were ruptured, was observed.
25–33.—Crescents and ovoid bodies. Figs. 30 and 31 represent one body, which was seen to extrude slowly, and later to withdraw, two rounded protrusions.
34, 35.—Round bodies.
36.—"Gemmation," fragmentation.
37.—Vacuolization of a crescent.
38–40.—Flagellation. The figures represent one organism. The blood was taken from the ear at 4.15 p. m.; at 4.17 the body was as represented in Fig. 38. At 4.27 the flagella appeared; at 4.33 two of the flagella had already broken away from the mother body.
41–45.—Phagocytosis. Traced with the camera lucida.

[1] These illustrations are reproduced by permission from the article by Drs. Thayer and Hewetson in *The Johns Hopkins Hospital Reports*, vol. v., 1895.

PLATE IV

The Parasite of Tertian Fever.



The Parasite of Quartan Fever.

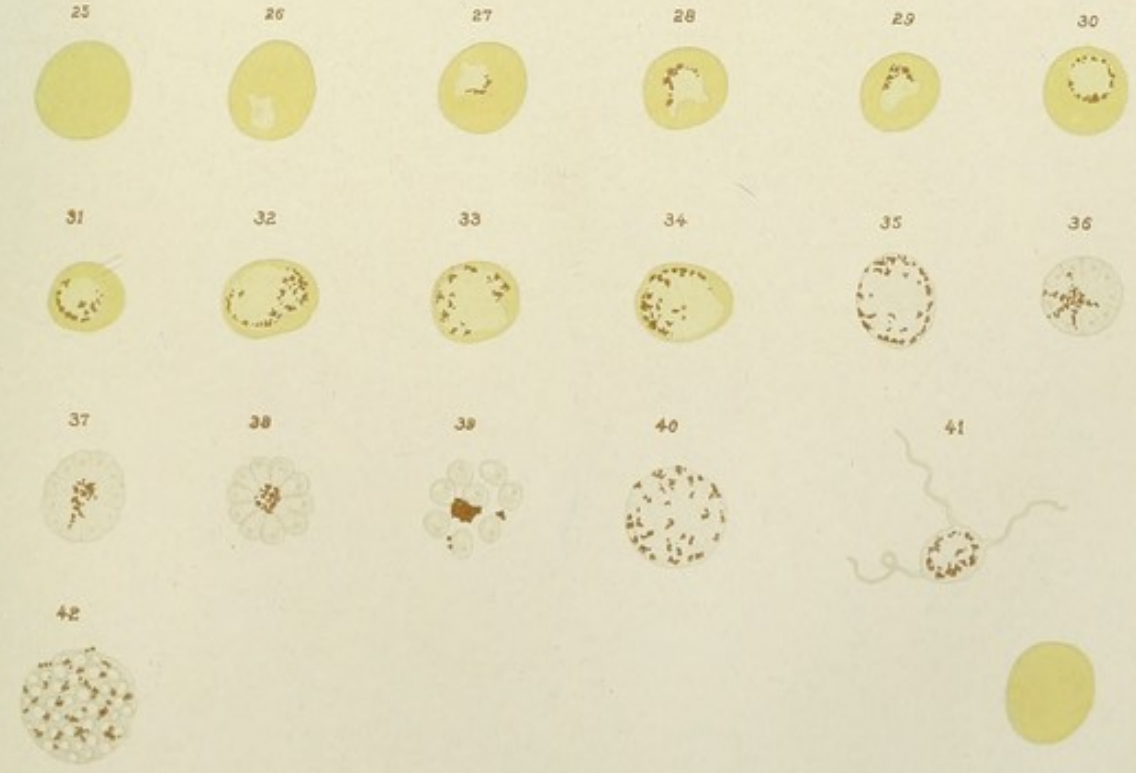
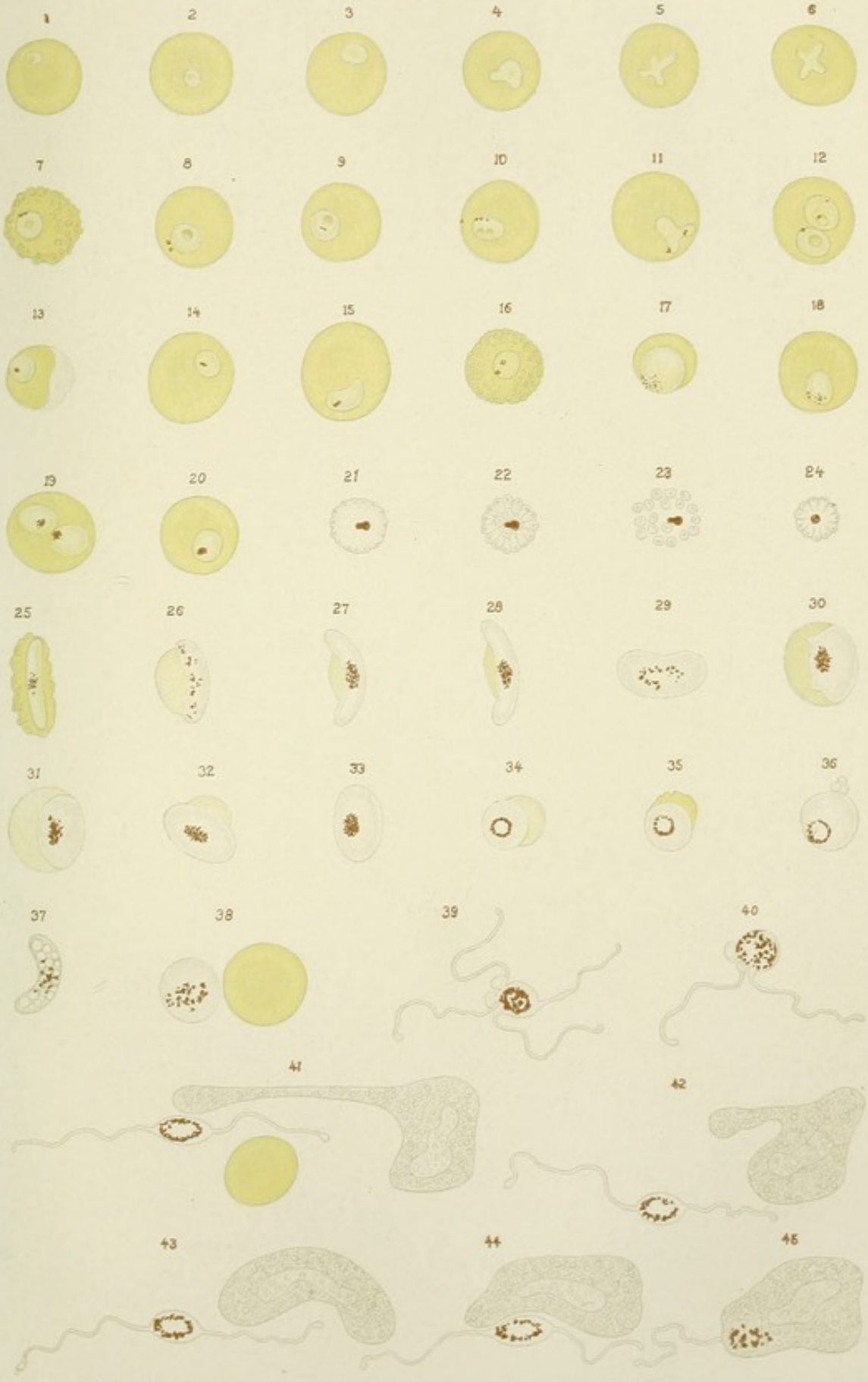


PLATE V

The Parasite of Aestivo Autumnal Fever.



sites are unpigmented rings, resembling the simple tertian rings, but are smaller and more delicate. Typical signet rings and rings without nodes are seen. The ring may be distorted or become broken and extended like a delicate thread or a narrow band. The largest rings are about one-half the diameter of the red cell. The pigment is sparse. Both the sporulating body and the individual spores are small. The central region of the crescent is almost achromatic, the extremities staining more deeply. Chromatin is not always visible in the crescents, but is usually seen, as is the pigment, in the achromatic area.

Mixed infections with quotidian and tertian estivo-autumnal parasites are very common.

The differences between these parasites are thus tabulated by Craig:[70]

THE HYALINE BODY

Stage of Development.	*Quotidian.*	*Malignant Tertian.*
Size.	Minute, one-sixth of corpuscle.	Larger, one-third to one-quarter of corpuscle.
Shape.	Ring or perfectly round.	Signet-ring shape.
Outline.	Indistinct.	Clear cut and refractive.
Motion.	Very active.	Sluggish.
Corpuscle.	Very dark green, wrinkled. Crenated.	Light green, less wrinkled.
Number.	More than one parasite in a corpuscle, common.	Very seldom more than one parasite in a corpuscle.

THE PIGMENTED BODY

Size.	One-quarter size of corpuscle.	One-half size of corpuscle.
Shape.	Round. Loses ring form before pigmentation.	Ring form becomes pigmented, afterward the parasite is round.
Motion.	Ameboid motion is lost.	Ameboid motion continues. Is sluggish.
Outline.	More sharply defined.	Very sharply defined and refractive. The protoplasm firmly granular.
Pigment.	One or two coarse granules, perfectly motionless.	Several minute grains, having a rapid vibratory motion.
Number.	May be more than one in a corpuscle.	Never more than one in a corpuscle.
Corpuscle.	Very green in color, often crenated.	Lighter in color, seldom crenated.

THE SEGMENTING BODY

Place of segmentation.	Within the red blood-corpuscles, as a rule.	Outside the red blood-corpuscles, as a rule.
Number of segments.	Six to eight.	Ten to fifteen or more.
The crescent phase.	Crescents small and plump, containing small amount of pigment. Always present double outline.	Crescents long, narrow, deeply pigmented. Double outline less common.
Cycle of development.	Twenty-four hours.	Forty-eight hours.

The following table will serve to distinguish the sexes of the gametes:

Microgametocytes.	*Macrogametes.*
Protoplasm stains very slightly.	Protoplasm stains more intensely.
Pigment distributed throughout the parasite.	Pigment collected near center, often in a circle.
Reniform, short, and broad.	Crescentic, longer and narrower.
Chromatin in several scattered masses.	Chromatin in one or two large masses near the center.

The chief characteristics of the species of malarial parasites may be tabulated as follows:

	Tertian.	*Quartan.*	*Estivo-autumnal.*
Length of asexual cycle.	48 hours.	72 hours.	24 hours, 48 hours, or irregular.
Site of sporulation.	May sporulate in peripheral blood, chiefly in visceral circulation.	Equally in peripheral and visceral blood.	Visceral circulation.
Movements.	Active.	Sluggish.	Active.
Pigment.	Fine, yellowish or dark brown, scattered, actively motile.	Coarse, dark brown or black (at periphery), slightly motile.	Scanty, fine.
Effect on red cell.	Enlarged, decolorized, Schüffner's dots in stained films.	Normal size or smaller, often dark and brassy.	Often shrunken, may be dark and brassy.
Size of adult.	As large as normal red corpuscles.	Smaller than normal corpuscles.	Much smaller than normal corpuscles.
Sporocyte.	Mulberry shape.	Symmetrical daisy shape.	Irregular.
Spores.	12-26, oftenest 16.	6-12, oftenest 8.	5-30.
Gametes.	Spherical.	Spherical.	Crescentic.

It is not infrequently difficult to differentiate young tertian from young estivo-autumnal rings, though the following table,

adapted from Ewing,[130] will enable a comparison of the main features:

Tertian.	*Estivo-autumnal.*
Nucleus achromatic to methylene-blue.	Nucleus stains intensely with methylene-blue.
Ring usually coarse and irregular.	Ring geometrically circular, delicate, usually a typical signet-like swelling.
One or two grains of pigment almost invariably present.	Pigment almost constantly absent.
Ring usually pigmented before chromatin subdivides.	Chromatin always subdivides before pigment appears.
Infected cell swollen.	Infected cell shrunken.

The Sporogonic Cycle.—If the anopheline mosquito obtains blood containing only schizonts, the latter soon perish in the digestive canal of the insect. However, if the blood contains mature gametes of both sexes these undergo the exogenous cycle, to be prepared to reinfect man bitten by the infected mosquito. The portion of the mosquito in which this transformation takes place is the stomach or midgut. Shortly after the infested blood has been sucked into the stomach the microgametocytes exflagellate, the microgametes become free, and the macrogametes emit small protuberances to receive the flagella or spermatozoa. The latter forces an entrance into the macrogamete at the site of the protuberance, and the resulting fertilized body is known as the zygote. All this has taken place within the first few hours. In its early stages the zygote resembles the ovoid body, but is larger. It is pigmented, it enlarges, becomes pyriform, and has the power of locomotion. The zygote burrows through the epithelial coat of the midgut to the tunica elasticomuscularis, becomes spherical and encysted, and is known as the oocyst. It enlarges so that it projects like a spherical excrescence into the body cavity or blood sinus, where it is nourished. The stomach of a badly-infected mosquito may be studded with these outgrowths. The oocyst attains a size of 40 to 70 microns in diameter. Its nuclear chromatin divides and subdivides, each portion surrounded by protoplasm, polygonal or irregular in shape from pressure, being known as the sporoblast. Each sporoblast splits into a large number of sporozoits, each enclosing a bit of chromatin. The sporozoits remain attached by one end to

the residual body of the sporoblast until the oöcyst bursts, when the sporozoits escape into the body cavity. Finally, through the lacunar circulation, they arrive at the salivary glands, where they congregate in hordes. The sporozoits number from a few hundreds to ten thousand or more, each measures about 14 microns in length, about eight times as long as broad, being very slender, tapering at both ends, and endowed with serpentine movements. From the salivary glands the sporozoits are injected by the mosquito, in the act of preying upon its victims, where each sporozoit soon enters a red cell and goes through the schizogonic cycle. The duration of the mosquito cycle varies from eight to sixteen or more days, depending mainly upon the temperature, but possibly also upon other factors.

The three species of parasites are closely similiar in their stages of exogenous development. The differences between the tertian and the estivo-autumnal organisms are that in the former the zygote is round or oval instead of pyriform or ovoid, the protoplasm is less refractive, the characteristic pigment maintains, the sporoblasts are larger and less numerous, the sporozoits are less dense and more regularly arranged, often radially within the sporoblast, and black spores have not been found.

The quartan parasite is the most difficult to develop within the mosquito.

The Parthenogenetic Cycle.—Parthenogenesis, or virgin birth, is reproduction by unfertilized females.

This phenomenon, known also as the "alternation of generations," has been most carefully studied in plant lice, the *Aphidæ*. The eggs, which are laid in the fall and have hibernated, hatch in the spring into females, having the power of giving birth, without fertilization, to viviparous young, which inherit the faculty of parthenogenesis, and procreate in this manner until the advent of cold weather or the failure of nourishment when males and oviparous females are brought forth. From these latter, after copulation, ova are produced, and the cycle recommences.

Parthenogenetic reproduction is known to occur in a number

of species, as hemoproteus, certain rotifera, jelly-fish, worms, entomostracea, acarina, and certain insects, the silk-moth, mosquitoes, gall-flies, ants, bees, wasps, chironomus, etc.

This life cycle of the parasite of malaria is the most recently recognized and least known of its cycles. Since the discovery of the parasite the gametes have been regarded as closely allied with the chronic malaria and relapses. Golgi plainly stated it as his belief that the crescent was the parasite of fevers recurring at long intervals.

Canalis,[131] in 1889, described and pictured spherical bodies derived from crescents in the act of sporulation. In 1890 Antolisei and Angelini[132] confirmed the observation of Canalis. Lewkowicz[132] reported, in 1897, that he had seen sporulating crescents some of which contained as many as thirty spores.

Grassi[133] expressed the opinion in 1901 that the parasites of malaria underwent a parthenogenetic cycle of development whereby the species was perpetuated after the death of the schizonts.

He cited a number of arguments in support of the theory, and referred to a similar process in other protozoa, *Adelea, Trichosphœrium,* and *Volvox.*

It was Schaudinn[134] who, in 1902, first observed and correctly interpreted parthenogenesis of tertian macrogametes. The case in which this was observed was that of Frau Kossel, who, during the spring and summer of several preceding years, had suffered occasional paroxysms. On April 29 and May 1 two severe paroxysms occurred. At the height of the fever on May 1 the blood was examined and tertian parasites found in abundance; besides schizonts, male and female gametes were numerous, showing that it was a typical relapse. During May the blood was examined regularly and found to contain tertian gametes in greater or less numbers. On May 25, at noon, the blood examination showed no marked variation from the usual findings, except that the parasites were somewhat more plentiful. In every preparation were 10-20 macrogametes and occasional microgametocytes. The temperature was normal. On the morning of May 26 a remarkable condition of the macrogametes, with noteworthy nuclear changes,

described below, were detected. The blood was examined every two hours, and the temperature was taken with the following results:

	Centigrade.
A. M.	
10.00	37.8
P. M.	
12.15	38.4
2.00	37.5
5.15	37.4
9.15	37.0

At 12.15 and at 2 P. M. parthenogenetic forms were most abundant. In the evening, besides unchanged sexual organisms, very young endoglobular schizonts were found.

On May 27 the blood was examined twice; at 7 A. M. only young endoglobular schizonts were found, the temperature 36.8; at 8 P. M. only scanty, half-grown schizonts were found, and the temperature was 37.

On May 28 the typical attack (depending on asexual sporulation) occurred, with the following temperature course:

	Centigrade.
A. M.	
7.00	37.60
10.00	39.00
P. M.	
12.15	39.85
1.15	40.75
2.15	40.40
3.30	39.10
5.15	39.00
7.00	37.80
9.15	37.45
May 29.	
A. M.	
7.00	36.40

The result of the blood examination was as usual in such attacks.

The next morning most of the young parasites were found to be gametes. Thus a true alternation of generations. It should be observed that, while the sporulation of the unfertilized macrogametes or parthenogametes (if it is permissible to coin a much-needed term) caused a slight rise of temperature, it did not compare to the height reached during schizogonic sporulation. It is indeed highly probable that sporulation of a small number of parthenogametes might occur with-

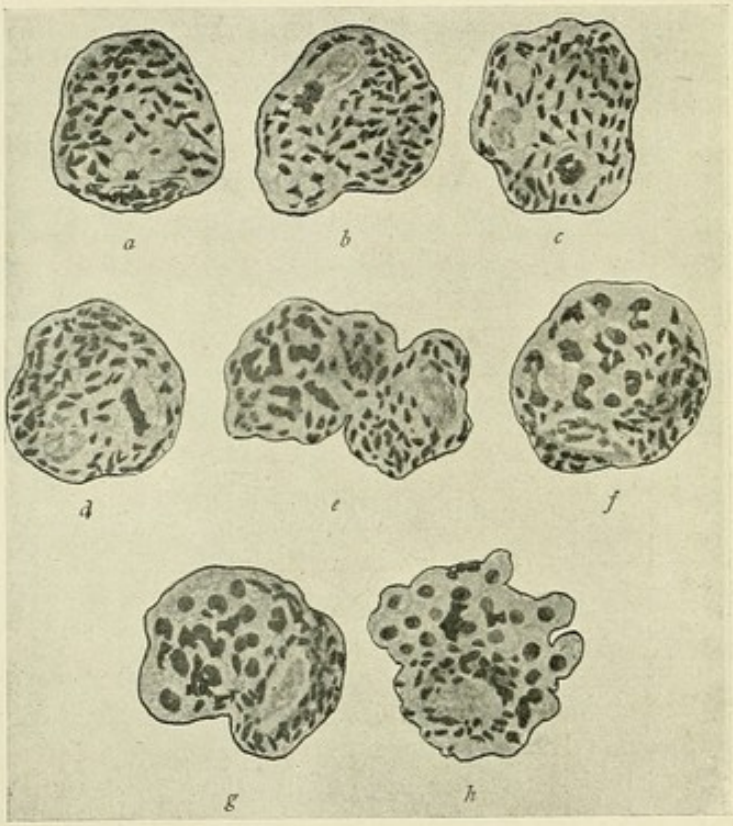


Fig. 48.—Parthenogenesis of the tertian parasite (after Schaudinn).

out perceptible rise of temperature, and that the paroxysm would ensue only when sporulation of schizonts occurred in sufficient numbers.

Schaudinn[134] thus describes the process of parthenogenesis as he observed it in tertian malaria (Fig. 48). The chromatin of the parthenogamete collects in coarse fragments and cords toward one end of the bean-shaped nucleus, and stains intensely, while the other somewhat larger half contains fewer and smaller chromatin particles and stains faintly. The nucleus then divides into two, one containing the coarse, deeply staining chromatin, and the other the fine, diffusely staining chromatin, the former resembling the nucleus of a schizont before nuclear proliferation. A constriction may be perceptible about the parasite almost separating a deeply staining, highly pigmented portion containing the pale-staining nucleus from a lightly stained and less pigmented portion in which lies the deeper stained nucleus. This nucleus now subdivides, and the portion of the plasma in which it lies proceeds to sporulation in a manner similar to schizogonic sporulation, the spores becoming typical schizonts.

Maurer,[135] in 1902, observed sporulation of estivo-autumnal gametes, and construed it as parthenogenesis.

Ziemann[48] believes that he has seen parthenogenetic reproduction of quartan gametes.

Blüml and Metz[136] observed sporulating parthenogametes in six preparations taken from 5 patients with tertian malaria. The process was identical with that described by Schaudinn. Young and sporulating schizonts and young gametes were present in these same preparations.

Are the parthenogametes identical with true macrogametes which do not proceed to sporulation? Such a doubt is hardly justifiable from a review of the scientific studies of the learned Schaudinn and of the other observers cited above. Craig,[137] however, has recently adduced evidence that latency and relapses are dependent upon resting bodies, the products of intracorpuscular conjugation of young schizonts. He does not, however, follow these forms further than the completion of conjugation, and while it is possible that this is the origin of

the parthenogametes, there is as yet no positive evidence that the latter are not true macrogametes.

Inasmuch as different terms are employed by various authors to describe the morphology of the malarial parasite, to the great confusion of the student, the writer has prepared a brief glossary of these terms. The definitions must not be taken in the wide zoologic sense, but only as applied by the majority of writers to the parasite of malaria:

Amphigony. See Sporogony.
Amphiont. See Zygote.
Androspore. See Microgamete.
Antheridium. See Microgametocyte.
Asexual Cycle, the schizogonic or human cycle of parasitic reproduction.
Blast. See Sporozoit.
Blastophore. See Sporoblast.
Copula. See Zygote.
Crescent, one form of the estivo-autumnal gamete.
Definitive Sporoblast. See Zygote.
Endogenous Cycle. See Schizogony.
Enhemospore. See Merozoite.
Exogenous Cycle. See Sporogony.
Exotospore. See Sporozoit.
Flagella, microgametes.
Gamete, sexual form of the parasite.
Gametoblast. See Sporozoit.
Gametocyte, cell giving origin to gametes.
Gametospore. See Zygote.
Germinal Rod. See Sporozoit.
Gymnospore, a schizogonic spore or merozoit.
Gynospore. See Macrogamete.
Hæmosporidia, the suborder of protozoa to which the malarial parasite belongs.
Human Cycle, the schizogonic or endogenous cycle.
Macrogamete, a female gamete.
Macrogametocyte, a female gametocyte.
Macrospore. See Macrogamete.
Merozoite, a spore the product of schizogony; also applied to the sporozoit after it has entered the red cell.
Microgamete, a male gamete, flagellum, spermatozoan.
Microgametocyte, a male gametocyte.
Microspore. See Microgametocyte.
Monogony. See Schizogony.
Monont. See Schizont.
Mosquito Cycle, the sexual or sporogonic cycle.
Nomospore. See Merozoit.
Ondeterospore. See Schizont.
Oöcyst, an encysted zygote.
Oökinete. See Zygote.
Ovoid, one form of the estivo-autumnal gamete.
Parthenogamete (new word), an unfertilized sporulating macrogamete.
Parthenogenesis, virginal reproduction.
Polymitus, an exflagellated microgametocyte.
Reproductive Cycle, the sporogonic or mosquito cycle.
Schizont, the asexual form of the parasite.
Schizogony, the asexual, human or endogenous cycle of development.
Sexual Cycle, the sporogonic, mosquito or exogenous cycle.
Sperm-mothercell. See Microgametocyte.
Spore-cyst. See Oöcyst.
Spore-mothercell. See Sporoblast.
Sporoblast, spherical or polygonal bodies contained in the oöcyst, giving origin to the sporozoits.
Sporocyte, a sporulating schizont.
Sporogony, the sexual cycle of development.
Sporont. See Oöcyst.
Sporozoa, the class of protozoa to which the malarial parasite belongs.
Sporozoit, a spore the product of sporogony.
Syzygies, the products of conjugating parasites.
Trophic Cycle, the asexual cycle.
Trophozoit, a young intracellular parasite of asexual origin; a merozoit which has entered the red cell.
Vermicule. See Zygote.
Zoöid. See Sporozoit.
Zygote, a fertilized macrogamete.
Zygotoblast. See Sporozoit.
Zygotomere. See Sporoblast.

Cultivation Experiments.—Coronado[138] claimed to have been successful in cultivating the malarial parasites from water which he believed infected. He stated that the entire cycle could be followed. Miller[86] also believed that he had cultivated the organisms. These experiments have been repeated, but the results could not be confirmed, hence were probably incorrect.

Sakharov, Rosenbach, Blumer, Hamburger and Mitchel[139] succeeded in maintaining the organisms alive for several days in the bodies of leeches which had sucked the blood from malarial patients. Hamburger's experiment is thus described by Thayer:[98] "Mr. Hamburger took the blood from a case of estivo-autumnal fever with quotidian paroxysms at a time when only small ameboid and ring-shaped, non-pigmented hyaline 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 eighth 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. The parasites, as in Dr. Blumer's case, showed no actual ameboid movement, though some slight change of shape could at times be made out. In both instances the parasites acquired after several days a peculiar refractive, glistening appearance. Specimens stained on the eighth day showed characteristic ring-shaped bodies."

PATHOGENESIS

Much fanciful speculation has been indulged in as to the cause of the paroxysms until Golgi and others of the Italian school showed that it was closely connected with the life history of the malarial parasites (Fig. 49).

The paroxysm is not immediately associated with the gradual vegetative growth of the parasite within the corpuscle, but, occurring more or less abruptly as it does, is simultaneous with sporulation and the sudden discharge into the blood stream of a new generation of parasites. In what manner does this process produce so peculiar a phenomenon as the malarial paroxysm? Golgi[67] was of the opinion that it was dependent

upon the entrance into fresh red cells of the young generation of parasites. This, however, is shown to be erroneous by the fact that a properly timed and adequate dose of quinine given before the chill is expected does not prevent the access though it does destroy the young parasites, preventing their invasion of the cells.

The true explanation of the origin of the paroxysm is through the agency of a toxin liberated by the sporulative act. The existence of a toxin, the product of the malarial parasite,

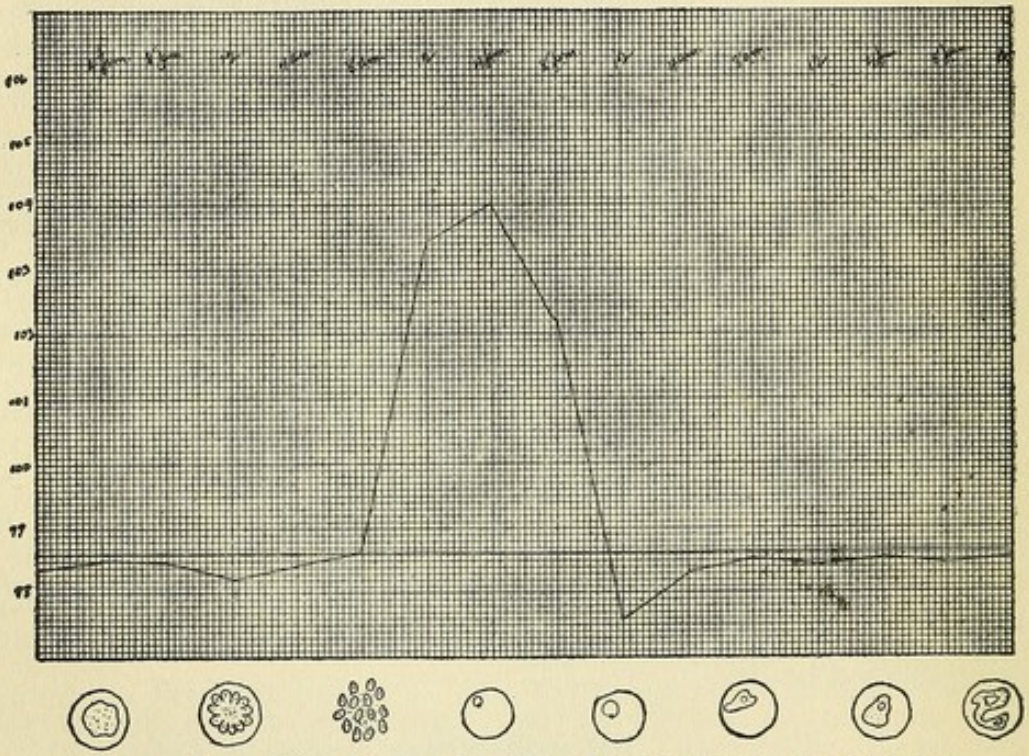


Fig. 49.—The relation between the stages of the parasite and the paroxysm.

is almost universally assumed by students of malaria. The grounds for this assumption may be recounted as follows:

1. An analogy with other infectious diseases.

2. Immunity; this immunity is not absolute, but that a relative immunity to malaria exists there is no room for doubt.

3. The formation of an antitoxin; Ford's[140] experiments being conclusive as to the existence of such.

4. Degenerative changes in the kidneys, liver, spleen, and other organs not otherwise explainable.

5. Blood changes, as anemia out of proportion to the num-

ber of parasites, and brassy degeneration, stippling, and polychromatophilia of the red cells.

6. Increased toxicity of the urine and sweat.

7. The existence of coma in malaria without parasites or pigment in the brain.

8. The fever and its relation to parasitic sporulation.

9. Experimental proof. The negative results of Gualdi,[79] Montesano,[79] Mannaberg,[141] and Celli[80] are devoid of weight against the convincing experiments of Rosenau, Parker, Francis and Beyer,[142] who demonstrated the existence in malarial blood of a poison capable of reproducing the symptoms of the disease when injected into the veins of other men. The details of their experiment with tertian malaria are reproduced as follows:

"Andrez Mendez (Case LXVI), 39 years old; born in La Luz, Estado de Guanajuato; never had fever in his native place. In 1878 had yellow fever (?) in San Antonio, Estado de Guanajuato, with which he says he was sick about one month. He came to Vera Cruz three years ago, and has had fevers five or six times since. Present illness dates from about November 3, but states that he had been troubled with mild attacks of fever for a month, which he describes as coming on alternate days, but not sufficiently severe to keep him from his work.

"The fever which initiated his present sickness began with a severe chill and was followed by fever and sweat, and was associated with some nausea and vomiting. He states that these paroxysms were repeated daily until his admission to San Sebastian Hospital, November 6, 1903.

"Blood examination showed that he had a heavy infection with tertian parasites, and he was immediately transferred to the laboratory of Working Party No. 2, Yellow Fever Institute.

"The man was physically robust, but very anemic, mucous membranes particularly pale, skin cold and damp.

"At about noon on this date (November 6) the patient was seized with a chill.

"By 12.30, half an hour later, the rigor was very marked; he

lay in bed with a blanket drawn over his head, and was shaking violently; he could not hold a thermometer in his mouth and the pulse was taken with difficulty. During this time the temperature was rapidly rising, it being now 39.1° C.

"At 12.40 blood was drawn from one of the superficial veins at the bend of the elbow. On account of the rigor there was some difficulty in introducing the needle. The blood flowed freely; 125 cc. were quickly drawn. It was permitted to flow into a porcelain dish and immediately defibrinated by whipping with sterilized forks. Clotting took place very quickly, so that the fibrin was readily and quickly separated from the fluid.

"Judging from the size of the clot and color, the fibrin had enmeshed a number of corpuscles. The defibrinated fluid showed no further tendency to clot, and on microscopical examination looked like fresh blood containing a normal number of corpuscles.

"To 25 cc. of defibrinated blood was added 25 cc. of physiological salt solution, and this diluted blood was filtered through the same Berkefield filter in the same manner as was done with the blood of Filomena Martinez. This filter when tested later, March 1, 1904, held back *Staphylococcus pyogenes aureus.*

"Nine cc. of the filtrate were injected into the right basilic vein of Louis Peredo as soon as this amount could be obtained. This injection took place at 1.40 P. M. It only took about forty minutes to defibrinate and filter the blood, which process was done as rapidly as possible.

"Stained smears of the filtrate showed no morphologic elements. The filtrate had a distinct red color.

"As a control, Jose Ojeira, at 2 P. M., was given an injection into his left basilic vein of 4 cc. of the unfiltered mixture. As the blood was diluted with equal parts of salt solution, he, therefore, received 2 cc. of Mendez's blood.

"The unfiltered mixture of defibrinated blood and salt solution, upon microscopic examination shortly after Ojeira received his injection, showed ameboid tertian organisms with dancing pigment.

"After drawing the blood from Mendez he continued to have

a chill, with a severe rigor and chattering of the teeth, accompanied by nausea and vomiting. His temperature continued to rise after the blood was drawn until it reached 40.2° C. The febrile period was followed by drowsiness and moisture of the skin.

"As will be seen by reference to the temperature chart, Mendez was kept under observation without quinine, and had another typical malarial paroxysm the next day. All the evidence in his peripheral blood, which was examined frequently, pointed to a severe double infection with the tertian parasite.

"He was then given quinine, which entirely controlled the disease and caused the complete disappearance of the parasite from his peripheral blood.

"The results caused by the injection of the blood of Andres Mendez into Peredo and Ojeira follow:

"Luis Peredo (Case LXIV), a volunteer, aged 25; born in Jalapa, State of Vera Cruz, where he has always lived. When examined at Jalapa, August 26, he was found to be physically sound; urine contained no albumin; peripheral blood showed no plasmodium.

"He was brought to Vera Cruz August 28 and taken from the station directly to the laboratory, from which time he was kept constantly within a mosquito-proof room.

"On October 27, after having been under daily observation two months, during which time he remained in normal health, he was injected with the filtered blood of Filomena Martinez, who at the time was suffering with a paroxysm of malarial fever of the estivo-autumnal type, his blood containing many young ring-forms and crescents.

"It will be noted by reference to the records of Filomena Martinez that the blood was drawn during the time of the decline of the paroxysm. It was then allowed to clot in the ice chest, the clear serum was pipetted off and diluted with an equal quantity of isotonic salt solution, and this filtered through a new Berkefield filter.

"Twenty cc. of the filtrate, which on account of the dilution represented 10 cc. of the blood serum, were injected into the left median basilic vein of Peredo.

"For further details of the manner in which the blood serum was obtained and the filtration performed, see the above records of Filomena Martinez.

"Peredo was carefully watched from the hour he was injected, but he remained in good health, and no deviation from the normal was detected.

"His temperature was taken every four hours during the night and day, both before and following the injection, as will be seen by the temperature chart. No symptoms developed.

"His blood was examined daily for plasmodium, but none was found. The result of this injection must, therefore, be considered negative.

"Ten days later he was again injected with filtered malarial blood under different circumstances, and with positive results.

"At 1.40 P. M., November 6, he was given an intravenous injection of the blood of Andres Mendez, passed through the same Berkefield filter as before. Mendez was suffering with a double tertian infection; his blood was drawn during his chill and before the height of the paroxysm, as will be seen by reference to the temperature chart.

"Thinking that allowing the blood to clot four or five hours in the ice chest in order to obtain a clear serum for filtration might be too severe a tax upon the vitality of the malarial parasite, we this time defibrinated the blood as quickly as possible, diluted it as before with an equal volume of physiologic salt solution, and filtered it through the same Berkefield filter in the same manner as was done with blood of Filomena Martinez.

"As soon as 9 cc. of the filtrate could be obtained it was injected into the basilic vein of the right arm of Louis Peredo. This injection took place at 1.40 P. M.

"About thirty-five minutes after receiving the injection he began having chilly sensations and headaches, and presently went to bed, covering himself with his blanket (2.25 P. M.). Five minutes later he was having a violent chill, his teeth chattering so that we could not trust the thermometer in his mouth. The rigor of the entire body was so marked that there was

difficulty in taking the radial pulse. The face was pale, and at this time he vomited most of the dinner he had eaten a short time before receiving the injection.

"The patient complained of headache, which he localized at the forehead and occiput; says he felt cold and had pains in the knees. At this time the skin was dry. The chill lasted somewhat over half an hour.

"At 3 P. M. the patient had transient chilly creeps, very slight rigor.

"At 3.15 P. M. he said he felt 'warm inside,' and all sense of chilliness had disappeared; still his headache.

"At 3.25 P. M. he complained of marked pain in his legs.

"At 3.30 P. M. he vomited the remainder of his dinner.

"It will be seen from the temperature chart that during this time his temperature was rapidly rising, and reached its highest point (38.7° C.) at 4 P. M., just two hours and twenty minutes after receiving the injection.

"The pains in the knees and back continued, and nausea and vomiting now became a distressing feature of the paroxysms for the patient.

"The fever gradually subsided, and reached normal at 4.30 A. M. the next morning.

"As the fever subsided the skin became moist, the nausea and pains gradually disappeared, so that by 6 P. M. the patient was quiet and dozing. The entire paroxysm, therefore, according to the temperature record, lasted about eight hours, although the patient was sleeping quietly five hours after receiving the injection.

"It is interesting to note that this man (Pedro) had what seemed to be a typical malarial paroxysm, beginning with a distinct rigor associated with a rise of temperature and followed by slight sweating. It is of particular interest to note that his paroxysm, so far as symptoms were concerned, was very much like the paroxysm from which Andres Mendez suffered, especially the nausea and vomiting.

"Pedro was kept under very close scrutiny until November 24, eighteen days following the injection, during which time he remained entirely normal and no plasmodium appeared in

his peripheral blood, which was frequently examined, as follows:

"November 6—4.30 P. M., 8 P. M. No malaria.

"November 7—4.30 A. M., 8.30 A. M., 12.30 P. M., 5 P. M., 11 P. M. No malaria.

"November 8—7 A. M., 1 P. M., 6 P. M., 9.30 P. M. No malaria.

"November 9—7.30 A. M., 1.30 P. M. No malaria.

"November 10—2 A. M., 3.30 P. M., 8 P. M., five minutes each. No malaria.

"November 11—4, 7, 10 A. M., 2, 6, 11 P. M., five minutes each. No malaria.

"November 12—1.30, 6.25 A. M., five minutes each. No malaria.

"November 13—7 A. M., 9.30 P. M., five minutes each. No malaria.

"November 14—8 A. M., 8 P. M., five minutes each. No malaria.

"November 15—8 A. M., 8.30 P. M., five minutes each. No malaria.

"November 16—7 A. M., 9.30 P. M., five minutes each. No malaria.

"November 17—8 A. M., 8 P. M., five minutes each. No malaria.

"Jose Ojeira (Case XXIII), a volunteer from Jalapa, 18 years old; he had never lived on the coast, and says that he never had fever of any kind. On examination in Jalapa, August 11, he was found to be physically sound, of robust physique; urine showed no albumin, and blood examination for malaria was negative.

"He was taken to Vera Cruz August 13 and immediately transferred to a mosquito-proof room in the laboratory, where he was kept under close observation.

"On August 28, at 9.30 A. M., he was bitten by four mosquitoes, two of which had bitten Antonio Leal (Case XXXV), a yellow-fever patient, fifteen days seventeen hours previously, and the other two had bitten the same case fourteen days twenty-three hours previously.

"The man was kept under close observation in a mosquito-proof room, but showed no reaction. There was no rise of temperature, nor did he present any untoward symptoms.

"On October 27, 7 P. M., he received intravenously 20 cc. of

diluted blood serum of Filomena Martinez (estivo-autumnal infection), passed through a Pasteur-Chamberland filter B. This represented 10 cc. of blood serum. For details of this filtration see Filomena Martinez.

"Ojeira showed no reaction whatever as a result of this injection.

"It will be noted that the blood of Martinez was drawn after the height of the paroxysm and while the temperature was on the decline.

"Martinez was suffering with a very severe estivo-autumnal infection at the time the blood was taken.

"Ojeira's blood was examined several times daily, both before and following this experiment, and at no time was anything resembling a malarial parasite seen in his peripheral blood.

"On November 6, the patient having continued in good health since the last experiment was used as a control for the experiment made on Peredo.

"On this date, at 2 P. M., he was given an intravenous injection of 4 cc. of the unfiltered, diluted, and defibrinated blood of Andres Mendez. At the time the blood was drawn from Mendez it contained a heavy infection of double tertian malaria, and the blood was taken from him during a chill and before the height of his paroxysm. It was at once defibrinated, diluted with an equal volume of physiologic salt solution and filtered through a Berkefeld filter. Nine cc. of the filtrate were given intravenously to Peredo, causing a malarial paroxysm without, however, the presence of the malarial parasite, and due, as we believe, to the toxin (?) in the blood of Mendez.

"Ojeira, who received 2 cc. of unfiltered blood (4 cc. dilution), reacted within an hour, with a slight rise of temperature and nausea, and four days following developed a typical malarial paroxysm, with many tertian parasites in the peripheral blood.

"There can be no doubt that the reaction to the 2 cc. of defibrinated blood injected into the vein of Ojeira caused a slight paroxysm, which it is reasonable to suppose was due to the same poison present in the blood of Mendez, and which also caused the reaction in Peredo.

"It will be noticed that 2 cc. of this blood caused but a slight reaction in the case of Ojeira, while 4.5 cc. caused a more marked reaction, with a rise of temperature to 38.7° C. in the case of Peredo, indicating in a very definite manner that the severity of the symptoms were directly due to the quantity of poison introduced. Ojeira did not have a chill or other manifestations of a malarial paroxysm other than a rise of temperature and nausea. He vomited gastric mucus several times.

"On November 10, the fourth day following the injection, Ojeira had a typical malarial paroxysm, with tertian parasites in his peripheral blood. He suffered with a double infection, having a chill every day, as will be noticed by reference to the temperature chart.

"The character of the parasites in his blood and the clinical course of the disease resembled in all respects those of Mendez, from whom the blood was taken. Both cases were entirely controlled by quinine."

The parasites of tertian and quartan infections develop uniformly, one generation at a time, hence typical paroxysms are the rule. Sometimes, it is true, sporulating forms are met with between the accesses, but a certain dose of toxin is necessary to excite a fit. The estivo-autumnal parasites, on the other hand, do not sporulate so uniformly, hence the poison is liberated in broken doses and typical paroxysms are more frequently lacking and the fever more continuous or irregular. If sporulation occurred more nearly simultaneously, as in the tertian and quartan forms of malaria, it is probable that the sudden discharge of the more highly poisonous estivo-autumnal toxin would be more often attended with serious consequences. The uniform sporulation of the tertian and quartan parasites may be likened to a body of soldiers firing by volleys, while that of the estivo-autumnal parasites is similar to soldiers firing at will.

The change of type of malarial attacks has been used as an argument for the unity of the malarial parasites. It is well known, however, that such occurrences are best explained by a number of different species. Quotidian malarial parox-

ysms due to two generations of tertian organisms may become tertian in character by the destruction of one generation. Quotidian paroxysms due to a triple quartan infection may become quartan or double quartan by the death of two generations or of a single generation of parasites. On the contrary, tertian and quartan accesses may become quotidian by the development into activity of one or two additional generations.

It is remarkable in multiple infections by different generations of the same species of parasite that they almost always sporulate on different days and very often about the same time each day. Thus it is very rare in double tertian infections that two paroxysms should occur within one day followed by a fever-free day. This is probably best explained by the mode of infection. It is known that the malarial mosquitoes feed almost solely at night and usually only once during the night. If a subject is inoculated by the mosquito on two successive nights it is obvious that the parasite would become mature with an interval of about twenty-four hours between the generations. If inoculation should occur upon three or more successive nights it is probable that the third and succeeding generations would sporulate, after incubation, simultaneously with the first and second. The interval between multiple quartan infections may be explained similarly.

Latency and relapses were formerly explained upon the theory that so long as the parasites remained below a certain level of asexual reproduction the disease was latent, and when the parasites exceeded in number this level a relapse occurred. Sims has estimated the greatest number of adult parasites which the body can endure without symptoms as about two billions. It is probable that brief periods of latency may be thus explained, especially in persons possessing a relative immunity, but it is evident that this is not a common mode, particularly of relapses at long intervals, since the asexual cycle is known to wear out spontaneously after certain periods. These relapses at long intervals can be explained by parthenogenesis alone. After the schizonts have perished, while the microgametocytes do not persist long, the macrogametes remain for indefinite periods. They may sporulate more or less

regularly, causing paroxysms at intervals of about a week, or multiples thereof, or may lie dormant until aroused into reproductive activity by exposure or dietary or other excesses. It is highly probable that the parthenogenetic cycle of reproduction is conducted almost altogether in the visceral circulation, particularly in the spleen. As evidence of this may be cited the outbreaks of malaria following cold douching, electrical stimulation, and trauma of the splenic region.

The anemia of malaria depends upon three factors: 1, the mechanical destruction of cells by the parasites; 2, the effect of toxins, and, 3, the activity of the blood-making organs. Liberated hemoglobin is transformed by the liver into bile pigment. When the hemoglobin is liberated too fast for the liver to utilize, hemoglobinemia results, and hemosiderin is precipitated from the blood. The increased activity of the liver results in polycholia and icterus. It is probable that jaundice is due also when the liver capacity is overtaxed to hemoglobinemia. When hemoglobinemia exceeds a certain limit the hemoglobin is excreted by the kidneys, resulting in hemoglobinuria.

Splenic enlargement is effected through hyperemia, deposition of detritus of destroyed erythrocytes, accumulation of parasites, and hyperplasia of the pulp.

Spontaneous cure is probably due to the natural weakening of the reproductive powers of the parasite, a phenomenon occurring in strains throughout the vegetable and animal kingdoms, and possibly also to the influence of an antitoxin. Phagocytosis plays, in the opinion of the writer, a much less prominent rôle than is usually attributed to it. It is probable that this function is exercised mainly after the parasites have lost vitality from other causes.

ETIOLOGY OF PERNICIOUS MALARIA

Pernicious malaria is that form of malaria so acute that, independently of complications, life is endangered in a few hours or a few days. This gravity may be due to the intensification of ordinary malarial symptoms or to the advent of unusual ones. It should be clearly understood that pernicious

fever is not a pathologic entity, but is a form of malaria, from the simple modes of which it sometimes differs only in degree.

In America pernicious malaria is rarely seen in the adult negro, by far the greater number of cases occurring in this race being in children under ten. This coincides with the experience of those who have practised among the blacks of Africa. It is not common among the natives of Algeria or Arabia. The natives of India are not immune, and the Chinese are very susceptible. Koch[143] relates that of 273 Chinese imported from Hong Kong to Stephansort in 1898, 125 died within the course of a year, mostly of malaria.

More cases occur in males than in females. This is not because of greater susceptibility, but on account of more frequent exposure of the male sex. Crespin[144] believes that pregnancy may render pernicious attacks that have no grave tendencies. Bell[145] reports a case of comatose malaria in a Chinese woman who was eight months pregnant. Premature delivery occurred on the second day, the child being dead, and the mother died on the seventh day. Dos Santos[146] describes a case of algid malaria in a woman, age twenty-seven, six months pregnant. Abortion occurred thirty-six hours after onset of the attack. The placenta was enormous. The woman recovered. Ten months later the same woman was assailed with a similar attack while six months pregnant. She aborted again and made a good recovery.

Children are prone to pernicious attacks, especially of the cerebral type. Sixty-nine cases observed by Martirano[147] give the following age distribution:

Under nine months	6
One year old	19
Two years old	12
From three to four years	8
From five to ten years	5
From ten to thirty years	5
From thirty to seventy years	14
	69

In another series of 25 under Martirano's[147] care, 13 were children and 12 were adults. In 31 cases of Tanzarella,[84] 19

were under ten years of age and 12 older. Caccini's[147] 99 cases show an unusually small per cent. in children, only 14 cases occurring in children under ten years of age.

The convulsive form is relatively frequent in children living in highly malarial countries. According to Thornhill,[148] in Ceylon during 1896, 40.52 per cent. of children dying under one year of age died of convulsions, most of which were due to malaria. Speaking of pernicious malaria in British Malaya, Travers says: "The infant mortality on some estates, where the coolies suffer much from fever, is terribly high. I know of one estate (since abandoned) on which a large Tamil labor force was employed where all the infants died. The manager offered a reward for the first child successfully reared on the estate, but that reward, I believe, was never claimed."

Convulsive pernicious is apt to attack children with nervous predisposition, either hereditary or acquired. It is rare in adults, though Maurel, Reynaud, and Duberge have seen such cases.[86] The aged are more susceptible to comatose attacks.

In the Southern States pernicious malaria is more prevalent at the height of the malarial seasons, especially in July, August, and September. In Southern Europe and in Algiers the season is said to be from July to November. In Greece cases appear in July are most frequent in autumn, and are rare in winter. In India it is at the acme of the malarial season that these attacks occur.

Eleven hundred and one cases from various sources are distributed as follows:

	Candé,[149] Cochin China.	Martirano,[150] Italy.	Tanzarella,[84] Italy.	Billett,[151] Algeria.	Caccini,[147] Italy.	Martirano,[147] Italy (1901).	Total.
January	39	..	1	..	..	..	40
February	43	..	..	..	..	..	43
March	80	..	..	..	..	..	80
April	99	..	1	..	..	..	100
May	110	..	1	1	..	..	112
June	126	..	2	1	1	..	130
July	115	1	8	2	4	5	135
August	79	5	10	11	18	25	148
September	54	10	3	13	7	21	108
October	52	5	2	12	12	7	90
November	47	4	3	..	12	6	72
December	36	..	..	..	2	5	43
Total	880	25	31	40	56	69	1101

The influence of inundations on the etiology of pernicious fever is well recognized. In 1826 Johnson[16] wrote: "There is no unmixed good in this world. The inundations of the Nile and the Ganges, while they scatter fertility over the valley of Egypt and the plains of Bengal, sow with a liberal hand at the same time the seeds of dreadful diseases." This is in all probability true of the Mississippi and other large rivers of our country. In 1854 Frerichs recorded an epidemic of pernicious malaria following an overflow of the Oder where there had previously been only mild cases of malaria.

The length of residence in a malarial region is probably not an important factor in the etiology of the affection. While Sims[152] and others believe that it occurs mainly in the early period of residence, most of Maurel's[75] cases were in persons who had been in the colony a long time. Plehn[5] mentions the case of a young physician who died of pernicious malaria six days after arrival at Banana.

Maurel[75] states that outbreaks of pernicious malaria may occur several years after return to France from the tropics, and without new infection. During and shortly after the war with Spain numerous cases which were infected in Cuba and the Philippines were treated in American hospitals. Rees[153] records the case of a man who had spent only five days in an endemic region and developed comatose malaria with fatal termination in a few weeks after his return to London. Satterlee,[154] Hall,[155] Neer,[156] and others have observed similar cases in America. In the majority of such cases the outbreak occurs within a few weeks after leaving the endemic area.

Occupations which subject not only to malarial infection, but to hardships and exposure, especially to the sun, predispose to pernicious attacks. Manson[59] cites the case of Hong Kong, formerly healthy enough, but when barracks and houses were being built and roads laid out the soldiers died by the hundred of pernicious fevers. Homem[157] asserts that these cases occur in Rio de Janeiro, particularly when the sewerage, gas, and water companies are making deep and extensive excavations in the more central streets of the city. Early in the last century, when the marsh of Chartreuse, near Bordeaux, was drained,

an epidemic of severe malaria prevailed, and in 1805 12,000 people were stricken, of whom 3,000 died in five months.

As it is especially in the laboring and poorer classes that primary infections do not receive adequate treatment, it is largely in this class that pernicious attacks are found.

Pernicious attacks may be first attacks or they may occur in cachectics, but it is chiefly between these extremes that most attacks originate, namely, in those having had previous attacks of malaria, but who are not saturated to the degree of cachexia. Laveran,[1] Marchiafava and Bignami,[22] and Sambon[9] have never seen pernicious attacks without previous malaria. Ruge,[158] however, states that such cases are not uncommon in India and both the east and west coasts of Africa. Colin and Antoniades have observed like cases.[159] Wurtz and Thiroux[160] say that the typhoid form is most often a fever of first invasion. Roux[161] knows of numerous examples of pernicious fever as the first manifestation of malaria. Mannaberg[141] asserts that it may attack those who have never before suffered from malaria, as well as those who have undergone repeated attacks. Homem[157] says that in many cases the pernicious paroxysm is preceded by simple ones; in others the patient is attacked while in perfect health. It is the comatose form that is most frequently seen in those who have not previously been attacked with malaria. Crespin's[144] experience is that the attacks are exceptional in chronic malarials. Smart[76] records it that during the Civil War pernicious attacks occurred not only in persons who were for the first time exposed to a highly malarial atmosphere, but also among those who had suffered more or less from the malarial influence before the superventionof the congestive seizure. In 50 cases observed by Cardamatis and Diamessis[35] only one developed as a primary attack Most of the algid and comatose cases of Maurel were in subjects of chronic malaria. Thayer[98] and Craig[70] say that it is customary for malarial paroxysms to precede. Schellong[92] agrees with Martin that pernicious fever attacks persons already rendered anemic from malaria.

While it is probably true that in the majority of instances typical paroxysms precede pernicious attacks, it is of the utmost

importance to bear in mind that the latter may be manifestations of first invasion. "If there are cases of pernicious fever, in which the patient has been attacked previously by paroxysms of simple, well-marked or masked intermittent, there are also cases, unhappily numerous, in which it is the pernicious attack that opens the scene, where the subject, in the enjoyment of the most flourishing health, is treacherously assailed by the terrible enemy without the least signal to warn of the enormous peril awaiting him." (Homem.)

Pernicious malaria is almost as varied in pathogenesis as it is in manifestations. Not only are its several forms associated with unlike conditions, but for the explanation of some the presence of several different factors is necessary. Thus comatose malaria may be associated with at least two different forms of the parasite; the peripheral blood may show very great numbers of these parasites or they may be scanty; in the brain they may be found in hordes, even to the occlusion of small vessels, or they may be entirely absent.

As may be inferred, no one etiologic element can account for all cases, even of the same type. Probably the only essentially common factor is the presence of the malarial parasite, the manifestations of which run the gamut from the mildest intermittent to the profoundest cachexia, from the most artfully masked to the deadliest pernicious.

Until comparatively recently it was believed that infections with the so-called benign organisms never gave rise to pernicious symptoms. Celli[80] states that the tertian and quartan parasites never cause pernicious fevers. Marchiafava and Bignami[162] say that there is no instance on record of a malignant fever following tertian and quartan infections, and that no autopsy has ever been made in connection with a malignant spring tertian or quartan. Mannaberg,[141] Van der Scheer,[163] and Maurer[135] believe that only the estivo-autumnal parasites have a rôle in the production of the pernicious fevers. Thayer, in his "Lectures on the Malarial Fevers," says that he never heard of a pernicious paroxysm occurring in tertian or quartan infections, with the exception of the case of French.

While the vast majority of cases of pernicious malaria are

due to the infection with the tropical parasites, it cannot now be maintained that tertian and quartan infections are not occasionally accompanied by perniciousness. Craig[164] says that any of the malarial parasites may cause pernicious infections, leading to death. Crespin[165] informs us that it is not rare to find on examination tertian and quartan parasites in these cases. Billet[151] found the large tertian in 6 of 40 cases of typhoid pernicious. Ziemann[96] observed a case of pernicious malaria due to the benign tertian. Thiroux[86] found this parasite in a case of convulsive pernicious in a mulatto infant. Ewing,[27] in 64 cases of the cerebral type of pernicious, found the large tertian parasite alone in 5. French[166] reports a case of comatose malaria in a man, aged twenty-one, whose blood harbored the tertian parasite. Hunt[167] observed a case of common tertian complicated by alarming hematemesis in a boy aged eleven. McElroy[168] had a case of comatose pernicious due to tertian infection in a negro male, aged thirty. Ficucci[169] records a case with a pernicious meningo-cerebellar syndrome due to tertian parasites. Fenner[170] gives the history of a case of the comatose type in an adult; the blood examinations showed crescents and large tertian forms.

Craig[164] makes the assertion that quartan infections are more apt to become pernicious than tertian. The writer, however, agrees with Davidson,[66] who says that pernicious symptoms occur more rarely in connection with the quartan infections than with simple tertian. The reasons for this are probably the relative rarity of quartan fever and the more even distribution of parasites throughout the circulation, there being slight tendency to form accumulations.

It is not yet known with certainty which variety of the estivo-autumnal parasite gives rise most frequently to perniciousness. Marchiafava and Bignami[162] and Mannaberg[141] hold that the tertian estivo-autumnal infections are the most dangerous, only a few cases showing the quotidian. Craig,[70] however, found the quotidian parasite most often in cases infected in Cuba and in the Philippines. This was also the experience of Wright[38] in British Malaya, who found the pigmented

quotidian parasite most frequently associated with the cerebral and gastro-intestinal types of pernicious malaria.

The part played by the crescents in the pathogenesis of pernicious paroxysms is worthy of brief consideration. Marchiafava and Bignami,[22] Celli,[80] Mannaberg,[141] A. Plehn,[171] Koch, [172] Manson,[59] Thayer,[98] and others believe that this form of the organism is non-pyrogenic. Ewing,[130] however, holds, with Laveran, that it is by no means certain that the formation and development of the crescents are entirely innocuous to the patient. Ewing, doubtless in part, bases this opinion on the finding of crescents alone in 33 of 64 cases of cerebral pernicious.[27] Whether the blood examined in these cases was peripheral or visceral is not stated, but as only three were fatal it may fairly be assumed that in most instances at least it was peripheral. That the crescentic form of the parasite has an intimate relation to the production of the pernicious fevers is improbable, for the following reasons: First, crescents alone may be found in the peripheral blood, and intense localization of active forms be present in the brain or other viscera. The number of parasites in the superficial circulation is not a reliable guide to the severity of the attack. Of Ewing's 64 cerebral cases no parasites were identified in 11, and in many of his 33 cases in which crescents alone were found the search was successful only after one and two hours. Second, crescents are rarely, if ever, present in the parasitic localizations and thrombi frequently observed in pernicious cases.

Of the pathogenetic factors which excite perniciousness the following are to be regarded as the most important and approximately of relatively equal importance:

1. An excessive number of parasites.
2. Localizations of parasites.
3. Toxins.
4. Individual predisposition and external etiologic influences.

Number of Parasites.—Golgi's law, that the number of parasites determines the severity of the attack, has been generally accepted. Cases in which the parasites are in very great numbers in the peripheral blood are usually accompanied by coma.

We have no means of estimating even approximately the total number of malarial parasites in the body of a malarial patient, as the distribution of the former varies within the widest limits. They may be numerous in the peripheral and visceral circulation generally; they may be scanty or absent in the peripheral circulation and numerous in most of the viscera; or they may exist in moderate numbers or be absent except in certain areas where they may be intensively localized. That the parasites are abundant, either absolutely in the body as a whole or relatively in certain areas, probably holds good in a great majority of the cases, though, as Celli[80] states, we cannot always attribute perniciousness to the large number of parasitic forms. Marchiafava and Bignami[22] call attention to certain grave cases of comatose, convulsive, delirious or mixed pernicious, in which from beginning to end and even at autopsy very few parasites are found. Mannaberg[141] says: "From the general impression which I have obtained naturally from the peripheral blood, the number in malignant fevers is perhaps larger, yet the difference scarcely seems so decided as to make this factor alone responsible for the perniciousness."

As applied to the number of parasites in the peripheral blood, Golgi's rule is applicable only in a very general sense. Bacelli[173] says that fatal cases of malaria occur in which there cannot be found any known form of the parasite.

Ziemann[48] states that the number of parasites in the peripheral blood is not always in direct relation to the severity of the attack. Crespin[144] acknowledges that he had difficulty in finding the parasites, which were always scanty in these cases. He gives the details of a case in which there were neither parasites nor pigment in the peripheral blood, but they were numerous in the vessels of certain viscera. This writer quotes Nocht as saying: "In pernicious attacks the hematozoa are not found in the peripheral blood, but only in the viscera." Moore[25] says: "I have often seen cases where the symptoms in no wise seemed commensurate with the number of parasites observed in the specimen of blood." According to Kendall,[30] there may be only a few parasites in the peripheral circulation, or it may be even impossible to find them. Mannaberg[141] states

that it sometimes happens that the peripheral blood is very poor in parasites. Marchiafava and Bignami[22] note the fact that the contradiction found so often during life between the number of the parasites and the gravity of the disease disappears when an autopsy allows of an examination of all the organs. Craig[70] asserts "that the number of the parasites found in the peripheral blood is not always a criterion as to the perniciousness, as one of the most rapidly fatal cases I have ever observed showed but few parasites in the peripheral blood." To quote Barker:[174] "In the estivo-autumnal infections the number of organisms circulating in the peripheral parts affords, as a rule, very insufficient data upon which to base an idea of the severity of the infection." Thayer[98] says that there may be very few parasites in the peripheral circulation. He mentions a fatal case of the comatose variety showing no active parasites in the peripheral blood and only a few ovoids and crescents after a careful search of the blood, obtained by puncture of the spleen. Marchoux[105] reported 3 cases of pernicious malaria in which the parasites were very scanty in the peripheral circulation. Zeri[175] records 4 cases of pernicious fever in all of which the parasites were few in number. Bloombergh and Coffin[176] treated a case ending fatally in which no parasites could be found until forty-eight hours after onset, notwithstanding repeated examinations. In 7 cases in which Fenner[170] examined the blood no parasites were found in 5. Ewing's[27] 11 cases of the comatose form, in which no parasites were identified, have been mentioned. The writer has observed 1 case of severe comatose malaria in a boy, aged twelve, in whose peripheral blood the parasites were scanty.

On the other hand, the superficial circulation may be teeming with parasites, while the patient experiences only a mild attack. Thus A. Plehn[99] gives the histories of 2 cases in which the symptoms were slight though the peripheral blood showed as many as thirty-five and forty-six tropic parasites, respectively, to each field of the microscope.

It is highly probable that an enormous number of parasites, equally distributed, depends for their power to elicit pernicious symptoms upon the increased quantity of toxin elaborated.

Localizations of Parasites.—Accumulations of parasites in the brain were first described by Planer (1854), and by Frerichs (1861); those in the liver by Guarnieri (1867). More recently the minute observations of Marchiafava and Bignami, Dock, Barker and Ewing have taught us that pernicious malaria, in many of its varied manifestations, is dependent on these localizations in one or more of a multiplicity of localities. Localizations in the brain have been found associated with a wide variety of cerebral symptoms; in the mucosa of the alimentary tract, the gastro-intestinal symptoms, and typical algid attacks; in the heart, with cardiac symptoms; in the medulla, with bulbar paralysis; in the retina, with amblyopia; in the pancreas, with hemorrhagic pancreatitis, etc. In proportion to the amount of damage sustained by the kidneys in malaria there is less tendency for parasites in pernicious attacks to accumulate in these organs than in any other of the body. The most carefully studied case of this condition is that of Ewing.[177]

These localizations consist, in the main, of parasite-infected red blood-cells. There may be, however, pigmented leucocytes and free parasites and pigment. The parasites in each particular case may be of the same or of different stages of development. The pigmented and sporulating forms are probably oftenest seen, but the earlier phases are frequently observed. It would seem reasonable that the crescents, on account of their size, would frequently form an important element in these accumulations of parasites, but such does not appear to be the case.

The cause of the parasitic concentrations is problematical. It cannot be due to the size, weight or loss of elasticity of the infected cells, for, as Mannaberg[141] states, the benign parasite would be more apt to form thrombi if this were the cause. Kelsch and Kiener[178] and others have observed endothelial swellings in the small cerebral vessels, with consequent constriction of calibre, but whether this is a cause or an effect cannot be said. Vasomotor disturbances and phagocytosis have also been invoked in explanation. The most probable theory is that of Mannaberg,[141] who attributes the condition to a sort of agglutination or adhesiveness that holds the erythrocytes to the vessel walls.

The symptoms present in cases in which, on post-mortem examination, localizations of parasites are demonstrated are not always referable to these aggregations alone, since changes are frequently observed which are secondary to parasitic thrombosis, and may outweigh the latter in pathogenic importance.

The most conspicuous of these changes are perivascular exudation, hemorrhage and necrosis. The hemorrhages are usually punctate, but Blanc[179] and Ziemann[48] report large cerebral clots.

This propensity of the parasites in pernicious fever to congregate undoubtedly explains the course of many cases, but by no means all. Fatal cases of comatose malaria have been observed with no parasites at all in the brain. Ford[180] reports a case with serious pulmonary symptoms in which the parasites were no more numerous in the lung than in the general circulation. "The severity of the renal lesion, with the absence of parasites in the renal vessels, also requires mention."[181]

It is not known whether parasitic thrombi may exist without producing symptoms. Frerichs,[96] who frequently observed thrombotic occlusions of the cerebral vessels, insisted that too much stress should not be laid on them on account of the rich collateral circulation. He likewise affirmed that he had more than once seen markedly pigmented brains without cerebral symptoms during life.

Based on a case in which the patient was suddenly attacked with transient coma three times in five days, Ewing[181] believes that the embolic processes are factors in some instances.

This is the most probable explanation of these cases.

Toxins.—The evidence of the existence of a toxin in malaria has been detailed above.

Individual Predisposition and External Etiologic Influences.—"We ought, then, in cases of pernicious fever, to seek in the conditions of the ground, whose quality is so different, and not in the quantity of the seed, the reason which shall explain to us the gravity of the disease."[157]

The quality of the soil, in the sense so aptly employed by Homem, as a factor in the pathogenesis of pernicious malaria has probably not received the attention it deserves. This influ-

ence, in many instances, doubtless not only induces the attack, but determines its type. Organs or systems enfeebled by antecedent ailments are apt to play the title rôle in the pernicious tragedy. Thus algid and choleraic attacks may be associated with a history of intestinal catarrh; the comatose and delirious cases, with a history of abuse of alcohol; the convulsive with epilepsy, etc. It is not improbable that some cases of dysenteric, cardialgic, syncopal, tetanic, cataleptic, paralytic, pneumonic, pleuritic, gastralgic, and other forms described by the older writers may be similarly explained. Mercier[182] goes so far as to say that all pernicious attacks are merely visceral complications.

Malarial subjects who are much exposed to the heat of the sun are liable to be stricken with pernicious fever, especially of the cerebral type. This danger is enhanced if to the solar heat are added fatigue, deficient or improper food, or other hardships. Certain psychic states have causative significance. Hertz[183] states that he has seen the localization of pernicious symptoms determined by injuries of the skull through a fall or a blow.

In addition to the four principal factors enumerated, congestion of viscera and parasitic obstruction of the hepatic capillaries have been regarded as important. It is probable that they have little influence.

A feeble phagocytic activity was considered by Golgi as predisposing to pernicious attacks. In the present state of our knowledge it is impossible to define the relation of this function to perniciousness.

A consideration of the relative frequency with which the several factors are concerned in the pathogenesis of the various forms of pernicious malaria will necessarily be brief. In the comatose variety any of the four chief agents may take part; idiosyncrasy and external influences may unite with any of the other factors; an extraordinary number of parasites in the general circulation, without accumulations in the brain, is productive of coma probably because of the toxin. Ewing[181] says that the majority of cases of comatose malaria coming to autopsy do not show a massing of parasites in the brain. He

attributes these cases to general toxemia. However, a study of the autopsy records of Marchiafava and Bignami[162] shows that in a great majority of their fatal comatose cases the parasites were markedly localized in the brain. Davidson[66] and Ruge[158] believe that almost always the cerebral capillaries are found filled with parasites in those who have died with coma.

Other pernicious cerebral forms are usually associated with parasitic localizations.

The algid variety, while possibly sometimes dependent on toxemia, is usually due to a massing of parasites in the gastro-intestinal mucosa. This is explained by Davidson[66] as follows: "Experiments show that the alimentary tract is in closer connection with the cardio-inhibitory center than other parts of the body, and that irritation of this tract, if sufficiently powerful, will produce cardiac inhibition, with pallor of the surface and accumulation of the blood in the abdominal vessels. That the intestinal canal is the center of mischief in this form of pernicious attack will appear all the more probable if we observe the character of the disturbances so frequently associated with the algid condition—the cardialgic pain, the choleraic vomiting and purging, and the dysenteric discharges."

ETIOLOGY OF HEMOGLOBINURIC FEVER

Etiologically hemoglobinuric fever stands in the same relation to malaria as do tabes and dementia paralytica to syphilis, and may, very properly, be regarded as a "paramalarial" infection.

