THE LIFE-HISTORY OF THE MALARIA GERM OUTSIDE THE HUMAN BODY

Patrick MANSON

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The Goulstonian Lectures

ON

THE LIFE-HISTORY OF THE MALARIA GERM OUTSIDE THE HUMAN BODY.

Delivered before the Royal College of Physicians of London,

BY PATRICK MANSON, M.D. ABERD., F.R.C.P. LOND.,

PHYSICIAN TO THE SEAMEN'S HOSPITAL, ALBERT DOCKS; LECTURER ON TROPICAL DISEASES AT ST. GEORGE'S HOSPITAL AND CHARING-CROSS HOSPITAL.

LECTURE I.

Delivered on March 10th, 1896.

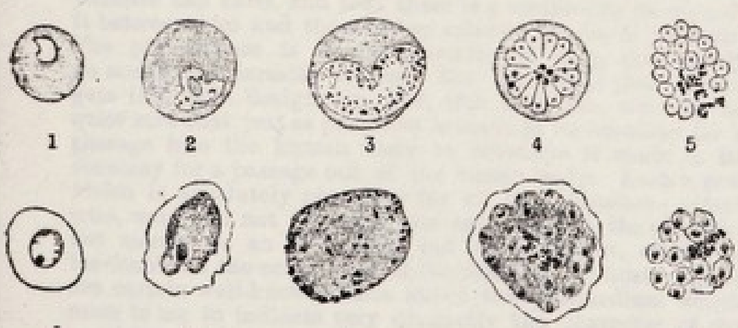
DISCOVERY OF THE MALARIAL PARASITE.

GENTLEMEN,—In his Croonian Lectures on the Climate and Fevers of India delivered before this College in March, 1882, Sir Joseph Fayrer, after briefly alluding to Laveran's then very recent discovery of a parasitic organism in the blood of the subjects of malaria, said: "We seem to be on the threshold of the discovery of unknown and almost unsuspected disease causes, and must watch the progress of investigation with great interest." Except by a very few, this great discovery was for years almost unnoticed. Laveran until lately, received little encouragement even from his own countrymen. For example, Corre a leading authority in France on tropical disease, writing in 1887, hardly mentioned Laveran's work; Kelsch and Kiener also, whose studies in malarial pathology are amongst the most careful and profound we possess, in their book *Traité des Maladies des Pays Chauds*, published so recently as 1889, did very scant justice to their compatriot, whose work they almost ignored. By degrees, however, Laveran's views gained ground. Richard in Algiers, Carter in India, Osler in America, Marchiafava in Italy, endorsed most of his statements, and when finally Golgi pointed out the very definite relation existing between the biological cycle of the parasite and the clinical phenomena of the fever cycle, the discovery was thoroughly established.

My purpose on the present occasion is to endeavour to throw some fresh light on the life-history of the malaria parasite outside the human body. I shall speak of the parasite as the plasmodium malariæ or the plasmodium—useful, though zoologically not very accurate terms.

THE MALARIAL PARASITE WITHIN THE HUMAN BODY.

If in a case of benign tertian ague we examine with the microscope blood procured from the finger in the usual way, it is not very difficult as a rule to see the parasite which is causing the disease. The exact form it assumes differs, however, according to the stage of the fever cycle it represents. A study of the different forms gives the key to a part at least of the life-history of the organism. If we select for



1 2 3 4 5

6 7 8 9 10

our examination blood procured during the state of rigor, or during an hour or two preceding the rigor, when the thermometer is gradually rising, we shall probably encounter a number of pale, morula-like bodies made up of some twelve to twenty spherules heaped together round one or two clumps of black pigment grains (Fig. 4). This morula-like body evidently lies inside a blood corpuscle, for very often we can make out that it is surrounded by a narrow, washed-out-looking rim of hæmoglobin. If, now, we stain these bodies, we can see that each of the little spherules constituting the morula-like mass consists of a deeply-stained nucleolus surrounded by a covering of more lightly-stained protoplasm (Fig. 9). In the same slide we may see similar bodies, but without the surrounding zone of hæmoglobin (Figs. 5 and 10); evidently these latter have escaped somehow from the blood corpuscles they had originally occupied. They appear to be falling to pieces; the little spherules no longer cling together and closely surround the pigment clump; they are scattered about irregularly, each spherule being independent of the other. In the same slide we may encounter individual spherules, which, so far as we can see, belong to no particular cluster system, being quite isolated and floating about in the liquor sanguinis. Further, we can perceive in or on certain of the blood corpuscles minute pale spots, which on careful scrutiny are seen to indulge in more or less active amœboid movement (Fig. 1). If, now, we stain these epi- or intra-corpuscular little bodies—say with methylene blue—they, too, are found to be made up of a deeply-stained nucleolus lying somewhat eccentrically in a larger circular unstained area—a nucleus which has come into view for the first time, the whole being surrounded by a narrow rim of lightly-stained protoplasm. These stained circlets look like tiny signet rings stuck on to the corpuscles (Fig. 6). If we wait for some hours and again examine the blood, we no longer find the pale, morula-like, pigment-enclosing bodies, no scattered spherules, no minute pale specks on the corpuscles; but we see in a proportion of the corpuscles actively moving, pale, amœboid bodies of some size, bodies which incessantly change their forms and keep pushing out pseudopodia, after the manner of amœbæ, into the surrounding hæmoglobin. Manifestly these amœboid bodies lie inside the blood corpuscles. On staining them we again recognise the eccentrically-placed nucleolus, the unstained vesicular nucleus, and the lightly-stained surrounding protoplasm, the latter having now very much increased in actual and relative size. An examination of the blood made several hours later reveals in a proportion of the corpuscles similar but larger pale amœboid bodies. And now a new feature has developed; each amœboid body carries one or more grains of an intensely black, or very dark, fiery-red pigment, which, if you carefully watch, is seen to be constantly changing its position (Fig. 2). Staining still shows the vesicular nucleus, the deeply-stained nucleolus, now larger and less distinct, and the lighter surrounding protoplasm (Fig. 7). If we examine the blood again a few hours before the next paroxysm of ague is due these pale bodies, now no longer actively amœboid, are seen to fill or nearly fill the corpuscles they occupy, and the pigment granules they contain are found to be coarser and more numerous, and hardly, or only very slowly, change their position (Fig. 3). On staining we can no longer bring out a nucleolus; the vesicular nucleus, too, is less distinct, and the now relatively abundant pigment is scattered through the lightly-stained protoplasm which constitutes the entire bulk of the body (Fig. 8). In a proportion of the parasites, for such they are, the pigment is seen to be collecting into little groups, or arranging itself in radiating lines, or becoming massed in a central clump. If these are stained neither nucleolus nor nucleus can be made out, both having become diffused, as it were, throughout the entire mass of the parasite. If we repeat the examination just before or at the time of rigor we again encounter the morula-like clusters of spherules already described and which we encountered at our first examination.

If we repeat our examinations, continuing to make them through a series of fever cycles, we shall find the same procession of forms occurring in the same order; and we conclude that the large pigmented intra-corpuscular body is the mature animal prepared for sporulation, the morula-like mass is the same with the sporules formed, and that the spherules into which it breaks up on leaving the blood corpuscle are spores. These spores, on becoming free, attach themselves to red blood corpuscles, enter the red blood corpuscles, and begin to grow at the expense of the hæmoglobin, which they convert into their proper tissue and into the black pigment which must be regarded as a sort of excrementitious product of the parasite's digestion. In about forty-eight hours they have attained their maximum growth and prepare for sporulation

the nucleus and nucleolus becoming diffused through the protoplasm. Presently the nucleolar matter collects at a number of points, and around these points the protoplasm arranges itself in the little spherules forming the elements of the morula mass, each little spherule or spore being the rudiment of the new being into which it may develop on the bursting up of the morula mass at the termination of the cycle. Although there may be differences of opinion on some minor points, pathologists and biologists in the main agree that this is substantially the history of the benign tertian parasite in human blood, and that the same account practically applies to all the malaria parasites.

[Dr. Manson here remarked that we have no explanation of the occasional latency, exhibited both by the parasite and by the clinical symptoms, which is so striking a feature in certain cases of malarial infection. He continued:—]

LIFE-HISTORY OF THE MALARIAL PARASITE OUTSIDE THE HUMAN BODY: METHODS OF INVESTIGATION.

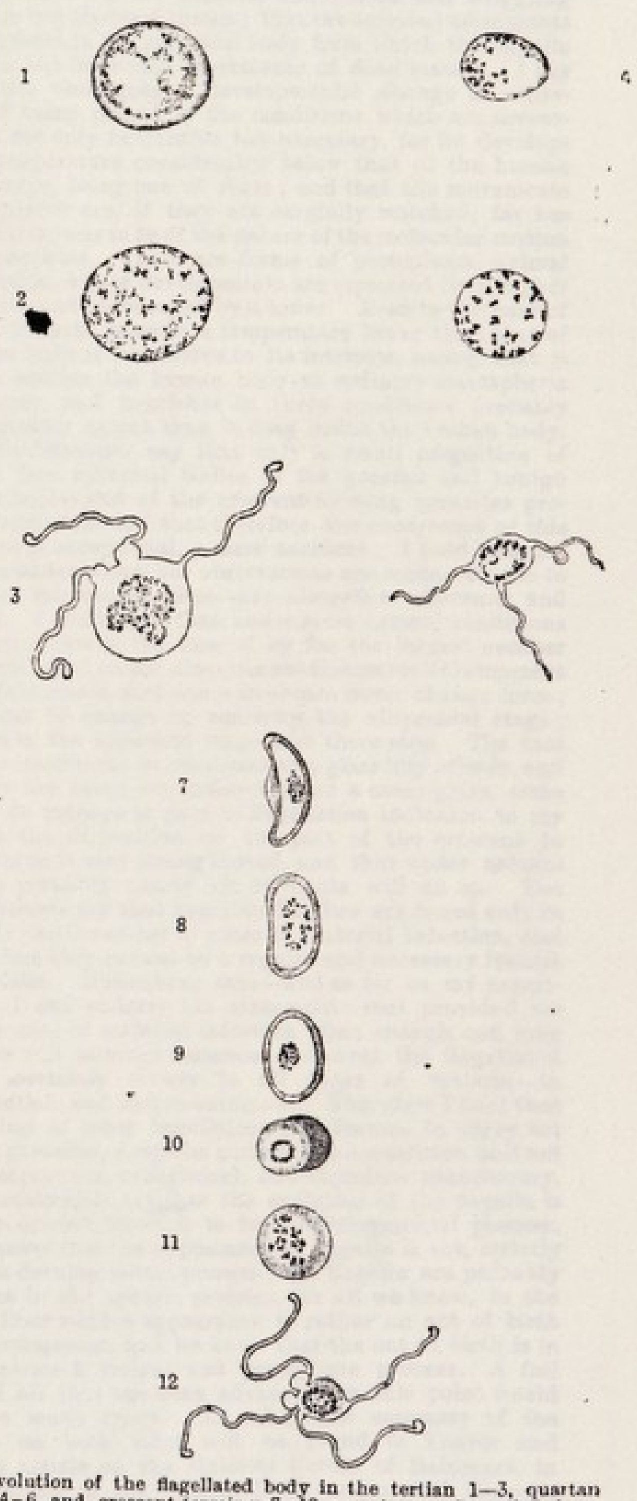
That this parasite, like all parasites, comes from without is certain. It is equally certain that in natural conditions it does not pass, like the germ of small-pox or the germ of measles, directly from one human being to another. There is abundant evidence to show that it does exist outside the body and independently of man; but, over and above this, there is ample evidence to prove that it can also multiply there, and multiply there indefinitely. There are two ways of searching for the extra-corporeal malaria germ: First, to grope about in external nature in a more or less blind way, trying to find some form which might be supposed to be the object sought for; secondly, to assume that the malaria parasite as found in the blood of man is present there as a normal circumstance in its life-history and to follow it out of the human body, tracing it into and through outer nature back to man again. By following the first very fallacious, very unpromising method of investigation many false hopes have been raised, but raised only to be very speedily dashed to pieces. Thus, not to mention many others, Massy's microscopic fungus, Salisbury's famous palmella, Balæstra's alga, Schurtz's oscillaria, and, latest of all, Klebs and Tommasi Crudelli's bacillus malariæ were all put forward as the malaria germ; each in turn held the field for a time, but only to be abandoned for some equally worthless successor. This being so, the only other hopeful method of arriving at a more complete knowledge of the life-history of this important parasite is to seek for its extra-corporeal form in the second way I mention.

