The history of malarial fever and contributions to it Ronald Ross.

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Thesis

THE HISTORY OF MALARIAL FEVER

and

CONTRIBUTIONS TO IT BY RONALD ROSS

by

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INTRODUCTION

My purpose in writing this thesis is to give the reader a brief history of malarial fever. Due to the nature of my particular work and to the tremendous amount of material that could be written on this subject, it is obvious that my treatment of it will include but a short portion of the entire history of this disease. I hope nevertheless, when the thesis is completed, to have given a clear understanding of certain definite facts relating to malaria.

These facts will deal with the ancient beliefs, and the important discoveries that were made from the time of Hippocrates up to the successful solving of the problem by Ross, and will also include the life-history of the parasites of the Anopheline mosquitoes, and will end with the medical aspects of the disease.

This disease was selected by me for several reasons, namely: its widespread distribution; its particular prevalence in certain localities; the general lack of active interest toward it, even after its cause was discovered and preventive measures suggested; and last, but not least, its importance as an economic factor.

In the first part of the thesis, some general information about the disease will be given, such as, definition, distribution, characteristic manifestations, ancient history in Greece and Italy, and the beliefs up to the discovery of cinchona bark.

From then on, the thesis is more specific in nature and it relates, in chronological order, the discoveries and discoverers of important facts pertaining to malaria. The more common theories are mentioned, together with their advocates, up to the
time that Ross took an active interest in the problem. The work of Ross is mentioned in detail, that is, the most important features of his work from the time he began up to the successful completion of his investigations. The men to first confirm his work are mentioned and there is also a reference to the Italian work, with the purpose of showing the result of laying too much stress on hypotheses.

The thesis then becomes more technical, containing the description of the actual parasites of malaria; their development in men and in mosquitoes; the complete life-history of Anopheles; and in closing, the etiology, pathology, symptoms, diagnosis, prognosis, and prophylaxis of malaria are given.
Malarial fever is the general term used to designate a group of specific fevers, their complications and sequelae which are caused by a living animal parasite called the Haematozoon malariae. The parasite invades the red blood cells of man and is transferred from man to man by mosquitoes. The name itself comes to us from the Italian "mal'aria"—bad air. This name was originally applied to the fever because of the belief that it was due to a miasm or poison. Now the name is used to designate the disease itself.

Some of the more common names by which this disease has been known are: Intermittent Fever; Chills and Fever; Fever and Ague; Paludism or Paludal fever; Swamp or Marsh fever; Miasmatic fever; Periodical fever; Autumnal fever; Jungle fever; and Telluric fever.

The most characteristic manifestations of malaria are, intermittent or remittent fever, certain forms which are called "pernicious", and a chronic cachexia which results in an enlarged spleen and anaemia. The parasite which was discovered by Laveran is always present in malarial cases and it produces from the haemoglobin of red blood corpuscles the brown or black pigment granules which are characteristic of the disease.

Malarial fever is truly a cosmopolitan fever, having broken out in practically all sections of the earth, at some time or other. However, it is in the tropics that the disease is most prevalent, and although enormous progress has been made and is continuously being made, it still remains the most common of
infectious diseases. In such places, as the tropics, it has been responsible for practically one-half of the people who have been patients in the hospitals; and it has been so widely-spread that approximately one-third of the entire population have suffered from it. Although comparatively few deaths have resulted from it, yet the disease has been responsible for a huge number of deaths either directly or indirectly. The most lamentable factor about the disease is that it occurs in the most fertile and well-watered parts of the world, thereby, causing to be deserted, many sections which otherwise would be well-inhabited; it, therefore, offers a serious obstacle to the march of civilization.

In the United States, the milder types of malaria are found in certain localities of the New England and Middle Atlantic States. The states covered by the Appalachian mountains, together with a number of the Central and Western states are almost free from the fever. However, the farther south we go, the more numerous become the cases of malaria. The tertian and estivo-autumnal types of malaria are commonly met with in the southeastern part of Virginia, the eastern half of North Carolina, in South Carolina, Georgia, and Florida. Also, in all sections of the states bordering the Gulf; Florida, Alabama, Mississippi, Louisiana, and Texas; and those bordering the Mississippi river, and the western parts of Tennessee, Kentucky, and Missouri. The estivo-autumnal type is found on the coast in certain parts of California, and to a less degree in Arizona, Utah, Washington, and Wyoming.
In general malaria prevails in all the countries within sixty degrees north latitude and thirty-five degrees south latitude. It is found in that part of Canada which is in the region of the Great Lakes. It is found a great deal in the West Indies, except in the islands of Antigua and Barbados; it is found on the Atlantic coast of Mexico and Central America, and to a less degree on the Pacific coast. It is also fairly common on the northern and eastern coast of South America, including Columbia, Venezuela, Guiana, and far into the interior of Brazil.

The fever is very widespread in Africa up to thirty degrees south latitude, except in the extreme southern part, the Cape of Good Hope, German Southwest Africa and the Orange river colony. Malaria in its most pernicious forms is encountered along the Gold and West coasts, along the Mediterranean coast, and especially in the valleys of the Nile and Congo rivers.

The fever is also prevalent in Asia; on the eastern and northern coast of Australia; and in Europe, where it is mostly found in Italy, Greece, Sicily, and Turkey.

The disease prevails especially in the tropics after rains, and at the beginning of what is known as the rainy season. In these places, all types of the fever are met with, although the type which is most commonly found is the severest type, namely, the estivo-autumnal fever.

In the sub-tropics, the disease reaches its height at the end of the summer season and the beginning of autumn. In the United States, it is most common during the months of July, August, September; and during October and November, it decreases
in its intensity until April, at which time, it again begins its upward march until its maximum is reached. Here the type of malaria which is most commonly met with is the tertian type. However the estivo-autumnal type is also found; but the quartan type is hardly ever encountered. In the temperate zones, the season is shorter, and it appears mostly during the latter part of the summer, the tertian type being the prevailing form of the fever.

The disease itself is an intermittent one, characterized by regular recurrences every day, every other day, or every third day, being known as quotidian, tertian, and quartan fever respectively. In fact the keynote of malarial fever is recurrence. These recurrences or exacerbations which take place at regular intervals are sometimes referred to as "Ague fits". They start with severe chills, which increase in intensity until the entire body shivers, and the teeth clatter; the face then becomes blue or livid in color; the fingers dead white, and nails blue. During this stage, the surface of the body is cold to touch, but the rectal temperature rises. There is also a copious flow of clear, watery urine. The next stage is referred to as the "dry heat" stage. The temperature during this stage is very high, often reaching one hundred and five degrees or more; the skin is distinctly flushed and feels to the patient as though it is on fire; the urine in this second stage is scanty and colored a great deal. This stage may continue in certain cases up to twenty or more hours. In the third stage the high temperature abates, accompanied by profuse sweating. In this stage the urine
is also scanty and it deposits a thick, brick-red sediment of urates on cooling. In most cases, the three stages together last about six to twelve hours. Then after twenty-four hours (quotidian), forty-eight hours (tertian), or seventy-two hours, (quartan), have passed from the start of the fit, (the time depending on the type of parasite which is present in the blood of the person), the cycle of symptoms, similar to the ones mentioned above, is repeated all over again.

Frequently in the quotidian and in the tertian types of malaria, a second attack of the fever begins before the first one has ended. When this happens the fever is known as a remittent one. When persons who are suffering from malaria are badly treated, recurrences may continue for weeks or even years separated by intervals of comparative quiescence. However, we should clearly understand that it is possible for a person to recover quickly after the first few attacks.

Although it is likely that malaria has existed from the earliest times, very scanty reference was made to it by the ancient Greek, Latin, and Italian writers. The ancients themselves recognized the fever in its various forms; and their writings seem to indicate that they were also well acquainted with the seasonal and local variability of the fever, and of its prevalence near marshes.

For over two thousand years, malaria has been known to exist in Greece and Italy, and the references of the earlier writers, although very scanty, bear out this fact. However, it is much more frequently referred to by the older writers. Homer (about
Hesiod (about 735 B.C.) lived in what is now a very malarious spot, Oreohomenos, along the bank of Lake Kopais, yet he never made any reference to malaria in his writings. From the medical writings of Hippocrates, Jones infers that paludism was known in the medical schools before his birth (about 460 B.C.). From the Wasps of Aristophanes, (425 B.C.) he infers that paludism was attracting special attention at Athens. The Athenians erected a statue to Athena Hygieia on the Acropolis about 429--B.C., and they started to worship Asclepius, which is inferred by Jones to mean that "ill health was distinctly on the increase". After this the references to malaria became more numerous.

Hippocrates in the fifth century B.C., described and wrote on periodic fevers, dividing them into quotidian, tertian, semiterrtian and quartan. He also noticed that the people who lived in low, meadowy, hot districts were usually wanting in courage and endurance, and this he ascribed to the fact that the fevers abounded in such regions.

Strabo in the first century, B.C., remarked in his writings that Alexandria, in spite of its site, was free from marsh fever. Commenting on this, W. H. S. Jones says, "It is to be inferred from this; that damp places were generally known to be unhealthy, so that exceptions to the rule were noticed by observers as remarkable phenomena." This further bears out the statement that the ancients were acquainted with the fact that malaria was prevalent near marshes.
Dahlgren is of the opinion that Asia was the original home of malaria, and that the fever spread from there to Europe. He believes that the fever was probably established in Greece around the fourth century B.C. and that it has been endemic in Europe ever since. Its prevalence in Italy and Greece has been historic, and he, together with many others, believes that the disease was a powerful factor in the decline of both these great nations.

W. H. S. Jones believes that malaria entered Greece and Italy during historical times; that it spread rapidly; and subsequently exerted much influence on the civilization of these two countries.

Ross is of the opinion that malaria was not very rife in Greece before the height of its prosperity, this, he claims, because of the warlike character and vigorous nature of the people at that time. Also, it would have been impossible for the Greek youths to have partaken in the gymnastics for which they were so well known, if they had possessed large spleens, which is one of the characteristics of malaria. Possibly the change took place around the fifth century B.C. either from the soldiers or from the slaves who came from abroad. Then by its spreading into the healthy towns, the fever, assisted by other causes, began to sap the vigor and physique of the race.

When we come to a discussion of Italy, we meet a repetition of what took place in Greece. Very scanty reference to malaria was made by the earlier writers, but the older ones referred to it more often in their writings. The general opinion is that
many sections of Italy, as in Greece, were at one time free from malaria, because many of the ancient settlements were situated on sites which are now extremely malarious; and it is very unlikely that the ancients would settle in unhealthy regions. This also, supports the belief of Ross, Jones and others who claimed that the disease was brought into both Greece and Italy by foreigners. The vast drainage system of cuniculi is said by some to have been built because of malaria, thereby enabling people to settle in sections which are now malarious. Others say that the cuniculi were built for agricultural purposes. The better view, and that which is more probable, is the one held by Jones, namely that the disease was introduced in Greece and Italy at the time of the first foreign expansions and became gradually intensified.

North, in his book, "Roman Fever", claims that the intensification of the disease was due to rural depopulation from the wars or from economic changes. Ross, on the other hand claims that malaria helped to bring about the depopulation. It seems as though the opinion advanced by Ross is more probable, since the disease can only be transferred by mosquitoes from persons who already have been infected, and if there are no people present, the mosquitoes cannot become infected themselves and consequently cannot carry the infection to any one else.

The effect of malaria was probably less in Italy than in Greece, due to the smaller proportion of malarious area. The Roman writers knew the leading facts of paludism, as did the Greek writers. Varro (116--B. C.) in his "Rerum Rusticarum"
claimed that in marshes there were animals too small to be seen, but which were able in some way to enter the mouth and nostrils of people and carry troublesome diseases. Columnela (first century B.C.) also connected malaria with insects which bred in the marshes. Cicero and Seneca claimed that certain districts were completely depopulated due to paludism. This supports the contention of Ross, namely, that malaria was a cause and not an effect of depopulation. Heroditus first noticed the use of mosquito nets (conopeum) in Egypt; and later reference was made to them by Varro, Juvenal and Horace.

