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From "THE PRACTITIONER" *for November*, 1898.

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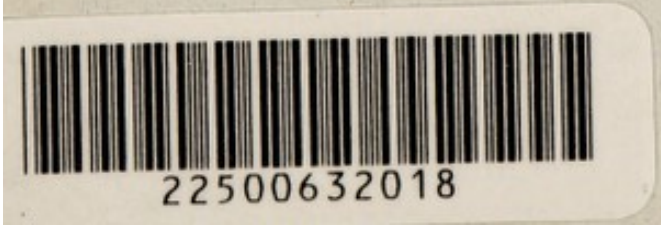
BY PATRICK MANSON, LL.D., M.D., F.R.C.P.,

Physician, Seamen's Hospital, attached to the Branch Hospital; Lecturer on Tropical Diseases, St. George's Hospital and Charing Cross Hospital Medical School.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A CLINICAL LECTURE ON THE PARASITE AND PATHOLOGY OF MALARIA.*

By PATRICK MANSON, LL.D., M.D., F.R.C.P.,

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Gentlemen,—The evolution of our present knowledge of the pathology of malaria has taken a long time. The Father of Medicine, Hippocrates, divided fevers into continued and intermittent, and in a vague way he recognised that somehow marshes and similar telluric conditions had something to do with the intermittent fevers and also with the development of that characteristic of malarial disease, enlargement of the spleen. Later medical writers, culminating in Celsus, recognised that intermittent fevers were of two or three types, quotidian, tertian and quartan. This meagre stock of knowledge remained without important addition until the introduction into Europe of quinine by Chincon, Viceroy of Peru. This drug enabled physicians to differentiate more distinctly between intermittent fevers produced by malarial poison and intermittent fevers produced by other causes. That was about 1640. In 1712, Torti, an Italian physician, made the important discovery that not only were intermittent fevers caused by the malarial poison, but that what are now recognised as the pernicious malarial fevers belong etiologically to the same category as ordinary quotidians, tertians and quartans. Then came Morton and Lancisi, who definitely connected malarial poisons with marshy conditions of soil. They had a clear conception that the cause of malaria was of a material nature, a something which could be floated up as it were by

* Delivered at the Central London Sick Asylum, Cleveland Street.

the air. Next Meckel, in 1837, demonstrated the presence in malarial blood of certain black particles, which were supposed to be included in the white blood corpuscles, in what were called pigmented leucocytes. Meckel's discovery was confirmed by Frierichs and also by Virchow.

When the bacterial idea of disease began to take hold of the medical mind it was, of course, extended to malaria, and malaria was ascribed by many to a hypothetical bacterial infection of the blood. Accordingly a great number of malarial bacteria were discovered, and were put forward by the discoverers as the material cause of the malarial diseases. The best known of these was the so-called bacillus malariæ of Klebs and Tommasi-Crudeli. Many believed that these pathologists had established a real connection between this bacillus and malaria.

All these bacterial hypotheses were completely upset, however, by the latest and most important advance of all in malaria pathology. This was made by Laveran in 1880. Laveran was engaged in Algeria as an army surgeon, and while there occupied himself in studying the pigmented leucocytes of Meckel, Frierichs, and Virchow. While investigating this subject, by accident he came across in one of his blood slides a peculiar organism which, by its striking and remarkable characters, at once fixed his attention. He saw what is now known as the flagellated body of malaria, a small organism consisting of a minute central, somewhat spherical, amœboid body, containing a large quantity of black pigment, and furnished with a number of long, actively moving flagella. This discovery stimulated Laveran's energy, and he proceeded steadily with his epoch-making work until he thoroughly established the fact that malaria was produced by a living protozoal organism, of which his flagellated body was but one phase.