The plasmodium certainly is not driven to enter man for the reason that man is in any way necessary for its existence as a species. We know that malaria abounds where man is rarely or never seen—in tropical wildernesses; this could not be the case were man necessary for its development and multiplication. So far from man being necessary for the evolution of this parasite, if anything his presence is inimical to it; in towns and other places, where men congregate, malaria is infinitely rarer than in the open country, where man is a comparatively insignificant feature. We are, therefore, forced to conclude that when the parasite does enter man, it does so as finding in him a suitable alternative host from whom it can escape and extend as a species, that man is only one of the media in which this parasite can exist, and that there is a reciprocity as regards it between him and those other external media or medium. The plasmodium is a true parasite of man, not merely an accidental parasitic visitor. The individual plasmodium gets into man designedly, and, this being so, we may be quite sure that just as provision is made in its economy for a passage into the human body, so provision is made in its economy for a passage out of the human body. Such a provision is absolutely necessary for all true parasites; otherwise, were this not the case, the extinction of the parasite, not merely as an individual but as a species, would be inevitable on the occurrence of the death of the host. There are certain well-known facts about the plasmodium which seem to me to indicate very distinctly the character of the provision we seek for.

THE FLAGELLATED BODY: FIRST EXTRA-CORPOREAL PHASE.

If we look at our slides of malarial blood some fifteen or twenty minutes, or longer perhaps, after they have been mounted, another body, whose appearances we had not remarked before, not infrequently comes into view. This is called the flagellated body (Fig. 11—3, 6, and 12). It is a strange, weird-looking, octopus-like creature, with long, whirling, curling, lashing, tentacle-like arms attached to a central, somewhat spherical, mass, in which are black melanin particles tumbling about in a state of continual agitation. If we keep on watching this body we sometimes see one or more of the tentacle-like arms break away and swim about in the liquor sanguinis with a spirillum-like movement. This peculiar looking flagellated body is certainly not present, or at least is not visible, in our slides immediately after they are prepared. It appears only after they have been put up for some time, that is to say, after the blood has left the vessels. It is, therefore, not a feature of the intra-corporeal parasite. At certain times in ordinary tertians and quartans, if we examine the blood with the microscope, we will find that though most of the large intra-corpuscular bodies have disappeared—doubtless having been resolved in the course of their development into sporulating forms and dispersed as spores—a few

FIG. 11.



Evolution of the flagellated body in the tertian 1—3, quartan 4—6, and crescent-forming 7—12 parasites. (Compiled from Thayer and Hewetson.)

large, pigmented, passive, intra-corpuscular forms still remain (Fig. 11—1 and 4). We may also see a few large spherical bodies which are not inclosed in red blood corpuscles (Fig. 11—2 and 5). If we select one of the former and watch it carefully, and if we are lucky, we may see it escape from the including corpuscle and assume the appearance of the other form—the free spherical body. From this we may conclude that the free spherical body originates from the intra-corpuscular body—that they are escaped intra-corpuscular bodies. If we keep on watching and fortune favours, we may after a time see the pigment in the free spherical body become violently agitated, the body itself become contorted and jerked about, and then suddenly we may see long flagella projected from its circumference and begin waving about. A flagellated body is formed (Fig. 11—3 and 6). If we prepare dozens of slides from the same patient's blood by rapidly drying and fixing the blood as soon as it is spread upon the slide in not one of those rapidly fixed preparations will we be able to find a free extra-corpuscular parasite, much less a flagellated organism, proving that the flagellated body does not exist as such in the circulation, but is formed only after the blood has left the vessels.

If we examine with the microscope the blood of a malarial patient who has been suffering for some time from one of the malignant forms of the infection—what has been incorrectly called æstivo-autumnal fever—in addition to those forms of the parasite already described as being devoted to intra-corporeal reproduction, we may see what is known as the "crescent body" (Fig. 11—7). This is a crescent-shaped parasite lying inside a blood corpuscle whose hæmoglobin it has evidently devoured. By careful looking one can make out as a delicate bow running between the horns of the crescent the shell, as it were, of the blood corpuscle inside which the parasite developed and is still lying. Keep one of these crescent bodies under observation. Presently, if you are lucky, or better still if you multiply your chances of success by keeping half-a-dozen crescents under as many microscopes, you will see the crescent slowly change its form. First it becomes stouter as it were, the ends rounding off more and the body becoming thicker (Fig. 11—8). Next it loses all appearance of being a crescent and becomes ellipsoid (Fig. 11—9). Then slowly the ellipsoid changes into a perfect sphere (Fig. 11—10). In the crescent there is always a mass of motionless pigment granules about its centre. During the change of form described this mass of pigment still remains passive and central. The sphere once formed, however, a change occurs in this respect, the pigment granules beginning to move, at first slowly, but presently more actively, dancing about in the most energetic manner in the centre of the parasite. By-and-by, their agitation increasing, they burst through what I take to be the delicate membrane hitherto enclosing them. The pigment now becomes diffused throughout the entire mass of the sphere, and continues to indulge in violent boiling-like movement (Fig. 11—11). At the same time the sphere itself becomes agitated—excited, as it were—changes form, writhes, is jerked violently about by some unseen force, and then suddenly flagella are projected from its circumference (Fig. 11—12), just as already described in the case of the free spheres of the quartan and the benign tertian parasite. That these ellipsoidal and spherical forms do not exist as such in the circulating blood may be proved, as in the case of the tertian and quartan plasmodium, by fixing the blood immediately on its removal from the body; on such slides—even although wet slides prepared simultaneously may exhibit crescents, ellipsoids, and spheres —we never find the two latter forms, but only crescents, and, of course, should fever be present or imminent the usual intra-corpuscular forms of the plasmodium. This transformation of the crescent into the flagellate body is a very striking phenomenon and must be referred to one of two things. Either it is a degenerative change in a dying or dead parasite or it is a vital evolutionary change—a normal step in the life of the parasite. My conviction is that it is the latter, and that the flagellated body is the first phase of the extra-corporeal plasmodium.

THE FLAGELLATED BODY NOT A DEGENERATED PLASMODIUM.

I know, however, that many good authorities, including biologists and pathologists of the highest standing—such as Blanchard, Labbé, Grassi, Marchiafava, Bignami, Golgi, and others—take an opposite view; but I humbly submit that their views are based on altogether insufficient grounds. The advocates of the degeneration hypothesis point to the fact that these flagellated bodies do not appear until the parasite is out of the body, and therefore they say they must be degenerations, seeing that they develop in what the degenerationists choose to regard as conditions unfavourable to life. But I would submit the flagellated body does not come into being until it is out of the body, because it is of no use inside the body, its function lying outside the body. It appears, or rather develops, only where and when it is wanted. The degenerationists say that the parasite is killed by the relative coolness of the microscope slip and concurrent changes in the blood; that its contortions and wriggling flagella are but its death throes; that the agitated movements of the pigment in the spherical body from which the flagella spring are but brownian movements of dead matter. I say the parasite undergoes a developmental change in consequence of being placed in the conditions which are favourable, and not only favourable but necessary, for its development, a temperature considerably below that of the human body, perhaps, being one of them; and that the movements of the pigment are, if they are carefully watched, far too gross and irregular to be of the nature of the molecular motion of dead particles. There are forms of protoplasm, animal and vegetable, whose developments are repressed by a higher temperature and encouraged by a lower. Even in the case of this same malaria parasite a temperature lower than that of the human body is conducive to its interests, seeing that it flourishes outside the human body at ordinary atmospheric temperatures, and flourishes in these conditions probably to a far greater extent than it does inside the human body. The degenerationists say that only a small proportion of the large free spherical bodies of the quartan and benign tertian parasites and of the crescent-forming parasites proceed to flagellation and that therefore the occurrence of this appearance is exceptional, a mere accident. I hold that the conditions under which our observations are made—that is to say, on our microscope slips—are altogether abnormal and unnatural. I shall show that under more natural conditions flagellation occurs in the case of by far the largest number of crescents; that on the glass the conditions for development are so unfavourable that some crescents never change form; others cease to change on reaching the ellipsoidal stage; others get to the spherical stage and there stop. The fact that under conditions so abnormal as a glass slip affords, and while they are being compressed under a cover-glass, some crescents do manage to pass to flagellation indicates, to my mind that the disposition on the part of the crescent to metamorphose is very strong indeed, and that under natural conditions probably nearly all crescents will do so. The degenerationists say that flagellated bodies are found only in a relatively small number of cases of malarial infection, and that therefore they cannot be a regular and necessary feature of the parasite. Mannaberg says—and so far as my experience goes I can endorse his statement—that provided we examine a case of malarial infection often enough and long enough, we will in every instance encounter the flagellated body. It certainly occurs in all types of malaria—in quartan, tertian, and æstivo-autumnal. Therefore I hold that at some time or other flagellation is a feature in every set of malaria parasites, a regular and normal occurrence, and not irregular, capricious, exceptional, and therefore unnecessary. The degenerationists say that the evolution of the flagella is too rapidly carried through to be a developmental process. I would answer that the appearance of flagella is not, strictly speaking, a developmental process; the flagella are probably pre-existent in the sphere, perhaps, for all we know, in the crescent; their sudden appearance is rather an act of birth than of development, and we know that the act of birth is in most organisms a violent and precipitate process. A full account of all that has been advanced on this point would occupy too much space. An admirable summary of the arguments on both sides will be found in Thayer and Hewetson's article on the Malarial Fevers of Baltimore, in the fifth volume of the "Johns Hopkins Hospital Reports, 1895," to which I would refer you. Laveran, Mannaberg, Danilewsky, Dock, Coronado, and others are, all of them, opposed to the degeneration theory of the flagellates.

FUNCTION OF THE FLAGELLATED BODY.

Admitting, then, that the flagellated body is a living thing, a phase of the parasite, how may we explain its object? Something has diverted these particular plasmodia from ordinary sporulation. What that something is I do not

pretend to say, any more than the biologist can pretend to say what it is that turns one embryo into a male and another embryo into a female in other departments of Nature. Had the plasmodium gone on to sporulation in the ordinary way the peripheral portion of its body would have resolved into the ordinary intra-corporeal spores, and the pigmented centre would have been discarded as residual matter; but, being diverted from sporulating in this way by some occult cause, the peripheral portion of the organism is converted into flagellated spores, the central portion remaining as dead residual matter. The flagellated plasmodium I therefore regard as a sporulating plasmodium whose spores, for certain reasons in the interests of the extra-corporeal parasite, assume a flagellate form.

This view is strongly supported by what one sometimes sees in those spheres which stop short of flagellation. The accompanying is a sketch (Fig. 12) of one of these abortive

FIG. 12.

crescent-derived spheres from a case of æstivo-autumnal fever. It represents a very definite body. Originally a crescent-derived sphere which, failing to project flagella, gradually developed a ring of pale, spore-like spheres in what is usually the clear zone around the central circle of pigment. The matrix in which the clear spore-like bodies were located had a slightly brownish tinge, and so showed up these minute bodies with great distinctness. When perfect, the little spherules numbered about fourteen. After a short time they gradually merged into one another, the septum between them disappearing as if from degeneration. Does not this arrangement of spherules recall the rosette body of the ordinary sporulating plasmodium? And does it not suggest by the fact that it occurred in a crescent-derived sphere that this ring of spherules was a ring of coiled-up flagellated spores which, failing to erupt in the usual way, underwent some molecular or degenerative change which by slightly altering their refraction rendered them visible?

