tions of the cause of this condition may be manifested, but it may be surmised that septic absorption has occurred from intestinal ulcers, or from a purulent focus in the spleen, or a mesenteric gland. In two of Osler's cases in this series numerous miliary abscesses were found in the kidneys, and in one of these typhoid bacilli were found and no other microbes. In other cases Eberth's bacilli were discovered in the kidneys together with other microbes, namely, the bacillus coli and the streptococcus. Sterilised cultures of the typhoid bacillus were found to produce nephritis in animals. The fact of ulceration of the bowels in enteric fever allows a ready entry into the system of specific bacilli, and Konjajoff has frequently found them in cases where albuminuria occurs in this fever. The kidneys appear to be one of the channels through which bacilli pass out of the body.

Having now considered the many and varied sequels which have been met with after enteric fever we may seek next for a rational explanation of them. If we can discover this we may fairly hope to find the clue to a settlement of the question, not only in respect of this particular fever, but of that which presses for solution in the case of all the specific infectious fevers and diseases. Modern bacteriological research leads us to regard it as highly probable, if not actually certain, that the toxins generated by the bacilli, specific in each case, are the active agents by which most of the sequels are induced in such instances. We have seen that many sequels may fairly be attributed to the extreme debility and exhaustion entailed by the acute manifestations of the disease. It suffices to examine with care the several viscera in fatal cases to be assured of the damage suffered in vital organs which is to be fairly set down to pyrexia alone. The softening of the cardiac walls, the shrinkage of the liver induced by atrophy and molecular degeneration, the condition recognised as "cloudy swelling" of this viscous witnessed on section, and the like state of the kidneys, all point to grave trophic disturbance with inadequacy of metabolic, secreting, and other functions. Although those changes are most obvious in the organs just mentioned, we may feel sure that they exist in all the textures of the body, and must during life have been potent for evil. Similar acute degenerations occur without doubt, though in lesser degree, in non-fatal cases, and we may cease to wonder at the low health, tardy recovery, and long failure to reach the normal level of health in these cases.¹⁸ That special organs or areas of tissue should suffer more in some cases than in others is probably to be explained by inherent and personal weakness, since we know that such visceral weakness and textual defects are hereditary, and we may thus account for many varieties of ailments and peculiarities met with in patients. Acute illness tests the integrity and functional adequacy of such parts, and they break down under the ordeal, revealing to us one or another failure as a sequel. We may thus speak of specific and non-specific sequels. In the former case we have to reckon with localised residues of the primal disease, manifested by invasion of parcels of toxin-generating bacilli, working out their malign effects. Actual proof of this is not far to seek. It has been shown that such definite and local invasions occur and fully account for the sequels. In the case of enteric fever we have the researches of Chantemesse and Widal¹⁹ showing the presence of bacilli in almost every tissue thus affected. These authorities affirm confidently that they have found the true bacillus of Eberth. My friend and colleague Dr. Kanthack, however, informs me that these and other observers in France had not sufficiently learned to distinguish the bacillus coli from Eberth's bacillus at the time they wrote, and that thus some doubt must still exist as to these particular researches. In Osler's case, already quoted, no such doubt can be entertained. Sultan and Burchke discovered, in one case six years after an attack of enteric fever and in another seven years after, living bacilli in abscesses of bone.²⁰ It is now

proved that these bacilli are very tenacious of life outside the body, and can exist in a potato culture for at least two years. Some of the sequels in enteric fever are not specific, but certainly due to invasion by other than the specific bacilli, to the ordinary microbes inducing suppuration, such as streptococcus, staphylococcus pyogenes aureus, and to the bacillus coli communis. These may be classed as septicæmic or pyæmic sequels, due to secondary invasion supervening, embolically or otherwise, on the specific fever, by way of venous or lymphatic channels, from purulent foci in the intestines, mesenteric glands, or spleen. Schmitzler records a case where the staphylococcus aureus had remained latent in a bone for over thirty-five years.²¹ Splenic enlargement is not always a simple matter. Rupture may occur on slight provocation, and has been known to occur even spontaneously.