Among the conditions other than blackwater fever under which hemoglobinuria can occur may be mentioned paroxysmal hemoglobinuria, scarlet fever, typhus and typhoid fevers, acute articular rheumatism, leukemia, pneumonia, streptococcus infection, chronic suppurative conditions, after extensive burns or freezing, occasional injuries, rupture of ectopic pregnancy, transfusion of blood, injection of tuberculin, poisoning with phenocoll, guaiacol, pirodin, salipyrin, salicylic acid, antipyrin, sulphonal, the salts of chloric acid, phenol, pyrogallic acid, sulphuric, nitric, and hydrochloric acids, naphthol, analine, chrysarobin, toluylendiamin, glycerine, nitrobenzol, potassium chlo-

rate, phenacetin, arseniuretted hydrogen, methylene blue, phosphorus, oxalic acid, certain illuminating gases, helvella esculenta, and snake venom. Hemoglobinuria is a common symptom of Texas fever in cattle, and is seen occasionally in sheep, dogs, goats, horses, and mules, following infection with hematozoa resembling the malarial parasite.

Race.—Hemoglobinuric fever is chiefly a disease of the white race. The negro is not absolutely immune, though not a few observers of wide experience have not seen cases in this race. This relative immunity can be explained only by natural selection. It varies markedly in different tribes, and members of an insusceptible tribe may be attacked on moving to a blackwater fever focus. F. Plehn[5] refers to an extensive outbreak that occurred among the Cameroon negroes, especially those who came from the interior to the coast. According to Dryepondt,[86] the negroes recruited for the Congo Free State in 1890 to 1892 paid a large tribute to this malady. DeGreny[8] saw 20 cases in negroes imported from the British Antilles for railroad construction work on the lower Congo. In the medical report from German East Africa for the official year, 1903-4, there were listed 8 cases in negroes. Corre,[8] Donny,[8] the younger Moncorvo,[8] Hanley,[184] A. Plehn,[99] Rudolph Plehn,[185] Wittrock,[49] Brunn,[49] Curry,[186] Eyles,[101] Doering,[187] Reynolds,[188] Easmon,[101] Wicke,[90] Gaertner,[90] Quartey-Papafio,[101] O'Sullivan-Beare,[90] Vieth,[90] Goltman and Krauss,[189] McElroy,[190] Bérenger-Féraud,[191] Ziemann,[86] Fisch,[191] Ollwig,[51] Greisert,[51] Lewis,[192] Francez,[193] Minor,[194] McKay,[195] Tyson,[196] Gorgas,[32] and Wendland[49] have seen cases in negroes. The writer has seen two cases in mulattoes and two in black negroes. Chinese imported into blackwater fever regions are almost as susceptible as whites. Manson[59] says that many of the Chinese laborers on the Congo railway died of hemoglobinuric fever. Imported Indians are affected, but, according to Daniels,[197] are only about one-fourth as susceptible as Europeans. As may be inferred from one of the names, "fièvre jaune des creoles," creoles are not infrequently attacked. Masterman[64] reports that it is common among the Jews of Palestine. Rothschuh[8] saw cases in mixed breeds and pure Indians in Nicaragua.

Sex.—Males are more often stricken than females, the latter being less often exposed to malarial infection. In the temperate zone the proportion of males to females is about 3 to 1. In persons under fifteen the proportion is more nearly equal. As we approach the equator the difference becomes wider, owing to the relatively small number of susceptible females and children. Daniels[57] says the proportion of male to female cases in British Central Africa is 15 to 1. Cardamatis[198] believed that pregnancy conferred immunity; however, Krauss[199] has reported a case in a pregnant woman, who made a tedious recovery after abortion. The writer[200] recently published brief notes of a case occurring in the practice of a colleague. The woman aborted on the third day of the disease and died on the fourth. Cases have often been observed to follow immediately after menstruation.

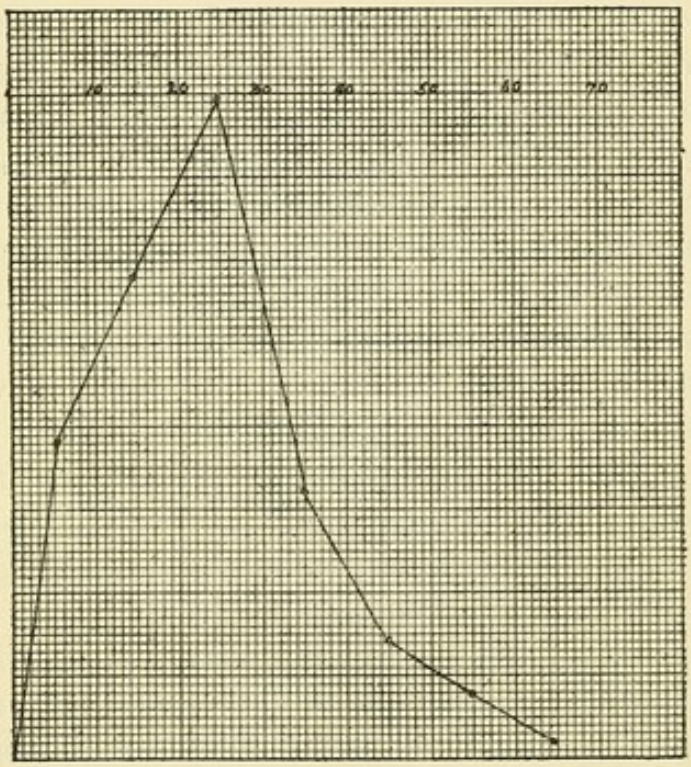


Fig. 50.—Age distribution of blackwater fever in America.

Age.—In America more than half the cases occur before the age of thirty, though very young children are relatively exempt. In the tropics it is commoner in the third and fourth

decades of life because most of the susceptible population is within these ages. Daniels[57] saw a case in a half-caste about five years old; Wendland,[49] Van der Scheer,[201] and Karamitsas[15] observed cases in children of four; Lipari[202] mentions 2 cases in children of three; Masterman[64] 1 in a girl of two, and Oetker[52] 1 in a two-year-old child; Fisch[203] saw cases in children of fourteen months and two and one-half years, and McElroy[204] 1 at twelve months.

Season.—In the tropics, like malaria, it is perennial, occurring without marked seasonal prevalence, though probably commoner in the transition period from the moist to the dry season. In the temperate zone it appears at the height of, or immediately following, the malarial season, the second half of the year showing by far the greater number of cases, especially August, September, and October. A few cases are seen in the first six months. In Greece it is during the months of November and December that the majority of cases occur.

Family Predisposition.—Tomaselli[205] believed in a well-marked family tendency, having observed cases in several members of the same family. Daniels[57] refers to three families in which he noticed this predisposition. Three such families are known to the writer. Cardamatis[206] relates the case of a family of seven, of which the father, mother, and one daughter were within a few days attacked and died with blackwater fever. The others, removing to Athens, were all subsequently attacked, but fortunately recovered. Nine years later a daughter had the fever again and recovered. Sutherland[168] speaks of a family of which all the children, six in number, died with hemoglobinuric fever.

Idiosyncrasy.—An idiosyncrasy in susceptible individuals has long been assumed and by many passively accepted as the sole explanation of the mysteries of pathogenesis. Foustanos[207] holds that idiosyncrasy is either congenital or acquired, as the result of debility or bodily changes due to syphilis, malaria, etc. There is not sufficient evidence to show that heredity plays an important part in whatever is meant by this vague term.

Previous Attacks of Hemoglobinuria.—Who has had

blackwater fever is prone to have recurrences. In the tropics about one-fourth of the subjects have more than one attack. Of 304 cases mentioned by Cardamatis, 81 occurred in persons who had previously had it. Several tropic physicians record repeated attacks in themselves. Thus F. Plehn[208] had five attacks, Crosse[209] at least ten severe attacks, and Banks[210] twelve or thirteen during eighteen years' residence in Congo. One of Koch's[172] patients had ten attacks in one year, and the Plehns[211] state that they know persons who have had fifteen or more attacks. There is, therefore, no active immunity; the only immunity except natural being conferred by prolonged residence in an endemic focus.

Length of residence in the home of the disease is an important factor. A curve showing the number of first attacks to each year of residence would rise from the first to the third years and then fall gradually. This is almost constant for observation in the tropics, being less noticeable in temperate regions. The following table of cases seen in the tropics will illustrate:

	First year.	Second year.	Third year.	Fourth year.	Fifth year.	Later.
Burot and Legrand,[211] 100 cases....	6	22	43	20	..	9
Daniels,[57] 114 cases.....	21	40	27	12	5	9
Bérenger-Féraud,[96] 185 cases.....	10	42	79	37	9	8
Vedy,[213] 54 cases.....	6	8	29	5	2	4
	43	112	178	74	16	30

Fifty cases observed by McElroy[214] in the Mississippi Valley were distributed as follows: Two in the first year of residence, 3 in the second, 6 between the second and the fifth, 23 between the fifth and the tenth, 11 between the tenth and twentieth, and 5 after twenty years.

Exceptionally are cases seen after only a short period of tropic residence, as Plehn's[5] Case XXXV, after two months in the Cameroon, and one of Brem's[215] cases, after two months on the Isthmus of Panama. Ziemann[48] mentions 2 cases beginning six weeks and twenty-seven days, respectively, after arrival in a malarial locality, and Oeconomou[15] observed a case occurring after ten days of residence in a malarial region. The case showing the longest period of residence before onset in

which this is specified is that of Howard,[216] twenty-three years in Central Africa, though in 5 of McElroy's[214] cases the length of residence was longer than twenty years.

Altitude.—Hemoglobinuric fever is often considered a disease of the lowlands, though cases are commonly observed at heights of 3,000 feet. The results of Daniels'[57] observations on the influence of altitude may be stated as follows:

The greater number of recorded cases have occurred in the highlands at or about 3,000 feet above the sea level. There are two reasons for this: First, the number of residents in these highlands is much greater than in the other districts. This correction alone reverses the figures; secondly, many of these cases were visiting the highlands on account of health or for other reasons. Others were passing through the highlands when invalided home. Some had recently visited the lowlands. A true correction that would attribute each case to the district in which the disease was acquired is impossible, but taking an arbitrary period of a fortnight as representing a not improbable latent period we should find that the place of residence a fortnight or more previous to onset would give a very different district distribution to that given by considering the place of onset. Corrected for proportional numbers of susceptible persons in each district and for place of residence two weeks previous to onset, the distribution per 10 of population is as follows: 1.04 in the highlands, 7.28 at the lake level (Lake Nyassa, altitude about 1,500 feet), and 3.8 in the lower shire regions. According to Laveran,[1] it was necessary, on account of the frequency of blackwater fever, to abandon certain posts in Congo established at heights of 500 to 700 meters.

Change of residence is a not uncommon cause for an outbreak, especially if the difference in altitude or climate is decided. In Africa not only those coming from the mountains to the lowlands, but also those moving from the insalubrious littoral to the refreshing high-lying districts are predisposed. This change seems to be independent of the hardships of travel.

After Leaving Endemic Region.—Such cases have been observed in England by Bassett-Smith,[217] Hughes,[218] Sylivan,[8] Crosse,[4] Manson,[219] Daniels,[57] and Parker;[220] in Ireland by

Mowbray;[221] in Germany by Schlayer,[222] A. Plehn,[24] Kleine,[223] Koch[224] and F. Plehn;[211] in France by Burot and Legrand,[225] Le Dantec,[226] Kelsch and Kiener,[178] Rouvier,[227] Vincent,[8] Boisson,[86] Troussaint[86] and Laveran;[1] in Belgium by Dryepondt and Vancanpenhout[228] and Bertrand;[229] and in Baltimore by Brem.[215] Many of these cases were not mere relapses; indeed, in the majority in which the number of previous attacks was specifically stated they were first attacks. The onset may occur from a few days to five months or more after leaving the endemic area. Inclement weather and fatigue seem to be factors in some of these cases. The mortality is low.

Occupation which requires residence in a malarial locality and which necessitates overturning of the soil, as gardening, farming, ditching, railroad construction, etc., is largely predisposing. Not a few cases occur among timber workers. The disease prevailed extensively among those engaged in the construction of the canal of Corinth. Manson[59] tells us that many of the Chinese laborers on the Congo railroad died of hemoglobinuric fever, and DeGreny[8] found many cases in both negroes and whites in the railroad work on the lower Congo. Crosse[209] says that it is significant that his first three gardeners died of blackwater fever, and that for some considerable time cases occurred only near the plantations, and as the plantations became more numerous the disease spread to the other stations in the territories.

Occasional Causes.—Of these, exposure to cold and dampness is probably the most efficacious, showing somewhat analogous to paroxysmal hemoglobinuria. Overexertion precedes some cases. The influence of alcohol has probably been overestimated. Trauma has a slight etiologic importance. Thus Mould[230] mentions a case developing after a sprained ankle; Plehn[61] one in which a man was wounded in a bush fight and bled considerably. Crosse[209] and Plehn[5] saw cases immediately following confinement. Psychic states, as anger, grief, and fear, exposure to sun, fatigue, excessive venery, syphilis, and the mercury cure have been mentioned as occasional causes. Cardamatis[86] lays stress on the association with rheumatic diathesis, 12 of his 30 cases being rheumatic. Alexander

Haig[231] believes there is an intimate relation, most probably causative, between an excess of uric acid in the blood and hemoglobinuric fever. He makes the unfounded statement that the ordinary acid sulphate of quinine is about one-fifth xanthin, which is physiologically and pathologically equivalent to uric acid, and herein, he believes, lies its supposed power to produce hemoglobinuria. Johnson[60] holds that a meat diet predisposes to blackwater fever.

Previous Malaria.—It may be said with almost absolute certainty that previous infection with malaria is essential. In fact, a majority of careful observers make the unqualified assertion. The extreme rarity of cases in which preceding malarial infection is denied almost forces us to the conclusion that it may have been overlooked, as might occur in latent or masked infection. It is, however, not impossible that hemoglobinuria may exceptionally accompany the first outbursts of malaria, as in cases of F. Plehn,[5] Goltman and Krauss,[189] and Brem.[215] In all of the cases of Tomaselli and Koch, the most ardent advocates of the quinine theory, there was a history of antecedent malaria. Tomaselli[205] states in italicized words that the two conditions which favor the hemolytic action of quinine are: 1, Malarial infection, chronic or sometimes recent; 2, a special idiosyncrasy often hereditary.

Cardamatis[206] cites several writers who have seen cases without preceding malaria, and Van der Scheer[201] is said to have seen such a case.

Pathogenesis.—There are three chief theories as to the nature of hemoglobinuric fever: 1, that it is malaria; 2, that it is quinine poisoning; 3, that it is a disease *sui generis*.

I. Against the malarial nature of hemoglobinuric fever may be urged the following objections:

1. The parasites are often absent; when present they are not numerically proportionate to the severity of the attack, and usually disappear as the disease progresses; sporulation does not correspond in time with the symptoms; hemoglobinuria may be associated with different forms of the malaria parasite.

2. In malaria very numerous parasites may be present without producing hemoglobinuria.

3. The geographic range does not coincide with that of malaria.

4. Its seasonal prevalence does not correspond with that of malaria.

5. Blackwater fever is not amenable to quinine.

The frequency with which the parasites are found is shown by the following list of examinations by various observers. The first column of figures shows the number of examinations made, the second the number in which the parasites were present:

Kanellis[232]	20	10
Bignami and Bastianelli[233]	2	1
Vincent[8]	5	1
Dryepondt and Vancanpenhout[228]	1	0
Powell[234]	11	5
Koch[172]	16	2
Hanley[184]	13	0
Cardamatis[108]	25	4
Burns[235]	3	3
Boisson[86]	3	3
Daniels[87]	16	4
Wellman[56]	1	1
Crosse[236]	1	1
Brem[215]	14	2
Krauss[199]	11	7
McElroy[214]	23	9
Thin[237]	1	0
Kleine[223]	15	6
Hoffman[49]	3	2
Curry[186]	2	0
Troussaint[88]	7	5
Pezopoules and Cardamatis[86]	7	3
Ketchen[238]	1	1
Mastermann[64]	1	1
Schlayer[222]	1	1
Ollwig[49]	15	6
Stephens and Christophers[57]	16	3
Howard[216]	1	0
Ruge[239]	1	1
Goltman and Krauss[189]	12	4
Woldert[240]	1	1
Hartsock[241]	1	0
F. Plehn[5]	33	22
Broden[242]	20	6
Marchoux[243]	9	1
Oeconomou[243]	3	0
Cardamatis[244]	25	4
Le Dantec[220]	3	0
Bernardo[245]	20	17
Gauducheau[245]	15	0
Da Costa[245]	20	15
Grattan[246]	11	4
Külz[247]	16	3
Kudicke[81]	17	9
Wellman[68]	34	3

As stated in the first objection, the parasites when present tend to disappear as the disease progresses. The following figures show the difference in results of examination at different periods. The great frequency with which they are found the day before the attack should be noted:

Stephens and Christophers:[118]

Day before attack parasites present in 95 per cent. of cases.
Day of attack parasites present in 70 per cent. of cases.
Day after attack parasites present in 20 per cent. of cases.

Mannaberg:[141]

Day before attack parasites present in 95.6 per cent. of cases.
Day of attack parasites present in 63 per cent. of cases.
Day after attack parasites present in 17.1 per cent. of cases.

The reasons for the rapid disappearance of the organisms are, first, that often quinine has been taken before the examination; secondly, that in the terrific hemolysis the weaker cells, including those containing parasites, are usually the first to succumb.

The hemoglobinuria occurring in Texas fever of cattle is cited with some show of reason as an argument for the purely malarial origin of blackwater fever. There are essential differences, however, in the occurrences of blackwater in malaria and Texas fever. First, malaria is followed by blackwater in a very small percentage of cases, malaria being common, hemoglobinuric fever much rarer; in Texas fever blackwater is a common symptom, occurring in nearly all severe cases. Second, in blackwater fever in man the number of parasites shows no proportion whatever to the severity of the disease. In Texas fever, on the other hand, as is shown by Smith and Kilbourne,[248] the number of parasites is in direct relation to the severity of the process and increases as a fatal termination approaches. In human malaria the parasites may exist in very large numbers without the development of hemoglobinuria; this is not the case in Texas fever. Bonome found in the icterohemoglobinuria of sheep the same relation between the number and behavior of the hematozoa and the intensity and progress of the attack as obtains with Texas fever.

The form of parasite found in blackwater fever is, in the great majority of instances, the estivo-autumnal. Only excep-

tionally is hemoglobinuria combined with infections with the benign organisms. The tertian parasite has been observed in cases of Ziemann,[48] Panse,[79] Orme,[249] Pecori,[69] Carducci,[69] Van der Horst,[250] Hughes,[218] Koch[234] (5 cases), A. Plehn[99] (3 cases), Ollwig,[49] McElroy,[214] Goltman and Krauss,[189] Brem,[215] Herrick[251] and Curl[251] (3 cases). The quartan parasite has occurred in cases of Vincenzi,[96] Grocco,[96] Kleine,[223] Kudicke,[51] and Otto.[53] Thiroux[86] and Laveran[11] are said to have found the large form of parasite, but whether tertian or quartan is not stated. The fact that parasites other than estivo-autumnal have been found is no argument against the malarial nature of blackwater fever, since cases of pernicious malaria in which only the large tertian parasites were found have been reported by French,[166] Ewing[181] (2 cases), Ziemann,[48] and others.

Some writers believe that in addition to the mechanical destruction of the red cells by the parasites the latter give off toxins which have hemolytic powers. The facts, however, that intense hemolysis may occur with very few parasites in the blood, and that the parasites when present do not bear a direct relation to the severity of the disease, but rapidly diminish as the disease progresses, speak strongly against the rôle of a parasitic toxin in blackwater fever.

The number of cases in which the parasite is found if the examination is made early constitutes conclusive evidence of an intimate relationship to malaria. This, however, is not all. The testimony furnished by the parasites is corroborated by the two subsidiary evidences of malaria: first, pigmented leukocytes; secondly, mononuclear leukocytosis. Given, therefore, the presence of the parasites in the first hours of attack, and the almost constant finding of pigmented leukocytes and mononuclear leukocytosis, it is impossible to deny that malaria plays an important rôle in its production.

The peculiarity of the geographic distribution of hemoglobinuric fever is no argument against its malarial nature. While it does not occur in all, even highly, malarial countries, it is not met except in markedly miasmatic regions. Neither does the distribution of quartan fever or some forms of pernicious fever coincide with that of malaria in general. Nor is

the slight difference of seasonal prevalence of any weight. The different forms of malaria have different seasons of prevalence, as "spring tertian," and estivo-autumnal.

Favorable, therefore, to malarial character are:

1. Geographic distribution.
2. Length of residence in endemic region.
3. Previous attacks of malaria.
4. Malarial prophylaxis is prophylactic of blackwater fever.
5. Blood findings: parasites, pigmented leukocytes, mononuclear leukocytosis.

The fact that hemoglobinuric fever does not respond to quinine is one of the strongest evidences that it is not an attack of malaria (*per se*).

The writer's opinion of the relation of malaria to blackwater fever is that the former is essentially and solely the predisposing cause, and that in some cases it may also act as the exciting cause.

II. Tomaselli first published his observations as to the etiologic relation between quinine and blackwater fever in 1874. More recently Koch has directed attention toward it. The widespread controversy that followed the publication of Koch's views was bitter in the extreme; the matter was even aired in the London lay press. The misunderstanding was probably due to two causes; first, ignorance of Koch's utterance at first hand; secondly, the somewhat non-committal manner in which he expresses his idea of the relation to malaria. While he is very emphatic that blackwater fever is not an attack of malaria, he is not clear as to the predisposing rôle of the latter. He does not even assert that quinine is the exciting cause in all cases, but admits that, although he saw no cases of blackwater fever in which quinine could be excluded, he could not go so far as to maintain that every case of blackwater fever is quinine poisoning.[172] There is no doubt but that this acrid dispute was productive of dire results, inasmuch as it brought the specific into discredit not only with the laity, but with many of the profession. Even yet it is necessary in some places on account of a fear of hemoglobinuria to disguise quinine before it can be given.

Tomaselli[205] was able to collect from the literature only 102 cases of quinine hemoglobinuria.

The objections to the quinine theory are:

1. Hemoglobinuria is restricted in geographic range, and is absent from some highly malarial localities where much quinine is used.

2. Hemoglobinuria does not follow the administration of quinine for maladies other than malaria.

3. In a considerable number of cases the antecedent use of quinine can be eliminated with certainty.

4. The same individual may have an attack following the administration of quinine, and later take it without harmful results.

5. The severity of the attack bears no relation to the size of the dose.

6. One dose of quinine could not cause intermittent hemoglobinuria.

7. The great majority of cases recover even under the continued use of large doses of quinine.

Objections 1, 2, and 6 go to demonstrate that other, and probably more important, factors than quinine are at work even in cases often attributed to it. Objections 4 and 7 are not potent if we assume that only a portion of the erythrocytes are susceptible to the effects of quinine, and that all these are destroyed by the first dose. Objection 5 proves that in cases where an outbreak occurs after quinine it cannot be regarded as mere quinine poisoning. The third is the strongest argument against the theory that all blackwater fevers are cases of quinine poisoning. That quinine is not always the exciting cause is fully attested by the numerous cases in which no quinine had been given, as observed by Boye,[252] Vedy,[213] Doering,[253] Broden,[242] Ellenbeck-Hilden,[254] Legrain,[255] Grall,[256] Rossoni,[257] F. Plehn,[208] A. Plehn[24] (22 cases), Marchiafava,[234] Celli,[234] Bastianelli,[234] Beyfuss,[234] Van der Scheer,[234] Seal,[258] Powell,[234] Von Diesing,[234] Carre,[234] Schellong,[234] Laveran,[1] Quennec,[234] Navarre,[234] Reynolds,[234] Etienne,[234] Sims,[234] Donny,[234] Dryepondt,[234] Mense,[234] Rothschuh,[8] Fluit,[8] R. Plehn,[185] Dempwolff,[185] Brin,[185] Crosse,[236] Thin,[237] Stalkarrt,[259]

Hopkins,[260] Cargill,[261] Mould,[230] Hoffmann,[49] Daniels,[57] Rankin,[262] Cardamatis[206] (32 cases), Yofé,[86] Moffatt,[263] Schlayer,[222] Curry,[186] McElroy,[264] DuBose,[265] Hearsey,[266] Ziemann,[86] Brem,[215] Bignami,[234] Doering[185] and Shropshire[267] (15 per cent. of his cases). The writer has seen 4 cases where quinine could be excluded from the etiology.

Hemoglobinuric fever occurring only in malarial subjects and quinine being specific for malaria, it is but a most natural sequence of events that a large number of the cases of hemoglobinuric fever have developed after the administration of quinine. The bare fact that blackwater fever often follows quinine is weak evidence for quinine etiology in the face of the numerous cases in which previous quinine could be absolutely excluded.

When, however, attacks can be produced repeatedly at will by a dose of quinine the question assumes a very different aspect. Such cases are those of Murri,[268] Hoffman,[49] Koch,[172] Manson,[213] Ketchen,[238] Hopkins,[260] Bertrand,[229] A. Plehn,[24] Ollwig,[49] Marsden,[269] Daniels,[57] Kleine,[223] Tomaselli,[205] Vincenzi,[96] and Grocco.[96]

As stated above, there is no relation between the amount of quinine and the intensity of the attack. Ketchen[238] precipitated an attack, experimentally, with 1½ grains. This patient stated that one-eighteenth of a gram had previously produced blackwater. Karamitsas,[86] Chomatianos,[86] Pampoukis,[86] Kanellis,[86] Koch,[172] Kleine,[223] Shropshire,[267] Moscato,[86] A. Plehn,[24] Boxer,[270] and others report outbreaks elicited by less than one-half gram. Panse[252] believes that the usual dose preceding an outbreak to be from one-tenth to 1 gram. Tomaselli[205] has observed attacks to follow the administration of doses as small as from one-twentieth to one-tenth gram, and Koch[271] reports a case after one-tenth gram had been administered. Kudicke[51] and Marchiafava and Bignami[22] state the minimum quantity as one-twentieth gram, Laveran[1] and Ziemann[48] as 1 centigram, and Ruge[158] as 1 milligram.

Tomaselli[205] examined various preparations of quinine to ascertain whether the toxic effect was dependent upon adulteration, and concluded that such was not the case, but that the

toxic properties were inherent to quinine itself and to all the preparations containing quinine.

The time intervening between the administration of quinine and the onset of hemoglobinuria is almost uniformly fixed by various observers at from one to six hours. With six hours as the maximum interval, the cases really due to quinine would dwindle considerably.

It is believed by some writers that quinine hypodermically does not produce blackwater, even in persons susceptible when administered orally. This, however, is not the case. Tomaselli[205] has shown that subcutaneous injections of quinine are followed more promptly by hemoglobinuria than is the oral administration. Kohlbrugge[7] thinks that only the inorganic salts of quinine are toxic, and states that the tannate, even in the largest doses given to susceptible persons, fails to cause hemoglobinuria. McKay[449] has recently attempted to show that hemolysis following the administration of the sulphate of quinine is due to the sulphate and not to the quinine. This view, however, is not supported by clinic experience. Furthermore, the results of experiments upon which McKay based his conclusion could not be verified by Christophers and Bentley. It is probable that neither the mode of administration nor the preparation used, if absorbed, gives any difference in results.

The rôle of quinine in hemoglobinuric fever is probably highly complex. It will be shown that it is of value as a prophylactic when systematically employed; if not thus used, and malarial infection be permitted to occur, it may, in some persons thus predisposed, act as the exciting cause. In the attack itself it is possibly of value in destroying the parasites when these are present, or it may act harmfully in aiding hemolysis.

Even after a careful study it is not easy to define precisely the respective potency of malaria and quinine as etiologic factors. To quote Shropshire:[267] "To establish the cause of any disease we must apply the agent to the subject, and have, as uniform result, the disease. But if there are two agents suspected as causative which applied together produce the disease,

but applied separately to the same individual, the one produce it, the other never, we can attribute only to the one a causative place, and to the other an accidental presence. Such is the case before us. Malaria taken as the cause and applied without quinine to an individual of such tendency, hemoglobinuria results in 15 per cent. of the cases before us. Quinine has probably been applied to all the cases before us without the presence of malaria and no hemoglobinuria resulting. Which produces it?"

Favoring malaria as against quinine we have:

1. Antecedent malaria essential.

2. Relative immunity of the negro. Racial immunity to disease well known; racial susceptibility to drugs rare or unknown.

3. Occurs often without the administration of quinine.

We may safely conclude that the predisposing cause is always malaria; the exciting causes are fresh malarial invasion, quinine or other medicaments, exposure, exertion, mental states, etc.

III. The most enthusiastic champion of the view that blackwater fever is neither malaria nor quinine poisoning, but a disease *sui generis,* is Sambon.[121] Manson[272] formerly advocated this theory. The two reasons for his belief are a similarity to paroxysmal hemoglobinuria and an analogy with Texas fever. Stalkarrt,[259] Rho,[273] Vincent,[8] and others believe that it is a distinct disease. While the similarity to paroxysmal hemoglobinuria cannot be denied, the relation to Texas fever, as we have seen, is far from close, and the evidence that it is a disease *sui generis* is inadequate. Yersin[274] found bacilli in the casts and epithelium in the urine of 2 patients, and believed that he had discovered the cause of the disease. Breaudat,[275] however, showed that these were the bacillus *Coli communis.*

Collet[276] has recently, without grounds, however, suggested that there may be a causal relation between the bacillus *Megatherium* and blackwater fever.

The theory that green beans and their blossoms were the cause of many cases of hemoglobinuric fever seems

to have perished in Greece, Sicily, and Sardinia, where it originated.

It is generally conceded that hemoglobinuric fever consists of a destruction of red blood-cells so widespread that, the liver being powerless to transform the liberated hemoglobin into bile pigment, the greater part is excreted by the kidneys. This conversion into biliary coloring matter is the physiologic fate of free hemoglobin, and indeed its pathologic destiny up to a certain limit—which, according to Ponfick's postulate, is the destruction of one-sixth of the entire number of red cells—beyond which hemoglobinuria ensues. This much seems to be rather unanimously accorded. The nature of the hemolysin is the missing link in the pathogenetic chain.

The modern study of immunity and cytolysis has thrown a flood of light on hemolysis. It is unnecessary to review in detail the development of our knowledge of hemolysis, but the following facts will be recalled. It has been known for some time that the serum of certain animals has the power of dissolving the blood corpuscles of certain other animals. Bordet showed that this effect may be produced artificially. The serum of guinea-pigs naturally has no hemolytic effect on the red cells of the rabbit, but if the rabbit's blood is injected into the guinea-pig and the process repeated the serum of the guinea-pig becomes hemolytic toward the rabbit. It has been shown that the hemolysins are formed by the interaction of two substances, one, the amboceptor or immune body, resisting moderate degrees of heat; the other, called the complement, inactivated by a temperature of about 55° C. Neither amboceptor nor complement alone is sufficient to dissolve erythrocytes, but for this it is necessary that both act, the amboceptor sensitizing the cells for the complement. The amboceptor may act alone, but the cells will only be rendered susceptible, not dissolved. The complement has no effect whatever on the red cells except through the immune body. The complement exists in normal serum. The formation of an anti-hemolysin is thus stated by Wasserman:[277] "Specific hemolysin, one, for example, specific for rabbit's blood, derived by treating a guinea-pig with rabbit's red cells, is highly

toxic to rabbits. Injected into the animals intravenously in doses of 5 cc. it quickly kills the animals, causing *intra vitam* a solution of red cells. Such a hemolytic serum then acts the same as a bacterial poison. For example, to keep to our illustration, rabbits are injected first with very small doses of this specific hemolytic serum. The dose is gradually increased until it is found that the animal tolerates amounts that would be absolutely fatal to animals not so treated. If some of the serum of this animal is now abstracted and added to the specific hemolytic serum it is found that the power of the latter will be inhibited. This shows that an antihemolysin has been formed."

These statements refer to the employment of heterologous serum; that is, the serum of different species of animals. Isolysis, due to the employment of blood of the same species, is exemplified in cases following the transfusion of blood from man to man. Examples of autolysis, due to the blood of the individual, are cases that have occurred after resorption of extravasated blood, as the rupture of ectopic pregnancy.

Based on these facts, which have been amply demonstrated, Bignami[22] states his theory as follows:

1. An alteration in the plasma which is effected, little by little, as a consequence of a specific change in the red blood corpuscles through which a certain number of them come to behave, in respect to the organism, like the corpuscles in the blood of another species of animal. 2. The formation in consequence of this change of a substance in the plasma which is capable, under certain conditions, of becoming hemolytic.

The writer[278] some time ago modified and elaborated Bignami's hypothesis, and expressed it for the first time in the terms of Ehrlich's side-chain theory.

For the better understanding of the writer's hypothesis the pathogenesis may be divided into the following stages: 1, erythrorrhexis; 2, hepatic stimulation and production of amboceptors; 3, action of complement; 4, hemolysis and hemoglobinuria, or the formation of an antihemolysin.

1. This primary blood destruction is due directly to the malarial parasite, chiefly through the act of sporulation, possi-

bly also by the production of a toxin. The hemoglobin thus liberated is carried to the liver, where it is elaborated into bile pigment. We have seen that this erythrorrhexis is insufficient to account for hemoglobinuria.

2. On reaching the liver the hemoglobin is acted upon by certain of the molecules or atom groups of the liver-cells, which have an affinity for it. When all of the atom groups have been combined with by the hemoglobin, which happens when this function of the liver has been frequently or recently exerted, or when the amount of liberated hemoglobin is very large, the liver is stimulated to the production of more such atom groups. This stimulation is responded to by an overproduction of atom groups, some of which gain access to the general circulation. Translated into the terms of Ehrlich's theory, it may be said that certain receptors of the liver cells have the property of transforming free hemoglobin into bile pigment; when these receptors are exhausted the deficiency is met by overproduction. When the cells become overfilled some of these side-chains are cast off into the general circulation. Here the receptor becomes an amboceptor. The pathology of the liver in this condition fully supports the view of overstimulation. Karyokinesis and other changes in the liver cells suggest that it responds to this stimulation. In the present state of our knowledge we cannot determine the chemic nature of the immune body.

3. Having gained access to the general circulation, the amboceptor meets the complement which is present in normal serum, and the complete hemolysin is formed.

4. The reaction of amboceptor with complement, if not antagonized by an antihemolysin, causes a hemolysis, which if sufficiently extensive results in hemoglobinuria. It is highly probable that when the production of the hemolysin does not proceed with too great rapidity there is formed, *parri passu,* an antihemolysin, which may exactly balance the hemolysin without destroying it. This is probably the symbiosis referred to by Krauss.[199] So long as the equilibrium between hemolysin and antihemolysin is maintained no hemolysis occurs, but let this equilibrium be greatly disturbed by fresh malarial

invasion, quinine, exposure, fatigue or other, and probably unknown, factors, hemolysis occurs and hemoglobinuria ensues. Under this exact equilibrium the subject may be said to possess idiosyncrasy, and is in a condition very similar to that of paroxysmal hemoglobinuria. Casagrandi[82] has recently found in malarial blood a hemolysin the presence of which is masked by an antihemolysin.

It is possible that a slight and temporary loss of equilibrium may result in a limited hemolysis producing hemoglobinemia, but not hemoglobinuria. In this way may be explained some cases of anemia, cachexia, and post-malarial secondary fever, in which the parasites, if present, are not in proportion to the results.

It is believed that this hypothesis explains the occurrence of hemoglobinuric fever during and after malarial infection, with or without the administration of quinine; it explains why the malarial attack may precede by months the appearance of blackwater; why exposure, exertion, etc., may elicit an attack; why the hemolysis does not always coincide in time with the sporulation of the parasites in the cases in which the latter are present; it accounts in a measure for the complex relation with quinine and explains obscure anemia, quinine fever, post-malarial secondary fever, and post-hemoglobinuric fever. Lastly, it coincides with the prevalent ideas of tropic physicians of an intimate relation between hemoglobinuric fever and "biliousness."

Christophers and Bentley,[279] constituting a committee appointed by the Government of India to conduct an inquiry regarding the nature of blackwater fever, have recently published an extensive monograph containing a record of their experiments and the conclusions which they reached as a result of these experiments. They exclude parasitic, osmotic, and chemic actions as causes of hemolysis, and show that the hemolysin is probably derived from auto-immunization against the organism's own red cells, an autolysin, confirming thus far Bignami's and the writer's theory. These experiments, which are the most complete and convincing that have been conducted in connection with hemoglobinuric fever, are too

extensive to be abstracted, and should be consulted in the original by those interested.

According to the conditions of its occurrence hemoglobinuric fever is classified by the Italian school as follows:

1. Malarial hemoglobinuria:
   (*a*) Cases in which the blood contains parasites.
   (*b*) Cases in which no parasites are present.
2. Quinine hemoglobinuria in malarial subjects, occurring:
   (*a*) During the malarial attack.
   (*b*) After the attack (post-hemoglobinuric).

CHAPTER IV

PATHOLOGIC ANATOMY

ACUTE MALARIA

THE pathognomonic anatomic feature of malaria is intravascular melanin, which is a product of hemoglobin converted through the biologic agency of the malarial parasites. Melanin occurs in the tissues also, but here there is some doubt as to its origin. It is brownish black in color, occurs in fine grains, coarse particles, or in lumps; does not yield the reaction for iron, and is insoluble in acids, but is readily dissolved by ammonium sulphide. This should not be confused with hemosiderin, which is a chemic derivative of the hemoglobin of broken-down red blood-cells; is yellowish in color; responds to the reaction for iron; is insoluble in acids, alkalies, alcohol, and water, and exists especially extravascularly. It is regarded as a result of prolonged hemoglobinemia following severe or chronic infections.

The general plan of distribution of melanin may be thus stated: In the blood current it may exist free or, more commonly, is contained within the phagocytes and the red cells infected with pigmented parasites, and is more abundant in the capillaries than in the larger vessels. In the viscera it is oftenest seen in the spleen, bone-marrow, brain, and liver, especially in the endothelial cells, but in the spleen and bone-marrow it exists also outside the vessels and either between or within the cells proper to these tissues.

The distribution of the parasites varies according to the type of the attack; it has been shown that the latter depends largely upon the localizations of the parasites. They are usually abundant in the splenic blood irrespective of the form assumed by the attack. It occasionally happens that death supervenes, notwithstanding a progressive diminution of the

PLATE VI



Fig. 1.

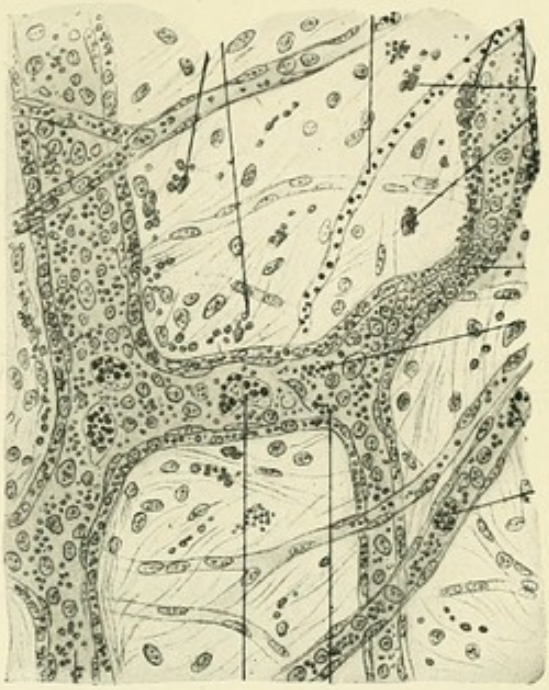


Fig. 2.



Fig. 3.

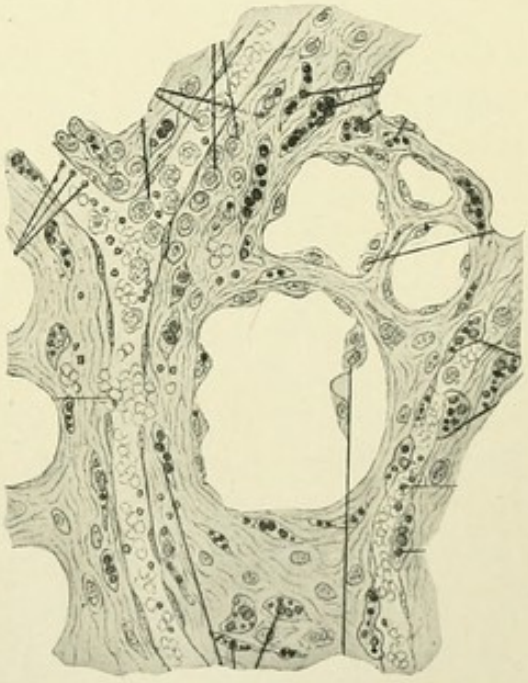


Fig. 4.

Fig. 1. Liver in acute malaria. Fig. 2. Pia mater in acute malaria. Fig. 3. Spleen in acute malaria. Fig. 4. Omentum in acute malaria. (Kelsch and Kiener.)

parasites, so that the latter may be scanty or even absent. In the spleen are found not only schizonts, but also numerous sexual forms, which are likewise usually found in the bone-marrow and even in the liver, but in the brain gametes are conspicuously few. Parasitic development is checked almost immediately upon the death of the host.

The **spleen** is always more or less enlarged, though perhaps slightly so in acute cases following recent infection. The edges are often rounded, the organ tending to lose its characteristic contour and to assume a spheric shape. The color varies from reddish brown to almost black, being darker in old malarials. In consistence it is usually softer than normal, often semifluid, sometimes resembling a bag of pulp. The capsule is thinned, occasionally adherent to the adjacent organs, and is very liable to rupture. The cut surface is dark in proportion to the age of the infection. The pigmentation is occasionally uniform and the tissues hardly distinguishable, though, as a rule, the Malpighian bodies stand out distinctly. The venous sinuses are often dilated. Microscopically there is enormous cellular hyperplasia with distention of Mall's pulp cords. The spleen cells are everywhere intercalated with red blood corpuscles, a large per cent. of which are infected. The parasites may be in the same or in different stages of development. The pigment is contained in the large mononucleated leukocytes, endothelial cells, and giant cells. The latter contain also red cells, parasites, and even small phagocytes, and are most abundant in the splenic vein. They sometimes show evidences of necrosis. The Malpighian bodies and the fibrous trabeculæ are usually unpigmented. Mitotic cells may be found in the pulp and in the Malpighian bodies. The circulation may be so obstructed that edema, interstitial hemorrhage, and cellular necrosis may occur.

The **liver** is generally enlarged, but in a less proportion as to frequency and size than the spleen. The color is usually a dirty brown, the surface is sleek, and the form is preserved. The consistence may be normal or somewhat diminished. The parenchyma presents a reddish-brown color after recent infection and the cut surface drips blood. The gall-bladder

is often distended with a quantity of dark, inspissated bile. Microscopically parasites are not so abundant as in the spleen. Pigment is found in the vessels, especially in the blood capillaries. Here are found also altered parasites, melaniferous leukocytes, and large endothelial cells containing coarse grains of pigment. The macrophages are sometimes of an enormous size. The pigmented endothelial cells are swollen and the capillaries are not infrequently entirely obstructed with pigmented cellular elements. The hepatic cells do not contain melanin, but are frequently charged with hemosiderin, and may show evidences of cloudy swelling, atrophy, or necrosis. Karyokinesis is occasionally noted. Areas of focal necrosis have been described.

The **kidneys** on gross inspection show few changes; they may be slightly enlarged and hyperemic. Microscopic examination shows a marked pigmentation of the Malpighian corpuscles, together with degenerated tubular epithelium. While the epithelium of the tubules may be healthy, it often shows cloudy swelling and necrosis. In the straight tubules there may be casts of various sorts. Melanin is found in the glomeruli, less often in the tubules. The cells may contain hemosiderin granules. Parasites are rare in the glomerular vessels, but may be found in the intertubular capillaries. Ewing's[177] case with massing of the parasites in the renal capillaries has been mentioned. A true glomerulitis has been found in cases of the algid type.

In cerebral cases the only variation from the normal condition of the **stomach** and **bowels** may be a slight pigmentation. In fatal cases of the algid and choleraic forms the gastro-intestinal tract may contain a bloody fluid and the mucous membrane may be swollen, hyperemic, pigmented, necrotic, or ulcerated. The follicles and Peyer's patches may be hypertrophied and prominent. Microscopically there is vivid injection, parasitic and pigmentary thrombosis of the capillaries, hemorrhagic points, and necrosis. The peritoneum is usually normal.

Macroscopically the **lungs** may show nothing abnormal save, probably, slight results of hypostasis, which in some cases may

be cadaveric lesions. Occasionally there are hemorrhagic areas. Microscopically neither pigment nor parasites are so evident as in certain of the other organs. The capillaries are congested, sometimes thrombosed, and contain infected erythrocytes, phagocytes, which often show signs of degeneration, and macrophages. The capillary epithelium may be swollen, but is only occasionally pigmented. The pleuræ show nothing abnormal.

The **heart muscle** is ordinarily pale and flabby, but the muscular fibers do not usually afford degenerative signs. The capillaries may contain parasites in greater or less number, and the endothelium may be swollen. Cases in which the parasites are very numerous in the cardiac capillaries, such as that of Ewing,[181] are very rare.

In cerebral cases the meninges of the **brain** are deeply hyperemic, and excess of serum is found in the meshes of the pia, in the ventricles, and at the base of the brain. The cerebral substance is commonly darkly pigmented and congested, and may show hemorrhages, usually punctiform, occasionally larger. The hemorrhages occur oftener in the cerebrum, but may be present in the cerebellum. In the abdominal form the brain may show but few pathologic changes. Microscopically in the cerebral cases the capillaries are seen to be filled, even to occlusion, with pigment, parasites, and phagocytes, the latter in the same or in different stages of schizogony; gametes are seldom found. In some instances nearly every red cell contains one or more parasites. Localization of parasites are found not only in the cerebrum, but also in the cerebellum and medulla. The capillary endothelium may be swollen, pigmented, and undergoing fatty degeneration. Secondary changes, such as perivascular exudation, hemorrhages, and necrosis, are not uncommon results of thrombosis. Degenerative changes in the ganglion cells have been detected.

The **bone-marrow** is of a dark color approaching that of the spleen, and sometimes diffluent. Microscopic examination reveals hyperemia, the capillaries being engorged with pigmented parasites and giant cells clinging to the vessel walls. The parasites exist as free spores, schizonts, which are fre-

quently sporulating, and gametes in large numbers. Extravascular parasites and free pigment are also found.

CHRONIC MALARIA

The **spleen** is always enlarged. The form is usually preserved. Its average weight is from 700 to 800 grams, though it may attain four or five times this weight. In consistence it is usually firmer than normal. The capsule is thickened, especially at the convexity. Upon the surface are scattered indurated whitish plaques of fibrous, occasionally calcareous, consistence, evidences of perisplenitis. Adhesions to the diaphragm or other parts are not infrequent. Subcapsular infarcts are occasionally encountered. In section the parenchyma is usually found firm, only rarely is it of diminished consistence. The color varies from that of muscular tissue to slate color. The thickened trabeculæ, like white bands, are very evident. The Malpighian follicles are sometimes conspicuous, sometimes indistinct. In old cases there is an overgrowth of connective tissue, particularly near the capsule. Histologically the chief changes found are trabecular hyperplasia and venous dilatation. The process sometimes resembles a hypertrophic cirrhosis. The fibrous trabeculæ are hypertrophied and there is formation of new connective tissue. The venules are notably dilated, the walls thickened, and the blood rich in pigmented leukocytes and macrophages. The deposition of pigment is in general similar to that in acute malaria. There is at times little change in the lymphoid tissue forming the arterial sheaths and Malpighian bodies, but this may be hyperplastic. Necrosis of the spleen pulp is observed, surrounded by evidences of regeneration. These regenerative processes consist chiefly of increased vascularization, formation of connective-tissue network enclosing giant cells, and hyperplasia of lymphoid tissue beginning in the Malpighian bodies.

The **liver** is not so constantly enlarged as is the spleen and never attains so excessive a degree of hypertrophy. It may weigh from 2 to 4 kilograms. In rare instances it is atrophic. The consistence is firm, occasionally somewhat doughy. The

PLATE VII

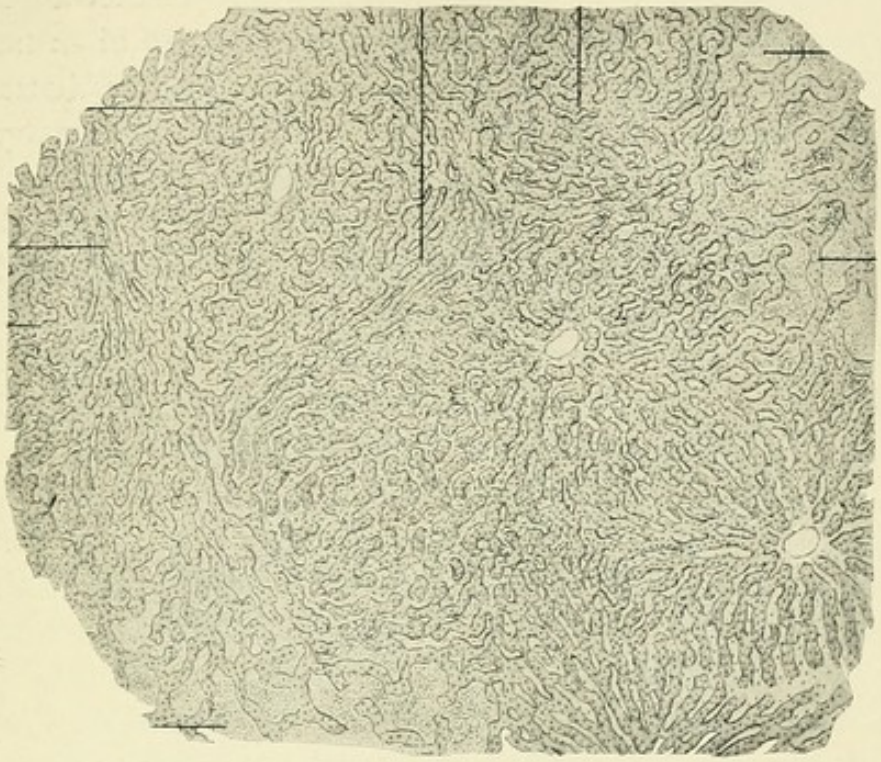


Fig. 1.



Fig. 2.

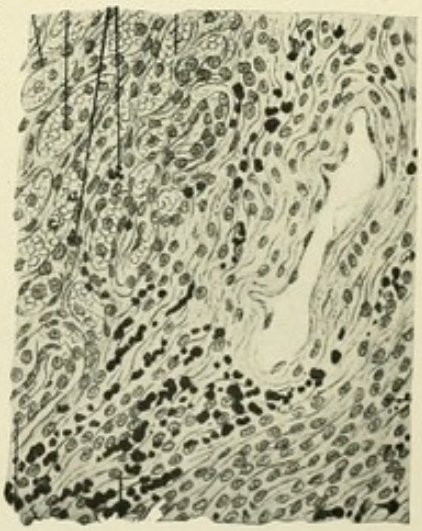


Fig. 3.

Figs. 1, 2. Liver in chronic malaria. Fig. 3. Spleen in chronic malaria. (Kelsch and Kiener.)

capsule is tense and may be thickened. There may be present whitish bands or patches, the results of perihepatitis. The color varies from reddish to almost black. The cut surface is usually found to be congested and may drip with blood. The color is more or less dark red. There may sometimes be detected on gross inspection an increase of connective tissue. Microscopically the hepatic cells are seen to be hypertrophied and hyperplastic, showing evidences of cloudy swelling and necrosis, or atrophied as a consequence of vascular dilatation. In certain areas there may be a complete disappearance of hepatic cells, which are replaced by connective tissue, Kupffer's cells, or beginning formation of new hepatic cells. The nuclei are frequently multiple, and when single may be much larger than normal and contain one or two nucleoli. The hepatic cells may be charged with hemosiderin. Pigment is contained in the endothelial and Kupffer's cells, especially in congested areas and in the periphery of the lobule. There is sometimes diffuse overgrowth of connective tissue. The blood capillaries are usually dilated and congested with blood rich in pigmented leukocytes; the circulation is commonly sluggish. The bile capillaries are ordinarily unaltered. The perivascular lymph channels may be dilated. Amyloid degeneration beginning apparently at the periphery of the lobules is not rare.

The **kidneys** are usually increased in volume and in weight. The contracted kidney has been described in connection with malaria, but there is some doubt as to the etiologic relationship. The surface of the kidney is smooth, the color is dark red, and the consistence is slightly increased. Upon section the cortical substance is reddish gray. The pyramids are markedly hyperemic, the red tint being most decided at the border of the pyramidal substance. Upon microscopic examination the convoluted tubules and ascending limb of Henle's loop are found dilated. The epithelium is swollen, charged with hemosiderin, and may be undergoing degeneration. In the collecting tubules the epithelium is, as a rule, only slightly altered. These tubules rarely contain granular or hyaline casts or desquamated epithelium. Bowman's capsule presents changes similar to those of the convoluted tubules.

The renal arterioles are congested and the capillaries are dilated and gorged with blood rich in leukocytes, more marked in the pyramidal than in the cortical substance. Melanemia is not so decided in the kidney even when profuse in the spleen and liver. There is generally little change in the connective tissue. Here and there is a slight thickening of the intertubular connective tissue. The blood-vessels, the glomeruli, and the walls of the renal tubules may undergo amyloid degeneration. This is more diffuse in the kidneys in chronic malaria than in the other organs.

The **alimentary tract** may show evidence of amyloid degeneration in the stomach or bowel and dysenteric lesions in the colon.

In the **lungs** may be pigmentation and anemia, and in the pleural cavity an effusion.

The **heart** is relaxed and often dilated and sometimes shows evidence of degeneration of the musculature.

The **bone-marrow** is of firmer consistence and more deeply colored than normal, especially toward the ends of the long bones. There is usually a decrease of fat and a proliferation of marrow cells, together with large cells, some undergoing karyokinesis, lymphoid cells, and nucleated red cells. The vessel walls are thickened. In some instances there is atrophy of the bone-marrow.

The elimination of the pigment probably consumes three or four months after the cessation of infection, though this varies with the activity of the eliminative processes.

HEMOGLOBINURIC FEVER

The pathologic findings vary in proportion to the proximity and intensity of the malarial attack. In addition to the changes characteristic of malaria there are found, in blackwater fever subjects, the results of hemoglobinemia and polycholia chiefly in the kidneys and liver. Occasionally post mortems do not reveal malarial evidences, as in two cases reported by Curry,[186] but this is very exceptional. The body is usually deeply jaundiced. There may or may not be edema. The muscular system is often icteric.

PLATE VIII

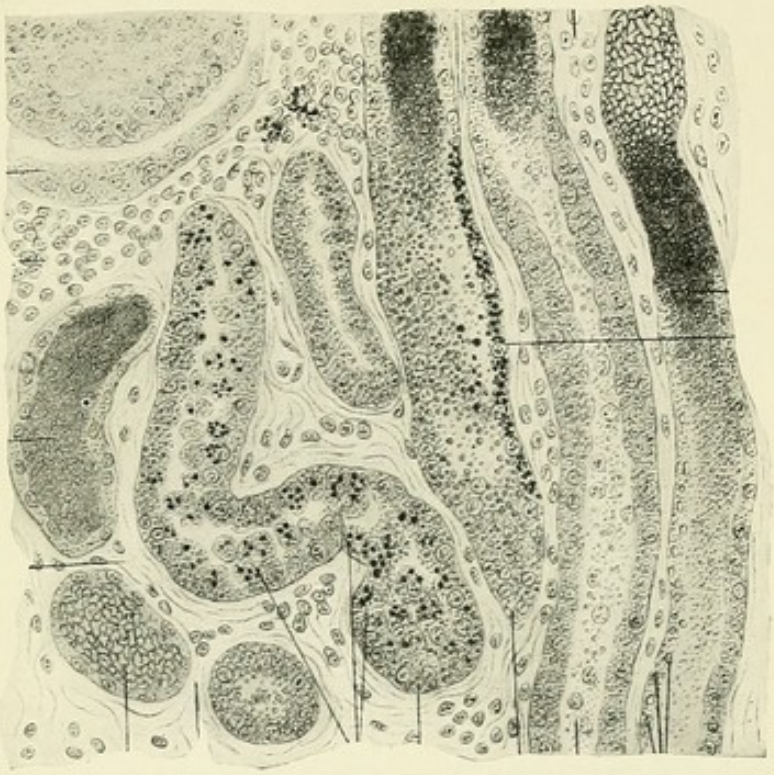


Fig. 1.

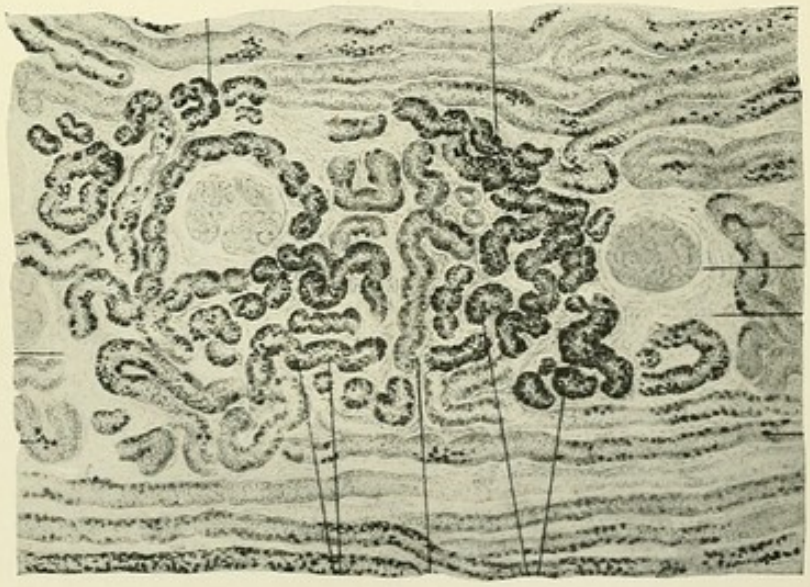


Fig. 2.

Fig. 1.—The kidney in chronic malaria with hemoglobinuric fever.
Fig. 2.—The kidney in malariæ cachexia. (Kelsch and Kiener.)

The **spleen** is enlarged, often enormously so, and congested. The surface color varies from grayish to reddish brown, almost black. The capsule is thickened and usually strips easily, but may be adherent. The consistence of the organ is often so diminished that it appears like a pulpy sac. The trabeculæ are thickened and fibrous; the pulp is decidedly increased. The Malpighian corpuscles are usually hypertrophied, sometimes giving the appearance of sago spleen. Pigment is usually abundant. It is contained within the cells or lying between them. The cells of the Malpighian bodies show the greatest quantity and largest masses. The large mononuclear cells and giant cells are pigmented. The leukocytes lying external to the walls of the small veins may show more pigment than those scattered here and there throughout the pulp. The color of the pigment varies from yellow to almost black, and may consist of hemosiderin or melanin. The walls of the smaller vessels are thickened, and the lumen may be obliterated. The sinuses may be obliterated with pigmented and other cells. The endothelial cells may be proliferating, and often contain granules of pigment. Parasites and pigmented leukocytes may be present in the spleen when not discoverable in the general circulation. There may be round cell infiltration around the trabeculæ.

The **liver** is enlarged, congested, and surcharged with bile. It varies in color from a decided yellow to a dark brown. The capsule is slightly adherent. The surface is usually smooth, but there may be subcapsular nodules from the size of a pinhead to that of a pea, which on section exude a thick, cheesy matter. There is abundant pigmentation, often rod-shaped, especially of the endothelial cells, macrophages, and leukocytes. The course of the capillaries may be well marked by the pigment contained in the endothelial cells and that between the wall and the adjacent liver cells. Both the yellow and black pigments are found, the former especially, in the liver cells. Pigmentation is often more pronounced in the center of the lobule. Thrombi of pigmented cells in the capillaries and sublobular veins occur, with cloudy swelling and fatty degeneration of liver cells. These retrogressive processes are in the

form of islands. The biliary injection, more intense in the center of the hepatic lobule, may extend to the smallest branches. Regenerative efforts on the part of the liver cells are very much more common than in pernicious malaria (Marchiafava and Bignami). Karyokinetic barrels and manasters predominate. This is interpreted by Bastianelli as evidence of hyperfunction of the liver. Marchiafava and Bastianelli both agree in believing that this multiplication of the hepatic cells is an attempt on the part of the liver to meet the increased demands for work in eliminating the detritus of hemoglobin (Thayer). The gall-bladder is usually distended with bile.

The **kidneys** are generally congested, weigh more, and are softer than normal. The capsule is loosely attached. On section the cortex is often yellowish; the pyramids may present brownish streaks, more intense toward the apices. In the cortex may be found wedge-shaped hemorrhages with bases toward the capsule and apices pointing toward the medulla. The medullary pyramids may show minute hemorrhages. The glomeruli often escape undamaged; there is rarely any pigmentation of the cells within Bowman's capsule; there may be cloudy swelling, and slight epithelial desquamation. The epithelia of the convoluted tubules usually show cloudy swelling, fatty degeneration, or coagulation necrosis. There may be pigmentation of the epithelial cells. The lumina are often plugged with hemoglobin casts holding the epithelia in place. The changes in the straight tubules are similar, but casts are more numerous. The epithelium of Henle's loops is better preserved, but the lumen is usually choked with casts of hemoglobin and epithelial detritus from the convoluted tubules. Biliary pigment also occurs here. Karyokinesis is sometimes seen in the epithelium of Henle's loops and of the convoluted tubules.

The **stomach** and **intestines** may be negative. The serous coat may be pale, the mucous membrane congested and bile-stained, especially near the opening of the common bile-duct. There may be isolated hemorrhages, excoriations, and pigmentation. The pancreas is normal.

PLATE IX

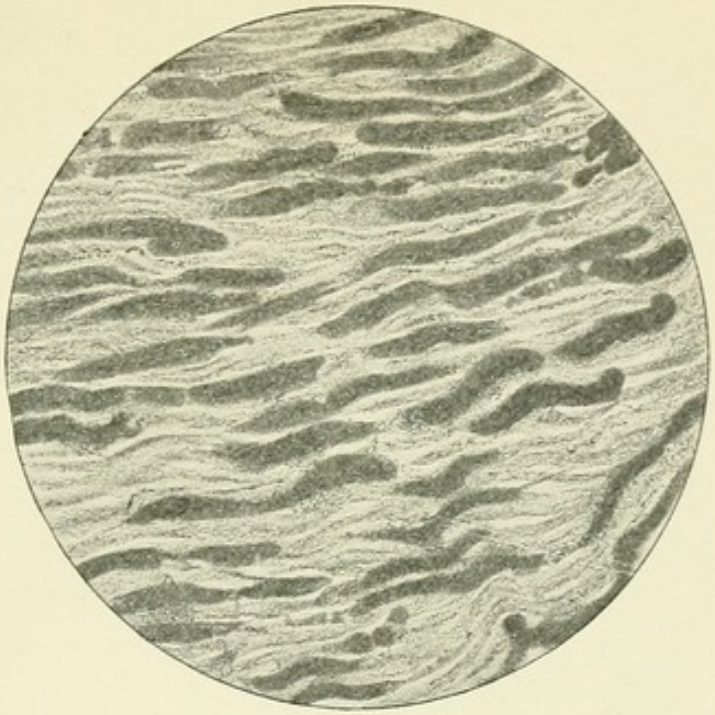


Fig. 1.

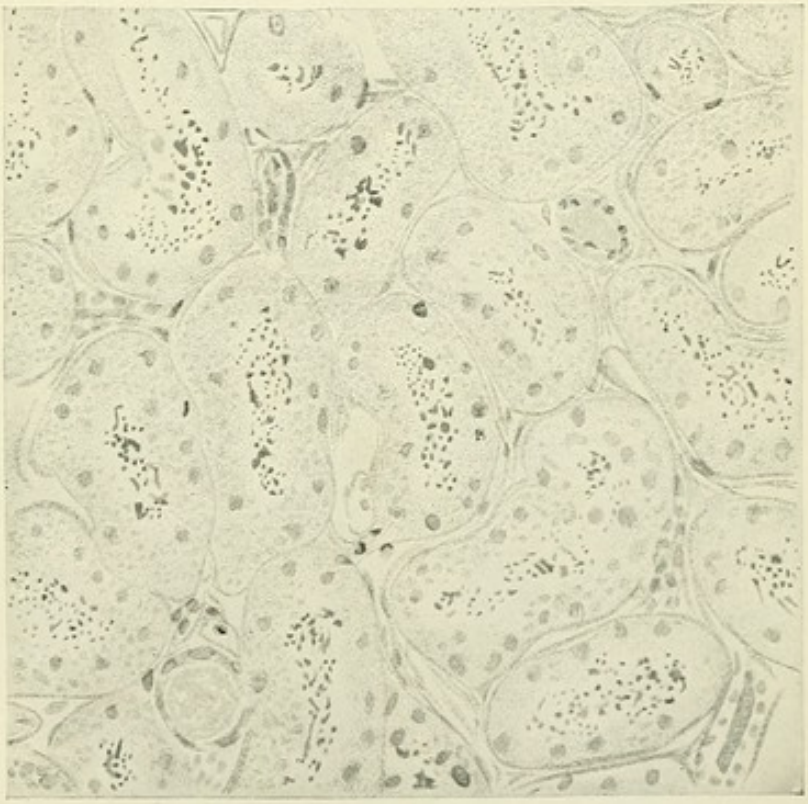


Fig. 2.

The kidneys in blackwater fever (Werner).

Fig. 1.—Occlusion of the straight tubules.
Fig. 2.—Iron reaction with potassium ferrocyanide.

PLATE X

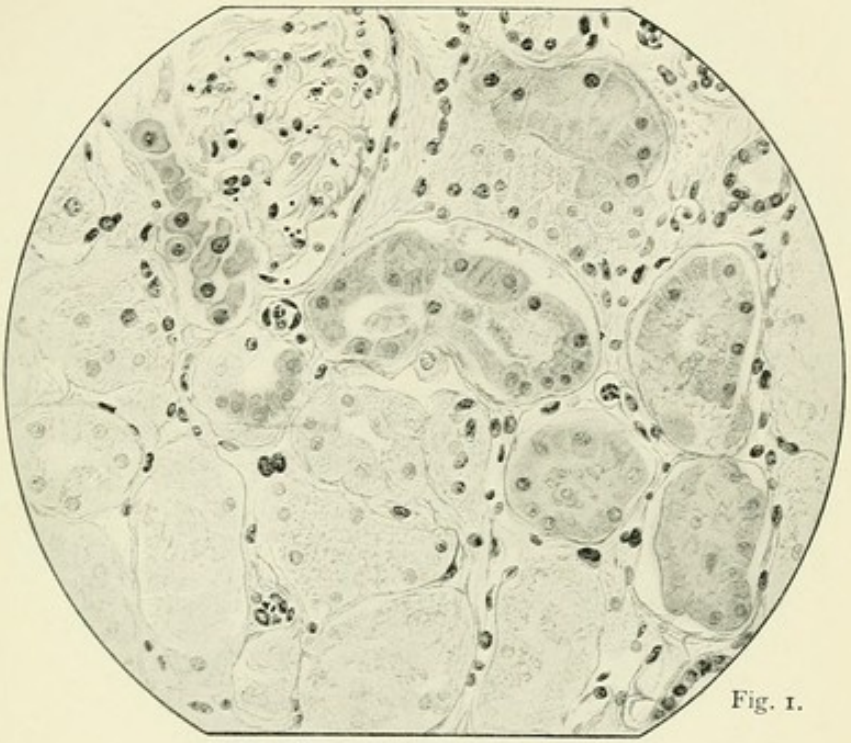


Fig. 1.

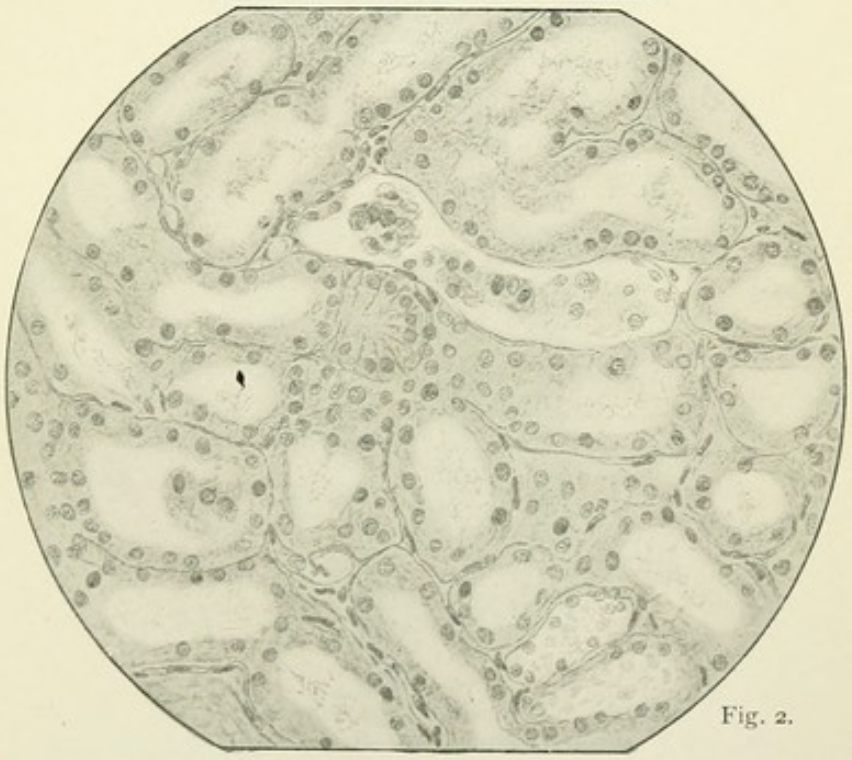


Fig. 2.