I conclude, then, that the crescent body, and the tertian and quartan spherical bodies which proceed to flagellation, are the extra-corporeal sporulating homologues of the intra-corporeal sporulating bodies; that the flagellum is the extra-corporeal homologue of the intra-corporeal spore. Both types of sporulating plasmodium have corresponding functions, both arise from the same source; one is the germ of the plasmodium inside the human body, the other is the germ of the plasmodium outside the human body; both function in the propagation of the parasite. Such is my view of the nature and significance of the flagellated phase of the malaria parasite and such are some of my reasons for entertaining this view. In the following lectures I propose to point out how under natural conditions the potential flagellated plasmodial spore leaves the human body and why this extra-corporeal plasmodial spore is flagellated. I shall then try to follow the parasite a little farther and endeavour to indicate what I cannot but regard as part at least of the extra-corporeal life of the plasmodium malariæ.

THE annual general meeting of governors of the Dental Hospital of London was held at the hospital on March 12th, Mr. F. A. Bevan, one of the trustees of the hospital, being in the chair.

THE ATTACK ON A MEDICAL PRACTITIONER AT RETFORD.—At the Nottinghamshire Assizes last week, before Mr. Justice Hawkins, George Mycroft, twenty-four, a foundry hand, was charged with unlawfully wounding Dr. Charles Westbrook at Retford on Jan. 18th. It will be remembered that Dr. Westbrook was attacked whilst helping the police to get a prisoner to the lock-up, and was severely injured about the head, being confined to his bed for ten days. Evidence for the prosecution went to show that Mycroft struck the blow, but the defence was that this was not reliable. Prisoner was found guilty and was sentenced to twelve months' hard labour, the judge stating that if Dr. Westbrook had died it would have been a clear case of murder.

The Milroy Lectures

ON

THE VALUE OF ISOLATION AND ITS DIFFICULTIES.

Delivered before the Royal College of Physicians of London

BY EDWARD SEATON, M.D., F.R.C.P. LOND.,

MEDICAL OFFICER OF HEALTH OF THE ADMINISTRATIVE COUNTY OF SURREY; LECTURER ON PUBLIC HEALTH AT ST. THOMAS'S HOSPITAL; AND EXAMINER IN PUBLIC HEALTH AND STATE MEDICINE TO THE ROYAL COLLEGE OF SURGEONS OF ENGLAND AND THE UNIVERSITY OF LONDON.

LECTURE III.[1]

Delivered on March 5th, 1896.

MR. PRESIDENT AND GENTLEMEN,—Typhus fever and small-pox afford examples of what may be accomplished by isolation along with the co-related measures of prevention. In what remains to be said of the value of isolation it is impossible to offer evidence as convincing, for the reason that other diseases, principally affecting children, have never as yet received the same amount of attention from public authorities. That which enables preventive measures to be carried out vigorously in the case of either typhus fever or small-pox is the fact that they may frequently strike down men in their prime. They consequently inspire fear among those who directly influence authorities, thus stimulating them to action. Neither whooping-cough, nor measles, nor scarlet fever, nor even diphtheria can give rise to panic such as that which immediately arises when the lives of bread-winners are specially endangered. This is the central fact we have to bear in mind when we come to consider the evidence respecting the advantages derived from such measures for controlling the prevalence of these last-named diseases as experience shows to be administratively possible. The disease of which we have had the most experience is scarlet fever. For the purposes of this lecture I have had charts prepared which show the prevalence of this disease in London and in the large towns of England generally. The experiences of London ought to be particularly instructive. The history of scarlet fever is, of course, not so dramatic (if I may so use the word) as that of the other two diseases. The death-rate has fallen very decidedly, as will be seen from the accompanying mortality chart. But the fall might have been greater, taking into account the largely increasing proportion of cases isolated at hospitals. The following table shows the annual death-rates per million for the last few years—namely, 1891, 1892, 1893, 1894, and 1895—as compared with those for previous periods.

Year.	Deaths.	Year.	Deaths.
1861–70	1133	1892	273
1871–80	600	1893	369
1881–90	330	1894	220
1891	142	1895	189

It will be noted that there was a very remarkable improvement shown during the decades 1871–80 and 1881-90, as compared with the period 1861–70, which may be described as the pre-isolation period. We are, therefore, justified in concluding that isolation has exercised a very great influence, but taking the experience of the last four years the history of scarlet fever would appear to be not altogether satisfactory. There was a rise in 1893 to 369. This was followed by a fall in 1894 to 220, and that has been followed by another fall in 1895 to 189. Scarlet fever is well known to be subject to cyclical fluctuations, and, therefore, the period would be considered too short to permit of definite conclusions. But it hardly looks as if scarlet fever were going to prove much less fatal in the decade 1891–1900, when over 60 per cent. of the cases are isolated, than in 1881–90, when less than half that proportion was so treated, so that it would appear that isolation under present conditions is not quite so efficacious in controlling scarlet fever as might have been hoped. At the same time the facts and figures show that the disease may be remarkably

1 Lectures I. and II. appeared in THE LANCET of March 7th, 1896.

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By PATRICK MANSON, M.D. Aberd., F.R.C.P. Lond.,

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LECTURE II.[1]

Delivered on March 12th, 1896.

The Escape of the Parasite from the Human Body.

Mr. President and Gentlemen.—I have endeavoured to show that the flagellated phase of the malaria parasite is in all probability the extra-corporeal homologue of the intra-corporeal sporulating body; that the latter provides for the propagation of the plasmodium inside the human body, whilst the former provides for its propagation outside the human body. I also dwelt on the fact that it is only when the plasmodium has escaped from the body that this flagellated phase can and does appear. The question now comes to be: Seeing that the escape from the body of its human host is necessary for the development of this, the first phase of the extra-corporeal plasmodium, how is this escape brought about?

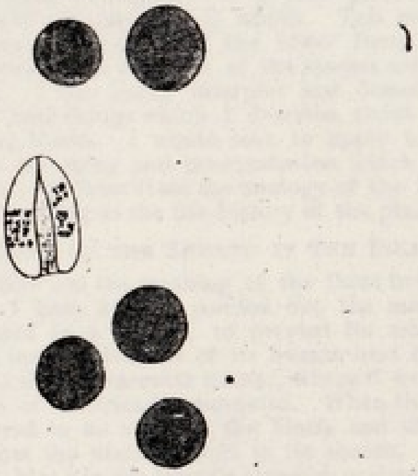
The Mosquito Theory.

Casting about for an agent that would meet the requirements of the case it occurred to me, as it had already occurred to Laveran, that as the plasmodium is a passive blood parasite its escape from the human body might be effected on the same principle that the escape of the passive muscle parasites is effected. As the latter obtain their opportunity by being swallowed by some flesh-eater—some carnivorous animal—I thought the former might get its chance of development by being swallowed by some blood-eater, some suctorial animal, such as the flea, the bug, the louse, the leech, the sand fly, or the mosquito. The geographical distribution of malaria and other very manifest considerations seem to point to one or other of the last two as the most likely liberating agent, and the notorious association of malaria and mosquitos with damp and stagnant water seemed to indicate more especially this insect.

Analogy with Filaria.

I was further impressed with the probability of the mosquito being the liberating agent of the plasmodium by a consideration of the remarkable similarity that obtains between the structure, habits, and requirements of the plasmodium, and the structure, habits, and requirements of the filaria—a parasite which I had already shown to be dependent on the mosquito for liberty and the opportunity for development. Thus, in the first place, the plasmodium and the filaria are both of them blood parasites, and both of them require to leave the blood in order to continue their respective species. Again, the filaria of the blood—filaria nocturna at all events—is enclosed in a loose sheath. Similarly the potential flagellated plasmodium, whether as sphere or crescent, while in the bloodvessels is enclosed in a blood corpuscle, which practically performs the function of a sheath. The filaria is sheathed to prevent its escaping from the bloodvessels into the peri-vascular tissues for the reason that, if it got there or escaped from the bloodvessels, it would be out of the way of the mosquito when this insect visited the body of the host. The filaria has a very elaborate and powerful oral armature—a piercing apparatus—which it seems always eager to use. To prevent the premature use of this weapon on the walls of the bloodvessels Nature has muzzled the filaria by enclosing it in the loose sac or sheath I refer to; so long as the parasite is inside this sac it cannot apply its oral armature to the walls of the bloodvessels. The plasmodium is similarly sheathed by the blood corpuscle it lies in, because, were it free in the blood, it would be set on immediately and destroyed by the phagocytes. The filaria is sheathed to prevent its committing suicide; the plasmodium is sheathed to protect it from being murdered. The sheathing in both instances has for its object the same thing, the preservation of the sheathed organism. The sheath in which the filaria is enclosed is easily demonstrated. It is not always easy, however, to make out the enveloping corpuscle which functions as a sheath or protecting agent for the plasmodium, either in its phase of potential flagella-producing sphere or as crescent. Sometimes, however, the former may be detected in the act of slipping out of or bursting their sheathing corpuscles; at such a moment the existence of the corpuscular sheath is very apparent. In the case of the crescent plasmodium the remains of the enveloping corpuscle can generally be readily recognised in the line that, bow-like, spans the concavity of the crescent. The preparation from which the accompanying drawing (Fig. 13) was made

Fig. 13.



clearly demonstrates the corpuscular nature of this bow. The drawing represents a double crescent of a peculiar type, the only one of its kind I have ever come across; nor do I recollect having seen either a description or a drawing of the same kind of double crescent. I fancy, therefore, it must be exceedingly rare. The case from which the preparation came was one of irregular fever and malarial cachexia in which the blood contained large numbers of crescents of the usual type. You can see that there are two separate and distinct crescents lying together and so disposed that their concavities face each other, the upper horns being in apposition, but the lower horns being separated by a considerable interval. You can also make out that a very delicate line unites the lower horns and that the space between the bodies of the twin crescents is occupied by a sheet of very pale hæmoglobin. This figure affords a convincing explanation, if such were needed, of the true nature of the arc line in the ordinary crescent. This line does not belong to the parasite, but to the blood corpuscle in which the parasite had developed and lies. If it belonged to the parasite, or were an integral part of the parasite, then, in the case of the twin crescents represented, each crescent would have its own special arc line—two crescents and two arc lines. This, you see, is not the case. The two crescents developing in the same corpuscle have been compelled to share the corpuscular capsule in common.

The Plasmodium and the Filaria both Cast their Protecting Envelopes.

Another parallel between the filaria and the flagella-producing forms of the plasmodium lies in the facts that not only are both parasites provided with a sheath, but both parasites cast this protecting covering when they get outside the body, and in both this casting of their sheaths can be artificially brought about on the microscope slide.

Escape of the Filaria from its Sheath.

To study this phenomenon in the case of the filaria we place an ordinary vaseline sealed preparation of filaria containing blood near a window in frosty weather, or, if the weather be mild, on a block of ice. The slide is left in the cold for several hours—say, overnight—and then examined

[1] Lecture I. was delivered on March 10th and published in The Lancet of March 14th.

walls of the bloodvessels. The plasmodium is similarly sheathed by the blood corpuscle it has to, however, were it free in the blood, it would be set on, immediately and destroyed by the phagocytes. The filaria is sheathed to prevent its escaping outside; the plasmodium is sheathed to protect it from being murdered. The sheathing in both instances has for its object the same thing, the preservation of the sheathed organism. The sheath in which the filaria is enclosed is easily demonstrated. It is not always easy, however, to make out the enveloping corpuscle which functions as a sheath of protection; except for the plasmodium, either in its phases of parasitic development, where we shall notice, however, the latter may be detected by the act of displacement of or pushing their containing corpuscle; as even a moment the existence of the corpuscular sheath is very apparent. In the case of the crescent plasmodium the remains of the enveloping corpuscle can generally be readily recognised in the line that, bow-like, spans the concavity of the crescent. The preparation from which the accompanying drawing (Fig. 13) was made

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THE PLASMODIUM AND THE FILARIA BOTH CAST THEIR PROTECTIVE ENVELOPES.

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ESCAPE OF THE FILARIA FROM ITS SHEATH.

To study this phenomenon in the case of the filaria we place an ordinary moist-chamber preparation of filaria containing blood over a window in frosty weather, or, if the weather be mild, on a block of ice. The slide is left to the cold for several hours—say, overnight—and then examined

The Croonian Lectures

ON THE LIFE-HISTORY OF THE MALARIA GERM OUTSIDE THE HUMAN BODY.