THE GOULSTONIAN LECTURES

ON

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

Delivered before the Royal College of Physicians of London, March, 1896,

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LECTURE III.

WHEN some time ago I had formulated in my own mind the theory I have endeavoured to explain, I saw little prospect of ever being able personally to put it to the test of further observation and experiment. I was so convinced, however, of its inherent probabilities and of its importance if established, that I ventured to publish in the BRITISH MEDICAL JOURNAL of December 8th, 1894, a *précis* of my views.

It appeared to me that as neither Laveran nor Mannaberg had connected the mosquito with the flagellum, and that as Calandruccio had failed to observe developmental changes in malarial parasites ingested by mosquitos, the logic of the situation had been missed.

For these reasons I ventured to call the attention of observers to what I could not but regard as a promising but imperfectly worked line of investigation, hoping that someone with better opportunities than I could command might take the matter up and endeavour to confute or confirm what appeared to me a very promising hypothesis.

When I wrote the short article in the BRITISH MEDICAL JOURNAL I refer to, I hardly ventured to hope that the views expressed would so soon receive the support—I hardly risk the word, confirmation—they have already done.

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.

PRINCIPLES GUIDING THE INVESTIGATION.

We considered that those forms of malaria in which the crescent body was a prominent feature were the most suitable for experiment, at all events to commence with. 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-corporal parasite of the quartan and benign tertian infections. The behaviour, therefore, of the crescent body in the mosquito was the first point to be studied. We concluded that what might be found to happen to it could be reasonably regarded as typical of what would happen to the other flagella-producing forms of plasmodium.

²¹ On Traumatic Infection: Lockwood, *Hunterian Lectures*, Royal College of Surgeons of England, 1895, p. 42.

¹⁸ According to the late Professor Aitken, of Netley, no patient having suffered severely from enteric fever is fit to resume active or laborious duties for three or four months subsequently. In many severe cases the patient has almost to be recreated anew before sound health is established, and a year not seldom elapses before this occurs, even under favourable conditions. ¹⁹ Société des Hôpitaux, Mars, 1890.

²⁰ Quoted by Dr. Washbourn, *Proceedings of the Royal Medical and Chirurgical Society*, November, 1895. *Vide* also report by H. C. Parsons, of Baltimore (*Annals of Surgery*, November, 1895.)

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 evolutionary change; or (b) that it would behave very much as crescents do on the microscope slide—that is, a large proportion of them would remain crescents, a certain proportion of them would become ovals and spheres, and a very small proportion of them would go on to flagellation; or (c) lastly, that 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; 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 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. Here, therefore, was a suitable case. 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.

ROSS FINDS THAT EVOLUTION OF THE FLAGELLATED BODY PROCEEDS IN THE MOSQUITO.

As a result of a prolonged study of the subject 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, that the crescent conducted itself in the mosquito's stomach very much as the flaria does, and exactly as if it had got into a proper medium for development—in fact, into the foster mother provided for it by Nature.

In describing his observations and the conclusions deduced from them, so far as possible, I shall use Ross's own words.

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, 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 6μ 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 noted 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. At 11.50 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; 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."

ROSS'S CONCLUSIONS.

Ross continued to experiment with his 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 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 enclosed 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 to two hours, the rest having given out flagella, been eaten by phagocytes, or having simply broken up."

These conclusions, 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 connection 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; 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, 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 evolutionary change into oval, sphere, 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.¹ 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 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.

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 for the time being his work on malaria.

EXPERIMENTS ON COMMUNICATION OF MALARIA TO MAN BY MOSQUITO WATER.

In the course of his investigations he received much en-

¹ This effect of quinine in inhibiting flagellation of crescent bodies is not always observed. I have seen flagellated bodies develop whilst the patient was thoroughly cinchonised.

couragement 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. Notwithstanding 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. Ross repeated the experiment in several other natives, but he did not again succeed in producing malarial fever of an unequivocal character.