The kidneys in blackwater fever (Werner).

Fig. 1.—Degenerative changes in the epithelium of the convoluted tubules.
Fig. 2.—Dilatation of the lumen of the convoluted tubules.

PLATE XI

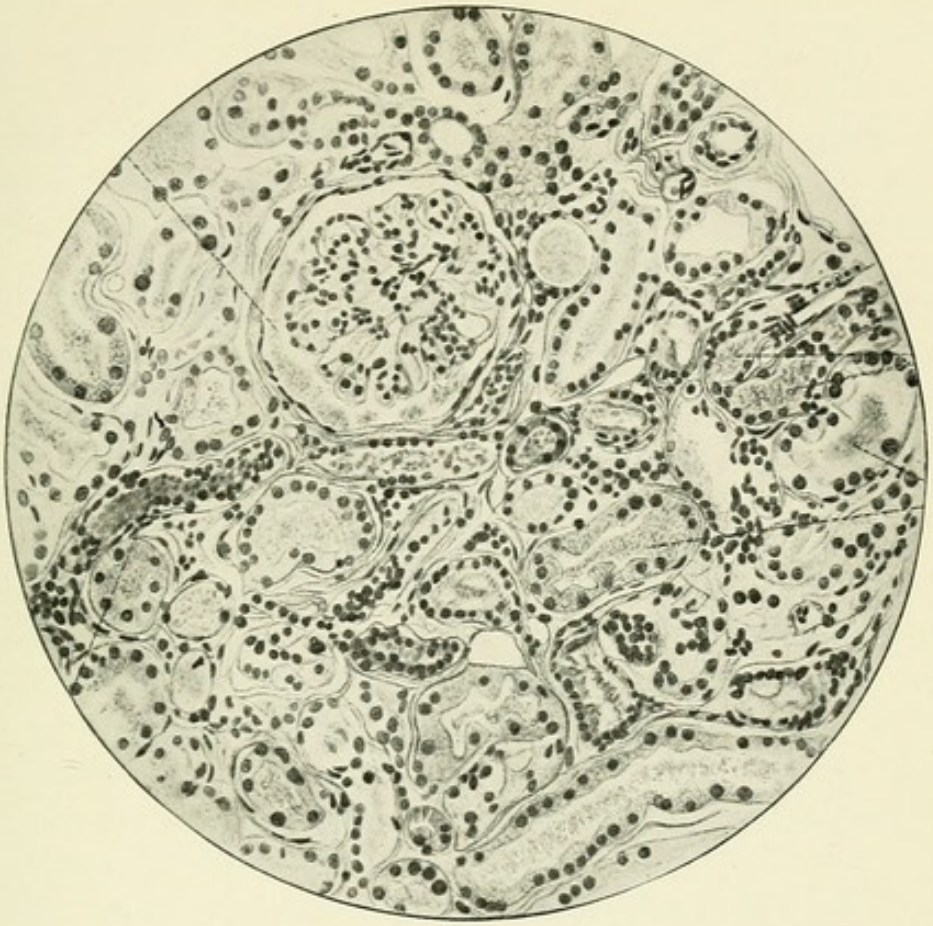


Fig. 1.



Fig. 2.

The kidneys in blackwater fever (Werner).

Fig. 1.—Different characters of included masses in the glomeruli, the convoluted tubules, the straight tubules, and the intercalary portion.

Fig. 2.—Different characters of coagula in the ascending and descending limbs of Henle's loops.

The **pleuræ** may show punctate hemorrhages and the cavity may contain a quantity of serous fluid. The surface of the lungs may show slaty specks and striæ. The cut surface is very pale, and exudes a very small amount of very pale, frothy, serous fluid. There may be an ashy discoloration in the course of the vessels, hypostatic congestion, and edema.

The **pericardium** may contain from a few drams to several ounces of a clear or sanguineous fluid, and may present hemorrhages varying in size from that of a millet seed to that of a cent. The heart is pale and often flabby. The muscular fibers are easily separable; the walls may be very thin. The left ventricle is usually strongly contracted, the right collapsed. Auricles and ventricles may contain coagula or thrombi. Microscopically the fibers stain well and show striations perfectly; there are some areas of slight pigmentation and some of connective-tissue proliferation; the nerve trunks in the transverse section show marked degeneration; empty nerve sheaths are seen, and some connective-tissue proliferation into funiculus (Goltman and Krauss).

The **brain** is usually pale and unpigmented; the latter ventricles may contain an excess of fluid. The convexity of the pia may show slight cloudiness in the course of the vessels. The puncta vasculosa may be scarcely visible. The bone-marrow shows the usual changes of malaria. Melanin, hemosiderin, and proliferating normoblasts may be found.

CHAPTER V

CLINICAL HISTORY

THE simplest and most logic classification of the malarial fevers is, according to the form of the several parasites causing them, into tertian, quartan, and estivo-autumnal. The endeavor to affiliate the tertian and quartan parasites with the intermittent fevers and the estivo-autumnal with the remittent is fruitless, for a remittent temperature is by no means a characteristic of estivo-autumnal infections. Neither is the division into quotidian, tertian, and quartan consistent. Quotidian paroxysms may be due to estivo-autumnal infection, double tertian, or triple quartan. Tertian paroxysms may be produced by estivo-autumnal parasites or by simple tertian. The three forms of malaria will be studied in their acute and chronic courses, larvated or masked forms, with the complications and sequelæ.

ACUTE MALARIA

Incubation.—The period of incubation varies within very wide limits. It may be stated as a general proposition that the incubation period is longest in quartan infections and shortest in the estivo-autumnal. The average period is, for quartan, twelve to eighteen days; tertian, six to fourteen days, and estivo-autumnal, two to ten days. Much longer periods, running into several months, have been reliably recorded. These must be regarded as cases of chronic malaria where the latent stage precedes the active, and are analogous to those cases of syphilis in which the secondary manifestations occur without recognized primary lesion, and are to be explained satisfactorily only by parthenogenesis.

General Description of a Malarial Paroxysm.—The forms of acute malaria have so many points in common that it is convenient to describe first the typic malarial paroxysm.

Prodomata may be perceived by the patient. They may correspond to the last few parasitic sporulations preceding that which causes the paroxysms or may occur only a few hours before the access. They are ill-defined, but usually consist of languor, anorexia, headache, aching of the loins and hips, thirst, epigastric distress, a disposition to stretch and yawn, and chilliness along the course of the spine. These symptoms may be so slight as to escape attention. The typic malarial paroxysm comprises three well-marked stages: the cold stage, the hot stage, and the sweating stage.

The cold stage presents itself with the rapid intensification of the prodromata described. The sensation of coldness spreads to every part of the body. The skin becomes pale, especially the lips, the ears, and the nails, and the papillæ of the skin stand out, forming the so-called "goose-skin." The patient shivers, sometimes so violently that he shakes the bed; he covers up, his teeth chatter, and he looks and feels cold. The slightest motion of the body or of the bedclothing increases the vehemence of these phenomena. Notwithstanding these evidences of coldness, the thermometer shows an elevation of internal temperature. The fever may even precede the cold stage. The patient complains of a tight headache, a backache, precordial oppression, and dyspnea. He often complains of general soreness, as severe as if having been beaten. He may suffer with nausea and vomiting of bile. There is apt to be frequent micturition of small quantities of limpid urine. The respiration is rapid and tremulous. The pulse is accelerated, diminished in volume, and increased in tension. The cold stage may last from a few minutes to two or three hours.

With the onset of the hot stage hot flashes alternate with cold until, the sense of heat becoming general, the patient presents a very different picture from that of the first stage. He begins to uncover, the skin is flushed and hot, the pulse full and bounding, the respiration deeper, and the urine is scanty and high colored. There may be constipation or diarrhea. The tongue is coated, bulky, and usually shows indentations produced by the teeth. Herpes appears upon the lips or nose. The spleen is enlarged and the upper half of the

abdomen is tender on pressure. The headache, soreness, nausea, and vomiting continue, there is often great thirst and epigastric pain, and the temperature continues to rise.

When the temperature is at its height the sweating stage is ushered in by crisis. Beads of perspiration begin to appear upon the face, then a universal sweat breaks out, and the skin, which was first cold and rough, then hot and dry, now becomes moist and natural. The temperature falls to normal, often a little below; the pulse and respiration resume their normal

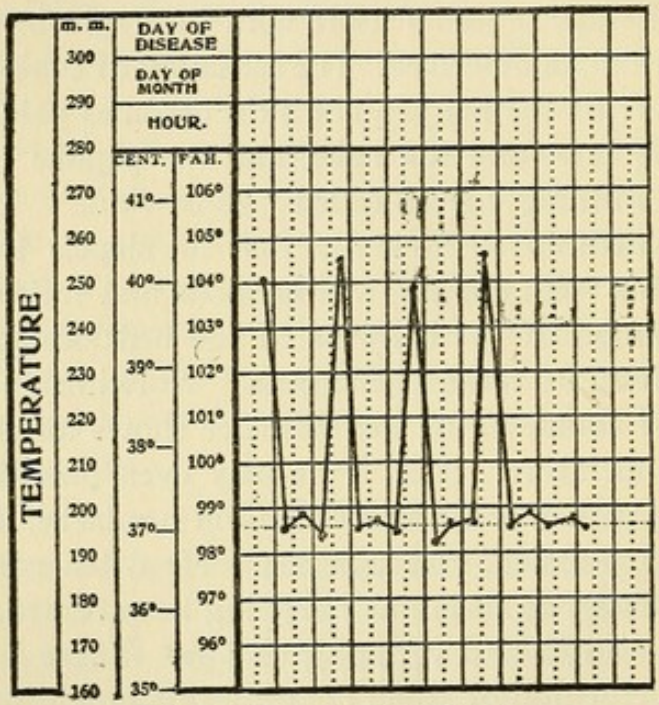


Fig. 51.—Single tertian infection.

features. The soreness disappears, the thirst ceases, and the patient often feels so comfortable that he takes a short nap.

Such is the typic procession of one of the most remarkable events in the category of disease. The conspicuous changes, the swift succession of stages, and the punctual periodicity of paroxysms are unparalleled in pathology.

In some paroxysms, however, one or two stages may be missing. The temperature may rise unaccompanied by a cold stage or may fall to normal unattended by sweats. This constitutes the so-called dumb chill. The cold stage is the least constant, the hot stage the most so. The cold stage is most

constant in quartan fever, least so in estivo-autumnal infections.

Simple Tertian Infection.—Infection with a single brood of simple tertian parasites causes a paroxysm every other day. The parasites being in the same stage of development causes great regularity in the course. From the beginning of one paroxysm to the beginning of another is almost precisely forty-eight hours. When the interval is not quite so long, as sometimes happens, the paroxysms are said to *anticipate;* when

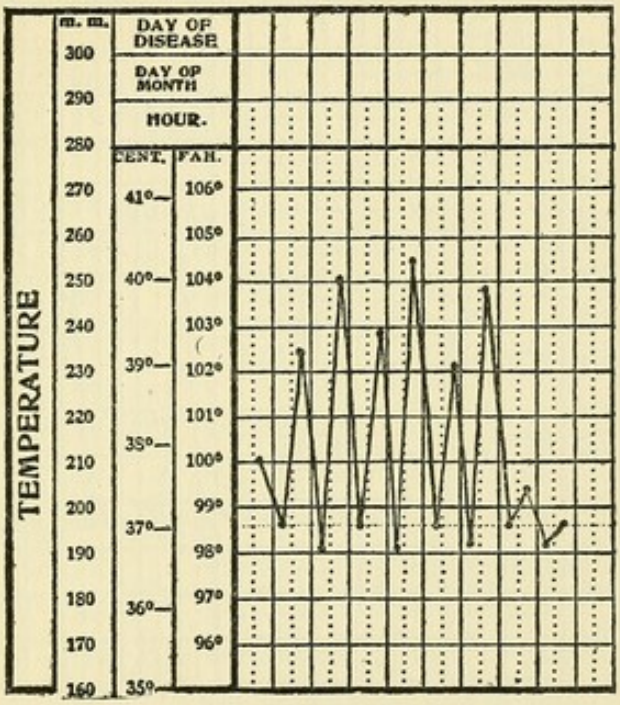


Fig. 52.—Double tertian infection.

longer, as is more rarely the case, they are said to *postpone* or to *retard*. Postponing is usually regarded as evidence of abating activity.

In more than half the simple tertian cases the infection is double; that is, there are two distinct generations of parasites. These generally mature on alternate days; two paroxysms on one day with an intervening day of apyrexia being extremely rare. The paroxysms may occur at the same time every day and be similar in every respect. Usually, however, there is a perceptible difference between the paroxysms of successive days, a difference consisting of time of onset, severity, and

relative length of the stages of the paroxysms. It very rarely happens that the paroxysms are so lengthened, and one so anticipates that its onset occurs during the latter stage of the preceding paroxysm. They are styled *subintrant* attacks.

A change of type from quotidian to tertian paroxysms, or *vice versâ,* is commonly observed. The change from quotidian to tertian may be spontaneous or the result of incomplete medication or improvement in hygienic conditions, one group of parasites perishing. A change from tertian to quotidian may

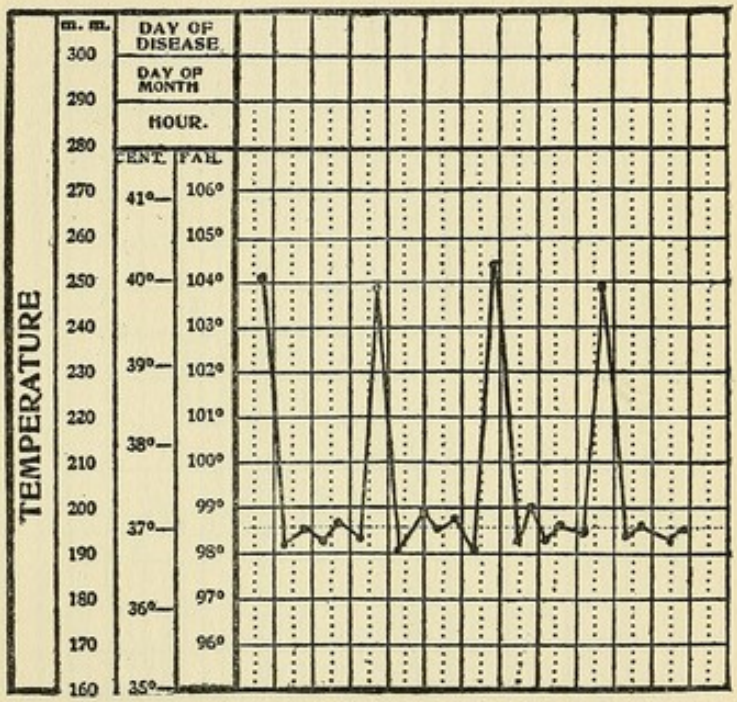


Fig. 53.—Single quartan infection.

occur without apparent cause or following indiscretions of various sorts.

The onset is probably more common during the morning, but this is neither constant nor of diagnostic dignity. The invasion is almost always with a chill. The temperature rises suddenly and falls likewise. Commonly there are no grave symptoms, but a mild delirium is not rare. The temperature usually goes as high as 103° to 105° F. The average duration of the paroxysm is from eight to twelve hours.

During apyrexia the patient may feel perfectly well except slight weakness, headache, or vertigo. He is usually able to

attend to his duties. The tendency to spontaneous cure is greater than in either of the other forms of malaria, the attack not infrequently subsiding after a number of paroxysms, without any medication or with only a purgative.

Quartan Infection.—The quartan parasite accomplishes its endogenous cycle in seventy-two hours. Hence infection with a single generation of quartan parasites produces a paroxysm followed by two days of apyrexia and a second paroxysm on the fourth day. Such attacks are popularly known in the South as "third-day chills." A double quartan infection reverses the

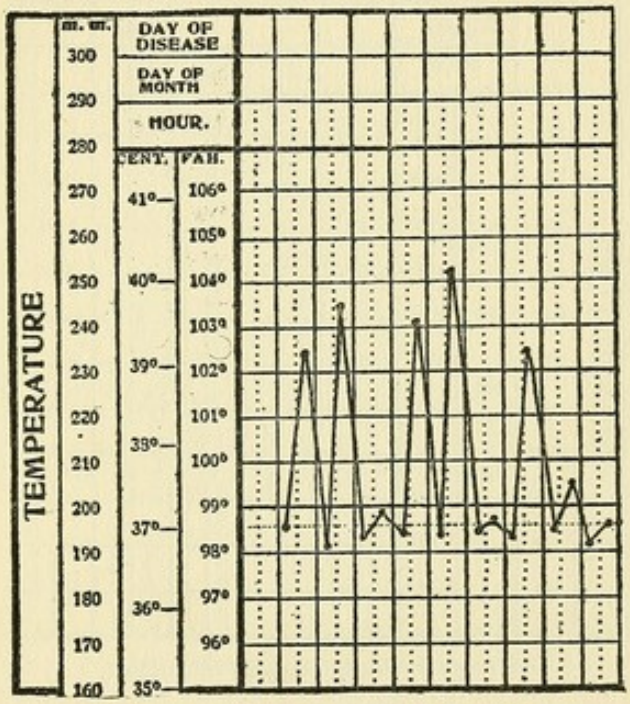


Fig. 54.—Double quartan infection.

course, causing two paroxysms on successive days, followed by a day of apyrexia. Triple quartan infections, the parasites maturing on successive days, give rise to quotidian fever. As in simple tertian intermittents, quartan accesses sometimes anticipate or retard. Subintrance in triple infections is rarely seen, due probably to the shorter duration of the paroxysms. Changes of type between single, double, and triple quartan are sometimes observed.

The onset, especially in single infections, occurs probably more often during the afternoon hours. The symptoms are

those of the typic paroxysm and are well marked. The cold stage is not only more constant than in the other forms, but is more intense and usually of longer duration. The three stages are sharply contrasted. Pernicious symptoms are very rarely observed in connection with quartan infections. This may be accounted for by the more equal distribution through the circulation of the parasites which show no tendency to congregate, and by the longer apyrexial periods between the paroxysms. The average duration of the paroxysm is eight or ten hours.

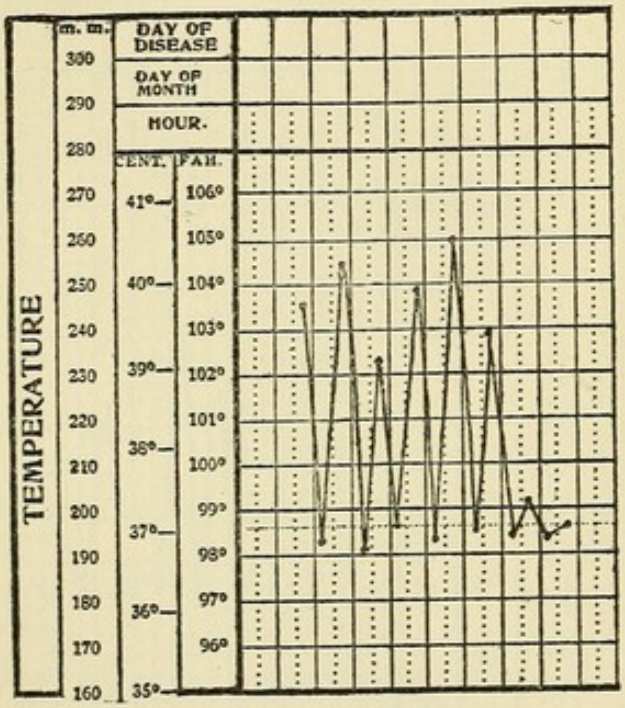


Fig. 55.—Triple quartan infection.

The obstinate disposition of quartan fever to recur has been a matter of common knowledge for centuries, and is still a popular idea. This may doubtless be accounted for at this day by the probability that, owing to the greater interval between the accesses, the specific is not properly taken. Most physicians will agree that quartan fever is just as amenable to appropriate therapy as the other acute forms. As in tertian fever, an almost complete feeling of well being may be experienced between paroxysms, the patient usually being able to attend to business.

Estivo-autumnal Infection.—The chief feature of infec-

tion with estivo-autumnal parasites is the irregularity of the course as contrasted with that of tertian and quartan infections. A classification is difficult and, while that into estivo-autumnal or malignant tertian and quotidian is perhaps best, these may be clinically indistinguishable.

Malignant Tertian.—This form of infection is due to parasites which tend to mature in forty-eight hours. It is characterized by a long paroxysm and a short apyrexia. The duration of the access is from twenty-four to forty-eight hours or more.

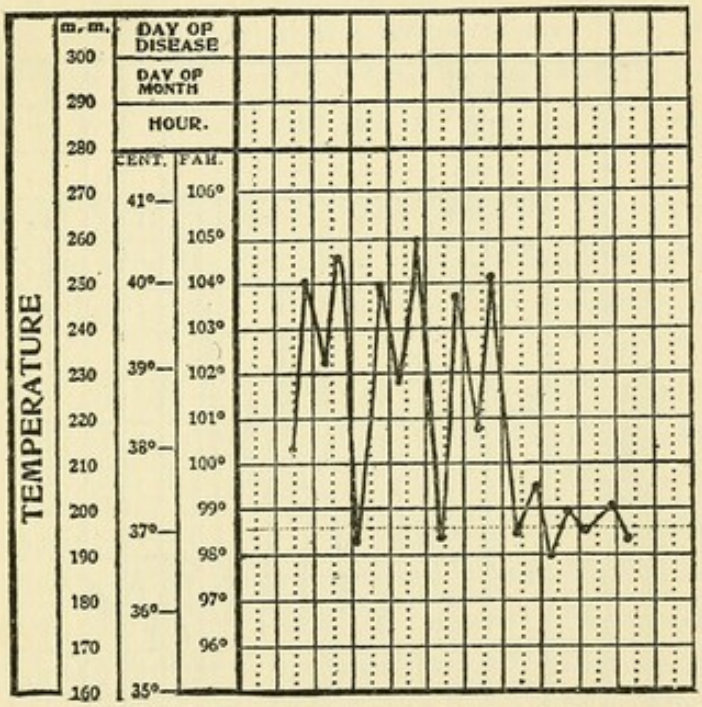


Fig. 56.—Tertian estivo-autumnal malaria.

Anticipation and subintrance are oftener observed here than in any other form of malaria.

Prodromal symptoms are usually pronounced. The cold stage is often not manifest; the sweating stage is less commonly missing. The typic temperature is characteristic. It rises abruptly, often as high as 104° F. On reaching its height it remits with slight oscillations for a few hours. It then makes a marked remission and again rises suddenly, usually higher than before. The final fall is by crisis. It is customary, following Marchiafava and Bignami, to divide this course into five stages: 1, the rise of invasion; 2, the fastigium;

3, the pseudocrisis; 4, the precritical rise; 5, the crisis. This curve is simulated only by simple tertian fever with subintrant attacks, which is uncommon. Unfortunately this typic sequence is far from constant; the modifications are very numerous and are too irregular to analyze.

The symptoms of the hot stage are more pronounced than in the infections previously described. The headache and backache are worse, the general depression is more profound, stupor and delirium may appear, and pernicious symptoms may arise. During the short interval the patient does not regain his ease

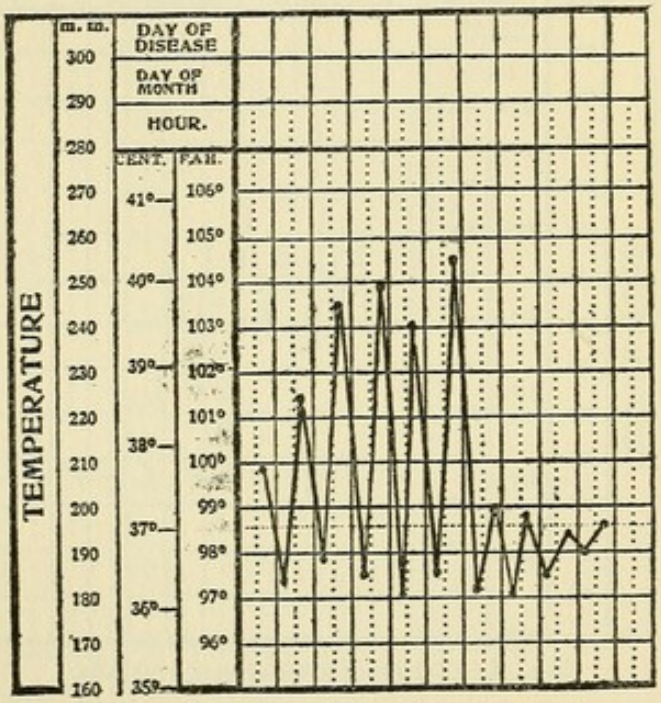


Fig. 57.—Quotidian estivo-autumnal malaria.

as in the simple intermittent fevers, but the aching and prostration continue, and he may be unaware that the fever has left.

Quotidian.—The quotidian estivo-autumnal fever is more regular in its course than the tertian, especially at first, though there is nothing characteristic in the temperature curve, which may closely resemble a double tertian or a triple quartan. Later it is apt to lose some of its regularity by anticipation or by lengthening of the paroxysms, whose average duration is from six to ten hours. The chill is rather more constant

than in the tertian, otherwise the symptoms are identical, the patient not regaining strength from one paroxysm to another. In the interval the temperature is prone to sink, even as low as to 95° F.

Mixed Infections.—Infections with two or more species of the malarial parasite are known as mixed or combined infections. The most frequent combination is of simple tertian and estivo-autumnal. As a rule, one parasitic form predominates and produces its usual picture; this may, however, be considerably modified by the other group of parasites. The most frequent modification in the temperature chart is a tendency to continuity. The paroxysms are not usually as typic as in simple infections and are not so regular in their occurrence.

Analysis of Symptoms.—*Temperature.*—The main characteristics of malarial temperature have been given when treating of the several forms. It remains only to consider a few general traits.

The feature of the temperature in uncomplicated and untreated malaria is periodicity. The temperature is, in a great majority of instances, intermittent. The fever of longest intervals, the quartan, has only one mode of causation, the quartan parasite. The fever of next longest intervals between times of onset, the tertian, has two modes, the simple tertian parasites and the tertian estivo-autumnal; while the fever of shortest intervals, the quotidian, may be due to triple quartan, double tertian, or quotidian estivo-autumnal infection. As intimated, quotidian fever may change to a single or double quartan or to a tertian, and both tertian and quartan may become quotidian, but tertian fever never becomes quartan, or *vice versâ*, without reinfection.

In tertian and quartan infections the temperature usually rises rapidly after the onset, reaching the acme during the second stage of the paroxysm and declining during the third to normal or a little below normal. This is also the usual course in quotidian estivo-autumnal, the temperature chart showing symmetric ascent and descent, producing an arrowhead appearance. In this infection the temperature descends

rather lower during the fever-free interval than in the others. The typic run of tertian estivo-autumnal has been given as follows: 1, the stage of initial ascent; 2, the fastigium, during which the temperature may show fluctuations of a half degree to a degree; 3, the pseudocrisis; 4, the precritical or final ascent; and, 5, the crisis.

Continued temperature in malaria is not as common as usually regarded; remittent fever was formally thought to be the rule in the summer-autumn malarial fevers. The causes of this error are three; first, in tertian estivo-autumnal infections the apyretic interval is short; secondly, this interval often occurs during the night or early morning hours; thirdly, the patient, guided by the discomfort which continues during the interval usually denies that he has been free from fever. Nevertheless, a continued temperature is occasionally noted in malaria, especially in tertian estivo-autumnal infections. It may be regularly remittent or may be irregular. The following are the chief causes of a continued malarial temperature:

1. Prolongation of the paroxysms.
2. Anticipation of the paroxysms.
3. Infection with more than one brood of the same species of parasite.
4. Infection with more than one species.
5. Complications.

So-called spontaneous recovery may occur in either form of malaria. As a rule, the recovery is only temporary and is merely the transition from the active to the latent stage, relapses usually occurring sooner or later. Favorable hygienic conditions encourage spontaneous cure.

The duration of untreated acute malaria is too indefinite to permit of exact statements. While simple tertian may terminate after a few paroxysms, an estivo-autumnal fever may continue three or four weeks if it does not in the meantime become pernicious.

A postmalarial secondary fever, or spodogenous fever, is occasionally observed after the infection, particularly estivo-autumnal, has lasted for some time. It persists for days or weeks uninfluenced by quinine. The blood examination is

negative for parasites. Resorption of débris, toxins, and visceral lesions have been offered as explanations of this process, but none of these are entirely satisfactory.

Circulatory System.—The Blood.—The blood, being the habitat of the parasites, furnishing their pabulum, containing their toxin, besides carrying one of the host's mechanism of defense against their depredations, shows important changes.

The volume of the blood as a whole is somewhat diminished. The specific gravity is only slightly lowered, and usually only in recent infections, the destruction of the solid elements being nearly compensated by the excretion of fluids. The density, at first lowered, approaches normal as the infection persists. The experiments that have been performed with reference to the tonicity of the blood in malaria have uniformly shown that this is increased.

The parasites of malaria have a very unequal distribution, some being almost constantly found in the superficial circulation throughout their asexual cycle, others only during the early stages of their development, modestly retiring to the recesses of the viscera for procreation. The organisms are sometimes scanty in the peripheral blood, occasionally entirely absent.

The tertian parasite, more abundant in the deep circulation, may be observed in the peripheral circulation throughout the course of the asexual cycle, excepting the sporulating forms, which are only exceptionally seen. The gametes are not infrequently detected.

The quartan parasite is most evenly distributed, being about equally common in the visceral and superficial blood. Furthermore, all stages of the asexual development, including the sporulating forms, may be followed in blood obtained from the peripheral circulation. Quartan gametes are rarely seen.

The estivo-autumnal parasites are seen in only the earliest phases. In some localities the gametes are very commonly observed after the infection has persisted a week or more; in others, even where severe infections of long standing are encountered, they are more rarely noted.

Pigment is most frequently contained within the large mononuclear, less often the polymorphonuclear, leukocytes, but may exist free in the blood current. It is of a dark reddish-brown or black color, and occurs as granules, rodlets, or irregular clumps.

One of the best-known facts in the study of malaria is the rapid and widespread destruction of the red blood-cells. A certain number of erythrocytes perish with each parasitic sporulation like soldiers after a volley from the enemy. It is not uncommon for a fourth to a half million red cells per cmm. to be destroyed during each of the first two or three paroxysms, and this may progress until the count is considerably less than one million per cmm. As a rule, in uncomplicated benign malaria this erythrorrhexis is greater during the early paroxysms, diminishing with each successive paroxysm, the cells apparently requiring some sort of immunity. It is likewise usual for the marked early destruction to be rapidly compensated, or nearly so, by the activity of the blood-forming organs. Later it is more difficult for these organs to replace even the smaller number of destroyed cells. Hence the anemia is commonly in proportion to the severity and duration of the attack. Restitution of the red cells is more rapid and certain with tertian and quartan than with estivo-autumnal infections. Race, age, and constitution are also factors in the rapidity of reconstruction.

There are certain changes that occur in the infected cells which should be mentioned. The cells containing the simple tertian parasites are swollen and somewhat decolorized. Those containing the quartan parasites are shrunken and somewhat darker in color. The cells harboring estivo-autumnal organisms have the appearance of old gold or of brass, and become somewhat smaller. A curious appearance of some infected cells is what has been termed stippling. This may be seen in both simple tertian and estivo-autumnal infections, but presents features more or less characteristic in each. In simple tertian the dots are fine and abundant. In estivo-autumnal they are coarse, irregular, maybe cleft-like, and few in number—from two to six. The fine stippling of tertian infection is also

known as "Schüffner's dots." Stippling is brought out by staining.

A mysterious property of infected cells is their apparent tendency to mutual attraction. For instance, it is very common to observe under the microscope two or more infected cells in juxtaposition, even where these are the only infected cells in the field. This property, whatever be its nature, probably explains the parasitic localizations in pernicious attacks.

Changes occur also in non-infected cells. The commonest of these are, in my experience, in the order named: the occurrence of macrocytes and microcytes, polychromatophiles, and poikilocytes. Nucleated reds are occasionally observed. Basophile granulation is sometimes noted. It was this lesion which Plehn formerly mistook for the latent phase of the parasite. These granules appear in a varying number of cells, occasionally in those containing parasites, as minute dots or streaks from one-quarter to one-half micron in diameter. When few in number they appear coarser. They stain best with the Romanowsky class of stains. Basophile granulation is not characteristic of malaria, but is found in a number of affections. Retraction of hemoglobin and vacuolization are common findings in malarial blood.

The hemoglobin generally falls decidedly. Its curve is apt to run parallel with and a little below that of the red cells, and is slower in returning to normal. The hemoglobin content is no guide as to the severity of the disease.

The leukocytes are, in benign malaria, usually slightly diminished. A leukocytosis is found only in pernicious malaria or in association with complications. The differential formula is the most noteworthy feature. Its peculiarity is the large mononuclear increase. Bastianelli[233] observed a diminution of the polymorphonuclears and increase of the large mononuclears, especially in advanced and pernicious cases, and less marked during the early paroxysms. Billings[280] noted a great absolute and relative increase of the large mononuclears, a decided diminution, both relatively and absolutely, of the polymorphonuclears, a wide variation of small mononuclears, and a slight diminution of eosinophiles. Stephens and Christo-

phers[57] have recorded that there is no increase of the large mononuclears during pyrexia, but that the increase is pronounced in the apyretic interval, or immediately following the rise of temperature, if only one such occurs. They also noted that in certain cases this change was extraordinarily marked, the large mononuclears during the interval even exceeding in number the polymorphonuclears. They observed further that in some cases the mononuclear increase was to be detected even during the fever stage, but in these cases it was still further evident during the interval. Rogers[44] concludes that the mononuclear increase is decidedly more marked and frequent in benign than in malignant tertians. He accounts for this by the shorter apyretic interval of the latter. Krauss[281] believes that it is not so much the absolute increase of the large mononuclear elements as the relative increase over the small lymphocytes, which is characteristic of malaria. Ziemann[48] states that in the beginning of the access there is often a transient polymorphonuclear leukocytosis, which recedes during the acme of the fever simultaneous with a relative increase of the large mononuclears, which may reach 15 per cent. or more.

Eosinophilia, in the writer's experience, denotes complications, ordinarily intestinal helminthiasis.

Billings'[280] 16 cases showed the following average:

	Per cent.
Small mononuclears	16.9
Large mononuclears	16.9
Polymorphonuclears	65.04
Eosinophiles	0.96

Krauss'[281] 204 cases:

	Per cent.
Small lymphocytes	14.8
Large lymphocytes	19.5
Polymorphonuclears	63.7
Eosinophiles	2.0

Rogers[44] found that the large mononuclear leukocytes numbered:

0-8 per cent. in	6 cases
8-12 per cent. in	10 cases
12-15 per cent. in	25 cases
15-20 per cent. in	16 cases
Over 20 per cent. in	20 cases

The leukocytes occasionally undergo degenerative changes, among which are fatty degeneration and vacuolization of the protoplasm and fragmentation and chromatolysis of the nucleus.

The blood platelets are somewhat increased in malaria, especially during the interval following a severe attack.

The carefully conducted experiments of Capograssi[84] tend to show that, while malarial blood possesses agglutinative properties, it is of no diagnostic importance.

Celli, Carducci, and Casagrandi,[147] investigating together, were unable to determine definitely the existence of an hemolysin, but concluded that such a body probably existed. Later Casagrandi was able to verify the presence of an hemolysin in malarial blood, and concluded that it was masked by an antibody. De Blasi[82] found in a watery solution of centrifugated red cells antihemolytic action in 15 cases out of 19. The 4 negative cases were in chronic malarias who had been under the influence of quinine a long time. This hemolytic action is not specific for malaria, occurring in measles, typhus, erysipelas, and scarlatina, but not in healthy persons.

At the height of the fever the pulse may reach 130 or more. During the interval it usually becomes almost quite normal in tertian and quartan infections. In estivo-autumnal fever it depends upon the severity of the attack and the resistance of the patient. Occasionally the rapidity of the pulse does not show the usual relation to the height of the temperature, but may be below 100, with high fever. This is sometimes observed during the attack, but is rather more common during convalescence. During the cold stage of the paroxysm the blood pressure rises decidedly, falling during the second stage, to become normal in the sweating stage. This is fairly constant, variations being due not to a difference of parasites, but to individual conditions. An anemic murmur may be heard over the heart. A sense of precordial oppression or acute pain are common complaints.

Respiratory Organs.—Respiration is usually accelerated in proportion to the temperature. Cough is a frequent symptom. In children a frequently repeated superficial hacking cough is

often an indication of nausea. Bronchial catarrh is not infrequently observed, accompanied by sibilant râles on auscultation. Epistaxis may occur and is occasionally alarmingly profuse.

Gastro-intestinal Organs.—While the paroxysm is on, the appetite is usually completely lost. In tertian and quartan malaria this may be regained during the interval, but in estivo-autumnal anorexia generally persists throughout apyrexia. The patient ordinarily complains of a bitter taste in the mouth and fulness, discomfort, or pain in the epigastric region. The tongue is large, flabby, thickly coated, usually anemic, and showing the prints of the teeth along the edges. Nausea is nearly a constant symptom, and retching and vomiting are distressing. The vomitus consists of matters ingested, bile, or slimy mucus. The bowels are constipated, regular, or loose, in the order of frequency named; choleraic or dysenteric discharges occasionally appear. More or less enlargement of the spleen is a usual occurrence, together with pain and tenderness in the left hypochondrium. In primary acute infections the enlargement may not be prominent; in later infections the spleen is often palpable beyond the costal margin. The spleen is rarely much enlarged in the negro. Enlargement of the liver is much less constant and less marked than splenic hypertrophy. There usually exists tenderness in the epigastric and right hypochondriac regions.

Genito-urinary Organs.—Urine.—As a general rule, the urine emitted during a cold stage is paler in color and that of the stage of fever highly colored, but individual circumstances may produce numerous exceptions to this rule. In certain cases of estivo-autumnal fever the urine may be very highly colored and contain a heavy deposit. In these cases the urine contains biliary coloring matters and an excess of urobilin. The diazo reaction sometimes obtains. The indican is frequently increased. In tertian and quartan cases the quantity of the urine is somewhat augmented, in estivo-autumnal diminished. Polyuria of tertian and quartan malaria and that occurring sometimes in estivo-autumnal occurs under two conditions, the polyuria of the paroxysm and that of convalescence or post-

malarial polyuria. In the former case the increase in the quantity of urine excreted coincides nearly with the paroxysm, the amount diminishing during the interval. The polyuria of convalescence ordinarily begins from three to six days after the attack and continues for a few days to several weeks. The reaction is acid, varying directly with the concentration of the urine. The specific gravity does not always bear a definite relation to the amount of the urine, as might be inferred, but may be relatively high when the urine is abundant, or low with scanty urine.

The output of urea is increased. The increase begins several hours before the attack, attains its maximum toward the end of the cold stage, declining to or below normal at the end of the paroxysm. A curious fact noted by Ringer and by Senator[227] is that when the return of the attack has been prevented by the administration of quinine, there is still to be observed an increase in the excretion of urea on the days upon which the paroxysm should have occurred.

The uric acid content of the urine is only slightly, if at all, modified. The amount of chlorides runs parallel with the quantity of urine. The phosphates are eliminated in quantities less than normal during the fever, and in greater quantities during apyrexia. The entire twenty-four-hour urine commonly shows an increase. The variations in the excretion of the sulphates are similar to those in regard to urea.

The elimination of the sodium and potassium bases is very inconstant, both as to quantity and as to the stage of the disease during which elimination takes place. Malarial urine contains an excess of iron, especially after the paroxysm. It is dependent upon and proportionate to the destruction of erythrocytes.

The occurrence of albumin in the urine is relatively infrequent in the mild attacks of simple intermittent which terminate after one or two paroxysms. In severe estivo-autumnal infections, however, it is exceedingly frequent. Its frequency varies not only with the type and severity of the attack, but also with locality and other circumstances. The following reports are tabulated to show the extent of these differences,

the denominator indicating the number of cases of malaria, the numerator the number in which albumin was found:

Costa[79]	$\frac{32}{103}$
F. Plehn[5]	$\frac{6}{198}$
Marchoux[96]	$\frac{39}{40}$
Borne[99]	3.8%
Thayer and Hewetson[29]	$\frac{133}{335}$
Solon[88]	25%
Schoo[89]	2%
Thayer[282]	$\frac{321}{758}$
Anders[283]	$\frac{14}{1780}$
Atkinson[285]	$\frac{11}{121}$
Chamberlain[42]	$\frac{0}{126}$
Frerichs[61]	$\frac{20}{51}$
Cook[285]	$\frac{75}{100}$

Marchiafava and Bignami[22] say that albuminuria is rare in their experience, though Kelsch and Kiener[178] hold the opposite view, and Craig[70] states that it occurs in a majority of the severe cases.

An increased toxicity of the urine has been found in large per cent. of cases of malaria, greatest during apyrexia and usually intensifying with each successive paroxysm. Brousse[86] arrived at the following conclusions: 1. The urotoxic coefficient, calculated by means of the formula of Bouchard, the average coefficient being .464, rises during the attack, and the physiologic effects observed are those usually noted after the injection of urine; dyspnea, miosis, fall of temperature, exophthalmia, besides convulsions. 2. This toxicity is diminished during the period of convalescence from the intermittent fevers very much below that of the urine during the access, and, furthermore, more feeble than that of normal urine.

Nervous System.—Headache is one of the most invariable symptoms of malaria. Backache and somatic soreness are severe. Sometimes hyperesthesia is seen. Vertigo is the rule, especially when the patient is upright. Neuralgia, facial or intercostal, is a not infrequent symptom. Stupor and delirium are present in grave cases, particularly in children.

Skin.—During the first stage of the paroxysm the skin is blanched and cold, during the second stage hot, dry, and perhaps turgid, during the third bathed with sweat, becoming natural toward apyrexia. Icterus is not a pronounced symptom

in acute cases except in certain pernicious forms. With the possible exception of pneumonia herpes is seen more frequently in malaria than in any other disease. Its commonest sites are the lips and nose, but it may appear elsewhere. It is not nearly so common in the negro as in the white. Urticaria and erythema are sometimes observed.

PERNICIOUS MALARIA

Malaria threatens or destroys life through its inherent dangers, acutely expressed, through the sequelæ of chronic manifestations, or through complications in any stage. Pernicious malaria is that form of malaria, extremely acute, which, independently of complications, endangers life in a few hours or a few days. This gravity may be due to the intensification of ordinary malarial symptoms or to the advent of unusual ones. It should be clearly understood that pernicious fever is not a pathologic entity, but is a form of malaria from the simple modes of which it sometimes differs only in degree. Its pathogenesis is intimately associated with the life history of the malarial parasite, much more so than is hemoglobinuric fever. Intermediate forms may be encountered which may be difficult to place, as cases with slight somnolence, abundant sweats, or cold surface.

Though the pernicious forms of malaria were alluded to by Hippocrates and by Celsus, they did not receive any detailed consideration until 1743, when Torti described them. This pyretologist divided the pernicious fevers into *solitariæ,* those characterized by the continuity or acuteness of the ordinary symptoms, and the *comitatæ,* in which one grave symptom predominated. The *comitatæ* he subdivided into the colliquative, including the choleraic, dysenteric, atrabiliary, cardialgic, and diaphoretic, and the coagulative, including the syncopal, algid, and lethargic forms.

Alibert, in 1804, distinguished twenty varieties of pernicious malaria.

Roux, following Jaccoud's classification, looks on all as originating in the vasomotor and sympathetic systems or in the cerebrospinal system.

Kelsch and Kiener adopt Torti's system with slight modifications.

Marchiafava and Bignami arrange the pernicious forms, according to the course of temperature, into tertian, quotidian, subcontinuous, and larval.

Manson groups them roughly into cerebral—including the hyperpyrexial, comatose, convulsive, and paretic forms—and algid, including the syncopal, choleriform, dysenteric, and hemoglobinuric forms.

Dantec classifies the varieties anatomically according to the organs which bear the brunt of the attack, namely: (1) The brain, (2) the medulla, (3) the spinal cord, (4) the heart, (5) the lungs, and (6) the digestive tube.

Homem describes fifteen definite forms, besides several undefined varieties.

Cardamatis distinguishes seventeen varieties.

More than thirty so-called varieties of pernicious malaria have been described. A partial list of these includes the apoplectic, ataxic, comatose, sudoral or diaphoretic, delirious, eclamptic or convulsive, tetanic, typhoid, amaurotic, aphasic, ardent, exanthematous, hemiplegic, hydrophobic, neuralgic, cerebromeningeal, cardialgic, dyspenic or asthmatic, pneumonic, pleuritic, syncopal, hemoptoic, algid, choleraic, dysenteric, gastric or gastralgic, hemorrhagic, bilious or hepatic, lymphatic, rheumatic, and nephritic forms.

This multiplicity is due to two causes: first, the fanciful and unnecessary subdivision of typic forms; second, the mistaking of complications for true pernicious attacks.

Any classification is not absolutely essential, and all are more or less arbitrary. Nevertheless, for convenience, all forms of true pernicious malaria may be easily and logically arranged into (1) cerebrospinal, (2) thoracic, and (3) abdominal forms.

Cerebrospinal Forms.—The representative type of cerebrospinal pernicious malaria is the comatose variety, which is, as well, the most frequent of all varieties.

Comatose malaria may make its appearance as the first manifestation of malaria or, more commonly, after the lapse of one or more paroxysms, typic or irregular. Violent head-

ache, stupid countenence, and somnolence, interrupted by frequent sighing, with a mild grade of mental aberration and defective articulation and vision, are not uncommon prodomata. These may, however, be so slight as to escape notice. The onset of cerebral symptoms may be with violent abruptness (the apoplectic form of some writers) or, as is most common, begins within a few hours after the commencement of the paroxysm with somnolence, which gradually deepens into

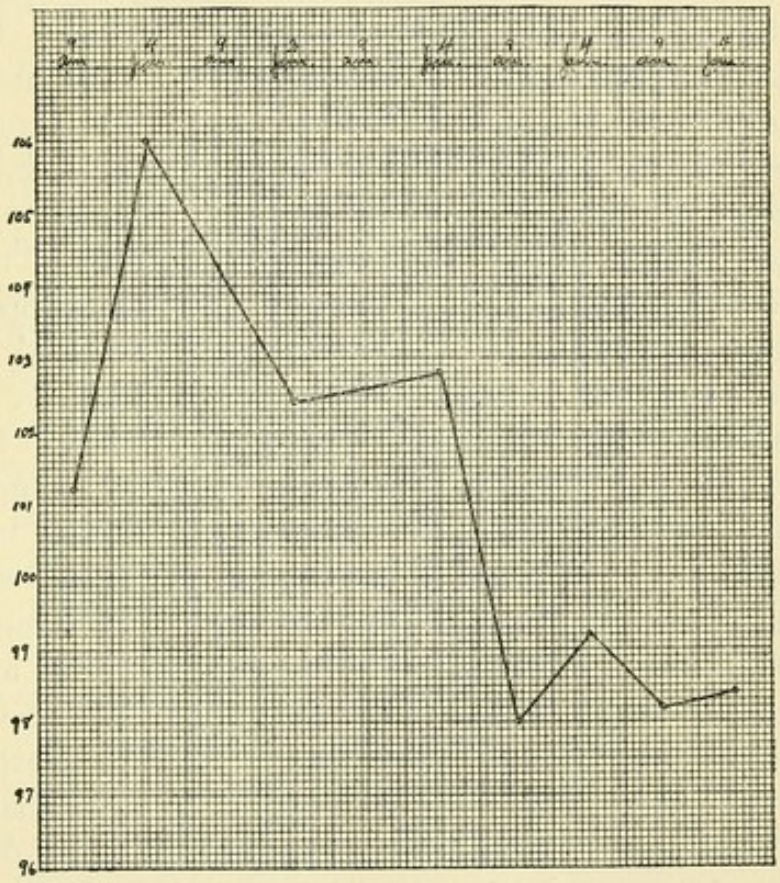


Fig. 58.—Comatose malaria ; recovery.

stupor and coma. It has occasionally happened that malarial coma has come on during natural sleep, the condition of the patient being discovered by accident. Convulsions may precede the coma, especially in children, or there may be extreme restlessness, gritting the teeth, and jactitation. The cerebral symptoms may vary from the marked drowsiness to profoundest coma. The eyes may be closed or open (coma-vigil). The pupils are usually equal and dilated or contracted, but may be

unequal and may or may not react to light. Strabismus is an occasional symptom. The face is congested in individuals recently attacked or pallid in older sufferers. The skin is at first hot and dry, perhaps slightly jaundiced; later it may be bathed with sweat. Petechiæ are occasionally seen. Trismus may be present, but the extremities are usually completely relaxed, though sensation and motion are often not entirely abolished, as sometimes evidenced by resistence to hypodermic medication. Cases manifesting muscular rigidity and tonic contractures have been reported by Schellong[92] and by Brown.[286] Hyperesthesia and muscular tremors are not infrequently present. The reflexes may be increased or diminished.

There may be twitching of the muscles of the face, usually confined to one side. Loud calls may not elicit response, and shaking only groans and unintelligible utterances. The coma may be intermittent, running parallel with the temperature. The fever in most cases varies from 101° to 103° F., but may be subnormal or hyperpyrexial. The pulse is at first full and bounding, later small, rapid, and feeble. Dilation of the right side of the heart may exist and an anemic murmur may sometimes be heard. The respiration may be quiet, slow or rapid, or blowing and stertorous, with Cheyne-Stokes characteristics late in the course. Edema of the lungs is an occasional late occurrence. Nausea and vomiting are seen early in the attack, if they are present at all. The mouth and tongue are dry, the latter deeply coated. Herpes and sordes are sometimes noted. Hiccough is an occasional symptom. The tongue when protruded may be drawn to one side. In cases of recent infection the spleen may be only slightly or not at all enlarged; in other cases it may be greatly enlarged, constituting a valuable diagnostic sign.

The liver may be tender, but is usually not much enlarged. The evacuations of bowels and bladder may be involuntary or there may be retention of urine. The bowels are often constipated.

In favorable cases the coma gradually fades, consciousness slowly dawns, the temperature drops to or below normal, the pulse regains its normal characteristics, and, save the physical

weakness and a degree of mental hebetude, all is well with the patient.

In unfavorable cases the coma becomes absolute, the pulse becomes rapid, thready, and irregular, the breathing is stertorous and of Cheyne-Stokes type, tracheal rattling appears, the face becomes cyanotic, and death ensues from convulsions or from collapse.

The duration of an attack is from a few hours to a few days.

Hertz[183] speaks of cases of "apparent death" arising in the course of comatose attacks. He describes these cases as follows:

"Under this form of pernicious intermittent must also be classed those cases of apparent death which may last from half an hour to four hours. Persons subject to such attacks may remain entirely conscious, seeing and hearing everything that occurs or is said around them, but unable to move or to utter a sound; or they may be entirely unconscious, respiration arrested, pulse and heart beat not to be recognized, and even the sharpest irritants applied to the body calling forth no signs of life until, at the beginning of the sweating stage, the patient comes to himself and the various organs again slowly manifest their activity. Trousseau reports the case of a man who had had fainting fits on two occasions in Algiers, and in a subsequent attack fell into this condition of simulated death. It was not until he had been carried into the post-mortem room that evidences of life were observed about him, whereupon he was returned to his bed and recovered under quinine treatment."

Relapses may occur after the apparently favorable defervescence of the symptoms. Laveran[1] saw three successive attacks in a soldier. Colin[86] reports several examples of pernicious attacks assailing the same subject repeatedly at intervals of fifteen to twenty days. Mayer states that in a third of the cases another attack supervened in eight or ten days. More than three are very rare, but Homem[157] records the case of a young student who died after having six pernicious paroxysms. It has long been maintained that the third attack is fatal. It

usually holds true that the successive paroxysms increase in severity and danger to the patient. In the interval the patient may be apathetic or may complain of headache. The relapse may appear in the form of a different type of pernicious paroxysm, as algid or choleraic, but such cases are very rare.

As intimated, the apoplectic form of pernicious malaria is merely a fulminant variety of comatose malaria. In these rare cases the onset is equally as sudden as in cerebral hemorrhage, whence the name. Laveran,[1] Cardamatis[287] and Crespin[144] are inclined to doubt the existence of this variety, but cases have been reported by Morris,[288] Davidson,[66] Maurel,[75] and others. Ewing's case is remarkable. "The patient, while sitting up in bed smoking, three times in five days suddenly became unconscious, his pipe fell to the floor, and he remained stuporous for three or four hours. At the end of that period he would wake up, at once pick up his pipe, and resume smoking."

Symptoms originating from the cerebellum are present in rare instances. Such are slow, monotonous speech, drowsiness, severe depression, and incoördination of voluntary movements.

Marchiafava and Bignami[22] describe as follows the interesting bulbar symptoms which occasionally present themselves: "When a physician unexpectedly encounters this disease he is easily inclined at the first glance to think that the case is one of a patient with bulbar paralysis who has become infected with malaria, but this suspicion disappears after a careful examination and after seeing the gradual resolution of the symptoms. 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 drools the saliva; a pendent lower lip; a dry and only slightly movable tongue; difficult or abolished deglutition. If the attack tends to a fatal issue we have the added symptoms of sopor, a thready intermittent pulse, labored and stertorous breathing, and clammy sweat. When, however, the result is favorable the patient recovers from the more severe symptom as soon as the fever falls; the bulbar symptoms usually persist for some days, although in milder form, and then gradually disappear, the dysphagia going first, then the dysarthria and

nasal voice, and the paresis of the lower part of the face. Two or three weeks may elapse before resolution is complete. If the malarial infection has not been properly treated we shall have an exacerbation or even a return of the bulbar symptoms in the relapses. With these symptoms there are sometimes associated disturbances of equilibrium which recall the staggering gait of cerebellar disease."

Cases in which hemiplegia occurs have sometimes been described as the hemiplegic form of pernicious malaria; cases with aphasia as the aphasic form. These two are not infrequently associated. Paraplegia is a very rare development in pernicious malaria.

A mild delirium is frequently present in the cerebrospinal forms of pernicious malaria. When it is conspicuous it forms the so-called delirious type. In this probably more than in any other form do predispositions have a causal part, especially alcoholism, nervous predisposition, mental fatigue, and exposure to solar heat. Delirium in this condition may vary from quiet to maniacal. Cases resembling rabies have been designated *Intermittens hydrophobica,* and are thus described: "Violent maniacal delirium, with a frequent pulse, red glowing face, and clonic spasms of the muscles of deglutition on drinking or even at the sight of water; these spasms then pass to the muscles of the face, the eyes, and the neck, and finally to those of the entire body, a disposition to bite being at the same time developed."[183]

Convulsive or eclamptic pernicious malaria is a variety of the comatose type in which convulsions are a prominent feature. It is especially common in children. The convulsions may be confined to certain muscle groups or may be general. In one of my cases the little patient had twelve convulsions in an hour. Epileptiform convulsions have been described, but it is probable that most of these cases are complicated with true epilepsy, as the case of Marchiafava and Bignami.[162]

Cases in which the symptoms resemble more or less closely those of tetanus constitute the tetanic type of some writers. These cases are said to have been relatively frequent in the French campaign in Madagascar.[226] Ziemann[48] records a

typic case. The most prominent symptoms are usually trismus and opisthotonos; emprosthotonos and pleurosthotonos are but rarely observed.

Occasionally amaurosis arises in the course of a comatose attack. It may be transient or, in rare instances, permanent. In the only case occurring under my observation vision began to improve at the end of the attack, but was not fully restored until after several weeks. According to Poncet,[101] the persistence of amblyopia in these cases is due to optic neuritis, peripapillary edema, extravasation of leukocytes, plugging of retinal and choroidal vessels by parasites or pigmented leukocytes, and consequent multiple hemorrhages.

A rare form of pernicious malaria, the ataxic, has been described, particularly by Angellini and Torti.[67] The principal symptoms are scanning speech, dysarthria, weakness of lower limbs, vertigo, unsteady gait with a disposition to fall forward, muscular tremors, and exaggerated reflexes. Maurel[75] records 22 cases, but it appears that some of these cases at least do not belong to the ataxic type.

Manson[59] thus describes the so-called ardent fever: "In the course of what seemed to be an ordinary malarial attack, the body temperature, instead of stopping at 104° or 105° F., may continue to rise, and, passing 107° F., rapidly mount to 110° or even to 112° F. The patient, after a brief stage of wild, maniacal, or perhaps muttering delirium, becomes rapidly unconscious, then comatose, and dies within a few hours or perhaps within an hour after the onset of the pernicious symptoms." Both the cases of this type observed by Homem[157] ended fatally.

Typhoid pernicious has been most carefully studied by Billet.[151] In these cases the clinic picture is almost identical with that presented in typhoid fever. The temperature is periodically intermittent or, as is more common, remittent, and usually ranges from 101° to 103° F., but may reach 106° F. There are headache, backache, rapid pulse, torpid digestive tract, sordes, splenomegaly, apathy, and stupor. There may be diarrhea or constipation, and bilious vomiting occurs in some cases. The abdomen is usually tympanitic and there

may exist tenderness and gurgling in the right iliac fossa. Epistaxis is frequent. Incoherent speech, delirium, and incontinence of urine and feces are symptoms of severe cases. All of Billet's 40 cases showed the presence of malarial parasites and a large mononuclear leukocytosis, and an absence of rose spots and the Widal reaction. The average duration was four or five days.

Thoracic Forms.—The immunity of the organs of the chest to localizations of the malarial parasites and to the effects of their toxins is remarkable. Indeed, the thoracic forms are much rarer than the records would import, for the older writers especially were prone to attribute any complication that might present itself to the effect of the mysterious malarial poison.

Ewing[179] has minutely recorded a case in which the autopsy showed an enormous number of parasites in the capillaries of the heart muscle. The symptoms referable to the heart were feeble pulse, 124 to the minute, and very feeble heart sounds on auscultation. The patient was comatose. Benvenuti[179] has reported a case in which the capillaries of the myocardium, brain, and kidney were filled with infected red cells. The principal symptoms were coma and dyspnea.

Formerly cases of pneumonic pernicious malaria were more frequently reported than at present. Since more exact methods of observation have come into use it is certain that many of these cases were complicating lobar pneumonias. That the malarial parasite is unable to cause true inflammation of lung tissue is now widely recognized, and was maintained by Colin,[233] Jaccoud,[289] Roux,[161] and Marchiafava and Bignami.[162] Nevertheless, grave symptoms referable to the lung, and more or less resembling pneumonia, may arise in malarial infections. Laveran,[1] who doubts the existence of a pneumonic pernicious, admits that in certain patients attacked with intermittent fever there may be observed, with each attack, pulmonary congestion, accompanied with subcrepitant râles, which may lead to a belief in the existence of a pneumonic intermittent. Bacelli proved the existence of a group of cases nearly resembling pneumonia in symptomatology. The characteristic cough,

dyspnea, and pain in the side are present. There may be moderate dulness and coarse, sonorous, and sibilant râles heard over the portion of the lung involved. Other writers describe intermittent lung symptoms and signs met in cases of pernicious malaria. Le Dantec[226] records the following case, occurring in the person of his friend, Dr. Grosset, who, after several paroxysms of intermittent, was taken in the course of an attack of fever with dyspnea. Percussion showed incomplete dulness throughout the entire extent of the chest. Auscultation revealed crepitant râles. The face and finger nails were cyanosed, the intelligence was unimpaired, but the peripheral sensibility had almost disappeared. The chest was covered with cupping-glasses, and several hypodermic injections of quinine were given. This alarming condition lasted almost twenty-four hours, when, at the moment a fatal issue was expected, the sensibility returned and every trace of pulmonary congestion disappeared as if by magic. Cases presenting profuse hemorrhages from the lungs and nose have been recorded but rarely.

The pathogenesis of this condition is not known, as there have been insufficient post mortems. From analogy with findings in other forms of pernicious malaria these cases must be attributed to accumulations of parasites in the pulmonary capillaries. Griesinger[290] early compared the filling up of the lung that takes place in these cases to the enlargement of the spleen.

Abdominal Forms.—The representative type of abdominal pernicious malaria is the algid. The reasons for classing this type as an abdominal form have been briefly stated when considering the pathogenesis of the different varieties. The picture presented is that of abdominal shock, it is peritonism minus the peritonitis.

Torti believed that the algid attack was merely the intensification of the cold stage of a malarial paroxysm. But there are essential differences. First, the algid attack almost always occurs during the febrile period and does not correspond in time to the first stage. Secondly, in the cold stage of the ordinary paroxysm the patient experiences a sensation of chilliness;

in the algid attack the patient feels that he is "burning up," while the skin feels cool to the observer. The algid symptoms may appear insidiously, but much more frequently supervene after the course of one or more simple paroxysms. Usually the first symptoms that attract the attention to the condition of the patient are the bad pulse and cold surface. Soon the Hippocratic facies is assumed. The eyes are deeply sunken and surrounded by dark circles, the nose appears sharp, the alæ nasi dilate with respiration, the tip of the nose and the ears are icy cold. The temples and cheeks are hollowed, the cheek bones project, the pupils are dilated, the conjunctivæ bluish white, the eyes have a peculiar anxious expression, and the breath is cool. The skin is pale, having the appearance of absolute bloodlessness rather than that of cyanosis. The surface of the body is bathed with a clammy sweat, is cold, and gives the sensation to the hand of handling a catfish. The fingers and toes often have the shrunken appearance of the washerwoman's hand. The prostration is extreme and the voice is weak, low, and cracked. The patient complains of burning heat within and begs piteously for cold drinks, which are, as a rule, immediately rejected by the stomach. The intelligence remains clear and occasionally "the patient, overcome by sad apprehensions, considers himself lost, bewails his situation, but is not delirious," though usually he is indifferent to his peril. The temperature may be subnormal or slightly elevated, seldom reaching 104° F. The pulse is rapid, filiform, of low tension, and often intermittent. Later it usually becomes imperceptible at the radial. The heart sounds are extremely feeble. The respiration is very rapid, superficial, and frequently interrupted with deep sighs. The tongue is tremulous, cold, and usually moist and smooth. Vomiting is a common symptom. The bowels are sometimes constipated, but often loose. The abdomen may be slightly tympanitic, or scaphoid and tender, especially in the upper half. The urine is scanty, highly colored, and of high specific gravity. The duration of the attack is short, rarely longer than twelve hours after the onset of algidity. In fatal cases the symptoms progress rapidly and the patient dies as if in peaceful sleep.

In favorable cases the character of the circulation and respiration improves, the body warmth is gradually restored, the patient ceases to complain, and convalescence is impeded only by the extreme weakness.

When, in addition to the symptoms of algidity already detailed, there exist symptoms simulating true cholera, there is the variety of algid malaria usually spoken of as choleraic pernicious. The onset is with profuse diarrhea and vomiting. The stools are thin and watery and often rice-water-like. There may likewise be shown the muscular cramps of the lower limbs frequent in cholera. The temperature is usually elevated and pains in the abdomen and precordia and singultus may be experienced. The urine is usually scanty and may become suppressed.

The condition of algor with which drenching diaphoresis occurs constitutes the so-called sudoral or diaphoretic form of pernicious fever. These sweats, which are so profuse that not only the clothing of the patient, but also the bedclothes are saturated, usually supervene toward the close of a paroxysm. The celebrated Torti, who was himself the victim of such an attack, says that he was just congratulating himself upon escaping the fever when the abundant sweats occurred to convince him that his condition was critical.

In the course of an algid access syncope occasionally occurs when any exertion, even the slightest, is attempted or when the patient's head is lifted from the pillow. This dangerous symptom usually comes quite unexpectedly, and if the patient survives the first onset a subsequent one may rapidly prove fatal.

The gastralgic or cardialgic type is characterized by excruciating pain in the abdomen, especially the epigastric region, or in the precordia. The pain is often so intense that the patient doubles up and rolls in agony upon the bed. The abdomen is tender and vomiting is a common symptom. There may be hematemesis, sometimes profuse. Diarrhea and singultus are occasional symptoms.

While the existence of dysenteric pernicious malaria has been denied by Colin[291] and more recently by Kanellis and Car-

damatis,[292] the frequent occurrence of severe dysenteric symptoms, due solely to malarial infection, has been definitely demonstrated by Craig.[293] The attack may follow other forms of abdominal pernicious or may come on suddenly. There are frequent actions of bloody mucus, violent tenesmus, colicky pains in the abdomen, elevation of temperature, and sometimes emaciation. Algid symptoms are not common. Occasionally abundant hemorrhages from the bowels occur. They may prove rapidly fatal, especially if the patient is already markedly anemic.

Icterus and bilious vomiting are not rare in malaraia. As a rule, these are not grave symptoms, but there are cases in which their persistence and intensity form a complex of symptoms described as bilious pernicious malaria. The fever is usually high, nausea constant, icterus marked, and vomiting of bile distressing. Bile is present in the urine, often in quantities, and sometimes albumin. Epistaxis and hematemesis have been noted. The epigastrium is often painful and singultus may add to the discomfort of the patient. Toward the end of the severe cases there are apathy and carphology, and the scene usually closes with delirium and coma.

Waton[290] observed a case with symptoms resembling those of peritonitis. Laveran[1] refers to several similar cases. Gillot[294] treated 3 cases in which the clinic picture was identical with that of acute peritonitis. One case which he diagnosed as perforation due to typhoid ulceration was operated upon. The operation proved a mistaken diagnosis. The blood was examined, malarial parasites found, and the patient recovered promptly after the subcutaneous injection of 1½ grams of quinine.

Wolf,[295] Chamberlain,[296] and Craig[297] report cases presenting symptoms which would lead to a diagnosis of appendicitis. Ford[180] records 5 such cases, one of which was operated upon and the appendix found to be healthy.

Ross and Daniels[298] performed an autopsy on a man who was not supposed to have died of malaria, and found a hemorrhagic pancreatitis with extensive massing of parasites in the pancreas. Parasites were also very numerous in the capil-

laries of the stomach and intestines, and these organs showed extensive necrosis.

The urine is usually highly colored. The amount varies inversely with the quantity of sweat, bowel movement, and vomited matter, the specific gravity varies inversely with the amount. Early in the attack albumin may be absent, though later it is often present in large quantities, together with numerous tube casts.

The blood in various forms of pernicious malaria shows, besides parasitic findings previously mentioned, a pronounced reduction of red cells, averaging a half to one million per paroxysm. Polychromatophilia of red cells may be observed. Contrary to the case of simple malaria, there is usually a pronounced leukocytosis. There may be as many as 35,000 per cm. Thayer[98] observed a case of the algid type in which there were 50,000 in number. The differential formula usual in malaria, the relative increase of large mononuclear elements, is maintained. According to Billet,[151] the average of these cells is 10-15 per cent.; in 9 of his 40 cases it varied from 20-25 per cent., and in 1 case they existed in the proportion of 30 per cent. Great numbers of these cells were pigmented.

HEMOGLOBINURIC FEVER

Hemoglobinuric fever is known by many names, some of which are mere localisms. Among the more general synonyms are: malarial hematuria, hemoglobinuric fever, swamp fever, blackwater fever, bilious hematuric fever, melanuric fever, etc.

After a severe chill the temperature rises rapidly and a copious discharge of red, almost black, urine is voided. The patient complains of headache and pain in the loins and epigastrium, and is afflicted with nausea and violent bilious vomiting. Thirst is torturing and insatiable because of the gastric disturbance. There may be more or less tympanites. The liver and spleen, especially the latter, may be enlarged and tender. In a few hours icterus begins and the patient soon becomes as yellow as a pumpkin. He is very restless and has an anxious expression. If the attack is mild the duration may not be

longer than that of an ordinary malarial paroxysm, the vomiting ceases, pain disappears, the urine gradually clears, the temperature falls to normal or a little below, and the patient is comparatively comfortable excepting a degree of weakness. The jaundice usually lasts a day or two longer. In rare cases the duration of the attack is extremely short, the urine voided at a single act only being hemoglobinuric.

