THE GOULSTONIAN LECTURES

ON

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

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LECTURE I.

DISCOVERY OF THE MALARIAL PARASITE.

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."

The progress of investigation has shown, has in fact proved, that what only seemed likely to Fayrer when he addressed the College, was, indeed, actually the case. A great discovery had been made, and a disease cause had been found in an organism belonging to a department of the animal kingdom hitherto hardly suspected as being a serious contributor to human pathology. Notwithstanding the startling and important nature of the discovery, the progress of investigation in connection with it, until the last five or six years, has been very slow; in fact, unless 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; and even where he does mention it he goes the length of refusing to attribute to the bodies Laveran described a parasitic, much less a pathogenic nature. 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. Doubtless these and other authorities recalled the many malaria germs which had already been offered to the public. Before Laveran's time, every year, almost, had brought forth a fresh malaria germ; and, just as regularly, every year had seen the promising germ wither and die. Consequently, the profession and the public were naturally shy about accepting this newest germ of Laveran; all the more so as it did not quite fall into line with the prevailing bacterial doctrine of infective disease.

By degrees, however, Laveran's views gained ground. Confirmation from different parts of the world came in. Richard in Algiers, Osler in America, Carter in India, Marchiafava in Italy and many others, one after another, endorsed most of the Frenchman's statements. When finally the patient work and remarkable intuition of Golgi had strung together in biological sequence most of the confusing variety of forms which Laveran and those other observers described, and when this talented Italian had 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 clenched and at length thoroughly established. Henceforth Laveran's parasite had to be classed among the leading facts of pathology. There cannot any longer be the slightest doubt that it is the germ of malaria; there cannot any longer be the slightest doubt that incidents connected with its multiplication in the human body are the causes of the clinical phenomena of malaria. These things are now abundantly proved, and are accepted by all who have taken the trouble to make themselves personally acquainted with the facts and the parasite.

The main incidents of the life-history of the malaria parasite inside the human body and of its pathological action there have been many times fully described. Further than is absolutely necessary for the elucidation of the special theme I have selected to speak about I do not

propose to occupy myself with that part of the malaria problem. My purpose on this occasion is rather to endeavour to throw some fresh light on, at all events to call attention to, a special and limited aspect of the subject, to one phase only of the parasite—an important phase, it is true, but one which has been somewhat neglected of late. This phase we know must certainly exist. A knowledge of it is not only likely to prove highly interesting from a scientific point of view, but it has very direct bearings on two highly practical questions—the prophylaxis of malaria and the hygiene of warm countries. I refer to the life-history of the malaria parasite outside the human body. England is not a favourable place for the study of this particular side of the malaria problem. I have, therefore, very few fresh facts to offer; but I trust that the few facts I shall bring forward and the inferences I shall draw from them may prove interesting, and perhaps have some influence in leading others more favourably circumstanced to look for something definite and convincing.

THE MALARIAL PARASITE WITHIN THE HUMAN BODY.

Before proceeding to deal with the life-history of the parasite as it exists outside the human body I think it advisable, in order to render my argument clear, to state very briefly the leading facts of its intracorporeal life. I would premise also that I shall speak of the parasite as the plasmodium malariae or the plasmodium—useful though, zoologically, not very accurate terms.

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 our examination blood procured during the stage of rigor, or during the hour or two preceding rigor when the thermometer is gradually mounting, we shall probably encounter a number of pale, morula-like bodies made up of some 12 to 20 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 morula-like 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; perhaps they are scattered about irregularly, each spherule being independent of the other. In the same slides 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 intracorporeal little bodies—say with methylene blue—they, too, are found to be made up of a deeply-stained nucleolus, which lies somewhat eccentric-

cally in a larger circular unstained area—the nucleus which has come into view for the first time; the whole is surrounded by a narrow rim of lightly-stained protoplasm. These stained circlets look like tiny signet rings stuck on to the affected 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 more numerous, and hardly, or only very slowly, changing 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. On staining, 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, although we cannot directly watch the evolution of any individual parasite, we are driven to the conclusion that one form passes into the other in a very definite and regular way, that we are contemplating the birth, growth, and multiplication of an organised being conducted on a regular and definite plan. We conclude that the large pigmented intra-corpuscular body is the mature animal prepared for sporulation, that the morula-like mass is the same with the sporules formed, and that the spherules into which it breaks up on its 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, both of fact and interpretation, pathologists and biologists in the main agree that the short account I have given is substantially the history of the benign tertian