ROSS HAS PROVED THE FIRST STEP IN THE MOSQUITO THEORY.

However we may interpret this case of experimental malarial infection, we may conclude with confidence that Ross has thoroughly proved by direct observation my hypothetical conjecture that the stomach of the mosquito is a suitable medium for the flagellated phase of the plasmodium malarie to develop in; and it seems to me that it is only a question of patience and technique to work out the remainder of the life-history of the parasite in this insect.

Fig. 18.

SUGGESTIONS FOR FURTHER INVESTIGATIONS.

It behoves us, therefore, to carry on Ross's work, and, starting from where he left off, to trace the progress and fate of the flagellum; a difficult task this, but not, I believe, an impossible one. I venture to suggest a procedure which, if properly carried out, might yield the knowledge we look for.

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 filarated mosquito is plunged into some hardening medium a few hours after it has fed, and in due course imbedded, 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 were so made (Figs. 18-19). Fig. 18 represents a somewhat oblique section

Fig. 19.

of a filaria which is still lying in the blood in the abdomen of the mosquito. It has evidently just succeeded in escaping from its sheath, part of which can be seen lying empty some 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 serial intervals from the time of feeding into $\frac{1}{2}$ per cent. osmic acid for a minute or two, might be hardened in formalin or some other suitable agent and then sectioned and stained in different ways. I can conceive that in insects so prepared, the shower of flagella, emitted about half an hour after feeding, might be traced in a more or less continuous stream setting from the blood in the abdomen towards the particular cells in which, as I have explained, it seeks to bury itself, and which we are in search of. Some of the flagella would perhaps be caught in the act of entering; 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.

I had hoped to show on this occasion such preparations. Whether they would have turned out as I expected I cannot say. Unfortunately, the vagaries of the Indian parcel post have for the time being postponed the settlement of the point I wished to demonstrate. But, had the malariated mosquitos which Ross was good enough to despatch to me some time ago arrived, I believe I could have demonstrated to you the

flagellum *en route* to its cell and, possibly, the developing flagellum actually lying in the cell itself.²

ROSS'S PREPARATIONS.

However this might have been, it seems to me that some such process of preparation as that which I suggest will have to be employed. Simple expression of the viscera of the mosquito, and groping about in their contents, will not suffice to discover the plasmodium after the stage of free flagellum has passed. In preparations which 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

Fig. 20.

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.

My critics may say that I ought to have waited for the advance which I so confidently anticipate before communicating such results as have already been arrived at in this matter of demonstrating the plasmodium in the mosquito. I feel that there is a certain amount of ground for such criticism. At the same time, I would plead that progress is favoured by publicity, that the co-operation of many workers is necessary, or at least desirable, in this as in all similar inquiries. It may be that someone, more fortunately situated as regards material and opportunity than either Ross or myself, may, by the publication of what has already been done, have his attention drawn to this line of investigation, and so be led to advance the inquiry still further, and perhaps, happily, to the completion of our work.

² Since this lecture was written I have received and examined some of the mosquitos referred to. The insects were first soaked over-night in acetic acid so as to get rid of the hæmoglobin, then placed in alcohol, then in celloidin, and sectioned. The sections were stained with hæmatoxylin. Thanks to the rare technical skill of Mr. Max Colhoun, Mr. Malcolm Morris's assistant, many exquisite preparations have been obtained. In these there is no difficulty in making out the pigmented spheres, and, in one instance at least, a flagellated body. I hope ere long to give a more complete description of these and similar preparations.

On first thought, and until we become familiar with the idea, it may seem a marvellous and almost incredible thing that the malaria germ, the worst of the animal parasites affecting man, should come to us through a familiar insect. But when we reflect on the circumstances of the life of the plasmodium; on the fact of its being a blood parasite; that the mosquito is a blood sucker, living on and intimately associated with man; on the certainty that the plasmodium is continually and in all parts of the world entering the mosquito; on the liability of insects to gregariniform infection; on the notorious association of malaria and mosquitoes with stagnant water—after all the idea does not seem so extraordinary and unnatural; in fact, when we come to think of it we are driven to conclude that it is just what we might expect. Certainly it is not a whit more marvellous than the relationship of the same insect with *filaria nocturna*.