In severer cases the temperature may drop, but not to normal; vomiting is incessant, the urine continues darkly colored and becomes scantier. Rigors may occur at irregular intervals, followed by a rise of temperature, deepening of the color of

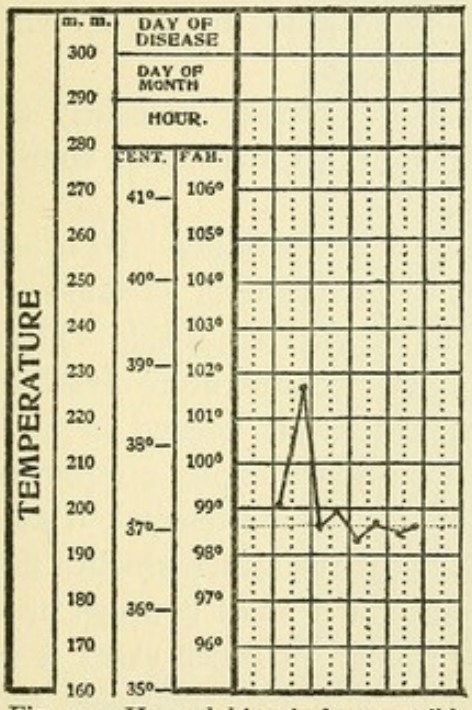


Fig. 59.—Hemoglobinuric fever; mild.

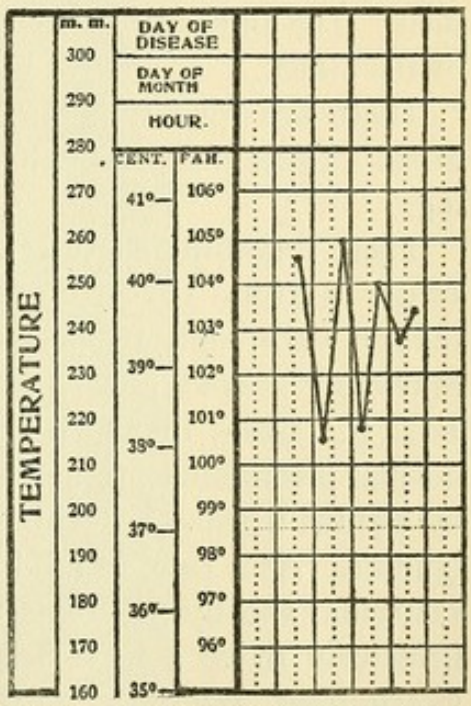


Fig. 60.—Hemoglobinuric fever; death.

the urine, and marked prostration. The urine may become suppressed and death takes place in a few days. Or the patient may die suddenly while being raised to use the vessel or to take medicine or nourishment.

The attack may be preceded by one or more malarial paroxysms or may come on suddenly. There may be prodromata consisting of general malaise, aching in the loins and head, nausea, and a slight rise of temperature, though this latter may be imperceptible to the patient. In more than nine-tenths of

the cases the onset is with a rigor, usually intense and protracted. Sometimes, as in ordinary malaria, the first stage is obscure or wanting, and the attack begins with fever and vomiting. Occasionally the passage of black water precedes the other symptoms, as in one of my cases, where the patient had had a mild rigor the day before, but felt well enough to ride out on horseback in search of his cow. While five miles from home he was dumbfounded at passing an abundance of almost black urine. He immediately set out to consult me, and had ridden six miles when he was prevailed upon to return home. Death from exhaustion occurred on the fourth day. Rarely the onset is characterized by violent pain in the abdomen. The intensity of the onset is no guide to the severity of the attack.

There are four symptoms which are present in nearly all cases. These are: fever, hemoglobinuria, icterus, and vomiting.

There is nothing characteristic in the temperature. Its usual range is from 101° to 105° F. Hyperpyrexia is unusual, though very high temperatures have been recorded. Thus Marsden[269] noted a case in which the temperature reached 109° F. Cases in which the temperature is normal or subnormal throughout are not unknown; for example, 2 reported by Baldwin Seal.[258] Neither of these patients had taken any quinine. As a rule, in mild cases the temperature reaches the fastigium shortly after onset, from which point it drops progressively to or a little below normal. In other cases it is intermittent, remittent, or irregular, and may resemble the curve of septic fever. When rigors occur during the course they are accompanied by a rise of temperature. Periodicity is not a conspicuous feature nor is the characteristic curve of Marchiafava and Bignami seen. The average duration of the fever is from a few hours to several days. It usually outlasts the hemoglobinuria, but not in all cases. The height of the temperature in hemoglobinuric fever is possessed of little or no prognostic import.

A rare occurrence is the obstinate tenacity or subsequent rise of the fever after hemoglobinuria has subsided. The duration



Fig. 61.—A convalescent from blackwater fever. The line indicates the border of the spleen.

of this posthemoglobinuric fever is variable. In 2 of Brem's[215] cases it was fourteen and eighteen days; in 3 of my cases twelve, nineteen, and twenty-eight days; in 1 of Bank's[210] over five weeks; in 1 of Howard's [216] six weeks. Outbursts of hemoglobinuria occasionally occur during this fever. In most of the cases the temperature rose higher than during the hemoglobinuric period. It is entirely uninfluenced by quinine and is probably related to the spodogenous fever of Marchiafava and Bignami,[22] or postmalarial secondary fever. The mortality of these cases seems to be low.

Schellong[92] observed a peculiar case which showed a postmortem elevation of temperature. The fever began to rise a few minutes after death, and more than an hour later, when last recorded, the temperature was 106.2° F. The thermometer registered higher in the right axilla than in the left throughout the observation.

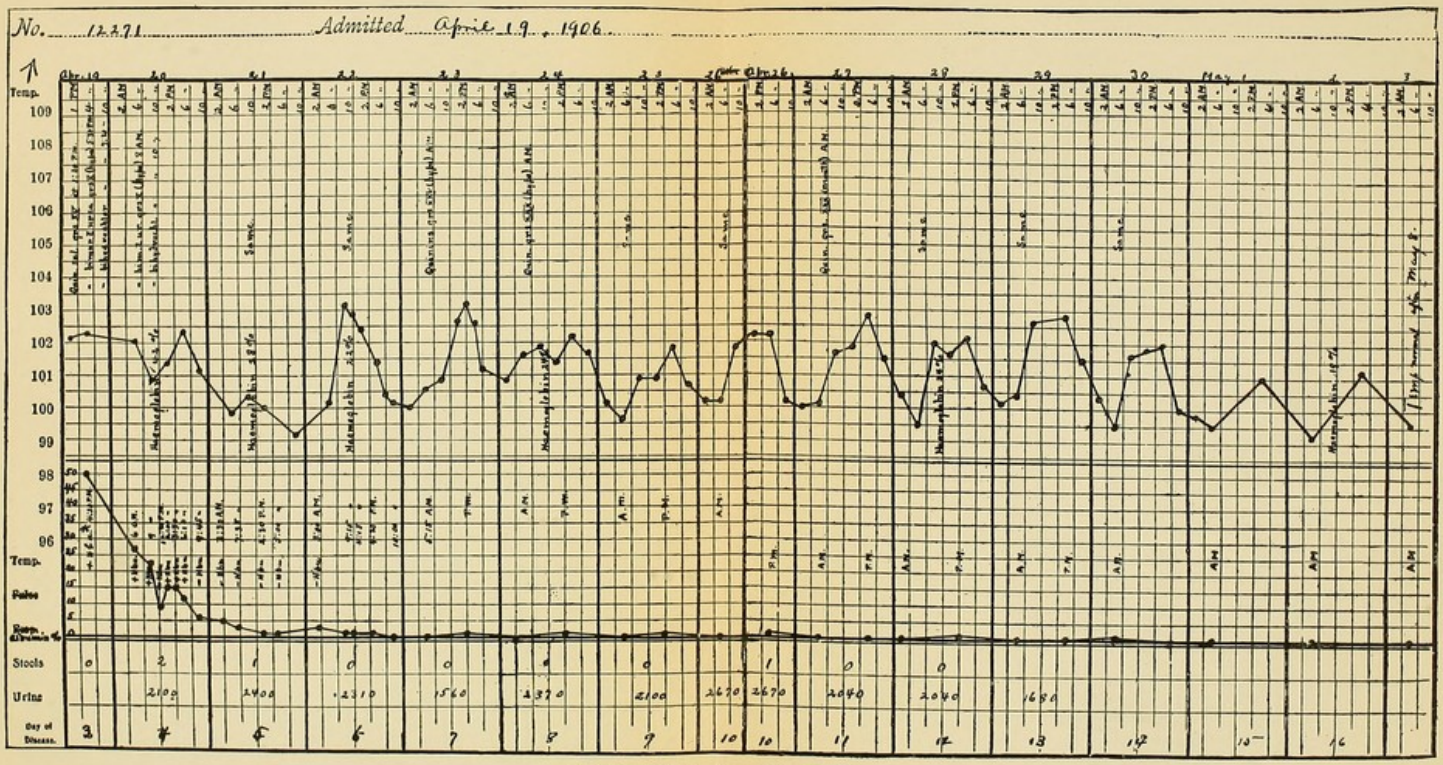
Probably in no other condition do we see such rapid and profound transition in the state of the urine. A few hours before the onset the urine is normal, afterward it may show all the characteristics detailed below. In favorable cases the return to normal is remarkable.

The quantity varies within very wide limits. In mild attacks it may not vary from that of health. Often at first there is an increase, a decided decrease at the height of the attack, gradually increasing to normal or above with improvement. In suppression cases there is usually a diminution from the first, resulting in total anuria or the passage of only a few ounces daily. Anuria is due to the plugging of the renal tubules and to diminution of blood pressure. Pain resembling that of renal colic may be experienced with anuria. The temperature may remain normal throughout suppression of several days' duration. It occasionally happens that urinary secretion is reëstablished after anuria has persisted, even as long as five days; in such cases, however, most die of complications during convalescence. The outlook is very grave when suppression lasts longer than twenty-four hours. Death usually takes place after three or four days, though Plehn[5] reports a fatal case where life was prolonged twelve days after the onset of sup-

pression, and Kudicke[51] observed 2 fatal cases in which anuria persisted thirteen days.

The color, often described as "port wine," varies from a light claret to that of black coffee. The latter color obtains when the urine of a severe attack is examined in a thick layer by reflected light. In a test-tube by transmitted light it appears of a lighter color. The froth varies from yellow to reddish; a greenish color is said to be due to the presence of bile. The coloring matter is more often in the form of methemaglobin, though oxyhemaglobin is found. It is probably not present in a true solution, since it is more abundant in the sediment of a centrifugalized urine than in the supernatant fluid, and disappears from the latter first with improvement. The hemoglobinuria may be intermittent or continuous. Stephens and Christophers[118] observed that blackwater urine made alkaline with potash and then boiled produced a purple color, giving the bands of hemochromogen, showing that the urine itself contained reducing bodies. A. Plehn mentions that on boiling the urine and allowing it to stand for some time a bright purple color appears. On standing an abundant dirty brownish sediment is deposited, the amount varying with the concentration of the fluid. The urine stains linen a dirty red. The reaction is generally slightly acid, but may be neutral or alkaline. The specific gravity varies inversely with the quantity. Albumin is always present. It is commonly in excess of the hemoglobin and persists for a longer period, though the curves run more or less parallel. Serum albumin, albumose, globulin, and nucleo-albumin are found. Plehn[5] gives the limits of quantity as ½-2 grams per liter, estimated according to Esbach's method. The writer has very frequently observed twice as much as his maximum limit, and in 1 of his cases the amount was 14 grams with the Esbach instrument. Some urines on being boiled become almost completely solidified. Bile is, as a rule, absent; it is never present in proportion to the polycholia. It was not found by the Plehns[5] or by Daniels[57] in any of their cases. Urobilin is common. Stephens and Christophers[118] assert that it occasionally appears before the attack, but more constantly after the oxyhemoglobin has dis-

PLATE XII



Posthemoglobinuric fever (after Brem).

appeared, or together with it. Marchoux[299] maintains that quinine cannot be detected in the urine during the hemoglobinuric period, but appears later. But the observations of Giemsa and Schaumann[300] do not sustain this opinion. They found the amount of quinine excreted with the urine during the attack is somewhat larger than otherwise, and that the excretion is extended over a longer period of time in a regularly increasing and decreasing curve which is uninfluenced by the hemoglobin content of the urine. This increased excretion of quinine in the urine in hemoglobinuric fever would lead to the inference that the organism is not capable, as it usually is, of protecting itself from the poisonous alkaloid by splitting the molecule. Marchoux[299] claims that hemoglobinuric fever urine has no hemolytic action on the red blood-cells of normal persons.

On microscopic examination the field appears littered with a brownish amorphous detritus, the products of broken-down red blood corpuscles. Whole red blood-cells are not generally found and rarely in considerable numbers. Casts are abundant, especially the granular; also hyaline and epithelial. These casts are sometimes almost covered with the granular pigment. Renal and vesical epithelium are common, and mucus and crystals of hematoidin may be found. Leucin and tyrosin are rare. Williams,[301] Mackey[302] and Brem[215] have described different peculiar bodies found in the urine. The nature and significance of these bodies are unknown.

There are often present vesical tenesmus and pain over the bladder. Retention of urine, burning in the urethra, and tenderness over the kidneys are not uncommon symptoms. The urine may be voided drop by drop.

After a few hours jaundice begins to appear and, except in the mildest cases, develops rapidly until the skin and sclera are of a pronounced saffron yellow. It usually outlasts the fever a few days. Itching of the skin is not common. Herpes is relatively infrequent and petechiæ are rare. The occurrence of the latter is said to imply a grave prognosis. Edema or anasarca may be encountered, especially in cases where there is unusual involvement of the kidneys. Sweats may occur with

the decline of the fever or with collapse. The skin is often dry. Sometimes the perspiration is charged with bile pigment. Banks[210] mentions a peculiar odor emanating from blackwater fever patients. He claims that it enables one, together with the expression, to make a diagnosis before the urine is examined. So far as the writer knows, he has not been corroborated, though in suppression cases a uremic odor may be perceptible.

Vomiting is usually one of the earliest symptoms and frequently the most distressing. After the stomach contents are voided the vomit consists of a yellowish or green bile. Occasionally it is a grass-green or peculiar bluish-green, or it may be very dark, almost black, somewhat resembling the black vomit of yellow fever. The vomiting is independent of the taking of food, and is probably more or less of central origin. In very mild cases vomiting may be very insignificant or absent. Nausea is usually in proportion to the vomiting. The bowels may be constipated or there may be a bilious diarrhea. Occasionally the dejections are thin and watery, of a reddish-brown color, and may closely resemble the urine.

This is thought to be due to the extravasation of hemoglobinuric serum into the intestine, and is usually seen in severe cases only. Dysenteric symptoms are infrequent. Hemorrhage from stomach or bowel is rare. Meteorism is not an infrequent symptom. There may be severe colicy pains in the abdomen. Pain is usually present in the epigastric region or over the liver and spleen. These are usually tender, the spleen often greatly enlarged, the liver less so. The appetite in all but mild cases is completely lost. Thirst is intense and cannot be alleviated for the vomiting. The tongue is anemic and heavily coated. Sordes of the teeth and lips are often seen in extreme cases. The saliva may stain the linen a brownish-yellow. The pulse is rapid, out of proportion to the temperature, at first full and bounding, later small and compressible. A hemic murmur, systolic in time, is sometimes heard over the precordia, not transmitted. Respiration is accelerated. There is often sense of oppression in the chest. Dyspnea may be a prominent symptom, due to anemia or to edema of the lungs.

There may be, especially after some days of severe illness, slight dulness and diminished respiratory murmur over the dependent portions of the lung, accompanied by slight cough, resulting from hypostatic congestion. Cheyne-Stokes respiration may appear toward the end. Hiccough is present in a large per cent. of fatal cases, and if obstinate is always to be regarded unfavorably. Epistaxis is occasionally seen.

Anemia increases with intense rapidity, half the red cells sometimes being destroyed in twenty-four hours. The number usually falls to one to two million during the attack. Except for the absolute diminution of the fluid portion of the blood as a consequence of purging and vomiting, the number of red cells per c.mm. would appear much smaller than it does. It is occasionally difficult to obtain a drop for examination by the usual method. It appears relatively thinner than normal and the cover-glass may adhere to the oil-immersion objective rather than to the slide. On coagulation the serum may appear yellow (cholemia) or reddish (hemoglobinemia), though neither is constant. Macrocytes, microcytes, poikilocytes, shadows, polychromatophiles, and basophiles are found, but not always, as pathologic cells may succumb early. One is often surprised to see, notwithstanding the extreme hemolysis, the erythrocytes presenting so few changes. Nucleated reds may be found, especially during convalescence. The color index shows nothing characteristic; it may be normal or above, at first falling gradually until convalescence is established. The hemoglobin per cent. usually runs parallel with the red cell count. It is generally reduced to 25 to 50 per cent., sometimes lower, as in a case of Hoffmann,[49] in which the patient recovered notwithstanding a fall to 12 per cent. It is often asserted that during pyrexia there is a leukocytosis, and the polymorphonuclears are increased often to 90 per cent. With falling temperature there is a pronounced large mononuclear increase with leukopenia. However, the average of a number of differential counts made at irregular intervals during the attack shows a marked increase in the large mononuclears, a decided diminution of small mononuclears, and a slight increase of polymorphonuclears. Pigmented leukocytes are common.

Christophers and Bentley[303] have made interesting observations on the phagocytosis of red blood corpuscles in the spleen of a case of blackwater fever. In a differential count of 2,200 spleen cells 1.7 per cent. were large macrophages containing red cells and 1.3 per cent. were small mononuclear cells containing red blood-cells. In both kinds of cells were seen blood corpuscles showing no evident alterations, corpuscles more or less decolorized, and clear vacuoles about the size of red blood-cells. The closest scrutiny of the engulfed cells failed to reveal the presence of parasites or other evidence of parasitic invasion. This extensive phagocytosis of apparently normal cells is of interest from the standpoint of pathogenesis. The platelets are numerous and of large size. The alkalinity of the blood is often diminished. In spite of the destruction of red cells the specific gravity remains relatively high. This is no doubt due to the quantity of material in solution in the serum. During convalescence the specific gravity falls. Stephens and Christophers[57] give the following as the result of their observation on tonicity: "In blackwater there is occasionally a remarkably low tonicity; in other cases it has the normal value or somewhat raised value, as in malaria. The low or normal value in blackwater may be due, as we have previously suggested, to the fact that the weak corpuscles—those of high tonicity—are destroyed, or it may be due to the fact that the tonicity of the corpuscles as a whole is changed after the liberation of hemoglobin." The presence of malarial parasites has been dealt with.

Blackwater fever is not a very painful affection, but the vomiting and thirst make the patient intensely wretched. Besides the abdominal pains there are headache and aching of the back and limbs. He is usually terrified at the appearance of the urine. His expression is one of anxiety and apprehension, and a fear of death often seizes him. He is restless and irritable. In children especially there is frequent tossing of the head from side to side. Later there is prostration, intense languor, perhaps somnolence. Formication and numbness in the fingers and toes are occasional complaints. Delirium when present is usually quiet. When suppression ensues the symp-

toms may be typic of those in uremia, but this is not constant; delirium may be of the low, muttering variety; convulsions are often missing, and the mind may be clear until shortly before death, when coma supervenes. There may be involuntary discharge of urine and feces.

The *causes of death* are three: Suppression of urine, exhaustion, and cardiac paralysis. Suppression is the commonest cause. This sometimes takes place when the urine is clearing or is already clear. Uremic symptoms do not result from suppression in blackwater fever as frequently as in other conditions. This is probably due to two causes. First, elimination through vomiting and purging is free; secondly, metabolism is diminished as the result of deficient oxygenation. Exhaustion is usually the result of the tremendous destruction of blood-cells, together with inability of the hematopoietic organs to meet the deficiency, or to pyrexia. Occasionally hiccough plays a rôle in exhaustion. The patient may die early with symptoms of shock or may linger several days in a typhoid state. Cardiac paralysis is usually due to thrombosis of the heart. Plehn[5] regards this as a common cause of death. Goltmann and Krauss[189] have shown that in some cases of death from syncope there exists a marked cardiac nerve degeneration and empty cylinders.

It would manifestly be of great practical importance if the symptoms of an impending attack of hemoglobinuria could be recognized. This is possible, if at all, only in a very general way. Plehn[24] says that an onset is to be feared when the patient has lived some six months in a blackwater fever area and has had malaria at short intervals, when this malaria has been treated improperly with insufficient quinine dosage, when he looks downcast, and perhaps shows a mild icterus of the sclera and skin. This might, however, forebode a relapse of ordinary malaria. Sometimes, he further states, there occurs a certain depressed condition, a characteristic mental apathy with physical restlessness, phenomena which are hard to describe, but have often been encountered by one who has seen many cases develop. Also the presence of albuminuria should cause suspicion, as this tends to be absent in simple

tropic fever, even with a temperature of 41° C. Koch[90] designates as "blackwater fever candidates" those in whom a few hours after taking quinine the temperature mounts to 38° C. or more, the urine becomes decidedly darker, and the next morning a mild icterus is evident. Ziemann[48] has frequently observed in blackwater fever candidates the following blood changes, which, however, are not constant:

1. The more frequent appearance of decided basophile and polychromatophile degeneration of the red cells.

2. The rapid solution of the red cells in a salt solution, in which normal cells do not dissolve.

3. A decided diminution of the coagulability of the blood.

This writer also regards urobilinuria as a valuable prognostic sign.

Relapses are not infrequent and several may occur, often befalling the patient when he is thought to be doing well. It may be difficult to distinguish relapses from recurrences. Convalescence may very properly be regarded as the dividing line, those occurring during convalescence being considered as relapses and those later as recurrences. Plehn[208] believes that recurrences are rare unless provoked by quinine. Of eighteen recurrences recorded by Vedy[213] one occurred after less than three months, fourteen from three to six months, two from six to twelve months, and one longer. It is remarkable that nine recurrences happened just three months from the date of the last attack. The writer's experience has been that in persons having more than one attack the attacks are more often separated by intervals of a year or more.

Complications and Sequelæ.—These are singularly few in variety. Nephritis in some degree is an almost constant complication, and may cause death from suppression during the attack. It may heal in a remarkably short time. As a sequela it is not infrequent and may persist for days or weeks, causing slow and incomplete convalescence or death. The changes in the kidney may be attributed to the irritating effect of hemoglobinuric urine and to the pyrexia.

In 16 cases the writer has been able to make examinations of urine at periods varying from a few days to fourteen years

after the last attack. In 8 cases the examination was negative. The others may be noted as follows:

F. S., white, male, æt. 17, one attack, 1899; urinalysis, February 27, 1907, showed a trace of albumin, no casts, no symptoms of nephritis.

A. J., white, male, æt. 18, two attacks, last one October, 1904; urinalysis, September 21, 1906, showed albumin ¼ gm. liter, very numerous cylindroids and hyaline casts, moderate number of granular. Anemia, edema of lids and ankles.

Mrs. H., white, female, æt. 25, one attack fourteen years ago; urinalysis, September 25, 1906, showed the presence of albumin and a few granular casts. No symptoms.

M. C., white, female, æt. 10, two attacks, last one September 24, 1906; urinalysis, on October 8, 1906, showed a moderate amount of albumin, no casts. Anemia, edema of face and ankles, indigestion.

E. C., white, female, æt. 7, five attacks, last one November 15, 1906; urinalysis, December 4, 1906, nitric acid test for albumin negative, microscope showed a very few cylindroids and hyaline and granular casts.

R. A., mulatto, male, æt. 44, one attack November 13, 1905; urinalysis, August 22, 1906, showed no albumin, moderate number of cylindroids, and a few hyaline casts.

J. P., white, male, æt. 37, several attacks, last one September 21, 1907; urinalysis, July 28, 1908, a slight trace of albumin, a few hyaline casts, very few granular.

W. S., white, male, æt. 42, one attack, which occurred February, 1905; urinalysis, June 27, 1908, no albumin, a few cylindroids.

The possibilities of the abnormalities of urine and the symptoms in the cases being produced by other causes than the hemoglobinuria should be borne in mind.

Anemia and consequent debility and digestive disturbances are not uncommon. Rare complications are: paraplegia, tetanic convulsions, purpura hemorrhagica, dysentery, pneumonia, pancreatitis, abscess of the liver, erysipelas, parotiditis, retinal hemorrhage, pleurisy, and neuralgia. The writer has seen tonsillitis once as a complication.

CHRONIC MALARIA

There is a great deal of confusion as to what is comprehended by *chronic malaria*. Much of this chaos is due to including the manifestations of malarial cachexia with those of chronic malaria, between which, however, there are essential differences. Chronic malaria implies a supply of vital resistance equal to the demand; malarial cachexia denotes an exhaustion of this supply. Chronic malaria is an antagonistic equilibrium between parasite and host; cachexia, a rupture of equilibrium. Chronic malaria is a conflict, cachexia a conquest. The relation between chronic malaria and cachexia has been fitly compared to that existing between a compensated heart lesion and broken compensation. Chronic malaria is an active form of malaria, cachexia is a sequel. Cachexia being a sequel, usually of chronic malaria, it may be difficult to say where the influence of the latter ends and the former begins. On the other hand, it is frequently difficult or impossible to differentiate between a relapse in chronic malaria and a reinfection.

For convenience of study, chronic malaria may be divided into a latent or passive stage and an active stage, or stage of relapse.

It is more frequently observed in children. It has already been shown that the frequency with which children native to the soil are infected constitutes the true endemic index of a locality.

Chronic malaria may be due to one infection, but occurring chiefly in regions where repeated reinfection is possible, it is highly probable that reinfection is an important factor.

An analysis by the writer of a large number of cases shows the following results: Quartan and tertian infections are more prone to relapse than estivo-autumnal. The percentage of relapses to total number of cases of quartan, tertian, and estivo-autumnal is, respectively, 65, 55, and 45. The pertinacity of quartan may be regarded as a conservative effort of nature to perpetuate the species. It is, indeed, remarkable how this form of the parasite is conserved in certain places where it is so very rare. However, the greater tendency to relapse shown by the

benign infections is more than counterbalanced by the severity of the symptoms of the estivo-autumnal relapses. Hence it is undoubtedly true that the estivo-autumnal parasites are the most important factors in chronic malaria.

It is the parthenogenetic cycle of the parasite that is chiefly concerned in the pathogenesis of chronic malaria, though the asexual forms also have a rôle. The parthenogametes are the parasites of the latent stage, the schizonts of the active stage. Parthenogenesis is the bridge across the gap caused by interruption of the schizogonic cycle.

The most frequent course is for chronic malaria to follow one or more acute attacks. In some instances, however, the latent stage may precede the active. Thus it is not extremely rare to meet cases with evidences of chronic malaria which have no history of active manifestations.

The latent stage of chronic malaria resembles in some respects a period of incubation; in fact, the cases reported with unduly long stages of incubation are doubtless nothing but latent stages of the chronic disease. During the latent stage parasites may or may not be found in the peripheral blood.

Symptoms during the latent stage may be altogether absent, in which case latency is absolute, or there may be present certain symptoms, subjectively insignificant, constituting relative latency. These symptoms are ordinarily similar to the prodromata of acute malaria: malaise, loss of appetite, aching of the back and legs, digestive disorders, etc., together with anemia and enlarged spleen. Latent malaria is the source of very numerous infections, and is of the utmost importance from the viewpoint of prophylaxis.

The duration of latency is exceedingly variable. Relapses occur at shorter or at longer intervals.

Relapses at short intervals have been recognized since the time of Hippocrates. Later the septenary periods were noted for a tendency to show relapses, and this idea is still largely prevalent among the laity. This shorter interval of latency corresponds more or less closely to the sexual cycle of the parasite and to the period of incubation. It is also in harmony

with the law of Treille[304] and with the studies of Cohen[305] upon the period of freedom from paroxysms following a single injection of quinine. The duration of this period is from five to twenty-one days, oftenest from five to ten. Relapses at shorter intervals occasionally exhibit a striking periodicity.

Relapses at longer intervals occur at from one to twelve months, exceptionally longer. Very long periods of freedom have been recorded, even up to sixty years.[306] Undoubtedly many of these are errors, due either to mistaken diagnosis or to the occurrence in the interval of unrecognized or masked paroxysms. However, periods as long as three years have been reliably recorded.[48]

It being clinically impossible to distinguish between a relapse and a reinfection, the writer has adopted Celli's[80] rule, it being equally adapted to the seasonal prevalence of malaria in this country. This authority regards as a relapse every case of fever which repeats itself in the same individual during the epidemic year of malaria, from July of one year to the end of the following June. It is true that this may include some cases of reinfection, but it is unquestionably the most practical guide and eliminates a maximum of error.

Secondary etiologic influences play a much more prominent rôle in relapses than in primary infections. Of these the most important are change of residence, fatigue, abuse of alcohol, exposure, and gastro-intestinal disturbances. All are familiar with the frequence with which a change of residence "brings the malaria out." These influences are much commoner factors in the relapses at long intervals than in those at shorter intervals.

It is ordinarily the relapse that brings the chronic malarial to the physician. The relapse may consist of one or more typic malarial paroxysms or they may be atypic. Very often the first stage of the paroxysm is wanting. They may exhibit quotidian, tertian, or quartan periodicity, or may be altogether irregular. The patient usually has an anemic tint and may, in advanced cases, be jaundiced. Occasionally the complexion may be earthy, at other times bronzed. The skin is dry and often scaly. The eyes may be deep set; they often bear a hag-

gard, restless expression. The patient appears aged beyond his years. The condition of nourishment is poor, and there may be edema of the face and feet. There are weakness of arms and legs and an indisposition to physical exertion. The pulse is accelerated, weak, and sometimes irregular. Percussion may reveal an increase in the cardiac dulness, and auscultation an anemic murmur. Dyspnea on slight exertion, a feeling of weight or pain in the precordia, and palpitation are not infrequent symptoms.

The extent of the blood destruction depends upon the severity and proximity of the paroxysms and the activity of the blood-making organs. The number of red cells frequently falls to one million per c.mm. or even less. In other cases the destroyed cells are nearly replaced within a short time after the relapse. The hemoglobin percentage is sometimes disproportionately lower than the red cell count, though occasionally it may be normal or above. The leukocyte formula is similar to that of acute infections. Parasites of the asexual cycle are usually found in the peripheral blood. Tertian gametes are frequently seen, while quartan are rare. The frequency of crescents and ovoids is very variable. In my experience they are very rarely seen in blood obtained from the superficial circulation. They are also infrequent in the experience of Manson[59] (in cases seen in the tropics), A. Plehn,[171] Craig,[307] Stephens and Christophers,[118] Ziemann,[308] Wellman,[309] Annett, Dutton and Elliott,[310] Kendall,[30] and others. The majority of observers, however, have seen estivo-autumnal gametes in a considerable proportion of their cases. In localities where this phase of the parasite is so rare it is rather difficult to understand how the species is preserved. The most probable explanation is that the sexual cycle is supplanted by the parthenogenetic cycle in the perpetuation of the species, the parthenogametes tending to congregate in the spleen.

Other blood changes, as nucleated red cells, microcytes, macrocytes, and poikilocytes, are more common in chronic than in acute malaria.

The respiration is usually quickened, especially after exercise. Chronic bronchial catarrh, usually of a mild degree, is

not a rare condition in chronic malaria, and epistaxis is sometimes profuse.

Digestive disorders are very common and marked meteorism may exist. The condition of the bowels is not constant, diarrhea sometimes alternating with constipation. Dysenteric manifestations are frequent.

The spleen may be of normal proportions in mild cases, but is usually enlarged, sometimes enormously so, passing the median line of the abdomen and the iliac crest. It may or may not be tender or painful; in the former case the pain is usually of a pulling nature and referred to the left shoulder. If perisplenitis with adhesions does not occur the spleen may be movable or floating. Often the spleen enlarges during the active stage to recede slowly during latency. The liver is often slightly enlarged and tender.

Headache, nervousness, restlessness, vertigo, insomnia, and, in severe cases, impaired memory, are observed. The urine is often albuminous.

Masked Malaria.—Masked or larvate malaria, like pernicious malaria, needs complete overhauling. Nearly every disease in the category has been confounded with malaria and classed as larvate. This heterogeneous group has been expanded to embrace diseases unrelated in any way to malaria, diseases complicating malaria, and symptoms and sequelæ of malaria. The frequency of masked malaria varies inversely with the care employed in diagnosis. Masked malaria is merely atypic malaria. The symptoms being of little value in diagnosis, this must be made by the anamnesis, the microscopic examination of the blood, and by the therapeutic test. Nervous, gastro-intestinal, and cutaneous disorders are those most frequently recorded as masked. Most of these are to be considered under Complications and Sequelæ.

COMPLICATIONS AND SEQUELÆ

Circulatory System.—Malaria is very frequently complicated by heart disorders. In the negro population of the South, in whom syphilis, abuse of alcohol and tobacco, pneumonia, and other etiologic factors are very prevalent, lesions of the cir-

culatory system, particularly valvular lesions of the heart, often add to the gravity of severe malarial infections. These are to be regarded almost invariably as complications and not as sequelæ. Circulatory lesions, the direct result of malarial invasion, are remarkably rare. Many such cases were reported before the discovery of the parasite, but are for this reason practically valueless.

Collin[227] found cardiac hypertrophy in 6 of 61, and Kelsch and Kiener[178] in 34 of 80 autopsies on malarial subjects. It is, however, by no means certain that malaria was responsible for the hypertrophy in these cases.

Probably the commonest cardiac sequel of malaria is myocarditis. Slight evidences of degeneration of the heart muscle are sometimes found after death in cases which presented no symptoms during life. Triantaphyllides[311] observed 26 cases with symptoms of myocarditis in 12,000 cases of malaria; these cases he believes due solely to malaria. The cases of so-called *asthenia cordis* following malaria are probably cases of myocarditis. Dilatation may follow myocarditis. Localizations of parasites in the blood-vessels of the heart have been mentioned when considering pernicious malaria.

Angina pectoris is occasionally observed in connection with malaria. It may exist as a complication or as the cardialgic type of pernicious malaria.

Much was formerly written about malarial endocarditis, aortitis, and endarteritis. These occur but rarely and only as complications. Ulcerative endocarditis has occasionally been observed after pneumonia complicating malaria. It should be borne in mind that the temperature of septic endocarditis may be similar to that of malaria. Pericarditis and aortic aneurism are unusual complications. Phlebitis and thrombosis have been seen, more often in cases of cachexia.

There is absolutely no evidence that malaria is a causative factor in either lymphangitis or lymphadenitis, the so-called malarial bubo, these conditions occurring only as complications. A suppurating bubo, like other septic processes, may be accompanied by an intermittent temperature.

Respiratory System.—Coryza may occur as a complication

to malaria, especially during unseasonable weather. Bronchitis is a common complication, during a portion of the malarial season occurring with marked frequency. It is observed oftener in the negro than in the white race. Subacute or chronic bronchitis is usually in chronic malaria and cachexia.

Ziemann reports the case of a healthy young man who, during an attack of estivo-autumnal malaria, was afflicted with intermittent spasm of the laryngeal muscles. The spasms coincided with the malarial paroxysms, parasites were found in the blood, and both the malaria and the laryngeal trouble yielded promptly to quinine.

A peculiar condition of the pulmonary apices has been described. It consists of a rapid and a transient congestion of the apex of one or both lungs, arising and disappearing with the paroxysm. The cough is dry and painful, the expectoration is scanty, occasionally bloody, and there may be bronchial breathing and increased vocal fremitus. The writer has had no experience with this complication.

Pneumonia was long considered a manifestation or a sequel of malaria, but it is now known that they are entirely distinct diseases.

Either lobular or lobar pneumonia may complicate malaria, the latter more frequently than the former. Lobar pneumonia sometimes occurs with acute malaria, but much more commonly with chronic malaria and cachexia. It is probably the most frequent mode of exit of the cachectic, in whom the pneumonia often assumes the low form and is especially liable to complications, as delayed resolution, gangrene, abscess, and pyothorax. Pneumonia complicating malaria is apt to be atypic, though the pneumonic symptoms usually predominate. Both lungs are more apt to be affected, profuse hemoptosis occasionally occurs, and malarial parasites may be found in the expectorated blood. Fibroid pneumonia sometimes complicates malarial cachexia. The prognosis in malaria complicated with pneumonia is grave.

Pleurisy is not a common complication of paludism. It has been maintained[312] that the enlarged spleen, especially if perisplenitis exists, predisposes to inflammation of the left pleura,

but this requires further evidence. Hydrothorax may rarely be present in cachexia. Jenness[313] has recently recorded a fatal case of abscess of the right diaphragmatic pleura during an attack of tertian malaria. The chief physical signs were flatness on percussion, and absence of respiratory and voice sounds; there was no bulging of the chest wall. At autopsy the liver was found normal.

Gastro-intestinal Tract.—Stomatitis is sometimes observed in malaria. Parotitis is an infrequent complication. Dyspeptic symptoms denoting chronic gastric catarrh are not uncommon in cases of chronic malaria and cachexia. Gastric ulcer in association with amyloid changes in the mucosa is rarely noted. Hematemesis occasionally assumes alarming proportions.

Enteritis is a much more frequent sequela of malaria than ordinarily regarded. The inflammation may advance to ulceration. The process has been frequently demonstrated by autopsies to be due to accumulations of parasites in the intestinal mucosa. Diarrhea is common, especially in persons improperly fed. Profuse hemorrhage occasionally occurs, in which case the microscopic examination of the blood is of the greatest value in differentiating the disease from typhoid fever.

Dysenteric symptoms arising in the course of malaria and the dysenteric form of pernicious malaria have been considered. Well-marked dysentery may be present either as a complication or as a sequela. Often the dysenteric symptoms predominate, thus constituting one of the commonest forms of masked malaria. Craig[164] has shown that 65 per cent. of the patients with malarial parasites in the blood observed at the Army General Hospital, Presidio of San Francisco, suffered at some time from acute or chronic dysentery, and of these more than 25 per cent. suffered from amebic dysentery. Thayer[98] says that nearly 12 per cent. of the cases of amebic dysentery treated at the Johns Hopkins Hospital have suffered simultaneously with malaria. In 36 cases of dysentery associated with malaria Ewing[27] found the *Amœba dysenterica* in the stools of 9. Dysentery aggravates the prognosis of malaria.

Besides the ameba, other intestinal parasites may complicate

paludism. Of these by far the most common is the *Ascaris lumbricoides*. Uncinariasis is not an infrequent complication in some sections. The writer has observed an infection with *Hymenolepis nana* associated with malaria. It is not improbable that intestinal helminthiasis aggravates the anemia and the gastro-intestinal and nervous symptoms. In examining the blood for the malarial parasite the presence of eosinophilia calls for an examination of the feces.

Cirrhosis of the liver, the direct result of malarial infection, described as relatively frequent in certain portions of the tropics, appears to be rare in this section. Hypertrophic hepatitis may result from prolonged infection. Ascites occasionally develops, particularly in chronic malaria and cachexia.

The Blood and Spleen.—Leukemia follows malaria only rarely, probably never as a true sequela. In 124 cases of leukemia Mosler[79] determined that only 8 or 10 bore any etiologic relation to malaria. Marchiafava and Bignami[22] observed a case of splenomedullary leukemia in an adult male, aged twenty-eight. The symptoms were enormous enlargement of the spleen and liver, diarrhea, and grave anemia. The case had been diagnosed malarial cachexia. Bastianelli[67] observed a similar case. Ziemann[48] treated a case in the ten-year-old daughter of a Duala chief; the girl had suffered repeated attacks of malaria, and pigmented leukocytes were found in the blood. Sakorraphos[79] described 10 cases of leukemia in persons who had formerly lived in malarial localities. However, the blood examination showed no parasites nor was there any elevation of the temperature. Brown[79] saw a case of lymphatic leukemia follow malaria. The writer has had no experience favoring an etiologic relation between leukemia and malaria.

The relation of splenic anemia (Banti's disease) to malaria is not clear. Two of Hemmeter's[314] cases followed malaria, and of 15 which Osler[316] observed malaria preceded 5. Cohen and Rosenberger[315] observed a case of chronic malarial infection with spleen and blood lesions closely resembling those of Banti's disease. Injections of quinine and urea were used with good results. Splenic anemia may come into consideration in differential diagnosis.

Malarial Cachexia.—In this condition the parasites have obtained undisputed possession of the host. The defensive forces have been completely conquered, the blood-making organs can no longer meet the demands made upon them, and toxins, unopposed, work changes, often irreparable, in important organs. Cachexia has been classified as dry or humid, according to the absence or presence of anasarca, and as acute or chronic. Acute cachexia is characterized by a rapid onset and development of symptoms, and usually follows acute malaria, occasionally after only one or two attacks. These cases are infrequent. Chronic cachexia, the usual form, is a sequela of chronic malaria.

Malarial cachexia is found where the severe forms of malaria are endemic. It may be stated as a general rule that the frequency of cachexia among the white race is an index to the prevalence of grave infections. It is much more common in the white race than in the negro. While negro children are not infrequently the subjects of malarial cachexia, it is much rarer in the adult negro. Of adults, males are more commonly cachectic than females; among children the proportion is about even. The condition rarely develops in persons of the better class, but is seen in those living under improper hygienic conditions and who neglect the treatment of acute malaria.

Cases of cachexia developing without preceding malaria have been reported, but are subject to question. The malaria may have been unrecognized, as might happen with latent or masked infections. In regions where kala-azar is endemic it is only recently that this disease has been differentiated from malarial cachexia. Infections with the estivo-autumnal parasites are followed by cachexia much more frequently than tertian and quartan infections.

The cachectic usually presents a singular appearance. The emaciated limbs are in marked contrast to the big belly, and the features are aged beyond the years. The most pronounced phenomena are the anemia and the enlarged spleen. The red blood-cells may be reduced to seven or eight hundred thousand per c.mm. The leukocytes are generally normal in number or a little below. Numerous differential counts have shown a

relative increase of the large mononuclear elements. The red cells may show basophile degeneration, polychromatophilia, poikilocytosis, and nuclei, but none of these changes are by any means constant. According to my experience parasites are rarely found in the peripheral blood. The spleen often extends to the umbilicus and to the crest of the ilium, sometimes beyond. It is usually hard and the anterior border presents a sharp edge. Pain and tenderness on pressure are not always felt. Occasionally a bruit is to be detected over the splenic area.

The pulse is small, compressible, and may be irregular. Palpitation of the heart and hemorrhages, especially epistaxis, may occur. An anemic murmur over the precordia is often heard. Myocarditis and dilatation are not infrequent. The breath is short, sometimes amounting to actual dyspnea. A cough is common and signs of bronchitis may be elicited. Pulmonary edema is a late symptom.

The temperature may be normal or subnormal for long periods, though evening rises are often observed. Typic paroxysms are not frequent. Fever often follows imprudences. Whether the fever of cachexia is due directly to parasitic activity or to organic changes is not definitely known. The appetite is generally poor and the digestion tardy. Epigastric pain, nausea, and vomiting may be complained of. The tongue and oral mucous membrane are pale. Diarrhea and dysentery frequently occur. Meteorism is common. The liver is usually somewhat enlarged at first; later it may become atrophic. Ascites is not a rare manifestation. When fever exists the urine is ordinarily scanty and highly colored. Delayed development of the genitals is common in the young and diminished sexual power is not rare in the adult. Indifference, intellectual torpor, somnolence, headache, and vertigo are observed in cachectics. Resistance to cold is lessened and rheumatic pains are experienced. The skin is pallid, dry, and rough, and may exhibit sores or purpuric spots. Anasarca may supervene.

Pneumonia, dysentery, hemoglobinuric fever, and nephritis are common complications of cachexia, and amyloid degeneration, especially of the kidneys, an occasional sequela. Peri-

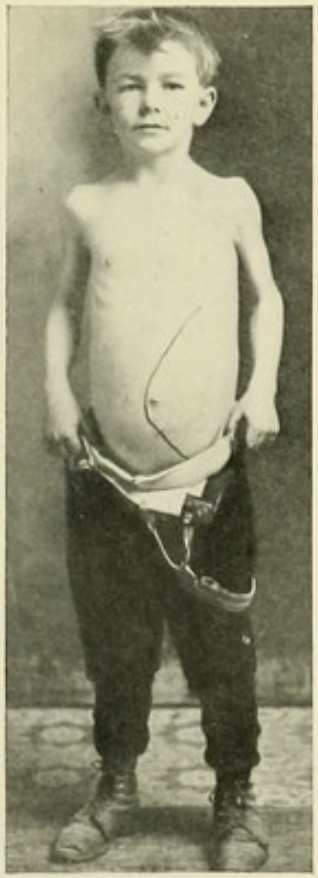


Fig. 62.



Fig. 63.

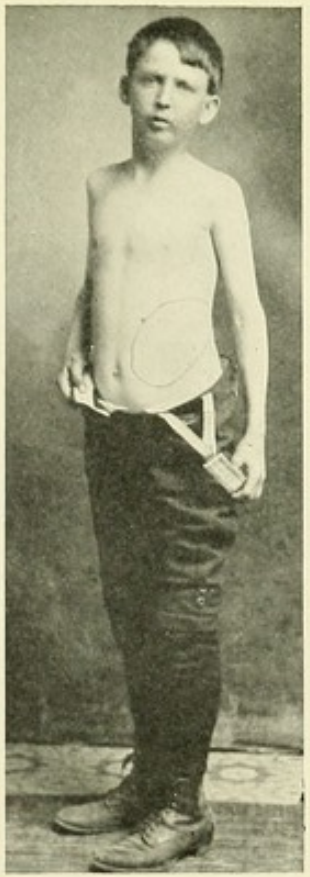


Fig. 64.



Fig. 65.

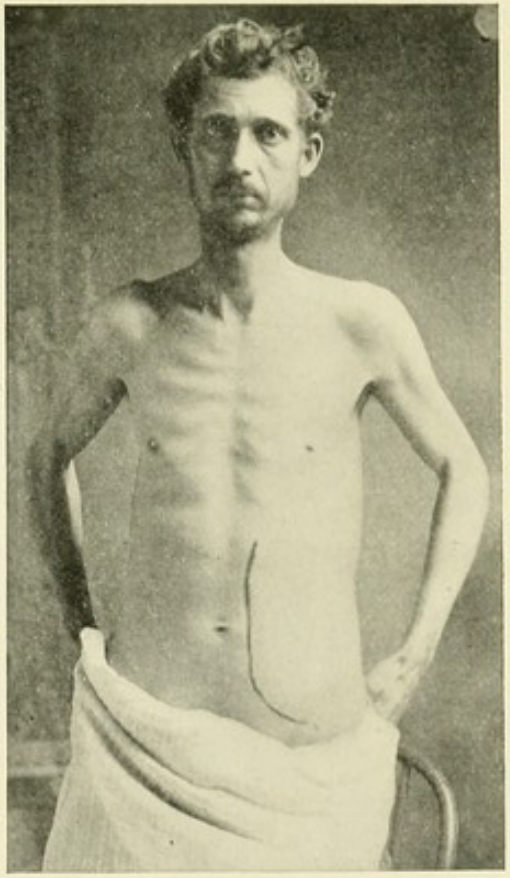


Fig. 66.

Figs. 62-66.—Types of malarial cachexia.

splenitis occasionally occurs and may be the cause of severe pain, especially if adhesions take place. A heavy spleen may cause relaxation of its supports and become "floating" or "wandering." This condition is seen more often in multiparous females. By pressure on neighboring organs a wandering spleen may cause pain, digestive disorders, or even intestinal occlusion. The pedicle may become twisted, as occurred in a fatal case of Marchiafava and Bignami.[22]

Rupture of the spleen is an infrequent complication of malarial cachexia. It is very rarely associated with acute malaria, though a case has been recorded by Palmer[317] in which rupture occurred within seven days of the onset of the fever. The writer observed a case in a subject of cachexia who had a large, hard spleen. Recovery followed, notwithstanding extensive hemorrhage. In some countries, especially in India, rupture of the spleen has assumed medicolegal importance. According to Brault,[318] it is popularly known in Kharkov that the malarial spleen is very friable, and that combatants engaged in fist fights strive to strike the region of the spleen, with the result that 5 per cent. of the official autopsies show ruptures of this organ. The rupture may be spontaneous or the result of blows and falls. Of 19 cases of rupture of the malarial spleen collected by Messerer[319] 15 were spontaneous and only 4 the result of trauma. However, 35 cases studied by Russell[95] were due to trauma, and no cases of spontaneous rupture were noted. A large, soft spleen is much more liable to rupture than a hard one, and fatal hemorrhage is more apt to occur in the former case. A full stomach predisposes to splenic rupture, especially of the concave side. The capsule is usually ruptured, but when thickened, as may result from previous perisplenitis, it may escape untorn. The capsule was not ruptured in only 1 of Russell's[95] 35 cases. The laceration occurs with about equal frequency on the concave and convex sides of the spleen. Tears of the inner aspect may occur without marks of violence of either the skin or the convex surface of the spleen. A light, sharp blow tends to injure the convex surface; a fall or crushing blow, the concave side. The symptoms of rupture of the spleen consist of violent pain in the splenic region referred to

the left shoulder, together with evidences of shock and hemorrhage. The mortality of cases not treated with splenectomy is exceedingly high. Death may occur in from a few hours to five days.

Abscess of the spleen is a rarer complication of malaria even than rupture. The writer is able to collect from the literature mention of not more than 50 cases. The common pyogenic cocci and the bacillus coli communis are the bacteria usually present in splenic abscesses. The symptoms are sometimes as vague as those of abscess of the liver. There may be pain in the left hypochondrium, especially if the abscess is superficial and the peritoneum is involved. The pain is often referred to the left shoulder. Pain may, however, be entirely wanting. The temperature is usually elevated, though in rare instances may be normal or subnormal. It is usually intermittent and associated with chills and sweats. Emaciation may be extreme, notwithstanding the appetite is sometimes voracious. Abscess of the spleen may be confused with uncomplicated malaria, and renal, gastric, or pancreatic disease. The presence of leukocytosis and the therapeutic test are valuable diagnostic points. Signorelli's spleen point may be a useful guide. This is a painful area corresponding to the fifth intercostal space near the left nipple. The examination of the urine may mislead. In a case of splenic abscess observed by Goltman[320] the urine contained albumin, casts, pus cells, renal cells, and some red blood-cells. Aspiration is attended with some danger, but may be done as a last resort, especially if the patient is prepared for operation. The abscess may rupture externally into the pleural cavity or lung of the left side, or into the stomach, intestine, or peritoneal cavity. Without operation the prognosis is very grave; with timely incision and drainage a considerable per cent. recover.

Infarcts and gangrene of the spleen are noted among the rare complications of the spleen in malarial cachexia.

Genito-urinary Organs. Nephritis.—The frequency of nephritis recorded as a sequela of malaria varies greatly with locality, type of fever, and with the idea of what constitutes nephritis. Thus, while Ford[180] observed acute nephritis in

only 1.5 per cent. of his cases of malaria, Moore[321] reports the percentage as 80. The real frequency of nephritis in malaria is in about ½ to 2 per cent. of the cases of tertian and quartan infections and 2 to 5 per cent. in estivo-autumnal. The negro is apparently more susceptible to the renal lesions of malaria than is the white. More cases are seen in the months during which the estivo-autumnal fevers prevail. The middle-aged and the old are less often attacked than the young. Nephritis is much more prone to result from chronic than from acute malaria. The nephritis is most often acute, but it is highly probable that malaria is an important factor in the etiology of chronic nephritis. Chronic nephritis may follow the acute form or may exist as such from the beginning. True hemorhagic nephritis is rare. There is ordinarily nothing characteristic either in the symptoms or pathologic histology of the nephritis of malaria. Ewing,[177] however, has observed an interesting and unique case of malarial nephritis with extensive massing of the parasites in the kidneys. Parenchymatous nephritis is the commonest type, though the contracted kidney may occur as a late lesion. Kelsch and Kiener[178] divide malarial nephritis into the diffuse or glomerular and the granular nephritis of Bright, each with acute and chronic forms. Amyloid degeneration is a renal sequela of malaria.

Occasionally intense lumbar pain, closely simulating renal colic, is experienced as a complication of malaria. This colic usually responds promptly to quinine, though the pathogenesis is not clear.

Forms of orchitis and epididymitis have for a long time been attributed to malaria. Either may complicate malaria. The writer has seen several cases of epididymitis associated with malaria, there being, however, in each case a history of venereal disease. There is at the present time absolutely no evidence that either orchitis or epididymitis is ever a true sequela of malarial disease. The same may be said of hydrocele, which some observers have ascribed to malaria.

It is doubtful whether genuine atrophy of the testicles ever occurs as the result of malaria. It is more probable that these cases are due to improper development, the result of cachexia,

climate, or other factors. Duprey[322] has recently described three cases of impotence following estivo-autumnal fever. Metrorrhagia and, more often, menorrhagia and amenorrhea are not infrequently seen with malaria. Sterility has been charged to paludism.

It was formerly believed that pregnancy conferred a degree of immunity against malaria. This is now known not to be true. If the pregnant woman is attacked less often with malaria it is because she is less often exposed to infection and not on account of any immunity which pregnancy confers upon her.

A list of cases is appended to give an idea of the frequency with which abortion and premature labor occur as the result of malaria complicating pregnancy. The first column of figures records the number of cases in which the complication appeared; the second column shows the number of abortions and premature labors which occurred:

Pascali[105]	34	25
Weatherly,[159] in India	88	28
Weatherly,[159] in England	58	2
Weatherly,[159] in Africa	97	22
Weatherly,[159] in Florida	52	22
Hospital, Rome[86]	51	33
Lwow[323]	26	10
Goth[324]	46	19
Bonfils[325]	105	73
Williams[326]	15	
	572	234
	24.4 per cent.	

This percentage is at least twice as large as that resulting from my experience.

The writer is inclined to the belief that the negro is much less liable to suffer abortion or premature delivery than is the white. This is in keeping with the well-known relative immunity of the negro to some of the effects of malaria. Mercier[182] has observed an unusually large number of abortions in Creole women infected with malaria. It is well known that this race is markedly susceptible to the severer forms of malaria.

Cases accompanied by continued high temperature, retching, and vomiting, and which are more resistent to treatment, are

those in which abortion most frequently occurs. Hence it follows that abortion is more often due to estivo-autumnal fever than to tertian and quartan, and to multiple infections than to single.

The danger of abortion and premature delivery is greater in proportion as the pregnancy is advanced. Thus of Goth's[324] 19 cases expulsion of the uterine contents occurred: once in the fourth month, once in the fifth month, three times in the sixth month, five times in the seventh month, and nine times in the eighth month.

The factors in the interruption of pregnancy are probably fever, retching, vomiting, anemia, and toxins. It is not improbable that in some cases parasitic localizations in the uterine vessels excite pains or cause placental separation, though for this theory there is as yet no pathologic proof.

If the malarial infection does not terminate the pregnancy the labor at full term is apt to be slow, especially the first stage.

Children born at full term of malarial mothers are apt to be smaller and lighter than normal, and the mortality is higher.

Labor often rekindles latent malaria, which, in the puerperium, is not infrequently atypic, the first or third stages of the paroxysm or complete intermission of the temperature sometimes lacking. Subinvolution, postpartum hemorrhage, and suppression of milk may occur with puerperal malaria.

Nervous System.—It is often impossible to determine whether nervous manifestations in malaria are complications or sequelæ. It is certain that many cases reported as due to malaria are purely complications. This is the case with multiple neuritis, of which numerous cases have been ascribed to malaria. In by far the majority of cases the existence of malaria was not established by blood examination; in others it is not certain that the neuritis was due to malaria.

Glogner,[327] in the East Indies, described 6 cases of polyneuritis occurring during and after malarial disease. In 4 cases the parasites were found in the blood. The chief symptoms were diffuse pains in the lower limbs, formication, tenderness of the nerves and muscles, and motor weakness, while the deep reflexes were sometimes intact, sometimes abolished. The elec-

tric excitability of the nerves and muscles was diminished, while sensibility was retained. Edema of the legs was present in some of the cases.

Price[328] records a case in a girl, eight years old, who following malarial infection, had multiple neuritis which lasted eighteen months. Her symptoms were pain, paresthesia, hand tremor, weakness of the extremities, with characteristic foot drop. Estivo-autumnal parasites were detected on blood examination, and quinine effected a cure.

Ziemann[48] observed a case of peripheral neuritis in a young German merchant who had been in Cameroon four months. Two days before his entrance into the hospital he was taken with high fever without a preceding cold stage. Simultaneously he noted almost complete paralysis of both legs, especially of the right. Neither the bladder nor bowel functions were affected, nor was there marked sensory disturbance. The temperature did not exceed 103.5° F. The peripheral blood showed an enormous number of estivo-autumnal parasites. While the paralysis of the left leg persisted only a few days during convalescence, that of the right leg was slow in diminishing, notwithstanding massage and electric treatment for several weeks, so that at the end of four months the patient was still compelled to walk with the aid of a stick.

It is not infrequently difficult to differentiate between polyneuritis and myelitis.

Laveran[1] describes a case of paraplegia which he observed in Constantine. The patient had had several attacks of malaria and underwent a relapse after admission to the hospital, during which the parasite was found on microscopic examination. The paralysis of the lower limbs was not accompanied by any alteration of sensibility nor of nutrition, and micturition and defecation were normal. Unfortunately for an exact diagnosis the patient had had syphilis also. Mercury and potassium iodide were prescribed without appreciable result. Quinine caused a disappearance of the parasites, but had no effect on the paralysis.

A fatal case showing paraplegia was treated by Ziemann.[48] The patient was a strong negro man. Bladder paralysis, re-

tention of urine, and coma were present. The blood contained estivo-autumnal parasites.

Da Costa's[329] case of paraplegia harbored the estivo-autumnal parasite and yielded to quinine.

Either persistent or intention tremors may be associated with paludism. The case of Da Costa just mentioned exhibited intention tremor. Fornaca[330] reports a case in a peasant, aged fifty-seven, whose personal and family history were good and who, during an attack of malaria, was affected with tremors of both arms and hands. These tremors were irregular and increased on voluntary motion, but did not cease during rest. They became exaggerated during the paroxysm and diminished in the interim. Simple tertian parasites were present in the blood and the symptoms disappeared upon the administration of quinine.

Torti[331] saw 2 cases in which there were symptoms of multiple sclerosis without a history of syphilis or the abuse of alcohol or tobacco. In both cases parasites were found, and both were cured with quinine.

Spiller[332] has reported a case closely resembling multiple sclerosis. The patient, a male, aged forty, gave a history of having had a chancre twenty years before. He came under observation three years before death, which resulted from acute diarrhea, lasting one week and probably of malarial origin. The symptoms were a very decided intention tremor of the left upper limb; marked ataxia of the left lower limb; alternating hemiparesis, first of one side of the body, then of the other; headache, drowsiness, vertigo, and diplopia; marked vertical nystagmus; scanning speech; exaggerated tendon reflexes and ankle clonus on the right side. Post mortem the spleen was found to weigh 550 grams. The crossed pyramidal tract was moderately sclerotic throughout the cord; this sclerosis could be traced as high as the left internal capsule. All the capillaries of the brain and cord were filled with estivo-autumnal parasites, and numerous small and recent hemorrhages were seen in the left paracentral lobule and other portions of the cortex. The capillaries observed under a low-power lens appeared to have been injected with black powder.

The sclerotic lesions are said not to have resembled those due to syphilis, and the symptoms are believed to have been due to the parasitic thromboses of the capillaries and not to the sclerosis.

Hemiplegia, paraplegia, and various monoplegias, either with or without aphasia or sensory disturbances, are not infrequently associated with malaria.

Cerebellar syndromes are rarely observed in malaria. They consist of general weakness, rigidity, and pain in the back of the neck, intense headache, ataxic gait with a tendency to fall backward and to the left, tremors, incoördination of movement, dysarthria, nystagmus, and vomiting. The tertian parasite is usually present in these cases.

Bulbar symptoms are occasionally encountered. Such are hypoglossal and facial paralysis, ataxia of arm, dysarthria or anarthria, and staggering gait. These symptoms are usually obstinate.

Various psychoses occur in connection with malaria, either during or following acute or chronic malaria. The commonest of these disorders are weakened memory, melancholia, mania, and delusional insanity. Suicidal and erotic tendencies may be observed. Below are brief notes on 4 cases under the care of Ziemann[333] in Cameroon:

1. A merchant, thirty-six years of age, slender, pale, with a history of neurasthenia but not of alcoholism, living in a very unhealthy locality, but using no prophylactic quinine, having had several moderate and light attacks of estivo-autumnal fever, was suddenly seized with a violent paroxysm. During the seizure he had strong delusions of persecution. He seized his gun in order to shoot down the neighbors whom he thought pursuing him. Energetic quinine therapy was followed by complete cure excepting that the idea that the neighbors had persecuted him during the night of his illness persisted.

2. A strong young merchant, with no hereditary taint nor alcoholic history, not having employed quinine prophylactically, had an attack of estivo-autumnal malaria. During the access he distinctly heard the voices of his father and other relatives in Europe, and conversed with them upon his prospects in

Cameroon. Complete cure followed the administration of quinine except the fixed idea that his relatives had visited him during his illness and that he was more quiet, peculiar, and neurasthenic. He was returned home on the failure of his firm.

3. A young merchant had been in Cameroon two years engaged in expeditions for the purpose of obtaining rubber. During these expeditions he did not use quinine as a prophylactic, although he suffered repeated malarial attacks. On a visit to another merchant he was suddenly taken with a paroxysm during which he distinctly saw an arm extended from the wall, holding a revolver aimed at him. Seized with terror, he fled to keep from being murdered. Quinine cured the fever, but the delusion of the arm and the revolver as to that particular time persisted.

4. A strong young merchant of healthy family and without history of alcoholism or nervous disorder was seized three weeks after arrival in Cameroon with a severe estivo-autumnal infection. During the attack he labored under the delusion that his colleagues, who in reality nursed him attentively, had planned to kill him. After energetic treatment with quinine a complete cure was effected excepting the persistence of the fixed idea of persecution by his colleagues.

Hysteria is not a rare phenomenon during paludism. It is probably the result of anemia in predisposed persons. As it may assume either of a multitude of forms, its chief significance is from the viewpoint of diagnosis.

A mild neurasthenia is probably due directly to malaria in some instances, and preëxisting neurasthenia is often aggravated by malarial infection. The usual symptoms are restlessness, nervousness, insomnia, and annoying distinctness of the heart beat on retiring.

It was formerly believed that intercurrent malaria exercised a beneficial influence upon epilepsy. So far from this being the case, however, epilepsy is frequently aggravated by paludal infection.

Violent choreic symptoms are among the rare nervous phenomena.

The Eye.—Injection of the conjunctiva is not infrequently associated with neuralgia of the fifth nerve. True intermittent conjunctivitis occurs but rarely if at all. Both interstitial and dendritic keratitis are occasionally observed with malaria, though it is doubtful whether either form can be attributed to malaria. The same probably holds true for vesicular keratitis or the so-called corneal herpes. In pernicious seizures with coma-vigil the eyes are more or less exposed to damage.

Iritis exists as a complication of malaria in rare instances. Choroiditis occasionally occurs in connection with retinitis. Optic neuritis is observed chiefly in cachectics. In the majority of cases it proceeds to atrophy.

Retinal hemorrhages are oftenest minute and located far forward, hence they may be easily overlooked. Occasionally, however, they are peripapillary or macular and of large size. In the latter case the prognosis is more serious. Persistent or periodic amaurosis without evident retinal changes is sometimes seen. The writer has seen one case of hemianopia following pernicious malaria of the comatose form which terminated in complete restoration of vision. Rarer optic manifestations occurring in conjunction with malaria are hemorrhage and infiltration into the vitreous humor.

The Ear.—Otalgia, labyrinthine vertigo, otitis media, and lesions of the internal ear and auditory nerve have been described as occurring with malaria, but in no case has the blood been examined.

The senses of taste and smell are said to be diminished or abolished in rare cases of malaria.

The Skin.—The frequency with which herpes occurs in malaria has already been mentioned. Next to herpes, urticaria is the most frequent cutaneous lesion associated with malaria. It may occasionally resemble the eruption of measles. The possibility of the eruption being caused by quinine should be remembered. Erythema is not an uncommon eruption with malaria, and may simulate the eruption of scarlatina. Pruritus may be present. Erythema nodosum has occasionally been observed. Petechiæ and large purpuric spots are not rare in

subjects of chronic malaria and of cachexia. In these patients ulcers and furunculosis may exist as complications.

The occurrence of herpes zoster in malaria is very variable. In 616 cases of malaria studied by Thayer and Hewetson[29] herpes zoster occurred only once, and this complication existed but once in 1,780 cases of malaria reviewed by Anders.[283] On the other hand, Winfield[334] found malarial parasites in the blood of 14 out of 25 cases of herpes zoster. The writer has recently observed 9 cases of herpes zoster. In 3 the blood examination revealed estivo-autumnal parasites; in 2 there was a history of recent malaria, but the examination of the blood was negative, while in 4 there was no history of recent malaria and the examination of the blood was negative.

As previously mentioned, purpura simplex is not an uncommon occurrence in malaria. Purpuric eruptions may also, but rarely, be noted in hemoglobinuric fever. But true purpura hemorrhagica is very rarely seen in malaria. Eisenmann, Wenmarning, and Tchouprina,[96] Bastianelli and Bignami,[335] Hirtz and Bernheim,[86] Marchiafava and Bignami,[162] and the writer[336] have reported such cases.

Malaria undoubtedly predisposes to the development of gangrene, especially when it has become chronic or has advanced to cachexia. More than this, however, cannot be said of the part played by malaria in the etiology of gangrene. Gangrene of almost every part of the surface of the body has been observed in malarial subjects. The gangrene is more commonly of the dry variety. Local asphyxia not followed by gangrene occurs also. Raynaud's disease, or symmetric gangrene, has been thought to be due to malaria in many instances, but reports of cases in which the malarial parasite was present in the blood are still rare.

Other Conditions and Diseases.—At various times malaria has been supposed to predispose to certain diseases. Such were typhoid fever and diabetes. It has also been thought to exert an antagonistic influence toward other diseases, as tuberculosis, cancer, and influenza. It is probable that any predisposing power on the part of malaria to other diseases is only indirect. It is *a priori* improbable that a disease conferring only relative

immunity toward itself should immunize against or antagonize other diseases, and such is the result of experience.

Typhoid Fever.—The complication of typhoid fever with malaria is not very rare. A search of the literature reveals records of 215 cases in which the presence of malarial parasites and the typhoid bacilli or the Widal reaction conclusively proved the association.

Typhoid fever is more frequently complicated with tertian than with estivo-autumnal malaria. Craig[337] has reported the only case of simultaneous typhoid fever and quartan malaria of which the writer has any knowledge.

Usually the malarial symptoms arise and the parasites are detected during convalescence from the typhoid fever, though they may be present during the course of the latter. When the onset of the malaria precedes that of the typhoid fever the malarial parasites often disappear from the peripheral circulation upon the advent of the typhoid fever, sometimes reappearing and producing symptoms during the convalescence from typhoid. This is analagous to the result of inoculating a given variety of malarial parasites into a malarial patient harboring a different form, the older infection usually surrendering to the fresh. Malaria occurring at the height of typhoid fever may or may not modify the course of the latter. The mortality of the complication of these two fevers is higher than that of uncomplicated typhoid.

The term "typhomalarial fever," if used at all, should be restricted to those cases in which exact methods of diagnosis prove it applicable. However, the combination of typhoid and malarial fevers is no more entitled, either by virtue of intimacy or frequency, to a hyphenated appellation than is tuberculosis or gonorrhea in association with malaria. It was formerly believed that a mysterious fusion of both diseases produced a hybrid pathologic entity. It is now definitely known that this is not the case. Such a diagnosis is ordinarily a compromise based on a lack of frankness to acknowledge inability to diagnose certain cases of fever in the earliest stages, and is not only loose and unscientific, but is, in many instances, actually harmful, as it often leads to the abuse of purgatives and quinine.

There is no question but that nearly all of the so-called "typho-malaria" is pure typhoid fever.

Diabetes.—In spite of the great frequency with which Burdel[86] claims to have found glycosuria complicating malaria (92 times in 382 cases of malaria), it must be considered a rare complication. Ziemann,[48] Wittrock,[49] and Marchiafava and Bignami[22] observed 1 case each, and Hemmeter[314] mentions records of 198 urinalyses in cases of malaria gathered from various hospitals, only 2 of which indicated diabetes mellitus. The writer recalls the case of a diabetic, passing more than 5 per cent. of sugar, who was attacked with estivo-autumnal malaria. The latter ran an uneventful course and seemed to have no effect on the sugar excretion. The patient died several months later of bronchitis.

Polyuria in malarial subjects has already been mentioned.

Tuberculosis.—In the South, where tuberculosis is very prevalent in the negro race, the negro death rate from tuberculosis ranging from 100 to 150 per cent. higher than in the white race, tuberculosis and malaria not infrequently concur, especially in the colored race. Malarial cachexia predisposes to tuberculosis only in a slight measure, if at all. The negro, who is less often the subject of cachexia than the white, more often shows the combination of malaria and tuberculosis. The malaria may prove rapidly fatal, both diseases may be unmodified in their progress, or the tuberculosis may assume a more rapid course. The old idea that the two diseases are antagonistic is disproved not only by their not uncommon occurrence in the same individual, but Kelsch and Kiener[178] have even found, in several autopsies, evidence of both diseases in the same organs, as the liver and spleen.