Delivered before the Royal College of Physicians of London

By PATRICK MANSON, M.D. ABERD., F.R.C.P. LOND.,

PHYSICIAN TO THE SEAMEN'S HOSPITAL, ALBERT DOCKS; LECTURER ON TROPICAL DISEASES AT ST. GEORGE'S HOSPITAL AND CHARING CROSS HOSPITAL.

LECTURE II.[1]

Delivered on March 19th, 1896.

ESCAPE OF THE PARASITE FROM THE HUMAN BODY.

MR. PRESIDENT AND GENTLEMEN,—I have endeavoured to show that the flagellated phase of the malaria parasite is in all probability the extra-corporeal homologue of the intra-corporeal sporulating body; that the latter provides for the propagation of the plasmodium inside the human body, whilst the former provides for its propagation outside the human body. I also dwelt on the fact that it is only when the plasmodium has escaped from the body that this flagellated phase can and does appear. The question now comes to be, seeing that the escape from the body of its human host is necessary for the development of this, the first phase of the extra-corporeal plasmodium, how is this escape brought about?

THE MOSQUITO THEORY.

Casting about for an agent that would meet the requirements of the case it occurred to me, as it had already occurred to Laveran, that, as the plasmodium is a passive blood parasite its escape from the human body might be effected on the same principle that the escape of the passive filaria parasites is effected. As the latter obtain their opportunity by being withdrawn by some blood-eater—some blood-sucking animal—I thought the former might get its chance of development by being swallowed by some blood-sucking, some suctorial animal such as the flea, the bug, the tick, the leech, the sand fly, or the mosquito. The geographical distribution of malaria and other very familiar considerations seem to point to one or other of the last two as the most likely liberating agent, and the notorious association of malaria and mosquitos with damp and stagnant water seemed to indicate more especially this insect.

ANALOGY WITH FILARIA.

I was further impressed with the probability of the mosquito being the liberating agent of the plasmodium by a consideration of the remarkable similarity that obtains between the structure, habits, and requirements of the plasmodium, and the structure, habits, and requirements of the filaria—a parasite which I had already shown to be dependent on the mosquito for liberty and the opportunity of development. Thus, in the first place, the plasmodium and the filaria are both of them blood parasites, and both of them require to leave the blood in order to continue their respective species. Again, the filaria of the blood—filaria nocturna at all events—is enclosed in a loose sheath. Similarly the potential flagellated plasmodium, whether in sphere or crescent, while in the bloodvessels is enclosed in a blood corpuscle, which practically performs the function of a sheath. The filaria is sheathed to prevent its escaping from the bloodvessels into the extra-vascular tissues for the reason that, if it got there or escaped from the bloodvessels, it would be out of the way of the mosquito when this insect visited the body of the host. The filaria has a very elaborate and powerful oral armature—a boring apparatus—which in some always eager to use. To prevent the premature use of this weapon on the walls of the bloodvessels Nature has sheathed the filaria by enclosing it in the loose sac or sheath I refer to; so long as the filaria is inside this sac it cannot apply its oral armature to the

[1] Lecture I. was delivered on March 17th and published in THE LANCET of March 21st.

with the microscope at the ordinary temperature of the room. We shall then find that, as the slide warms up, the chilled and languid filariæ gradually resume their usual active movements. But, in addition to this, in addition to the wriggling about like a worm on a hook seen in ordinary unchilled preparations of fresh blood, the filaria begins to indulge in a peculiar rushing, butting movement of quite a new character. Lying inside its long, loose sheath, it ever and anon retires towards the tail end of this, and then suddenly and rapidly darts forward, throwing itself with great force against the head end of the sheath. Evidently this butting movement is an endeavour on the part of the parasite to break through and escape from the sheath. The chilling to which the blood had been subjected has had the effect of causing the hæmoglobin to leave the red blood corpuscles and become diffused through the liquor sanguinis. This diffusion of hæmoglobin has thickened the blood, and so favours, and perhaps has provoked, the efforts of the worm to escape. We can see that the thick and viscid blood clings to the sheath and holds it, as it were, thereby enabling the

FIG. 14.

little animal within to butt the sheath more effectually. Sooner or later it succeeds in effecting what is manifestly the object of these butting movements; it breaks through the head end of the sheath, and finally wriggles itself free from the trailing encumbrance (Figs. 14 and 15). And now

FIG. 15.

another thing is noticeable about the movements of the filaria. While still in its sheath, though very active in wriggling about, the filaria never changed materially its position on the slide and there was no need to shift the slide about to keep the parasite in the field of the microscope, but now when it has succeeded in ridding itself of the sheath, the style of movement undergoes a complete change; the worm is no longer stationary, but begins to travel about all over the slide, moving restlessly from one part of the preparation to another as if searching for something, so that to keep it under continuous observation the slip has to be constantly shifted. The wriggling stationary movement is changed into a locomotive movement.

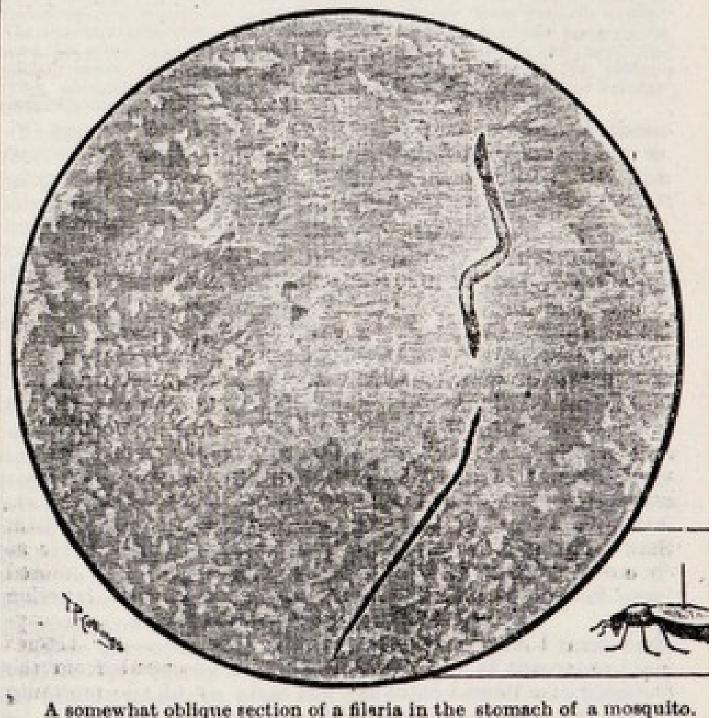
ESCAPE OF PLASMODIUM FROM BLOOD CORPUSCLE.

Similarly, as I have pointed out, the crescent form of the plasmodium, when newly abstracted from the circulation, lies motionless in its sheath—the sheltering blood corpuscle; it is stationary; but when the crescent has been outside the body for a very little time it often commences to change its shape, and in doing so ruptures its corpuscular capsule; the parasite then—like the filaria on the chilled slide—becomes free in the blood. And just as the filaria, freed from its sheath, acquires a locomotive faculty and travels away, so the flagella, which develop on the disappearance of the corpuscular capsule, tend to break away and to swim to a distant part of the preparation. Both parasites on ridding themselves of their sheaths develop locomotor habits. These may seem small and insignificant facts to dwell on. Not so; the most trifling anatomical or physiological fact has a meaning could we but read it aright. This meaning has nearly always—particularly in the lower forms of life—a direct reference to the interests of the species exhibiting the phenomenon. I can easily interpret and demonstrate the meaning of these things which I describe about the movements of the filaria. I would seek to apply to the plasmodium the reasoning and interpretation which hold good for the filaria; to draw from the analogy of the filaria some assistance in getting at the life-history of the plasmodium.

FUNCTION OF THE SHEATH IN THE FILARIA.

Let us follow out the meaning of the facts in the case of the filaria. I have already pointed out the reason for its being enclosed in a sheath, to prevent its using its oral armature on the bloodvessels of its human host and thereby escaping into the perivascular tissues, where it would be out of the reach of the friendly mosquito. When the mosquito has transferred to its stomach the filaria and the blood in which it floats the filaria is still in its sheath. Presently, however, the blood in the insect's stomach undergoes exactly

FIG. 16.

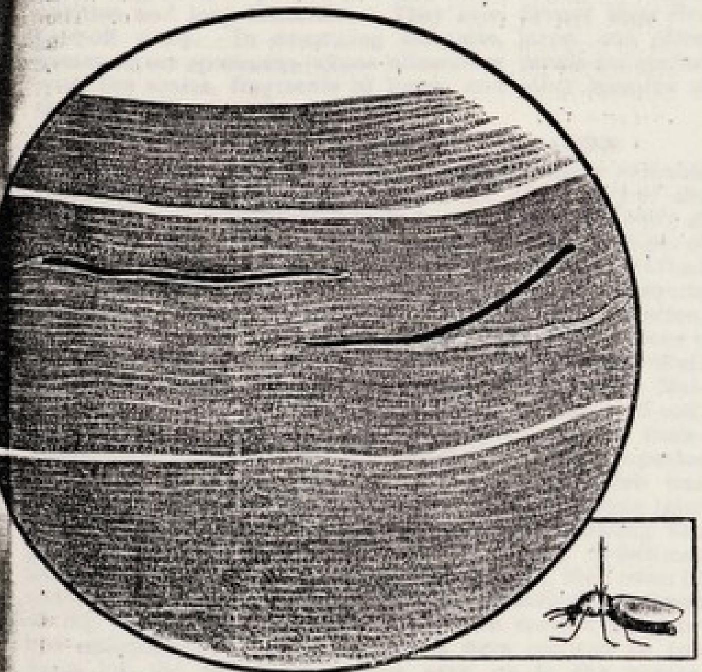


A somewhat oblique section of a filaria in the stomach of a mosquito. The darker object is the filaria; it has just escaped from its sheath, the more lightly shaded object lying above the free filaria.

the same thickening from escape of hæmoglobin into the liquor sanguinis which we produced artificially on our chilled slides. Thus, in the mosquito the filaria is provided with the physical conditions which prompt it to try and which are necessary for enabling it to break through its sheath; this in time it succeeds in doing (Fig. 16); but when it has

got through its sheath it is still relatively a long way from its destination, from the end of its journey. The filaria has to get into the thoracic muscles of the mosquito before it can utilise this insect as an intermediate host in which to complete its metamorphosis, this being effected in the thorax and not in the abdomen. It has to travel from the centre, perhaps, of the mass of blood in the mosquito's stomach to the walls of the stomach, and thence to the thoracic muscles (Fig. 17), a long journey, if

FIG. 17.



Two filariæ lying between the muscular fibres in the thorax of the mosquito.

we bear in mind the size and equipment of the traveller. Accordingly a physiological change comes over the unsheathed parasite; the wriggling movement which had previously characterised it is changed into a locomotive movement. This locomotive movement has for its first object to transfer the filaria to the walls of the insect's stomach; and now we understand the object of the armature with which nature has provided the parasite and why she had previously sheathed this armature so carefully, and why she has unsheathed it later. When the filaria gets to the end of this first stage of its journey and arrives at the walls of the mosquito's stomach it employs the now naked beak and hooks to tear through this viscus, and then, boring and squeezing along and between the fibres of the thoracic muscles, to work its way to the destination, where it will subsequently undergo the metamorphosis qualifying it for further life. I have many times followed out the little drama I describe. These drawings made from actual preparations illustrate the main facts very well.

[Dr. Manson here argued that the analogy between the structure, habits, and requirements of the filaria and the plasmodium respectively might be applied to their life-histories as well. He described the affinity of the plasmodium to the sporozoa and continued:—]

The gymnosporidia, as the order to which the plasmodium belongs has been named by Labbé, are in many respects like the gregarines, in other respects like the coccidia. The members of the three orders are all of them intracellular parasites during either a considerable part or the whole of their lives; they all propagate, of course, by the production of spores, and in all of them the spores have to get transferred somehow from one host to another in a more or less passive way. The gregarines and coccidia do not propagate outside the bodies of their respective hosts; I hold, therefore, as probable that their close allies the gymnosporidia—such as the plasmodium of man and the halteridium and proteosoma of birds—do not live at any time as free organisms, unless, perhaps, it be sometimes as a resting spore, but are always parasitic during their active propagating life. And so I consider that the reason why the plasmodium on entering the mosquito pushes for the walls of the insect's stomach is that it may get at some cell in the mosquito's body, therein to curl itself up and grow and sporulate just in the same way as it does in the blood corpuscles of man, and as is the habit of its allies the gregarines and coccidia. Where in the mosquito's body and what the particular cell is I do not pretend to be able to indicate. Perhaps, owing to the minuteness of the objects we are dealing with and the many practical difficulties attending the investigation, it may be long before that cell is found and the full history of the parasite in the mosquito is thoroughly worked out; but I feel certain that in time these things will be established on the lines I indicate, and that the life-history of the plasmodium will be revealed as completely for the mosquito as it already is for man.