Laveran found that in the blood of all malarials certain protozoal organisms are to be found. For example, he found that in some malarials a proportion of the blood corpuscles are occupied by a pale, feebly amœboid body containing scattered about the pale substance a number of black particles. This pale, pigmented, amœboid body nearly filled

the corpuscle. He also found at times a body somewhat similar to these, but in which all the black particles were concentrated in the centre, the periphery of the body being made up of a number of little pale spherules; "rosette bodies" he called them. He also ascertained that occasionally these rosette bodies became free and broke up in the liquor sanguinis, the little clump of black pigment floating beside the pale spherules. Moreover, he found in certain phases of some malarial fevers that the parasite-invaded blood corpuscles contained a much smaller pale and non-pigmented body, and that this body indulged in active amœboid movement, changing its shape rapidly even while under the microscope. He also found bodies intermediate in size, connecting, as it were, by gradation the smaller unpigmented with the larger pigmented corpuscle-parasites. Besides these he found another well-defined pigmented body which from its shape he called the "crescent body."

So the discovery of Laveran remained for some time. By and by the Italians took the subject up. At first they were sceptical, being more or less committed to the bacillus malariæ. But, as they proceeded, they and many others found that Laveran's observations were true to nature; and now his great discovery is abundantly confirmed and almost universally accepted.

The Italians have shown that there are different types of this malaria parasite, and that each form is associated with its own special clinical type of disease. Golgi was the first to show this. He showed that in ordinary tertian infections the parasite when mature was very much larger than those in any of the other forms of infection; that it was made up of some sixteen or twenty spherules, and that the corpuscle containing it was markedly enlarged, hypertrophied, and paler than normal. He found that in other clinical types the blood corpuscle containing the parasite retained its original size—at all events, was not hypertrophied as in the tertian form. In quartans he pointed out that the blood corpuscle was not enlarged, although it was completely filled by the parasite at maturity, a mere rim only of hæmoglobin remaining as evidence that it really was included in a blood

corpuscle. He noticed, too, that in the quartan parasite the pigment was very much larger and coarser than it was in the tertian. He found that the parasite in quartan blood, instead of having sixteen to twenty spherules, had only eight or ten spherules.

In another type of fever, in the more malignant fevers (which, because in Italy they occur as primary infections in summer and autumn only, are called æstivo-autumnal), he and others found that although the including blood corpuscle might or might not be slightly hypertrophied, the parasite never attained a size above a quarter or one-third of the blood corpuscle, and carried only one or two minute grains of pigment. Sometimes he saw what seemed to be the final or rosette stage of this form of the parasite, in which there were only from three to six or eight spherules. In the same type of disease he found what appeared to be an early stage of the parasite occupying a very limited area of the corpuscle, and that it indulged in amœboid movement of a much more active nature than is the case in the other types of malaria.

These three forms—the tertian, the quartan, and the æstivo-autumnal—represent all that is positively known about what may be called the intracorporeal form of parasite. That which belongs to the benign tertian infection is recognised by the large size of the parasite, the hypertrophied corpuscle, and pallid hæmoglobin. That which belongs to the quartan infection fills when mature the whole corpuscle, does not cause hypertrophy of the corpuscle or paling of the hæmoglobin, and carries a pigment larger and coarser in grain than in the tertian. Those infections in which the parasite is very small and with very little pigment are found to be characterised by a type of fever prone to assume an adynamic and even a pernicious type.

Investigation has further shown that the different phases of these three types of parasites correspond with different phases of the clinical cycle of malaria. When the parasite occupies the entire corpuscle an attack of ague is imminent. When rosette bodies are found a rigor as a rule is present or imminent. When the small unpigmented forms are found it is during or towards the end of the pyrexial stage, and

when the larger pigmented forms are alone present it is usually during the apyrexial interval. This relation of the forms of parasite to the clinical cycle of malaria was distinctly established by Golgi and the Italians, and has been confirmed elsewhere.

The history of the parasite in the blood seems, therefore, to be something as follows:—Assuming that the parasite is mature when it has attained its largest size, by and by the pigment, which hitherto had been scattered all through the little animal, in virtue of some vital process becomes concentrated about its centre. When this occurs, the protoplasm of which the rest of the body of the parasite is composed divides it into a number of minute spheres. By and by, when these spheres are perfectly formed, the corpuscle surrounding them breaks away, and the cluster of spherules is set free and the individual spherules are scattered about in the blood. Most of them are attacked and destroyed by phagocytes; some few escape, and attach themselves to red blood corpuscles, which they contrive to penetrate, and there grow and attain in time the stage of maturity. Sporulation then occurs once more, and a fresh generation is started; and so on indefinitely.