Influenza.—Anders[337] believes that there exists a decided antagonism between malaria and influenza. Simms and Warwick,[85] however, mention simultaneous epidemics of malaria and influenza in Alabama, when, "of those infected with malaria, 60 per cent. were brought down with this disease, and it was much more severe than in those who were not infected."

Cancer.—Based on the supposition that cancer is not so frequent in tropic latitudes, and on the report of Krzowitz, in

1776, of a case of cancer of the breast healing after an attack of double tertian malaria, Löffler[338] assumed an antagonism between the two diseases, and proposed, as a therapeutic measure, the inoculation with malaria of cancerous patients. A few experiments and numerous reports of cancer among tropic people and malarial subjects have shown the absolute uselessness of such a procedure. On the other hand, it is believed that malaria of long standing predisposes to cancer of the liver.

Smallpox is an infrequent complication of malaria. Laveran[1] observed several such cases in Constantine. The malarial parasites usually disappeared from the blood with the onset of the smallpox where the onset of the latter succeeded that of the former. The mortality of these cases was unusually high. Pyemic foci and hemorrhages were observed.

Syphilis is a common complication of paludism. Under these circumstances syphilis is more rapid in its course and is rebellious to treatment in proportion to the chronicity of the malarial infection. In malarial cachectics antisyphilitic treatment is sometimes all but impotent. Syphilitic buboes are more apt to suppurate and become ugly indolent ulcers. Malarial invasion may arouse latent syphilis.

Vincent[159] is of the opinion that the colon bacillus often assumes pathogenic importance in malarial infections, and he terms the result "coli-malarial fever." The patients are profoundly malarial; they present a fever of continued type and typhoid phenomena, subdelirium, coma, diarrhea, etc. At autopsy there are no intestinal lesions save a few psorenteric plagues. Some show extensive foci of necrosis in the spleen or small miliary abscesses; others suppurating points in the kidneys. Siderosis is found in the spleen and liver. Bacteriologic examination shows a generalized infection with the bacillus coli communis. The eccentric and iconoclastic Legrain[255] believes that the rôle of the colon bacillus in exotic pathology is immense.

In the present state of our knowledge it is impossible to determine the part played by the colon bacillus in the fevers of warm countries. In subtropic and tropic climates, with an exuberant flora, it is theoretically not impossible that the colon

bacillus may acquire an unusual degree of virulence and give rise to auto-intoxications. Every Southern physician is familiar with ephemeral fevers, usually attributed to "biliousness," which disappear after the administration of an antiseptic purge, as calomel.

The association of scorbutus and malaria was formerly frequently encountered in military practice during campaigns. It is now rarely seen, especially in civil practice.

Valenti[339] and Lioubenetzy[340] have each observed in malarial subjects symptoms recalling Addison's disease.

Malaria in Children.—In older children there is nothing unusual in the malarial attacks. In infants and young children there are several points which deserve a brief consideration.

The type of fever is most often quotidian, sometimes tertian or double quotidian, rarely quartan. The paroxysm occurs more often during the night than is the case with the adult, the fever being often detected for the first time in the morning.

The first stage is rarely typic, the rigor being replaced by coldness of the extremities, pallor, slight cyanosis, especially of the lips and nails; vomiting, drowsiness, and sometimes convulsions. During the second stage the fever is ordinarily higher than in the adult. Gastro-intestinal symptoms, particularly vomiting and diarrhea, are common. Thirst is usually intense. The most common complaints are pain in the head and epigastric region. Enlargement of the spleen is more constant than in the adult. Torticollis and erythema may be noted. Atypic forms and dangerous symptoms, especially on the part of the nervous and gastro-intestinal systems, are frequent. Edema, ascites, and purpura are not uncommon.

Malaria in the Negro.—The relative immunity of the negro race to the severe manifestations of malaria and to hemoglobinuric fever has been mentioned. It remains only to cite a few clinic features of malaria in this race.

Estivo-autumnal malaria is much more common in the colored race than are tertian and quartan. The paroxysms usually occur during the day, but night paroxysms are more common than in the white race. A well-defined and severe cold

stage, while not at all rare in the negro, is more frequently lacking than in the accesses in the white. Herpes is relatively rarer in the black. Uncontrollable vomiting is not nearly so frequent in the colored race as in the white. Marked splenic enlargement is much less common in the negro, palpable spleens in the adult negro being infrequent. The extremely low hemoglobin percentages, which are not rare in chronic malaria and cachexia of white persons, are far less frequently observed in the negro. As previously stated, cachexia is decidedly more prevalent in the white race. Malarial parasites are altogether absent from the peripheral blood of negroes in a larger per cent. of cases than they are wanting in white patients. When present they are more frequently scanty. On the other hand, the negro may harbor large numbers of parasites without manifesting any symptoms. Pulmonary complications, bronchitis, pneumonia, and tuberculosis are more frequent in the negro. Nephritis is another complication of which this is true. Hysteria and other neuroses are probably more common in the colored female. The abuse of snuff, which is undermining the nervous stability of the majority of adult negro females in the South, may help to account for this. There is less tendency to abort during pregnancy complicated with malaria in the colored female than in the white. Spontaneous cure after only one or two paroxysms is a common termination of malaria in the negro. Every physician practising among this race is familiar with the frequency with which their attacks of malaria end after a "round" of purgative and a potion of "tea" of some sort. The grave forms of malaria occurring less often, the mortality is consequently lower in the negro race.

The Surgical Aspect of Malaria.—Trauma may aggravate active malaria or arouse it from latency. On the other hand, malarial infection reacts upon wounds. Slight wounds, such as that caused by the extraction of a tooth, may in cachectics give rise to excessive hemorrhage. Fractures heal more slowly in malarial subjects. The writer has more than once observed suppuration, ulceration, and sloughing in the wounds, aseptically treated, of malarial persons, especially sawmill employes

and timbermen. If surgical measures are contemplated in patients with a history of recent malaria the blood should be examined carefully for evidences of malaria, which, if present, might figure in the result.

With reference to the surgical relations of malaria the following conclusions are justifiable:

1. In subjects of active malaria, wounds are apt to aggravate the malaria.

2. In subjects of latent malaria, trauma is apt to excite the latter into activity.

3. Chronic malaria and cachexia may complicate wounds by increasing the tendency to hemorrhage, suppuration, sloughing, indolence, or even gangrene.

4. The mere presence of parasites in the blood without producing symptoms (absolute latency) is no bar to operation, as the specific treatment may be pursued with the surgical.

5. In badly debilitated subjects of chronic malaria and of cachexia only operations of necessity should be undertaken, and then quinine and tonics should form part of the after-treatment.

CHAPTER VI

DIAGNOSIS

MALARIA is the scapegoat of tropic pathology and quinine the high priest.

Too often is the mocking equation of Legrain,

Fever=Malaria=Quinine,

employed to solve the diagnostic problems of the fevers of warm climates.

There are three sources from which information may be drawn to make a diagnosis of malaria; first, from the symptoms; second, from the examination of the blood; and third, from the effect of quinine upon the symptoms.

1. Of the clinical history the most important feature to be considered is **periodicity.** Tertian and quartan periodicity are pathognomonic of malaria. Sometimes the statements of patients cannot be relied on with respect to the course of their ailments, and tertian and quartan periodicity must be absolutely determined to be of diagnostic value. By this is not meant that the disease must be observed by the physician untreated until such periodicity is established, but that value of this symptom is in proportion to the reliability of the source from which the history is derived. Unfortunately this periodicity is of little value in estivo-autumnal infections, in which the importance and difficulty of diagnosis are greater.

Quotidian periodicity is not only worthless, but actually misleading in the diagnosis of malaria. It is especially in septic conditions that mistakes are oftenest made, where not infrequently is the rhythmic quotidian succession of chill, fever, and sweat mistaken for the metric march of malaria. A noted clinician has said that he has rarely seen a case of abscess of the liver that had not been drenched with quinine, and his experience is not unique in this respect. Malaria is

by no means the only condition accompanied with cold, hot, and sweating stages, and one or two of these stages are sometimes wanting in malaria. Abscess of the liver, gall-stone disease, tuberculosis, and numerous other diseases may exhibit temperature charts closely resembling that of malaria.

It should be borne in mind, however, that *quotidian fever* in malaria may show *tertian* or *quartan periodicity*. Thus in double tertian the paroxysms of the first and third days may occur at a certain hour in the morning, and those of the second and fourth days at a certain hour in the afternoon. Tertian periodicity in quotidian fever is valuable from a diagnostic view in proportion as the paroxysms on successive days are separated from a given hour and those on alternate days approach a given hour, or, in other words, as the alternate paroxysms approach a forty-eight-hour interval, while the accesses on successive days are distant, by more or less, from a twenty-four-hour interval. Quartan periodicity in quotidian fever rarely comes into consideration in diagnosis on account of the relative rarity of the triple quartan infections, the promptness with which the microscope decides the matter, and the more frequent tendency of one or two of the three groups of parasites to sporulate approximately twenty-four hours after the last preceding. The course of a double quartan infection, two successive fever days followed by a fever-free day, is pathognomonic.

It may be stated as a general rule that tertian and quartan periodicity are of importance in diagnosis in proportion to the length of the series of paroxysms, since it is not impossible that fever on only two days separated by one or two days of apyrexia might occur adventitiously from causes other than malaria. It is the repetition of this succession that indicates malaria, hence the periodicity must be perfectly established.

The characteristic curve of tertian estivo-autumnal fever is probably pathognomonic, but can be obtained in only a small proportion of cases in private practice. The clinical course of estivo-autumnal infections is of much less value in diagnosis than that of tertian and quartan.

The value of enlargement of the spleen in the diagnosis

of malaria has certainly been overrated. In regions where there is little malaria, the endemic index being low, it is probably a point of some worth. On the other hand, in malarial regions of high *index endemicus* it is worth much less. It is almost valueless in malaria occurring in negroes, as it is infrequently sufficiently enlarged to be palpable, and unless palpable is of no diagnostic value. Physicians in malarial regions are all familiar with the frequency with which the enlarged spleen of the subject of chronic malaria or cachexia complicates other diseases. If the physician is sufficiently familiar with the patient to know that the splenic enlargement is acute, it becomes a matter of some importance, but the statement of the patient as to the former condition of the organ, even when the latter is immense, is not always to be relied upon.

Herpes when present is an aid to diagnosis. The only disease in which it occurs with anything like the frequency it does in malaria is pneumonia.

2. The **microscopic examination of the blood** for the diagnosis of malaria determines the presence or absence of parasites, pigment, and leukocytosis, and the numeric relation of the leukocytes.

Before attempting the diagnosis of malaria by the microscopic examination of the blood the beginner must become thoroughly familiar with the appearance of normal blood and with the technic of examination, and he should not rely too much upon the result of an examination until he has had considerable experience with malarial blood.

While Laveran made his discovery with a one-sixth-inch lens, only a one-twelfth-inch oil immersion lens, with appropriate condenser and diaphragm, should be employed, and the mechanic stage greatly facilitates the work. Thin slides and cover-glasses should be used.

While stained films of the blood have a wider field of usefulness to the general practitioner than preparations of the unstained blood, he should become familiar with the technic of each.

When about to obtain blood to be examined, fresh and unstained, several slides and cover-glasses, having been washed



Fig. 67.—Making the puncture.

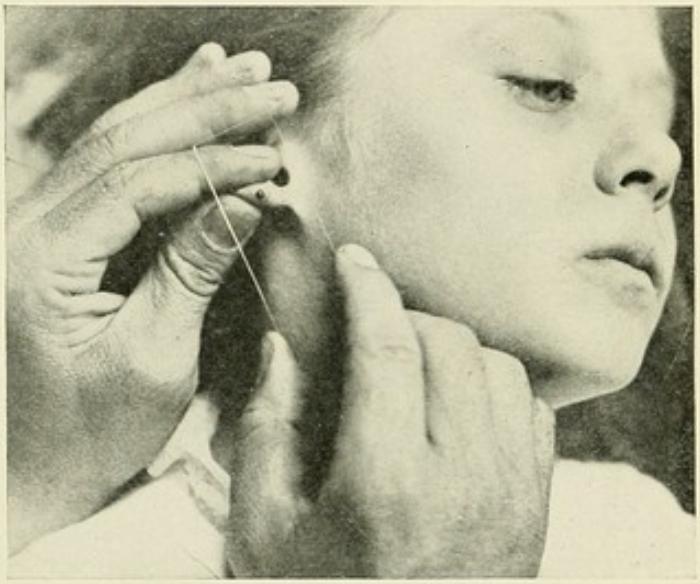


Fig. 68.—Obtaining the blood.

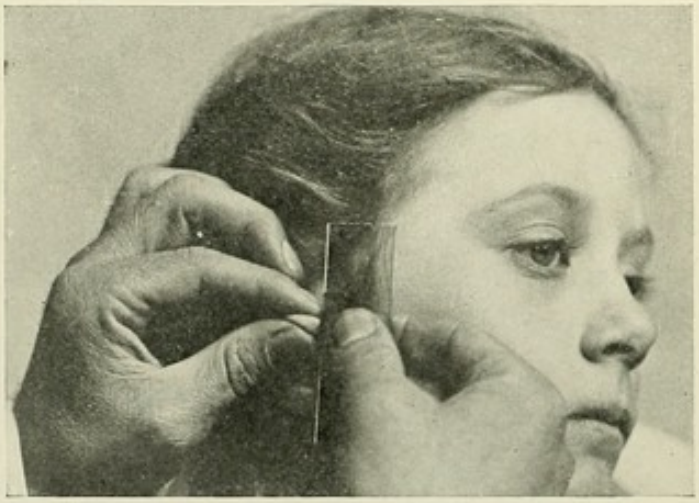


Fig. 69.—Obtaining the blood between slide and cover-glass.

thoroughly with soap and water, then with alcohol, should be rubbed thoroughly with an old, clean handkerchief and gently warmed. While the blood may be obtained elsewhere, the lobe of the ear has advantages over other locations; it is less sensitive, it being possible to obtain blood from sleeping children without awakening them; the instrument and the blood may be kept from the view of the patient, an advantage when dealing with children and nervous persons. More blood is easily obtained if desired to make a hemoglobin estimation, blood count, or Widal test. The lobe of the ear should be cleaned with soap and water, then with alcohol, and should be dried thoroughly. It is then grasped between the thumb and forefinger, the latter uppermost. The puncture is made preferably with a large straight Hagedorn needle (Fig. 67), and should be made quickly to the depth of about one-eighth inch. The first one or two drops should be wiped away and one chosen which is not too large.

The cover-glass, held by diagonal corners between the thumb and forefinger, or, better, by means of forceps applied to the summit of the blood-drop and laid face down upon the slide. Care must be taken to touch only the top of the drop and not the skin, otherwise the blood smeared upon the cover-glass will have begun to coagulate around the margin and will not spread freely. It is a common mistake to take too large a drop of blood, and if the blood extends to the edges of the cover-glass and the center of the film has a ground-glass appearance it should be discarded. If the blood does not spread freely and evenly it is better not to use pressure, but the cover-glass may be gently pushed by the needle applied to its edge. Several preparations should be made to insure a good one, and each time the ear should be wiped free of blood and a fresh drop taken. A rim of vaseline around the edges of the cover-glass will preserve the specimen longer.

As simple as this seems it requires considerable practice to obtain films in which the red cells lie side by side and not in rouleaux.

Hayem's method gives better results in the hands of the amateur. A square cover-glass is placed upon a slide in such

a manner that one edge of the cover-glass coincides exactly with the edge of the slide near its middle. Held rather firmly in this position by the thumb and forefinger, the coapted edges are applied to the blood-drop when the blood spreads evenly between the slide and cover-glass (Fig. 69). When the blood has almost reached the opposite edge of the cover-glass enough blood has been obtained. Two cover-glasses may be used instead of a slide and cover-glass, and when ready to be examined one of the cover-glasses cemented at the corner or edge to a slide by means of Canada balsam.

The advantages of dried films over fresh preparations of blood are several. Cleanliness of the part from which the blood is taken and the size of the drop are not so important. This advantage is appreciated by the practitioner who often has to make the preparation in the remote corner of an ill-lighted cabin. The slides may be laid aside and examined at leisure, weeks or even months later. The differential leukocyte count can be made on the same slide.

It is not necessary that the region from which the blood is taken should be perfectly clean, but if perspiration is present this should be wiped off. The ear is held and the puncture made as described for wet films. The slide, held in the right hand, is rested against the thumb and forefinger holding the lobe of the ear, and gradually lowered until it receives the drop of blood near one end.

The smear may be made by either one of three useful methods. The simplest is to hold the slide in the left hand and with the right lay the shaft of the needle across the drop of blood (Fig. 70). After waiting a few moments for the blood to spread out between the needle and the slide, the needle is evenly and gradually drawn to the opposite end of the slide. Drying the film by rapidly waving it in the air preserves the form of the red cells.

Instead of the needle the end of another slide may be applied to the drop of blood (Fig. 71) so that the two slides meet at an angle of about 45 degrees; after waiting for the blood to spread along the edge of the slide, the upper slide is then

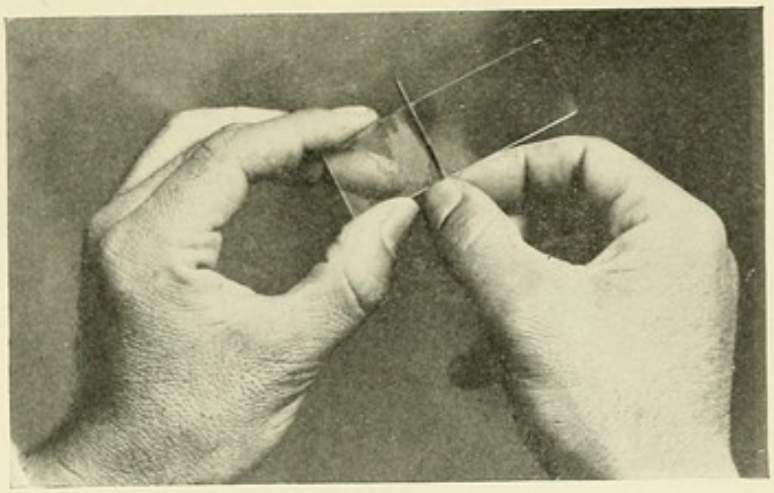


Fig. 70.—Making the spread.

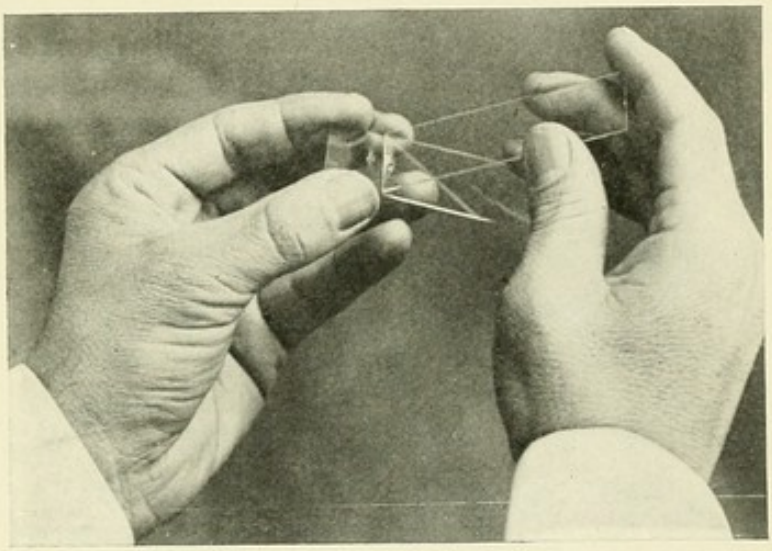


Fig. 71.—Using another slide to spread the blood.

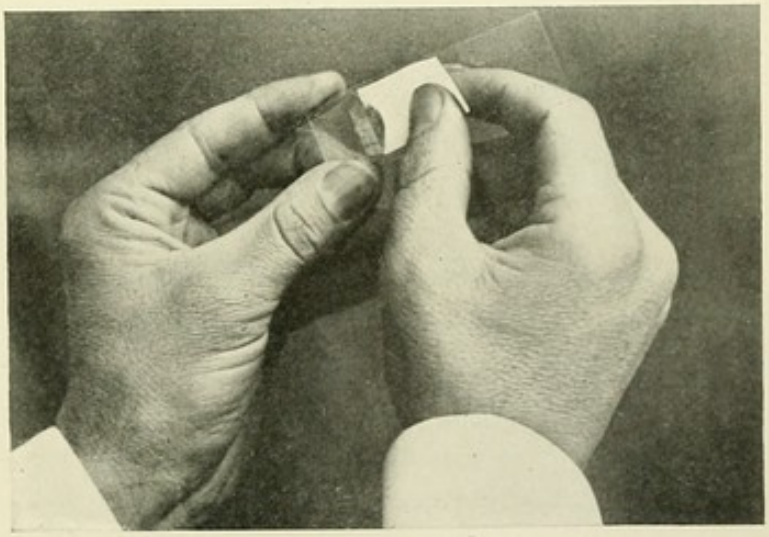


Fig. 72.—The cigarette-paper method.

drawn to the opposite end of the lower, and the film dried by waving.

Cigarette paper may be used as follows: Strips about three-fourths of an inch wide are cut perpendicularly to the ribs of the paper; the end of one of these strips, the original machine-cut edge, is applied to the blood-drop near the end of the slide, and after a few moments drawn to the opposite end of the slide. Other paper may be employed if cigarette paper is not available, but does not answer so well (Fig. 72).

If flies gain access to unstained films they will rapidly devour the blood.

Many staining methods have been proposed to demonstrate the malarial parasite in the blood. A common mistake for the student to make is to attribute bad results to the stain, and to discard a method before he has become familiar with it. In no branch of pathology is attention to minute details of technic of greater influence upon results, and a method should be thoroughly mastered before passing judgment upon it.

Malarial parasites take basic stains, of which methylene-blue is most frequently employed.

The parent of our modern stains for the malarial parasite is that of *Romanowsky*. The films are made upon cover-glasses by obtaining a drop of blood upon the center of one cover-glass and laying another diagonally across it. As soon as the blood has spread the cover-glasses are drawn apart in the same plane, not lifted. When dry the films are fixed by immersion in absolute alcohol for ten minutes, or in equal parts of absolute alcohol and ether for thirty minutes, or by heating in an oven to 150° C., when they are removed and allowed to cool.

The Romanowsky method necessitates two solutions, a saturated watery solution of methylene-blue, and a 1 per cent. watery solution of eosin. Old solutions of methylene-blue give better results than recent. The staining solution is mixed immediately before use as follows:

Methylene-blue solution, 2 parts;
Eosin solution, 4 to 5 parts.

A precipitate will form, which should not be filtered out,

though the methylene-blue solution may be filtered before mixing with the eosin if desired. The mixture is poured into a watch-glass and the films floated blood side down upon its surface for two or three hours. They are then washed in water, dried, and mounted.

Ewing[130] describes Nocht's modification of Romanowsky's method as follows:

1. To 1 ounce of polychrome methylene-blue (Grubler) add 5 drops of 3 per cent. solution of acetic acid (U. S. P. 33 per cent.).

2. Make a saturated (1 per cent.) water solution of methylene-blue, preferably Ehrlich's rect. (Grubler), or Koch's, dissolving the dye by gentle heat. This solution improves with age, and should be at least one week old.

3. Make a 1 per cent. solution in water of (Grubler's) aqueous eosin.

The mixture is prepared as follows:

To 10 cc. of water add 4 drops of the eosin solution, 6 drops of neutralized polychrome blue, and 2 drops of 1 per cent. methylene-blue, mixing well. The specimens fixed in alcohol or by heat are immersed for two hours, specimen side down, and will not overstain in twenty-four hours. The density of the blue stain may be varied to suit individual preferences. The above proportions need not be rigidly followed, but the polychrome solution should be accurately neutralized.

Leishman's solution combines the fixing and staining properties into one solution, the whole process requiring only a few minutes. Its manufacture is, however, rather tedious. Two solutions are necessary. The first consists of Grubler's methylene-blue, 1 part; sodium carbonate, 0.5 part; distilled water, 100 parts. This solution is rendered polychrome by heating to 65° C. for twelve hours, then exposing to room temperature for a week or ten days. The other is a 1 : 1000 watery solution of Grubler's eosin. Equal parts of these solutions are mixed and allowed to stand for six to twelve hours, stirring occasionally. The mixture is then filtered and the filtrate thoroughly washed with distilled water and dried. The dried filtrate is the stain, and 0.15 gram is dissolved in 100 cc.

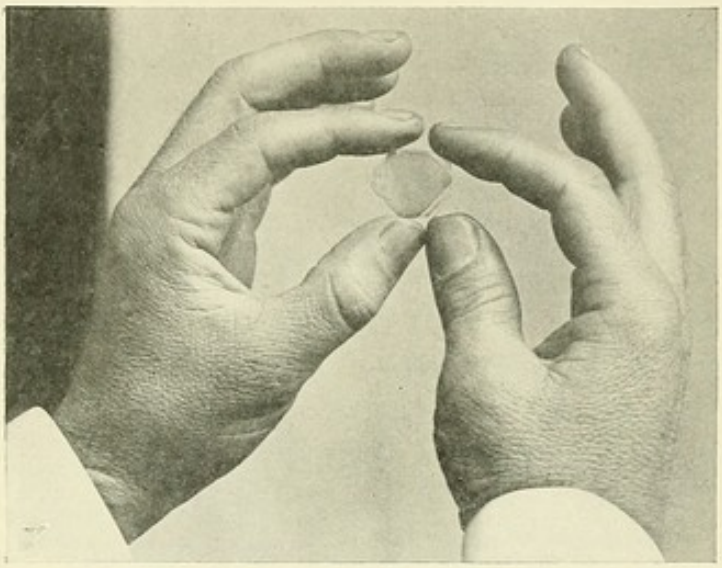


Fig. 73.—Making films upon cover-glasses.

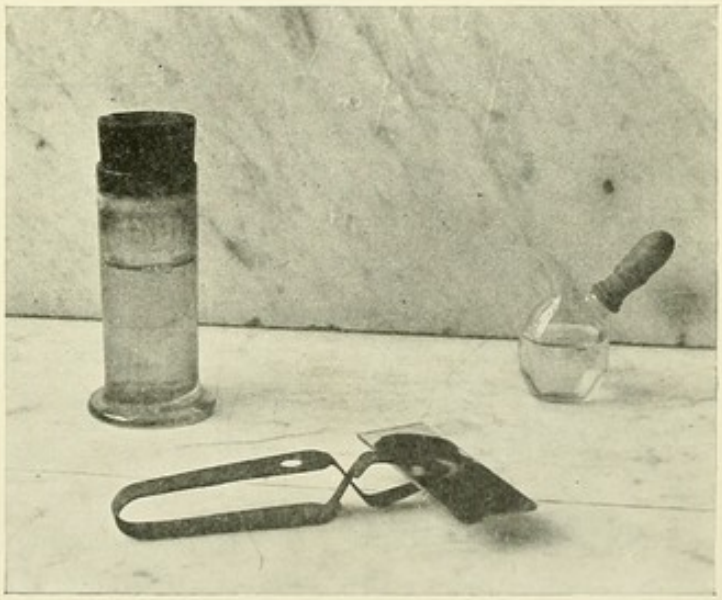


Fig. 74.—If the forceps are applied to the center of the slide the stain will not run off.

pure methyl alcohol and kept tightly stoppered. For staining a few drops are placed upon the dried, unfixed blood film and allowed to stand one-half to one minute, when about twice the quantity of water is added, or until the precipitated stain is seen floating upon the surface. After five minutes the slide is washed in water for about a minute and dried between filter paper.

The most easily prepared of the combined fixing and staining solutions, and giving results as satisfactory as any, Wright's, is described by the originator as follows:[341]

"This staining fluid is an improvement on one devised by W. B. Leishman because it requires only a few hours and an ordinary steam sterilizer for its preparation, while Leishman's required at least eleven days and the employment of a thermostat regulated at 65° C. Leishman deserves great credit for originating a method of staining blood films and malarial parasites which combines the important 'Romanowsky' staining with the great advantages of the methyl-alcohol method of Jenner. Wright's stain is applied in the same manner and gives the same results.

"It is preferred to Ehrlich's stain because it does not require the difficult and uncertain fixation of the blood film by heat and because it gives constantly satisfactory results even in the hands of inexperienced workers.

"This stain makes visible in the blood smear not only all that the Ehrlich stain does, but more, for it gives the differential Romanowsky staining to mast-cells, blood-plates, certain degenerate products in the red corpuscles, and to malarial and other protozoan parasites, thus accomplishing at one and the same time all that which usually requires the employment of several special staining methods separately applied.

"It is prepared as follows:

"Dissolve 0.5 gm. of sodium bicarbonate in 100 cc. of distilled water, add 1 gm. of methylene-blue (Grubler). Any of the methylene-blues of Grubler, known as 'BX,' 'Koch's,' or 'Ehrlich's rectified,' may be used. It seems to be important that the bicarbonate of soda be all dissolved before adding the methylene-blue.

"The mixture is next to be steamed in an ordinary steam sterilizer at 100° C. for one hour, counting the time after 'steam is up.' The heating should not be done in a pressure sterilizer, or in a water-bath, or in any other way than as stated. This steaming of the alkaline solution of methylene-blue effects certain changes in the methylene-blue whereby a polychromatic property is given to it, so that the compound with eosin, which is later to be formed with it, has the property not only of differentially staining the chromatin of the malarial parasite, but also of differentiating and bringing out more sharply the nuclei and granules of the white blood corpuscles.

"When the steaming is completed the mixture is removed from the sterilizer and allowed to cool, the flask being placed in cold water if desired. When it is cold, without filtering, pour it into a large dish or flask and add to it, stirring or shaking meanwhile, a sufficient quantity of a 1 : 1000 solution of eosin (Grubler, yellowish, soluble in water) until the mixture, losing its blue color, becomes purple in color and a scum with yellowish metallic lustre forms on the surface, while on close inspection a finely granular black precipitate appears in suspension. This will require about 500 cc. of the eosin solution for 100 cc. of the alkaline methylene-blue solution. These are quantities which are convenient and suitable to employ.

"The precipitate is collected on a filter and, without washing, is allowed to dry thereon. When thoroughly dry dissolve this precipitate in *pure* methyl-alcohol in the proportion of 0.5 gm. to 100 cc. of alcohol. This alcoholic solution is the staining fluid. It is not necessary to filter it. It will keep indefinitely, as will also the dry precipitate. Precautions should be taken to keep the alcohol from evaporating, for thus the solution may become too saturated and precipitates may form on the blood film in the process of staining. If the staining fluid deposits such precipitates it should be filtered and a small quantity of methyl-alcohol added to it.

"The films of blood, which should be spread thinly, are allowed to dry in the air. When dry, as much of the staining fluid is poured upon the film as the cover-glass will readily

hold without draining off. Allow the staining fluid to remain in contact with the film for one minute. This chiefly serves the purpose of fixing the blood corpuscles. The cover-glass is most conveniently manipulated by means of cover-glass forceps.

"Next add to the staining fluid on the cover-glass distilled water, drop by drop, until a delicate scum with iridescent metallic lustre forms on the surface. The amount of water required will vary with the amount of staining fluid on the preparation, but, in a general way, it may be said that six or eight drops will be required if a seven-eighth-inch square cover-glass is used. The amount of water added must not be sufficient to make the fluid transparent.

"The staining fluid, thus diluted, is allowed to remain on the preparation for two or three minutes, during which time the real staining of the preparation takes place, and is then washed in water.

"The blood film will now be seen to have a blue or purple color, and if examined with the microscope the red blood corpuscles will be seen to be stained blue.

"The next step is to develop the differential staining of the various elements in the preparation. This is done by washing the preparation in water—preferably distilled water—until the better spread portions of the film appear yellowish or reddish in color. Some tap waters may spoil the staining. If desired, the process of differentiation may be readily observed by placing the cover-glass film side uppermost on a slide, covering it with water, and examining it with the microscope under a low magnifying power. The red blood corpuscles, which, as before stated, at first have a blue color, will become greenish, then yellowish, and finally orange or pinkish in color, depending upon the depth of the original staining, which varies with the length of time that the diluted staining fluid has been allowed to act and with the degree of its dilution.

"The differentiation by washing in water seems to be essentially a process of decolorization by which some of the blue constituent of the dye is removed, for the water that drains off from the preparation has a blue color. This differentiation or

decolorization proceeds slowly, and may require one or more minutes, depending upon the intensity of the staining and upon the tint sought to be obtained in the red corpuscles.

"It is apparent from the above that with a little experience with the method the color of the red corpuscles may be made either orange or pink, as the operator desires. When the desired color is obtained in the red corpuscles the preparation is then quickly dried between layers of filter paper and mounted in balsam. It is important to stop the decolorization by drying the preparation as soon as the desired tint in the red corpuscles is obtained, for it may be carried too far.

"Dried stains on the upper surface of the cover-glass may be easily removed with ordinary alcohol.

"In the light of the foregoing explanations the following summary of the method of staining blood films will be intelligible:

"1. Make films of the blood, spread thinly, and allow them to dry in the air.

"2. Cover the preparation with the staining fluid for one minute.

"3. Add to the staining fluid on the preparation sufficient water, drop by drop, until a delicate iridescent, metallic scum forms on the surface. Allow this mixture to remain on the preparation for two or three minutes.

"4. Wash in water, preferably in distilled water, until the film has a pinkish tint in its thinner or better-spread portions and the red corpuscles acquire a yellow or pink color.

"5. Dry between filter paper and mount in balsam.

"The preparations retain their colors as long as any preparation stained with aniline dyes.

"Unstained blood films may be kept for some weeks without impairment of their staining properties. Films months old will probably not give good results.

"The red cells are orange or pink in color. Polychromatophilia and punctate basophilia or granular degeneration are well brought out. The nucleated red cells have deep-blue nuclei and the cytoplasm is usually of a bluish tint.

"The lymphocytes have dark purplish-blue nuclei and rob-

in's-egg-blue cytoplasm, in which a few dark blue or purplish granules are sometimes present.

"The polynuclear neutrophilic leukocytes have a dark blue or dark lilac-colored nucleus, and the granules are usually of a reddish-lilac color.

"The eosinophilic leukocytes have blue or dark lilac-colored nuclei. The granules have the color of eosin, while the cytoplasm in which they are imbedded has a blue color.

"The large mononuclear leukocytes appear in at least two forms. Each form has a blue or dark lilac-colored nucleus. The cytoplasm of one form is pale blue, and of the other form is blue with dark lilac or deep purple-colored granules, which are usually not so numerous as are the granules in the polynuclear neutrophilic leukocytes.

"The mast-cells appear as cells of about the size of polynuclear leukocytes, with purplish or dark blue-stained, irregular-shaped nuclei, and with cytoplasm, sometimes bluish, in which numerous coarse spheric granules of variable size are imbedded. These granules are of a dark purple color and may appear almost black.

"The myelocytes have dark blue or dark lilac-colored nuclei and blue cytoplasm, in which numerous dark lilac or reddish lilac-colored granules are imbedded. In leukemia more color differences are brought out among the leukocytes than by the ordinary methods of staining.

"The blood-plates are well stained. In the best preparations they appear as round or oval, very pale blue bodies with smooth contour, containing many small dark lilac or blue-stained granules. In many instances, however, only the deeply stained granules in their substances are visible. They are usually of a diameter of one-third to one-half of that of a red blood corpuscle. Frequently they occur in groups or masses, and at first sight may be regarded as precipitates."

The powdered stain keeps well, but the solution after a time tends to lose its blue-staining property, hence small quantities only of the solution should be prepared. If too intensely blue at first some old stain may be added until the desired tint is obtained. Films prepared upon slides are more easily dealt

with than those upon cover-glasses. The cedar oil is dropped directly upon the stained film.

The examination should be protracted for thirty minutes before being pronounced negative. While parasites, if present, are usually found within five or ten minutes, it is not uncommon to detect the first organisms after a search of twenty to thirty minutes.

Cedar oil may be removed from the film by wiping gently with a soft cloth moistened with xylol.

The "thick film process" is occasionally useful where the parasites are very scanty. The blood is smeared upon the slide in a much thicker layer than for other methods. After drying, a little distilled water is added and allowed to remain fifteen minutes, which causes the dissolution of the hemoglobin. After drying again the film is stained by one of the usual methods. While the outlines of the red cells are still visible, the cells are transparent and parasites may be detected, though lying under several cells. The advantage of this method is that a much larger volume of blood may be examined in a shorter space of time than is the case with the thin film.

Flagella are much more easily demonstrated in the gametes of the estivo-autumnal than of the tertian and quartan parasites. The crescent becomes oval and then spheric before exflagellation is observed. To encourage this process the method of Stephens and Christophers[118] is most practical. A number of rather thick drops of blood are placed upon a series of slides. The slides are then inverted, with the hanging drops over holes cut in blotting paper, moistened with water, and spread on a pane of glass. A series of moist chambers is thus made. A slide is removed at intervals of five minutes, the blood spread in the usual manner and stained. Exflagellation is also observed in preparations of fresh blood. The warm stage, breathing upon the specimen, and the addition of a little water are recommended to hasten the process.

Sources of Error.—In the examination of blood for malarial parasites there are several objects which may mislead. Pitfalls are probably more common in fresh blood than in stained films.

Vacuoles and retractions of hemoglobin in red cells of fresh preparations are delusive and not infrequently mistaken for the young hyaline forms of the parasite. They are most common in the center of the cell, while parasites are found in any portion. Vacuoles are highly refractive, having well-defined, clear-cut edges; the margins of the parasites are dim and fade gradually into the substance of the red cells. The vacuoles may show slight changes of form, but do not possess true ameboid motion nor pigment. While the vacuoles are perfectly clear, the parasites show a slight opalescence. In stained specimens areas which do not take the stain may deceive. These areas may be of circular form in the center of the cell, or of ring form surrounding the center, or may be oval, horseshoe shaped, crucial or irregular. When present they are apt to be abundant in some portions of the film and entirely absent elsewhere.

Crenations of red cells may present a hyaline appearance somewhat resembling an ameboid parasite. Their nature may be determined by changing the focus.

Bent or buckled corpuscles occasionally resemble crescents. The absence of pigment and the size of corpuscle should, however, enable a distinction. Overlapping of the corpuscles may produce a ring or crescent appearance which deceives the beginner.

The object in stained spreads which proves most deceiving to the inexperienced is probably the blood platelet. These corpuscles may lie upon or within the red cells, in the center, near the periphery, or only partially enclosed by them. They are from one-seventh to one-half the size of a red blood-cell, and are round, oval, or elongated in shape. They are often of mulberrry shape and reticular structure, and, with the Romanowsky class of stains, approach more nearly purple or lilac than the characteristic blue of the parasites. The margin is surrounded by a pale or unstained area resembling a halo. There is, of course, an absence of pigment and chromatin. Occurring in groups, as it frequently does, it has not rarely been mistaken for a sporulating body, and isolated for a free

spore. Bodies resembling free spores should, however, be disregarded for diagnostic purposes.

The nuclei of nucleated red corpuscles may be mistaken for parasites, but this should rarely occur if the morphology and staining reactions of both bodies is borne in mind.

Cabot[342] and others have found in the blood of patients afflicted with pernicious anemia, leukemia, and lead poisoning ring-shaped bodies occurring within the red cells and not unlike malarial parasites. Their origin or significance is not known, but they are thought to represent nuclear remains.

Pigmented leukocytes have been mistaken for parasites, but the ameboid motion of the former in fresh specimens and the staining reactions in dried films should prevent confusion.

Hemokonia, or blood-dust, may be confused with free spores. They are small, highly refractive, micrococcus-like bodies averaging one-half micron in diameter and possessed of very animated motion. As stated, free spores should not be sought for diagnosis, and bodies resembling them should be ignored.

Extraneous dirt, leukocyte granulations, and stain precipitates must be carefully distinguished from pigment.

The amateur in examinations of malarial blood is apt to become decidedly discouraged, even when he has satisfactorily mastered the technic in the laboratory. Most students gain the impression that all that is necessary to find the parasites is to locate a malarial subject with any form of the disease and obtain the necessary blood at any stage of parasitic development, to stain it properly, and to inspect it under a high-power lens. Usually this is what he has been taught by text-books and by teachers, and when he fails to detect the characteristic organisms in undoubted cases of malaria he is disgusted. The results of such teaching throw discredit upon a discovery whose practical importance is unsurpassed in modern medicine.

To estimate the value of a report on the result of microscopic examination of the blood for malarial parasites it is always desirable to know something of the experience of the examiner. In addition to competence and proper technic there are several factors which influence the result of the examination for parasites. The most important of these are: (*a*) the

previous administration of quinine; (*b*) the stage of development of the organisms; (*c*) the stage of the disease; (*d*) the type of infection; (*e*) race; (*f*) locality, and (*g*) individual circumstances.

(*a*) The previous administration of quinine, even in small quantities, renders it almost useless to examine the blood with the expectation of finding parasites. Even where the quantity of the drug is insufficient to have any effect on the symptoms, it will ordinarily cause a disappearance of the parasites from the peripheral circulation. The half-poisoned parasites which persist in some instances are frequently unrecognizable with reference to type.

(*b*) The quartan parasite is nearly evenly distributed in all its phases, from the youngest form to the sporulating body, throughout the superficial and deep circulation. Hence, when dealing with this type it makes little difference at what period the blood is examined. But with the estivo-autumnal organism it is only the early stages, the small rings, that are observed with any degree of frequency in the peripheral blood, and if the examination is made when the parasite has reached a later stage of development it will probably be missed. Instead of resembling the quartan parasite in habit of distribution it seems to imitate its more distant relative, the Leishman-Donovan parasite. Later phases of the simple tertian hematozoön are less commonly found in examinations of the peripheral blood than are those of the quartan, but are much more frequently observed than those of the estivo-autumnal. Sporulating bodies of the quartan type are not uncommon in the cutaneous blood, while those of the tertian are much less common and those of the estivo-autumnal extremely uncommon.

The frequency with which crescents are detected varies within the broadest confines. In the experience of some they are rare, while other observers note them frequently in estivo-autumnal infections. Tertian gametes are not rarely observed in the blood of the superficial circulation, while quartan gametes are scarcely found.

(*c*) In acute untreated malaria the parasite can be detected at some stage of its growth in almost 100 per cent. of cases.

If not found at the first examination, as frequently occurs, subsequent searches are usually successful. On the contrary, in chronic malaria the parasites are far from constant during the stage of latency, and prolonged search may fail to reveal them during the relapse. Parasites are often absent from the peripheral blood of malarial cachectics. In the paramalarial syndrome, hemoglobinuric fever, the parasites, if present before onset, afterward disappear in the majority of cases.

(*d*) The behavior of the different kinds of parasite in their various stages has been referred to. As a rule, the quartan parasite is most certainly found on first examination, the estivo-autumnal least so, on account of its habit of resorting to the deep circulation when approaching maturity. It is very unfortunate for rapid diagnosis that the estivo-autumnal parasites are less readily detected than those of the benign infections, but, fortunately, are usually easily found in pernicious cases of estivo-autumnal infection.

(*e*) That malarial parasites are found less frequently and in smaller numbers in the superficial circulation of negroes with malaria the writer is convinced, though the difference is slight. This opinion is confirmed in part by the observations of Külz,[247] who found malarial parasites much less frequently in his negro malarial patients than in white.

(*f*) Along the Northern borders of malarial distribution the parasites are probably more readily detected. This may be accounted for partially by the greater relative frequency of simple tertian infections. Whether the more northern negro shows the same scanty distribution of parasites in the peripheral blood as manifested by his southern brother the writer has no means of determining. It is surprising with what frequency crescents are found in higher latitudes in the blood of patients moving from highly malarial localities where crescents are not so frequently observed. Whether this is a conservative measure related to the relative rarity of anopheline mosquitoes cannot be stated positively, but it is known that the life histories of animals are, in some instances, peculiarly interdependent, especially in the case of parasite and host.

(*g*) Why it is that in certain unquestionable cases of malaria

which have received no quinine and in which every condition seems favorable to finding the parasites prolonged and repeated examination shows none is not known, but such cases are sometimes encountered.

As before said, where the specific can be withheld and repeated examinations made by a competent microscopist if not found at the first examination, the parasite may be found in almost 100 per cent. of cases of malaria. The question, which is of the utmost practical importance to the physician, arises: In what proportion of cases is the parasite to be found at a single examination? On this depends in great measure the practical value of Laveran's discovery, for in not a few cases in general practice for reasons of convenience the examination cannot be repeated, in others in which the diagnosis seems more or less clear urgent symptoms are demanding the specific. The two factors which more than the others influence the result are whether or not the patient has received quinine and the phase of parasitic development attained when the blood is withdrawn for the examination. Neither of these factors is always within the control of the physician who desires to make a diagnosis upon examination of the blood taken when the patient first comes under his observation. Since a very large proportion of the malaria of the land is treated by country doctors, the *practical* value of a diagnostic test is largely in proportion as it is applicable by them.

With reference to the number of cases in which the parasite can be found at the first examination the writer will state his experience. From a record kept of the number of malarial cases which had taken quinine in some form before coming under observation it was learned that this reached something over 50 per cent. of the total number of cases treated. The diagnosis in these cases was obviously based upon the clinical history and the therapeutic test, since the search for parasites in the blood of persons having received quinine is so discouraging that this has not been done in routine work, but only in special cases. Allowing for errors in diagnosis might reduce this number to 50 per cent. A specimen of blood was always taken from malarial patients who had not recently received

quinine when they came under observation for the first time, irrespective of the stage of the access. The blood from frank cases only has been included, no cases of atypic or latent malaria or of cachexia figuring in the result. Parasites were found in approximately two-thirds of the cases and the examination was negative in about one-third. No difference as to clinic course, severity, or the efficacy of quinine could be detected between the cases in which parasites were found and those in which none were observed. From this experience may be inferred that in localities in which half of the malarial subjects take quinine in some form before consulting a physician the parasite can be detected at a single examination of the peripheral blood taken at random with respect to the stage of parasitic growth in approximately one-third of the cases only. The prevalence of self-medication with quinine products depends largely upon local custom and upon the energy of the patent medicine industry.

The experience of the writer being somewhat at variance with the conventional text-book teaching, he feels it incumbent upon him to cite the experience of others in this matter of the most vital interest.

Craig[70] says, "Often if the blood be examined but once none at all will be found."

Fornario[343] observes that the parasites are missed with extreme frequency, and Soliani,[147] in an analysis of 612 cases under his care, says that in many cases the first examination was negative.

McElroy[344] says, "I have been struck with the frequency with which I have been unable to find parasites in cases where I am strongly impressed with the malarial nature from the clinical history."

Plehn[345] states that the parasites are frequently lacking in the malaria of natives, or at least they are not found in the peripheral blood, where the temperature curve is typic and pigmented leukocytes indicate malaria.

The experience of Ewing[27] at Camp Wikoff is interesting. "In the 605 cases of malaria the plasmodia were found in the blood in 335 cases, while in 270 cases the diagnosis was based

upon the clinical history and the discovery in the blood of evidences of malarial infection. The evidences of malarial infection in the blood consisted (1) usually in the presence of intracellular bodies so much affected by quinine that their exact type could not be positively determined; or (2) in the presence of typic pigmented leukocytes; or (3) in chronic cases of distinct clinical character in the presence of marked anemia."

Leonard Rogers,[86] than whom there is no more competent observer, says: "As long ago as 1896 I showed from an examination of 100 cases of consecutive malarial fever before the administration of quinine that in only one-third of them could the malarial parasite be found by means of a prolonged search of a single blood film."

Delaney's[346] experience is even more disheartening. He concludes: "I think that I shall be supported by most competent observers in India that this (17 per cent.) about represents the percentage of success in finding malarial parasites in the malarial fevers of India at a single examination, and on this point both text-books and writers on the subject are, I consider, very misleading."

Such quotations from practical workers and keen observers could be multiplied, but could add no further weight to the authority of those cited.

The above statements are not meant to cast the slightest doubt upon the etiologic rôle of the parasite of malaria, or its presence in every case of acute untreated malaria, or its great diagnostic value under certain circumstances, but are intended to demonstrate that the detection of the parasite is subject to several conditions. In probably no other disease, associated with a pathognomonic sign which can be elicited in almost 100 per cent. of cases, is its detection so dependent upon conditions beyond the control of the physician.

What is the value of a positive result of examination of the blood for malarial organisms? This parasite is thoroughly established as the sole cause of malaria, and its pathogenic reputation has never been marred by rumors of etiologic association with other diseases, but is the parasite, when present,

responsible for the symptoms which instigate the blood examination?

In localities where a considerable per cent. of the inhabitants carry malarial germs in their blood without showing malarial symptoms it is manifestly possible that parasites might be found in the blood of such inhabitants during the course of other ailments. And such is actually the case in certain regions with a very high endemic index, to such an extent, indeed, that the widely experienced Albert Plehn,[99] in Cameroon, declared that the presence or absence of malarial parasites in the blood of the West African coast negro is of no diganostic value.

In cases of coma in which malarial parasites are detected and which give a history of exposure to violent heat or of the abuse of alcohol, it is not infrequently difficult to determine the part played by the parasite. In cases of coma accompanied by malarial parasites in the blood and albumin and casts in the urine the diagnosis may be obscure. Fever occurring during the puerperium in subjects of former malaria will make the thoughtful physician uneasy for a short while at least, even if parasites are found on blood examination.

These are mainly problems, however, which are involved in other fields of diagnosis and serve to impress the fact that complications must be excluded or, if found, weighed. While these contingencies should not be lost sight of, in the immense majority of cases in this country *active* forms of the malarial parasite detected in the blood are responsible for the symptoms which bring the patient under the care of the physician or which prompt the physician to make the examination.

It will be noted that the word *active* is emphasized. What, then, is the value to be attached to the discovery of gametes alone?

Formerly it was believed that the sole function of these peculiar bodies was the perpetuation of the species through the mosquito cycle. Under this limited view the detection of gametes alone was on a diagnostic par with anemia and splenomegaly, sequelæ of malaria, and not necessarily proof of existing malaria, even latent. Since it has become known, however, that under certain not well understood conditions the macro-

gametes can immediately, by the process of parthenogenesis, give rise to pyrogenic parasites without undergoing the mosquito cycle, our views must be modified, and these forms must be regarded clinically as the parasites of latent malaria. Relative to active malaria, they may be looked upon as evidences of past and potential, but not necessarily of present, active malaria.

In regard to the number of parasites in a given film of blood the following classification applies to estivo-autumnal infections:

Abundant when there is an average of two or more parasites to each field of the microscope; they are detected immediately.

Moderately numerous when present in only one of several fields; found after a few minutes' search.

Scanty when only a few parasites are detected in the entire film, as commonly prepared, aften ten to thirty minutes' search.

While there are many cases of estivo-autumnal infection in which the parasites are scanty, large numbers of estivo-autumnal parasites are occasionally observed in the peripheral blood, especially of pernicious cases. As many as 75 per cent. of the red cells have been found infested in several cases reported, and Rogers[44] mentions a rapidly fatal case in which the blood showed more parasites than erythrocytes.

What is the diagnostic value of a negative result?

The writer can by no means agree with those who maintain that such a result positively excludes a diagnosis of malaria. The failure to find parasites in the blood of a single film taken without reference to the period of the paroxysm, while of some value, is not conclusive, and if the patient has recently received quinine is absolutely worthless. On the other hand, if the blood of a patient who has not recently taken quinine be examined repeatedly by a competent person with the result that no parasites are found, it is very strong evidence against malaria. The diagnostic value, then, of a negative finding depends upon the presence or absence of the conditions which have been enumerated, the chief of which is the administration of quinine.

When the examination of the peripheral blood is negative puncture of the spleen has been advised, as the parasites in all

stages are easily detected in the blood of this organ. This procedure, however, is attended with some degree of danger, especially of hemorrhage, and should be resorted to only in cases where an immediate diagnosis is imperative. It has been estimated that the mortality of aspiration of the spleen is 1½ per cent.[158] Many fatalities have resulted in India recently from this method of obtaining blood for the study of the Leishmann-Donovan parasites.[44] When decided upon the following precautions should be observed: An aspirating syringe or even an ordinary hypodermic syringe may be employed. A flexible connection between needle and nipple, such as comes with the regular antitoxin syringe, is valuable to prevent laceration of the capsule of the spleen in the event of sudden respiratory movements. Both the syringe and the site of injection should be rendered sterile. Cutaneous sensation may be deadened with cocaine or with ethyl chloride. The patient should be instructed to hold the breath on deep inspiration, and the spleen should be steadied against the ribs and diaphragm. The needle should be inserted deeply and when the syringe is half filled should be partially withdrawn, then filled, to obtain the blood from two points. The operation should be performed quickly, that the patient may not have to breathe during the process, as the danger of laceration is thereby increased. Afterward the cutaneous puncture should be sealed with collodion, the patient kept at rest in the recumbent position for twenty-four hours, and cold applications placed over the region of the spleen. A dose of calcium chloride administered half an hour before the procedure might lessen the tendency to hemorrhage.

Upon failure to discover parasites in the blood there are two other blood signs which must be considered. These are the presence of pigment and a relative increase in the large mononuclear leukocytes. These signs are termed subsidiary evidences of malaria, because, being secondary in diagnostic importance to the parasites, they are generally called upon only in the absence of the latter.

Melanin is pathognomonic of malaria, and its presence is not contingent upon the stage of development of the parasites or upon the previous administration of quinine. Theoretically,

therefore, it should be of the greatest significance in the diagnosis of malaria. There are, however, certain circumstances which detract from its practical value. Free pigment, or that lying upon the red blood-cells, should be ignored in the diagnosis, as it cannot be distinguished from adventitious detritus. Within the large mononuclear leukocytes, the leukocytes in which it is most frequently found, it must be carefully distinguished from the minute pigment-like granulations which may occur normally in these cells to the number of one, two, or three to each cell. This requires a considerable degree of experience and deceived a no less accurate observer than Vincent.[347] Coarse granules of pigment are much more readily recognized, especially in fresh blood. In stained films precipitates may prove very confusing. Pigment may persist for two or three days after the last paroxysm in tertian and quartan infections, and for a much longer period in estivo-autumnal. It is more valuable as a diagnostic sign of chronic malaria than of acute.

The second subsidiary sign of malaria, a relative increase of the large mononuclear leukocytes, is under some conditions a valuable aid to a diagnosis. The proportion of large mononuclear elements in the differential count is modified by certain factors which detract somewhat from its value.

In early childhood there is normally an increase of mononuclear leukocytes, hence this sign need not be sought for in the malaria of young children.

As with other diagnostic evidences of malaria, this sign is unfortunately more constant and more marked in tertian and quartan infections than in estivo-autumnal.

The increase of the large mononuclear leukocytes in malaria is generally in inverse proportion to the height of the temperature, being most decided in the interval and may be absent during pyrexia. An increase may be wanting also early in first attacks.

In making the differential count the leukocytes lying in the middle third of the film should be counted and the slide moved from side to side and not from end to end. If the colorless cells are calculated at random or only near the ends of the

smear it will make quite a difference, particularly in the relation of the small lymphocytes to the large mononuclears, and this relation is significant. It is an interesting experiment to make and compare differential leukocyte counts at both the beginning and the end of the spread. For accuracy at least 500 cells should be counted, though 250 give a fairly correct estimate.

Perhaps the chief difficulty in the procedure is the almost arbitrary distinction between the small mononuclear and the large mononuclear leukocytes. An investigation of the literature upon the subject convinces that the definitions of the large mononuclear leukocyte are essentially different. Furthermore, since the chief difference, size, is one of degree only, it is obvious that there is much room for error in the application of any one of these definitions and that it requires a good deal of experience to become skilful in the employment of this diagnostic measure.

When there is evidence of leukocytosis the differential count alone must not be relied upon, since an absolute increase may exist under these circumstances when the differential count will show only a small per cent. Here the absolute count must be made also.

In differentiating malaria from typhoid fever the differential count is of value only in the first two weeks of a fever, since after that time the relative proportions of the leukocytes are similar in the two diseases.

Notwithstanding its difficulties, the differential leukocyte count made by an experienced examiner may render important aid in the diagnosis of malaria where the parasite cannot be detected, and a mononuclear leukocytosis reaching 15 per cent. must be regarded as strong evidence of malaria.

Besides the presence of pigment and a large mononuclear increase there is another point ascertained by microscopic examination of the blood, this is the presence or absence of leukocytosis. Between malaria and typhoid fever this point has no differential value, and it will be remembered that a leukocytosis is frequent in pernicious malaria. It is, however, in septic conditions which sometimes so closely resemble mala-

ria in which a marked leukocytosis may serve to exclude malaria.

3. **The Therapeutic Test.**—The diagnostic value of the **therapeutic test** has been known since the days of Torti, though neither its value nor its limitations are yet widely realized. On the one hand, there are theoretic and ultrascientific writers, apparently valuing a microscopic diagnosis more highly than human life, who advocate withholding the specific indefinitely until the parasite may be found. On the other hand, there are physicians who continue the administration of quinine in heroic doses for days, or even weeks, in fevers which do not show the slightest susceptibility.

Here diagnosis and treatment meet very closely, the former encroaching somewhat upon the field of the latter, the diagnostic test often becoming a therapeutic and life-saving measure. The therapeutic test is of especial value in cases which have already had insufficient quinine, thereby causing only the disappearance of the parasites from the superficial circulation and distortion of the fever curve. In these cases it has at least as much standing in clinical medicine as antisyphilitics in obscure cases thought to be syphilis or antitoxin in cases of suspicious angina in which a bacteriologic examination is impossible. When properly applied it can hardly be productive of harm.

A fever which resists quinine is not a malarial fever. In order to test the resistance of a fever to quinine the drug must be continued for a sufficient length of time and in proper doses at suitable intervals, and, what is most important, it must be absorbed.

The maximum period of resistance of malaria to quinine is ordinarily stated as four days. As far as the writer's observations go, they tend to show that in many cases the fever is broken by the end of thirty-six hours, in at least half the cases in forty-eight hours, and in three-fourths the cases in sixty hours. It is highly probable that in cases of malaria persisting longer than four days the specific is not being absorbed. A case is recalled in which the fever continued notwithstanding the administration in capsules of 24 grains of a soluble salt of quinine during the twenty-four hours for nearly six days.

Parasites having been found before the quinine was begun, the drug was then given in solution, when the fever responded during the seventh day. There had been no evidences of cinchonism until the solution was employed. Cinchonism, however, is not a guide in the employment of the therapeutic test; the specific is directed toward the parasites and not toward the patient, and patients manifest various degrees of sensitiveness toward quinine.

Owing to the conditions under which the therapeutic test is usually employed it is better to use moderate doses at regular intervals during both day and night. Three or 4 grains every three hours are sufficient. Pills and tablets of quinine should never be relied upon; the result may be not only misleading but dangerous. Capsules, if fresh, are usually satisfactory; a few pin punctures in each end aids solution. Where the fever persists and there is reason to believe that the medicine is not being absorbed it should be given in solution or even intramuscularly.

In connection with the therapeutic test the law of Treille[304] is interesting. It may be stated as follows:

In malarial fever quinine given in a single proper dose at the beginning of a paroxysm does not influence that paroxysm, but always suppresses the following for a minimum period of five days. Designating the day upon which quinine is administered as 1, the minimum duration of apyrexia as 5, and the day of recurrence as 1, the formula may be graphically represented as 1-5-1. In the case of quotidian and quartan fevers the duration of apyrexia is often a multiple of 5. The formula is, then, 1-m5-1. Treille regards as a proper dose: for quartan fever, 25 centigrams; for quotidian, 2.5 grams, and for tertian, 2 grams.

The writer cannot vouch for the details of these propositions, but the general principle has ample support. In thorough accord are the recently recorded and accurate observations of Cohen,[305] who ascertained that a single subcutaneous injection of 15 grains of quinine and urea, given preferably during the paroxysm or shortly after, produced an apyretic period of approximately six and a half days or approximately thirteen days.

This period of apyrexia following a single dose of quinine corresponds closely to the parthenogenetic cycle. The conquest of the schizonts seems to be a signal for the macrogametes to lay aside the conventionality of slow sexual reproduction and to conscript recruits rapidly by parthenogenesis.

Not every fever which discontinues after the administration of quinine can be considered malarial, since such an occurrence is occasionally coincidental. Furthermore, it is well known that quinine has no little antipyretic influence upon certain conditions, particularly septic.

It is probably superfluous to say that the diagnosis of malaria does not always consist alone in the mere mechanic application of a single test, but that in some cases the keenest clinic judgment is required. Of the several diagnostic signs which we possess each is valuable and each has its limitations.

It should be a routine practice to take a specimen of blood from each fever patient.

In dealing with a disease in which the blood examination affords pathognomonic evidence and for which we possess a specific the dilemma is often faced, where the examination of the first specimen of blood is negative, of having to decide whether it is best to wait a few hours for an absolutely certain diagnosis or to take advantage of every hour and begin the treatment immediately. If quinine has already been taken the chances are that further examinations would also be negative, and the better course would be to proceed with the specific. If quinine has not already been taken and the symptoms are not urgent the case may be treated symptomatically for a little while, during which time the blood is examined at appropriate intervals.

In hospital practice the practical value of the blood examination for malarial parasites is inestimable; in general practice, especially in the rural districts, its value is more limited. In general practice, especially in the country, the therapeutic test is of great value; in hospital practice it is less often justifiable.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis between the malarial infections can best be made with the microscope. In only one type of infection, the quartan, either single or double, can the differential diagnosis be made clinically with certainty.

The differentiation of chronic malaria from cachexia is sometimes very difficult, the relation being one of disease entity and sequel, and the difference sometimes one of degree only.

The diagnosis of latent malaria must be based solely upon the detection of parasites in the blood. Basophile granulation of the red cells and urobilinuria cannot be relied upon as evidences of latent malaria.

Abscess of the Liver.—Septic conditions are very often diagnosed as malaria; this is especially true of hepatic abscess. There are two classes of cases of abscess of the liver that may be difficult at first examination to distinguish from malaria; first, where the local symptoms are absent or not well defined; second, where there is enlargement of both liver and spleen and a history of both dysentery and malaria. The fact that these patients have usually been drenched unsystematically with quinine may complicate the diagnosis. In typic cases of hepatic abscess there is usually a history of dysentery, and amebæ may be present in the feces. There is usually a dragging pain in the liver, sometimes referred to the right shoulder, increase of liver dulness, and tenderness on pressure. The spleen is not necessarily enlarged. The temperature does not often rise high, and there is apt to be profuse perspiration, especially during sleep. On microscopic examination of the blood there is usually a leukocytosis to be found, though this is wanting in a few cases, and its absence should not be taken to exclude abscess. There are neither parasites, pigment, nor a relative increase of the large mononuclear leukocytes. Exploratory aspiration is valuable in some cases. Jaundice is a very variable symptom and may be misleading.

Infective endocarditis may present periodic paroxysms of chill, fever, and sweat. The physical examination of the heart and the microscopic examination of the blood should establish the diagnosis.

Puerperal Septicemia.—Women who have had malaria during pregnancy are prone to suffer relapses during the puerperium. In this condition malaria is not infrequently atypic: the first or third stages of the paroxysm are sometimes lacking and complete intermission of temperature is often wanting. The following may serve to differentiate typic cases of malaria and puerperal sepsis:

Malaria.	*Puerperal Septicemia.*
Onset from a few hours to twenty-one days after labor.	Rare after the fifth day.
Often a history of malaria.	Malarial history usually absent.
Temperature curve more or less typic.	Irregular.
Symptoms decline with temperature.	No relation between symptoms and temperature.
No local symptoms.	Local symptoms present.
Blood examination positive.	Negative.
Therapeutic test positive.	Negative.

The so-called *urethral fever* may be accompanied by paroxysms somewhat resembling those of malaria. The writer has recently seen a case in which the introduction of a steel sound every other day was accompanied for a short time by corresponding paroxysms not due to malaria. The differentiation from malaria should present no difficulties.

Perinephritic abscess, pyelitis, cholecystitis, and other *septic processes* may be associated with fever which bears a more or less close resemblance to that of malaria. Local symptoms, the blood examination, and the therapeutic test rarely leave the diagnosis in doubt but a short while.

Typhoid Fever.—Since Laveran's discovery and since the knowledge of the prompt efficacy of quinine in malaria and the value of the Widal reaction have become thoroughly established mistakes in the diagnosis of typhoid fever and malaria should be relatively infrequent. This is unfortunately not the case. Witness the lesson of the Spanish-American War: Of 20,738 cases of typhoid fever occurring in the American army, 10,428, or 50.27 per cent., were correctly diagnosed by regimental or hospital surgeons. Most of the remainder were called malaria; ten thousand mistakes in one season, and the board of investigation concludes that in recognizing about half the cases of

typhoid fever the army surgeon probably did better than the average physician throughout the country does in his private practice.

In proportion to the reliance placed upon symptomatology in the differentiation of typhoid and malarial fevers so frequently will mistakes occur. Chills, continued fever, bronchitis, enlarged spleen, slight tenderness and gurgling in the right iliac fossa, tympanites, diarrhea, the Diazo reaction, delirium, and the typhoid state may occur with either disease. Herpes is strongly indicative of malaria and rose spots of typhoid fever, but these spots are more frequently absent than present in the typhoid fever of warm countries.

A correct diagnosis must rest upon the results of the examination of the blood and the therapeutic test.

The number, either absolute or relative, of the leukocytes is not as valuable in this connection as elsewhere, and if the case is seen early the diagnosis may be made before the Widal reaction is applicable, but this latter test is eminently useful in many cases.

Proper prophylactic precautions should be observed from the start in cases of doubtful diagnosis.

Tuberculosis is sometimes similar in its course to malaria. It is especially so in the early stage when the local signs and symptoms are ill-defined or absent and the bacillus cannot be detected, and in the stage of secondary infection when septic symptoms supervene. Miliary tuberculosis has not infrequently been mistaken for malaria. For the diagnosis between tuberculosis and malaria the microscopic examination of the blood and sputum, the physical examination, and therapeutic test are usually ample.

Influenza has sometimes been confused with malaria. If the epidemic occurrence, different seasonal prevalence, catarrhal and other symptoms are insufficient upon which to make a diagnosis, the absence of characteristic blood findings are generally conclusive.

Yellow fever in some cases so closely resembles the so-called bilious remittent fever that in regions where both diseases occur the differential diagnosis by clinical history alone is impossible.

In such instances the microscope becomes an instrument of the greatest good not only to the individual, but to the community.

The frequency with which *dysentery* is associated with malaria as a complication and as a sequel renders the microscopic examination of the blood very important in these cases.

Patients with *syphilis* manifesting quotidian fever not infrequently receive quinine instead of antisyphilitics. The microscope, the therapeutic test, and the history should form the basis of the diagnosis.

Before the geographic distribution of the hookworm and its importance in the production of anemia became recognized uncinariasis was not distinguished from chronic malaria and cachexia. The detection of the ova in the feces and the presence of eosinophilia and the absence of parasites and the subsidiary evidences of malaria in the blood render such a mistake at the present time inexcusable.

Leukemia must occasionally be taken into consideration in the differential diagnosis of malaria, in which case the microscopic examination of the blood is absolutely essential.

The differentiation of *Banti's disease* from chronic malaria and cachexia may be extremely difficult. We will not solve the mysteries of splenomegaly until we learn a safe method of obtaining blood from the spleen.

THE DIAGNOSIS OF PERNICIOUS MALARIA

It is only since Laveran's revolutionizing discovery that the diagnosis of pernicious malaria has been reduced almost to exactitude. Cases have already been recited where the parasites were scanty or even missed in the blood, but these are only rare exceptions. In the immense majority of cases examination of the peripheral blood will reveal the presence of the organisms. The value of this is inestimable and is paralleled only by the importance of making blood examinations in all cases. It may be safely said with Craig[70] that hundreds of lives have been sacrificed to pernicious malarial fever which could have been saved had an examination of the blood been made. It is not extremely uncommon in our cities for subjects

of pernicious attacks found in coma to be taken to the police station instead of the hospital and the true condition not suspected until the patients fail to "sober up" in due time, when it is usually too late for treatment to avail.

Negative examinations of the peripheral blood in desperate cases justify risking the dangers of splenic puncture.

In cases showing the presence of parasites complications must be rigidly excluded. In some cases this is attended with difficulties.