parasite in human blood; and that the same account, modified somewhat as regards the length of the cycle, certain details affecting the amount, colour, shape, and movements of the pigment granules, amœboid movements of the parasite, its effect on the blood corpuscle, and its distribution in the vessels and organs of the body, applies to the quartan and to the various forms of what may be termed the malignant malaria parasite. It is not necessary for my purpose to enter into details about these modifications. The account I give of the tertian parasite practically applies to all the malaria parasites, and indicates sufficiently in what way the plasmodium maintains itself during the acute manifestations of malarial disease, and how it contrives to propagate itself in the circulation.

LATENCY OF THE MALARIAL PARASITE.

In this description we look in vain for an explanation of two other and important matters in connection with malaria. It affords 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; and it does not explain the *rationale* of the primary infection—how the parasite enters the human body in the first instance; and it does not give us any clue to the life of the parasite outside the human body.

It is a well-known fact that the subjects of malarial infection may for a time lose their disease symptoms, becoming, so far as ordinary clinical tests can show, perfectly healthy; and yet, after remaining well for weeks, months, or even years, suffer a relapse of acute symptoms, the plasmodium, which had completely disappeared from the peripheral circulation, reappearing once more in the finger blood concurrently with the return of the symptoms. Such occurrences are in many instances of the nature of true relapses; for they may take place under conditions in which reinfection from without is extremely improbable, if not impossible, as in persons who, though infected originally in a malarial country, may have for a long time been resident in a non-malarial country and quite beyond the geographical range of the plasmodium. In such instances it is manifest that during the period in which clinical evidences of infection were absent, and in which the parasite could no longer be found in the blood, in one form or another the plasmodium must have been lying dormant in some out of the way corner of the body. It would be interesting to know what the particular form is which, under these circumstances, the parasite assumes; and, also, what part or tissue of the human body it inhabits during this period of latency. It would also be interesting to know what are the physical conditions that rouse it from its sleep and permit it again to run riot in the blood—conditions on the withdrawal of which it once more assumes its latent form. This is a subject about which we as yet know absolutely nothing. It is an important one, for it is probable, if we knew the conditions which cause the malarial parasite to become latent and the conditions which rouse it into activity, that we might be able, by reproducing the one or avoiding the other, to obtain a therapeutical and prophylactic mastery over this germ of the utmost value to humanity. I have no new fact to offer on this subject. I merely note the important hiatus in our knowledge, and pass on to the matter with which I propose more particularly to occupy your attention.

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. This is so evident and so universally admitted that the proposition does not call for discussion. I purposely say "pass directly from one human being to another." This does not mean that it cannot pass at all, or indirectly, from one man to another. It does imply, however, that it exists at one time or another outside the human body, and in a condition independent of man. There is abundant evidence to show that it does thus 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.

How to find this extra-corporeal form of the plasmodium is the problem I would first discuss; this is the first step to make before we can hope to get at its extra-corporeal life-history.

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, from morphological and other considerations, might be supposed to be the object sought for; next, when such a form is found, to endeavour to prove by experiment its identity with the malaria germ; and then, having satisfied ourselves in this way of its identity, to set about studying its habits as we would those of any other object of natural history. 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—in its own interests, as it were—and to follow it out of the human body, tracing it into and through outer Nature back to man again.

Until the intra-corporeal form of the malaria parasite was discovered the only line of investigation possible was the first of the two I have indicated; and on these lines, by this process of blind groping, many attempts were made to find the hypothetical germ in outer Nature. It would serve no useful purpose to recall in detail these attempts. They all ended in failure. It is difficult to understand how it could have been otherwise. The soil, the water, the air of reputedly malarious places were diligently scrutinised with the microscope. Myriads of suspicious animal and vegetable forms can be, and were, found in this way; but, unless the nature and appearance of the malaria parasite were already known, how could an investigator hope to recognise it among the myriad forms with which it might be associated? How could he be certain he had captured it, that it was present even, on the glycerine plates he had hung up to catch it; in his condensed atmospheric vapour; in his wash bottle; in his samples of water and soil? Is it even probable that this deadly parasite is in such profusion in the air of malaria-haunted spots that it is inhaled in every breath, present in every few gallons of air filtering over or through the collector's apparatus? Such a line of investigation postulates this improbability; otherwise what hope has the investigator of finding it in the insignificant amount of concentrated atmospheric dust that goes to make up a slide of his microscope? It is unreasonable to suppose that the germ of the parasite is so abundant in the atmosphere of even the most malarious spots. If it were so abundant, as this would imply, no one who entered these districts could hope to escape malarial disease; the effect on anyone breathing such an atmosphere would be deadly; he would be overwhelmed.