The entire history of malaria can be divided into three major periods:

First period: From the time of Hippocrates up to 1640.
Second period: From 1640 to 1880.
Third period: From 1880 up to the present time.

The theory of the parasitic origin of the disease dates back to Varro (116–37 B.C.). It was later revived by Lancisi (1717) and others, and it was finally confirmed by Laveran in 1880. It was the discovery of Laveran in 1880, that marked the first great step in the etiology of malaria, since it enabled us to distinguish malarial fever from fevers which were not malarial.

Up until the end of the sixteenth century, no noticeable advance was made in the study of malaria, from what was already known. However, at that time, Mercatus, while working on malignant fevers, described various forms of pernicious paroxysms in association with intermittent fever, especially with the tertian
type. Nevertheless, no marked interest was as yet evident in the study of malaria.
IMPORTANT DISCOVERIES

In the year 1640, the next great advance was made in the study of malarial fever. This is the year which marked the beginning of the second period in the history of malaria. It was during that year, that the Countess d'El Cinchon, wife of the Viceroy of Peru, contracted a fever while she was in that country. This in itself was not of importance, but what is important, is, that she was cured of the fever by the use of Cinchona bark, which a group of Indians had discovered near Loxa (?). It was the discovery of this bark which was later to become of tremendous importance in the treating of malaria infected persons. Foreseeing the value of the bark, the Countess, together with her body-physician, Juan del Vego, brought it back to Europe, and its use was therefore introduced and established.

Where previously very little attention and interest was shown in the study of malaria, it now began to receive a great deal of attention; so that besides its curative value, Cinchona bark is important because it furnished a much needed impetus to the study of the disease itself. The result is that during the last half of the seventeenth century and the beginning of the eighteenth, much literature was published on the subject. Previously, we must remember, very little literature was published which directly related to the subject, for most of the references were made in an indirect way. Besides this, the discovery of Cinchona bark enabled Morton in 1697 and Torti in 1753 to separate the types of malarial fevers which were cured by it,
from those on which it had no influence; and as a result, they were then able to differentiate between the two types and study the symptoms of the former, (those which were cured by it). The alkaloid quinine was not extracted from the bark until almost two hundred years after its discovery. This was accomplished by Pelletier and Caventou in 1820.

The old hypothesis, in which the fever was connected with marshes, was recalled by Morton, and he also claimed that the fevers disappeared after drainage. He even went so far as to study mosquitoes, having advanced the suggestion that inoculation by them was a possible means of infection, and that their larvae fouled drinking water. Then, in order that the paludic connection might be explained, the paludic miasma hypothesis was advanced. According to this hypothesis, there was an infecting emanation from stagnant water, which was either of a chemical or of an organic nature. However, because certain facts still remained unexplained, the paludic miasma hypothesis was extended to the telluric miasma. This hypothesis suggested that there was poison present not only in marshes, but anywhere in suitable soil, and that it arose either at night or whenever the soil was disturbed. The name mal’aria (bad air) is derived from this latter hypothesis.

We now reach the next important step or advance; and this took place in the year 1847. In that year, Heinrich Meckel examined the blood of an insane person who had died, and who had suffered from malaria fever. While he was examining the blood, Meckel observed the presence of a peculiar black granular
substance, both in the blood itself and in some tissues. This substance was composed of ennumerable black granules, which eventually became known as malarial pigment or melanin. For a long time after its discovery, this malarial pigment or melanin was thought to be due to a chemical action of the paludic miasma on the red cells of the blood. Its presence was next observed by Virchow who found the same substance in the body of a man who suffered from chronic malaria (1849).

These observations were directly responsible for the great discovery of Laveran in the year 1880. This discovery marked the beginning of the third period in the history of malarial fever. Laveran had observed that the granules, which made up the granular substance, were very frequently contained within cells possessing active amoeboïd movements. He had also noticed that in those persons who were infected with malaria, many of the red blood corpuscles contained small, pale, circular patches, without the yellow color of the corpuscles; and that these patches in the fresh blood were capable of amoeboïd movement and contained one or more minute black particles of melanin. He further observed that these patches kept increasing in size until they almost completely filled up the corpuscle; and when they reached that stage, they contained a large number of melanin granules. When they became mature, he noticed, the patches broke up into separate portions called SPORES, then the corpuscle which had served as their host, ruptured, and the spores were liberated in the serum to infect fresh corpuscles. These were the ASEXUAL forms of the malaria parasite which was
subsequently, known as the PLASMODIUM.

Besides these forms, however, Laveran also saw some bodies, which evidently belonged to the same class, but which were not contained in the corpuscles. In other words, these latter bodies which he observed, were full of melanin like the previous bodies, but unlike them, they were lying by themselves in the serum. Turning all his attention to these latter bodies, he finally, on the sixth of November, 1880, at Constantine, Algeria, "saw the melanin granules become violently agitated and then observed that long filaments issued from the parent body and wriggled about violently as if attempting to escape from it". At first he thought that the filaments, which issued from the parent body, were flagella, similar to the flagella found in many small organisms to enable them to move about in water; and he named the entire body, including the so-called flagella attached to it, the flagellate body. Now, however, these bodies are known to be, not flagellate bodies, but the male SEXUAL forms of the Plasmodium, the filaments being the SPERMS.

The entire history of the researches carried out by Ross and which eventually led to a complete, solution of the problem, depended upon these SEXUAL forms. Although, at that time, it was known that many diseases were due to vegetable parasites called bacteria, it was clearly evident that the organism discovered by Laveran was not a vegetable parasite, but was an animal, a living parasite of the human red corpuscles.

Laveran clearly showed that his parasites were found only in people infected with malaria, and were never found in healthy
persons; yet he could not work out their complete life history. About this same time C. Gerhardt proved that healthy persons could be infected by the inoculation of blood of persons suffering from paludism (1884). His work proved conclusively that the disease was a true infection of a living virus. In 1886 and subsequently, C. Golgi, showed clearly "That the parasites reproduced by simultaneous sporulation; that the febrile paroxysm in the patient commenced at the same moment when these spores were liberated; and that the parasites of quartan and mild tertian fever were morphologically different". These researches were verified by many observers in various parts of the world.

After Laveran made his remarkable discovery, much work was performed, and certain conclusions were reached in regard to malaria. These were:

1. That Laveran's parasite was the cause of malarial fever, because it was always found in persons suffering from malaria, but never found in healthy persons.

2. That the parasite was a sporozoan which belonged to a group probably allied to the Coccidiidae, of which other members were found in birds; and that somewhat similar but more distantly related haemocytosoa were found in other Vertebrates.

3. That the organisms, once they gained entrance in the blood, propagated rapidly by spore formation.

4. That there are probably at least three varieties of the human parasites, which caused respectively
the quartan, tertian and irregular types of fevers. Golgi had already shown that the parasites which caused quartan and mild tertian fever were morphologically different from each other.

5. That the paroxysm of fever commenced with the release of the spores.

6. That with all varieties of the parasites there were certain forms which did not produce spores, but which, shortly after blood containing them was drawn from the host, emitted certain singular motile filaments. The nature and function of these filaments still required further investigation.

It is clearly evident, at this time, that a tremendous advance had been made in knowledge pertaining to malaria. Where from the earliest times, practically all knowledge centered about the paludic and telluric miasma theories, now the malarial fevers could be distinguished from non malarial ones due to the discovery of the Cinchona bark; and what was most important, the actual parasite which caused the fever was now known, and was being very closely studied.

Now that the parasite which caused the fever was known, the question as to what causes malarial fever, could be answered. However, it was now necessary to answer another question, namely, how do these parasites enter into the blood of men and animals? This question was still unanswered, and all those concerned in the problem, now bent all their efforts in finding the solution
to this problem.

Some were of the belief that the parasites were capable of saprophytic life in stagnant water. According to this belief, the parasites entered the body either by the inhalation of watery vapour or by infected drinking water. Calandruchio and Celli even carried on investigations, in an attempt to prove this. Their process was to bring water from notoriously unhealthy sources, and then give it to healthy persons to drink. They believed that when the healthy persons drank the water, they would become infected with malaria. However, the results of their experiments were entirely negative.
ROSS' WORK

Ross first became attracted to the malarial problem in India in the year 1889, when he observed many facts, concerning the disease, which were at variance with the hypotheses instilled in him during his curriculum. He had at first believed, that the disease might be due to intestinal autointoxication. For several years he had carefully examined the blood of malarial persons, and he had failed to find the true parasites, which Laveran had discovered and which others had confirmed. In fact, due to his continued failure in attempting to find them, Ross was even beginning to doubt that Laveran's parasites existed. However, in the year 1894, while he was in England, he called on Dr. Manson, who showed him the malaria parasites. In November of that same year, Ross received a communication from Manson, in which he (Manson) stated his hypotheses, which he had just formed and in which he suggested that the mosquito was the intermediary host of the malaria parasite.

Manson's suggestion that the mosquito was the intermediary host of the malaria parasite was not the first such suggestion that had been put forth. Previous to his, the following theories had been advanced in which it had been suggested that the mosquito played an important part in the spreading of malarial fever.

Ross was informed by Dr. R. H. Kennan that when he (Kennan) had been in Freetown, Sierra Leone, he had come across an old ordinance, dated 1812, in which the inhabitants were enjoined to keep the road in front of their property in good condition, in
order that the formation of "stagnant pools which generate disease and mosquitoes over the town", might be prevented.

Dr. Josiah Nott, of Mobile, Alabama, in the year 1848, stated that he believed both yellow fever and malaria could be transmitted by mosquitoes; and he further stated that the speculation, as regards malaria, had already been advanced.

In 1854, Louis Daniel Beauperthuy, a French medical man, mentioned the same hypothesis in greater detail. He studied both malarial fever and yellow fever microscopically, and after close study and observation, he came to the conclusion that both fevers were produced by "a venomous fluid injected under the skin by mosquitoes". He even went farther and claimed that marshes were dangerous, not because of their effluvia, but because the mosquitoes, which were responsible for the diseases, bred in them. His theory was evidently a speculation which he based upon general thought and observation, since he performed no experiments whatever to support his opinions. As we shall see later, subsequent events and experiments proved that his theory, although merely a speculation, was correct.

Another hypothesis similar to the one mentioned above was advanced in 1881, by Charles Finlay of Havana. However, it is significant to note that Finlay's views differed from those of Beauperthuy in one important particular. Where Beauperthuy believed that the mosquitoes originally obtained the disease-giving poison from the marsh in which they bred; Finlay believed (in regard to yellow fever) that the mosquitoes obtained the poison from sick people, that is, those people who already had
the disease. His theory, therefore, was that the mosquitoes acted merely as carriers or conveyers of the fever from people already infected to those in a healthy condition. His work however, was practically the same as that of Beauperthuy, mostly conjectural, and the few experiments that he was supposed to have performed were very doubtful.

In the year 1883, a paper was published by Dr. A. W. A. King, in which he advanced the view that the malarial poison was carried from the marsh to the human being by the bites of mosquitoes which bred in them. This theory, as we can see, was fundamentally the same as that of Beauperthuy, and it, like that of Beauperthuy, was wrong in its claim that the mosquitoes obtained the poison from the marshes in which they bred. Finlay, in his theory had not made the same error, but he had given the correct explanation, only that he did not prove it by actual experimentation, as he should have. King, in order to support his hypothesis, gave nineteen reasons, all of which were based entirely on epidemiological considerations. They were:

1. Both paludism and mosquitoes are connected with marshes.
2. They both require a temperature of over sixty degrees.
3. Are checked at freezing point.
4. Abound most near the equator and sea coasts.
5. Have an affinity for dense foliage.
6. Can be screened off by trees.
7. Can be transported by winds.
8. Are encouraged by turning the soil.
9. Are affected by "bodies of water".
10. Are diminished by cultivation and settlement.
11. Keep near the surface of the ground.
12. Abound most after sundown;
13. And in the open.
15. Are not so common in cities.
16. Are most prevalent in autumn.
17. Are arrested by mosquito nets.
18. Affect infants (which are generally protected by nets) less than adults.
19. Attack whites more than other races.