In comatose malaria, besides the evidence obtained by an examination of the blood, a history of exposure to or attacks of malaria, the general appearance and age of the patient, the absence of atheroma, the early elevation of temperature, and perhaps the enlargement of the spleen and slight jaundice should exclude cerebral hemorrhage. The differentiation of malarial coma from sunstroke is often hard; in fact, the two not infrequently co-exist, in which case it may be impossible to apportion the etiologic share of each in the clinic picture. Cardamatis[287] states that in this type of pernicious malaria coma is the dominating symptom, while in sunstroke are observed coma, convulsions, delirium, and hyperpyrexia. Uremic coma may simulate that due to malaria. Unfortunately, the urinalysis throws no light on the diagnosis, as in both conditions we may find albumin and casts. The blood examination, the temperature, and the anamnesis serve to make the diagnosis. For the differentiation of alcoholic from malarial coma the blood examination is essential. The history may be of value, but the odor of the breath may be misleading. To discriminate between malarial coma and diabetic coma the presence of the parasites, on one hand, and of glycosuria, on the other, are sufficient. In differentiating between the various comas with reference to malaria two points should be remembered: First, that comatose malaria may occur in persons with the odor of alcohol on the breath, and, secondly, that coma from causes other than malaria may attack malarial cachectics. To distinguish epilepsy, opium poisoning, tetanus, and meningitis from pernicious malaria should rarely present difficulties if the blood is examined. The following table of different features of

amblyopia due to quinine and to malaria is borrowed from Manson:[59]

Quinine Amblyopia.	*Malarial Amblyopia.*
History.—Quinine taken in large doses, not less than 30 grains.	History.—Quinine may have been taken, but not necessarily in large doses.
Onset.—Sudden, accompanied by deafness; both eyes are affected.	Onset.—Not usually sudden, but it may be so if hemorrhage has occurred in the macular region. There is no deafness, and both eyes are not necessarily affected.
Pupils.—Widely dilated, and while loss of vision continues they do not react to light.	Pupils.—React to light.
Vision.—Completely lost for a time.	Vision.—Never completely lost.
Ophthalmoscopic Appearances.—A white haze over fundus; cherry-red spot at macula; optic disk pale; retinal vessels markedly constricted.	Ophthalmoscopic Appearances.—There is optic neuritis; optic disk is of characteristic grayish-red color; retinal hemorrhages and sometimes vitreous opacities.
Termination.—Usually some permanent defect in the field of vision or in color vision. Central vision recovers first; optic disk is unusually white, and retinal vessels small.	Termination.—Some cases recover completely; in others greater or less permanent defect of vision remains.
Treatment.—Stop quinine. Amyl-nitrite has been recommended to induce dilation of retinal vessels.	Treatment.—Give quinine.

Algid attacks sometimes resemble perforation, or typhoid, or gastric ulcers, or rupture of the spleen. The microscope and the local symptoms should render the diagnosis certain. The cases resembling appendicitis and peritonitis have been mentioned; here, again, the microscopic examination of the blood may save lives. In countries in which cholera is endemic the diagnosis between this disease and the choleraic type of pernicious malaria was formerly difficult or impossible. Laveran's discovery has removed this difficulty and rendered possible a diagnosis of the utmost importance. The finding of the hematozoa differentiates the hemorrhagic, bilious, and typhoid types from typhoid and yellow fevers.

DIAGNOSIS OF HEMOGLOBINURIC FEVER

This is usually made and, as a rule, correctly before the physician arrives. The history of malaria, the fever, vomiting, jaundice, and black water are pathognomonic. Though the parasites are so frequently missed, on examination of the blood

there is usually a mononuclear leukocytosis, and pigmented leukocytes may be found.

The diagnosis from paroxysmal hemoglobinuria might prevent difficulties. In this rare condition the attacks usually follow chilling of some portion of the body, and the attack is usually of short duration and seldom fatal. In hemoglobinuric fever there is given a history of several years of residence in an endemic region, repeated attacks of malaria, with often the presence of parasites, pigmented leukocytes, and a mononuclear leukocytosis in the blood.

The conditions which have been most frequently confounded with hemoglobinuric fever are yellow fever and bilious remittent fever.

In localities where yellow fever and blackwater fever prevail their differentiation is not easy. The following are the chief points of difference:

Hemoglobinuric Fever.	*Yellow Fever.*
Endemic.	Epidemic.
One attack predisposes.	One attack confers immunity.
Occurs usually after several years of residence.	Attacks also new comers.
Malarial history always given.	May be no history of malaria.
Prodromata common.	Uncommon.
Icterus intense, early, always present.	Icterus usually slight, begins on third or fourth day; may be absent.
Conjunctiva jaundiced.	Usually congested at first.
Hemoglobinuria.	Albuminuria or hematuria.
Blood may show malarial parasites, pigmented leukocytes, and mononuclear leukocytosis.	Absent.
Bilious vomiting.	Vomit clear or black.
Hemorrhages uncommon.	Relatively common.
Spleen usually much enlarged.	Enlargement slight.
Increasing pulse.	Pulse retards with stationary or increasing temperature (Faget's sign).
Albuminuria from beginning.	Usually appears from second to fourth day.

A rather striking coincidence is the relative immunity of the negro to both diseases.

Certain cases of bilious remittent fever present points of striking similarity. This is well illustrated by the following case which was represented to me by the messenger and by the family on my arrival as one of "hematuria":

A. H., white, male, aged thirty-nine, timberman, lived in a malarial country eighteen years. Never had hemoglobinuric fever. He had been having chills at intervals all summer and fall, slight fever, "dumb chills," and slight jaundice for three weeks; no quinine for two months; badly salivated from seven large doses of calomel taken several days ago. Examination November 29, 1906, four and a half hours after first passage of "bloody water." Temperature, $99^{4}/_{5}$; pulse, 92; marked jaundice of skin and sclera; has been vomiting; liver region tender; spleen extends to anterior superior spinous process and to within 1½ inches of the umbilicus. Blood examination showed two large pigmented, intracorpuscular parasites, hemoglobin 65 per cent. Urine "port wine" color, acid 1.014; nitric acid test for albumin negative, biliary coloring matter abundant, no hemoglobin. Microscopic examination negative. Under quinine treatment the urine cleared in thirty-six hours and the fever left in a few days, going no higher than 101½. The anemia and enlarged spleen were yet present when I last saw the patient, two weeks after the attack.

The following scheme will help to differentiate hemoglobinuric fever and bilious remittent fever:

Hemoglobinuric Fever.	*Bilious Remittent Fever.*
Onset sudden.	Onset slower.
Jaundice develops rapidly and becomes intense.	Jaundice develops more slowly and is not so intense.
Parasites frequently absent.	Parasites usually present.
Albuminuria constant.	Albuminuria not constant.
Urine colored by hemoglobin or its derivatives.	Urine colored by bile.

The differential diagnosis, as attempted by some writers, from "quinine poisoning in malarial subjects" is futile and impossible, as this condition is a mode of hemoglobinuric fever.

CHAPTER VII

PROGNOSIS

Spontaneous Recovery.—It is a familiar fact that malaria, after the manner of other infectious diseases, not infrequently undergoes what is termed spontaneous cure. Physicians in malarial regions often see patients whose paroxysms, typic and with characteristic periodicity, have ceased without medication or after nothing but a purgative dose.

It is doubtful, however, whether this cessation may with propriety be termed a cure. In the majority of instances relapses follow at shorter or longer intervals. It is better, therefore, for practical purposes to consider this but a transition from active malaria to latency. The greater frequency with which gametes are found after the so-called spontaneous recovery justifies this assumption.

Spontaneous cure occurs more frequently in tertian and quartan infections. This statement applies merely to the temporary cessation of paroxysms and not to the tendency to relapse.

It is more frequently observed in the negro than in the white race, permanent cures occurring not rarely in the former race in the absence of all medication.

Sex may exert a slight influence upon the tendency to spontaneous recovery, the female, on account of less severe exposure to deleterious influences, probably manifesting a greater disposition.

The discontinuance of paroxysms may be sudden or more often gradual, the accesses becoming less severe or the interval longer, or in infections with more than one generation of parasites one may be suddenly destroyed, the others later.

Prognosis.—This is influenced to some extent by locality. It is manifest that in regions where only the tertian and quartan

infections are prevalent the mortality is less than where severe estivo-autumnal fevers are widespread. There is, furthermore, quite a difference in the mortality rate in countries where the estivo-autumnal infections are equally distributed.

Race as a factor in the mortality of malaria has already been dealt with.

A majority of deaths from malaria occur in children. There is no doubt but that many children die of malaria which has not been diagnosed in time. In the young pernicious symptoms, especially cerebral, are prone to supervene, or the attack may be followed by extreme anemia and dropsies. Malaria is likewise much more serious in advanced age than in the intermediate ages.

Occupation and social conditions play a part in prognosis. Excessive toil and exposure may render pernicious attacks otherwise benign, and timely treatment, usually resorted to by the better classes, enhances the chance of recovery.

The outlook is probably more favorable in attacks occurring without the malarial season than within.

Manifestly the condition of the patient with reference to the results of previous disease is of importance. Anemia, alcoholism, dysentery, and other conditions not fully recovered from contribute gravity to the prospect.

The type of malarial infection is of the greatest importance. In the tertian and quartan types it is only very rarely that serious symptoms result. It is not yet certainly known in which variety of estivo-autumnal infection the prognosis is most grave. While Marchiafava and Bignami[162] and Mannaberg[141] hold that the tertian estivo-autumnal infections are most often attended with danger, Craig[70] and Wright[38] maintain the opposite view.

Postponement and anticipation of the paroxysms were formerly regarded as favorable and unfavorable, respectively. However, owing to the irregularity of the estivo-autumnal fevers, these can be said strictly to be properties of tertian and quartan infections only, and are consequently of little prognostic import. Violent headache, somnolence, sighing respiration, slight mental aberration, defective articulation and vision,

cold surface, and rapid, feeble purse are some of the symptoms which forebode evil.

The prognostic value of the microscopic examination of the blood is limited. While, as a general rule, the severity of the attack is in proportion to the number of parasites, these are sometimes scanty in the peripheral circulation even in grave cases. Sporulating and advanced stages of estivo-autumnal parasites are rarely seen in the superficial blood except in extremely severe cases.

Delaney[346] regards a reduction of leukocytes to or below 1,500 as of grave prognostic value. The writer is unable to verify this from his experience, since in his cases of pernicious malaria there has existed a leukocytosis.

While in tertian and quartan infections a paroxysm may be predicted approximately from the results of blood examination, such an attempt with estivo-autumnal malaria may prove misleading. An impending paroxysm dependent on mature parasites in the visceral circulation cannot be foretold.

Intercurrent diseases complicating malaria aggravate the prognosis. This is especially the case in chronic malaria and cachexia, with which pneumonia, dysentery, and other diseases form frequently fatal associations.

The gravity of pregnancy as a complication of malaria has been considered.

In nephritis of malarial origin the prospect is, as a rule, good. If, however, the patient is repeatedly subjected to malaria or other harmful influences the prognosis is not propitious.

The prognosis of the nervous sequelæ is ordinarily favorable. The various paralyses and mental symptoms are generally transitory, but may occasionally become persistent. Bulbar symptoms are usually slow to disappear.

The course of chronic cachexia may be extended for years; acute cachexia runs a more rapid course. In mild cases a change of climate and tonic treatment do a great deal for the patient; advanced cases rarely recover. Death may occur from exhaustion, but is more commonly due to pernicious malaria and to complications, of which the most frequent are

pneumonia and nephritis. Hence the danger to the cachectic is not confined to the malarial season, but he is in danger throughout the entire year.

Mortality.—The true mortality of malaria is difficult to estimate. While statistics are not lacking, the different conditions under which they are compiled must be considered, some being from charity hospitals, some from private practice, some from military practice, from various localities, etc. It is, furthermore, undoubtedly true that a considerable proportion of malarial cases does not come to the notice of physicians. The variety of forms which malaria assumes is another obstacle. It is probable that many cases ascribed to complications, fancied or real, are due to malaria.

Bearing these points in mind, the following figures are presented, showing a mortality of 2.89 per cent.:

Author.	Locality.	Cases.	Deaths.
Laveran[1]	Turko-Russian War	140,000	1,092
Laveran[1]	Constantine	1,310	
Laveran[1]	Italian Army	4,856	13
Schellong[32]	New Guinea	1,954	22
Ross[248]	Greece	960,048	5,916
Ross[249]	Hong Kong	7,352	984
Ewing[27]	Camp Wikoff	605	39
Smart[76]	Civil War	1,373,355	15,423
Travers[58]	Malay States	3,397	348
Terburgh[64]	Dutch Indies	2,308,128	114,490
Cardamatis[65]	Athens	22,618	15
Koch[24]	Grosseto	281	
Koch[172]	East Africa	63	2
Hagen[350]	Papua	301	23
British Colonial Reports[351]	British Colonies	12,617	618
Wright[38]	British Malaya	17,468	680
Haw[352]	Baberton	449	14
Hope[40]	North Bengal	1,784	
Laveran[353]	Algiers	98,774	7,432
Gorgas[354]	Panama	1,055	5
Erni[81]	Dutch Indies	116,879	731
United States Marine Hospital[355]	General	6,618	20
Various Hospital Reports	Southern States	1,294	30
German Protectorate Reports[356]	German Protectorates	5,003	32
Malaria Society[37]	Italy	22,792	120
		5,109,001	148,055

Prognosis of Pernicious Malaria.—The prognosis of pernicious malaria is extremely grave. It depends upon the physic condition and age of the patient, the type and severity of the attack, and the promptness and efficiency of the treatment.

Anemia from previous attacks of malaria or other causes, alcoholism, or organic disease of important viscera add to the gravity of the case. The cerebral types are less serious in the young and vigorous, very fatal in the aged. As a rule, patients seen early and treated skilfully and energetically have a better chance for life, but many cases end fatally in spite of the best and most timely treatment.

The number of parasites in the peripheral circulation is not always a reliable guide as to the severity or progress of the attack. With apparent amelioration of the symptoms the physician should be circumspect in his prognosis and bear in mind the possibility of further paroxysms.

In the writer's opinion, the algid type is the most lethal, the typhoid and the dysenteric least so, though this is not exactly in accord with Colin,[291] who arranges the types according to the following descending scale of gravity: Syncopal, algid, cardialgic, delirious, comatose, icteric, choleraic. Schellong[92] regards the comatose as the most dangerous, and Le Dantec,[26] the delirious and algid.

Parry[357] states that average mortality of pernicious malaria is 1 out of every 8 cases; Wharton[358] estimates it as 1 of every 12 or 15; Haspel[86] and Borius,[149] one-third; Pampoukis,[86] 21.4-25.4 per cent.; Le Dantec,[226] 20-50 per cent., and Crespin,[144] 20-70 per cent. The algid type is said by Pampoukis[86] to be fatal in 55.5 per cent. of cases. Cardamatis[287] states that the comatose variety is fatal in 20-40 per cent.; Bergeand[359] believes the mortality of this type to be 50 per cent.

The following list of 27,039 cases of pernicious malaria, compiled from the literature, shows a mortality of 26.6 per cent. The first column of figures shows the number of cases, the second the number of fatalities:

	Number of Cases.	Number of Deaths.
Laveran[1]	104	53
Bailly[360]	886	341
Nepple[88]	14	6
Antonini and Monard[86]	39	9
Maillot[85]	186	38
Grall[256]	117	75
Burot and Legrand[212]	210	142
Smart[76]	16,209	4,164
Travers[38]	260	81

	Number of Cases.	Number of Deaths.
Martirano[150]	19	9
Pezza[84]	2	1
Tanzarella[84]	31	8
Thayer and Hewetson[29]	3	2
Plehn[5]	10	1
Maillot[362]	7	6
Theophanidis[362]	5	2
Cardamatis[363]	3	2
Pampoukis[362]	52	20
Billet[151]	40	2
Segard[79]	24	15
Maurel[75]	156	77
Caccini[147]	135	56
Martirano[147]	6	3
Charity Hospital, New Orleans[361]	8	6
Neer[156]	3	3
Celli[83]	8,032	1,879
Cardamatis[68]	50	9
Colonial Reports[251]	252	133
Kelsch and Kiener[178]	89	51
Albini[82]	87	11
	27,039	7,205

Six hundred and eighty-nine cases of specified type give the following respective mortalities:

	Comatose.	Delirious.	Algid.	Typhoid.	Ataxic.
Maillot[86]	77-14	61-12	48-12		
Schellong[52]	7-6				
Plehn[5]	10-1				
Maillot[362]	.....	....	7-6		
Theophanidis[362]	....	....	5-2		
Cardamatis[363]	....	....	3-2		
Pampoukis[287]	52-20				
Billet[151]	.....	....	....	40-2	
Maurel[75]	279-103	....	78-23	....	22-17
Neer[156]	3-3				
Total	428-147	61-12	141-45	40-2	22-17
	34%	20%	32%	5%	77%

The Prognosis of Hemoglobinuric Fever.—The prognosis of hemoglobinuric fever is grave, and should be "guarded and Delphic." Probably the most valuable prognostic sign is the quantity of urine; the chemic analysis and microscopic examination are not of great value in prognosis. Anuria, the most dreaded symptom, is to be feared if the daily quantity of urine falls below 200 cc. If suppression supervenes the outlook is extremely serious and is unfavorable in proportion to early onset. When a patient is tided over a period of suppression,

as occasionally happens, he usually dies during convalescence of exhaustion, subsequent nephritis, or embolism.

Excessive and uncontrollable vomiting is a bad omen, exhausting the sufferer and interfering with nutrition and medication. Diarrhea is probably in many cases, with suppression or a tendency thereto, a life-saving measure, and may be partially responsible for the relative rarity of uremic symptoms under these circumstances. Singultus is present in a majority of fatal cases, and when obstinate is always unfavorable. Remittent or intermittent temperature is usually favorable. Somnolence, with diminishing amount of urine; coma, especially of early onset, petechiæ, epistaxis or other hemorrhage, and algor forebode evil.

Thrombus formation in the heart or large vessels may cause sudden death when the patient is thought to be progressing favorably. Plehn[5] believes that loud heart murmurs accompanied with weak, irregular pulse denote heart thrombus. This condition is almost certainly fatal, usually in five to eight days.

The larger the share partaken by quinine in the etiology of the individual case the better the prognosis, provided the case is not further aggravated by quinine.

Cases occurring in victims of malarial cachexia or of complications are usually more serious.

The mortality varies unaccountably from year to year, some seasons evincing a series of mild cases, others an appalling mortality. In a certain parish of Louisiana in 1867 many cases are said to have occurred, of which not less than 95 per cent. died.[366] Fisch,[191] who placed the mortality on the Gold Coast at 20 per cent., states that until two or three decades previously nearly all who were attacked died. On the other hand, Banks[210] makes the well-nigh incredible statement that he treated over 100 cases in the Congo State without a death.

Pampoukis[96] gives the mortality of blackwater fever as 6.6 per cent.; Crosse,[4] 20 per cent.; Kanellis,[867] 22.4 per cent.; Bérenger-Féraud,[96] 23.1 per cent.; Barthèlemy-Benôit,[96] 25 per cent.; Bertrand,[229] 25 per cent.; Carré,[191] 27 per cent.; Cassan,[96] 32.1 per cent.; Michel,[368] 33 to 50 per cent.; Schellong,[191] 42 per cent.; Reynolds,[367] 50 per cent.; Scott,[367] 60 per cent.

The following list of 6,037 cases, with 1,268 deaths, shows a mortality of 21 per cent. It is compiled from various sources. The first column of figures shows the number of cases, the second the number of deaths:

TREATED WITH QUININE, 1821 CASES, 472 DEATHS, 25.9%

	Number of Cases.	Number of Deaths.
Vieth[8]	14	3
Dryepondt[8]	28	1
Mense[234]	22	
Powell[234]	9	7
Gelpe[234]	3	2
Diesing[234]	2	2
Hagge[234]	7	2
Schellong[234]	7	3
Reynolds[234]	1	1
Doering[187]	6	
Hanley[184]	13	3
Moffatt[263]	9	2
Gorgas[354]	20	3
Steudel[96]	18	3
Malone[369]	120	14
Brem[215]	14	2
Coste[370]	15	7
Steggall[371]	3	
Woldert[249]	5	
Otto[53]	1	
Schlayer[222]	1	
Austin[372]	1	
Herrick[251]	8	
Curry[186]	1	1
Burot and Legrand[225]	3	1
Cardamatis[206]	1,352	354
Broden[242]	12	7
Theophanidis[373]	23	14
Oeconomou[373]	18	5
McDaniel[374]	85	35

TREATED WITHOUT QUININE, 1006 CASES, 112 DEATHS, 11.1%

	Number of Cases.	Number of Deaths.
Tomaselli[232]	30	6
Navarre[8]	2	
Henric[375]	2	
Kohlstock[376]	48	8
Koch[172]	16	3
Hopkins[260]	6	1
Bertrand[229]	21	2
Ollwig[49]	15	
Wittrock[49]	4	1
Ziemann[49]	12	4
A. Plehn[191]	53	5
Kleine[223]	15	1
Krauss[199]	15	
McElroy[214]	25	4
Goltman and Krauss[189]	12	9

TREATED WITHOUT QUININE, 1006 CASES, 112 DEATHS, 11.1%

	Number of Cases.	Number of Deaths.
Malone[369]	35	
Coste[370]	10	4
Hearsey[266]	15	4
Seal[258]	6	1
Ruge[239]	1	
Dryepondt and Vancampenhout[228]	1	
Howard[216]	1	
Ketchen[238]	1	
Masterman[64]	1	1
Herrick[251]	1	1
Curry[186]	1	1
Cardamatis[206]	456	33
Ensor[377]	11	1
Broden[242]	25	2
Pancot[242]	7	1
Theophanidis[373]	9	
Oeconomou[373]	31	2
McDaniel[374]	93	16
F. Plehn[5]	25	1

TREATMENT MIXED OR NOT RECORDED, 3210 CASES, 684 DEATHS, 21.3%

	Number of Cases.	Number of Deaths.
Kanellis[232]	20	4
Poole[8]	56	15
Rothschuh[8]	20	18
Guiol[378]	185	49
Gouzien[379]	53	
Meixner[49]	40	6
Hofft[49]	14	6
Wendland[49]	10	
Daniels[57]	184	41
Wellman[56]	34	5
Ipscher[99]	20	1
Krueger[99]	11	2
Simon[90]	17	3
Kerr Cross[389]	27	9
Osborn[14]	10	5
Bérenger-Féraud[96]	286	66
O'Neill[96]	50	2
Burns[235]	16	6
Shropshire[267]	177	35
Dempwolff[381]	17	2
Lipari[202]	19	5
Gouducheau[245]	15	4
Cochran[282]	642	158
Kelsch and Kiener[178]	109	35
Bolton[283]	175	38
Grall[256]	113	13
Forde[284]	2	1
Grenet[372]	68	8
Rousseau[372]	22	6
Carmouze[372]	30	9
Mericourt[372]	22	3
Koryllos[372]	28	5
Pampoukis[372]	156	35

TREATMENT MIXED OR NOT RECORDED, 3210 CASES, 684 DEATHS, 21.3%

	Number of Cases.	Number of Deaths.
Cardamatis[385]	30	6
Parathyris[372]	23	3
Prout[386]	24	8
Jacobs[387]	147	16
DeCruz[388]	13	6
DeBlasi[389]	3	
Orme[390]	2	
Thompstone[391]	27	5
German Protectorate Reports[356]	293	45
Total	6,037	1,268

F. Plehn[5] asserts that mortality is highest in first attacks, but the following table of Daniels[57] does not bear him out:

Of 136 first attacks.....31 or 22.7 per cent. were fatal
Of 33 second attacks..... 8 or 24.0 per cent. were fatal
Of 15 third or fourth attacks. 2 or 13.3 per cent. were fatal

CHAPTER VIII

PROPHYLAXIS

THE immortal discovery of Ross is to the prophylaxis of malaria what that of Laveran is to the diagnosis, and, although recent, has already been instrumental in saving untold suffering, incalculable economic loss, and thousands of human lives.

It has been explained how the parasite is abstracted by certain species of mosquitoes with the blood of infected individuals, undergoes essential changes in the body of the mosquito, and is then inoculated into healthy persons. It is, therefore, evident that if this cycle be broken at any point infection cannot occur, and that if it were universally interrupted during a sufficiently long period of time the disease would be annihilated. Hence prophylactic measures may be directed against the destruction of the malarial parasites within the body of man, the destruction of the mosquitoes which are capable of transmitting the parasites, and the prevention of mosquitoes gaining access to man. The parasite may be opposed either in man or in the mosquito. The mosquito may be combated either in its aquatic or in its aerial stage. Prophylaxis may be conducted by a community or by an individual, may be public or private, offensive or defensive.

As is well known, malaria is now almost or entirely absent from regions in which it was formerly very prevalent, and in other places is rapidly diminishing. In the regions in mind the change was independent of designed efforts for the eradication of the disease; in fact, it occurred in most instances before the discovery of either the malarial parasite or of the rôle of the mosquito in the dissemination of the disease, and was an unexpected result of the progress of civilization. This unconscious prophylaxis was probably the product of several factors, which may be classed as agricultural, therapeutic, and hygienic.

1. Lowering of the ground water and consequent diminution of breeding pools through drainage for reclamation of swamp lands, clearing and cultivating of lands, construction of levees, etc. 2. More radical cures of malaria by means of cinchona bark and its derivatives, lessening the number of cases of latent malaria, thereby diminishing the sources from which parasites might be obtained. 3. Improved hygienic conditions, better homes and food, the installation of water and sewerage systems, improved road and street grading, the use of screens, mosquito bars, etc. For very few other diseases has unconscious prophylaxis done so much as for malaria. This is still exemplified in regions where malaria is yet endemic; those who live under the best hygienic conditions suffer least from malaria, though they may even be ignorant of the manner of its propagation.

With the tediously attained and in many cases incomplete results of this unconscious prophylaxis are in decided contrast the consequences of well organized and vigorous sanitary measures directed toward the prevention of malaria. Many instances could be adduced where within a comparatively short space of time highly malarial localities have been almost completely freed from the disease, but a few examples will suffice.

One of the most successful campaigns against malaria was that at Ismailia, a town of about 8,000 inhabitants, near the middle point of the Suez Canal. The town was founded in 1862, and was celebrated for its salubrity until 1877, when malaria was introduced and spread rapidly; in 1886 nearly all the inhabitants were attacked. In 1901 the president of the Suez Canal Company, learning something of the results of modern prophylactic methods, dispatched Pressat, a member of the medical staff, to Italy to study the subject, and invited Ross to inspect the place and advise upon the most suitable manner of conducting the campaign. In September, 1902, Ross arrived in company with MacGregor and with Pressat returning from Italy. An abundance of anophelines were found in the houses of the employes, and the larvæ, especially in small, brackish marshes, in the sand, and in some of the waters of irrigation, but not in the main canal, where they

were probably destroyed by fish. It was evident that mosquito reduction was to be the chief end, though old cases of malaria received vigorous treatment. Marshes were filled with sand and the irrigation channels were deepened or treated with oil. This preliminary work was conducted with a brigade of only four men, though many others were employed later for the extensive permanent work. From 1885 until 1902 inclusive the number of cases of malaria at Ismailia had averaged nearly 1800 annually. In 1903 there occurred 214 cases; in 1904, 90, and in 1905 only 37. It is said that it is now possible to sleep with comfort in the place without nets. The cost of the campaign is estimated at an initial expenditure of 6.25 francs, and an annual outlay of 2.3 francs per head of population.

The results of the campaign conducted by Travers and Watson at Klang and Port Swettenham, in the Federated Malay States, are hardly less striking. Klang had 3,576 inhabitants in 1901. Port Swettenham, five miles away, had a population of about 700. The population of the district surrounding the two towns was about 14,000. In the latter part of 1901 malaria was so extensively prevalent that probably not more than three houses in Klang escaped infection, and Port Swettenham was being abandoned by the workmen. The antimalarial campaign, which was confined to the towns of Klang and Port Swettenham, began in 1902. Swamps were filled, a contour drain established to intercept incoming water from surrounding springs, and forest and mangrove trees were felled. After the epidemic had begun to subside screens were furnished many of the houses and quinine was distributed. The cost of the operations to the end of 1905 consisted of a primary expense of £10,100 and an annual expense of £410.

The following table shows the mortality from malaria within the towns as compared with that of the unprotected district:

	1900	1901	1902	1903	1904	1905
Towns	259	368	59	46	48	45
District	173	266	227	230	286	351

The most brilliant results in the prophylaxis of malaria were those obtained by Gorgas in Panama, one of the most insalubrious regions upon the face of the earth, having been called



Fig. 75.—The barrels and one of the buckets contained many larvæ.



Fig. 76.—Anopheles larvæ in the barrel. A fatal case of comatose malaria occurred here a few weeks before the picture was taken.



Fig. 77.—Unmindful of the danger lurking in the barrel.



Fig. 78.—Fire barrels containing larvæ.



Fig. 79.—Water barrels may prevent the spread of fire, but will breed mosquitoes unless covered.

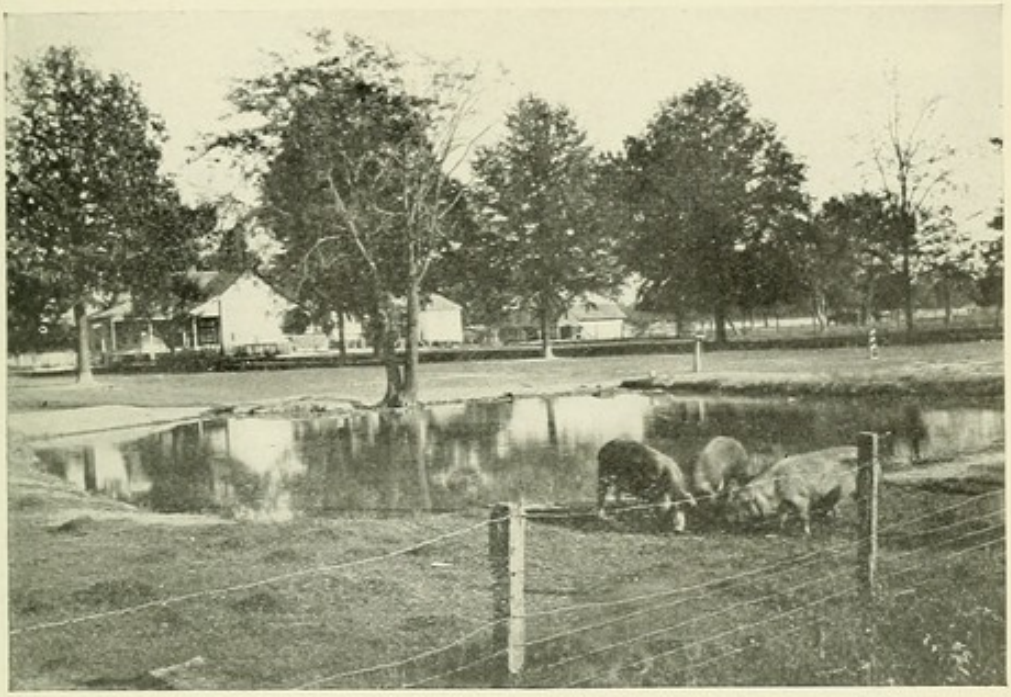


Fig. 80.—Stock pond containing anopheles larvæ. Too near the dwelling.

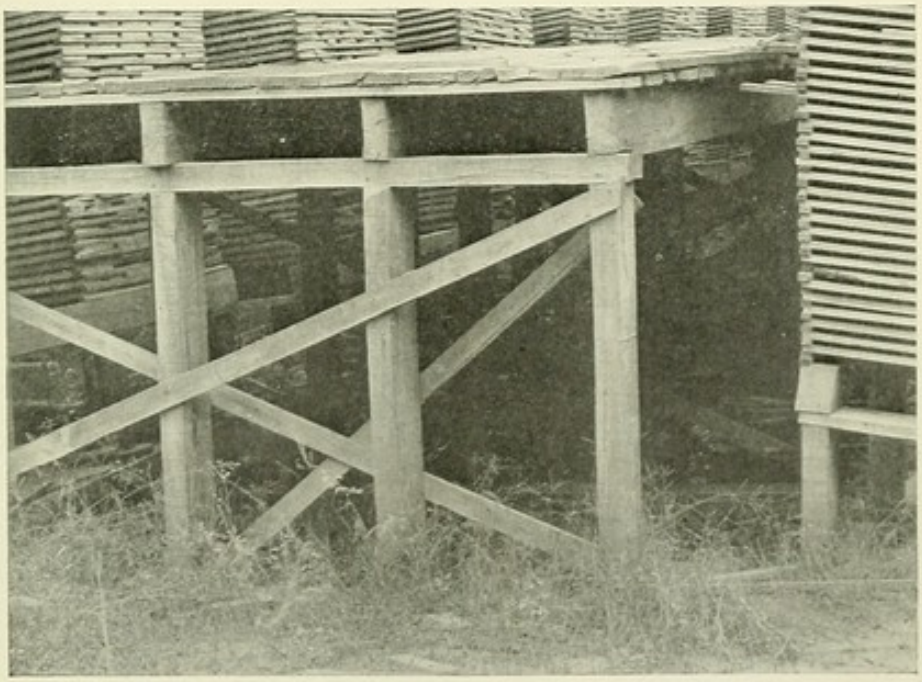


Fig. 81.—A protected pool in a lumber-yard containing myriads of anopheles larvæ.



Fig. 82.—A typical "bayou," the headquarters of malaria.

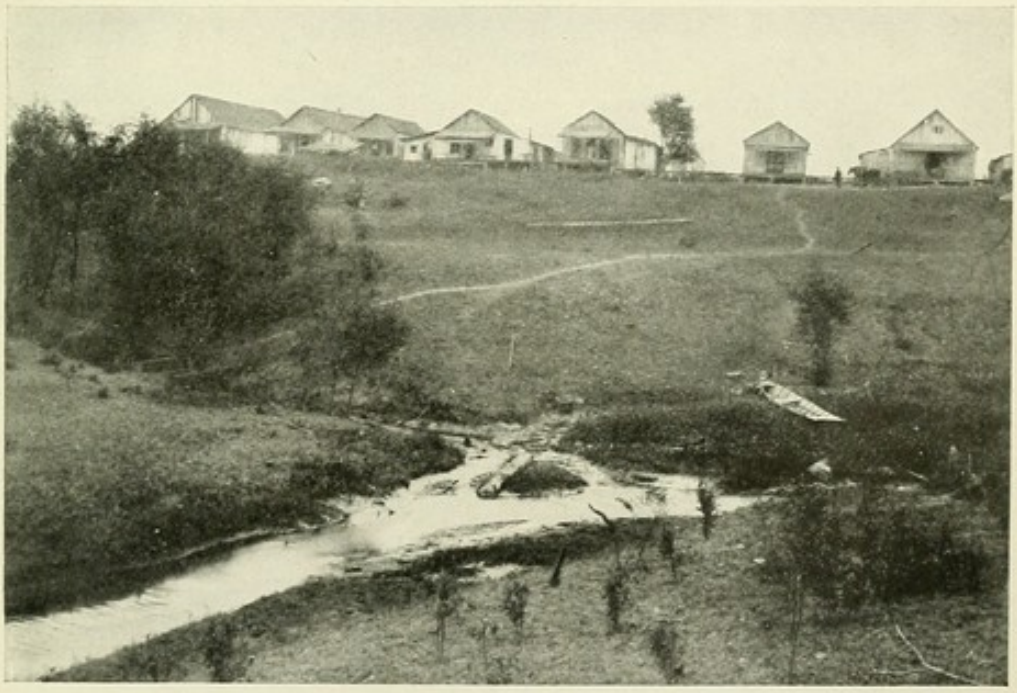


Fig. 83.—An ill-chosen town site along the bayou.

during French occupation "the Frenchman's Grace." It is a common report that in the railroad between Panama and Colon every cross-tie represents the corpse of a laborer.

The canal zone is fifty miles in length, with Panama and Colon at each end. The average number of employes is 40,000. The efforts consisted in the destruction of breeding places only within 200 yards of the camps and villages, no attempts being made to deal with those farther off. All the houses were screened and the people were urged to use mosquito bars. Quinine was furnished them and they were advised to take 3 grains daily. The abolition of the breeding pools was regarded as a most important measure. Owing to the heavy rainfall and the luxuriant vegetation the ditches filled rapidly with grass, and it was found much cheaper to concrete them. Subsoiling by means of the tile drain covered with rock and soil was used wherever possible.

The result is that the death rate has been lowered until it does not exceed that of New York City.

I. MEASURES DIRECTED FOR THE DESTRUCTION OF MOSQUITOES

Destruction of breeding pools for the anopheles is an efficient preventive measure. It is chiefly through the eradication of breeding places that so-called unconscious prophylaxis has accomplished its results. This method has received the chief consideration in the greatest antimalarial campaigns. It is more permanent and possesses the further advantage in many instances of being cheaper in the end.

It is neither necessary nor in every case advisable to remove the surface water from the whole of a malarial country, but only in the region of habitations or where anopheles are known to breed. In the Panama campaign the area of destruction extended only 200 yards from camps and habitations. This should probably be the minimum radius, though work at a much greater distance is only a useless expense.

In the area to be protected the land should be cleared of weeds, undergrowth, bushes, and unnecessary trees to promote evaporation and prevent the formation of puddles.

Grocery cans, broken bottles, buckets, and old tinware which might retain water should best be buried. Water-barrels, tanks, cisterns, and wells should be emptied, filled, or screened. Gutters should be maintained in such a condition that water cannot accumulate.

The stock pond, so common in the vicinity of habitations in some sections, is a menace to both man and beast and should not be tolerated.

The care of streams and large bodies of water is ordinarily simple, since these rarely threaten sanitation as anopheles breeders. Within the protected area the banks should be cleared of dense weeds and bushes, eddies prevented where possible, and pools along the edges drained into the channel.

In the case of streams that get very low after the rainy season, leaving a chain of pools along the river-bed, these pools should be drained into each other and an attempt made to reëstablish a flow and to permit of scouring and the access of fish from the larger pools. Where the pools are small much water can be gotten rid of by the use of brooms.

In the case of large bodies of water subject to overflow the problem is more difficult. The primary effect of the submerging of land, while the water is high, is to diminish malaria. The secondary effect, after the waters have receded, is to cause a marked increase. A remarkable example which illustrates this occurred in Holland in 1748. The Dutch allowed the land, for defensive purposes, to become overflowed. Peace being concluded during the middle of the summer, the inundation was caused to subside, whereupon a serious outbreak of malaria occurred. The epidemic was not successfully combated until the land was again submerged and kept so until the advent of winter. The effect upon malaria of inundations is almost yearly observed in the valleys of the Nile, of the Mississippi, and of other large streams. Levées, dykes, and other engineering means of large dimensions are the only remedies; these being expensive are rarely employed merely for sanitary purposes.

Marshes and swamps when too extensive to be filled may be effectively drained. The drains should be narrow, of suffi-



Fig. 84.—Anopheles breed among the cypress knees.



Fig. 85.—Many breeding-places are left upon the lowlands after the overflow has receded.

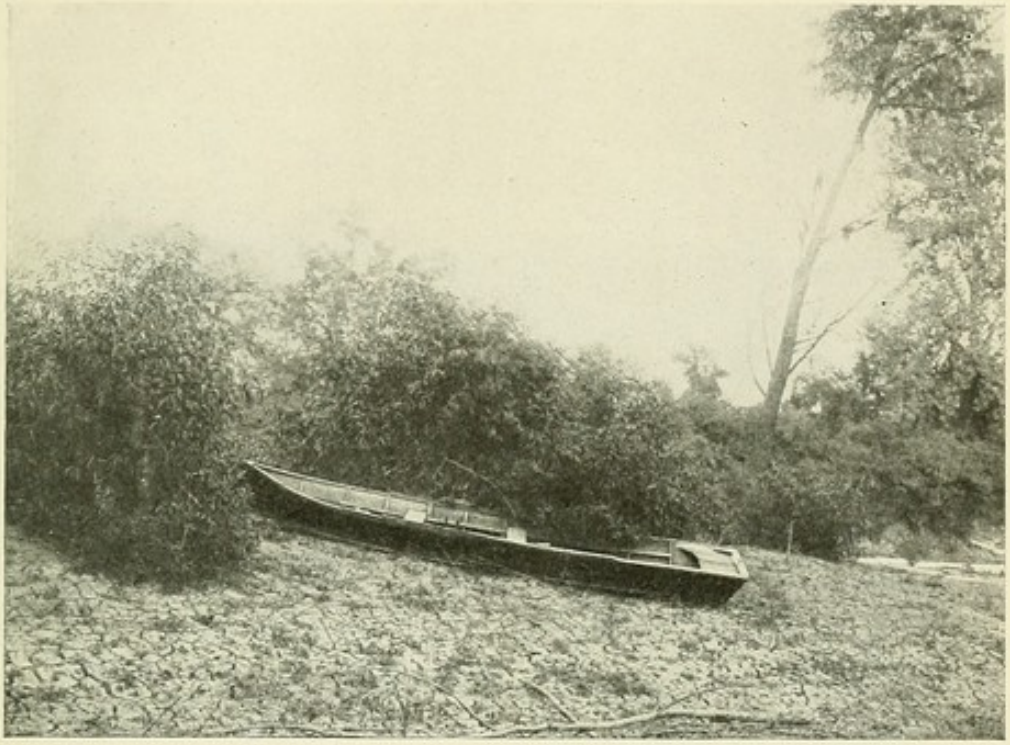


Fig. 86.—A stranded skiff containing a little water and many anopheles wrigglers.



Fig. 87.—The cyclone as a factor in malaria.



Fig 88.—This pool, fed from the ice-plant, contained larvæ weeks after most other pools had disappeared.

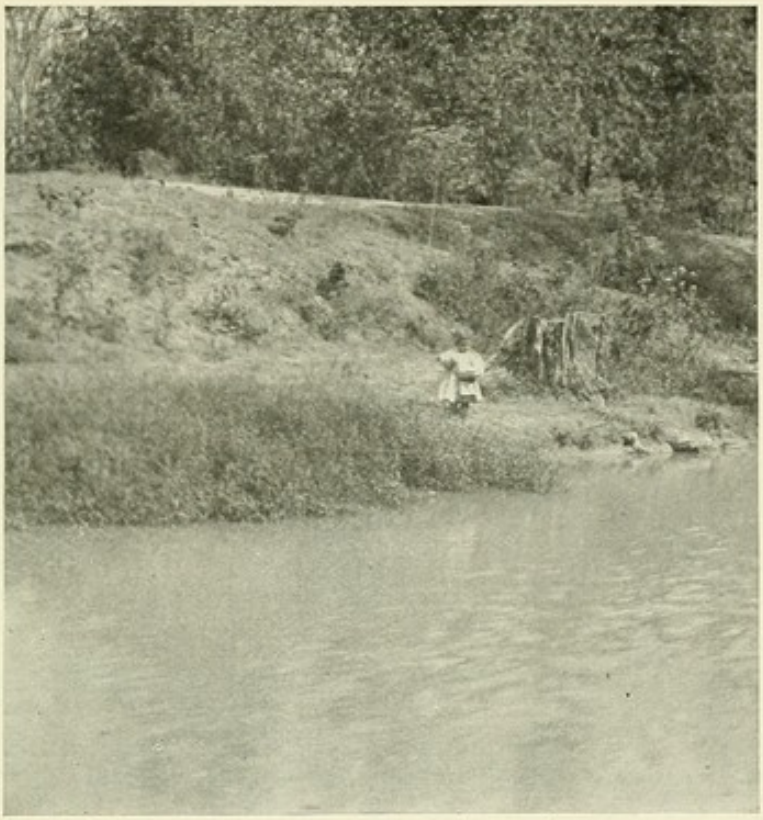


Fig. 89.—Hunting for anopheles larvæ along the levée.



Fig. 90.—An embryc scientist searching for anopheles larvæ.



Fig. 91.—Breeding pools in the borrow pits along a railroad.



Fig. 92.—Breeding pools along the roadside.

cient depth and fall to drain effectively, and may be parallel, crowfoot fashion or otherwise, as best suited to local conditions. If concreted they require less after-treatment and may be cheaper in the end. If not concreted they should be frequently inspected to prevent caving, deposit, or filling with vegetation. Tile-drains are usually very efficient.

Large swamps in the vicinity of streams have been rendered unfit as breeding places by directing the course of the stream through them. The water is thus given a current, and if the stream contains much mud in suspension the bed of the marsh is gradually filled.

Fresh-water ponds close to the sea have been successfully treated by filling with salt water. It is said that a large fresh-water lake back of the hotels at Virginia Beach which bred numerous mosquitoes was filled with salt water by means of machinery with a satisfactory result. Water strong in salt is not attractive for breeding purposes, though brackish water may harbor numerous larvæ.

The rendering innocuous of borrow pits along railroad lines (Fig. 91) is difficult. It is much easier to prevent the stagnation of water during the construction of the road than it is to remedy the defect after completion. Filling and drainage are the best correctives. It should be the duty of some one to see that the construction of railroads, canals, and similar enterprises does not render a country more unsanitary.

The destruction of smaller pools and puddles is usually simple and goes far toward prophylaxis, since it is in such places that anopheline mosquitoes breed by preference. Filling is by far the most permanent, hence the cheapest and most desirable method by which to deal with these collections of water. Pools in ditches along the sides of roads (Fig. 92), wheel ruts, hoofprints of stock in soft ground, water remaining in natural inequalities in the ground and in excavations for various purposes should be assiduously attended. The work should be conducted by one who is familiar with the rudimentary principles of drainage. The organization for this purpose of "mosquito brigades" was first suggested and put into practice by Ross,[392] whose advice is as follows: "Attack

first those collections of water the obliteration of which will remove the largest number of mosquitoes for the least amount of money. Thus it is quite useless to drain stagnant water simply because it is stagnant water. The superintendent should first assure himself that it does actually contain larvæ, and, better, that it constantly contains them. As already mentioned, some pools are too large, others are too small, and others are subject to scouring, and, though these conditions often change at certain seasons, when, for instance, large pools dry up, yet some pools appear to be habitually unsuited to the larvæ. It is useless to spend much money over these. Again, it is not advisable to attack without discrimination even the pools which do contain larvæ. Some contain many more larvæ than others do; and, in my experience, while larvæ do occur in some considerable bodies of water, such as marshes or ponds, they are generally much more numerous in small pools. Now, it is evidently bad economy to spend large sums over draining large bodies of water when small puddles, easily dealt with, really cause more mischief. The superintendent must *suppose* nothing—he must never *suppose* because a marsh exists in a neighborhood that it is the only or the principal cause of malaria. He must study the point by careful search for *anopheles* larvæ; and may often find that a small, unobserved pool in the street is more dangerous than a marsh a mile away.

The number and nature of the breeding pools depend so much upon the configuration of the ground, the character of the soil, and the amount of the rainfall that it is impossible to give very minute directions regarding the method of dealing with them. The superintendent must be guided by his own judgment, remembering only the maxim, which applies to most kinds of work, "The simplest measures first."

The height of the ground water is very intimately associated with the prevalence of malaria, since the quantity of surface water depends largely upon the height of the ground water, and the latter, when appearing upon the surface, is a favorite breeding site for malarial mosquitoes. Hence, measures directed toward the lowering of the ground water are of the highest efficacy in the prophylaxis of malaria. This is evi-

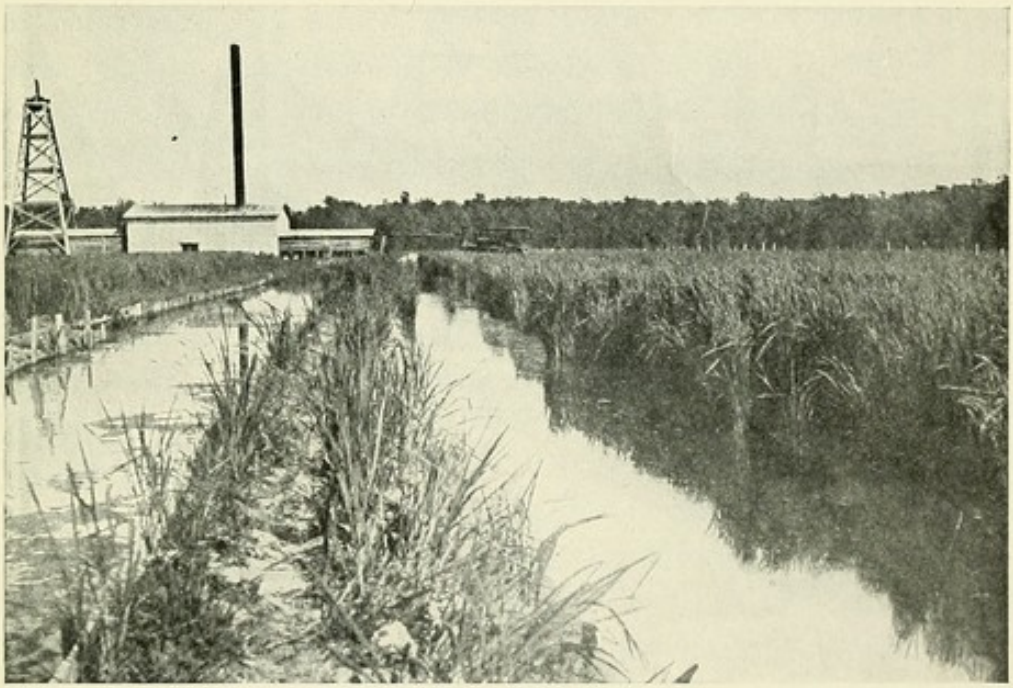


Fig. 93.—Breeding pools on a rice farm.

denced by the results of the "tiling" of land and by the formation of drainage districts for the reclamation of swamp lands. Such procedures often render unnecessary the expenditure of labor or money for the removal of breeding pools or other antilarval steps.

Ground water is lowered by various methods, the most primitive of which is ditching. These ditches are left open or are partly filled with gravel or stone, then with earth. The unglazed tile drain is very effective; perforated drains have been employed also.

In certain regions where the hardpan or impervious stratum is responsible for a high-ground water excellent results have been obtained by boring through this, thereby allowing the water to escape into the permeable earth beneath. These are the so-called *absorbing wells.*

It is well known that rice culture increases the malaria of a region to a great extent (Fig. 93). In some of the Oriental countries the crop is a necessity, but in regions not absolutely dependent upon the crop the cultivation of rice must be looked upon as an evil. In fact, some governments have either thrown certain restrictions around the industry or have altogether prohibited it.

Since the time of Pliny it has been the theory that trees render a locality more salubrious by filtering out miasmatic exhalations. The *eucalyptus globulus* has attained considerable reputation in this respect, probably from a belief that it absorbs moisture from the soil and renders it drier. Recent experiments in Italy have, however, shown that this tree has no effect in decreasing malaria, and that it even affords an excellent shelter for *anopheles* mosquitoes.

Sunflowers and castor-oil plants, which are reputed to be beneficial in the prophylaxis of malaria, are probably devoid of such virtue.

There are circumstances under which it is impossible to destroy the breeding pools. Here the use of petroleum is indicated. This oil is also useful in antimalarial campaigns as a temporary measure in part of the work while permanent means are being employed elsewhere.

While the value of petroleum as a larvicide was known early in the nineteenth century, to Howard belongs the credit of its practical application.

An oil should be chosen which spreads rapidly and evaporates slowly. The refined illuminating oil evaporates readily, hence is too expensive for work on a large scale. The most suitable is the fuel oil or blast-furnace oil. The oil, forming a film upon the entire surface of the water, chokes the air tubes of the larvæ, which come to the surface to breathe. The pupæ expire even earlier than the larvæ, since they require more air. Furthermore, not a few adult female mosquitoes in the act of oviposition are thereby destroyed.

The pool should be cleared, as far as possible, from weeds and algæ which interfere with the spread of the oil. The oil should be poured from a watering pot, sprayed by means of a force pump, or painted over the surface with saturated cloths tied to the ends of sticks. An automatic oiler may be improvised by placing a barrel of oil a few feet above the water to give the oil the necessary spread, and having a perforation in the bottom of the barrel to drop about twenty times to the minute.

The quantity of oil which has been found amply sufficient is 1 ounce for each 15 square feet of surface. It has been estimated that a barrel of oil costing only a few dollars is sufficient to cover 96,000 square feet of surface.

Evaporation, rains, and winds prevent permanent results, so that the oiling must be repeated. Intervals of two or three weeks are the proper average, and certain days of the month should be systematically chosen. It is best to begin the oiling in the spring to prevent the first generations.

Nearly every antiseptic and poison has been employed for the destruction of mosquito larvæ. The aniline derivatives are valuable, especially that known as *Larvicide,* which destroys also fish and other forms of life which may be useful in killing larvæ. The same objection applies to *Phinotas Oil,* a cresol combination, and saprol, which are effective larvicides. Formalin, corrosive sublimate, carbolic acid, and lysol are too slow in their effects upon larvæ to be of practical value. Perman-

ganate of potash has proved disappointing in all trials made of it. Tar, creosote, tobacco, pyrethrum, sulphate of iron, and numerous other substances have been used and abandoned. Nothing is so efficacious, so free from danger, and so inexpensive as kerosene.

Where it is not feasible either to drain or oil a breeding pool the introduction of small fish has been practised with success. Certain species of fish prey upon the eggs, larvæ, and pupæ of mosquitoes, and even upon adults when about to emerge from the pupal shell or when in the act of oviposition. The common top minnows (*Gambusia* and *Fundulus*) and the sunfish are excellent for this purpose. The former being very voracious and top-feeders, are especially adapted for the destruction of *anopheles* larvæ. They are fast breeders and resist the drying of pools in a remarkable degree. Sticklebacks, gold-fish, and roach are also larvivorous. It is doubtful whether the common German carp, on account of its feeding habits, is of any use for this purpose. The tadpole is valueless for the destruction of larvæ.

The larvæ of dragon-flies devour the mosquito larvæ among other prey. Feeding upon the bottom, however, they are not very effective, as to *anopheles* larvæ especially, unless the pool be shallow, in which case they may destroy great numbers.

The water boatman (*notonectidæ*) is an efficient enemy, and many mosquito larvæ are cannibalistic among the smaller forms, even of the same species.

The hair worm, a species of *mermis,* is sometimes a fatal parasite of mosquito larvæ. During a certain summer Stiles[114] found that many of the larvæ which he collected died in the laboratory. Upon dissection he found them infested with the hair worm. It was noted that in years when mosquitoes were scarce this parasite was plentiful.

Giles[119] in India found larvæ infested by a parasitic stalked infusorian, and suspects that they may be the cause of the inexplicable disappearance of larvæ from places where they were formerly abundant.

Galli-Valerio and de Jongh[82] observed from laboratory and field experiments that *aspergillus niger* and *glaucus,* especially

the former, exercised a very unfavorable influence upon the development of mosquito larvæ.

The cultivation of the water pest (*anacharis alsinastrum*), which so thickly covers the surface of the water as to prevent the larvæ and pupæ from gaining access to the air, has been recommended as a prophylactic measure. It is said that in certain localities the disappearance of malaria coincides chronologically with the appearance of the water pest.

The natural enemies of adult mosquitoes are few and practically insignificant. Dragon-flies, night-hawks, whip-poor-wills, swallows, bats, and certain species of lizards destroy a number and some are killed by parasitic mites and a small suctorial fly.

An ideal prophylaxis destroys the breeding pools or the aquatic stages of mosquitoes, but remedies against the adult insects are sometimes necessary. For this purpose a great variety of substances has been tried. One of the most primitive of measures is the smoldering fire of chips, rags, and feathers, to be seen in summer twilight to the windward of nearly every negro cabin.

The most practical means are the fumes of burning sulphur and of pyrethrum powder. The room to be fumigated should be made as nearly airtight as possible.

Of sulphur, from 2 to 5 pounds should be used for every 1,000 cubic feet of space. Its deleterious effect upon metals and delicate fabrics limits its use somewhat. Sulphur dioxide fumes have been found to be an excellent insecticide. Rosenau[393] says of it: "Very diluted atmospheres of the gas will quickly kill mosquitoes. It is as efficacious for this purpose when dry as when moist, whereas the dry gas has practically no power against bacteria. Contrary to formaldehyde, it has surprising powers of penetrating through clothing and fabrics, killing the mosquitoes even when hidden under four layers of toweling, in one hour's time, and in very diluted proportions. This substance, which has been so long disparaged as a disinfectant because it fails to kill spores, must now be considered as holding first rank in disinfection against yellow fever, malaria, filariasis, and other insect-borne diseases."

The room should be kept closed for several hours to insure the complete extermination of the insects.

Pyrethrum powder may be burned in the proportion of a few ounces to a pound for each 1,000 cubic feet of space. It may be moistened with water, molded into cones, and dried, or the powder may be slightly dampened at the summit with alcohol and lighted. The mosquitoes are suffocated by the fumes and must be swept up and destroyed.

Formaldehyde has been tried and found wanting, but may be effective when very large quantities are rapidly liberated in a tight room with few hiding places for the insects.

The pulverized leaves and stems of the common jimson weed (*Datura stramonium*), mixed with saltpeter, and burned in the proportion of 5 ounces to 1,000 cubic feet of space, have been successfully used by the New Jersey Mosquito Commission.

Chlorine gas, generated by adding a few drams of sulphuric acid to an ounce of chloride of lime, is said to be efficient, and burning tobacco leaves are useful.

The following table copied from Celli[80] shows the effects of various odors, fumes, and gases upon adult mosquitoes according to his experiments:

Action of culicidal substances on mosquitoes (*C. annulatus, C. pippens, A. claviger*):

I. Odors

No.	Substances used.	Time in which death is manifested. Apparent.	Actual.
1.	Essential oil of turpentine	1 min.	1 min.
2.	Iodoform	10 min.	40 min.
3.	Menthol	10 min.	45 min.
4.	Nutmeg	10 min.	2 hours
5.	Musk	30 min.	3 hours
6.	Camphor	4-5 min	4-5 hours
7.	Leek	5-10 min.	5 hours
8.	Crushed pepper	20 min.	6 hours
9.	Naphthalene	10-35 min.	8 hours
10.	Roman wormwood	6 hours	24 hours
11.	Onion	4-6 hours	Survive
12.	Salvia	.....	Survive
13.	Rosemary	.....	Survive
14.	Dry and fresh basil	.....	Survive
15.	Cinnamon bark	.....	Survive
16.	Asafetida	.....	Survive

II. Fumes

Substances used.	Time in which death is manifested. Apparent.	Actual.
1. Tobacco	Instantly	1-3 min.
2. Larvicide	Instantly	5 min.
3. Chrysanthemum powder (unexpanded flowers)	5 min.	1 hour
4. Valerian root	5 min.	2 hours
5. Fresh leaves of eucalyptus	3-5 min.	3 hours
6. Quassia wood	16 min.	5 hours
7. Pyrethrum powder	5 min.	6 hours
8. Dry leaves of Mentha pulegium	5 min.	8 hours
9. Pitch	10-13 min.	8 hours
10. Dry leaves of basil	2-6 min.	24 hours
11. Dry rosemary	7-12 min.	24 hours
12. Culicidal cones	2-10 min.	36 hours
13. Dry chamomile flowers	2-10 min.	36 hours
14. Dry leaves of Saturgia hortensis	2-10 min.	36 hours
15. Salvia leaves	8-10 min.	36 hours
16. Wood	5-7 min.	12-48 hours
17. Guaiacum resin	12 min.	Survive
18. Myrrh	15 min.	Survive
19. Elemi	15 min.	Survive
20. Incense	15 min.	Survive

III. Gases

Substances used.	Time in which death is manifested. Apparent.	Actual.
1. Sulphur dioxide	Instantly	1 min.
2. Hydrogen sulphide	Instantly	1 min.
3. Ammonia	1 min.	2 min.
4. Illuminating gas	1 min.	2 min.
5. Formaldehyde (Trillat's apparatus)	2 min.	10-15 min.
6. Sulphuret of carbon	15-30 min.	Survive
7. Acetylene	...	Survive

Ross'[392] summary is a fitting conclusion to the consideration of mosquito destruction:

Summary of Objects

1. We do not propose to exterminate mosquitoes in any entire continent. We propose only to deal with them in the town in which we live and in its suburbs.

2. We do not propose to get rid of every mosquito even in this town. We aim only at reducing the number of the insects as much as possible.

3. We do not think it possible to drain or otherwise treat every breeding place in the town. We aim at dealing with as many as possible.

4. We cannot exclude mosquitoes which may just possibly be blown into the town from miles away. We content ourselves with preventing the insects breeding in the town itself.

Summary of Methods

1. We start work at once with whatever means we can scrape together.

2. We operate from a center outward.

3. We clear houses, backyards, and gardens of all rubbish, empty tubs and cisterns containing larvæ, or destroy the larvæ in them by means of oil.

4. We show people how to do these things for themselves, and how to protect tubs and cisterns by means of wire gauze.

5. When we have cleared as many houses as we determine to deal with we clear them over and over again.

6. We fill up or drain away all the pools, ditches, old wells, and puddles we can—especially those which contain most larvæ.

7. Such pools as cannot be filled up or drained are deepened and cleared of weeds if they contain larvæ.

8. Streams and water-courses which possess larvæ are "trained."

9. Where we can do nothing else we destroy larvæ periodically with oil, or by brushing them out with brooms, or by other means.

10. We endeavor to interest our neighbors in the work, and to educate the town into maintaining a special gang of men for the purpose of keeping the streets and gardens absolutely free of stagnant mosquito-bearing water.

Motto:

Our motto should be one which, I think, will shortly become the first law of tropic sanitation, namely:

"NO STAGNANT WATER."

II. MEASURES DIRECTED TOWARD THE DESTRUCTION OF PARASITES

Efforts to destroy the malarial parasites in the human body assume two modes. The first consists of the radical cure of the malaria-infected individual, the prevention of a relapse, thereby benefiting the individual and annihilating a source of

danger to the community. The second mode consists of the administration, to persons not necessarily infected, of a drug which destroys the parasite soon after the latter is introduced into the body, before the incubative stage is completed.

Cases of latent and atypic malaria (Fig. 94) are of greater importance to prophylaxis, being sources of greater danger to communities than are typic acute cases. The duration of the acute attack is short, the patient is apt to be placed under relatively favorable conditions and to receive quinine; he does not wander and disseminate the disease, and his blood may contain but few sexual forms of the parasite. On the other hand, the subject of latent malaria may harbor parasites for months, and, the condition being unrecognized or ignored, he does not take quinine, and is a fountain of infection in diverse places and for prolonged periods.

Koch has maintained that the prompt and permanent cure of all acute cases of malaria and the systematic search for, and appropriate treatment of, all latent cases in a region will result in the extermination of the disease from such a locality. This is theoretically possible, but could be practised only in small communities under perfect control. Nevertheless, it is certainly the duty of physicians to endeavor to effect radical cures of the cases which come under their observation, a duty owed not only to the patient, but to the public, and such efforts will go far toward the eradication of the disease.

Quinine Prophylaxis.—Theoretically the administration of quinine to healthy individuals for the prevention of malaria is not an ideal method of prophylaxis, for, strictly speaking, it does not prevent infection, but destroys the parasites in the incubative stage after inoculation into the human body. But no one method satisfies all conditions; each has its advantages and its limitations, and frequently two or more methods must be employed simultaneously.

Quinine prophylaxis is indicated in proportion to the difficulty of pursuing more permanent methods. It is valuable where screens and bars are not available, as in camping, marching, traveling, or where the occupation takes one out at night. When residents of non-malarial countries go into mala-



Fig. 94.—Carriers of latent infections are disseminators of the disease.

rial localities, especially in the rural districts, for short spaces of time quinine is a most valuable prophylactic. After infection is known to have occurred quinine is, of course, essential not only as a cure, but as a preventive. It may be employed effectively where it is impossible to destroy mosquitoes or as an adjunct to other measures.

Numerous experiences attest the value of quinine in the prophylaxis of malaria.

The observations of Logan,[394] made upon soldiers of the Civil War, were as follows: Of 230 men who took no quinine 134 had fever, a ratio per 1,000 of 582. Of 246 men who took quinine irregularly 96 had fever, a ratio per 1,000 of 390. Of 506 men who took quinine regularly 98 had fever, a ratio of 193 per 1,000.

Jilek[86] reports that among 736 soldiers, living under similar conditions, 5,000 took 0.10 gram of sulphate of quinine each morning and only 18 per cent. had fever, which was mild and recurrences few. Among the 236 men who took no quinine 28 per cent. had fever.

At Melaboe, in the Dutch Indies, there were, during 1896, in the garrison 1,237 days of sickness and 33 men excused for malaria; in 1897, 1,841 days of sickness and 44 cases of malaria. Beginning with November, 1907, each soldier took 0.50 gram of quinine twice a week. During 1908 there were only 214 days of sickness and no one dismissed on account of malaria.[1]

At the prison of Bhagalpur the average mortality had been 48 per 1,000. With cinchonidine prophylaxis it fell to 9 per 1,000 in 1895, and to 7.2 per 1,000 in 1896. The civil population suffered heavily from malaria during this time.[1]

During 1901 the malarial morbidity in the Grossetane marsh, which was formerly 55 per cent., was reduced to 24.53 per cent.

In Italy, Mori[79] gave to persons over sixteen years of age 0.50 gram euquinine daily, and to children 0.25 gram, with the result that of these only 6.25 per cent. were attacked, while of those who took no prophylactic 81 per cent. took the disease.

Ziemann[48] observed in Cameroon that among 25 persons who

did not use quinine all were attacked with malaria, with a mortality of 36 per cent. Of 69 who used quinine regularly according to his method 16 per cent. remained free from malaria, and among those attacked only 4.35 per cent. died.

Babes[395] employed Koch's method of quinine prophylaxis in Roumania. In one locality of 214 inhabitants who took quinine prophylactically no case of malaria occurred, while among 32 who used no preventive there were 15 cases. In another locality, in which 1,800 inhabitants were thus treated, not a single case occurred, though in 800 who did not employ the prophylactic the morbidity was 20 per cent.

During a severe epidemic in 1907 in Marathon, a highly malarial locality, Hadjimichalis and Cardamatis[93] had the following experience with Koch's method:

Of 67 persons who took quinine for 21-24 weeks none were infected; of 145 who took it for 16-20 weeks 20.6 per cent. were attacked; of 220 who took the drug for 11-16 weeks 48.6 per cent. were attacked; of 820 who took it for 1-10 weeks 56.5 per cent. were infected.

The following table shows the effect of quinine prophylaxis in the community of Stroppiana:[83]

Year.	Cases of Malaria.	Grams of Quinine Consumed.
1903	87	800
1904	57	2500
1905	44	4025
1906	26	5832
1907	11	4500

The Society for the Study of Malaria in Italy, beginning prophylactic experiments on a small scale in limited areas, have extended their practical efforts until the results are felt throughout the entire country.

Quinine has been the chief reliance of this organization.

The following figures give the malarial mortality in Italy from 1900 to 1907:

Year.	Deaths.	Year.	Deaths.
1900	15,865	1904	8,463
1901	13,558	1905	7,845
1902	9,908	1906	4,871
1903	8,517	1907	4,160

Malarial admissions to the hospital of Marcianise:

Year.	Cases.	Year.	Cases.
1900	601	1904	138
1901	410	1905	124
1902	227	1906	112
1903	126	1907	47

The distribution of quinine by the Italian Government has had a decided effect upon the prevalence of malaria, as evidenced by the following:

Year.	Number of persons.	Morbidity.
1902	3,055	7.7
1903	19,021	5.6
1904	52,690	8.0
1905	59,340	5.8
1906	110,804	6.4
1907	100,816	4.1

The decrease of malaria at Pontepossero and Uniti, the result of a "mixed" prophylaxis, screening and quinine, is remarkable:

Year.	Per Cent. of Population Attacked by Fever.
Before 1902	60.8
1902	55.0
1903	40.0
1904	30.0
1905	16.0
1906	9.8
1907	2.0

Notwithstanding the favorable experiences recorded, there are disadvantages in the employment of quinine as a prophylactic. The obstacles are much greater in its use as a public measure than private.

One objection, varying considerably with individuals, is cinchonism, which may even amount to very unpleasant nervous or gastric disturbance.

To be efficient as a preventive of malaria quinine must be taken in sufficient dose during the entire malarial season. It is difficult to make ignorant people realize the importance of taking treatment during several months to prevent, maybe, merely a chill, and few governments have the authority to force them to do so. No permanent results are to be obtained

in this way unless all take the drug throughout the malarial season and all cases of malaria are radically cured.

The expense of public prophylaxis with quinine on a large scale is enormous; in fact, in some instances prohibitory. Money spent for quinine to be given in inadequate doses at irregular intervals is wasted.

The size of the dose and the interval at which the prophylactic is administered are of the utmost importance. Very varying quantities have been employed at different intervals, but the established methods have about settled down to those described below:

The method canonized by Koch consists in giving 1 gram of quinine every sixth and seventh day, seventh and eighth, eighth and ninth, or ninth and tenth day, according to the danger of infection. This manifestly leaves several intervening days in which there is no quinine in the circulation. In localities, therefore, in which estivo-autumnal malaria is prevalent, the shorter interval of administration should be preferred on account of the shorter period of incubation of this form of malaria.

This method has proved very valuable in many hands.