By following this 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, Balestra's alga, Schurtz's oscillaria, and, latest of all, Klebs and Tommasi-Crudeli's bacillus malarie 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.

THE METHOD FOLLOWED IN THE PRESENT INQUIRY.

For the reasons I have given, research carried on on these lines is almost bound to end in failure. 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—namely, to trace it out of the human body, to follow its destinies step by step—never to lose sight of it, so to speak, until we trace it back to the human body again. This is the plan I propose to pursue for a little way. Laveran's great discovery has made possible to us what was impossible to our predecessors.

The method starts with the assumption that the plasmodium is present in the human body in a natural way, in pursuance of the interests of the species it belongs to, not, so to speak, without meaning in reference to its life-history.

Before proceeding to indicate a way of following out this line of investigation, it is desirable to examine briefly what grounds there may be for the assumption with which I start.

The plasmodium enters and multiplies in the human body for one of three reasons. First, because a residence in the human body is, in some way, necessary for its evolution and existence as a species. Secondly, it may enter the human body accidentally, stray into it as it were; and find the human body a suitable medium in which to maintain itself, though not a suitable place from which to propagate its species. Lastly, it may enter the human body, as finding there, not only an asylum, but also a suitable place to propagate its species from, although at the same time it possesses elsewhere in Nature other hosts or media; that is to say, man may be one of the alternative hosts or media for the plasmodium, a reciprocity as regards the parasite existing between man and the other medium or media; in other words, malarial infection of man may be an example of optional parasitism.

MALARIA NOT AN ACCIDENTAL BUT AN OPTIONAL PARASITISM.

The plasmodium certainly is not driven to enter man for the first of these reasons, namely, because 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 most do congregate, malaria is infinitely rarer than in the open country, where man is a comparatively insignificant feature. Malaria is acquired from places, not from people; as Blanchard puts it, the plasmodium pre-exists man. The malaria parasite must, therefore, enter man either accidentally or, it may be, optionally, making use of him as an alternative host.

One of the characteristics of accidental parasitism is its comparative rarity. Malaria does not conform in this respect; for it is well known that in many places every human inhabitant is a host, at some time or another, of the plasmodium. Another frequent characteristic of accidental parasitism, especially animal parasitism, is that the strayed parasite does not multiply. We have seen how the plasmodium not only multiplies in man, but, also, how when circumstances unfavourable to multiplication in the blood arise, provision is made for its remaining latent until circumstances favourable to renewal of activity shall again recur. Surely this device—if I may use the expression—to multiply the chances of maintaining the species is a work of supererogation on Nature's part if it be the case that the plasmodium is present in man merely as an accident, and, as this would imply, that it has to die out without any chance of further extending its species being afforded it. Nature does not work in this way. Moreover, if the plasmodium is present in man as an accident, and for no purpose as regards its own interests, we must conclude from analogy that all the many members of the daily increasing family of hæmocytozoa, which we now know to be represented extensively in the lower animals, are also present in their respective hosts merely as accidents—hopelessly stranded. As Danilewsky and others have pointed out, nearly every individual in certain species of birds lodges a hæmocytozoon very similar to that of man. If man's hæmocytozoon is an accident, why not those others? Nature does not get her species into a corner in this wholesale manner; accidents do happen in Nature, it is true, but not wholesale accident of this description; she does not walk systematically with aimless feet.

If, then, the malaria parasite is present in man neither as a necessary circumstance in its life history, nor as an accident; and if, as is universally admitted, the malaria parasite can increase and multiply and lead a life perfectly independent of man, we are forced to conclude that when it 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.

This seems to be a perfectly legitimate conclusion. The plasmodium is, therefore, a true parasite of man, not merely an accidental parasitic visitor. The individual plasmodium gets into man designedly; not in its own individual interest merely, but also in the interest of the species to which it

belongs. 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. We may not assume that the plasmodium is different from other parasites in this respect; rather, we must assume that it conforms to the general law.