Reasons (4), (13), (14), (18), and (19) are not very sound; while reasons (5), (6), (7) are doubtful. All his reasons are stated with one view in mind, namely that the insects brought the poison from the marshes and then proceeded to inoculate it into healthy persons, by their bites.

Laveran, in 1884, suggested the same idea, when he said; "do mosquitoes play the same role in paludism and in filariasis?" "The thing is not impossible, and we must note that mosquitoes abound in all marshy places". Seven years later, Laveran again suggested the same idea, still very briefly and without giving many reasons to substantiate it.

Going back now to the hypothesis of Manson, which he communicated to Ross, (1894) and in which he suggested that the mosquito was the intermediary host of the malaria parasite, we find that the entire hypothesis was based upon Manson's own parasitological argument, Laveran's work had clearly established
the fact that the general life cycle of the parasites within the vertebrate host consisted of a process of asexual spore formation. He had also, as has been pointed out, observed that besides those sporocytes which existed for the purpose of asexual spore formation, there were, also, certain large cells, which evidently did not exist for the purpose of producing spores. He had also, by actual experimentation, demonstrated that if the blood which contain these cells (the ones which did not produce spores) was withdrawn from the circulation, the cells underwent a peculiar change, "they gave issue to a number of long, actively motile filaments, which could separate themselves from the parent cell, and progress independently among the blood corpuscles."

According to Grassi and a few others, the motile filaments were the products of a kind of death agony In Vitro. These men explained their stand by claiming that the motile filaments contained no chromatin. Later study proved this to be untrue.

Laveran, Danielewsky and Mannaberg had come to the conclusion that the motile filaments represented in some way the highest stage of the parasite; Mannaberg even went so far as to suggest that the motile filaments were concerned "in the passage from the intracorporeal to the extracorporeal stage of the organisms. However, he did not, in any way, indicate the route by which he thought that the passage was made.

It was precisely at this point that Manson's speculation broke in. He fully agreed with the opinion advanced by Mannaberg; but he noticed further that there must have been some means whereby parasites could pass from an already infected
individual into a fresh or healthy individual; and since observation and experimentation had demonstrated that the parasites of malaria were contained within the closed cavity of the circulation, Manson claimed that it was impossible for the parasites to escape from the circulation, except by the intervention of some external agency; this agency he claimed was the mosquito.

He went further and claimed that if we considered the epidemiological laws of malarial fever, we would see a possible connection with mosquitoes. He immediately came to the conclusion that "the motile filaments were really flagellate spores which, when the parent cells were ingested by the mosquito, escaped and entered the insect's tissues developing in them into some form analogous to that of the organisms in the human blood", therefore, he reasoned, after the death of the insect, the parasites entered the water and infected men either through the medium of drinking water, or by the aerial miasma.

We can see therefore, that Manson, in his hypothesis, suggested a clue which related only to the departure of the parasite from the human host; it did not, in any way, attempt to explain the route by which the parasite entered the human host, that is, it did not suggest the exact mode of infection. Later on, we shall see how he was wrong in his latter points and in his belief that the motile filaments were flagellate spores. However, it was through the fundamental part of his hypothesis, namely that "the motile filaments and the parent cells from which they spring must be meant to infect the mosquito in some way", that the necessary clue to further research was furnished.
It is altogether possible that without this very important clue, the malarial problem would probably not have been solved at all, or at least much later than it actually was.

Ross, before departing from London, discussed with Manson what would be the best method of procedure after he arrived in India. Both of them agreed that the best method to employ would be to carefully select persons whose blood contained gametocytes (this was the name that had been given to those particular forms of the parasite of which some produced motile filaments); then allow mosquitoes to bite these persons; and then "attempt to trace in the tissues of these insects the development of the above mentioned motile filaments (which they thought were flagellate spores)". For they reasoned, that after they had observed the motile filaments in the ingested blood in the mosquitoes' stomach, it would merely remain for them to follow said filaments to their ultimate destination. This destination, they supposed, was within some kind of cells of the insect's tissues.

They were well aware of the fact that not all species of mosquitoes would be amenable to the malarial infection; but they were of the opinion, that they would be able to pick out the proper species by its particular prevalence in very malarious localities. What, they believed would be their most difficult task, would be to trace the motile filaments to their habitat in the particular cells of the insect; for once this was accomplished, it would be a simple matter to observe the further development of these filaments; and to watch how they escaped into the water after the host's death. The solution of the problem would
then be manifest, for they would be able to identify the extra-corporeal form of the parasites in water, air, or dew, and they would also be able to ascertain exactly the route of infection in man.

Ross conducted his preliminary observations in 1895 at Secunderabad, where he had been appointed medical officer of a regiment of native soldiers suffering much from malarial fever. He immediately began to study the mosquitoes which abounded in the vicinity, and being unable to secure any literature concerning them he was forced to rely on his own observations. He took the various species of mosquitoes which he observed in that locality and divided them into two groups. For his own convenience, he called these two groups, Brindled mosquitoes and Grey mosquitoes. (It was not until two years later that he clearly recognized a third group which he called Spotted-Winged mosquitoes). He then allowed a number of the grey and brindled mosquitoes to be fed on persons, who contained the gametocytes of estivo-autumnal fever (crescents) in their blood.

The first point which had to be cleared up was the process by which the motile filaments escaped from the parent cells (gametocytes) within the stomach cavity of the mosquitoes. In order that he might find this out Ross killed the insects from one minute to several hours after they had been fed on a patient. He then extracted the stomach and examined its contents in the fresh state. The first thing he observed was that in the insect's stomach about sixty per cent of the crescents gave issue to the motile filaments; previously when this same process
had been studied "In Vitro", only about five per cent of the crescents gave issue to the motile filaments. He also noticed the fact that in the preliminary stages of the process, in which the crescents swelled up and rounded out, were much more constantly seen in the blood ingested by the insect than "In Vitro". This was a noteworthy discovery because it at least showed that the insect's stomach was a more favorable locus for the process than an ordinary specimen of blood was. He further observed that approximately one-third of the crescents never produced motile filaments at all; and these had a slightly different appearance than the others which did emit them.

One fact, therefore, was now established, namely that the gametocytes were not immediately killed in the mosquitoes' stomach, but they issued their motile filaments there more readily than "In Vitro". This much being now settled, it was now necessary to seek the destination of these filaments in the insect's tissues. This was by no means an easy task, for it must be borne in mind that the motile filaments were exceedingly delicate bodies, and their movements were very difficult to follow, even with the highest powers of a good microscope and in the clear spaces of an ordinary preparation of blood. The task became even more difficult for Ross, for he was dealing with the blood of a mosquito's stomach, which in a very short time became a thick grumous mass in which it was impossible to even see the filaments unless they were in active movement. Ross therefore, because of the limited means with which he was forced to work, was unable to discover what became of the filaments,
for within a few minutes of their escape, they seemed to lose their movements. He, then determined to give up his quest of following the motile filaments in an attempt to discover their destination; and it turned out to be a fortunate decision. For later events showed that the motile filaments migrated nowhere, and in fact, they did not enter the mosquito’s tissues at all.

After his determination of abandoning the quest of following the motile filaments, the first method which Ross adopted and which ultimately led him to success was as follows: By hypothesis, he reasoned that when the motile filaments reached the particular cells of the mosquito for which it was believed they were destined, they should grow in them into some unknown but larger form; they should become more visible; and then if they were to pass into the water, as it was believed they would do, they should take on some definite form of resistance which would be easy to recognize.

Instead of killing the mosquitoes a short time after they had been fed on a patient, as he previously did, Ross now waited several days before he dissected them. For according to his hypothesis, after a lapse of a few days, the filaments should have developed into something more tangible. His entire plan was, first to feed the mosquitoes on persons who contained crescents in their blood; second, to keep the insects alive for several days; and then to search their tissues for any parasites which might occur in them. Once the parasites were found it would be an easy matter to find out if they were derived from the motile filaments, for all that would be necessary, would be
to ascertain if the same parasites also occurred in mosquitoes of the same kind fed on healthy blood. In the experiments which he performed, Ross used only those mosquitoes which were freshly hatched from the larva in captivity, for by so doing, any doubt as to whether the insects had been previously contaminated, was dispelled.

He then conducted many experiments in an attempt to find out if the infection was carried by drinking water. The result being always negative, he began to consider the possibility of the infection being carried by some other means. He came to the conclusion that "Manson's induction was exigent only as regards the entry of the parasites into the mosquitoes, and that his secondary hypothesis regarding their escape from the insects and their infection of man through drinking water was not so strong". His first conjecture was that the insects first became infected themselves, either from diseased persons or from other mosquitoes, and then, they either inoculated the parasites into healthy persons during puncture, or deposited them on the skin during haustellation.

The hypothesis that infection might be caused by inoculation had previously been considered by Bignami, and the same idea had been mentioned long before and in much greater detail by King. However, we must note an essential difference which existed between the opinions of Bignami, King, and Ross. The first two believed that the poison existed in the marshes themselves, and that the mosquitoes brought the poison from the marshes to man; Ross, however, believed that the mosquitoes were
infected from persons who already had the disease (according to Manson's induction) and possibly also from other malaria infected mosquitoes, and then they communicated the parasites to healthy persons—perhaps by inoculation. Such a belief would also explain the connection that had always existed between malaria and marshes, because the mosquitoes bred in stagnant water. Manson's secondary hypothesis was that "the motile filaments, after living for some time in the mosquito, passed from it into the water, and thence by ingestion or inhalation into man". This, Ross concluded, did not hold, for if there was such an infection of water, as Manson claimed, it must be very limited, because after their escape from the dead mosquito, the parasites could neither travel far in the water nor live long there. For if they could do this, it would be logical to conclude that all the water in India would be infected. The result of this would be that the disease, instead of being confined, as it was, to certain spots, would be universal. Obviously then, logical reasoning, coupled with the previous history and knowledge of the disease, did away with Manson's secondary hypothesis.

Ross, as has been pointed out, had now roughly classified three types of mosquitoes; Brindled Mosquitoes (now recognized as belonging to the genus Stegomyia); Grey Mosquitoes (now recognized as belonging to the genus Culex); and the Dappled-Winged or Spotted-Winged Mosquitoes (now recognized as belonging to the genus Anopheles). Up to now, Ross had conducted numerous experiments with the first two types of mosquitoes, and the results of all these experiments were the same, negative. He
followed, in all cases, a definite form of procedure which was as follows: Larvae were collected by employed natives from far and wide round the barracks. These larvae were kept in separate bottles, and when the adult insects appeared they were released within mosquito nets in which the patients had been placed. The insects were applied sometimes during the day in a darkened room; and were sometimes fed all night. After feeding, the gorged insects were collected in small bottles containing a little water and were kept for several days before being dissected. Then every cell was examined; even the integument and legs were not neglected; the evacuations of the insects found in the bottles, and the contents of the intestine were scrupulously searched. Numerous grey and brindled mosquitoes were exhaustively examined, and the results were negative.