Ziemann[48] describes his method of "universal prophylaxis" as follows:

1. One gram of quinine is given every four days, three days intervening. The drug is given in solution with 5 drops of hydrochloric acid. If cinchonism is marked, 1 gram of potassium bromide is given.

2. If 1 gram of quinine is not well borne, 1 gram of euquinine is given.

3. If this produces too decided cinchonism, ½ gram of quinine is given as above.

4. If ½ gram of quinine cannot be taken, ½ gram of euquinine is administered.

The drug is given early in the morning or one and a half to two hours after a meal. The rule is to give a dose on the first of each month and thereafter on each day of the month divisible by four.

By this method it is believed that quinine is constantly in the blood current, and that this result is accomplished with a

minimum amount of the specific necessary for efficient prophylaxis.

The method of Plehn,[171] ½ gram of quinine every fifth evening, has already borne the test of experience.

The administration of small doses of quinine daily is the oldest method of giving quinine prophylactically. From 1½ to 6 grains have been given daily. It is probable that the smaller amount is almost entirely a waste, though in Italy 40 centigrams daily is the universally adopted dose and accomplishes good results. It is very doubtful, however, whether such doses would prevent relapses in those already infected.

Nocht's method is to give 0.2 gram of quinine five times daily. Though said to be efficient, this method is entirely too tedious to become popular.

Doses varying from 0.25 to 0.50 gram given every other day or every three days have been recommended with favorable experience.

A method of giving quinine for the prevention of malaria should be chosen by experience in the region. The Koch method, every sixth and seventh day, has been satisfactory in the writer's hands.

The best form in which to employ quinine in prophylaxis and the size of the dose for children do not differ from those in the treatment, and will be considered in that section.

The use of "bitters," a solution of quinine in whisky, is not to be recommended. Such a mixture usually contains too little quinine to be of benefit, and the use of whisky in the hot season, especially when followed by exposure to the sun, is to be condemned.

Prophylactic quinine should be continued for two or three months after leaving a possible source of infection, even if the disease has not been contracted, and, in the latter event, for yet a longer period.

The Italian Government has undertaken the sale of quinine at a low price and its free distribution.

The law of December 23, 1900, authorized the Minister of Finance to sell publicly the hydrochlorate and the sulphate of quinine through the pharmacies, tobacco offices, etc. These

preparations are sold in the form of tablets of 20 centigrams, and the price of a tube containing ten tablets is, for the hydrochlorate, 40 centimes, and, for the sulphate, 32 centimes.

The law of November 2, 1901, prescribes that laborers are to be furnished gratuitously with quinine. The law considers malaria as a disease from which the landlord should protect the laborer, and the quinine is furnished by or charged to the landlord. If the laborer dies of pernicious malaria and it is evident that death was due to a lack of quinine, the family of the laborer is entitled to indemnity from the landlord. Government employes in malarial localities receive free quinine from the Government.

Combinations in pill form of quinine, iron, and arsenic, known as antimalarial pills, are valuable as tonics and are mildly prophylactic. They do not, however, contain sufficient quinine to be reliable prophylactics, at least in this region. Such pills, Grassi's esanophele pills, were tried in comparison with the sulphate and hydrochlorate of quinine by the Italian Antimalaria Society and found to be less efficient.[147]

Arsenic, so long vaunted as an antimalarial, has been thoroughly tried and abandoned.

Narcotine has some prophylactic value, though, as evident from the experience of Duncan,[396] it does not compare with quinine. In 1896, 50 men taking 3 grains of quinine had no cases of malaria; 50 taking 2 grains of narcotine had 3 per cent. of malarial cases, while those taking no drug had 6.5 per cent. of malaria. In 1897, 50 men taking 3 grains of quinine had no malaria, 50 taking 2 grains of narcotine had 6 per cent. of malaria, while those taking no drug had 9.8 per cent. of malaria.

Tea, coffee, and lemons have very slight preventive virtue.

III. MEASURES TO PREVENT THE ACCESS OF MOSQUITOES

Exclusion of Mosquitoes.—The prophylactic value of excluding mosquitoes is in proportion to the number of anophelines and the proximity of infected persons.

A properly protected house should have every door and window screened. In some localities it is advisable to cover

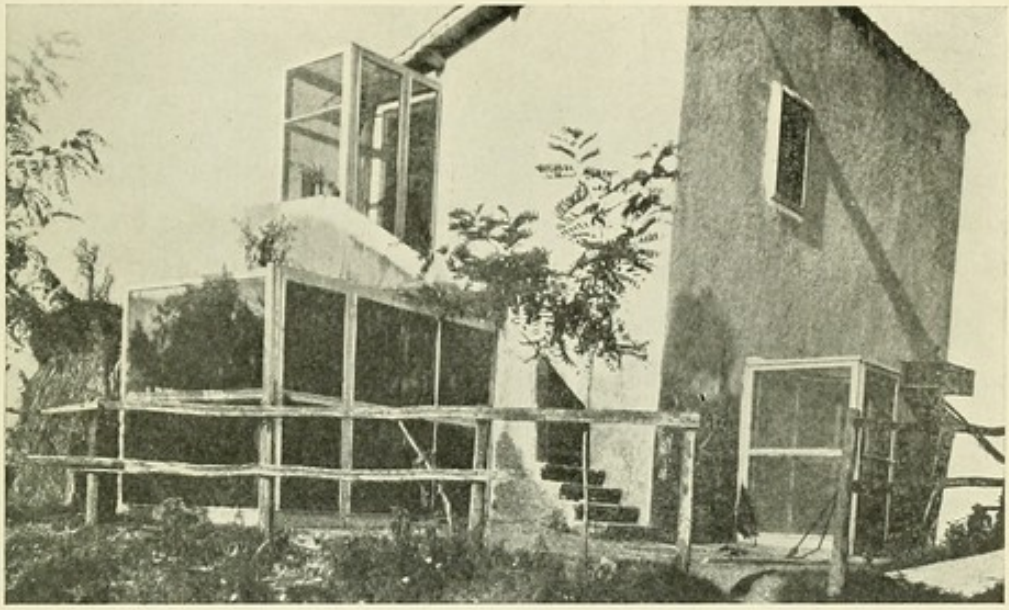


Fig. 95.—The screened vestibule as employed by the Italians (Celli).

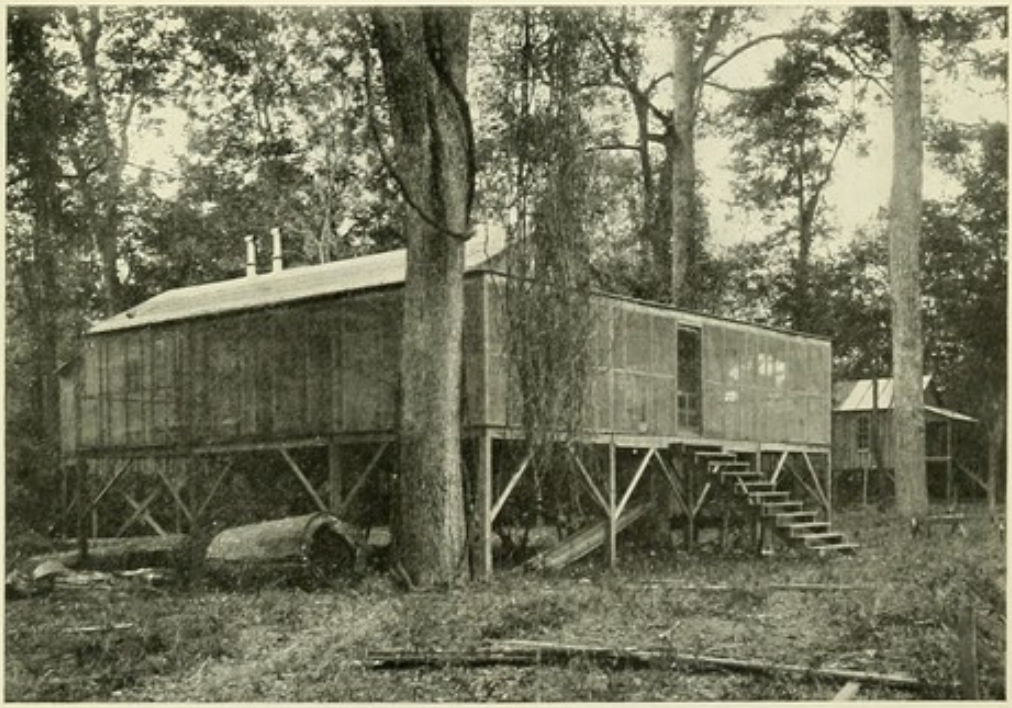


Fig. 96.—A model of house screening.



Fig. 97.—The importance of screens is appreciated by the shanty boatman.

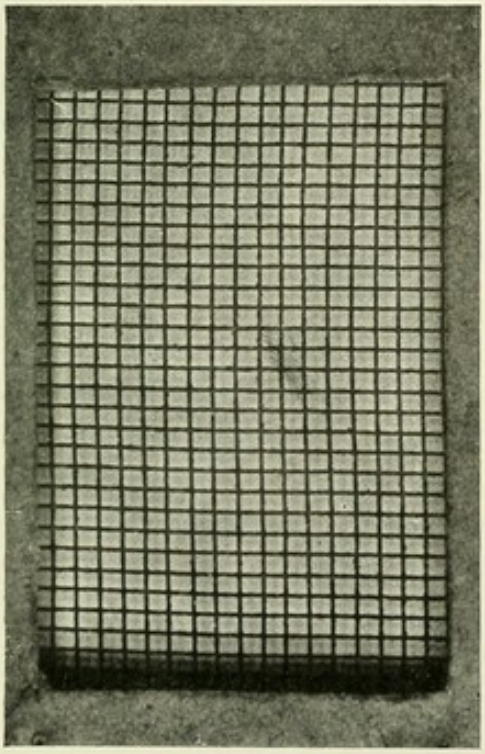


Fig. 98.—Improper size of mosquito netting.

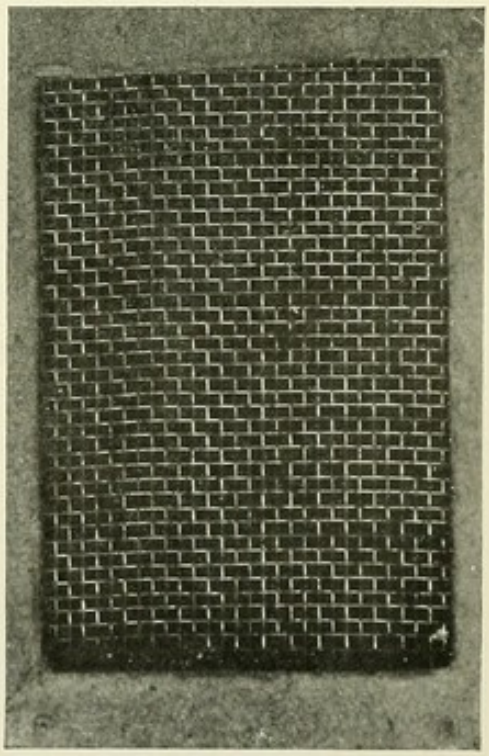


Fig. 99.—Proper size of mosquito netting.

even the chimneys with wire netting. Doors should be provided with springs to necessitate closure. Where mosquitoes are plentiful, and a door is much used, a double door, with an intervening vestibule, after the manner of the Italians (Fig. 95), is to be preferred. A screened porch permits of sitting in the air in the evening when it would be dangerous to do so otherwise.

The selection of the gauze for screens is of the highest importance. The mesh of the wire netting often used, No. 12, is too large, permitting small mosquitoes to pass (Figs. 98 and 99). None should be used with fewer meshes than 18 to the inch. In the absence of wire gauze, cotton mosquito netting may be employed, but, being frail, soon becomes torn and useless.

Persons whose ocupations keep them out at night in highly malarial places, as watchmen and others, should be protected with veils and with leather gloves having gauntlets.

The mosquito bar is indispensable in malarial countries. Besides being very effective when properly adjusted, it is the most inexpensive of all prophylactic methods.

Stephens and Christophers[113] relied personally almost entirely upon the protection afforded by the mosquito bar. They say: "The net should be square (not a bell net); should not have a single, even minute, hole; should hang outside the poles, if these are used; should be tucked *under* the mattress, and should *not* trail on the ground. A piece of closely woven material, fastened on all round at the level of the body, is a necessary addition in order to protect the limbs during sleep from bites *through* the net. When not in use the ends of the net should be twisted up somewhat and then thrown over the top. We always arranged our nets ourselves, never trusting to servants, and, further, to be doubly certain, we always carefully searched the interior with a candle before going to sleep. To these minute precautions solely we attribute our absolute freedom from malaria. Employed without care and attention a mosquito net is of little protection in such malarious places as most up-country African stations."

The Public Health and Marine Hospital Service issues the

following instructions in regard to screening against mosquitoes:[397]

1. The netting used should have meshes fine enough to prevent the passage of mosquitoes (at least 18-20 to the inch).

2. It is important to screen the windows and doors of the house. It is doubly important to screen the beds of fever patients.

3. Mosquitoes can bite through the mosquito nets when any part of the body is in contact with the netting.

4. Frequent examinations should be made to see that there are no torn places in the netting or that no mosquitoes have found a lodging inside.

5. The netting should be well tucked in to keep mosquitoes from entering.

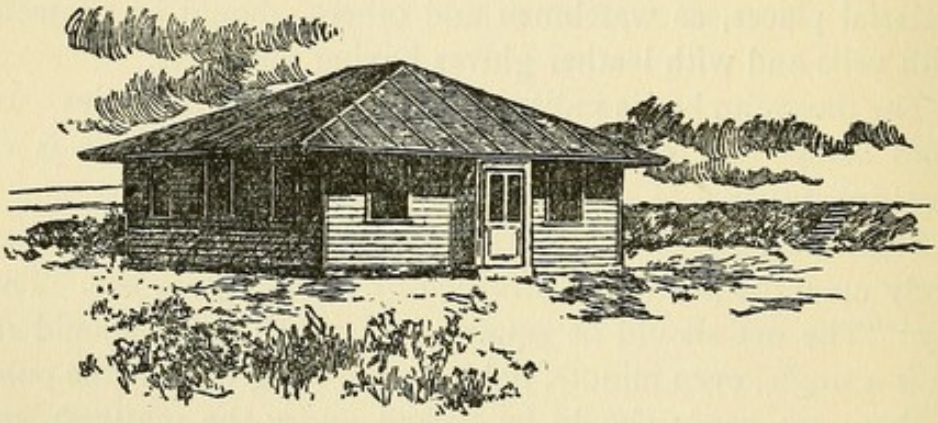


Fig. 100.—British experimental hut near Ostia (Manson).

6. If mosquitoes are found within the netting they should be killed inside, and not merely driven or shaken out.

The results obtained from mechanical prophylaxis have been very satisfactory. The celebrated experiment of Sambon and Low[398] is striking. Under the auspices of the English Colonial Office and the London School of Tropic Medicine these scientists spent the entire malarial season of 1900 near Ostia, in one of the most malarial parts of the Roman Campagna. The hut in which they lived was constructed in London for the purpose, and was thoroughly screened. They drank the same water and worked in the marsh with the natives. They took no quinine, and, in fact, observed no prophylactic precautions excepting to

remain in the house from sunset to sunrise. Though malaria and anopheline mosquitoes were abundant about them, they remained the entire season without becoming infected with malaria.

The following figures show the results obtained by the Italian Society for the Study of Malaria.[147] Of 802 persons incompletely protected 10.9 per cent. had primary infections; of 5,165 protected more or less completely there were 3.3 per cent. of primary infections; while among 4,363 persons completely protected there were only 1.9 per cent. of primary infections. Among unprotected persons in the same regions the proportion varied between 40 to 60 per cent.

The following experiment was conducted by the Japanese military authorities upon the Island of Formosa. A company of 115 men was completely protected against mosquitoes, with the result that not a single case of malaria occurred in the company. The rest of the battalion, numbering 646 men, was unprotected, and 282 cases of malaria, with a mortality of 1.12 per cent., occurred among them.[86]

At the custom-house barracks at Porto-Vecchio there were in 1901 among 23 persons 14 cases of malaria. In 1902, after the installation of metal screens, there was not a single case in the same force.[86]

In one of the most insalubrious localities in Corsica there were in 1904 among 153 individuals 80 cases of malaria. Screens were put up in 1905, and during the year there were only 7 primary cases.

Schoo's[90] results with screening in Holland were favorable. Among 47 inhabitants there were 18 cases of malaria in 1901. Screens were installed March, 1902, and not a single fresh infection occurred. Of 58 unprotected persons there were 8 cases of malaria in 1901, and in 1902 there were 19 cases.

As with every other method for the prevention of malaria, screens have certain shortcomings. It is evident that if malaria is to be eradicated by these means from a locality every house should be screened, otherwise only those in the protected houses would be exempt, and only so long as they remain in such houses. It is out of the question in many malarial places to

consider the screening of all the houses, both on account of the expense and because of the poor construction of many of them, permitting mosquitoes to enter through crevices and other openings. The fact that screens offer a slight hindrance to the free circulation of air in hot countries is of little moment in the face of the benefits derived from their use, and they must be considered as one of the most effective means of private prophylaxis.

Of *local applications to drive away mosquitoes* many substances have been tried, particularly the essential oils, of which the oils of citronella, eucalyptus, and lavender are probably the most efficacious. Petroleum, infusion of quassia, naphthaline, powdered sulphur, camphor, garlic, the oils of cloves, tar, pennyroyal, chrysanthemum, and anise have been employed with varying degrees of success.

The following preparations are highly recommended:

Cedar oil ..... 1 ounce;
Oil of citronella ..... 2 ounces;
Spirits of camphor ..... 2 ounces.—M.
Sig.: Apply a few drops to a cloth and hang upon the bed.[120]

Castor oil, } āā 1 ounce;
Alcohol }
Oil of lavender ..... 1 dram.—M.
Sig.: Apply to the skin.[122]

Quinine-glycerine..... 1 : 1000
Sig.: Apply to the skin.[48]

Ether, } āā 5.0
Alcohol }
Aq. colomensis, } āā 10.0
Ol. eucalyptus }
Tr. pyrethrum ..... 15.0.—M.
Sig.: Dilute with four or five parts of water and apply to the skin.[48]

For the local relief of mosquito bites, touching with water of ammonia or with glycerin are efficient.

In India the *punka* is employed to keep the air in motion, and for this reason is found to be of service in driving away mosquitoes. The electric fan has this effect also, but for obvious reasons should not be employed for this purpose during sleep.

The value of smoke against mosquitoes is well known, though it is not always entirely effective. The writer recalls an occason while on an island off the Gulf coast of Florida where

smoke was of no avail against the terrific onslaught of blood-thirsty mosquitoes, and it became necessary to bury himself up to the neck in the sand and to cover the head with a coat.

Isolation of the malarial patient is as truly indicated as in yellow fever, both diseases being conveyed in the same manner. Mosquitoes must become infected before they can infect man; breaking the vicious circle at this point would extirpate malaria. Isolation is demanded not only for the good of the community, but to prevent reinfection of the patient, who should be confined under a well-adjusted bar until a radical cure is effected. It is not to be expected, however, that as much can be accomplished from the isolation of malaria as from isolation of yellow fever. Many cases of malaria entirely escape medical treatment, and a malarial subject may be a source of infection for a year or more, while yellow fever is infectious for only a few days.

Since it has become evident that so great a proportion of the inhabitants, especially the children of tropic countries, harbor malarial parasites in the blood, segregation of the whites from the natives has been proposed and in some instances practised with success. While the question is of some import in this country, the negro quarters in most of our towns are fairly well defined from those of the white. Upon the premises the householder should see that his servants' quarters are as thoroughly screened as his own. In the choice of camp sites native houses should be avoided beyond the limit of flight of mosquitoes, if possible.

Great good is being accomplished in the prophylaxis of tuberculosis by education, keeping the main facts in the etiology and prevention constantly before the eyes of the people. So much cannot be expected for malaria on account of the ignorance and carelessness of the class and race of people most scourged, but undoubtedly some good may accrue from this method. The Europeans, at home and in their colonies, have obtained some results in the prophylaxis of malaria by teaching the people the elements of the cause and prevention of the disease.

Lectures, illustrated by stereopticon views, are held publicly.

Publications in simple language, in the form of circulars and tracts, and even appropriately illustrated postcards are scattered broadcast. The Italian Society for the Study of Malaria has distributed about two millions of these circulars. The principles of prophylaxis are instilled into the minds of the school children, and made attractive and impressed by means of illustrated charts. The lay press has been used to advantage. With such means the formation of an antimalarial league can do much for a community. A little can be accomplished by education, and this little should not be neglected.

Schools and departments of tropic medicine have done a great deal to disseminate a knowledge of this very important subject, and even more stress should be laid upon this important branch of medical science.

To be thorough, malarial prophylaxis should be handled by the Government. Destruction of the breeding places of the mosquitoes, which is by far the most radical method, is, in many instances, too expensive to be done by individuals. The formation of drainage districts, the expenses of which are paid by those benefited, is an effective plan, and so enhances the value of real estate, from both agricultural and sanitary standpoints, that there should be no opposition. The writer is convinced that these districts, which are being formed in various parts of the South, are decreasing the malaria in a decided degree. It is highly probable that malaria will be exterminated as a natural consequence of the drainage of the soil before the Government or the people are educated to the point of taking prophylactic steps. Governments will spend millions of money in the eradication of malaria from foreign laborers in order to further gigantic commercial enterprises, but make no prophylactic efforts against the malaria undermining the vitality and destroying the lives of citizens. Individuals who should know better permit anopheles mosquitoes to breed at their doors and to have access to their houses, and allow their malaria to go untreated.

The International Congress of Hygiene at its Brussels meeting, September, 1903, recommended to all Governments the adoption of the following measures:[144]

1. All officers, administrators, or employes before entering the service of the country should give proof of a knowledge of the epidemiology of malaria and its practical application.

2. In all countries, places of instruction, depending upon either the Government, missions, or otherwise, are urged to include in the curricula a teaching of the knowledge of the propagation of malaria, and the practical applications which proceed therefrom.

3. Officers, administrators, or employes ignorant of these facts or persistently refusing to apply them are to be considered unfit for service in malarial countries.

The almost miraculous results in the prophylaxis of malaria which may be obtained by a willing and wealthy Government are exemplified in the sanitation of the canal zone previously referred to. The means of accomplishing this end are thus briefly described by Busck:[399]

"In the beginning the land is cleared by the removal of all brush, undergrowth, and grass; only shade and fruit trees are left, and these are thinned out to admit sunlight and free ventilation. Where possible, swamps and lowlands are filled in, the immense excavations at the Culebra cut furnishing abundant material. Then the whole area is drained to carry off the surface water or any constant flow from springs or seepage from the hills. This drainage is extended to all new work in the canal cut and to railroad work or dumps near settlements. The drainage is accomplished by subsoil tile-drains, open ditches, and open concrete or stone and cement ditches. Drain tiling or cement ditches are made where possible, as they require very little care afterward, while the open dirt ditches must be constantly cleaned and regraded to prevent 'pocketing' and the consequent formation of breeding pools for mosquitoes. In open dirt ditches the algæ will form in two or three days after cleaning, and to prevent this drip cans are placed at the head of those ditches with a solution of sulphate of copper, 5 pounds to a barrel of 50 gallons of water. This is also used in all running streams after the removal of algæ.

"Open ditches in which the water flows sluggishly have oil

drip-cans at their heads. The oil cans are raised three feet above the water to give a wide spread to each drop, and are arranged to drop about 20 drops to the minute. The oil used is a rather heavy dark grade, which costs the department $4.34 a barrel. About 3,200 barrels of oil were used within the last year.

"All streams are kept free from algæ and are kept within restricted banks as far as possible; this is done by blowing out the rapids or falls to produce a uniform flow, and the edges are filled in by hand.

"All swamps, pools, or even temporary collections of water are oiled at least weekly, and in the rainy season oftener; this applies to the smallest collection of water, even animal tracks, ruts from wagon wheels, and crab holes. It entails a great amount of work, which is done by colored labor under continual supervision.

"All receptacles holding water must be screened or oiled. Water barrels are screened by covering with a board with a small, screened opening in the center for the inflow. Below this board are two screened holes for the overflow, and the water is drawn from a faucet at the bottom. Buckets and pails in daily use in a household are not permitted to stand filled more than twenty-four hours. All tin cans, bottles, etc., must be buried. No gutters are allowed on houses. There is a daily inspection of all water receptacles, and weekly the inspector at the head of the station must make a personal inspection and report any receptacle found containing mosquito larvæ. The second offense, after a warning, means the arrest and fine of the householder.

"All old machinery, which is found in great quantity all over the zone canal, left from the French occupation, is drained by punching holes in any part that will hold water or, where this is not possible, such places are filled with dirt.

"Even patent car couplings on the trains in use must be inspected and oiled, as they are often found to contain mosquito larvæ.

"When any house or camp is found to contain any number of mosquitoes it is fumigated with sulphur by the dry method.

All cracks or openings are pasted over with paper; enough pots, each containing 5 pounds of sulphur, are placed at intervals on the floors to make about 1 pot for each 1,000 cubic feet of space. After fumigation the house is left closed from three to four hours.

"All barracks, whether for black or white laborers, bachelor quarters, married quarters, offices, churches, lodge-rooms, and other rooms used for sleeping, living, or eating quarters are screened. The Sanitary Department is responsible for all repairs of this screening, and employs a large force of carpenters for this purpose.

"The physicians in each district make a weekly report on the number of cases of malaria in the different camps; these reports are tabulated in the central office of the Sanitary Department and compared with the previous records, and if an increase of even a fraction of 1 per cent. is shown for any locality the local inspector is telephoned and ordered to locate the point of infection and eradicate the breeding places. Long-continued statistics show how nicely this system works. If any more serious increase occurs a special mosquito inspector is sent out from the central office to locate the trouble and report on the best measures to be taken.

"The difficulties of this work are numerous. The constant increase of population requires new sites for camps to be made in the unimproved, brush-covered country; the ever-changing conditions due to the canal work are a continued source of trouble; the progress of each steam-shovel or of each of the extensive dumps produces new problems to be solved in the way of drainage, and, above all, the recurring deluges of the rainy season cause rising creeks and rivers and overflow of lowlands so irregular as to be impossible to foresee.

"The Sanitary Department has, aside from its office force, about thirty sanitary inspectors and employs between 1,200 and 1,300 laborers. The total cost of the Sanitary Inspector's Department is between three and four hundred thousand dollars."

It should be the duty of the authorities of every malarial

country to remove the duty from quinine and to maintain a high standard of purity and a low price.

In military practice permanent quarters should be properly screened, and all breeding pools within the radius of danger should be destroyed. Temporary quarters should be chosen with reference to the breeding of mosquitoes, and the force should, if necessary, be subjected to Koch's quinine prophylaxis. Ships should not anchor too near the shore of malarial localities.

Private prophylaxis consists of measures having reference to the person and to the premises. Personal prophylaxis is synonymous with proper hygiene. Suitable food, water, and clothing are essential. Regular hours must be kept, and constipation, chilling of the body, and excesses of all kinds must be avoided. Prophylactic quinine is not constantly necessary for residents if the premises are in proper condition, but is suitable for strangers and under conditions where mosquitoes cannot be excluded. Persons sleeping upstairs are less liable to infection than those upon the first floor.

Pools are to be filled, drained, or oiled, and vessels emptied. It has been suggested that a tub of water be kept on the place to tempt mosquitoes to breed, and that this be emptied every few days. Stock ponds should be drained, oiled, or stocked with fish. The houses should be thoroughly screened, and where these are not effective, or if infection occurs, bars must be employed.

PROPHYLAXIS OF HEMOGLOBINURIC FEVER

A. Plehn has shown that hemoglobinuric fever is preventable to a greater degree even than malaria. In 1897-99 among the officers of Cameroon who used no prophylactic there occurred in 578 months of residence 287 cases of malaria and 31 of blackwater fever, or 1 malaria case for every two months and 1 of blackwater fever for each 18.5 months. Ten per cent. of the blackwater cases terminated fatally. During the same period among those who used prophylaxis there were in 446 months of residence 90 cases of malaria and 6 of hemoglobinuric fever, or 1 case of malaria for each five months

of residence and 1 of hemoglobinuric fever for each seventy-four months, none of which were fatal. Thus, while malaria was reduced by half, the morbidity of blackwater fever was lowered to one-fourth. The lowered mortality of these cases is even still more remarkable; similar results were observed by Moffatt.[263] Even Koch[90] believes that through appropriate quinine prophylaxis not only malaria, but blackwater fever in an overwhelming majority of instances can be exterminated.

The prophylaxis of hemoglobinuric fever consists of the prophylaxis and proper treatment of malaria. There are two chief methods in vogue for the use of quinine as a preventive of hemoglobinuric fever: Plehn's method, ½ gram every fifth evening, and Koch's, 1 gram on two successive days.

The results of A. Plehn, recorded above, were obtained with ½-gram prophylaxis, but Ruge[158] maintains that better consequences follow Koch's method, and gives the following figures: According to the 1903 statistics of Cameroon, there were among those who used quinine regularly 12 cases of blackwater fever, of which 8 employed the Plehn method, 3 first Plehn's, then Koch's, and only 1 Koch's method regularly. Of 35 cases among irregular users 17 employed the ½-gram method and only 3 the 1-gram method. From these figures it is evident that Koch's method is preferable even when not systematically employed.

It is necessary to persist in prophylaxis not only while in the blackwater fever district, but for several months thereafter. As a majority of the first cases occur from the second to the fourth year of residence, it is evident that greater care should be exerted during this period.

CHAPTER IX

TREATMENT

THE use of cinchona, whose discovery, made by an uncivilized people, was one of the most valuable in the history of medicine, was at first bitterly opposed by the medical profession. Sydenham, Morton, and Torti had in a measure removed the prejudice against the drug when the work of Johnson,[16] the most pernicious medical book of the nineteenth century, appeared and largely undid their teaching. After much suffering and waste of life quinine has come to be regarded as almost specific for malaria.

The word "almost" is used intentionally, for, while quinine is more nearly specific than any other known drug, it has limitations. While the clinical manifestations of malaria usually subside readily after quinine, a radical cure is sometimes difficult. A few grains a day will relieve many cases, though a dram a day will not save some patients. A few of the sequelæ of malaria are but little, if at all, influenced by quinine.

Among the alkaloids of cinchona bark quinine is the one now generally used. The following table shows the alkaloidal strength of the various salts of quinine, as well as their solubility:

Salt.	Per Cent. of Alkaloid.	Solubility in Parts of Water.
Quinine, anhydrous	100	1,750
Quinine acetate	84	Slightly
Quinine bimuriate (or acid hydrochloride)	71	Less than its weight
Quinine bisulphate	59	8.5
Quinine citrate	67	820
Quinine hydrobromide	76	40
Quinine lactate	78	10
Quinine hydrochloride	81	18
Quinine salicylate	68	77
Quinine sulphate	74	720
Quinine tannate, about	30	800
Quinine valerianate	76	53
Euquinine	81	12,500

The duration of malaria under quinine treatment has been considered. Acute infections are usually more amenable than chronic, though it has been repeatedly observed that it requires less quinine to control the paroxysms after the lapse of four or five than when the specific is given early in the attack.

Absorption and Elimination of Quinine.—Most of the salts are readily absorbed from the stomach. It has been shown, however, that the tannate is more largely absorbed from the small intestine.

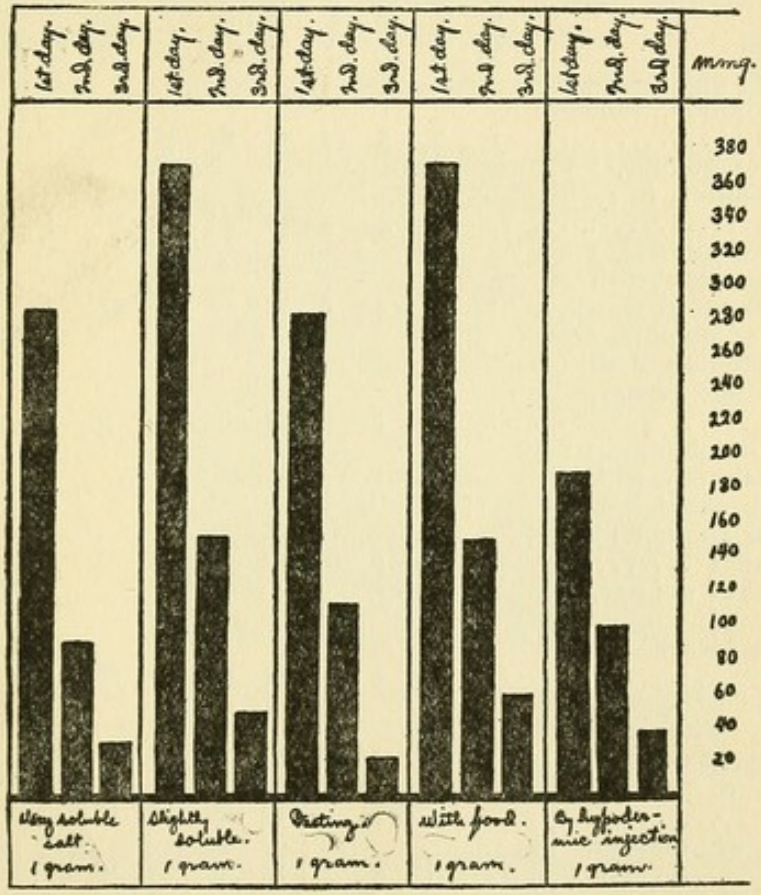


Fig. 101.—Average results of the quantitative determination of the excretion of quinine in the urine (after Mariani).

The rapidity of absorption varies with the different salts, and is estimated by the length of time required to appear in the urine. The time from the administration of the drug until it begins to appear in the urine is represented as follows:

Hydrochloride	15 minutes
Bisulphate	30 minutes
Sulphate	45 minutes
Acetate	30 minutes
Citrate	30 minutes
Tannate	3 hours

The method of administration of quinine also influences the rapidity with which it is absorbed.

Given by the mouth, a highly soluble salt will begin to appear in the urine within fifteen to thirty minutes, and is eliminated in the greatest quantity within three to twelve hours.

Mariani[84] thus tabulates the results of his experiments:

Form and mode of administration.	Contents of each individual portion of urine. Date of successive emissions of urine.											
	15 minutes.	30 minutes.	45 minutes.	1 hour.	3 hours.	6 hours.	12 hours.	24 hours (night urine).	36 hours.	48 hours (night urine).	60 hours.	72 hours.
Muriate of quinine, 25 per cent. solution, subcutaneously	1	3	5	12	24	18	25	7	1			
Muriate of quinine, 1 per cent. solution, in spring water	..	1	4	5	12	24	20	16	5	2	1	
Muriate of quinine, 1 per cent. solution with 200 cc. carbonated water	1	4	4	8	15	19	30	12	2	1		
Muriate of quinine, 1 per cent. solution with 150 cc. spring water, by rectum	..	1	4	9	16	16	14	9	2			
Muriate of quinine, 1 per cent. solution with 150 cc. carbonated water, in an hour another 150 cc., by rectum	1	5	5	10	19	28	15	5	4			
Bisulphate of quinine, with sugar of milk and sodium bicarbonate, by mouth	..	1	2	6	14	26	19	16	6	2		
Carbonate of quinine, by mouth, with 200 cc. carbonated water	1	4	4	10	12	22	15	12	10	3		
Sulphate of quinine, by mouth	..	..	5	6	13	25	18	15	8	4	1	
Acetate of quinine, by mouth	..	2	5	6	13	27	16	12	8	3		
Citrate of quinine, by mouth	..	1	4	7	15	29	14	10	7	4	1	
Chinoidin with gum arabic, by mouth	..	..	..	..	..	8	10	38	22	8	5	2
Tannate of quinine	..	..	..	..	1	2	9	28	14	4	2	2
Pulverized bark, suspended in water	..	..	..	..	..	2	3	4	9	6	3	1

With reference to the influence of food in the stomach upon the rate of absorption, Kleine's[400] experiments tend to show that quinine is much more slowly absorbed from a full than from a fasting stomach. The minute researches of Mariani prove, however, that, while the presence of food in the stomach

retards the absorption of quinine during the first six hours after administration, the quantity absorbed during the entire twenty-four hours after administration is greater from a full than from an empty stomach, and is absorbed in greater quantities even during the second and third days. He explains this by the theory that the liver is able to dispose of only a small quantity of the alkaloid when it arrives together with the products of digestion.

Giemsa and Schaumann[300] investigated the subject, with the following results: After the administration of 1 gram of quinine upon an empty stomach the excretion by the urine

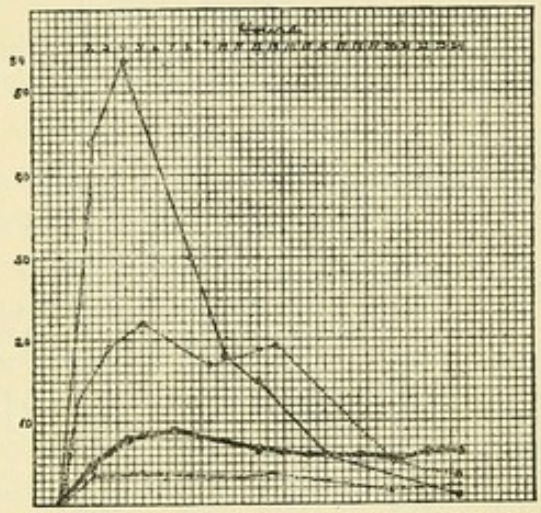


Fig. 102.—Excretion of large doses of quinine (after Kleine).

——— Quinine muriate, 1.0, by mouth, empty stomach.
..... Quinine muriate, 2.0, in enema.
▬▬▬ Quinine muriate, 2.0, by mouth, three hours after eating.
—.—.—.— Quinine muriate, 0.5, subcutaneously.

during the first twenty-four hours reached 23.6 per cent.; the same amount administered during a meal was followed by the excretion of 22.7 per cent. during the first twenty-four hours. The quantity excreted during three days after the administration of 1 gram upon an empty stomach was 38.93 per cent.; during the same period following 1 gram at meal time the quantity excreted was 39.8 per cent.

These investigators found that the elimination of quinine by the urine is about one-sixth greater when administered in five daily doses than in a single dose. The results of their experiments are thus tabulated:

TABLE I

One gram daily of quinine hydrochloride in water, at a single dose, by mouth.

	No. Patient.						
	1.	2.	3.	4.	5.	6.	7.
	Total quantity of urine excreted in per cent.						
First day	18.5	26.0	31.5	8.5	24.4	24.8	26.5
Second day	20.8	28.5	32.4	12,5	29.2	25.5	28.5
Third day	19.0	29.5	33.2	10.0	27.4	25.9	28.0
Fourth day	19.8	29.8	42.2	18.3	27.2	14.4	
Fifth day	19.2	29.6	24.2	18.1	24.2	18.4	
Sixth day	20.4	27.4	29.4	12.2	26.2	14.2	
Seventh day	...	29.9	30.6	12.8	...	24.2	
Eighth day	...	28.4	...	15.4	...	24.9	
Ninth day	...	28.6	...	15.0			
Tenth day	...	29.6					
Average	19.6	28.7	29.3	13.6	26.4	21.5	27.6

Total average, 23.8 per cent.

Remarks.—In patient No. 4 the feces were examined, in which only a trace of quinine could be detected with the thalleo-quinine reaction.

TABLE II

One gram daily of quinine hydrochloride in wafers, .2 gram every two hours.

	No. Patient.							
	1.	2.	3.	4.	5.	6.	7.	8.
	Total quantity of urine excreted in per cent.							
First day	16.8	14.3	14.4	18.8	14.9	16.6	18.9	16.0
Second day	28.9	31.8	26.9	32.0	26.1	30.1	34.5	
Third day	29.2	29.7	26.8	32.1	24.1	30.4	35.4	
Fourth day	29.4	33.8	29.1	29.2	24.1	30.3	35.0	
Fifth day	30.1	33.9	29.2	28.0	28.2	29.2	32.8	29.9
Sixth day	27.3	32.9	...	29.4	27.9	31.4	...	30.2
Seventh day	27.1	29.0	...	29.4	...	29.2	...	30.4
Eighth day	...	29.8	...	29.9	...	28.1	...	29.1
Ninth day	...	33.2	...	...	...	...	...	29.4
Tenth day	...	33.0	...	...	...	...	...	28.6
Average	27.0	30.1	25.2	28.6	24.2	28.1	31.3	27.6

Total average, 27.8 per cent.

Remarks.—In patient No. 8 the urine of second, third, and fourth days were thrown out by mistake. In patient No. 3 the feces were examined: only traces of quinine could be detected by the thalleo-quinine reaction.

While it is a widely prevalent belief that the soluble salts of quinine are much more rapidly and completely absorbed from the stomach than are the insoluble preparations, experiments show that such is not the case.

Mariani[84] records his results as follows:

	Administered on an empty stomach. Per cent.	On a full stomach. Per cent.
Easily soluble quinine salt	36.28	44.45
Hardly soluble quinine salt	45.50	68.43

Giemsa and Schaumann[300] observed that the average percentage excreted within the first twenty-four hours after administration of a soluble salt of quinine was 22.9 per cent., while with an insoluble salt it was 24.33 per cent., and they conclude that the salts of quinine, hardly soluble in water, are *at least* as energetically absorbed from the digestive tract as the soluble ones.

The results of clinical experience with euquinine and the tannate of quinine fully support such a conclusion.

Briquet and Quevenne[401] formerly maintained that the absorption and excretion of quinine proceeded one-sixth more rapidly in females than in males. This conclusion, as yet unconfirmed, should be determined only after a long series of experiments.

Employed hypodermically the rapidity and thoroughness of absorption depends upon the solubility of the salt and the concentration of the solution. The latter is of the utmost importance, since, no matter how soluble the salt, if given in strong solution it will not be absorbed.

In order to determine the effect upon human blood and serum of quinine injections, Giemsa and Schaumann[300] added to 1 cc. of light red human serum 1 cc. of solutions of different strengths of various salts of quinine. Their results were as follows:

Preparation.	Strength of solution.	Contents equivalent to anhydrous quinine (per cent.).	Behavior of the mixture. Immediately.	After twenty-four hours.
Sulphate	1 : 160	.45	Cloudiness.	Precipitation.
Bisulphate	1 : 12	4.92	Marked precipitation.	More decided precipitation, gray colored.
Hydrochloride	1 : 35	2.33	Marked cloudiness.	Increased precipitation, coagulation.
Bimuriate	1 : 2	40.8	Clear coagulum, gray colored.	Cloudy gray coagulum.
Bimuriate with urea.	1 : 2	29.61	Clear coagulum, gray colored.	Cloudy gray coagulum.
Bisulphate	1.69 : 50	2.0	Cloudiness.	Precipitation.
Hydrochloride	1.22 : 50	2.0	Marked cloudiness.	Precipitation.
Bimuriate	1.22 : 50	2.0	Cloudiness.	Precipitation.
Bimuriate with urea	1.69 : 50	2.0	Cloudiness.	Precipitation.

These investigators claim that coagulation and precipitation always follow the injection of concentrated solutions of quinine into the tissues, and that this accounts for the slower absorption.

The rate of excretion after injection of solutions of bimuriate of quinine, 1 gram to 10 cc. of water and 1 gram to 1 cc. of water, is recorded in the following tables, respectively:

	Total daily elimination estimated in per cent. of anhydrous quinine. Number of patient.		
	1	2	3
1 : 10—			
One day	21.0	24.1	19.8
Two days	26.2	24.9	22.0
Three days	...	26.9	
Average	23.6	25.3	20.9
Average of 3 cases, 23.3 per cent.			
1 : 1—			
One day	10.3	12.1	8.3
Two days	16.3	15.1	5.2
Three days	18.2	19.3	2.2
Average	14.9	15.5	5.2
Average of 3 cases, 11.8 per cent.			

Mariani[84] found that after the injection of 1 gram of the bimuriate of quinine dissolved in 10 cc. of water the maximum excretion occurred between the sixth and the twelfth hours, while after the injection of the same quantity of the salt dissolved in 2 cc. of water this period occurred between the ninth and the eighteenth hours.

As compared with the oral administration of quinine the hypodermic method has been ascertained to be followed by the absorption of a smaller proportion of the drug. The proportion is, according to Giemsa and Schaumann,[300] 38.5 : 17.5; according to Mariani, 45.63 : 31.86, and according to Schmitz,[402] 27.7 : 16.1.

On account of the fact that a portion of the quinine injected remains at the site of injection, the period of absorption and elimination extends over a longer period, and the drug has been detected in the urine a week or more after injection.

After intravenous administration quinine has been detected

in the urine in ten minutes. In a small series of observations Mariani[84] found the average daily elimination after intravenous injection as follows:

	Per cent.
First day	20.54
Second day	6.33
Third day	1.07

Injected into the rectum quinine appears in the urine in twenty to twenty-five minutes. On account of the tenesmus which quinine solutions are prone to produce when introduced into the rectum, experiments are not very numerous, but those performed show that the drug, even in a highly soluble form, is much less easily absorbed than when given orally.

Besides with the urine, quinine is excreted with the feces, the milk, the sweat, the tears, pathologic transudates and exudates, the amniotic fluid, and the first urine of the newborn children of cinchonized mothers.

Action of Quinine Upon the Malarial Parasites.—Binz, in 1867, was the first to assume that the effect of quinine in malaria was due to its action as a protoplasmic poison upon the organisms which he believed to be the cause of the disease. This conclusion was reached from a knowledge of the action of quinine upon infusoria.

In 1881 Laveran found that the parasites were killed by the addition of a 1 : 10,000 solution of quinine, and concluded that "it is because it destroys the parasites that quinine causes the disappearance of the manifestations of paludism."

Since the introduction of practical staining methods numerous observations upon the action of quinine on the malarial parasites have been made, of which those of Craig[403] are especially valuable and from which the following is quoted:

"*The Tertian Plasmodium* (*Plasmodium vivax*).—The morphologic changes produced by quinine in the tertian plasmodium, as shown by stained specimen, will first be described.

"In order to study these it is necessary to give the drug in divided doses to single tertian infections, the first dose just before segmentation; specimens of the blood should then be taken and stained at intervals of every three hours for the

next forty-eight hours. Given just before segmentation and repeated at intervals of three hours, the drug acts upon the plasmodia not only while free in the plasma, but also upon every stage of their human life cycle, and it is thus possible to study the morphologic changes produced by quinine in every stage of their development.

"The young 'ring forms' stain very intensely after the administration of quinine, the protoplasm staining a much darker blue than normal, while the chromatin stains a dark crimson. Besides the increase in the intensity of the stain, the only other morphologic change observed is the loss of the unstained area, which, in normal specimens, always surrounds the chromatin.

"In tertian plasmodia a little further advanced in development the staining reactions are the same as in the 'ring forms,' but the increased motility of the parasites is shown in the great number and the 'bizarre' arrangement of the pseudopodia. Fragmentation is observed even before the formation of pigment, some of the plasmodia at this stage being broken up into deeply stained portions, the chromatin lying in one of these portions or free near the periphery of the erythrocyte.

"After the formation of pigment, and especially after the plasmodia are from one-half to three-quarters grown, the evidence of fragmentation and of extrusion of the chromatin from the parasite become more marked. Many of the erythrocytes contained portions of deeply stained protoplasm, the chromatin of the plasmodium lying free at some portion of the red cell. The latter is often situated at the extreme periphery or partly outside of the erythrocyte.

"At this stage numerous extracellular plasmodia are seen, either undergoing fragmentation or hydropic degeneration. Many of the fragments are entirely devoid of pigment, staining a uniform deep blue throughout, while some may be almost filled with pigment granules. The unstained area about the chromatin is always absent, nor is there any indication of an increase in the amount of chromatin which is so noticeable in the normal plasmodia at this stage.

"While at this stage many fragmented plasmodia are usually observed, in some instances no evidence of this process is

seen. The protoplasm stains a uniform dark blue, the pigment being collected, as a rule, about the periphery, while the chromatin stains intensely and may be situated at any portion of the organism, but usually near the periphery. There is no unstained area surrounding the chromatin.

"In many instances the chromatin is situated at the extreme periphery of the plasmodium or may lie partly or wholly outside of it within the erythrocyte, thus proving that quinine possesses the power of causing extrusion of the chromatin, thus rendering the plasmodium sterile.

"Together with the absence of the vesicular portion of the nucleus, as shown by the loss of the unstained area surrounding the chromatin, there is but seldom, even in those organisms which are not undergoing fragmentation, any evidence of increase of the chromatin, and never any evidence of its division.

"When the tertian plasmodium is nearly full grown quinine very often causes fragmentation, many of the fragmentated organisms being free from chromatin, but the characteristic change from the normal at this stage of growth consists in the fact that, although the chromatin may be present and stain very intensely, 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 influenced by quinine and have reached this stage of development, the chromatin has always increased largely in amount and divided into several small clumps, which are scattered throughout the organism. The morphology of the plasmodia at this period of their growth indicates clearly that quinine prevents an increase in the amount of the chromatin, and either hinders division or stops it altogether.

"At this stage the protoplasm of the organism stains deeply, and the pigment is collected about the periphery in blocks or granules, or distributed throughout the protoplasm in the form of fine granules or small clumps.

"The unstained area about the chromatin is always absent. Those plasmodia which sporulate after being exposed to the action of the quinine throughout their entire cycle of develop-

ment present very marked morphologic evidences of the injurious effect of the drug. While sporulation may not be entirely prevented, the majority of the spores are devoid of chromatin and are undoubtedly sterile. The segments are also decreased in number and may be distorted in shape, while in the segments which show the presence of chromatin the latter is in the form of irregular masses, very distinct from the usual form as seen in normal plasmodia. Very often sporulating bodies are observed in which only two or three of the segments possess chromatin; in such segments the protoplasm stains a deep blue and there is no unstained area surrounding the chromatin.

"Associated with the chromatin containing segments are from six to eight, or perhaps more, deeply stained segments containing no chromatin.

"In the segmenting plasmodia the pigment, instead of being collected in a dense, compact mass, as is the rule in the normal tertian plasmodia, is reduced in amount and scattered in small clumps or granules between the segments.

"From the morphologic changes described it is evident that quinine, administered in divided doses, exercises a markedly injurious effect upon every stage in the human life cycle of the tertian plasmodium, either causing the death of the organism at some period of its development or preventing normal sporulation by restraining the division of the chromatin prior to segmentation. The death of the organism is evidenced by fragmentation or the extrusion of the chromatin, while the effect upon sporulation is shown by the limited division of the chromatin and the large number of segments which are devoid of this essential portion of the nucleus.

"If quinine is administered in one large dose, which is not repeated, at any stage of the development of the tertian plasmodium prior to segmentation, the changes produced are the same in kind as those already described, but a comparatively large number escape entirely or are but little injured.

"When quinine is administered just prior to segmentation it does not, as has been maintained by numerous authorities, prevent segmentation, nor do the stained preparations show any distinct morphologic changes in the segmenting bodies.

"The Quartan Plasmodium (Plasmodium malariæ).—The changes produced by quinine in the quartan plasmodium, as shown by stained preparations, are the same as those described for the tertian plasmodium, and I cannot agree with Golgi and Antolisei that upon the adult plasmodium the drug has no effect. 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.

"The Estivo-autumnal Plasmodia (Plasmodium immaculatum).—I have not been able as yet to study the effect of quinine upon the full-grown or segmenting estivo-autumnal plasmodia, but have studied many specimens containing the 'ring forms' and the young pigmented forms. The results of my observations are opposed to those of Marchiafava and Bignami, who claim that no morphologic changes are produced in these plasmodia by the drug, and that the unpigmented parasites do not become pigmented after its administration. I have repeatedly seen pigmented forms of both the tertian and the quotidian estivo-autumnal plasmodia develop after quinine had been administered for as long as three days, while the morphologic changes produced are similar, but not as marked as those observed in the tertian and quartan plasmodia.

"In the 'ring forms,' which are most easily studied, the staining capacity of both the chromatin and the protoplasm is increased, but the unstained area surrounding the chromatin disappears. A large number of the 'ring forms' may appear normal, but careful examination will always show that numerous parasites show the loss of the unstained area and the 'rings' are distorted in shape owing to increased ameboid movement. In a few instances I have observed the separation of the chromatin from the body of the plasmodium, thus showing that extrusion had occurred. I have never observed fragmentation of the 'ring forms.'

"The changes produced in the young pigmented estivo-autumnal plasmodia are similar in every respect to those occur-

ring in the tertian and quartan plasmodia, consisting in fragmentation, loss of the unstained area surrounding the chromatin, and extrusion of the chromatin."

It is well known that the sexual forms of the malarial parasites are very resistant to quinine, persisting in the blood for weeks and months despite the liberal use of quinine.

While young and half-grown tertian and quartan gametes are sometimes destroyed by quinine, those of the estivo-autumnal variety are exceedingly difficult to kill. In fact, it has been maintained that the administration of quinine to patients harboring only the asexual forms favors the development of crescents.

Schaudinn[134] infected anopheles mosquitoes with tertian gametes from the blood of his servant girl, who had been taking a gram of quinine three times weekly for a month.

Gualdi and Martirano[150] arrived at the following conclusions with respect to the effect of quinine upon crescents:

1. Quinine administered in a single dose of 2.50 grams or of 1.00 to 1.50 grams for many consecutive days is not able to cause the disappearance of crescents from the blood.

2. Quinine in doses sufficient to destroy ameboid forms of the parasite not only do not destroy the crescents, but do not inhibit their development within the body of the mosquito.

3. Quinine does not appreciably shorten the period during which crescents remain in the blood after the cessation of fever, the period which represents the contagious term of the disease.

Macrogametes are more resistant to the effects of quinine than are the microgametocytes. This may possibly be due to the thicker protoplasmic body of the former, and explains the difficulty of interrupting the parthenogenetic cycle, the cycle of chronic or latent malaria.

Binz observed that infusoria were stimulated to increased movement by quinine. The same has been noted with the parasites of malaria.

According to Mannaberg,[404] a short time after the administration of quinine medium-sized tertian parasites are often observed in very active, even convulsive, movement, from which it appears that the parasites are at first irritated to

increased movement. Bacelli[131] observed the same in quartan parasites.

Cohen[305] believes this action of quinine to be useful in diagnosis. He states that in cases of doubtful diagnosis the injection of a quantity of the drug not sufficient to insure a definite freedom period will frequently cause the appearance in the peripheral blood of organisms recognizable as normal or atypic forms of the hemameba of malaria, and this has been observed so frequently and in so many diverse conditions that he is inclined to look upon its absence after, say, half a dozen injections, varying from three days to a week apart and in doses increasing from 0.3 to 1 gram, as virtually excluding malarial infection. He is of the opinion that in such cases the organism is resting in some larval form, probably in the spleen or bone-marrow, and that its appearance peripherally is part of a defensive, reproductive reaction to the paratoxic effect of quinine.

That small doses of quinine are able to arouse latent malaria is, in the writer's opinion, unquestionable. This can only be explained satisfactorily by assuming that quinine stimulates the parthenogametes into a compensatory reproduction.

The relation of the time when the quinine is administered to the temperature curve and the behavior of the parasites has been carefully studied by Marchiafava and Bignami,[22] the results of whose observations may be summarized as follows:

1. If the quinine is administered during the crisis of an attack and continued during the apyrexia, which follows in the majority of cases, the next expected attack is inhibited or there is merely a slight elevation of temperature, with a slight sense of discomfort. In a smaller number of cases, even when strong doses of quinine are given during the crisis and the period of apyrexia, the attack is not prevented, but is delayed and abortive.

2. If quinine in the usual dose is administered within the six hours preceding the expected attack it may have no influence at all upon the temperature of the succeeding paroxysm. In other cases there is noticed a slight delay in the attack, which also is less severe than the preceding one, but even in

this case the temperature curve is the typic one of an estival tertian. Subsequent attacks, as a rule, do not occur.

3. If the remedy is administered at the onset of the attack in the majority of cases the attack will come on in the usual way, and may even be grave and prolonged; very often, however, there are some modifications in the curve. A subsequent attack does not usually occur, although there may be frequent irregular elevations of temperature.

4. When the quinine is given during the febrile attack beginning shortly after the onset and continuing throughout the course of the fever in a series of cases the characteristic curve of the tertian is not appreciably modified, while in another series there are various modifications. In a whole series of cases when the quinine has been given in large amount during the attack, there are apt to be no subsequent attacks, or on the following day or days there are only slight elevations of temperature.

5. If quinine is given near the time of the crisis when the blood contains only young non-pigmented parasites, and if its administration is continued for about twelve hours, the parasites continue to be seen in the peripheral blood for nearly twenty-four hours, together with pigmented leukocytes.

6. If quinine is given in the last hours preceding the attack, when the only bodies found in the blood are the pigmented adult parasites, or these predominate, then the parasites go on to their development up to fission, but the new generation, as a rule, does not present itself in the following attack. In other cases, while we do not see the generation of young parasites, we have bodies belonging to the crescent group; it would appear that in this case the parasites, instead of going on to sporulation, take the other road which leads to the formation of crescent forms.

7. When the remedy is given at the beginning of the attack, at the time when in the blood we find fission forms, or those that have already become divided, the action of the remedy is subsequently recognized by the fact that the ameba of the new generation become extremely scarce, and if the quinine be

continued they disappear entirely from the blood within the twenty-four hours.

It is the uniform result of experience that the stage of the parasite most susceptible to the action of quinine is the merozoite, the spore before it has assumed the protection of the red cell. Hence it is desirable to have in the blood as strong a solution of quinine as possible at the time of sporulation, that the young parasites may be born into a toxic medium.

The exact manner in which quinine destroys the parasite of malaria is not certain. Whether it acts as a direct poison to the parasite, or by stimulating phagocytosis, or by increasing the fluorescence of the blood, or by forming indigestible combinations with the blood elements has not been determined.

Golgi's[131] scale of susceptibility of the parasites to quinine, with reference to the variety of the parasite, is, 1, tertian; 2, quartan, and, 3, estivo-autumnal; and, with reference to the stage of the parasite, 1, spores; 2, mature forms before beginning sporulation; 3, endoglobular young forms.

Some Effects of Quinine Upon the Human Organism.—Quinine is one of the few drugs possessed of great therapeutic power which has relatively little toxic property; nevertheless, in exceptional instances, untoward effects result from its use. Reference is not made to the group of symptoms known as cinchonism, ringing in the ears, slight deafness, roaring, the fulness in the head, dizziness, nervousness, a bitter taste, and slight nausea. But manifestations of a more serious nature occasionally arise.

Practitioners are very often told by patients that they cannot take quinine. The writer has made it a rule to disregard such statements and to administer quinine where indicated, disguised if need be, and in only two instances has he had cause for regret.

One case was that of a rather nervous woman in whom 3 grains of the bimuriate of quinine, given orally, produced within half an hour distressing urticaria and nervousness, and alarming dyspnea and depression which lasted for several hours. There was no lesion of the heart or other organs. This

same effect had several times formerly resulted from small doses of quinine.

The other case was that of a woman with a mitral regurgitant murmur, who stated that every time in her life that quinine had been given her she thought she would die of suffocation. Three grains of euquinine in powder were given her, and in a short time she was prostrated, suffering with severe dyspnea and fear of death. These symptoms lasted about an hour.

Gudden[405] observed in several patients as a result of 1 gram of quinine, headache, nausea, vomiting, a sense of burning heat, a chill, and elevation of temperature to 102.2° F., and pulse to 164. The urine contained no albumin.

Plehn[406] records a case of a woman who, a few minutes after taking ½ gram of quinine, was seized with itching of the skin, an erythematous rash upon the neck and breast, a chill, and rise of fever to 102° F. After the intramuscular injection of 1 gram of quinine the temperature became 104° F. The urine was normal and the elevation of temperature lasted only a few hours.

Trousseau and Pidoux[86] report the case of a patient who took at one dose 3 grams of quinine for the cure of asthma, which recurred every day at a certain hour. Four hours later he experienced ringing in the ears, dizziness, and terrific vomiting. Seven hours after taking the drug he was blind and deaf, delirious, and unable to walk on account of vertigo. He was vomiting constantly. These symptoms ceded spontaneously during the middle of the night.

Grenier[407] cites the example of a girl of fifteen years who took a moderate dose of quinine for an attack of fever. A short time later she had nausea, vertigo, deafness, visual disturbances, swelling of the face, dyspnea, profound prostration, general urticaria, edema of the hands and feet, and vomiting. These symptoms disappeared in the course of six hours, but returned each time even a small dose of quinine was given, even though unrecognized.

Large doses of quinine may even prove fatal. Laveran[1] speaks of two soldiers, intending to take sulphate of soda as a purgative, took by mistake 12 grams each of quinine. In

half an hour they were taken with cramping in the stomach, vomiting, facial pallor, dilatation of the pupils, superficial respiration, chilliness; pulse small, irregular, sometimes insensible, and a tendency to syncope. One of the patients recovered, the other died in collapse.

Quill[408] reports the case of a patient who took ½ ounce of the sulphate of quinine. Toxic symptoms appeared within two minutes; these were retching and vomiting, unconsciousness, slow and labored respiration, a barely perceptible pulse, convulsions, affecting chiefly the lower extremities. Death followed soon.

Numerous other cases of quinine poisoning could be cited. The symptoms most frequently recorded are headache, delirium, muscular weakness, staggering gait, dyspnea, collapse, deafness, amaurosis, psychic disturbance, cutaneous eruptions, hemorrhages, and fever.

Fever caused by quinine was recognized as early as 1790 by Hahnemann.[409] He says: "For experiment's sake, I took 60 grains of cinchona bark twice daily for a few consecutive days; my feet and hands became cold, followed by a feeling of malaise, palpitation of the heart, pulse hard and rapid, a feeling of apprehension, then a beating headache, flushing of the cheeks, thirst, and all the usual symptoms of intermittent fever. These symptoms lasted two to three hours each time and returned after each dose. I stopped the bark and I was healthy."

Numerous cases have since been observed. F. Plehn,[5] who had a number of cases, believes that, while it appears more often in tropic than in temperate climates, it may occur in those who have never suffered with malaria, and occurs oftener in old residents than in newcomers. The fever may be preceded by a chill, is accompanied with other evidences of cinchonism, and is sometimes associated with the cutaneous manifestations of quinine.

For the report of a case in this country, with an interesting review of the literature and a bibliography, the reader is referred to the article of Goodman.[409] This writer believes the

explanation of this untoward effect of quinine to be that some chemic changes in the blood act on the heat-dissipating apparatus in persons who have, or have had, malaria.

The condition is as yet too obscure to warrant any conclusions. A careful study of the blood might reveal the pathogenesis. Some cases probably bear an analogy to the condition produced by quinine in certain persons whom Koch designates "blackwater-fever candidates."

Quinine in large doses is undoubtedly somewhat depressing to the heart, as exemplified in some of the cases recited. It may cause syncope, or even collapse and death. In fatal cases the heart is said to be arrested in diastole.

Quinine may cause temporary psychic disturbance, even insanity and delirium. The latter occurs either in an active, noisy form, with loquacity and agitation, or in a quiet form, with stupor and depression.

The chief digestive disorders referable to quinine are nausea, vomiting, anorexia, and gastric and intestinal catarrh. Gastric and intestinal hemorrhages have been attributed to the use of the drug, as well as hemorrhages from the mouth, gums, nose, lungs, skin, and conjunctiva.

The cutaneous eruptions of quinine origin may be caused by small doses. They are most apt to follow the administration of the sulphate. The writer has seen persons in whom the sulphate had always produced annoying urticaria, take the bimuriate with no untoward effect. The pruritus attending some of these eruptions is sometimes agonizing, the patients declaring that the remedy is worse than the disease.

It is said that laborers in the manufacture of quinine often experience pruritus of the hands and forearms, followed by redness and a lichenoid eruption, sometimes with swelling of the face and genitals.

Urticaria is, in the experience of the writer, the most frequent of these manifestations. It may be general or quite local, and is sometimes attended with edema of the face and hands. The writer has seen only one such case in the negro race.

Erythema, scarlatinal or morbilliform in appearance, is some-

times observed. It may be followed by desquamation and prove difficult of diagnosis.

Vesicular eruptions are but rarely seen as the result of quinine administration. Petechiæ are occasionally noted, and Kulz[90] has reported a case of purpura hemorrhagica referable to 1 gram of quinine. The hemorrhages proceeded from the stomach, intestines, mouth, nose, skin, and conjunctiva. The entire skin was covered with petechiæ from the size of a lentil to that of a dollar. Even the pinching between the fingers of a fold of skin resulted in a purpuric spot. Quantities of blood were vomited and purged. The temperature remained normal and the general condition was surprisingly little disturbed. Under rest, opium, diet, and tamponning of the gums the hemorrhages ceased upon the first day. Eight days later the administration of .05 gram of euquinine was followed in three hours by similar symptoms. Afterward an injection of quinine precipitated an attack of hemoglobinuria, which terminated in recovery.

The pathogenesis of these skin lesions is not clearly understood, but it is probable that they are produced by some action of the drug upon the skin in its elimination through the sweat glands.

Considering the fact that quinine is in great part eliminated by the urinary organs, these organs suffer but few untoward effects. The drug has only a slight diuretic action. Albuminuria has been observed following the administration of the drug to malarial subjects, but whether this was due to the drug or to the disease is questionable. Cases of so-called hematuria have been reported as a result, but many of these cases were undoubtedly hemoglobinuria, the result of hemolysis rather than of local irritation.

The rôle of quinine in the production of hemoglobinuria has been considered.

Uterine colic may result from quinine, and the writer has seen several instances of metrorrhagia and menorrhagia.

Inasmuch as abortion not infrequently occurs in the course of malarial fever treated with quinine, this effect is often attributed to the drug. While quinine undoubtedly strengthens

preëxisting uterine contractions, it is extremely doubtful whether it initiates labor pains except in a very limited number of cases. The writer has several times seen patients threatened with miscarriage whose pains were promptly quieted by the immediate administration of quinine, and he believes that abortion in these cases is oftener due to too little quinine than to too much. Pregnant women may take quinine prophylactically for long periods, and if they keep free from malaria they show no tendency to abort.

The effect of quinine upon the eye is sometimes a matter of much concern. Total blindness may result, but fortunately this severe degree does not last long, though some constriction of the visual field may persist permanently. Quinine amblyopia is usually accompanied by other toxic effects, being due ordinarily to large doses of the drug continued for several days. The condition is usually bilateral and attended with photophobia, dilated pupils, diminished pupillary reaction, color blindness, concentric restriction of the visual field, retinal anemia, with vascular constriction and atrophy of the optic nerve. DeSchweinitz found quinine and urea more toxic with reference to the eye than any other preparation he employed. The prognosis is usually good, normal vision being entirely regained in the majority of cases, but the condition may persist for months. The differentiation of this condition from malarial amaurosis has been considered.

Tinnitus and a degree of deafness are common results of quinine. The deafness may be temporarily complete. Congestion of the malleolus, with opacity and retraction of the drum, are the common conditions present.

The action of quinine on the spleen is doubtful. While Catani,[410] Rochfontaine,[410] Herrlich,[409] and Piorry[86] maintain that it causes a contraction, even of the healthy organ, their results could not be confirmed by Valleix and Briquet.[86]

The behavior of the leukocytes under the influence of quinine is disputed. Vincent and Bastianelli[86] observed that the administration of quinine caused an increase in the number of mononuclear leukocytes. Billet[86] noted that within three to five hours after administration there occurred a diminution of the

leukocytes, and in ten or twelve hours a mononuclear increase, even greater than the average for untreated malaria.

Binz maintained that quinine interfered with the movements of the leukocytes and with diapedesis, but Hayem was unable to verify these observations.

Marchiafava and Bignami[162] observed a remarkable development in the phagocyte phenomena after the administration of the salts of quinine, but believed that it was not due to an increase in the phagocyte energy brought about by the drug, but to the greater quantity of necrotic forms, and of free pigment, which is diffused in the blood in consequence of the direct action of the remedy on the parasites, the phagocytes removing the dead forms which render the blood impure. All that these writers could say with certainty was, that the salts of quinine do not hinder the phagocyte activity of the white blood corpuscles, nor is their mobility modified.

Disselhorst and others[233] proved by experiments upon frogs that the motility and the phagocyte function of the leukocytes is unimpaired by quinine. Mannaberg[404] considered that the phagocytes in the internal organs have their functions rather weakened than stimulated by quinine.

Contra-indications to the Use of Quinine.—The mere statement of the patient that he is unable to take quinine should constitute no bar to the use of the specific. The history of the invariable sequence of very severe skin manifestations should perhaps lead the physician to employ one of the substitutes for quinine.

Cardiac depression and dyspnea are a decided contra-indication to the administration of the drug.

The treatment of malaria complicating pregnancy is essentially the same as under other conditions. A fear, probably more fancied than real, of the oxytocic properties of quinine is widely prevalent, but of the dilemma, malaria or quinine, the latter is certainly the shorter horn. The pregnant patient runs far less risk of abortion with rational quinine treatment than without. Malaria during pregnancy is notoriously stubborn, and, while the attack should be treated with the smallest doses necessary to effect a prompt cure, systematic and prolonged

quinine prophylaxis is necessary to prevent recurrences. If labor pains have begun opium should be administered with the quinine.