MODE OF ESCAPE OF THE PARASITE FROM THE HUMAN BODY.

In consequence of the location of parasites inside the bodies, in the organs and in the tissues of their respective hosts, special arrangements of a kind very unlike anything occurring in non-parasitic animals have to be made to provide for this necessary escape from the body of the host. Those arrangements are often very strange and complicated; often appearing, until one has become accustomed to think about them, as almost incredible, unnatural, in some instances grotesque even; as if they were the outcome of some weird, reasoning, designing faculty in Nature. These provisions for escape from the body of the host often entail marvellous adaptations of the habits of the parasite to the habits of the host, of the intermediate host or hosts, and to the phenomena of external Nature. Thus the intestinal parasites get their chance of passing out of their respective hosts by emitting their eggs into the dung of those hosts; the lung parasites by emitting their eggs or young into the bronchial mucus; the muscle parasites by being swallowed by some animal which preys on the flesh of their hosts; the blood parasites by being picked out of the circulation by some suction animal, or by escaping in the secretions; the connective tissue parasites in some instances by drilling a hole through the integuments, and so on.

Manifestly, then, the first thing to be done towards forwarding our attempt to track the plasmodium is to ascertain what provision there is in the economy of the malaria parasite for this necessary passage out of the human body. When we have ascertained this we may be in a position to understand how the passage is effected.

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; analogy will, I think, help us a step farther, and indicate to us the way this provision has an opportunity to come into operation; and actually observed facts, facts which I can demonstrate, can be invoked in support of the teachings of analogy.

I have already described the leading features presented by the plasmodium as it is seen in the blood, appearances which are readily and satisfactorily accounted for as belonging to a sporozoön actively engaged in ordinary reproduction. In newly-drawn blood these, or modifications of these, are, with one exception, all the appearances presented by the un mutilated plasmodium. We can see and trace the spores attacking the blood corpuscles; we can trace their growth into adult hæmocytozoa; we may note the preparations for sporulation; we can see the sporulating body before it breaks up into spores; and we see this process in every variety of malarial infection repeating itself over and over again. The inter-relationship of the various bodies is sufficiently obvious; and so is their purpose—the reproduction and maintenance of the intra-corporeal phase of the parasite.

THE FLAGELLATED BODY: FIRST EXTRA-CORPOREAL PHASE.

But 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 appearance we had not remarked before, not infrequently comes into view. This body is called the flagellated body (Fig. 11, 3, 6, 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 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. This is a fact which I wish to accentuate. The flagellated body comes into existence only after the blood has been withdrawn from the circulation. What is the nature of this body? Whence comes it? What is its purpose and interpretation?

Fig. 11.—Evolution of the flagellated body in the tertian I-III, quartan IV-VI, and crescent-forming VII-XII parasites. (Compiled from Thayer and Hewetson).

If we study its genesis and habits we may get some light on these points. 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-corporeal bodies have disappeared—doubtless having been resolved in the course of their development into sporulating forms and dispersed as spores—a few large, pigmented, passive, intra-corporeal forms still remain (Fig. 11, 1 and 4). We may also see a few large spherical bodies which are not enclosed 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-corporeal body—that they are escaped intra-corporeal 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, 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-corporeal 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 called incorrectly astivo-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 para-

site lying inside a blood corpuscle, the hæmoglobin of which 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 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-bye, their agitation increasing, the pigment granules 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. 10, 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, 13), just as already described in the case of the free spheres of the quartan and 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 free spherical and of the crescent bodies 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-corpuscular 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, perhaps Golgi, and others—take an opposite view; but I humbly submit that their views are based on altogether insufficient grounds.

If movement be an evidence of life, then at no stage of its existence in the blood does the plasmodium show so much vitality as when transformed into the flagellated body. If definiteness of form be an evidence of organised life, then no feature of the parasite is more regular, more definite than these flagella. If locomotive properties be an evidence of life, then at no time of its existence does the parasite exhibit this quality so markedly as when the flagella break off and swim about, not for seconds merely, but for hours, as I shall show. If I can also show, as I hope to do, that these flagella are admirably adapted for a certain purpose in the interests of the plasmodium, I think you will agree with me that they cannot be simply freaks of Nature brought about by degenerative processes in dead or dying protoplasm, as the authorities I mention maintain.