We know very well that in the economy of all parasites provision must be made, not only for the life of the individual parasite and for its propagation, but also for its spread from one host to another. It is evident that unless some such arrangement is called into operation the parasite would in time become extinct as a species. If a man is affected with the malarial parasite, just as would be the case with a tapeworm or any other parasite, unless it is possible for it to escape from one host and get into another, the species would come to an end. The question then comes to be, What is the provision in the malarial parasite subserving this necessity? I believe that that strange body originally first remarked by Laveran—the body which first arrested his attention and led to his great discovery, the flagellated body—is really a provision which nature has instituted for securing a continuation of the species of what has come to be called the plasmodium malariæ. My reason for believing that is this: If you examine the blood in

the æstivo-autumnal type of malarial disease you will find a peculiar body—which from its shape is called "the crescent body"—in a certain phase of the disease; and in other forms of malaria you will find large spherical bodies which do not sporulate, and which seem to be analogous to the crescent body, the different sorts being peculiar to different forms of the disease. Now, if you keep either of these bodies, crescents or spheres, under observation, you will find that in a proportion of instances they evolve into the flagellated body. A striking fact about the flagellated body is that if you examine malarial blood immediately after you have taken it out of the human body you never will find them; but if you wait half or three quarters of an hour you may find plenty of these bodies—that is to say, the flagellated body does not appear until the blood has been outside the human body for a certain time. That fact, to my mind, almost proves that the flagellated body is intended to live outside the human blood-vessels, that its purpose can only be fulfilled when it gets outside the human blood-vessels.

Another fact tending to prove that this supposition is correct is this. In certain cases of tertian fever, if you look carefully and long enough, you will find that in some of the blood corpuscles you get what appears to be but the ordinary form of the parasite before concentration of the pigment and before the division of the protoplasm into spores; you will find these large pigmented spheroidal bodies still enclosed in the red blood corpuscle, and you may make out the surrounding rim of hæmoglobin. If you watch you will find by and by that the parasite slips out of the blood corpuscle and becomes free in the liquor sanguinis. If you still keep watching, you will find later that the pigment granules take on a peculiar boiling, swarming movement, and that not only do the pigment granules move about, but the whole body of the parasite becomes agitated, convulsed, and twisted about. Then, suddenly, you will see shot out from the periphery of the little animal several long, slender arms, which begin to wave about, until, perhaps, one or more of them break away and swim free in the liquor sanguinis. If you watch the quartan parasite, you will occasionally see exactly the same

thing happen, the parasite at first lying inside the blood corpuscle, then escaping from the blood corpuscle, becoming agitated, and finally projecting flagella.

In the æstivo-autumnal form the same occurs, but the process is somewhat different. About seven to ten or twelve days from the commencing of an æstivo-autumnal fever you will find certain crescent-shaped bodies begin to appear in the blood. At first they are very few in number; but by-and-by they become more numerous, and at the end of a week you may find in certain cases, and in every microscopical field, one, two, or three of these peculiar crescent-shaped bodies. If you examine very closely, you will find that these bodies are made up of two elements. There is the usual white protoplasmic mass so characteristic of all the forms of the malarial parasite, and concentrated towards the centre of this a number of rods or specks of equally characteristic black pigment, similar in physical characters to the black pigment in many of the other forms of the parasite. This crescent body comes into the blood, as I have stated, from seven to twelve days after the commencement of the type of fever, the æstivo-autumnal, with which it is associated; sometimes, it may be, several days after the fever has disappeared; sometimes even when the patient is under the influence of quinine. If you keep observing the patient's blood you will often find that these crescent bodies gradually go on increasing in number for some days, and then, later, gradually decrease in number, and finally disappear. If you make a film preparation of malarial blood containing these bodies, dry it at once, and, after fixing it with alcohol, stain it with methylene blue; you will find the bodies are invariably of the crescent form. But if, in newly-drawn blood, you keep one of these crescentic bodies under observation under the microscope, you will find that in a few minutes the crescent slowly changes shape, becoming shorter and broader. In about eight or ten minutes it is still more transformed, and has probably become spherical. Later, you may find that the pigment which originally was lying in the centre is now arranged as a central ring, or that it is more or less diffused,

and that the parasite is becoming affected with a peculiar jerking, writhing movement. Continue your watch and you will find that from the periphery of this sphere flagella are shot out, and that after a time one or all of these flagella break away and swim free in the blood.