THE ADVENTURES OF A FLAGELLUM.

So far as I am aware no one has seen the plasmodium flagellum enter a cell; but that it has the desire and the power to do so seems to be certain. I have lately received a letter bearing on this point from Surgeon-Major Ronald Ross, I.M.S., whose remarkable work on the plasmodium in the mosquito I shall fully describe in my concluding lecture. In this letter there occurs a passage which describes very graphically what I may call the adventures of a flagellum. Referring to the examination of a certain malarial patient's blood he writes:—

"I said I was going to watch free flagella. I found one in my first specimen and watched it continuously for three hours. So much for the statement that free flagella soon become quiescent and vanish in the serum. At first it wriggled about for twenty minutes like a trypanosoma, so that I could hardly follow it. Then it brought up against a phagocyte and remained there so long that I thought the phagocyte had seized it. Not so; it was neither killed nor sucked in, but was actively engaged in attacking the phagocyte. The flagellum kept at this for about a quarter of an hour and then wriggled away across two fields and in the direction of another phagocyte. Into this second phagocyte it pushed in several places with one of its ends, and the phagocyte seemed to rear up and try in vain to get round and envelop the flagellum. At last the phagocyte seemed to give the struggle up, and flattened itself against an air bubble, the flagellum still attacking it. After fifty minutes, and when the flagellum seemed to be getting exhausted, a very curious thing happened. A third phagocyte approached, coming rapidly across the field, but it had no sooner got near than the flagellum left its fallen foe and attacked the new one, holding on to it and shaking like a snake on a dog. In one minute the third phagocyte turned sharp round and quickly made off; it went right across a whole field, the flagellum, holding on to it. This continued for five minutes, after which the flagellum left the phagocyte. By this time the flagellum had become much more visible and had a large swelling in the middle. I watched it steadily as its movements became gradually slower. It was certainly able to attach itself to the cover-glass (as shown by touching it with a pen) by either end, and even perhaps by the swelling. At last this swelling moved to one end nearly and became very large and distinct until, after three hours, the creature evidently died; at any rate, it curled up and ceased to move." Surgeon-Major Ross goes on to say: "Is not this interesting? I think it shows, first, that the phagocytes have no more power over free flagella than they have over trypanosomes; secondly, that the beast was evidently attacking the phagocytes, probably mistaking them for some other kind of cell, so I judge by its leaving the phagocytes after a time."

I agree with Surgeon-Major Ross in considering these observations most interesting; more than that, in addition to being interesting they are highly important, for they not only establish the fact that the plasmodial flagellum attacks—that is, seeks to enter cells—but also that in the free state it can resist the phagocytes; and, contrary to the statements of many of the writers on the malarial parasite, that it does not die within a few minutes of its quitting the sphere from which it was originally emitted.

THE PLASMODIUM A PARASITE OF THE MOSQUITO.

I think I have advanced many cogent reasons for believing that the plasmodium malariæ on leaving man, and as a normal step in its life-history, becomes parasitic in the mosquito, and that in this insect it enters some cell—as any gregarine or coccidium would do—and probably develops into its reproductive sporulating form just as it does in the blood corpuscles of man. What then? How can its spores get out of the mosquito so as to increase and multiply and preserve its species from extinction when in the course of nature the mosquito dies? How, too, does it spread over the land, and how does it get back to man again?

Before attempting to answer these questions, I must first describe very briefly a passage in the life of the mosquito. The female mosquito, after she has filled herself with blood—the male insect is not a blood-sucker—seeks out some dark and sheltered spot near stagnant water. At the end of about six days she quits her shelter, and, alighting on the surface of the water, deposits her eggs thereon. She then dies, and as a rule falls into the water beside her eggs. The eggs float about for a time, and then in due course each gives birth to a tiny swimming larva. These larvæ, in virtue of a voracious

appetite, grow apace, casting their skins several times to admit of growth. Later they pass into the nympha stage, during which, after a time, they float on the surface of the water. Finally, the shell of the nympha cracks along its dorsal surface and a young mosquito emerges. Standing, as on a raft, on the empty pelt the young mosquito floats on the surface of the water while its wings are drying and acquiring rigidity. When this is complete it flies away. The young mosquito larvæ, to satisfy their prodigious appetites, devour everything eatable they come across; and one of the first things they eat if they get the chance is the dead body of their parent, now soft and sodden from decomposition and long immersion. They even devour their own cast-off skins. In examining mosquito larvæ one often comes across specimens whose alimentary canals are stuffed with the scales, fragments of limbs, and other remains of the parental insect.

THE HISTORY OF A MOSQUITO GREGARINE.

I am indebted to Surgeon-Major Ross for many valuable facts in support of my views as to the life-history of the plasmodium; amongst other facts for the instructive story of the gregarine which inhabits the stomach and appendages of the Secunderabad mosquitos and their larvæ. He tracked the germs of this gregarine into the stomach of the mosquito larva, where after an intracellular stage of short duration, and which was not quite satisfactorily made out, it became a large, free, actively moving gregarine. At maturity the adult gregarines crawled out of the stomach and into the Malpighian tubes, along which they crept towards the cæcal end. There, with or without conjugation, they encapsuled themselves and generated in the interior of their capsules multitudes of pseudo-navicellæ. At maturity, which was attained at the nympha stage of the insect, or a little later in the perfect insect, the capsule ruptured liberating the pseudo-navicellæ in such numbers that they sometimes seemed to completely fill, and even to distend, the lumen of the Malpighian tubes. Many of the pseudo-navicellæ escaped in the fæces of the nympha, others were carried away by the mosquito when it emerged, and were emitted in the fæces of the insect, sometimes even on to the human skin, while she was in the act of sucking blood. As mentioned, the development of the gregarine was sometimes effected so rapidly that numerous pseudo-navicellæ were emitted before the nympha stage of the mosquito was concluded, so that it was a common thing to find the empty nympha pelts thickly sprinkled over with multitudes of tiny gregarine germs. As we have seen that the mosquito larva devours its own and its neighbour's exuviæ, we can readily understand how, once gregarines have been introduced into a pool of water, the larval mosquitos in that particular pool become infected by the parasite. But as the mature mosquito when she quits her nympha husk also contains numerous gregarines, we can also understand how she, too, carries the infection with her, scattering it about the country in her fæces or conveying it to any other pool where she may lay her eggs and afterwards die. Her body is then devoured by her progeny or by any other mosquito larvæ that already chance to be in the pool. Along with her body, of course, the larvæ swallow any gregarine germs it may contain if they have not already been picked up by the larvæ when feeding on the mud at the bottom of the pool. Does not this little story of the gregarine indicate the way, or a way, in which that other mosquito sporozoon—the plasmodium malariæ—multiplies? Does it not indicate how this parasite, in which man is so much interested, passes from mosquito to larva, from larva to mosquito, in never-ending series? Does it not indicate how the plasmodium disease of mosquitos spreads from pool to pool and is scattered broadcast about the country, and does it not indicate how it may get back to man again?

DIFFUSION OF THE PLASMODIUM BY THE MOSQUITO.

We can readily understand how the mosquito-bred plasmodium may be swallowed by man in water as so many disease germs are, and we can readily understand how it may be inhaled in dust. Mosquito-haunted pools dry up. The plasmodia in the larvæ, and those that have been scattered about in the water, finding themselves stranded by the drought, and so placed in a condition unfavourable for development, pass into a resting stage, just as they do when by quinine or other means man is rendered temporarily unsuited for their active life. They may, probably do, become encysted as so many of the protozoa do in similar circumstances. The dried sediment of the pool, blown about by winds and currents of air, is inhaled by man, and so the plasmodium may find its way back again to the host from whom its ancestors had, perhaps, started generations back. I would conjecture that on entering man and on entering the larval mosquito it develops into a flagellated spore similar to the flagellated spore into which it develops in the mosquito's stomach. In this way it would be enabled to penetrate the mucous surfaces and get into the human blood cell. Many mosquitos die without getting to water; all male mosquitos die without seeking water. They may die far from water, blown away, as we know mosquitos are, by high winds. The bodies of such mosquitos fall in time on the soil and decompose. The parasites they contained pass into the resting stage, and in this form they also may be carried into the air by currents, or be blown about as dust, or be shaken out by man when he disturbs the soil. In this way the plasmodium may find a route back to man again. In this way, too, we may explain the occurrence of those cases of malaria which apparently, though not really, are unconnected with swamp or stagnant water. Such is my view of the life-history of the malaria parasite, and the *rôle* of the mosquito with regard to it, and of the process by which man becomes infected. In my concluding lecture I shall bring forward further evidence for the truth of this theory, and endeavour to answer certain objections which have been, or which may be, brought against it.

A CASE OF DOUBLE UTERUS WITH SUBMUCOUS FIBROID TUMOUR.

BY ARTHUR H. N. LEWERS, M.D. LOND.,
OBSTETRIC PHYSICIAN TO THE LONDON HOSPITAL.

A MARRIED woman, thirty-eight years of age, was sent to me by Mr. Snowman and admitted into the London Hospital under my care on Oct. 16th, 1895. She had been married fourteen years, but had never been pregnant. The catamenia appeared when she was fifteen, but she was not regular till she was twenty-one, several months intervening at times between the periods. Since she was twenty-one she had been quite regular every four weeks till seven months ago, but nearly always had some pain during menstruation. She complained that for the last seven months she had been losing too much at her periods, and for the last six months there had been a constant red discharge between the periods, but till recently she could still tell when the menstrual periods occurred. For the last six months she had passed clots during menstruation, but had never done so previously. The dysmenorrhœa had been relieved during the last seven months by lying down, but this is said to have had no effect in lessening the excessive flow. She had had some pain and smarting during micturition ever since her marriage, but this had been worse during the last seven months. She had been losing flesh during the last six months. On vaginal examination the uterus was found considerably enlarged. A curious falciform fold of mucous membrane (F) was felt at the upper part of the vagina running from before backwards and from right to left. The sound passed four and a half inches. At this time it was not recognised that there was a second vaginal portion, as the finger passed to the right of the fold just described. After disinfecting the vagina a laminaria tent, specially rendered aseptic by prolonged immersion in absolute alcohol containing 1 per cent. of corrosive sublimate, was inserted into the cervix (A)—that on the right side—on Oct. 16th at 5 P.M., a strip of iodoform gauze being packed below the tent to keep it in position. The next day at 2 P.M. an anæsthetic was given, and the patient placed in the lithotomy position. The iodoform gauze was removed and a vaginal douche of perchloride of mercury (1 in 1000) given. The upper part of the vagina and the cervix into which the tent had been inserted were then thoroughly exposed with Sims's speculum and retractor. It was then seen that there was a second vaginal portion (B) to the left side. It was perfectly well formed, but slightly smaller than the vaginal portion on the right side. The falciform fold of vaginal mucous membrane (F) passed between the two vaginal portions, running, as already mentioned, from before backwards and slightly from right to left. The tent was now removed from the right about by winds and currents of air, is inhaled by man, and so the plasmodium may find its way back again to the host from which its ancestors (or, perhaps, started generations back). I would remember that on quitting man and on entering the larval mosquito is devoured but is assimilated upon similar to the flagellated spore form which is develops in the mosquito's stomach. In this way it would be enabled to reinstate the mosquito's existence and get into the human blood cell. Many mosquitoes die without getting to water: all male mosquitoes die without seeking water. They may die far from water, blown away, as we know mosquitoes are, by high winds. The bodies of such mosquitoes fall in time on the soil and decompose. The remains they contained pass into the resting stage, and in this form they also may be carried into the air by currents, or be borne about as dust, or be shaken out by man when he disturbs the soil. In this way the plasmodium may daily come back to man again. In this way, too, we may explain the occurrence of those cases of malaria which apparently, though not really, are unconnected with swamp or stagnant water. Such is my view of the life-history of the malaria parasite, and the rôle of the mosquito with regard to it, and of the process by which man becomes infected. In my concluding lecture I shall bring forward further evidence for the truth of this theory, and endeavour to answer certain objections which have been or which may be brought against it.