As yet, dappled-winged mosquitoes had not been used by Ross in his experiments, and therefore, the results were concerned only with the grey and brindled mosquitoes. The reason that the dappled-winged type had not been experimented with was because their larvae could not be located. However on the fifteenth of August, one of Ross' assistants brought him a bottle of larvae, a number of which hatched out on the following day. Among the number which hatched out, several of the dappled-winged type of mosquitoes were found. As soon as they were recognized, they were immediately fed on a case with crescents in the blood. One by one then, they were all closely examined, and the results, until there were but two more mosquitoes remaining, were entirely negative. However, while Ross was examining the next to the last
remaining mosquito, he observed nothing unusual until he reached the insect's stomach; there he noticed a "very delicate circular cell which was apparently lying among the ordinary cells of the organ, and which was hardly distinguishable from them". He further noticed that there was not only one but several similar cells in the same region. He then closely examined one of these particular cells and found that it contained a few minute granules of some black substance exactly similar to the pigment of the malarial parasite. On the next day, he dissected and examined the last remaining mosquito and found similar cells in it.

Now that he had discovered what he believed was the malarial pigment in the mosquito's stomach, he summarized his work. He had bred both of the mosquitoes, in which he had found the pigment granules, from larvae in captivity; he had fed both of them on the same person (a person suffering from malaria); he had never, in the hundreds of mosquitoes which he had hitherto examined, noticed bodies which resembled the pigmented cells he had found in the last two mosquitoes; these cells did not lie in the stomach cavity of the insects, but in the thickness of the stomach wall; these cells contained a number of black granules, which were exactly like the granules that had been discovered in the malarial parasites; they were also unlike anything that had been formerly observed in any mosquito. "Lastly, these two mosquitoes, (in which the pigmented cells were found) were the first of the kind which Ross had ever tested". Two quantities, previously unknown, had now been solved by Ross, namely "the kind of mosquito implicated and the position and appearance of
the parasites within it".

Ross and his assistants had yet to find the breeding places of the dappled-winged mosquitoes, with the result that, neither the larvae of the small nor of the large species of these mosquitoes could be found. One day, however, swarms of small grey larvae were found in an isolated pool of rain water. When these larvae hatched out, it was discovered that they were the long-sought larva of the small dappled-winged mosquitoes. The first striking feature which Ross noticed was their lack of breathing tubes, and that, compared with the larvae of other mosquitoes, they had a peculiar attitude. He then examined the pool in which they had been found, and he remembered that the larvae of other mosquitoes were never found in such shallow pools as this one was. These few facts which he immediately observed concerning the mosquitoes themselves and their breeding place, seemed unimportant at the time, but they became of tremendous value later on, in connection with the prevention of malaria.

The larvae were kept in breeding bottles, and when the adults appeared, they were set free in large numbers within the mosquito net of a patient with crescents in his blood. On the following day, Ross found that only two of the mosquitoes had fed themselves; one of these he killed on the next day, and after examining it found nothing; the second one he killed on the following day, and in this one he found a large number of small pigmented cells. The matter was practically clinched then, and Ross communicated to Manson, stating in his letter that within a few weeks, he (Ross) would know the full life-history
of the parasites of malaria in the mosquito.

Mao Callum, in the meantime, while working on the halteridium of birds, in America, discovered just what the motile filaments were and how they acted. In studying the gametocytes, he had observed that they were of two kinds. One of these produced motile filaments, while the other did not. In order to see if there was any connection between the two different types, he placed one of each of the cells under a microscope; "he observed that the filaments escaped from one as usual; that it moved about actively for a time; and then approaching the other gametocyte actually entered it". The result of this experiment proved two important facts for the first time, that the filaments contained chromatin, and that they escaped and moved about in the blood.

Mao Callum concluded, therefore, that the filaments were really sperms, which were emitted from the one kind of gametocytes (males), and then fertilized the other kind of gametocytes (females). He further observed that the female cell, which was motionless before fertilization, afterwards became vigorous. It was now clear why Ross had found that only a percentage of crescents emitted filaments in the mosquito's stomach, the rest, which did not, were females. The question concerning the motile filaments was at last clear.

Now that the pigmented cells had been discovered, the question naturally arose, "what are the pigmented cells?" Manson, who had received the results of Mao Callum's work a short time after Ross had discovered the pigmented cells, immediately
connected the two groups of facts, that is, the results of Ross and of Mac Callum. He concluded, that the PIGMENTED CELLS WERE THE FERTILIZED FEMALE CELLS, WHICH HAD BURROWED INTO THE INSECT'S TISSUES FOR THE PURPOSE OF UNDERGOING FURTHER DEVELOPMENT THERE." This would also account for the presence of pigment in the cells.

After the pigmented cells had been discovered, Ross was unfortunately transferred to Calcutta. I say unfortunately because at Calcutta, he was unable to work with actual malaria patients as he had been doing up to that time. He therefore, shifted his work to birds, because the malarial parasites of birds were very closely related to those of men.

The true malaria parasites were distinguished by their generally amoeboid character, by their containing the characteristic black or brown pigment (melanin); and by an "identical life-history as regards the production and appearance of the spores within the corpuscles, and of the motile filaments shortly after the blood containing them is drawn from the host". The only differences between the parasites of birds from those of man were in some small morphological details.

Ross, in his work, used crows, pigeons, larks, and sparrows, and his results were what he had expected, so that the theory of the parasites of malaria developing in mosquitoes became practically established. While he was studying their development, he noticed that the pigmented cells kept growing in size, until about the eighth day, when they had grown to such a degree that they were almost visible to the naked eye, then, they evidently became mature and burst within the insect, and in order to
support this claim, Ross offered the proof that when he dissected mosquitoes which had been infected more than eight or nine days, he never found in them the mature pigmented cells, but only their empty capsules.

Up to that time the commonly accepted opinion was that the female mosquito, a few days after her meal of blood, laid her eggs and died. Ross, himself, had accepted this opinion, although he had on many occasions noticed that the insects did not die immediately after laying their eggs. One day he was busily engaged in watching the pigmented cells grow in size, but although they kept growing larger and larger, they did not seem to ripen, even five days after the insect had been fed. All at once the reason why the mosquitoes died so early occurred to him, namely, because they had never been fed anymore after the first time. He then set out to see if this was so, and he found that by feeding the infected mosquitoes more than once, he was able to keep them alive for a month. By this discovery he was able to work out the development of the malaria parasite completely.

Ross had, up to the present time, succeeded in tracing the development of the pigmented cells to their maturity, rupture and discharge of their contents into the body-cavity of the mosquito. To be able to definitely explain what the route of infection was, depended on finding out what happened to the contents after their discharge from the pigmented cells. The contents consisted of a multitude of delicate thread-like structures, which, upon the rupture of the parent cell were poured into the insect's body-cavity, and which were evidently spores.
Manson claimed that these spores escaped into the water; Ross claimed that they were voided by the intestine; King and Bignami claimed that the spores worked their way into healthy persons during puncture.

Ross, on the second of July, found several of these so-called spores in a large cell which was in the thorax of a mosquito. Two days later, he noticed that towards a certain region in the thorax, these spores seemed to become abundant in number, and in that particular region he also observed many cells similar to the one which he had noticed two days previous.

All of these cells were contained within the same capsule and were attached to a duct, forming a sort of gland-like structure. All of these cells contained hundreds of the aforementioned spores (thread-like structures), and very close by where the gland-like structure was, he noticed another lobe of the same structure, which was likewise filled with spores.

On the eighth of July, Ross finally discovered what the gland-like structure was. It was situated in the neck and upper thorax (the throat) of the mosquito. It consisted of three lobes on each side, the ducts of which were all united together, and the duct so formed on each side, went forward and joined the similar duct from the other side under the chin—so to speak—of the mosquito. The common duct which was thus formed, went farther and entered through the round base of the central stylet or stabbing weapon of the mosquito's probosces. The gland was, therefore, the SALIVARY GLAND. And it was this particular gland which secreted the irritating fluid which the mosquito
injected in the wound made by her in the skin. He had, at length, finally discovered the exact route of infection.

The process of infection is as follows: "the mosquito (Anopheline) bites a person who is suffering from malaria, and when it sucks the patient's blood, it also sucks up a number of malarial parasites with the blood. These parasites burrow themselves into the insect's tissues, grow rapidly, and after a week or two produce many spores. These spores enter the poison or salivary gland of the insect, and they lie in a fluid which is secreted by this gland. When the insect bites another person, it injects this fluid through its proboscis into the person's skin, and the spores being released mix with the person's blood and produce infection".

Ross believed that the infecting Anopheline probably injected anywhere from a few to several thousand spores of one or more species of Plasmodium at a single feeding. Although many of the injected spores may perish, those which survive enter haematids and they begin to multiply, the rate of which depends on their particular species, and possibly, other factors.

When the number of parasites reaches something like fifty per c. mm. of blood, the patient begins for the first time to show definite symptoms of illness. Also about this same time, some kind of germicidal power comes into play, which opposes the invasion of the parasites and which tends, in the majority of cases, to limit the number of parasites below a fatal number. There is also some increasing anti-toxic power which tends to reduce the effect of the parasites on the host. The result is
that there is probably a constant struggle between the parasites and the germicidal power, tending, in most cases, to bring about the victory of the latter. This struggle, in the case of untreated or non-immune persons, usually produces a long series of relapses, which tend to be precipitated by many secondary influences acting on the host. Usually after this series of rallies and relapses, the person often appears to reach a stage of partial (or complete) immunity.

An average of about one-half the cases tend to recover spontaneously every three months, if reinfection does not occur. The exact effect of reinfections upon the severity or upon the duration of the disease has not been estimated. We must remember that the disease can be cut short at any time by death, spontaneous recovery, or quinine.

Certain conditions are required for the production of new infections in a locality; there must be living either in or near the locality, a person, whose blood contains a sufficient number of sexual forms of the malarial parasite; a mosquito (Anopheline) which is capable of carrying the parasite must suck enough of that person's blood; the Anopheline must live for a week or more afterwards under conditions which are suitable for the parasites to mature in; the Anopheline must then bite another person who is neither immune against the disease, nor is protected by quinine. Numerous investigations conducted for the purpose, have shown that very few or no new infections will occur in a community unless the persons with the sexual forms in their blood and the carrying Anophelines are sufficiently numerous. The
latter statement is the foundation upon which public prevention is built.

After Ross returned to England, he consulted well known zoologists in order that he might secure proper nomenclature in regard to the developmental stages of the parasites in mosquitoes.

The motile filaments were called microgametes; pigmented cells were called zygotes; the thread-like structures in the salivary glands were called blasts. The mosquitoes which he had used were classified as: Anopheles, the dappled-winged mosquitoes; Culex, the grey mosquitoes; Stegomyia, the brindled mosquitoes.

The conditions under which the Anopheles bred and propagated were studied at Sierra Leone. At the time that the studying was going on, it happened to be the rainy season, and the place was full of stagnant pools. It was observed that the larvae of the dappled-winged mosquitoes were always found to be present in such pools; the larvae of the grey and brindled mosquitoes, on the other hand, were always found in tubs and pots. "THE GREAT LAW OF MALARIA---ITS CONNECTION WITH STAGNANT WATER ON THE GROUND---WAS FINALLY EXPLAINED."

After the work of Ross was made known, the first ones to verify it were Koch and his assistants. Koch, himself claimed that he had believed in the mosquito theory from 1883, but he also admitted that he had never published anything about it. He was also one of the first to attack the mosquito theory by actual experiment. His discovery of frequent infections in the native children of the tropics furnished the necessary explanation as
to the source of most malarial infections in the tropics. It also furnished some valuable information as to the possibility of immunity in malaria.

Some mention of the Italian work will be made at this point. The best advantages possible for the study of malaria were available in Southern Italy, and because of these advantages, the Italians were able to add additional information to many facts discovered in other places.