I repeat this remarkable transformation of the crescents occurs only when the parasite is outside the human body. There can be no other purpose for this extracorporeal transformation than that it subserves the interests of the parasites. That the malaria parasite does live outside the human body we may be sure, because it is found in countries where man may never or very rarely have previously resided. We are, therefore, driven to infer that the malarial parasite can live independently of man, and that for an indefinite time; and not only live, but multiply. The question now arises, In what condition, where, or in what form is it to be found outside man? I think we have in the facts I have just described distinct guidance towards determining the proper answer to this question.

Observe, first, that the malaria parasite is a blood parasite, and that while in the blood it is an intracorpuscular parasite. As the blood does not in normal conditions escape from the human body in any secretion or excretion, and as it does not escape as a pathological discharge in malarial disease, the inference is that the parasite, being thus confined in the blood corpuscles, cannot spontaneously escape from the human body. If it cannot spontaneously escape from the human body, and if it must exist outside the human body, the inference is forced on us that some agency must remove it from the circulation. Now, what agencies existing in nature can remove blood corpuscles from man? We know leeches can; we know fleas can; we know sand-flies can; we know mosquitos and a considerable number of other blood-eating animals can. There are certain facts which may aid us in fixing on the particular animal probably connected in this way with the malaria parasite. The facts of paludism suggest that this animal is one common in warm climates, and at the same time paludal in habit. What animal answers to this description? I hold that animal to be the mosquito.

That much is hypothesis; but here is fact. If you raise mosquitos (which can readily be done from the larvæ to be found floating in almost every puddle of water in the tropics) and get them to bite a man with malarial crescents, it will, just as in the case of an ordinary individual, fill its stomach with the patient's blood. If you capture the insect immediately and at once separate the abdomen from the thorax, and express the blood in the abdomen on to a microscope slide, you will find that in this blood probably a large number of crescent bodies are present. If you express the blood from a quarter to half an hour after the mosquito has fed, you will find that a very large proportion of the crescent bodies have undergone the transformation I have described, and that they are now flagellated bodies. If you dissect the mosquito half to three-quarters of an hour after it has fed, you will find that the flagellated bodies have now lost their flagella, and that there remain now merely the pigmented cores of the flagellated bodies. These facts have been demonstrated many times by Surgeon-Major Ross.

Lately, Ross, in dissecting a certain species of mosquito fed on crescent-containing blood, found in the stomach-wall rounded cells containing pigment grains closely resembling the pigment of malaria. Sometimes this pigment was scattered through the cell; often it was arranged in the form of a rude circle, exactly as one sometimes finds it in the crescent and spherical forms of the malaria parasite.

These are the facts; the interpretation is a little difficult. As yet we do not know for certain if the presence of these pigmented cells represents a phenomenon or phase of the malarial parasite; or whether they are merely the outcome of more or less accidental inclusion of the pigment of dead malaria parasite by the cells of the mosquito's stomach. My idea is that it represents an essential stage in the life-history of the malaria parasite. I believe that just as the malaria parasite while inside the body of man is intracapsular, that is, an intracellular parasite, so, while outside the human body, it still retains its intracellular habits. My idea is that the flagellated bodies are developed from intracorpuscular plasmodia.

that the flagella which break away are really flagellated spores, and that they are endowed with powers of locomotion for a purpose. One must bear in mind that the anatomical and physiological peculiarities of every organism have a direct reference to the life-interest of the animal exhibiting them. This power of locomotion exhibited by the flagella is, I believe, intended to carry the spore of the parasite while it lies in the mosquito's stomach into some cell free in the cavity of, or in the lining of, the mosquito's stomach. So far investigation bears out this view. By-and-by, I feel confident, we shall hear of important results from the work in which Surgeon-Major Ross is engaged. We may find that the extra-corporeal phase of the various malaria parasites is passed in certain species of mosquito. I believe the quartan, the tertian, and the æstivo-autumnal parasite has each its special species of mosquito as its special extracorporeal host; that the malaria parasite inhabits man when it gets the chance, that it can pass from man to the mosquito, and that it can pass from mosquito to man.*