A CASE OF DOUBLE UTERUS WITH SUBMUCOUS FIBROID TUMOUR.

By ARTHUR H. N. LEWERS, M.D. Lond.,
OBSTETRIC PHYSICIAN TO THE LONDON HOSPITAL.

A MARRIED woman, thirty-eight years of age, was sent to me by Mr. Sylvester and admitted into the London Hospital under my care on Oct. 14th, 1895. She had been married fourteen years, but had never been pregnant. The catamenia appeared when she was fifteen, but she was not regular till she was twenty-one, several months intervening at times between the periods. Since she was twenty-one she had been quite regular every four weeks till seven months ago, but nearly always had some pain during menstruation. She complained that for the last seven months she had been losing too much at her periods, and for the last six months there had been a constant red discharge between the periods, but till recently she could still tell when the menstrual periods occurred. For the last six months she had passed clots during menstruation, but had never done so previously. The dysmenorrhœa had been relieved during the last seven months by lying down, but this is said to have had no effect in lessening the excessive flow. She had had some pain and smarting during micturition ever since her marriage, but this had been worse during the last seven months. She had been losing flesh during the last six months. On vaginal examination the uterus was found considerably enlarged. A narrow falciform fold of mucous membrane (F) was felt at the upper part of the vagina running from before backwards and from right to left. The sound passed four and a half inches. At this time it was not recognised that there was a second vaginal portion, as the finger passed to the right of the fold just described. After disinfecting the vagina a laminaria tent, specially rendered aseptic by prolonged immersion in absolute alcohol containing 1 per cent. of corrosive sublimate, was inserted into the cervix (A)—that on the right side—on Oct. 18th at 5 P.M., a strip of iodoform gauze being packed below the tent to keep it in position. The next day at 3 P.M. an anæsthetic was given, and the patient placed in the lithotomy position. The iodoform gauze was removed and a vaginal douche of perchloride of mercury (1 in 1000) given. The upper part of the vagina and the cervix into which the tent had been inserted were then thoroughly exposed with Sims's speculum and retractor. It was then seen that there was a second vaginal portion (B) to the left side. It was perfectly well formed, but slightly smaller than the vaginal portion on the right side. The falciform fold of vaginal mucous membrane (F) passed between the two vaginal portions, running, as already mentioned, from before backwards and slightly from right to left. The tent was now removed from the right

this poor space, casting their skins several times to natural growth. Later they pass into the nymph stage, during which, after a time, they float on the surface of the water. Finally, the shell of the nymph cracks along its dorsal surface and a young mosquito emerges. Standing, as on a raft, on the empty pelt the young mosquito floats on the surface of the water while its wings are drying and hardening rapidly. When this is complete it flies away. The young mosquito larvæ, to satisfy their prodigious appetites, devour everything eatable they come across; and one of the first things they eat if they get the chance is the dead body of their parent, now soft and sodden from decomposition and long immersion. They even devour their own cast-off skins. In examining mosquito larvæ one often comes across specimens whose alimentary canals are stuffed with the scales, fragments of limbs, and other remains of the parental insect.

THE HISTORY OF A MOSQUITO GREGARINE.

I am indebted to Surgeon-Major Ross for many valuable facts in support of my views as to the life-history of the plasmodium; amongst other facts for the instructive story of the gregarine which infests the stomach and appendages of the Secunderabad mosquitoes and their larvæ. He tracked the spores of this gregarine into the stomach of the mosquito larva, where after an intermediate stage of short duration, and which was not quite satisfactorily made out, it became a large, free, actively moving gregarine. At maturity the adult gregarines crawled out of the stomach and into the Malpighian tubes, along which they crept towards the cæcal end. There, with or without conjugation, they encapsuled themselves and generated in the interior of their capsules multitudes of pseudo-navicellæ. At maturity—which was attained at the nymph stage of the insect or a little later in the perfect insect—the capsule ruptured, liberating the pseudo-navicellæ in such numbers that they sometimes seemed to completely fill and even to distend the lumen of the Malpighian tubes. Many of the pseudo-navicellæ escaped in the fæces of the nymph; others were carried away by the mosquito when it emerged, and were emitted in the fæces of the insect, sometimes even on to the human skin, while she was in the act of sucking blood. As mentioned, the development of the gregarine was sometimes effected so rapidly that numerous pseudo-navicellæ were produced before the nymph stage of the mosquito was concluded, so that it was a common thing to find the empty nymph pelts thickly sprinkled over with multitudes of tiny gregarine spores. As we have seen that the mosquito larva devours its own and its neighbour's exuviæ, we can readily understand how, once gregarines have been introduced into a pool of water, the larval mosquitoes in that particular pool become infected by the parasite. But as the mature mosquito when she quits her nymph pelt also contains numerous gregarines, we can also understand how she, the carrier of the infection, with her wandering, is able to carry the infection to a new pool by conveying it to any other pool where she may lay her eggs and afterwards die. Her body is then devoured by her progeny or by any other mosquito larvæ that already chance to be in the pool. Along with her body, of course, the larvæ swallow any gregarine spores it may contain if they have not already been picked up by the larvæ when feeding on the food at the bottom of the pool. Does not this little story of the gregarine indicate the way, or a way, in which that other mosquito parasite—the plasmodium malariæ—multiplies? Does it not indicate how this parasite, in which case it is so much interested, passes from mosquito to larva, from larva to mosquito, in never-ending series? Does it not indicate how the paludal disease of mosquitoes spreads from pool to pool and is scattered broadcast about the country, and does it not indicate how it may get back to man again?

DEPENDENCE OF THE PLASMODIUM ON THE MOSQUITO.

We can readily understand how the mosquito-bred plasmodium may be swallowed by man in water as so many disease germs are, and we can readily understand how it may be inhaled in dust. Mosquito-infested pools dry up. The plasmodia in the larvæ, and those that have been scattered about in the water, finding conditions abnormal, are placed in a condition unfavourable for development, pass into a resting stage, just as they do when by failure or other causes they are rendered temporarily unsuited for their active life. They may, probably do, behave as so many of the parasites do in similar circumstances. The dried sediment of the pool, blown

The Goulstonian Lectures

ON

THE LIFE-HISTORY OF THE MALARIA GERM OUTSIDE THE HUMAN BODY.

Delivered before the Royal College of Physicians of London

BY PATRICK MANSON, M.D. ABERD., F.R.C.P. LOND.,

PHYSICIAN TO THE SEAMEN'S HOSPITAL, ALBERT DOCKS; LECTURER ON TROPICAL DISEASES AT ST. GEORGE'S HOSPITAL AND CHARING-CROSS HOSPITAL.

LECTURE III.[1]

Delivered on March 17th, 1896.

MR. PRESIDENT AND GENTLEMEN,—When some time ago I had formulated the theory enunciated in my last lecture there was little prospect of my being able personally to put it to the test of further observation and experiment, and as neither Laveran nor Mannaberg had connected the mosquito with the flagellum, and Calandruccio had failed to observe developmental changes in malarial parasites ingested by mosquitos, I hardly ventured to hope that my views would so soon receive the support which has been given to them.

SURGEON-MAJOR ROSS'S INVESTIGATIONS.

Surgeon-Major Ronald Ross, to whom I have already referred, was in England last winter, and, being favourably impressed with the mosquito hypothesis, determined to work it out on his return to India. After much discussion we fixed on a certain line of experiment and observation which my experience in former years in filaria work seemed to indicate as being likely to lead to some definite result one way or other. Those forms of malaria in which the crescent body is a prominent feature are the most suitable for experiment, at all events to commence with, for of all the forms of the plasmodium the crescent is the most definite, the most readily recognised in the blood, and the easiest to work with, much more so than the potential flagella-forming intra-corpuscular parasite of the quartan and benign tertian infections. We concluded that when the mosquito ingested the crescent plasmodium one of three things must happen: (*a*) either the crescent would be killed and digested without exhibiting any evolutional change; or (*b*) it would behave very much as crescents do on the microscope slide—that is, a large proportion of them would remain crescents and a certain proportion of them would become ovals and spheres, and a very small proportion of them would go on to flagellation; or (*c*) a very large proportion of the crescents ingested would proceed to flagellation, the flagella subsequently becoming free. We concluded that if the first turned out to be the case, then this mosquito hypothesis was wrong; if the second, that it was at best doubtful; and if the last, that it was probably correct, or, at all events, that it was worth pursuing further. On his return to India in April of last year Surgeon-Major Ross was stationed at Secunderabad, in the Deccan, where malaria is common enough. After some searching among his hospital patients he found a complacent native, one Abdul Kadir, a sepoy, who was suffering from malarial cachexia, and in whose blood the crescent form of the plasmodium abounded; several crescents could be found in nearly every field of the microscope. Surgeon-Major Ross placed this man under a mosquito net, introduced mosquitos which he had previously reared from the egg, and then collected the insects after they had filled themselves with the patient's blood. He then made systematic examinations at short serial intervals of the blood in the malariated mosquitos' stomachs, being careful at the same time to compare the results so obtained with control slides of finger blood prepared at corresponding times from the same patient. As a result of a prolonged study of the subject Surgeon-Major Ross found that, so far from being killed and digested by the stomach of the mosquito, with the exception of an insignificant proportion, all the ingested crescents rapidly proceeded in development; almost all became spheres, and at least 40 or 50 per cent. of them proceeded to flagellation and liberation of flagella; that is to say, the crescent conducted itself in the mosquito's stomach very much as the filaria does, and exactly as if it had got into a proper medium for development. In explanation of some of the terms employed I may mention that the expressions "spent spheres" and "pigment bodies" refer to the more or less passive spherical pieces of pigmented plasmodial protoplasm which remain after the flagella have broken away from what I may call the mother sphere: these pieces of protoplasm represent the discarded body of the flagellated organism, and, biologically, may be regarded as residual matter left after sporulation. In a letter dated May 25th, 1895, Surgeon-Major Ross says:—