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, namely, cold, coagulating, dead blood. But I would submit that 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 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 molecular motion of dead particles. There are forms of protoplasm, animal and vegetable, whose developments are repressed by a higher temperature, 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 larger 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 some time or another 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. The best argument I can supply for the interpretation I would put on the nature of these bodies is supplied by the contemplation of the actual bodies themselves. Whoever watches the flagellated organism and the flagella for a little while will rise from his microscope with the conviction that he has been looking at a living thing. It would seem as if the degenerationists started and advocated their peculiar hypothesis simply because they have been unable to explain the meaning and purpose of the phenomenon they cannot deny.

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? Observe that it does not come into existence until the spherical or crescent body from which it proceeds has left the body. Why is this? Because, as I have said, its purpose lies outside the body. It is found where it is wanted, and only there. And what is it wanted for? To carry on the life of the plasmodium outside the body. Observe from what phase of the intra-corporeal organism it arises. From a large, fully-grown, adult, intra-corporeal parasite, one which might very well to all appearance have proceeded to ordinary intra-corporeal sporulation. This is certainly the case in the quartan and benign tertian parasite; and it is in the highest degree probable that it is also the case in the crescent parasite, for it, too, is an intra-corporeal plasmodium—somewhat different in shape, it is true, but functioning in the same way, and therefore probably originating in the same way. 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 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.¹

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 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 malarie.

THE MILROY LECTURES

ON

THE VALUE OF ISOLATION AND ITS
DIFFICULTIES.

Delivered before the Royal College of Physicians of London.

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[ABSTRACT.]

LECTURE III.

THE DIFFICULTIES OF ISOLATION.

[AFTER discussing the influence of isolation on scarlet fever (which under present conditions was not controlled so efficaciously as might have been hoped), diphtheria (which appeared to increase in spite of sanitary measures), and measles, Dr. Seaton proceeded to deal with the difficulties of isolation. He said:]

OPPOSITION TO INFECTIOUS HOSPITALS.

First and foremost has been the growing dislike of land-owners and householders to the propinquity of "infectious hospitals." The opposition to the establishment of small-pox hospitals has been most violent. It is true that a distinction is made by the medical department of the Local Government Board as regards the dangers which attend the isolation of small-pox on the one hand, or the isolation of scarlet fever, typhoid fever, or diphtheria on the other. Still it is probable that the fear engendered by the numerous reports which have been made of late years as to the dangers of hospitals has not been without its influence in increasing the opposition raised to their establishment, or of "infectious hospitals" of any kind whatever. Certain it is that year by year the difficulties have increased to such an extent that some authorities, after numerous attempts, have felt inclined to abandon the project altogether. That such opposition should be kept within reasonable limits is a thing which authorities have a right to expect at the present day. In county districts the establishment of infectious hospitals is, I believe, practically without danger, and yet in some countries the attempts to provide them have been almost at a standstill.

HOSPITALS AS EXCHANGES FOR INFECTION.

By far the worst difficulty is that to which Sir George Buchanan specially refers in the Government report of 1881: the "misfortunes," as they are termed, which have occurred from time to time within infectious hospitals, that is to say, the accidental infection of persons with another disease than that for which they were removed. This constitutes, to my mind, one of the gravest difficulties connected with the system of isolation. Unless its extent be fully appreciated and unless the directions of medical officers be loyally followed by hospital or sanitary authorities, the isolation system, a valuable auxiliary to our preventive forces, may be jeopardised. For administrative reasons there are strong inducements to relax stringent rules as to admission of different kinds of diseases when there are vacant beds. I feel it therefore my duty in these official lectures to declare emphatically that it is vital to the whole question of

¹ I would venture to conjecture that all forms of the flagellated bodies proceed from conjugation forms, the result of multiple injection of a blood corpuscle—as Mannaberg maintains is the case in the crescent body; single injection of a blood corpuscle going on to the formation of the intra-corporeal sporulating body—intra-corporeal propagation, multiple injection of a blood corpuscle going on to the formation of the conjugated form, resulting in the flagellated body, extra-corporeal propagation. The fact of non-conjugation or of conjugation, determines the direction of development shall take. The relatively large size of the free flagella-forming sphere in tertian and quartan, and of the crescent body in æstivo-autumnal to the ordinary amebæ in their respective injections, would be explained by such an hypothesis. The mathematical figure of the crescent body I regard as the result of a mechanical rather than of a vital process.