After Laveran had made his remarkable discovery, most of the Italian workers claimed that the motile filaments were "agoniforms." Bignami believed in this theory to such an extent, that he completely rejected Manson's induction. Grassi rejected the entire mosquito theory because of the following beliefs; that mosquitoes did not bite birds; that there were mosquitoes present in places where there was no malaria; and that the malarial parasites died in the stomach of mosquitoes. He was of the firm opinion that the extracorporeal stage of the parasite was a free-living Amoeba.

The Italian theory of the motile filaments was destroyed by Simond, Mac Callum and Ross. Ross, in his papers, showed the life-history of the parasites in the mosquito and also the genus which was concerned in the spreading of estivo-autumnal fever. These papers were all published in the British Medical Journal, and therefore were made accessible to every one. Grassi, however, in his first publication, told all about the work of Ross, but did not mention his (Ross) name once. His later publication showed that he knew about the work of Ross, before he himself
got any definite results.

Unquestionably, the Italians did much work and contributed greatly to the malarial question. However, their one great fault seemed to be a fondness for hypothesis. That is, when some particular fact was discovered, they immediately attempted to explain the entire problem by building an hypothesis on that fact. Then after some experiments did not bear out their hypothesis, they set about for some other means to support their theories, instead of disregarding the hypothesis entirely. The most notable example of this was in regard to the belief that the fever was in some way received through drinking water. They conducted countless experiments in an attempt to prove persons were infected from drinking water, and all their results were negative. Yet, instead of considering the possibility of infection by other means, they kept their efforts bent in an attempt to find out how the infection was transmitted from the water.
MALARIAL PARASITE

The following classification of the malarial parasite, has been suggested by Craig.

Division------Protozoa
Class--------Sporozoa
Order--------Haemosporidia
Genus--------Plasmodium
Species------1. Plasmodium malariae (Marchiafava and Celli). The quartan malarial Plasmodium.
2. Plasmodium vivax (Grassi and Feletti). The tertian malarial plasmodium.
4. Plasmodium falciparum (Craig). The estivo-autumnal plasmodium, quotidian type.

For the continuation of the life of these parasites two distinct forms of evolution are necessary, each complete in itself, but nevertheless depending on the other. One of these is of an asexual nature and it takes place in the blood of man and is termed Schizogony. The other is of a sexual nature and takes place in the body of certain species of mosquitoes (Anopheles) and is termed Sporogony. The forms undergoing evolution in both the human and mosquito cycles have been carefully studied by Ross, Marchiafava, Grassi, Mac Callum, Celli and others; and all
those who have studied the morphology of the parasites have confirmed the observations of these workers.

Schizogony: In discussing the forms of the parasite observed in Schizogony, three zoological terms must be understood; schizont, this term is applied to all asexual forms resulting from the sporozoite, which has been injected by the Anopheline in the biting process, and it also refers to those asexual forms which result from the merozoite; merozoite, this term refers to the forms which result from the sporulation of the fully grown schizont, and which re-enter the corpuscle to continue schizogony; trophozoite, this term refers to the young hyaline forms which develop following the penetration of the corpuscles by the sporozoites and the merozoites.

These forms which have been mentioned, were not seen in the mosquito and they were not known to develop outside of the human body, until their successful cultivation in vitro by Bass.* The schizonts are "thin bodies which result from the injection of sporozoites from the mosquito and from the merozoite, the product of sporulation". The sporozoites are "needle-shaped structures that penetrate the red corpuscle and immediately take on ring shapes, which are termed trophozoites". These are at first not motile, but as they gather pigment from the assimilated haemoglobin, they begin to be active, and this activity in-

*Used a culture medium composed of blood from the malarial patient, to which had been added one-tenth c. c. per cent solution of dextrose. Only the schizonts, the forms concerned in the human life cycle undergo any development in cultures.
creases up to a certain age of the parasite and when this age is reached, the activity decreases. Accordingly, then, depending on the species to which they belong, they assume various shapes and develop certain distinctive points in their morphology, and as development continues, the corpuscles, which are occupied, undergo certain changes, the changes also depending on the species.

The corpuscle is destroyed when the sporulation stage is reached; the adult plasmodia are divided into a number of spores known as merozoites; the merozoites re-enter the red corpuscles, and the evolution is once more under way. This cycle is completed in twenty-four, forty-eight, or seventy-two hours, depending on the species, and hence we have the quotidian, tertian, and quartan types of malaria. In order that there will be no misunderstanding as to the exact meaning of the hours involved in the three common types of malaria, we must understand that when we speak, for example, of tertian fever, we mean that the cycle of the parasite is completed within forty-eight hours, but the resulting chill takes place every third day, and therefore it is called tertian fever. In other words, the cycle itself does not take three days for its completion, so that if a chill took place on a Monday, it would be followed by another on Wednesday, (the third day), the cycle of the parasite, however, being completed in forty-eight hours. The same holds true of the quartan type, the cycle of the parasite being completed in seventy-two hours, but the chill occurring every fourth day.

Sporogony: This cycle takes place in the mosquito, but the sexual bodies (gametes) themselves originate in the blood of man.
They are only formed in the blood of man, and are incapable of further development in the human circulation. These gametes are either macrogametes (female), or microgametocytes (male).

If a mosquito feeds on the blood of a man infected with malaria, assuming that this person has both the sexual forms of the parasite, the first form of evolution, known as ex-flagellation takes place in the male form. In this process of exflagellation, the microgametocyte throws out from one or two to eight long thread-like filaments; they become detached from the parent body and also actively motile; the parent body, from which these filaments were emitted, undergoes degeneration. This process occurs normally in the body of the mosquito within half an hour from the ingestion of the infected blood. We can also observe this same process in the human blood, "if it is withdrawn from the circulation", but it does not take place in the circulation of man under any circumstances.

These motile thread-like filaments or flagella are the fully developed microgametes, and they dance about very rapidly until they come in contact with the macrogamete, which they penetrate and fertilize, and the resulting body is known as a zygote. The zygote, after a short time, becomes situated in the muscular walls of the mosquito's stomach; it is then known as an ookinete, and in this condition it is a motile, protoplasmic body, containing pigment, and a nucleus in the center, and this develops into an oocyst. The oocyst eventually becomes from four to eight times its original size and it contains the fully developed sporoblasts. Thin, elongated, needle-shaped filaments
EXPLANATION OF DIAGRAM I

Schizony: Mosquito (A) biting man injects sporozoites (I) which immediately upon entering the circulation assume ring forms (2); as evolution advances the young schizont (3) is formed which enlarges as evolution proceeds (4). Toward the end of the human cycle the sporulating form (5) is seen, which in turn produces a number of merozoites (6). Each of these young merozoites (7) re-enter other red cells (follow a) and, repeating the process begun by the original ring form (2), continues schizogony indefinitely; thus multiplying the number of parasites by many times every sporulating period.

Sporogony: After schizony has continued for a certain number of days, certain of the merozoites undergo a transformation evolving to sexual forms known as the macrogamete or female (8) and the microgametocyte or male (9). Neither of these forms can proceed further in the process of evolution so long as they remain in the circulation of man, but as soon as they are ingested by the mosquito (B) evolution is again under way (follow b). The first change is flagellation of the microgametocyte, resulting in the formation of the flagellate body (10), which in turn produces the fully developed microgamete (11). This form penetrates and fertilizes the female form (12) resulting in an oocinete, a body that becomes lodged in the muscular walls of the mosquito's intestine (13), this later evolves to the oocyst (14) from which evolve the sporozoites (15), these becoming lodged in the salivary glands and being free in the saliva of the mosquito with which they are injected by the insect into man's circulation (as shown at 1)—the cycle being thus completed.

This diagram is merely to bring out the salient points that take place in the evolution of the parasite.

N.B. This explanation and accompanying diagram (I) have been taken from: Henson, G. E., (Ref. No1 20) after page 30.
Cycle of the Malarial Parasite in man and the mosquito

Diagram I

A. Mosquito, Injecting (1) Sporozoites

2. Young ring form
3. Young schizont
4. Older schizont
5. Sporulating plasmodium
6. Young merozoites
7. Merozoite, continuing process of schizogony
8. Macrogamete (female sexual form)
9. Microgametocyte (male sexual form)

B. Mosquito becoming infected with the sexual forms while feeding on blood of infected man.

10. Flagellate body
11. Microgamete
12. Microgamete fertilizing female
13. Ookinete
14. Oocyst
15. Sporozoites
(sporozoites), come from the external layers of the sporoblasts, and they embed themselves in the salivary glands of the insect. Eventually these sporozoites get into the ducts of the salivary gland and from there into the saliva. With the saliva secretion they are injected into the blood of man by the insect, in the biting process. Thousands of these sporozoites can be harbored in these glands (salivary) and the number injected at a single feeding varies anywhere from a few to hundreds.

Briefly, then, the evolution stages of the two cycles summarized is "gametes forming in the human circulation are withdrawn by the mosquito when biting, and by a series of stages of development in this insect, sporozoites are formed, which become lodged in the salivary glands, and are injected by the mosquito into the blood of man. These penetrate the red corpuscles, and by another series of changes of development in man, reach maturity and sporulate in certain fixed periods, depending on the variety; but this series of stages does not end the cycle in man, for the merozoite, the product of sporulation, now re-enters the red corpuscle, continuing the cycle by schizogony. After this has taken place for some days, certain of the merozoites go on to the formation of gametes, which are then ready to be taken up by the mosquito, and the cycle of sporogony repeated in this insect".* (Diag. I)

As yet, we do not know whether man or mosquito had the infection first, or in which of the two the parasite originated.

*Bibl. No. 20, P. 32
What we do know is that the parasite does alternately occur in man and mosquito, thereby perpetuating the species; and that, as far as we know, they are the only factors necessary for the perpetuation of the parasite, which cannot reproduce except by this alternation of hosts.

A few distinguishing characteristics about the particular parasites responsible for the different types of malaria will now be given. These characteristics have been derived from medical and veterinary entomology and are as follows:

1. *Plasmodium falciparum*: This is the parasite which is responsible for estivo-autumnal malaria, also referred to as subtertian or pernicious malaria. It is the most severe type of the disease and many times its result is fatal. The fever is tertian in form, but there is much irregularity in both the occurrence and the duration of the febrile stage. This is explained by an irregularity in the sporulation of the parasites themselves. The corpuscles which become infected, remain usually normal in size. The trophozoite or intracorpuscular parasite never increases in size over two-thirds of the size of the corpuscle. There is not as much melanin present as there is in the *P. vivax* or *P. malariae*. There may be two or three signet rings present in one corpuscle. From eight to fifteen merozoites are produced from the segmented state. The crescent shaped bodies, which are the sexual forms (gametocytes) and which occur in only this species of *Plasmodium*, appear in the peripheral
blood about ten days after infection. In the female form, the chromatin granules are well concentrated in the mid region, while the male form is more hyaline in appearance.

2. *Plasmodium falciparum quotidianum*: This is the parasite responsible for quotidian malaria. The paroxysms in this type, occur every twenty-four hours. This form of malaria is found in almost every region where the estive-autumnal form is found. It may be the result of multiple infections from the tertian parasites. The parasite itself resembles *P. falciparum* very closely, although usually the corpuscles which have been infected, are smaller than normal.

3. *Plasmodium vivax*: This is the parasite responsible for tertian fever, sometimes referred to as benign tertian malaria. The paroxysms of this form of malaria occur every forty-eight hours. The pigment granules in this parasite are very fine and are distributed throughout the entire corpuscle. The infected corpuscles are noticeably enlarged. The signet ring is very conspicuous. This species contains no crescents and except for their more regular form and denser pigmentation, the sexual forms are fairly difficult to distinguish from the asexual forms. From twelve to twenty merozoites are produced from the segmented state and they may be seen in the peripheral blood, (in the first species, these merozoites could not be seen in the
peripheral blood).