"The result was my first perfect specimen of mosquito blood. About twenty minutes had elapsed since the mosquito had begun sucking; the hæmoglobin had commenced to diffuse. The blood swarmed with perfect spherules, not very large, about 6 microns (= 0·006 mm.) in diameter, but showing an almost eruptive movement of pigment, as if flagella were about to burst forth in a moment. I looked in vain, however, for flagellates; to my surprise not one was to be seen. In a very few minutes the pigment oscillation, the intensity of which was much greater than in the control specimens, began to quiet down. Many of the spheres were shaking, but, as I have said, not one was flagellate. The general view, however, was very different from an ordinary specimen. All the spheres had perfect circular contours, and I now noticed that they seemed to be in much larger numbers than in finger blood, contrary to my first impression. Here are my notes of the number of spheres mostly in thin fields: 7, 3, 9, 7, 1, 2, 3, 2, 2, 0, 2, 2, 1, equal to an average of 3 per field. The fields were consecutive. The numbers will give you some idea of the quantities of parasites. I made a specimen of a second mosquito at three-quarters of an hour after beginning to suck, and the results were precisely the same. On counting the numbers of crescent spheres and pigment masses respectively I obtained: First specimen: 7 crescents, 80 spheres, 8 pigment masses; second specimen, 14 crescents, 30 spheres, 9 pigment masses. On counting the second specimen next day I found 0 crescents, 8 spheres, and 32 pigmented masses. In both specimens the number of crescents appears a great deal too favourable, as it was possible to examine field after field without finding one. Next day I began with a finger-blood specimen, which gave, when fresh, crescents and ovals 39, spheres 10, pigment masses 1. Then I made two more mosquito specimens at about half an hour, my 18th and 19th mosquitos. Up to date I had observed only two flagellate bodies, both in finger blood. I was astonished I had not met with more. Always the spheres seemed ripe for flagella, but they did not come. The temperature of the air was 95° F. Now directly I looked at mosquito 18 I saw flagellated organisms in every field. I saw 9 altogether in a few minutes, but instead of counting them I wasted my time looking at them. Two fields held 2 each, and I could have found numbers, I do not doubt, if I had looked at once over the specimen. As it was the spectacle afforded by mosquito 18 was amazing. All the spherules seemed bursting with excitement and were exceedingly numerous. I noticed in contiguous fields 6, 10, 8, 7, 10, 14, 12, 16, an average of 10 a field; but when I came to examine special fields I found 60 in one field, 72 in the next, all endeavouring and ready to burst. I think you will confess that no one has had such an experience as this in finger-blood. On looking through mosquito 19 I found the same swarm of spheres but no flagellate organisms. Next day I began with mosquito 20, fed the day before. I found mostly pigment masses, but about 20 per cent. of the parasites were still cellular—that is, spheres. I made a specimen of a fresh mosquito—No. 21—at half an hour from feeding, with a presentiment of what I was going to see: 4 flagellates and 20 spheres in the first field, 5 flagellates and 12 spheres in the second field, and 3 flagellates and 10 spheres in the third field. Flagellate organisms everywhere; one, or two, or more in every field. I must have seen over 30 or 40, though I examined only a few fields, being hardly able to tear myself away from individual organisms. The flagella were excessively fine, quite invisible in open spaces, but visible in hæmoglobinous serum. The flagellated organisms were unmistakable, because they were being dragged about all over the field generally, or were quivering and being shaken as a dog shakes a rat. The 'manifestation' nearly ceased in a few minutes, though I saw flagellates for half an hour afterwards. Mosquitos 22 and 23, at seventy and ninety minutes, gave no flagellates and but few parasites comparatively. The patient was put under the net again. Mosquito 24 gave the same results at half an hour as mosquito 21. Five flagellates in one field of 12 parasites. Flagellate organisms everywhere, especially in open parts. The 'manifestation' lasted in its intensity only for about five minutes."

SURGEON-MAJOR ROSS'S CONCLUSIONS.

Surgeon-Major Ross continued to experiment with mosquitos going over the ground again, and again generally obtaining similar results. Writing on May 28th he says:—

"The progress of things, then, is this: 1. Almost all the crescents are converted into spheres very shortly after they enter the mosquito's stomach. Sometimes a fair number of crescents may be found at ten, fifteen, twenty, or more minutes, but these are almost always seen in the same part of the specimen, and, therefore, belong probably to the last intake of blood. It is very rare to find more than one or two crescents in an entire preparation of mosquito blood made at longer intervals. Ovals are not often seen. Untransformed crescents are, I believe, aborted ones. 2. The spheres are always found. They have a perfect contour, and contain a clear material, which distinguishes them markedly from the masses of corpuscles in the midst of which they are generally found. At first the pigment is clustered together; then the outermost pigment particles begin to oscillate; lastly, all pigment particles commence swarming, while the whole cell may take on a slight jerking movement. 3. Flagellate organisms may be found at from seven to thirty-five minutes or more. When seen they lie almost always in great numbers

[1] Lectures I. and II. were delivered on March 10th and 12th and were published in THE LANCET of March 14th and 21st respectively.

in contiguous fields, suggesting that they belong to the same intake of blood and have ripened at the same time. So far as I have experienced, they are always found within a minute or two of the lens being brought to a focus. The whole 'manifestation' ceases in a very few minutes. Owing to this circumstance, and probably owing to the process of making the specimen causing the flagella to break away, the flagellated organisms are sometimes not to be found. 4. The spent spheres or pigment masses may sometimes be seen very early—even at eight minutes, but then are few in number. Their number steadily increases, almost without fail, in successive mosquitos of the same batch as regards time of feeding until, as in mosquito 39, they may reach 60 per cent. of all parasites not enclosed in phagocytes. Their appearance is quite characteristic, simply because they are not inclosed in the clear, well-defined cells of the spheres. They are easily seen to be mere dead clusters of pigment—sometimes with very feeble oscillations. They may be in masses, rings, or drawn-out clusters. Their absence in the blood of the earlier killed mosquito and their large numbers in the blood of the later killed show conclusively that they are due to a progressive metamorphosis inside the mosquito and not to crushing in making the specimen. 5. Phagocytes containing spheres and pigment begin to be seen later than the spent pigment (at about twenty minutes or so), and increase in number up to about two hours. 6. About 30 or 40 per cent. of the parasites fail to throw out flagella and remain as spheres. The above developments may be shortly stated in two sentences:—(*a*) Practically all crescents become spheres a few minutes after being taken into the mosquito's stomach. (*b*) From 30 to 40 per cent. of the spheres die after one or two hours, the rest having given out flagella, been eaten by phagocytes, or having simply broken up."

These conclusions, Surgeon-Major Ross informs me, were borne out by a number of similar experiments on three other patients having crescent parasites in their blood. In these cases, too, the evolution of the flagellated form occurred as in Abdul Kadir, so that there can be little doubt that the conclusions founded on the Abdul Kadir experiments apply equally to the crescent parasite in every case.

EFFECT OF QUININE ON THE EVOLUTION OF THE FLAGELLATED BODY IN BLOOD AND IN THE MOSQUITO.

I may mention a curious circumstance in connexion with Abdul Kadir's crescents which gives, perhaps, a certain amount of additional support to the claim the mosquito has to be regarded as a suitable nurse for the plasmodium. After a number of days the patient began to be feverish and it was evident that an attack of acute malaria was impending. Not feeling justified in exposing the man to what might prove to be a serious illness Surgeon-Major Ross administered some doses of quinine, and at the same time continued his mosquito observations. The effect of the drug on the parasite was curious. Hitherto a certain proportion of the crescents in finger-blood underwent evolutional change into oval, spherical, and, in a very few instances, into flagellated bodies; but, after the administration of quinine, the crescents in finger-blood remained crescents in every instance. Apparently the drug had at least impaired their vital energies if it had not killed them outright. But when the crescents which had been swallowed by the mosquito in the cinchonised blood were examined it was found that the usual evolution into sphere and flagellated body took place as before, only with this difference, it was delayed for about a quarter of an hour beyond the usual time. This would seem to show that the conditions afforded by the mosquito's stomach are so favourable to the evolution of the crescent that they can with time overcome the paralysing influence of quinine on the plasmodium. Surgeon-Major Ross had commenced the difficult task of following up the flagellum to its destination in the tissues of the mosquito, when, unfortunately, official duties called him away from Secunderabad and forced him to suspend his work on malaria.

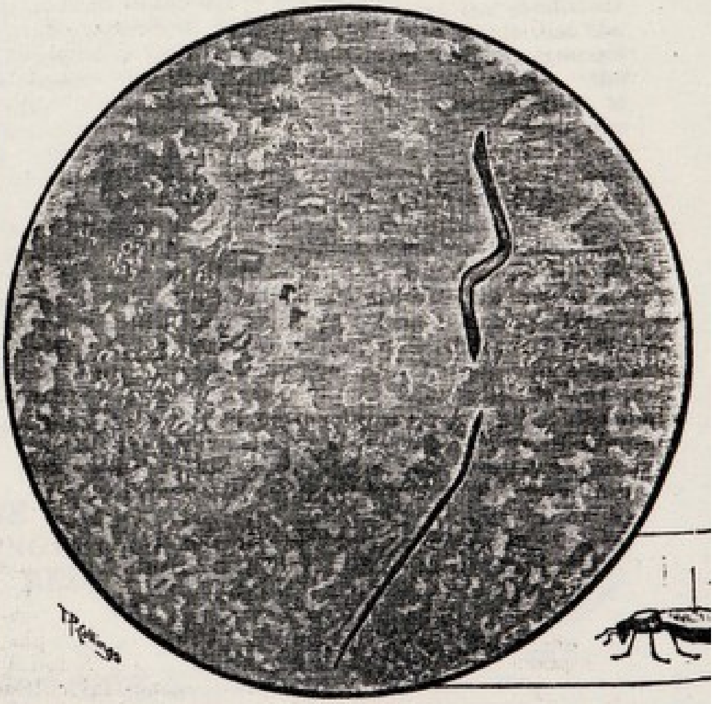
EXPERIMENTS ON COMMUNICATION OF MALARIA TO MAN BY MOSQUITO WATER.

In the course of his investigations Surgeon-Major Ross received much encouragement from an experiment he performed. After due explanation he administered to a healthy native the drachm or two of water in which a couple of malarialised mosquitos had died after depositing their eggs. The remains of the insects had been removed, but the eggs and some mosquito grubs which had just been hatched out from some of the eggs were swallowed. Eleven days (the incubation period in experimental malaria, be it noted) after this peculiar draught the man got an attack of fever characterised by headache, rise of temperature to 103°F., lassitude, and so forth, but no rigor. The fever lasted three days and then subsided spontaneously. In the blood a considerable number of the ring form of the plasmodium were found; but although many examinations were made during the next week or two no crescent form appeared nor was there any relapse. Nothwithstanding the absence of crescents and of relapse and the spontaneous subsidence of the fever, which, clinically, was of the æstivo-autumnal type usually associated with crescents, there can be little doubt that this was a case of malarial disease. Whether it was the result of the mosquito water, or whether its occurrence eleven days after the administration of this was simply a coincidence, it is impossible to say. Surgeon-Major Ross repeated the experiment in several other natives, but he did not again succeed in producing malarial fever of an unequivocal character.

SUGGESTIONS FOR FURTHER INVESTIGATIONS.

Surgeon-Major Ross has proved by observation the correctness of my conjecture that the stomach of the mosquito is a suitable medium for the flagellated phase of the plasmodium malariæ to develop in; and it behoves us, starting where he left off, to trace the progress and fate of the flagellum. The first thing we have to do is to find out where the flagellum goes after it has been set free in the blood of the mosquito's stomach, and this is only possible by systematic observation from hour to hour and day to day. When working out the life-history of the filaria in the mosquito the relatively enormous size of this parasite made the task of tracing it a comparatively easy one, even with the imperfect apparatus I had at my disposal. With modern methods of sectioning the task would have been still easier. I find that if a living filariated mosquito is plunged into some hardening medium a few hours after it has fed, and in due course embedded, sectioned, and stained, it is a very easy matter to trace the filaria in its progress from the abdomen of the insect to the thoracic muscles, and through its subsequent metamorphosis. The preparations represented by Figs. 18 and 19 were made in this way. Fig. 18 represents a somewhat oblique section of a filaria which is still lying in the blood of the abdomen of the mosquito. It has evidently just succeeded in escaping from its sheath, part of which can be seen lying empty some

FIG. 18.



A somewhat oblique section of a filaria in the stomach of a mosquito. The darker object is the filaria; it has just escaped from its sheath, the more lightly shaded object lying above the free filaria.

distance behind it. Fig. 19 represents a longitudinal section of the thoracic muscles of the same mosquito. Two filariæ can be made out. One is still *in situ* and lies stretched out among the muscular fibres between which it doubtless had been boring its way; the other, which when alive had occupied a similar position, has been partially turned out from its bed by the stroke of the section knife. From such and similar preparations it is easy to read the story of the filaria in the mosquito. Now I would suggest that the progress of the flagellum might be made out and demonstrated in the same way. Malariated mosquitos, after being plunged at relapse. But whether the absence of crescents and of relapse and subsequent absence of the fever which, naturally, was [illegible] with quinine and [illegible] cannot be [illegible] that this was a case of [illegible] disease. Whether it was the result of the mosquito bites, or whether its recurrence seven days after the administration of the quinine was simply a coincidence, it is impossible to say. Surgeon-Major Ross repeated the experiment in several other natives, but he did not again succeed in producing malarial fever of an unequivocal character.