It may be said that this organism is simply an epiphenomenon in the malarial condition, that it may not be the cause of malarial fever. It may only be that malarial blood is a suitable nidus for its development; though found in malaria it does not necessarily follow that it is the cause of malaria. Although it is true that this parasite has not been proved with mathematical certainty to be the cause of malaria, the presumption, nevertheless, is very strong that it is; the

* Since this lecture was delivered MacCallum has observed that the flagellum enters certain free plasmodial spheres (crescent derived in the case of æstivo-autumnal infection); that after this impregnation, in the case of at least one form of plasmodial infection of birds, the impregnated sphere changes shape, becoming a sort of vermicule with remarkable powers of locomotion and penetration. It seems probable that the pigmented cell in the stomach wall of the mosquito is this travelling vermicule arrived at its appropriate nidus. Ross has further shown that the pigmented cell grows to a considerable size and then bursts, discharging into the body cavity of the mosquito a prodigious number of very minute rods. These rods are taken up by the blood of the insect, and finally by the cells of the veneno-salivary glands. When the insect bites again it discharges the irritating secretion which it instils into its avian victim, inoculating it with plasmodial disease. About a week or ten days later plasmodia can be found in abundance in the bird's blood, and the bitten bird very often dies of the infection.

principal reasons for this belief are:—First, in all malarial cases which have not been interfered with by therapeutic measures, such as quinine, this parasite is to be found. In common with many other observers, I have examined the blood in a large number of cases of malaria, and in no instance in which I have had adequate opportunity have I failed to discover some form of the malaria parasite; so if its occurrence in malaria be merely coincidence it is an uncommonly frequent coincidence; an invariable coincidence generally implies a cause and effect relationship. Secondly this malarial parasite is found in no other disease; for instance, it has never been found in a phthisical patient unless he was also malarial, nor yet in dysentery unless it be complicated with malaria, and so on. A third reason for believing in the causal relation of the parasite to the disease is that the life-cycle of the parasite corresponds exactly with the cycle of the disease. If you want to see a sporulating form you will only find it during the early stage of an attack, either immediately before rigor, during rigor, or at the first part of the hot stage; it is much more rare in the sweating stage, or in the stage of apyrexia. If you want to find the early unpigmented amœboid form you will only do so during the late fever or early in the apyrexial stage. If you want to find the mature bodies you must look at the end of apyrexia or at the commencement of pyrexia. Again, our best remedy for malaria is quinine. We know that given a case of quartan or tertian fever, if we adminster thirty grains of quinine we shall for the time cure the disease; strange to say we also at the same time cause the parasite to disappear from the blood. Lastly, if you take a syringeful of malarial blood containing the parasites, and inject that blood into the veins of an individual who has never been in a malarial country and is not suffering from malarial disease, in eight or ten days that individual will have an attack of malarial fever. All this is true; nevertheless no one has cultivated the malarial parasite and from a culture produced malarial disease, and until this is done the mathematical proof is lacking. The reason of failure in cultivation is obvious; the parasite is not a bacterium. You cannot cultivate an intracellular parasite in ordinary culture media; it

requires a cell, in this case a blood cell, to grow in; you cannot manufacture or keep alive red blood corpuscles in a test tube. Still, apparently, with the assistance of the mosquito you can conduct an equivalent experiment, and I look to the future with great confidence for conclusive proofs supplied by such mosquito-culture experiments.