4. Plasmodium malariae: This is the parasite responsible for quartan malaria and the paroxysms occur every seventy-two hours. This is considered the rarest form of malaria and in its distribution, it coincides with the estivo-autumnal fever. The pigment is coarse and usually appears in marginal streaks or in bands. The infected corpuscle remains normal in size. The sexual forms are very rarely observed. The merozoites produced from the segmenting stage are arranged in a "daisy" form and vary from six to twelve in number.
ANOPHELINE MOSQUITOES

Before giving a detailed description of the life-history of the Anopheline mosquitoes, I will first mention some general facts concerning them.

There are about one hundred and fifty species of Anophelines determined and of this number about forty are pretty well known to act as hosts for the malaria parasites. Experiments have shown that not all species of Anopheles can become infected, and some can only be infected by certain species of the plasmodium.

Their eggs are usually laid on water, although they are sometimes laid on blades of grass, sticks, etc. Usually they prefer and select clean water where vegetation exists, for their breeding places. Some natural breeding places are creeks, swamps, branches, shallow pools, pockets of streams, etc., where grass, algae, weeds, sticks, moss, and other vegetation is present.

Most of their flying is done between sunset and sunrise. They do not bite a person who is active or moving about. They attack, however, very quickly and their sting is less irritating than that of other mosquitoes. Ovulation is greatly stimulated by blood food.

The body axis of Anopheles is very straight; its wings are generally spotted; its proboscis is long and thick. If we were to observe the insect seated on some surface, we would notice that its body projects away from the surface at an angle, with its head being nearest to the surface and the extremity of the tail furthest from it. Most of its biting is done in the dark.

The larvae float about flat on the surface of the water
like sticks. When they are disturbed, however, they skate with a backward jerk on the surface and then they dive to the bottom. These larvae live in the majority of cases, in pools of water on the ground and very seldom in vessels of water. They are not found in all pools, but they are limited to those pools that are not so large as to contain minnows, nor so small as to dry up within a week or so, and which are not liable to scourging out during heavy rains.

Such places as these are usually found "in flat, marshy country, valleys, on the margin of lakes and rivers, in forests, on badly drained roads, and in unkept back yards", and for this reason places such as these, are very often termed malarious.

Anopheles abound in forest, bush, and open country covered with shrub, in all of which places they feed on villagers, animals, and birds, and attack travellers in camps or rest houses. Investigations have proved that in and near the houses of natives, whose children so frequently contain the parasites, many Anopheles are often infected, with the result that those travellers who sleep in or near native villagers always run a grave risk.

Another peculiar characteristic of Anopheles is that they do not hover and hum around their victims as much as other kinds of gnats do. And it is due to the fact that they usually enter houses only at night, that they are not generally noticed, and many times people will go away from some particular region thinking that there were no mosquitoes there at all, whereas the truth of the matter is that there were many mosquitoes there,
but they were not perceived.

The Anopheline mosquito goes through the typical four stages which are characteristic of all those insects in which complete metamorphosis takes place. They are the egg, larva, pupa and adult stages.

The egg of Anopheles is boat-shaped, with one end pointed and the other rounded. The lower surface, or what in analogy would be the bottom of the boat is strongly convex and reticulated; the upper surface is more flattened. On each side the egg has corrugated air chambers which act as floats. When the eggs have just been laid, they are white, but they quickly begin to darken and within the space of a few hours, they become almost completely black. The eggs are deposited separately and they may usually be found arranged in various patterns on the surface of the water, where they either form star-shaped groups or by adhering side by side to form miniature pontoon bridges.

When it hatches out, the larva of the Anopheles is very minute; its body is cylindrical and exceeded in diameter by the small rounded head. The larva begins to feed, as soon as it is freed from the egg. It then proceeds to grow rapidly and if there is a sufficient quantity of food about and the temperature of the water is not too low, it may reach its full size within a few days.

The body of the larva is divided into three sections, the head, thorax, and a cylindrical abdomen of nine rings or segments. At first, the latter regions are difficult to distinguish, but as the larva grows, the three fused segments of the
If the thorax become enlarged and flattened. The larva has no legs, but on the thorax and abdomen there are many symmetrically placed pairs of branched, feather-like hairs, which project laterally and aid in maintaining equilibrium; it is probable that these hairs serve also as organs of touch and possibly respiration.

On the back of the head there are many smaller but similar hairs as the one just mentioned. In addition, there are many very small hairs on the entire body especially along the back and sides. When the larva is at rest, it floats about on the surface of the water by means of five or six pairs of brown, palmate structures which are situated on the back of the abdomen. These structures also aid in keeping the horizontal position of the body, which is a definite characteristic of the larvae belonging to the genus Anopheles.

Situated on the next to the last segment on the upper side, is a short siphon, which reaches the surface of the water, when the larva floats. The openings of the two main tracheae or respiratory tubes are located in the siphon.

It must be kept in mind that the larvae are strictly air breathing and the only time that they stay away from the surface of the water, is when they are disturbed, and even then, they stay away for only a very short time. It is precisely due to the fact that larvae need air to live, that we can destroy them by various means, as will be shown when the prophylaxis of malaria is considered.

Terminally located on the last segment of the abdomen are two pairs of bristles and four elongated sac-like appendages
with thin walls, the so-called "blood-gills". On the under side of this same segment there is a fairly large fan-like arrangement of branched hairs which seem to serve as a keel or rudder.

The head of the mature larva is large, rounded, and brown in color. It is joined to the thorax by a membranous neck, which allows free movement. On the upper surface of the head there are dark brown spots and rows of branched hairs. On the sides of the head are antennae, which extend forward; and behind these are the eyes. The mouth, surrounded by a formidable armature, is in front, on the under side and over-hung by the elongated anterior portion of the head. Over-hanging the mouth parts and at the most anterior part of the head, are two moustache-like brushes; below these brushes and slightly behind, are two mandibles which move in a lateral direction and on which there are strong, spine-like teeth for the purpose of crushing food. The maxillary palps which are cylindrical in shape, project on either side of the mandible, below which are the flattened maxillae with numerous fine hairs. Located below all of these afore mentioned mouth parts is the small, triangular, so-called "lower-lip".

The larva feeds in a peculiar way, having its head turned so that the lower side, which bears the mouth, is directed upward. The moustache-like brushes, which are located at the most anterior part of the head, set up a current, by rapidly sweeping the under side of the surface film of water, and by means of this current the food is carried into the mouth. Any small particles that may become entangled in the brushes, are combed out by
stout curved hairs, three or four of which are borne on each mandible, the brushes bending back into the mouth for this purpose from time to time.

The food of the larvae consists of microscopic animals and plants which are found in great quantities on the surface of the water. The intestine is practically a straight tube, which can be seen in the rather transparent living animal, colored dark by its contents. Sometimes, due to ingested algae, the entire larva appears to be green in color.

We can distinguish the Anopheline from the Culex due to the short siphon and horizontal position in the water which the Anopheline has. The common "wrigglers" have an elongated siphon and they hang obliquely or vertically, head down, with only the tip of the siphon reaching the surface of the water.

The duration of the larval stage varies from seven to fourteen days, and during this time all the various parts of the adult insect are being formed under the larval skin. We may even see the adult eye in the older larvae appearing as a crescentic dark mass lying near the larval eye. Changes in the strictly larval internal organs and tissues go on while the adult structures are being formed. When the process has proceeded far enough, there is a T-shaped split along the back of the larval skin and through this, the insect emerges as a pupa.

The pupa like the larva is also aquatic, but it lives a comparatively short and quiet life. During this stage of its existence, the insect does not feed. When resting the pupa floats on the surface of the water, breathing through a pair of
funnel-like tubes. It has the ability to dart downward when it is disturbed. Outlined under the transparent integument of the pupa may be seen the body and appendages of the developing mosquito. The pupal stage usually lasts from two to four days, however, it may, if the temperature conditions are unfavorable, last for weeks. On the other hand, threatening danger may hasten the emergence of the adult.

The entire pupa stage "represents that period in the metamorphosis of the insect, during which the internal changes which began in the larva and which will eventually result in the formation of the adult mosquito, are carried on and completed".

When the mosquito fly is fully formed, the pupa skin splits along the middle of the back and the adult emerges from its floating case. The legs and wings are at first very delicate, but they become hardened after a short time.

The adult mosquito is from six to eight mm. long. Its body is covered by a dense, thin continuous layer of chitin. This chitin protects the body and forms a kind of external skeleton. The body is divided into three regions, head, thorax, and abdomen. On the head are the mouth parts and special sense organs. The thorax, of three segments, bears the legs, wings, and a pair of minute balancers or halterers. The abdomen consists of eight rings and except on the terminal segment, it has no appendages.

Two large compound eyes are situated on the anterior portion of the head each of which is composed of several thousand simple eyes or facets. In front of the eyes are two, slender
antennae, which are organs of hearing, and also, it is through them that the male is able to detect the presence of the female. At the very front of the head and below the antennae, are the mouth-parts making up the proboscis.

The proboscis is composed of various parts, such as; the labrum, which has a deep groove along its lower side; the hypopharynx, which lies under the labrum and is closely applied to it in such a way that it closes the groove from below, thereby forming a tube through which the mosquito sucks up blood and other liquid food; running along the median line of the hypopharynx, there is a tubular channel which serves to conduct the poison that the mosquito pours into the wound when sucking blood; two pairs of slender rods, the mandibles and maxillae lie along the sides of and below the tube which the labrum and hypopharynx formed; the maxillae are stouter and have the larger teeth and they serve to brace the head while the sucking-tube is thrust forward into the wound made by the point of the labrum; the labrum, hypopharynx, mandibles and maxillae all form a compact mass which is contained within a groove on the upper surface of the lower lip or labium, when they are not actively engaged. Only the female of the species sucks blood. The maxillae are not present in the male and the tip of the labrum is blunt and unfit for piercing.

On either side of the proboscis are the maxillary palps, which serve as organs of touch. In Anopheles, these palps are long and equal in length to the proboscis and they are covered with scales. In the female, they are slender and of uniform
thickness; in the male, the terminal segment is enlarged and bears long hairs. The characteristics of the maxillary palps furnish a ready means of distinguishing Anopheles from Culex.

A slender neck unites the head and thorax. The middle segment of the thorax is larger than the other two and it forms the entire dorsal portion of the thorax. The wings are membranous and they are strengthened by ribs, or veins. On the margin of the wings, there are several rows of scales. A pair of club-like structures termed halteres, are located on the third segment. These halteres are also known as balancers and they maintain the equilibrium for the insect. On each thoracic segment there is also a pair of legs. These legs are connected to the body by the "coxal" or hip joints, which are constructed so that much freedom of movement is allowed. The parts of the leg, beginning with the hip-joint or coxa are: coxae, trochanter, femur, tibia, five tarsal joints. The leg proper is made up of the femur, tibia, and tarsal joints. On the last one of the five tarsal joints, there is a pair of claws.

The abdomen which is closely united to the thorax consists of eight segments. Each segment consists of an upper and lower chitinous shield and a soft connecting membrane. This membrane permits of movements of respiration and of the distension which is common to mosquitoes after a full meal. On the last segment of the female mosquito, there is an ovipositor, while the last segment of the male terminates in a pair of claspers.

Internally the mosquito contains two pumps by which blood is pumped up into the "sucking-tube". One of the pumps is just
above the junction of the labrum with the head, while the other is further back in the head. When the latter pump collapses, the liquid is forced into the oesophagus, which gives off three food reservoirs just beyond its entrance into the thorax. The stomach is a direct continuation of the oesophagus, and is narrow in front but dilates into a sac posteriorly. A chain of connected nerve ganglia make up the nervous system; and in the head region, several pairs of the ganglia fuse to form the brain. There is also a fusion of ganglia in the thorax. The thorax is almost filled with muscles, which consist of two masses at right angles to each other.