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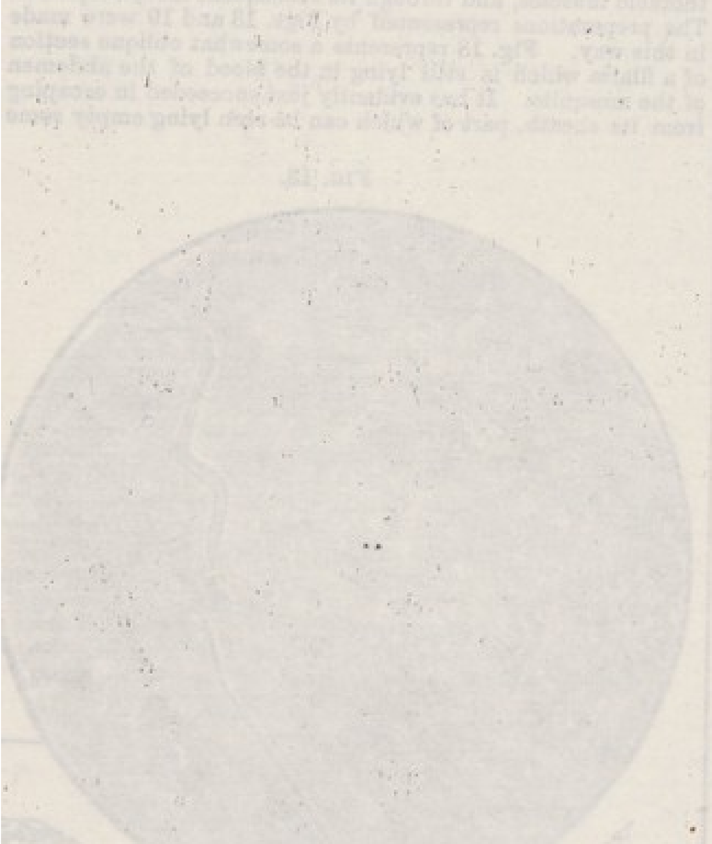

A somewhat oblique section of a filaria in the stomach of a mosquito. The darker object is the filaria; it has just escaped from its sheath, the more lightly shaded object lying above [illegible].

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[illegible] pentagonous forms, suggesting that they belong to the same phase [illegible] of the same time. So far as I have [illegible], they are [illegible] found within a minute or [illegible] very few minutes. Owing to their vacuolation and colourlessness, [illegible] the flagellated organisms are sometimes apt to be ignored. [illegible] but these are few in number. [illegible] of all parasites but [illegible] well-defined cells of the spheres. They [illegible] clumps of pigment [illegible] in the blood of the [illegible] mosquito and [illegible] conclusively that they are due to a [illegible] in the mosquito [illegible] pigmented bodies [illegible] in number up to about [illegible] per cent. of the parasites [illegible] sheath [illegible] of the spheres [illegible] hours [illegible] or having already developed.

These conclusions, Surgeon-Major Ross informs me, were borne out by a number of similar experiments on three other patients having crescent parasites in their blood. In these cases, too, the evolution of the flagellated form occurred as in Abdul Kadir, so that there can be little doubt that the conclusions founded on the Abdul Kadir experiments apply equally to the crescent parasite in every case.

EFFECT OF QUININE ON THE EVOLUTION OF THE FLAGELLATED BODY IN BLOOD AND IN THE MOSQUITO.

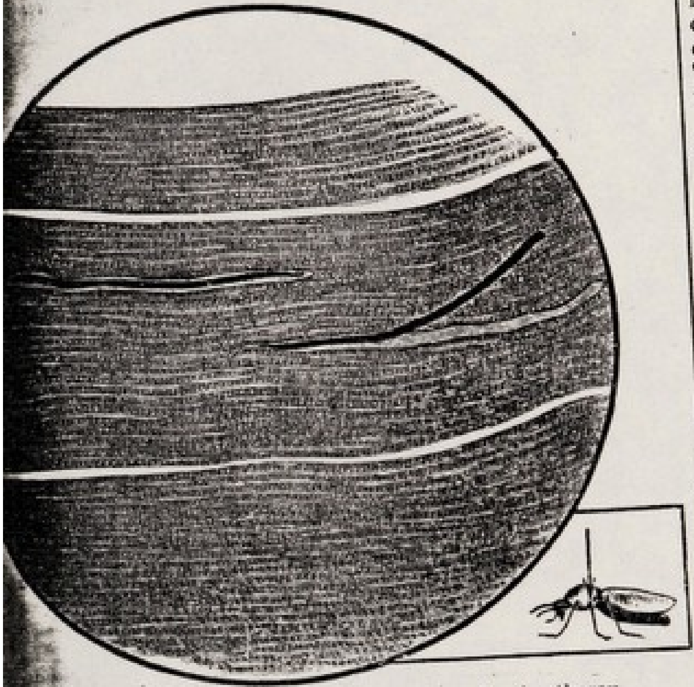
I may mention a curious circumstance in connexion with Abdul Kadir's crescents which gives, perhaps, a certain amount of additional support to the claim the mosquito has to be regarded as a suitable medium for the plasmodium. After a number of days the patient began to be feverish and it was evident that an attack of acute malaria was impending. Not feeling justified in exposing the man to what might prove to be a serious illness Surgeon-Major Ross administered some doses of quinine, and at the same time continued his mosquito observations. The effect of the drug on the parasite was curious. Hitherto a certain proportion of the crescents in finger-blood underwent evolution, change into oval, spherical, and, in a very few instances, into flagellated bodies; but, after the administration of quinine, the crescents in finger-blood remained crescents in every instance. Apparently the drug had at least impaired their vital energies if it had not killed them outright. But when the crescents which had been swallowed by the mosquito in the quininised blood were examined it was found that the usual evolution into sphere and flagellated body took place as before, only with this difference, it was delayed for about a quarter of an hour beyond the usual time. This would seem to show that the conditions afforded by the mosquito's stomach are so favourable to the evolution of the crescent that they can with time overcome the paralysing influence of quinine on the plasmodium. Surgeon-Major Ross had commenced the difficult task of following up the flagellum to its destination in the tissues of the mosquito, when, unfortunately, official duties called him away from Secunderabad and forced him to suspend his work on malaria.

EXPERIMENTS ON COMMUNICATION OF MALARIA TO MAN BY MOSQUITO WATER.

In the course of his investigations Surgeon-Major Ross received much encouragement from an experiment he performed. After due explanation he administered to a healthy native the drachm or two of water in which a couple of malariated mosquitos had died after depositing their eggs. The remains of the insects had been removed, but the eggs and some mosquito grubs which had just been hatched out from some of the eggs were swallowed. Eleven days (the incubation period in experimental malaria, be it noted) after this potion drank the man got an attack of fever characterised by headache, rise of temperature to 102°F., lassitude, and so forth, but no rigor. The fever lasted three days and then subsided spontaneously. In his blood a considerable number of the ring form of the plasmodium were found; but although many examinations were made during the next week or two no crescent form appeared nor was there any

...al intervals from the time of feeding into half per cent. ...ic acid for a minute or two, might be hardened in ...malin or some other suitable agent and then sectioned ...d stained in different ways. I can conceive that in insects ...prepared the shower of flagella, emitted about half an ...ur after feeding, might be traced in the blood in the ...domen, a more or less continuous stream setting in towards ...e particular cells in which, as I have explained, the

Fig. 19.



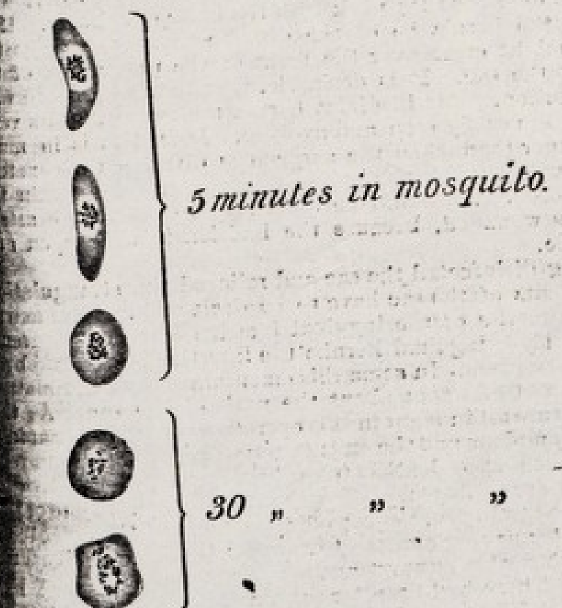
Two filariæ lying between the muscular fibres in the thorax of the mosquito.

flagellum seeks to bury itself and which we are in search of. Some of the flagella would perhaps be caught in the act of entering; and some of them, perhaps, might be seen already coiled up in the interior of these cells. This particular cell once discovered the remainder of the task would be easy enough.

Surgeon-Major Ross's Preparations.

Simple expression of the viscera of the mosquito, and groping about in their contents, will not suffice to discover

Fig. 20.



the plasmodium after the stage of free flagellum has passed. In preparations which Surgeon-Major Ross sent me last year I have been able to follow, to some extent, the transmutations he describes. The bodies represented in Fig. 20 were drawn from such preparations, and, so far as they go, they unmistakably bear out his statements. They are sufficiently confirmatory to warrant us in placing implicit reliance on the description he gives of the phenomenon of ex-flagellation in the mosquito. The flagella are structures so delicate and so difficult to stain that the rude preparations these drawings were made from cannot be expected to show them. Short of this, however, they are convincing. The upper figures, representing the crescent bodies, are from a mosquito killed five minutes after it had fed. One can easily pick out in the preparation every variety of developmental form, from crescent to ellipsoid. The two lower figures are from a preparation made thirty minutes after the mosquito had fed. In it we can make out here and there forms belonging to the flagellated organism, to the spent spheres, and to the pigment masses. The pigment they contain suffices to establish the plasmodial nature of the bodies in which it lies.

[Dr. Manson here enumerated the more debatable points of his argument. He continued :—]

Objections to the Mosquito Theory.

Until malarial disease is communicated by the administration of plasmodial forms that have been passed through the mosquito, until the theory is proved up to the hilt, it is probable that various objections will be raised. For instance, there are many places in the world where, though mosquitos abound, malaria is rare; and, again, there are certain places on the west coast of Africa and elsewhere where malaria is notoriously prevalent although mosquitos are absent; but the most serious difficulty in the mosquito theory is the fact that as yet we have not been able to trace the flagellum into the tissues of the mosquito. The reasons for this I believe to be the delicacy and minuteness of the object, the complicated character and abundance of cell forms, with which we are as yet very imperfectly acquainted, in the mosquito, and our ignorance of a suitable technique. Until the flagellum has been traced into some cell in the mosquito it is possible that I may have been misled by the marvellous analogy between the requirements and structure of the plasmodium and those of the filaria, and by the apparent suitability of the structure and habits of the flagellated plasmodium and the flagellum to the conditions they encounter in the mosquito. It is just possible that the invariableness with which the metamorphosis of the crescent is effected in the mosquito, the certainty with which "the manifestation" of flagellation occurs in from twenty to thirty minutes after ingestion of malarial blood by the mosquito, are mere coincidences. One may say, the phagocytes live for a time in the mosquito, why not the flagellated body? It can live on the microscope slide, why should it not live in the mosquito's stomach? While acknowledging that these are points requiring further investigation I do not recognise in them grave arguments against the validity of my theory, and I hold that Surgeon-Major Ross's investigations have rendered it so probable that I look confidently to him and to other workers in India and elsewhere to forge the links that are still wanting to complete the chain of evidence.

THE OPERATION FOR STRANGULATED INGUINAL HERNIA CONSIDERED IN RELATION TO RECENT ADVANCES IN SURGERY.

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During the last few years when called upon to operate for strangulated inguinal hernia I have performed an operation which differs in many ways from that which used to be done. It is highly probable that other surgeons follow exactly the same course as that which I am about to describe, but even such modern works upon operative surgery as those of Mr. Jacobson and Mr. Treves illustrate the operation for strangulated inguinal hernia with figures which go back to Fergusson and describe an operation unlike the following. Briefly defined it is simply the operation for the radical cure of inguinal hernia, but differs in that the contents of the sac are strangulated. The objects aimed at are not only to relieve the strangulation but also to cure the hernia, or, at least in older people, to make it amenable to a light truss.