The history of hemoglobinuric fever is no contra-indication to the use of quinine. While the administration of the drug is sometimes the occasion of an outbreak of blackwater fever, the latter is generally due to too little quinine rather than to too much. Nor is it advisable to restrict the size of the dose unnecessarily through fear of an attack, since it has been shown that the amount of quinine is of little importance in the etiology, very small quantities being as prone to occasion the attack as moderate amounts.

Choice of Preparation.—This is influenced by the age of the patient, the mode of administration, the severity of the attack, and other factors.

The sulphate, on account of its cheapness and ease with which it is obtained, is widely employed. The writer, however, now rarely employs it, and then only in suspension in syrup of yerba santa for children. It is probable that it gives rise to more gastro-intestinal and nervous disturbances than any other salt of quinine, and it is these manifestations produced, as a rule, by this salt which cause so many persons to say to the physician that they cannot take quinine.

The bisulphate, the hydrobromide or bromide, and the hydrochloride are useful preparations, being easily dissolved and readily absorbed.

The bimuriate, or acid hydrochloride, or bihydrochlorate is the most valuable salt of quinine. Its great solubility adapts it for solution to be given by mouth, by rectum, intramuscularly, or intravenously.

Euquinine, or quinine ethyl carbonate, has been thoroughly tried and has given satisfactory results in the writer's hands. Being practically tasteless, it is easily administered, either in powder or suspended in a neutral syrup, to children. An acid with the drug or immediately following develops a bitter taste. The objections to the preparation are its expense and the fact that it is patented.

The tannate of quinine, on account of its small proportion of

alkaloid and slight solubility, has been until recently only rarely employed in the therapy of malaria. The Italian Government, in an effort to supply a tasteless salt of quinine for children, has been dispensing tannate of quinine in the form of chocolate confections. A commission of members of the Superior Council of Health, appointed to investigate the results obtained by this method of administration, reported adversely. They concluded that the tannate of quinine is one of the most insoluble preparations of quinine, and that it is weakly and slowly acted upon by the digestive fluids; that the fat of the cocoa retards the action of the digestive fluids upon the quinine and causes it to deteriorate under the influence of the air. This report was the occasion of a unanimous remonstrance by numerous physicians who obtained excellent results from the use of the tannate.

The experience of the writer with this salt, together with the reports of the Italian physicians, leads to the following conclusions:

1. The tannate of quinine is almost completely absorbed from the alimentary tract.

2. It is more slowly absorbed and more slowly eliminated than the other salts of quinine, and remains in the system longer.

3. A small quantity only of the salt is acted upon by the gastric juice, but is largely absorbed from the bowel after contact with the bile and pancreatic juice.

4. It is not absorbed when injected into the rectum.

5. It is better tolerated by the stomach, intestines, and nervous system than the sulphate.

6. The clinical results with the tannate of quinine are entirely satisfactory.

7. Being nearly tasteless, it is especially adapted to the treatment of malaria in children.

8. It has a good effect upon diarrhea and dysentery complicating malaria.

9. It is several times less expensive than any other tasteless preparation of quinine.

Methods of Administration of Quinine.—*Administration*

by the Mouth.—In simple cases of malaria, administration of quinine by the mouth is the rule; by other methods the exception. It is probable that ninety-nine-one-hundredths of the quinine consumed is given by the oral route.

There are those, not objecting to the taste of quinine, who will take it in the powdered form; in fact, it is a common method among the Southern negroes to lick it from the palm of the hand. The taste is, however, so repulsive to most persons that, with the exception of the tannate and euquinine, it must be given in some other form.

The same objection applies to giving the drug in solution, though this is unquestionably the most reliable form in which to give it by the mouth, but for obvious reasons it cannot be so extensively employed in this manner in private practice. The solution is more quickly and completely absorbed. The bimuriate and the bisulphate are the salts most suitable for solution, but if neither of these is at hand the sulphate may be employed by adding a drop of dilute hydrochloric or sulphuric acid for each grain of the quinine.

The most efficient vehicle for disguising the taste of the sulphate of quinine is the syrup of yerba santa. Two grains of quinine to the dram of the syrup is the suitable proportion. Syrup of chocolate, fluidextract of licorice, ginger, coffee, milk, honey, olive oil, and other media have been recommended, but are far from satisfactory. Acid fruit juices and syrups usually enhance the bitter taste.

Where prejudice against quinine makes it necessary to disguise the appearance of the drug, this may be accomplished effectively by adding a small quantity of charcoal, turmeric, or methylene-blue to the bimuriate, bisulphate, or other salt.

Pills and tablets are convenient to administer and not unpleasant to take, but cannot be relied upon. The coating often becomes so hard as to make solution difficult or impossible. The writer has several times seen quinine given in this form pass from the bowel wholly unaffected. Pills and tablets should not be given when capsules can be obtained. Capsules, when fresh, are easily dissolved. If there is any doubt as to their quality they may be punctured several times in each

end with a pin, or may be followed by a few drops of a dilute mineral acid.

In the absence of capsules quinine has been rolled in a little ball with cigarette paper. Absorption is extremely slow and uncertain, and this method should not be resorted to.

The tannate of quinine has been compounded with the chocolate confection for administration to children, and in this form, if reliably made, is readily taken, and in sufficient dose is efficient.

Hypodermic Method.—Quinine was used hypodermically at least as early as 1863, when Bourdon[289] employed the sulphate dissolved in water with tartaric acid. The same year Moore[411] recommended the use of 30 grains of the sulphate of quinine dissolved in ½ ounce of water by means of 8 or 10 drops of dilute sulphuric acid, from 1 to 1½ drams of this solution to be used at a dose. Bad results were common. Arnould,[412] in 1867, reported in 95 cases thus injected 2 indurated nodes, 4 eschars, and 15 abscesses. In 1888 Beurmann and Villejean[412] introduced for hypodermic use the bimuriate in the following formula, which is still widely employed:

Quinine bimuriate	5 gm.;
Distilled water to	10 cc.

Kobner[86] recommends:

Quinine hydrochlorate	.5-1 gm.;
Glycerine, Distilled water	āā 2 gm.

Grimmaux:[86]

Quinine hydrochlorico-sulphate	5 gm.;
Aqua dest.	6 cc.

Klein:[96]

Quinine hydrobromate	2 gm.;
Sulphuric ether	12 cc.;
Alcohol	q. s. 20 cc.

Triulzi[86] added antipyrine to promote solution and diminish pain:

Quinine muriate	3 gm.;
Antipyrine	2 gm.;
Aqua	6 cc.

Vincent and Burot:[96]

Quinine muriate	3 gm.;
Analgesin	2 gm.;
Aqua	6 cc.

Gaglio:[86]

Quinine hydrochlorate	3 gm.;
Urethane	3 gm.;
Aqua	5 cc.

The addition of cocaine has been recommended also to lessen the pain.

The most suitable salt of quinine for injection is unquestionably the bimuriate. The tablets of bimuriate of quinine and urea are convenient and insure accurate dosage. The 3-grain tablets contain approximately 2½ grains of the quinine salt.

The advantages of giving quinine by the needle in pernicious malaria are obviously being able to administer it to patients unable to swallow or to retain it, and the certainty and promptness of absorption. Nevertheless, these great benefits are somewhat discounted by the bad results which sometimes appear. Formerly tetanus was to be feared. Bartholow[413] mentions several such cases reported from New Orleans and 2 occurring in one regiment of the British Indian Army. Vincent,[414] in a late report, recalls the numerous cases following the subcutaneous use of quinine. McCampbell[415] speaks of a fatal case of tetanus shortly following a hypodermic injection of the hydrochlorate of quinine, though the experiments of this writer fail to corroborate those of Vincent to the effect that the injection of quinine favors the development of the tetanus bacillus. In the late French campaign in Madagascar 6 cases of tetanus subsequent to hypodermics of quinine came under observation. But there are other consequences which, while not so deadly, are more commonly met. Nodules, necrosis, sloughing, and abscess formation are referred to. Plehn[171] and Blümchen[416] have frequently seen necroses and abscesses result from hypodermics of quinine. Thayer[98] says there is always danger of subsequent abscess or necrosis. Laveran[1] states that injections made into the skin often give rise to

eschars. Manson[417] has often seen induration, if not abscess, follow the hypodermic injection of quinine conducted in the ordinary way. Bonnette,[412] Mauviez[412] and LeDantec[226] say that, in spite of the greatest aseptic precautions, eschars and abscesses will sometimes result. Craig[418] has observed abscesses in about 20 per cent. of the cases, and often had nodular elevations at the seat of puncture which persisted for some time. Gros,[419] Shoemaker,[420] and Tyson[421] have abandoned the method on account of the frequency of inflammation and abscess formation.

These results, however, should not prevent the use of quinine injections in the treatment of pernicious malaria, as such effects are, in a great measure, preventable. To this end there are three measures of importance: First, asepsis; second, dilute solutions, and, third, deep injections.

The first is at the present day probably the least often neglected, as most physicians realize the importance of sterilization, and a spoonful of water and a few matches are sufficient to effect it on the part of the solution and needle, and soap and water are almost omnipresent.

The necessity of employing a dilute solution has been all but ignored. Nearly all writers on the subject lay great stress on the need of asepsis, but with few exceptions even mention the evils of too concentrated solutions. Strong solutions of quinine injected into the tissues cause a wall of necrosis around the solution, preventing absorption and paralyzing phagocytosis, resulting, even if the solution is sterile, in nodes or ugly chemic sloughs. It is in all probability this chemic irritation of the cells which allows of bacterial infection following the injections of solutions not properly sterilized, and, no matter how sterile the solution, if too concentrated, a nodule or chemic slough is apt to result. Witness the frequency with which unsterilized solutions of morphine and other drugs are given without the slightest bad consequence.

For injection purposes the following formula is most suitable:

Quinine bimuriate	1 gm. (gr. xv);
Water	10 cc. (dr. iiss).

As much of this as needed may be injected in one or several locations.

The solutions should not be injected hypodermically, but intramuscularly, since in the latter location the injection is more certainly absorbed, is less apt to cause induration and abscess, and is less painful. In some cases of pernicious malaria the superficial circulation is very poor, absorption correspondingly inadequate, and necrosis almost inevitable if the quinine is not deeply injected. In a case of algid malaria in my practice where the quinine was given hypodermically the site of injection began to turn blue within ten minutes and was almost black within two hours.

The initial dose should ordinarily be 15 grains. Afterward from 5 to 10 grains should be injected every six or eight hours as long as the symptoms demand it. For children under five years the first dose may be 1½ grains for each year of age. The statement of Homem,[157] that in the administration of quinine in pernicious malaria it is best rather to sin by prodigality than by parsimony, is open to question. While there are few drugs so potent as quinine having so few toxic effects, bad results do sometimes follow excessive doses. Schellong[92] noticed that large doses added to the insult to the nervous system and had a depressing effect on the heart. As Plehn[5] expresses it, there is a universal tendency to attribute all bad phenomena to the disease and all favorable ones to the remedy. However, after using in 5 cases 5 to 6 grams in divided doses, repeated at short intervals during the height of fever, this accurate observer noted considerable depression of the heart, nervous system, and general condition of the patients.

Most of the continental writers recommend the Pravaz or Luer syringes, with platin-iridium needles, but the ordinary antitoxin syringe, as used by Sutherland[168] for this purpose, answers as well. A soft-rubber tubing connection between the needle and the nipple of the syringe is advantageous, as it may prevent the breaking of a needle in a struggling patient. One of these syringes, a small sterilizing pan, and alcohol lamp do not occupy much space, and, being almost indispensable in these cases, should be easily accessible during the malarial season to

the physician in a malarial locality, who often sees these cases miles from his office, when time is a matter of life and death. The ordinary hypodermic syringe may be used in an emergency, but to use a sufficient quantity of a properly diluted solution a number of injections have to be made.

The best location for injection is in the gluteal region well above the ischial tuberosities, though the interscapular region is often chosen.

The technic of intramuscular injections of quinine may be summarized in these precautions: Have the solution freshly made, thorough, dilute, and sterile; render the syringe and the injection site aseptic; insert the needle into muscular tissue, and avoid breaking the needle.

Intravenous Method.—In 1890 Bacelli[422] introduced the intravenous administration of quinine in the treatment of pernicious malaria, claiming thereby to have reduced the mortality from 17 to 6 per cent. The following formula was used:

Quinine hydrochlorate	1.00 gm.;
Sodium chloride	.75 gm.;
Distilled water	10.00 cc.

The arm is bound above the elbow in order to distend the veins of the forearm, into one of which the needle is introduced in the direction of the blood current, and the solution injected very slowly after removing the constriction. The puncture should be covered with a sterile dressing. The solution should be warm and sterile, and care should be taken that no air is injected. If swelling occurs at site of the injection it is evident that the vein has not been entered. It is said that 1 gram of quinine thus injected produces a solution in the blood of 1 : 5,000, which is the strength deemed necessary by Binz to destroy protozoa. Rogers[44] thinks well of this method, and has abandoned in favor of it the subcutaneous route. However, it probably has no advantages over the intramuscular administration. Moreover, it is not infrequently almost impossible to locate the veins, especially in young negroes.

Hypodermoclysis.—Quinine dissolved in normal salt solution given by hypodermoclysis has been recommended by Grall[256]

and others. From 10 to 30 grains of the bimuriate are dissolved in a pint of normal salt solution, and as much as desired is injected into the loose subcutaneous tissue. It is extolled especially by Glatard[86] in the treatment of children suffering with pernicious malaria. This method is probably not adapted to the treatment of algid malaria on account of the deficient superficial circulation. Besides, the necessary apparatus is frequently wanting.

Gutierrez[423] had success with injections of quinine directly into the spleen, but such a dangerous procedure is entirely unjustifiable. Fleury,[424] acting upon the theory that the nearer the spleen the quinine is injected the better the result, injected deeply into the structures below the ribs in the midaxillary line upon the left side. His results do not appear to have excelled those following injections in other sites.

Jousset[159] treated pernicious malaria with injections of quinine into the trachea by inserting the needle immediately below the cricoid cartilage and injecting a 10 per cent. solution drop by drop.

Le Dantec[226] suggests that in cases of tetanic pernicious malaria the subarachnoid injections of quinine, after the method of Jaboulay, might prove efficacious. So far as known, this method has not been tried in this condition.

Rectal Administration.—This method, though uncertain, is of value where quinine cannot be retained by the stomach, and there are objections to the intramuscular injection, especially in children. It may also be used as an adjuvant to the intramuscular or intravenous injection in pernicious cases. A soluble salt should be used, preferably the bimuriate. The water should be about the temperature of the body, and should not exceed a few ounces in quantity. Two or three times as much quinine should be given by the rectum as by the mouth, and the injection should be made high into the bowel. Ten or 15 drops of tincture of opium should be added to prevent tenesmus and aid retention. Antipyrine has been recommended by some, but should be used with care where there is depression. A cleansing injection should be given first if the patient is conscious.

The writer has had no experience with quinine given in rectal suppositories, but these are highly recommended by Shoemaker.[420] Five or 10 grains should be contained in each suppository, in which may also be included a small quantity of the extract of belladonna to facilitate retention.

Epidermic Administration.—The use of quinine mixed with fats and oils and rubbed into the skin is not to be relied upon, since little, if any, quinine is absorbed by the skin.

Time of Administration and Dose.—With reference to the time when the drug is given, there are three chief modes of giving quinine:

(1) The method of Torti, a single dose before the paroxysm; (2) the method of Sydenham, a single dose in the decline of the paroxysm, and (3) the method of fractional doses.

The first two methods are adapted only to the benign infections.

The efficacy of the *method of Torti* rests upon the fact that the parasites are most susceptible to the action of quinine immediately after sporulation, while free, before having entered the red cells. It presupposes an accurate knowledge of the hour at which the next paroxysm will occur, based obviously upon a definite history of repeated paroxysms, a temperature chart, or blood examinations sufficiently accurate to determine not only the type of the organism, but its exact stage. It is evident that in private practice, in the patient seen in the first access, the prediction of the next paroxysm must usually depend upon the results of the examination of the blood, and that this must be repeated if the stage is not recognized at the first examination. Unless this can be done quinine should not be administered in this way, for, even if the type of malaria present is known, there are two conditions which may render the single dose futile: first, anticipation of the paroxysm; second, a multiple infection. Even where the blood is carefully examined, it may happen, in double infections, that only one group can be detected in the peripheral blood.

By this method, also known as the *Roman method,* the quinine is given in a single dose of about 15 grains from four to six hours before the next succeeding paroxysm. This

paroxysm is not prevented; in fact, it may be entirely unmodified; but such a dose, properly timed, usually secures apyrexia subsequently for several days.

In double tertian infections a single dose given in this way may change the quotidian paroxysms into tertian, and if repeated, in multiple tertian and quartan infections, constitutes a sort of fractional sterilization of the blood.

The method of Sydenham, the *English method,* consists of a single dose, averaging 15 grains, given in the sweating stage or the decline of the paroxysm. This dose usually prevents succeeding paroxysms; if one should occur it is usually abortive.

This method requires less knowledge of the exact nature of the infection and of the stage of development than the former method, hence it may be more effectively applied by the busy practitioner. What experience the writer has had with it has been satisfactory.

The third method, that of small doses at frequent intervals, has numerous advantages over the one-dose methods.

1. Quinine given in this way is better borne by the digestive and nervous systems.

2. The loss of one dose by vomiting or failure of absorption is not of so much importance.

3. The method is adapted to tertian, quartan, or estivo-autumnal infections; this is important, for sometimes these cannot be differentiated clinically.

4. It is adapted especially to estivo-autumnal infections where sporulation is not so nearly synchronous.

5. The time of administration is not dependent on parasitic findings or definite stages, both of which may be obscure where the patient has previously taken quinine.

6. An experience in many hundreds of cases has proved its value.

The writer gives quinine in this way almost exclusively. The average dose is a grain an hour, given usually 2 grains every two hours, 3 grains every three hours, or 4 grains every four hours day and night. It is especially important that the drug be given during the night, since thus only may the

blood be charged during the day, when sporulation usually occurs.

It is not necessary to defer or discontinue the use of quinine on account of fever, as is believed by some. More than four-score years ago Maillot showed that to withhold the drug for this reason was not only useless, but dangerous.

Cinchonism is no guide to the quantity to be given; it is not the patient toward which the quinine is directed, but the parasites.

The specific should not be discontinued as soon as the temperature is normal, but should be kept up for at least two days longer in the quantity employed during the fever. Thereafter about 15 grains on two successive days of each week should be given for at least two or three months to prevent relapse, even though the patient leave the malarial locality. A few days' treatment with quinine no more cures malaria than does a few weeks' rubbing with mercury cure syphilis.

Hygienic and Symptomatic Treatment.—Rest is important in the treatment of malaria not only during the stage of active symptoms, but during convalescence. Exercise may counteract the benefits of quinine; it is not uncommon to see cases yield after confinement to bed which had previously resisted quinine. A relapse may be provoked by a too-early resumption of duty. Rest is especially important in the treatment of estivo-autumnal infections.

Buttermilk is one of the most acceptable and easily retained articles of diet. Sweet milk, meat broths, vegetable soups, fruit juices with egg albumen, soft-boiled eggs, and toast are usually allowable. Where there is much gastric disturbance food had better be withheld temporarily.

The room and bed should be screened; in this way only can other members of the household be satisfactorily protected. The room should be thoroughly ventilated and the patient protected from draughts.

It is customary to begin the medical treatment with a purge. Calomel is the drug most easily administered and retained. The drug need not exceed 5 or 6 grains, and should be followed by a saline. The quinine should not be delayed for the action

of the purgative. As has been said, "cases originally violent almost invariably die while *preparing* for the quinine, and those of moderate severity become worse under the *preparation.*"[66] Calomel has been frightfully abused in most malarial countries. It was formerly the universal practice to give the drug until the gums were "touched" and the teeth irreparably damaged. It was more the abuse of calomel than of any other drug that led Oliver Wendell Holmes[425] to declare that, excepting a few drugs, "if the whole *materia medica, as now used,* could be sunk to the bottom of the sea it would be all the better for mankind—and all the worse for the fishes."

During the cold stage blankets, hot drinks, and the external application of heat are indicated. Atropine hypodermically is useful, and morphine is indicated in some cases.

In the hot stage, if the temperature runs high, cold applications to the head, tepid sponging, and cold rectal injections may be used. The coal-tar antipyretics are not often indicated. Cold drinks may be given.

For the headache cold applications, codeine, and acetanilid, or chloral and bromide of soda are useful, and, if the pain demands it, morphine need not be withheld. If nervousness is marked the monobromated camphor should be administered with the quinine in capsules, or the bromide of soda, in solution, with each dose of the specific.

For vomiting, if intense and not relieved by the application of a mustard plaster to the epigastrium, morphine should be employed subcutaneously.

Chronic Malaria.—In the treatment of chronic malaria two parasitic cycles have to be combated, the schizogonic and the parthenogenetic. The treatment of the asexual cycle of parasitic evolution in chronic malaria is that of acute malaria.

The tendency to relapse at multiples of approximately seven days has long been recognized, these periods being known as the *septenary periods.* It is now known that these relapses depend upon the sporulation of the parthenogametes, a cycle difficult to interrupt except during the stage of free spores.

After successively meeting the active symptoms by quinine, administered as above outlined, the prevention of a relapse is

to be accomplished by giving 15 grains of quinine every sixth and seventh days for a period of not less than three months. The administration of a valuable salt of quinine in this manner has rarely failed, in the writer's experience, to cure the most obstinate case of chronic malaria. The quinine is usually given in 3-grain doses every three hours until five are taken.

The hygienic treatment is even of greater importance in the management of chronic malaria than in acute. Many secondary factors may arouse latent malaria, and these, which have been mentioned in the section on Etiology, should be assiduously avoided.

Cachexia.—Nothing is more discouraging to the physician than the treatment of cachetics in whom the poor hygienic conditions cannot be corrected, which is not rarely the case. The two chief principles involved in the treatment of cachexia are, first, the prevention of active outbreaks of malaria, and, second, the improvement of the general condition of the patient by appropriate hygiene.

Quinine is most effectively given upon two successive days in each week, as described. This alone, however, will rarely effect a cure except in the mildest cases.

Where it is practicable a complete change of climate should be advised. Without this very little can be accomplished for cases of severe degree. A wholesome, nutritious, and digestible diet should be prescribed. The digestion is often impaired and stomachic tonics may be indicated. Exposure to inclement weather must be avoided on account of the dangers of pneumonia. Occupations which subject the cachectic to violent exertion or to bodily harm should be interdicted for fear of rupture of the spleen. Regular hours must be kept and constipation overcome.

Of drugs other than quinine, arsenic has the best reputation. It should be given in rather large doses of the arsenous acid or Fowler's or Donovan's solutions. Atoxyl has recently been introduced into the treatment of malarial cachexia. It is employed hypodermically, one-third grain being a moderate dose. The writer's limited experience with this method has been rather favorable than otherwise. The possibility of

amaurosis as a toxic result of atoxyl should be borne in mind.

Iron is nearly always indicated; the organic preparations of iron and manganese are usually well borne by the stomach. The pill of Blaud's mass, 2½ grains; atoxyl, one-third grain, may be tried, or the classic antimalarial pill of iron, quinine, arsenic, and strychnine.

Injections of medicaments directly into the spleen, as sometimes advised, are unjustifiable.

Counter-irritation over the splenic area may aid in the reduction of the enlarged spleen. The best agent is the ointment of the red iodide of mercury. A piece the size of a pea or larger should be thoroughly rubbed in, the splenic region being bared to the sun's rays or to the heat of a fire. This should be repeated daily until the skin becomes so irritated as to make friction painful, when it should be discontinued, to be resumed again when the condition of the skin will permit. Iodine, turpentine, mustard, firing with the actual cautery, and other counter-irritants have been recommended.

Hydrotherapeutics and electricity have not given general satisfaction. Their use is sometimes followed by an active outburst of malaria.

While the *x*-rays have a destructive effect upon certain protozoa, they do not appear to have such action upon the parasites of malaria within the circulation. Demarchi,[426] as a result of his experiments, is convinced that, while these rays are useless against the infection itself, they appear to have a beneficial effect upon the enlarged spleen when the parasites have disappeared spontaneously or as the result of medication.

Splenectomy may be performed in very anemic patients with large, painful spleens, especially if freely movable, in whom a change of climate is impossible and therapeutic measures have failed. The writer had the opportunity of treating an obstinate case of estivo-autumnal malaria in an adult female who had had, several years previously, the spleen removed on account of malarial cachexia. Hemoglobin percentage was only slightly affected by the attack, and convalescence was rapid.

Brachio[427] has recently suggested a unique method of treat-

ment of splenomegaly. He had observed that in patients with splenic enlargements who suffered suppurative complications, as mastoiditis, empyema, cancrum oris, etc., the spleen rapidly diminished in size. At the same time a leukocytosis was produced where these cells had previously been diminished, and to this phenomenon he attributed the improvement. In order to produce leukocytosis this writer injected subcutaneously 5 minims of turpentine in the splenic region, which resulted in abscess formation and a consequent increase in the number of leukocytes. Nearly 20 cases were treated in this manner with the most encouraging results. While in cases with very large spleens it was necessary to repeat the injection, in only 1 case was the third injection required.

Treatment of Malaria in Children.—In the treatment of malaria in children it is the practice of the writer to administer the quinine at short intervals every two or three hours.

While children bear quinine in relatively larger doses than adults, the size of the dose should be regulated by the severity of the attack and the age of the patient. In average cases children from one-half to two years of age may be given from ½ to 1 grain of quinine every three hours, from three to five years from 1 to 2 grains, and from six to ten years from 2 to 2½ grains. These quantities may be increased in severe attacks.

The drug is ordinarily given by the mouth. Where capsules cannot be used, recourse must be had to a tasteless preparation or to a disguising vehicle. Euquinine and the tannate of quinine are the best of the tasteless preparations. The former must be given in slightly larger doses, the latter up to double the doses indicated above. The most efficient liquid for disguising the taste of the sulphate of quinine is the syrup of yerba santa, at least 1 dram of which should be given for each 2 grains of the quinine. In cases with pernicious symptoms the drug should, of course, be injected intramuscularly. Rectal administration of a solution or suppository may be employed to supplement other modes. The buttocks should be pressed together for half an hour after insertion to aid retention.

Calomel, mercury with chalk, and castor oil are efficient purgatives in the treatment of malaria in children.

Treatment of Complications.—When malaria is complicated with other diseases each should receive appropriate treatment. The malaria should be promptly treated as under ordinary circumstances. Only a few complications need special consideration.

For rupture of the spleen immediate laparotomy should be performed. With early operation over half recover, without operation the mortality is nearly 100 per cent.

Abscess of the spleen is a surgical condition. The choice of operation between splenectomy and splenotomy must be based upon individual conditions. Two cases reported by Bell[428] and by Goltman[429] recovered after operation.

In the treatment of quinine amaurosis the quinine must, of course, be discontinued. Nitrite of amyl and nitroglycerine, with tonics, are recommended.

Substitutes for Quinine.—In the treatment of malaria there is no other drug that can compare in efficacy to the salts of quinine; nevertheless, in rare instances, it becomes necessary on account of idiosyncrasy to resort to the use of other remedial agents.

Of the newer preparations of quinine, euquinine, saloquinine, aristochin, etc., while purported to be free from the toxic properties of the official salts, the writer has seen 1 case in which euquinine caused distressing dyspnea, and another case in which this preparation caused violent urticaria. Euquinine is probably the most valuable of these preparations.

The alkaloids of cinchona, other than quinine, are now but rarely employed, and opinions vary widely as to their merits. Cinchonidine is probably the most useful of these alkaloids. It must be given in doses about twice as large as of quinine. These alkaloids, especially cinchonine and quinidine, are more toxic than quinine, producing nervous and gastric disorder and, in toxic doses, convulsions.

In order to determine the value of these alkaloids in the treatment of malaria the English Government, in India, in 1866, appointed a commission to investigate the subject.[161]

410 patients were treated with cinchonine, of which 400 were cured
350 patients were treated with cinchonidine, of which 346 were cured
375 patients were treated with quinidine, of which 365 were cured

These results are, however, much better than those obtained by other observers.

Good results have been obtained with *Warburg's tincture.* It is claimed that quinine may be given in this form when not tolerated otherwise. The liquid contains, among its many ingredients, about 10 grains of quinine to the ounce, and the dose is ½ ounce repeated in two to four hours. It is probable that as good effects can be obtained by quinine alone in solution as with this unpalatable and unscientific conglomeration of "quinine concealed in a farrago of inert substances for purposes of mystification." Its composition was for a long time a secret.

Methylene-blue was introduced into the treatment of malaria by Guttmann and Ehrlich[430] in 1891.

In the writer's experience this is the best substitute for the derivatives of Peruvian bark. While it does not compare favorably with quinine, requiring a longer time to effect a cure, and failing altogether in not a few instances, it seems to possess some specific action upon the parasites of malaria, and is the most valuable drug where the cinchona preparations are absolutely contra-indicated. Wood[431] collected from the literature 425 cases of malaria treated with methylene-blue with 362 cures. De Blasi[432] tried it in 100 cases with 62 cures. Ruge[158] considers methylene-blue as efficacious as quinine against quartan fever, or even more so under some circumstances. Koch[33] had good results in the cases in which he tried the remedy, and commends its use in cases where quinine cannot be taken. Ziemann,[48] F. Plehn,[5] Laveran,[1] and others have, however, had poor results with the use of methylene-blue.

Only the purest preparation should be employed for medicinal purposes, otherwise untoward results may follow.

The dose is from 1½ to 3 grains given every three hours until from 7½ to 15 grains have been given in twenty-four hours. The drug may be continued in this manner for several

days. Ruge[158] has given as much as 15 grains daily for four weeks without bad results. It is best given in capsules. Kunst[90] injected subcutaneously 5 cc. of a 5 per cent. solution; in some cases he gave even as much as 1 gram in this manner. In the latter cases the patients became greenish-blue all over, the injection site remained painful for ten days and became partially gangrenous.

It is believed by some observers that methylene-blue has more decided curative effect upon chronic than upon acute malaria. It is probably most effective in tertian and quartan infections than in estivo-autumnal. It is thought that methylene-blue affects especially the plasma of the parasites, and is consequently most effective in the stage where this cell element abounds. The drug causes a diminution of ameboid motion of the parasites and a splitting of the plasma substance into several spheric masses.

Untoward symptoms caused by the administration of methylene-blue are headache, nausea, vomiting, diarrhea, strangury, and albuminuria. These effects are less apt to supervene when a pure article is given. De Blasi[432] is of the opinion that it causes contractions of the pregnant uterus. The addition of 2 or 3 grains of powdered nutmeg lessens the tendency to strangury. The patient should always be forewarned of the blue color imparted to the urine and feces.

Thayer[433] reached the following conclusions after using methylene-blue in a few cases:

1. Methylene-blue has a definite action against malarial fever, accomplishing its end by destroying the specific organism; but it is materially less efficacious than quinine, failing to accomplish its purpose in many cases where quinine acts satisfactorily.

2. The action appears to be rapid, the chills disappearing or the temperature, in the remittent cases, falling to normal during the first four or five days; but later, however, if a sufficient number of organisms have resisted the drug, they appear to develop again directly under its influence, causing a return of the symptoms.

3. Methylene-blue seems to have no advantages over quinine which would warrant its further use.

Moore and Allison,[434] who treated 10 cases of malaria with 20 grains daily of methylene-blue, give the following as their conclusions:

1. Methylene-blue will destroy malarial parasites in many cases, but is less certain than quinine.

2. Methylene-blue is probably most valuable in chronic cases, but has no advantage over quinine.

3. The effects of methylene-blue are ordinarily more unpleasant than quinine.

4. It is useful in cases that cannot take quinine on account of some idiosyncrasy toward it. Its use in cases of pregnancy is undetermined.

5. It is probably valuable in treating hematuric and hemoglobinuric fevers on account of its diuretic action; this has as yet to be determined. We have had no chance to test its use in such cases.

6. We believe that quinine is quicker and more certain, and would rely upon it rather than upon methylene-blue.

After its introduction in 1842 by Boudin *arsenic* enjoyed, until recently, considerable reputation in the treatment of malaria. The old school of physicians claimed results but little inferior to those with quinine. More recent observations show that if this agent has any value in the treatment of malaria it is in the chronic form. Whether its good effects here are chiefly upon the anemia and as a general tonic or whether it has some action upon the parthenogenetic cycle is not determined. Fowler's solution and the arsenous acid are the preparations usually employed. The dose at the beginning should be small and gradually increased. Upon the appearance of puffiness of the eyelids, colicky pains in the abdomen, and diarrhea the dose should be diminished or its use temporarily discontinued. The arsenous acid may well be combined with iron, quinine, and strychnine in the treatment of chronic malaria.

Two recent preparations of arsenic, arrhenal or disodic methylarsenate, and sodium cacodylate have been vaunted as

antimalarials by Gautier and others. They are rich in arsenic, but less toxic. Both preparations have been used in cases where abortion threatened, and good results have been claimed. They are usually given hypodermically in doses of from ¾ to 1½ grains daily.

The benefits derived from *atoxyl* in the treatment of trypanosomiasis led to an investigation of its merits in malaria. Chemically, atoxyl is sodium aminophenyl arsenate, containing about 25 per cent. of arsenic and soluble, at 20° C., in 4.3 parts of water. The usual dose is from one-third to 1 grain, given every day or every other day, usually hypodermically.

Grosch[435] cured with atoxyl a case of malaria that obstinately resisted quinine for a long period. Fusco had satisfactory results in 3 cases. Koch, in reporting his experience with atoxyl in the treatment of sleeping sickness, states that in cases that were complicated with malaria, usually of the estivo-autumnal variety, the malarial parasites diminished markedly, but were not so decidedly influenced by the drug as were the trypanosomes.

Slatineano and Galesesco, employing large doses of atoxyl in 15 cases of malaria, had 10 cures and 5 failures. The failures were experienced mostly with double infections. Georgopulos, after its use in 14 cases, reported that the paroxysms ceased, the spleen diminished in size, the parasites disappeared from the blood, and the general condition of the patient improved. In 6 cases treated by Gonder and Dapas the patients improved during the treatment; in 2 cases the splenic enlargement diminished considerably, but in only 1 case did the parasites disappear entirely. The resistance of the gametes, especially the macrogametes, to the drug was noteworthy.[436] Vassal[437] claims good results, especially in malarial cachexia, by the use of atoxyl with the quinine.

While the experience of the writer with atoxyl has been limited, he believes that it is a valuable adjuvant to quinine in the cases where the latter is insufficient, particularly in cases of cachexia and extreme anemia. Its good effect in these cases may be due to the increased amount of arsenic which may be

administered in this form. In employing atoxyl its possible toxic effects should not be lost sight of.

The value of *opium* in the treatment of malaria was discovered accidentally by Lind,[71] in 1766. He says:

"The effects of opium given in the hot fit of an intermitting fever are: (1) It shortens and abates the fit, and this, with more certainty than an ounce of bark, is found to remove the disease; (2) it generally gives a sensible relief to the head, takes off the burning heat of the fever, and occasions a profuse sweat; this sweat is attended with an agreeable softness of the skin instead of the disagreeable burning sensation which usually affects patients sweating in the hot fit, and is more copious than in those who are not under the influence of opium; (3) it often produces a soft and refreshing sleep to patients before harassed with the fever, from which they awake bathed in sweat, and in a great measure free from complaint.

"I have always observed that the effects of opium are more uniform and constant in intermitting fevers than in most other diseases, and are then more quick and sensible than those of most other medicines. An opiate thus given, soon after the commencement of the hot fit, by abating the violence and lessening the duration of the fever, preserves the constitution in a great measure uninjured. Since I have used opium in agues, a dropsy or jaundice has seldom attacked any of my patients in these diseases."

Opium is not only effective against certain symptoms of malaria, but it has been shown by Drake[65] and others to possess antiperiodic virtue. This is, in all probability, due to the narcotine contained. For this reason opium, in the form of the powder, Dover's powder, laudanum, or paregoric, is more effective than morphine. In order to test the value of narcotine as compared to quinine, Duncan[438] treated 78 cases of malaria with quinine, with an average duration of fever of 2.11 days and 20.5 per cent. of failures; with 66 cases of malaria treated with narcotine the average duration of the fever was 2.77 days and the per cent. of failures only 1.06. The immunity of opium smokers to malaria has been remarked upon by a number of tropic physicians.

A large number of other substances have been recommended as substitutes for quinine. The chief of these are *phenocoll, eucalyptus, salicin, salicylic acid, sodium hyposulphite,* etc. Their antimalarial value, if, indeed, they possess any, is so slight as to render a detailed consideration not worth the while.

The *serum treatment* of malaria has not yet reached the stage of practical utility. Indeed, the experiments of Ford[140] alone have resulted in the isolation of an antitoxin. In his first series of 9 cases of benign tertian malaria 7 were cured, 1 was temporarily benefited, while in the other the result was negative. In his second series of 20 cases of benign tertian 17 were cured, while 3 were apparently quite uninfluenced.

Critzmann[86] had several cachectic patients eat three times daily 50 grams of chopped beef spleen mixed with the yolk of an egg and 10 grams of bone-marrow. Burot and Legrand[225] used the same treatment in numerous cases of cachexia in the hospital of Rochefort. In the course of about fifteen days the patient acquired a disgust for the repast. While the preparation had no effect upon the fever, it seemed to act as a reconstituent.

More recently Carpenter[439] claims remarkable success in the treatment of malaria with powdered splenic extract in the dose of 5 grains every two to four hours, preferably in capsules. He says: "In more than six years' continuous experience and in the treatment of hundreds of cases of malarial infections of all types, both simple and complicated by all sorts of conditions, not a single case has been met with which did not yield to this remedy." He further states that it is equally as reliable a remedy as quinine.

The Treatment of Pernicious Malaria.—There are certain cases apparently on the borderline between benign malaria and pernicious malaria of the cerebral type which may cause hesitation as to the mode of administration. In these cases, usually in children, the patients, though stupefied, or even semicomatose, can be aroused and made to swallow and usually retain the medicine. In such cases, if the patient can be watched, the quinine may be given in solution by the mouth.

If vomited or if the symptoms do not rapidly improve, the drug in dilute solution should be injected intramuscularly. Where the injection mode is chosen it is advisable to supplement this with oral administration of the solution where it can be swallowed, and even the rectum may be employed also.

As previously stated, quinine for intramuscular injection should be in dilute solution; 15 grains to 2½ drams of water is a suitable proportion. The gluteal region, above the ischial tuberosities, is the best site for injection. In pernicious cases about 15 grains is the quantity to be used at first injection. Subsequent doses may be from 5 to 10 grains injected every six to eight hours as needed. The technic of such injections has already been given.

Just as antisyphilitics may cause the gumma to melt rapidly but are powerless to restore the tissue it has destroyed, so quinine has its limitations in the therapeutics of malaria. It should be borne in mind that in its relation to the parasites quinine is a toxin, but not an antitoxin. It is possible that where the parasites are accumulated to the extent of thrombosis the quinine in solution in the blood does not reach them in toxic quantities, and where perivascular exudation, hemorrhage, and necrosis have resulted from these thrombi the annihilation of the parasites avails nothing. This is corroborated by those cases ending fatally, notwithstanding a rapid disappearance of the parasites, and in which post mortem these secondary changes are found. All that can be expected of quinine is to destroy the parasites, and this it may fail to accomplish from not being absorbed or not being present in the blood in sufficient quantities or at the time when the parasites are most susceptible to its action, or on account of thrombotic occlusions it may not gain access to the parasites causing the symptoms. Quinine is probably a true specific in those cases of pernicious malaria only in which, in the absence of irreparable changes due to toxins or to thrombi, the prompt destruction of the parasites would be attended by an almost simultaneous cessation of symptoms.

Other than the specific treatment there are important symptomatic indications to be met.

In cases with high temperature and hot dry skin cooling baths should be used. For heart depression strychnine or digitalis are useful.

In the cerebral types the ice-bag to the head is called for and an active cathartic should be given if possible. Where this cannot be swallowed, a drop of croton oil on the back of the tongue may be tried. If delirium is marked, a solution of chloral and the bromides should be given by the rectum. Where there are convulsions, chloral and bromides by the rectum, morphine hypodermically, or even inhalations of chloroform may be necessary. Bell employed lumbar puncture in a case of malarial coma to relieve the increase in the cerebrospinal fluid which usually exists in these cases, but the result was disappointing.

In algid attacks for the relief of cold surface and dyspnea, especially if choleraic symptoms are present, nothing is so suitable as a combination of morphine and atropine. The heart usually requires stimulation by strychnine and digitalis. Hypodermics of ether may be necessary. If dysenteric symptoms arise they should be treated with opium and bismuth, together with saline irrigations.

If complications appear they should receive appropriate treatment.

During convalescence a tonic of arsenic, strychnine, iron, and quinine is usually indicated. In cases where it is feasible, a change of climate should be ordered until recovery is thoroughly established.

Treatment of Hemoglobinuric Fever.—The discussion of the treatment of hemoglobinuric fever has probably been productive of more harsh and prejudiced controversies than has any other question in therapeutics. The bone of contention is quinine.

It is unnecessary to review the history of the discussions or to rehearse the arguments for or against the etiologic relation of quinine to blackwater fever. No valid conclusion can be reached except through results of a large series of cases treated with and without quinine. The collection recorded under Prognosis shows a mortality of 25.9 per cent. in cases

treated with quinine, and 11.1 per cent. in cases in which no quinine was used. This number of cases probably eliminates all errors and should be convincing.

While the results of the series prove that the mortality is higher under the routine treatment with quinine, they should not be taken to exclude absolutely the use of quinine in some cases of hemoglobinuric fever, for under certain circumstances quinine may be of value. It is difficult—in fact, sometimes impossible—to say whether quinine is indicated or contraindicated in a certain case.

Mannaberg[141] gives the following general rules to aid a decision:

1. When, without quinine preceding, hemoglobinuria occurs and the blood examination shows the presence of malarial infection, quinine is undoubtedly to be exhibited.

2. When the hemoglobinuria occurs after one dose of quinine, while the anamnesis shows that the patient previously took quinine without bad effect, and the parasites are present in the blood, quinine is also to be exhibited. If a paroxysm of hemoglobinuria should follow within a few hours, the repetition of the drug should be made dependent upon whether or not the parasites have in great part disappeared. In the former case the quinine may be stopped, at least for a time. But if the blood examinations show that the parasites have increased in number the quinine is to be continued.

3. When the anamnesis shows that the patient suffered previously from hemoglobinuria following quinine and the blood examination is negative, quinine is to be absolutely avoided.

4. When the case manifests a severe malarial infection (numerous parasites on examination) and at the same time an assured intolerance to quinine in the shape of hemoglobinuria the decision is very difficult.

Marchiafava and Bignami[22] believe that the only guide indicating to the physician whether to give or to withhold quinine ought to be the result of a blood examination.

Bastianelli's[101] canon is as follows:

1. If a hemoglobinuria occurs during a malarial paroxysm and parasites are found in the blood quinine should be given.

2. If parasites are not found in the blood quinine should not be given.

3. If quinine has already been given before the hemoglobinuria has appeared and no parasites are found, its use should be suspended; but if parasites persist it should be continued.

Thayer[98] states his rules, modified from Bastianelli, thus:

1. If the attack occurs spontaneously with a malarial paroxysm, the blood showing the presence of parasites, quinine should be freely administered hypodermically or intravenously.

2. If the parasites have disappeared, either as a result of the paroxysm itself or of doses of quinine already given, it may be as well to abstain, at least for a time, from the administration of the drug. It cannot ameliorate the further course of the paroxysm, and the possibility, if it has been already given, that the symptoms may be in part due to quinine may be thought of.

3. If an attack arise in the middle of an ordinary malarial infection, after taking quinine, it is best to abstain, for a time, at any rate, from the further use of the drug. That which has been given may have been enough to control the affection.

4. If, however, in an attack coming on after quinine, the parasites continue to develop, quinine should be again administered, despite the slight possibility of its injurious action. The dangers from the further development of the parasites are probably the greater.

5. In postmalarial hemoglobinuria quinine is, of course, useless.

The following rules of Vedy[213] are practical:

1. If living parasites (not merely evidence of their former existence, pigment) are detected twenty-four hours after the beginning of the attack 80 centigrams of a salt of quinine may be injected subcutaneously.

2. If the parasites are not visible do not administer quinine.

3. If in doubt, that is to say, if the microscopic examination of the blood cannot be made, do not give quinine.

It may be seen that the authorities quoted lay great stress on the presence of the parasite as a guide to the administration of quinine. The writer, however, cannot agree with those who

hold that quinine should be exhibited in every case where the microscopic examination shows the presence of parasites. It has been shown conclusively that parasites are present in a very large proportion of cases examined early. It has also been shown that in an equally large number of cases the parasites disappear spontaneously. In these cases quinine is, to say the least, superfluous.

In the writer's opinion, *the only conditions in which quinine is indicated are: first, where the parasites show no tendency to disappear after forty-eight hours from onset; second, in the infrequent cases of intermittent hemoglobinuria where the outbreak corresponds with parasitic sporulation.*

If it is decided to give quinine it should be injected, in dilute solution, into the muscles as directed for the treatment of pernicious malaria. Given by the mouth it upsets the stomach and may not be absorbed.

Even in cases of mildest onset the patient should be confined to bed from the start, and should be kept quiet either by suasion or by sedatives. Sudden death on slight exertion sometimes occurs. The patient should not be transported from one place to another; the Plehn brothers observed anuria as a frequent consequence of moving patients from place to place. Chilling of the body, especially when the temperature is low, should be carefully avoided. When vomiting is not a prominent feature liquid nourishment may be given freely; buttermilk and albumen water are the most suitable. Sweet milk is often ejected as a thick curd, molded ropy by the esophagus in the act of vomiting. Animal broths, barley and oatmeal water, lemonade, and orange juice are allowable. Rectal alimentation is unsatisfactory.

There is no specific. *Methylene-blue* has proved disappointing. Besides being a renal irritant, it masks the color of the urine, a most serious objection. Salicylic acid probably has no effect further than to upset the stomach and increase the discomfort. With the false idea that a hemorrhage has to be checked, gallic and tannic acids, ergot, and similar drugs are frequently given; these cannot possibly be of any benefit. Carbolic acid and other renal irritants should not be used.

The bowels should be moved early and often, and calomel possesses advantages over other purgatives; it is more easily retained, is a bland diuretic, and is the best of intestinal antiseptics. Too large doses are usually advised; 3 to 5 grains are, as a rule, sufficient, repeated *pro re nata.*

Quennec's[440] *chloroform treatment* has been successful in some hands. The originator claims for the method three points of value:

1. Controls vomiting.
2. Increases output of urine.
3. Diminishes albuminuria.

He treated more than 50 cases with no mortality. The following is his formula: Chloroform, 6 grams; gum arabic, 8 grams; sweetened water, 250 grams. This amount is used daily, a sip taken every ten minutes. In addition, Quennec used quinine, 1 gram daily subcutaneously, and sulphate of soda and senna by rectum. The excessive administration of chloroform might be harmful, as it is a cardiac depressant, renal irritant, and lowers the blood pressure.

Cardamatis[206] gives *ether* in every case of hemoglobinuric fever. In ordinary cases he prescribes a teaspoonful in sweetened water every three hours, and increases the dose if the urine diminishes in quantity. In cases of suppression he gives as much as a teaspoonful every hour, at the same time injecting hypodermically 1 cc. every two or three hours. He maintains that by this means the pulse is strengthened, precordial anxiety, dyspnea, and vomiting are relieved, and a profuse diuresis is provoked.

The writer has had no experience with ether in the treatment of blackwater fever, but would consider it too irritating to the kidneys for general use.

Hearsey[266] used with good results a modification of *Sternberg's yellow-fever treatment.* The original Sternberg formula is: sodium bicarbonate, 150 grains; mercury perchloride, one-third grain; water, 2 pints. Sig.: 1½ ounces every hour. Hearsey gives sodium bicarbonate, 10 grains; liquor hydrargyri perchloridi, 30 minims; every two to three hours.

A method of treatment recently introduced and extrava-

gantly extolled by its originator is that of *Vincent.*[441] This writer maintains that calcium chloride is not only a preventive, but has extraordinary curative powers. During the attack from 4 to 6 grams are given daily by the mouth, or from 1 to 2 grams dissolved in normal salt solution hypodermically. He asserts that it acts as an antihemolysin, and that in persons in whom an attack of blackwater may be provoked at will by a dose of quinine, the previous administration of calcium chloride will forestall the outbreak. It is worthy of mention that this drug has been used successfully in paroxysmal hemoglobinuria by Saundby, and in hemophilia by Wright and others.

The writer has recently employed *calcium chloride* in 6 cases, of which 3 ended fatally. The series is too small to permit of very definite conclusions as to results of treatment, but it would appear that the results claimed by Vincent were not obtained. The 3 fatal cases were in persons whose health was probably not more undermined from previous malaria or other causes than the average patient who is attacked with hemoglobinuric fever. It is worthy of note that the cause of death in these 3 cases was not syncope nor suppression, but exhaustion due directly to hemolysis, the very process which calcium chloride was used to combat. No treatment other than supportive was used which might modify the antihemolytic effects of the calcium chloride.

Hyposulphite of soda introduced into the treatment of malarial conditions by Polli,[442] in 1867, has been used extensively in the treatment of hemoglobinuria. Its use is probably not attended with any signal results. O'Sullivan-Beare[443] used with good results a decoction of the root of *cassia beareana,* a native plant. Gouzien employed an infusion of the leaves of *cassia occidentalis.*

Teas made from the leaves of *folia combreti alti* and of *aphloia theæformis* are also highly recommended.[86]

The fever does not usually run sufficiently high to call for treatment. The coal-tar preparations should be assiduously avoided. Cold baths may be productive of harm by increasing the blood destruction, but in hyperpyrexial cases sponging with tepid water may be resorted to.

Vomiting, if not intense, is often benefited by a mustard plaster on the epigastrium. The fly-blister formerly used should be abandoned. Draughts of hot water or carbonated water sometimes assist in relieving this troublesome symptom. Cracked ice may be tried. Morphine hypodermically should be given unhesitatingly when other measures fail. Any evil effects are more than outweighed by its enabling the stomach to retain liquids.

An important measure toward the prevention and relief of nausea and vomiting is to maintain the recumbent position. Medicine, water, and nourishment should be taken through a drinking tube or the ordinary invalid's cup, and the bed-pan or urinal should be used when evacuating the bowels or bladder.

It is imperative to allay the restlessness often present in these cases. For this purpose chloral and bromide of soda by rectum, morphine hypodermically, or sulphonal or small doses of chloroform by mouth are useful.

Probably the most important indication in the treatment is the prevention of suppression. *Medicinal diuretics* usually do harm. One, turpentine, widely used in some sections, should be condemned in the strongest terms. It is one of the most violent renal irritants, and in some persons small doses may cause suppression or hematuria. Water is the best diuretic, and as much should be given by mouth as will be retained. Lewis,[192] of North Carolina, was the first to recommend the use of normal salt solution by hypodermoclysis and by the rectum in the treatment of hemoglobinuric fever, though Laveran[1] attributes the priority to Gouzien. The latter recommends the daily injection of 100 to 300 grams of a nine-tenths per cent. solution, in conjunction with the rectal injection of 200 grams, four to six times in twenty-four hours. The use of salt solution is the very best means of combating and treating anuria. It is probably better to use a hypertonic solution. In mild cases where the urine is free the rectal use is usually sufficient, but in cases where suppression threatens or is imminent the solution should be used subcutaneously or intravenously and in larger quantities and oftener than advised by

Gouzien. Mild counterirritation over the region of the kidneys may be tried.

Werner,[444] in 1902, suggested nephrotomy for anuria. Such an operation has been recorded in only three instances. Ziemann[48] mentions a case in a young female patient in whom suppression had existed two days. The capsule of the right kidney was split and peeled off to the hilum and nephrotomy performed through the convexity of the organ. The operation was well borne, and subsequently 200 cc. of cloudy, albuminous urine was voided from the bladder. During the following days complete suppression recurred, and the patient died.

In Kruger's[445] case decortication of one kidney was done five days after the onset of anuria, and, although the secretion of urine was profusely reëstablished, the patient died of progressive weakness.

Külz[446] reports a case in a man during his second attack. Three and a half days after the onset of anuria nephrotomy upon one kidney was performed through Simon's incision. Vomiting, which was formerly uncontrollable, ceased immediately. Three hours after the operation 30 cc. of blood were voided from the bladder. In eight hours the dressing was saturated with bloody icteric urine, which necessitated changing the dressing every three hours. Twenty-four hours after the operation the patient died. Though a microscopic examination of the kidney could not be made, upon gross inspection the nephrotomized kidney appeared much more nearly normal than the other.

Supportive measures are essential. Alcohol in all its forms is inadmissible. Strychnine is useful, and should be given hypodermically when circumstances permit. Digitalis has proved serviceable in the writer's hands. Doering[187] had good effects from strophanthus. The aromatic spirits of ammonia and hypodermic injections of ether have been recommended. Transfusion of blood has been used, it is said, with excellent results. The elder Plehn[61] says that he had four attacks, in which Kohlstock treated him with inhalations of oxygen, and that nothing else did him so much good. Unfortunately, this method of treatment is not often possible in private practice.

The after-treatment should have a care for the diet, which should be non-nitrogenous and consist largely of liquids at first. A tonic of organic iron is indicated, and digestive disorders when present should receive appropriate treatment.

A question of practical importance is, how soon after the attack to begin the administration of quinine. A dose given too early might possibly, in some persons, precipitate hemolysis. On the other hand, delay may permit an outbreak of malaria accompanied by hemoglobinuria. Upon the ground that most of the sensitive cells have succumbed during the attack and that the newly formed cells are probably more susceptible than those that have withstood the attack, the writer is of the opinion that quinine should be begun, carefully at first, a short time after the attack has subsided and before blood regeneration is fairly established. One grain of quinine three times daily, increased gradually every other day, is a safe procedure. If the temperature rises or the urine becomes distinctly darker no further attempt to increase the dose should be made.

In the present state of our knowledge it is probably Utopian to discuss the treatment of hemoglobinuric fever by antihemolytic sera, but such has recently been successfully accomplished by Widal and Rostaine[447] in paroxysmal hemoglobinuria.

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INDEX

Abdominal forms, 212
Abortion, 242
Abscess of liver, diagnosis, 284
  of spleen, 240
Absorption of quinine, 335
Action of quinine on parasites, 341
Acute malaria, 184
Administration of quinine, 357
Adult mosquitoes, 81
Aëdeomyia, 100
Aedes, 93
Age, 55, 253
  and hemoglobinuric fever, 155
  and immunity, 53
  and pernicious malaria, 141
Agglutinin, 199
Albuminuria, 201
Algid form, 212
Alkaloids of cinchona, 343
Altitude, 45
  and hemoglobinuric fever, 158
  and mosquitoes, 104
Amaurosis, 210
Amblyopia, diagnosis, 289
Anemia, pathogenesis, 140
Anopheles, 88
  breeding places of, 75
  crucians, description, 86
  maculipennis, description, 84
  mosquitoes, 74
  punctipennis, description, 85
Anophelinæ, 87
Anopheline larvæ, 77
  ova, 76
Apoplectic form, 208
Apparent death, 207
Appendicitis, 215
Ardent form, 210
Ataxic form, 210

Bacillus malariæ, 20
Banti's disease, diagnosis, 287
Beans and hemoglobinuria, 168
Bilious form, 215
    remittent fever, and hemoglobinuria, 27
      diagnosis, 291
Biology of parasites, 113
Biting of mosquitoes, 105
Blackwater fever. See *Hemoglobinuric fever.*
Blood, 195, 216, 223
  complications, 236
  examination, 258
Bone-marrow, pathology, 177, 180, 183
Brain, pathology, 177, 183
Breeding mosquitoes, 109
  places, 75
Bulbar symptoms, 208

Cachexia, 237
  productive of immunity, 54
  treatment, 369
Cacomyia, 101
Cancer, complication, 251
Cardialgic form, 214
Cellia, 89
Cerebellar symptoms, 208
Cerebrospinal forms, 204
Change of residence, 53, 60
    and hemoglobinuric fever, 158
    and pernicious malaria, 143
  of type, 139, 188
Children, malaria in, 55, 56, 253
  pernicious malaria in, 141
  treatment, 371
Chill, description, 184
Choice of preparation, 356
Choleraic form, 214

Chronic malaria, 228
treatment, 368
Cinchona, history, 28
Circulatory system, complications, 232
symptoms, 195
Civilization, 61
Classification of mosquitoes, 86
of parasites, 112
of pernicious malaria, 203
Clearing of land, 48
Climate, 38
Clinical history, 184
Colon bacillus, 252
Colors and mosquitoes, 106
Comatose malaria, 204
Complications, 232
of hemoglobinuric fever, 226
treatment, 372
Congenital immunity, 54
malaria, 64
Contra-indications to quinine, 355
Convulsive form, 209
Coquillettidia, 100
Crescents, 231
pyrogenic properties, 147
Culex, 98
Culicella, 97
Culicinæ, 87, 90
Culiseta, 98
Cultivation experiments, 129
Cycles of the parasites, 114
Cycloleppteron, 89

Deinocerites, 101
Deinoceritinæ, 87, 101
Dendromyia, 103
Destruction of mosquitoes, 305
of parasites, 315
Diabetes, complication, 251
Diagnosis, 256
differential, 284
of hemoglobinuric fever, 289
of pernicious malaria, 287
Diaphoretic form, 214
Differential diagnosis, 284
Disappearance of malaria, 73
Dissection of mosquitoes, 110
Dissemination by mosquitoes, 69
Dosage of quinine, 365
Drinking-water, 62
Duration of larval stage, 79
Dysenteric form, 214

Ear complications, 248
Earthquakes, 46
Eclamptic form, 209
Education and prophylaxis, 327
Eggs of mosquitoes, 76, 107
Elimination of quinine, 335
Endemic index, 56
Endocarditis, diagnosis, 284
Endogenous cycle, 114
Epidemics, 63
of hemoglobinuric fever, 37
Error, sources of, 268
Estivo-autumnal infection, symptoms, 190
parasites, 119
differentiation, 121
Etiology, 38
of hemoglobinuric fever, 153
of pernicious malaria, 140
Europeans and hemoglobinuric fever, 29
Examination of blood, 258
Exclusion of mosquitoes, 322
Exflagellation, 117
Exogenous cycle, 123
Exposure, 60
to wind, 49
External etiologic influences, 151
Eye complications, 248

Family predisposition and hemoglobinuria, 156
Feeding of mosquitoes, 70, 110
Females, susceptibility of, 54
Fertilization of mosquitoes, 70, 107
Fish and prophylaxis, 311
Flagella, 117, 268
Flight of mosquitoes, 105
Food in etiology, 61
of mosquitoes, 70, 104

Gametes, differentiation, 117, 122
estivo-autumnal, 120
quartan, 119
tertian, 117
Gastralgic form, 214
Gastro-intestinal organs, complications, 235

Gastro-intestinal organs, symptoms, 200
Genito-urinary organs, complications, 240
symptoms, 200
Geographic distribution, 31
of hemoglobinuric fever, 34
Glossary of terms, 128
Grabhamia, 97
Ground water, 43, 308
Gymnometopa, 101

Habits of mosquitoes, 104
Hæmamœba immaculata, 119
malariæ, 118
parva, 119
præcox, 119
quartanæ, 118
tertianæ, 115
vivax, 115
Hæmatozoön falciform, 120
Hæmocytozoa, 112
Hæmogogus, 101
Hæmomenas præcox, 119
Hayem's method, 259
Heart, pathology, 177, 180, 183
Hematuria. See *Hemoglobinuric fever*.
Hemiplegia, 209
Hemoglobinuric fever, complications, 226
diagnosis, 289
etiology, 153
geographic distribution, 34
history, 23
pathogenesis, 160
pathology, 180
prognosis, 297
prophylaxis, 332
quinine and, 26
sequelæ, 226
symptoms, 216
treatment, 380
Hemolysin, 199
Hemosiderin, 174
Hibernation of larvæ, 107
mosquitoes, 108
ova, 107
parasites, 71
pupæ, 108
History of cinchona, 28
of hemoglobinuric fever, 23
History of malaria, 18
Howardina, 101
Human cycle, 114
Hydrophobic form, 209
Hygienic treatment, 365
Hypodermic method, 359

Idiosyncrasy, 156
Imago of mosquitoes, 81
Immunity, 50
congenital, 54
Incubation, 184
Index endemicus, 56
Individual predisposition, 151
Infection, modes of, 63
Influenza, complication, 251
diagnosis, 286
Inheritance of parasites by mosquitoes, 71
Inoculation, 67
Insecticides, 312
Intestines, pathology, 176, 180, 182
Intravenous method, 363
Introduction, 17
Inundations, 47, 143
Isolation of patients, 327
Isostomyia, 99

Janthinosoma, 92

Key to mosquitoes, 86
Kidneys, pathology, 176, 179, 182
Killing mosquitoes, 108

Larvæ, differentiation, 79
hibernation, 107
Larval stage, duration, 79
Latent malaria, 228
pathogenesis, 139
Laverania malariæ, 118
præcox, 119
Leishman's stain, 262
Length of flight of mosquitoes, 105
of life of mosquitoes, 107
of residence, 59, 143, 157
Lepidoplatys, 93
Lepidosia, 92
Leukemia, diagnosis, 287
Leukocytes, 197, 223, 279
Life of mosquitoes, length, 107

Limatus, 103
Liver, pathology, 175, 178, 181
Localizations of parasites, 150
Lungs, pathology, 176, 180, 183
Lutzia, 97

Malaria upon ships, 49
  without mosquitoes, 72
Malaria-bearing mosquitoes, 74
Malarial parasites, 112
Malignant tertian, 191
Marshes, 43
Masked malaria, 232
Megarhinæ, 87, 89
Megarhinus, 89
Melanin, 174
Melanoconion, 99
Methods of administration, 357
Methylene-blue, 373
Micrædes, 99
Microscopic examination of blood, 258
Midgut, dissection, 110
Mixed infections, 193
Modes of infection, 63
Mononuclear increase, 279
Mortality, 295
  of hemoglobinuric fever, 298
  of pernicious malaria, 296
Mounting mosquitoes, 109
Mythology and malaria, 18
Myzomyia, 88
Mosquito cycle, 123
  larvæ, 77
  pupæ, 80
Mosquitoes as malaria carriers, 22
  classification, 86
  description of adult, 81
  destruction of, 305
  hemoglobinuric fever and, 36
  hibernation of, 108
  list of malaria-bearing, 74
  malaria-bearing, 69

Negative results, 277
Negro, 141, 253
Nephritis, 240
Nervous system, complications, 243
    symptoms, 202
Nobel prizes, 18
Nocht-Romanowsky stain, 262
Notes of mosquitoes, 105
Nototricha, 89
Number of parasites, 147

Objections to mosquito theory, 72
Occasional causes of hemoglobinuria, 159
Occupation, 60, 143, 159
Ochlerotatus, 93
Odors and mosquitoes, 106
Opium-eating and immunity, 62
Ova, hibernation, 107
  of anopheles, 76
  of mosquitoes, 107
Overflows, 47, 143
Oviposition of mosquitoes, 107

Palmate hairs of larvæ, 78
Parasites, biology, 113
  classification, 112
  estivo-autumnal, 119
  in hemoglobinuric fever, 161
  localizations, 150
  number, 150
  quartan, 118
  table of differentiation, 122
  tertian, 115
Paroxysm, description, 184
Parthenogametes, 126
Parthenogenesis, 139, 229
  in mosquitoes, 107
Parthenogenetic cycle, 114, 124
Pathogenesis, 129
  of hemoglobinuric fever, 160
  of pernicious malaria, 145
Pathology, 174
  of hemoglobinuric fever, 180
Pericardium, pathology, 183
Periodicity, 256
Peritonitis, 215
Pernicious malaria, diagnosis, 287
    etiology, 140
    prognosis, 295
    symptoms, 203
    treatment, 378
Perpetuation of parasites, 71
Petroleum in prophylaxis, 309
Phagocytosis, 224

Phoniomyia, 103
Physiologic effects of quinine, 349
Pigment, 278
Plants and malaria, 48
Plasmodium falciparum, 120
  immaculatum, 119
  malariæ, 118
  præcox, 119
  vivax, 115
Pleuræ, pathology, 183
Pneumaculex, 101
Pneumonic form, 211
Positive results, 275
Postmalarial fever, 194
Pregnancy, 55, 242
  and quinine, 353
Previous attacks of hemoglobinuric fever, 156
  of malaria, 144
Private prophylaxis, 332
Prodromata, 185
Prognosis, 292
  of hemoglobinuric fever, 297
  of pernicious malaria, 295
Prophylaxis, 302
  of hemoglobinuric fever, 332
Psorophora, 90
Psorophorinæ, 87, 90
Puerperal septicemia, diagnosis, 285
Puerperium, 55
Pupæ, 80
  differentiation, 80
  hibernation, 108

Quartan infection, symptoms, 189
  parasite, 118
Quinine, 334
  absorption and elimination, 335
  action on parasites, 341
  and pregnancy, 353
  contra-indications, 355
  effect on parasites, 271
  in etiology of hemoglobinuric fever, 26, 164
  methods of administration, 357
  physiologic effects, 349
  prophylaxis, 316
  substitutes, 372
  test, 281
Quotidian estivo-autumnal, 192

Race, 50, 253
  and hemoglobinuric fever, 154
  and pernicious malaria, 141
Rainfall, 41
Rectal administration, 364
Relapse, 228
  in pernicious malaria, 207
  pathogenesis, 139
Residence, change of, 143, 158
  length of, 59, 143, 157
Respiratory system, complications, 233
    symptoms, 199
Resting position of larvæ, 79
    of mosquitoes, 84
Rice culture, 60
Ring forms, differentiation, 123
Romanowsky stain, 261
Rupture of spleen, 239

Sabethes, 103
Sabethoides, 103
Salivary glands, dissection, 111
Salt marshes, 45
  water and mosquitoes, 75
Schizogonic cycle, 114
Schüffner's dots, 197
Screens, 322
Season, 39
  and hemoglobinuric fever, 156
  and mosquitoes, 103
  and pernicious malaria, 142
Secondary fever, 194
Sequelæ, 232
  of hemoglobinuric fever, 226
Sex, 54
  and hemoglobinuric fever, 155
  and pernicious malaria, 141
Ships, malaria on, 49
Sitting position of mosquitoes, 84
Skin complications, 248
  symptoms, 202
Smallpox, complication, 252
Social condition, 61, 144
Soil, 42
Solubility of quinine salts, 334
Sources of error, 268
Spleen, abscess of, 240
  pathology, 175, 178, 181
  rate, 58
  rupture of, 239

Splenic enlargement, pathogenesis, 140
Spodogenous fever, 194
Spontaneous recovery, 292
pathogenesis, 140
Sporogonic cycle, 123
Stegomyia, 93
Stippling, 196
Stomach, pathology, 176, 180, 182
Study of mosquitoes, 108
Substitutes for quinine, 372
Sudoral form, 214
Surgical aspect, 254
Swamps, 43
Symptoms, 184
analysis, 193
of hemoglobinuric fever, 216
of pernicious malaria, 203
Symptomatic treatment, 367
Syncopal form, 214
Syphilis, complication, 252

TÆNIORRHYNCHUS, 100
Technic of blood examination, 258
of mosquito study, 108
Temperature, atmospheric, 38
and mosquitoes, 103
clinical, 193, 218
Tertian estivo-autumnal, 191
infection, symptoms, 187
parasite, 115
Tetanic form, 209
Texas fever, 162
Theobaldia, 98
Therapeutic test, 281
Thick film process, 268
Thoracic forms, 211
Time of administration, 365
Tinolestes, 99
Topography, 43
Toxin, 130, 151
in hemoglobinuric fever, 163
Treatment, 334
of hemoglobinuric fever, 380
of pernicious malaria, 378
Trees, effect on malaria, 48
in prophylaxis, 309
Trichoprosopon, 102
Trichoprosoponinæ, 87, 102
Tuberculosis, complication, 251
diagnosis, 286
Typhoid fever, complication, 250
diagnosis, 285
form, 210

UNINHABITED regions, malaria in, 74
Unity of the malarial parasites, 113
Uranotænia, 102
Uranotæniinæ, 87, 102
Urine, 200, 219

VEGETATION, 48
Verrallina, 93
Volcanic eruptions, 46

WATER, contagion through, 62
Weeds and malaria, 48
Wind, malaria borne by, 48
mosquitoes borne by, 106
Wings of mosquitoes, 83
Wright's stain, 263
Wyeomyia, 103

YELLOW fever and hemoglobinuric fever, 28
diagnosis, 291

ZOOLOGIC relations of the parasites, 112

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