Air is supplied by a system of branching trachea, which open to the outside by two main openings on either side of the thorax and by eight smaller ones in the abdominal membrane. The only blood vessel in the mosquito is the heart, a tubular organ. It is into the blood in the body cavity of the mosquito, that the malarial spores escape and through the circulation of the blood, these spores find their way into the salivary or poison glands.

These glands lie beyond the neck, within the anterior part of the thorax. Each gland is three-lobed and its secretion is carried forward into the head by the salivary duct. The two ducts join in the head and the common duct empties into the salivary pump. The salivary pump, together with its continuation, the salivary channel in the hypopharynx, forms a syringe by which the poisonous saliva is automatically forced out at the point of the proboscis during the act of feeding. Nuttall and Shipley
thought that the saliva served to prevent the clotting of the blood in the sucking-tube of the mosquito, but this was not proved. However, its irritating effect is known and it is, also, with this salivary secretion that the malarial spores are injected into the human circulation.

The life-history and description of the Anopheles which has been given is for the most part, technical and therefore of not much practical use to the average person. However, the untrained observer can always know if he is dealing with a mosquito and not some other insect resembling a mosquito, by making sure that there is a fringe of scales along the posterior border of the wings and even along the wing veins. Because only the female bites, we can see the importance in being able to distinguish between the sexes. Probably one of the easiest methods of determining the sex is to notice the antennae, which in the female are sparsely covered with hairs, and in the male are very heavily covered with hair. Also, the palpi in the female are as long as the proboscis.

The wings of Anopheles are distinctly spotted and when the mosquito is resting or biting, its proboscis, head, thorax and abdomen form one straight line.

In the United States, three species of Anopheles are commonly met. They are:

1. Anopheles—puncipennis
2. Anopheles—quadrimaculatus
3. Anopheles—crucians

The Anopheles puncipennis contains a large white or
yellowish patch at the anterior margin of the wings near the outer end. The anterior margin itself is dark. This type breeds in running water and in streams that are subject to freshet from rains. They are often found in porches, outbuildings and under houses.

The Anopheles quadrimaculatus, sometimes called maculipennis, usually has from three to five black spots, which are patches of black scales, on the second and fourth wing veins. It breeds in quiet water and it invades human habitations.

The Anopheles crucians has dusky wings and prominently marked veins with three small spots of black on the sixth vein, (on the thoracic end-posterior margin).
BRIEF REVIEW OF FACTS

Before discussing the etiology, pathology, symptoms, diagnosis, prognosis, and prophylaxis of malaria, I am going to give a brief summary of facts regarding the disease, in order that certain points will be impressed and a clearer understanding will result.

Malarial fever occurs most commonly in all warm climates, especially near marshes. It is caused by an enormous number of minute parasites which get into the blood circulation and which are called Plasmodia and were discovered by Laveran in 1880. They gain admittance into the blood stream through the proboscis of certain species of mosquitoes called Anopheles. After the Plasmodia once gains admittance, they enter the red corpuscles, where they live, and grow. When maturity is reached, each parasite produces many spores, which escape from the corpuscle in which they were held, and enter fresh corpuscles. This particular method of propagation may be continued indefinitely for years.

The person who is infected may remain in apparent good health, while the number of parasites is still small, however, as soon as the number becomes large enough, he begins to suffer from fever. The parasites tend to produce their spores all at the same time, and consequently when these spores escape, the patients' fever begins. The actual causal agent is probably a little poison which escapes from each parasite with the spore. From six to forty hours later, the poison is eliminated from the patient's system, and as a result the fever tends to leave him,
however, another generation of parasites may be approaching maturity and these may cause another attack of fever similar to the first attack. This process may continue for weeks or months and therefore, the attacks of fever follow each other at regular intervals.

Even without treatment, the number of parasites may decrease after a time and the patient improve temporarily. But eventually the number of parasites usually increases again and when they do, the patient again suffers from another series of attacks. Such relapses may also be encouraged by fatigue, heat, chill, wetting, dissipation, and attacks of other illnesses. It is possible for such relapses to occur at intervals for a long time after the patient was first infected and even after he has moved to localities where there is no malaria. "As long as one parasite remains alive in the patient's blood it is probable that he may remain subject to such relapses".

The parasites of malaria can produce besides fever, anaemia and enlargement of the spleen, especially in persons who have suffered from many relapses. Sudden and grave symptoms, such as Blackwater fever, or Haemoglobinura, which generally occur in old and neglected infections, may result in death. Due to the constitution already being enfeebled by the parasites of malaria, other diseases, such as pneumonia or dysentery, may cause death during the course of a malarial infection. The parasites which cause malaria are at least of three kinds, all of which can be distinguished in blood placed under the microscope. They are; Plasmodium falciparum, which causes the most severe type of
malaria (estivo-autumnal), and in which paroxysms occur every twenty-four hours. (This type is also called quotidian or malignant fever); Plasmodium vivax, which causes the tertian type of malaria, in which the paroxysms occur every forty-eight hours; Plasmodium malariae, which causes quartan malaria, in which the paroxysms occur every seventy-two hours.

Years of experience have conclusively proved that cinchona bark, from which quinine is made, possesses the power of destroying the parasites and curbing the infection. The necessary requirement in the administering of quinine is that it be given in sufficient doses and continued for several months, in order that all the parasites in the body will be destroyed.

There are, besides the forms of the malaria parasites which produce spores in the human body, other forms, male and female. When an Anopheline mosquito feeds on a person in whose blood there are the parasites of malaria, these parasites are drawn with the blood into the mosquito’s stomach. The sexual forms of the parasites undergo certain changes once they reach the mosquito’s stomach; the females pass through its wall and fix themselves to its outer surface (between the stomach and the skin of the insect), where they grow much in size and produce, after a week, a number of spores.

The average incubation periods for the different species of parasites are:

a. Benign tertian, from eight to twenty-five days.

b. Quartan, about eleven days.

c. Estivo-autumnal, from ten to thirty-five days.
Ross says that the average incubation period of all the species is anywhere from three to twenty days.

These spores get into the salivary gland of the insect, and it is from this gland that the irritating fluid is secreted which the insect injects through its proboscis under the human skin when it begins to feed. Therefore, if a certain species of Anopheline, which has more than a week before fed upon a patient in whom sexual forms of the malaria parasites were present, bites another person, it injects these spores, with its saliva, under his skin, usually into his blood. Infection or re-infection to this second person, is thereby caused by the spores and in this way the malaria parasites pass alternately from men to certain mosquitoes, and back from these mosquitoes to men. Malaria is therefore, without any doubt, an infectious disease that is communicated from persons who already have it, to those who are healthy, by the agency of certain mosquitoes belonging to the genus Anopheles.

The parasites of malaria are carried by mosquitoes which breed in marshy pools and streams; from which they enter the adjacent houses, and feed on the inmates, mostly at night. It is when there is an infected person present in the house that the mosquito becomes infected itself and carries the infection to the other inmates and to neighboring houses. The result is that the entire neighborhood tends to become infected and such a neighborhood is termed "malarious". A locality of this type may remain malarious for years by the infection being constantly passed on from the older to the younger persons.
MEDICAL ASPECTS OF MALARIA

We will now consider the etiology, pathology, symptoms, diagnosis, prognosis and prophylaxis of malaria, in the order in which they are mentioned.

Etiology: No races are immune to malaria, though some races, through repeated infections in early life, become largely immune to the poisons produced by the plasmodia and as a result do not show definite symptoms of an infection. Such people will nevertheless develop and show the symptoms if they are exposed to infection under conditions which greatly depress their powers of resistance.

Age has no definite bearing on susceptibility to malarial infection. However there is a much greater chance for infection in children, because they do not notice the biting of insects as much as adults and because in malarious localities, the adults might have developed a relative immunity.

The sex relationship to malaria is more or less artificial. Men are more frequently infected than women owing to their being bitten more frequently by mosquitoes because of their occupations.

Infection is favored by occupations that depress the general health or that expose the individual to the chance of being bitten by mosquitoes.

Certain regions are considered malarious due to local conditions favoring the breeding of transmitting mosquitoes. Certain types of malaria are found only in certain localities.

The only relation that climate has to the transmission of malaria, is its favoring the breeding of the mosquitoes that
transmit the disease, or the growth of the plasmodia in man.

Soil, altitude and moisture influence the prevalence of malaria, only because they influence the breeding and development of the transmitting mosquitoes.

The most important factors which influence the transmission of malaria are divided into two kinds. The first is concerning the development of the Plasmodia in man. In this, it is necessary that there be present in the blood of a human, both the male and female sexual forms of the gametocytes. The second is concerning the development of the Plasmodia in the mosquito. In this, temperature is the most important factor and the optimum temperatures for the development of the three common types of malaria parasites are: 25 degrees C. (77 degrees F. ) for Plasmodium vivax; 22 degrees C. (72 degrees F. ) for P. malariae; and 30 degrees C. (86 degrees F. ) for P. falciparum. The minimum temperature for the development of any of the three species is sixty degrees. The plasmodia may remain alive in the mosquito through the winter and renew their development in the spring.

Pathology: Distinct changes are produced in the blood and blood-forming organs by the malaria toxin or toxins. The anemia which is always present in malarial infection is a result of the growth of the plasmodia within the red blood corpuscles and the consequent destruction of these corpuscles. The number of red cells are reduced after every febrile paroxysm. Besides the reduction of the red blood corpuscles, there is also a reduction in the number of leukocytes. Another characteristic of malaria infection is the appearance, in the peripheral blood and in the
capillaries of the viscera of leukocytes, of pigment, which is
derived from the hemoglobin of infected red corpuscles through
the action of the plasmodia and is liberated in the blood plasma
at the time of segmentation.

There may be some pathological changes in the urine in
estivo-autumnal infections, but there are usually none in the
tertian and quartan type. In the estivo-autumnal type, the
specific gravity may be increased during the paroxysm, the urea
may be increased in amount, albumin may appear, or hyaline and
granular casts may be observed.

In chronic malarial infections, the chief pathological charac-
teristic is the marked anemia and the enlargement of the spleen
and liver, with marked pigmentation of these organs.

Symptoms: In tertian malaria, the paroxysms of fever occur
every forty-eight hours; the incubation period varies between
eleven and twenty-one days, with eleven or twelve being the
average period. This type best illustrates the three stages of
malaria, namely, chill-fever—sweating. Paroxysm begins with a
severe, shaking chill; the face becomes cyanotic, the lips blue
and the hands and feet cold. Pulse is rapid and may be irregu-
lar. Chill lasts from one fourth of an hour to two hours.

Hot stage begins as flushings of heat succeeded by cold
sensations, but soon the heat sensation becomes continuous and
the temperature reaches one hundred and four degrees or one
hundred and five degrees. The skin of the entire body is redden-
ed, and hot and dry to touch. The pulse is increased in fre-
quency. This stage lasts from four to six hours.
As the temperature begins to decline, the sweating stage commences. When the fever reaches the normal point, perspiration is very profuse, and with this there is a disappearance of all disagreeable symptoms and the patient recovers rapidly from the paroxysm. This stage lasts from two to three hours. The entire tertian paroxysm lasts from ten to fourteen hours, but it may reach twenty-four hours in severe infections. Many times a person is infected with two generations of tertian plasmodia, segmenting at different times and when this happens, we have a quotidian paroxysm in a tertian infection, the two generations segmenting on successive days.

In quartan malaria, the paroxysms of chill, fever and sweating occur every seventy-two hours; the incubation periods varies between ten and eighteen days, with fourteen being the average. The symptoms are practically the same as in the tertian type, only that they may be more severe; especially affecting the nervous system. The entire quartan paroxysm lasts from eight to ten hours, but in severe cases, may reach twenty-four hours. There are a few more fatal quartan cases than tertian ones, although both are very rare when compared with the estivo-autumnal type.