The leading pathological features found in malarial fever are these—enlargement of the spleen, often enlargement of the liver, generally congestion of the whole portal system, diminution in the number of red blood corpuscles. You also find *post mortem* that the bone marrow is congested; and you will find, particularly in the spleen, brain, bone marrow, and liver, what is called pigmentation—that is, these organs are dark-tinted by scattered grains of malarial pigment deposited in them. In what way does the parasite produce these appearances? The malarial parasite is a parasite of the blood corpuscles. Every blood corpuscle attacked by a malarial parasite is destroyed; in that way you can account for the oligocythæmia. In the finger blood in a case of malaria you will not find more than one or two parasites in a thousand blood corpuscles; at the most you will find perhaps one in a hundred. Nevertheless that patient, after two or three attacks of ague, will become pronouncedly anæmic, and there will be a loss after each fever fit of five hundred thousand corpuscles perhaps in every cubic millimetre of blood. You will say, if the corpuscles attacked by parasites are so few, as evidenced by what we find in finger blood, why all this rapid anæmia? The explanation of this and many other things in the symptomatology and morbid anatomy of malaria lies in the fact that the principal habitat of the malarial parasite is not the peripheral blood. If you examine patients who have died of the comatose form of pernicious malaria there will be only a very few corpuscles in the peripheral blood affected, but in the capillaries of the man's brain you will find the parasite in enormous profusion. It is evident, then, that what we see in the finger's blood is but a feeble echo of the drama which is being enacted in the central organs. There is not only oligocythæmia, but there is also a loss in hæmoglobin value of the surviving corpuscles. My explanation of

this is that when the sporulating form of the parasite breaks up, and its elements become free in the liquor sanguinis, a toxin, or perhaps several toxins, are liberated at the same time, and among these toxins I believe there are some which have the power of dissolving the hæmoglobin. We know that the parasite itself devours and digests the hæmoglobin while it occupies the blood corpuscle, and it must do this in virtue of some digestive agent, some solvent of hæmoglobin. Now, when the parasite breaks up, this solvent must also escape and I believe that it still continues its digestive action on the blood, and so washes out, as it were, a portion of the hæmoglobin in the surviving blood corpuscles. If you make sections of the different organs in malaria, say of the spleen, you will find the black pigment which represents the centre of the sporulating parasite present in the cells of the organ. If you examine the liver you will find a good deal of this same pigment in the white blood corpuscles in the vessels, in the endothelium, and some of it in the walls of the vessels, and even in the lymphatic spaces around the vessels. If you examine, at a later stage of the disease the lymphatics occupying the hilum of the liver, you will find that these lymphatic glands are highly pigmented, more highly than any other lymphatic gland in the body.

The inference from these and similar pathological facts is that the pigmentation of organs in malaria is the product of the malarial parasite, that the pigment is carried to the spleen and to the liver, and there included by various kinds of phagocytic cells, and ultimately disposed of by the lymphatic apparatus. If you examine sections of the brain in cases of pernicious and fatal malaria, you will often find the capillaries full of blood corpuscles containing the parasite. In every case of comatose malaria in which the patient has died you will find the parasite blocking up the capillaries of the brain. This embolism of the brain explains many of the phenomena of pernicious fever. Many of the fevers are characterised by profound coma, doubtless from plugging of capillaries by parasites. Others are characterised by hyperpyrexia; probably in these the parasites are infesting those parts of the brain which

control the body heat. You also sometimes meet with forms of aphasia in malaria; the aphasia in these is no doubt due to the parasite infesting the portion of the brain subserving speech. The fever itself, common to all malarial attacks, is presumably produced by the release, at the time of sporulation of the parasites, of toxins. In malarial fevers what is called biliousness is generally a very pronounced symptom; the graver the fever the more pronounced, as a rule, are the bilious symptoms. The patient may have enormous discharges of bile by the mouth or by the anus; there may be bilious diarrhœa and bilious vomiting, and at the same time the skin may be suffused with an icteric tint sometimes of a bright saffron colour. In a still severer form of malaria hæmoglobinuria may occur, and the urine may become almost black. The explanation of these bilious phenomena is this:— When the blood corpuscles are destroyed by the parasites, when a proportion of the hæmoglobin is dissolved out from the surviving corpuscles, an enormous quantity of hæmoglobin is set free in the blood and is eliminated by the liver as bile pigment. If the amount of hæmoglobin liberated is not more than the chemistry of the liver can deal with then there may be only an increase in the bilious discharge, possibly bilious vomiting or diarrhœa. If the hæmoglobin is in excess of what the liver can immediately deal with then the hæmoglobin is deposited in the cells of the various organs of the body, including the skin, and there is an icteric tinting of these organs, and a hæmotogenous jaundice. If the amount of blood destruction is still greater then there are not only bilious symptoms and hæmotogenous jaundice, but there is also a discharge of the free hæmoglobin through the kidneys and a hæmoglobinuria.

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