In the estivo-autumnal type of malaria, the paroxysms occur every twenty-four hours. The incubation period varies between seven and fifteen days with ten to twelve days being the average period. The cold stage begins with yawning and a feeling of general malaise accompanied by nausea, and, in some instances, by vomiting. There is no severe, shaking chill as in tertian
malaria, but the chill is limited to chilly sensations along the spine. The pulse is increased in frequency and decreased in tension. This condition lasts about one half an hour.

The hot stage begins with localized flushings which soon become general. Headache is usually unbearable in this type of fever and there are severe neuralgic pains in the back and limbs, temperature reaches one hundred and four degrees or higher; pulse is increased; urine contains albumin and sometimes hyaline and granular casts. This stage lasts from sixteen to twenty-four hours.

The sweating stage is not as well marked as in tertian and quartan infections. The temperature rapidly declines, accompanied by slight perspiration and the disagreeable symptoms disappear, leaving the patient feeling as well as usual. This period of absence of symptoms is however, very short, lasting only a few hours.

In the sub-tertian type of estivo-autumnal fever, the paroxysms cover about thirty-six hours and occur every forty-eight hours. The temperature curve of this type is not met in any other febrile condition. In the quotidian type of estivo-autumnal fever, about the only difference from what has already been mentioned is that the chill is more severe and sweating more pronounced. When this type becomes pernicious, it is more fatal than the sub-tertian type.

Pernicious malaria is not a disease "per se", but it is the term applied to those malarial infections, in which the symptoms are so severe as to endanger life or actually cause the death of
the patient. It may be caused by any of the species of malaria plasmodia, but it is usually caused by the estivo-autumnal type. Any estivo-autumnal infection may develop into pernicious symptoms, which will cause the death of the patient within a few hours.

**Diagnosis:** The most accurate and scientific diagnosis of malaria depends upon the presence of the malaria plasmodia in the blood of the suspected person. When a blood examination is impossible we must depend upon the symptoms present in order to differentiate malaria from other infections or diseases they may be present. Under the following circumstances, a fever is likely to be malarial; if the fever comes on suddenly without any previous local symptoms, such as, continued pains in the stomach or chest, diarrhoea or dysentery, abscess, inflamed wounds or sores, large boils, persistent cough or cold in the head, and great weakness of the legs; if the fever begins in a locality which is known to be very malarious, or from five days to some weeks after the patient has been in such a locality; if, after the fever has lasted for some days, the temperature falls below normal and then suddenly rises again, and if this procedure is frequently repeated, and especially if the fever occurs regularly every day, every other day, every third day or at irregular intervals, then the fever is almost certain malarial; also, if the fever leaves off after large doses of quinine have been taken regularly for several days.

A method used by Dr. C. L. Urriola is mentioned in the *Lacet*. He collected the urine of a patient, and centrifugalised
a specimen of it; then he examined the deposit under a high power of magnification and found that in the urine of every malarial patient, there were granules of pigment present.

**Prognosis:** This is favorable in the case of benign tertian and quartan fever. Even in cases that have not been properly treated, fatalities are rare, except in the case of young children and infants. Prognosis in estivo-autumnal infections should be guarded, for although it is good in treated cases, it becomes very grave if the fever is improperly treated or oft-recurring. Certain cases of pernicious malaria will prove fatal, regardless of the best treatment given, so that the prognosis is always grave.

**Prophylaxis:** The prophylaxis of malaria is based on two principles: That malaria is naturally contracted only through the bite of an Anopheline mosquito and that man is the only known host of the malaria parasite, which is the only source of mosquito infection. We, therefore, consider man and mosquito in a discussion of malaria prophylaxis.

First, we will consider the mosquito and we will treat it under two general headings, destruction, and prevention.

Probably the best way in which malaria can be checked is by the destroying of the mosquitoes themselves. This is best done by attacking all those places where Anopheline larvae are found. We should drain any and all standing water or bring about a movement of the water, so that it is unfavorable for breeding. When there is any kind of a movement or current in the water, larvae of Anopheles will not grow there.
The spreading of light fuel oil over the surface of the water will produce a thin film and this prevents the larvae from breathing, so that they suffocate. The use of larvicides is also very effective in destroying larvae, especially a mixture of crude carbolic acid, rosin and caustic soda which kills the larvae in five minutes. One part Paris Green to one hundred parts of sand distributed by a spray is another effective larvicide.

Another way of ridding stagnant pools of these larvae is by the introduction into those pools, of top-feeding minnows, water boatmen, larvae of dragon flies and even the larvae of certain other mosquitoes, all of which will eat Anopheline larvae.

Adult mosquitoes can be destroyed inside houses by fumigation, by burning sulphur and by hydrocyanic gas. Outside the house if places of shelter such as tall grass, weeds, vines, etc., are removed, they cannot rest during the day and consequently will not be near the house at night, when they do most of their flying and biting.

In regard to the prevention of infections from mosquitoes, we must keep them away from man. There are many ways of doing this, the most common of which are; use of screens, mosquito bars, mosquito nets and electric fans; if there is constant motion of some sort the Anophelines will not bite. All these measures will serve to prevent the mosquito from gaining access to man.

There are also certain substances which can be rubbed over the surface of the skin and which tend to keep the mosquito away; some of these are citronelle oil and kerosene. However,
it is best to use other measures than the last two, when possible. Of all the measures, the best ones are probably the use of screens and of mosquito nets.

Coming to man, the other agent in malaria prophylaxis, we will consider him in the light of treatment.

Our main object when dealing with man is to free him of the parasites, if he already is infected; and to prevent him from being infected, if he is in good health.

For a person in good health, the best suggestion is to take the means of prevention already mentioned and to be on the safe side, especially if he is in a malarious locality, to take regular doses (moderate) of quinine.

For a person already infected, the best known treatment is quinine also. The object of treatment with quinine is to completely exterminate and not merely reduce the number of parasites present in the blood. One who has been infected should take quinine regularly for at least three or four months, whether he gets fever or not and he should continue the doses for about three months after his symptoms have completely gone.

The therapeutic use of horse serum in the treatment of severe forms of malaria, such as Blackwater fever, has been used advantageously. The serum inhibits the action of an autohaemolysin and its destruction of red blood cells in the body. In the tropics, intramuscular and intravenous injections of the byhydrochloride of quinine have been advocated by some clinicians in the treatment of serious cases.

Local conditions, must in most cases, determine the best
mode of prophylaxis. There should be several methods of control combined, and among them there should be an educational propaganda program.

Summed up, our work is to prevent the mosquito from becoming infected; destroy the Anophelines in which parasites of malaria develop; prevent their biting and inoculating the parasites in the blood of man. Our results for this will not only be good health, but also good economic returns.
Malaria is caused by a living animal parasite that invades the red blood cells of man and is transmitted from man to man through the agency of certain mosquitoes belonging to the genus Anopheles. Although the disease is usually restricted to certain localities, it has nevertheless broken out in all sections of the earth at some time or other. It has been a great barrier to the progress of civilization by its prevalence in many of the most fertile and well-watered sections of the world.

The disease is especially characterized by recurrences which take place every day, every other day, or every third day, being called quotidian, tertian, and quartan fever respectively. These recurrences which are referred to as paroxysms, consist of three stages, namely, the chill stage, dry heat stage, and sweating stage. The paroxysm begins with severe chills, which increase in intensity until the entire body shivers and the surface of the body is cold to touch. Then the temperature rises (dry heat stage) and the skin is distinctly flushed, feeling to the patient as though it was on fire. During this stage, the temperature often reaches one hundred and five degrees or more. Then in the last stage, the fever abates, accompanied by profuse sweating, and the patient feels well again. However, these same stages are repeated again in twenty-four, forty-eight, or seventy-two hours, depending on the type of parasite which is present in the patient's blood.

The parasites which are responsible for the different types of malaria are: Plasmodium malariae, which causes tertian fever,
the paroxysms of which occur every forty-eight hours; Plasmodium vivax, which causes quartan fever, the paroxysms of which occur every seventy-two hours; Plasmodium falciparum, which causes estivo-autumnal fever, the paroxysms of which occur every forty-eight hours, in the case of the sub-tertian type and every twenty-four hours in the case of the quotidian type. (Note: when we say the paroxysms occur every forty-eight hours, we mean that the cycle of the parasite is completed in forty-eight hours, but the resulting chill takes place on the third day, therefore, it is called tertian.)

The following contributions eventually led to the complete solution of the malarial problem. The separation of malarial fever into quartan, tertian, and sub-tertian types by Hippocrates. The discovery of the curative value of cinchona bark by the Countess D'El Cinchon, and her body-physician in 1640. The extraction of the alkaloid quinine from the bark in 1820, by Pelletier and Caventou. The discovery of the malarial pigment (melanin) in 1847, by H. Meckel. The discovery of the actual parasite of malaria by Laveran in 1880. And finally the discovery of the actual process of infection by Ross in 1898.

The life-cycle of the malarial parasite consists of two stages, asexual and sexual. The asexual stage is carried on in the blood of man, while the sexual stage is carried on in the body of the Anopheline mosquito. We do not know whether man or mosquito had the infection first, nor do we know in which of the two the parasite originated. However, we do know that the parasites occur alternately in man and mosquito, both of which are
necessary for the perpetuation of the species.

The connection which malaria has always had with stagnant water is due to the fact that the mosquitoes, which transmit the disease from the sick to the healthy, breed in such water. The name malaria, which in Italian means bad air, was originally given to the disease because of the belief that it was caused by a miasm or poison.

Malaria is only transmitted by certain species of Anopheles mosquitoes. The most distinguishing features of Anophelines, from other species of mosquitoes, are noticed in their larval stage. The common "wrigglers" have an elongated siphon and they hang obliquely or vertically, head down, with only the tip of the siphon reaching the surface of the water. The Anopheline larvae, on the other hand, have a short siphon and they lie in a horizontal position in the water.

Some races through repeated infections in early life become largely immune to the poisons produced by the plasmodia and as a result do not show definite symptoms of an infection. However, if they are exposed to infection under conditions which depress their powers of resistance, they will develop and show the symptoms; so that, if we wished to make a positive statement, we could say that "no races are immune to malaria".

Two factors are necessary for the transmission of malaria; the development of the plasmodia in man and the development of the plasmodia in the mosquito. In the first, there must be present in the man's blood, both the male and the female sexual forms of the gametocytes. In the second, temperature is the all
important factor, and the optimum temperature at which any one of the species of parasites may develop in the mosquito is eighty-six degrees; the minimum sixty degrees.

The most distinct pathological changes occur in the human blood due to the reduction in number of both the red blood cells and the leukocytes.

The most important factors in the prophylaxis of malaria are: destruction of the mosquitoes which transmit the disease and proper treatment of persons already infected. We can most effectively destroy the malaria transmitting mosquitoes by finding their breeding places and destroying the larvae either by the use of oil, or by the use of certain larvicides, both of which will kill the larvae.

Persons who are infected should be treated with quinine, until they no longer suffer from the paroxysms and then they should be given smaller doses of quinine for at least three months after their last attack. Those who are healthy, but are in malarious localities should take proper preventive measures (use mosquito nets--screens--mosquito bars, etc.) to prevent infection.

This is the exact process of infection: "An Anophine mosquito bites a malaria patient, and when it sucks the patient's blood, it also sucks up a number of malarial parasites with the blood. These parasites grow rapidly in the insect's tissues and produce spores after a week or two. The spores get into the salivary gland of the insect and lie in a fluid which is secreted by this gland. When the mosquito bites another person, it injects
this fluid through its proboscis into the person's skin, and the spores being released mix with the person's blood and produce infection. Thus the cycle goes on from man to mosquito to man."
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