If we reject this hypothesis of the extra-corporeal life of the plasmodium, how explain the singular behaviour of the crescent body in the stomach of the mosquito? Must we regard that wonderful display of developmental activity, what Ross calls "the manifestation"—the sudden and nearly simultaneous projection of flagella by the crescent-derived spheres—occurring in the mosquito some twenty or thirty minutes after ingestion of malarial blood, as a mere accident? Surely this extraordinary event, which has been so carefully, so skilfully—if I may use the expression—led up to by Nature is not a meaningless, accidental phenomenon.

OBJECTIONS TO THE MOSQUITO THEORY.

Plausible as this theory of the extra-corporeal life of the malarial parasite may be, and fascinating as it is, until the whole story of the plasmodium in the mosquito is thoroughly worked out, and 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, I make little doubt that many objections will be raised and many critics will attack it. But, while admitting that it has not as yet been fully proved, so far as I can see at present, I know of no insuperable reason for not entertaining it.

MOSQUITOS ABOUND WHERE THERE IS NO MALARIA.

One objection which might be advanced, and which at first sight seems a strong one, lies in the fact that there are many places in the world where, though mosquitoes abound, malaria is rare. This is a fact which I admit; but though I admit it as a fact, I do not admit it as an unanswerable argument against my theory. Admitting—what is by no means certain—that the mosquito of these places is the same in species as the mosquito of malarious countries, it does not necessarily follow that it harbours the plasmodium. The same argument might be advanced against the mosquito being a necessary agent in the distribution of *filaria* disease. A similar argument might be advanced against the rôle of the sheep and the dog in transmitting hydatid disease; against cyclops as transmitting guinea-worm disease; and against many a well-established theory in biology as well as in pathology.

What I may designate as test-tube experiment with living things is one affair; what I may call natural experiments with living things is a very different affair. Last year, as a test-tube experiment, I satisfied myself that the guinea-worm could be raised in England. Why, then, does not guinea-worm occur endemically in England? It is often introduced, the cyclops (its intermediate host) is in abundance in our pools and ditches, and man (its definitive host) is everywhere; yet the parasite, which is so common in Africa and India, does not spread here. I think I could produce an epidemic of guinea-worm disease in London by simply pouring into one of the water mains a bucketful of cyclops in which I had raised young guinea-worms. I think in a year's time there would be hundreds of guinea-worm cases attending the hospitals. But the epidemic would not spread; it would cease with the first crop of cases. Why? One obvious reason—though probably not the only one—is the circumstance that Englishmen wear shoes and stockings. The mere facts that we cover our lower extremities, and do not wade about in ponds and puddles, would prevent the young guinea-worms from getting to water and to cyclops, and so spreading the

disease. I mention this as an illustration of how some trifling circumstance—the presence or absence of something—favours or destroys the chances of organic forms in the struggle for existence. The malaria germ is not exempt from the operation of the general laws of Nature.

MALARIA SAID TO EXIST WHERE MOSQUITOS ARE ABSENT.

Another objection which has been raised to my theory is to the effect that in certain places on the West Coast of Africa and elsewhere, where malaria is notoriously prevalent, mosquitoes are absent. I have made inquiries about this, and I am told that at certain places on the West Coast, where fever is common enough, mosquitoes are not very troublesome; but I am also told that if ever at such places water is allowed to stand about in pools, or in uncovered tanks or vessels for any length of time, mosquitoes soon begin to appear; and, moreover, that in close proximity to places where mosquitoes are little troublesome, there are other places in which they are abundant enough. One can easily understand how winds may blow malaria-charged mosquitoes, or their remains, from one place to the other, or how their dead bodies, or their larvæ, or the disease germs they had harboured, may be floated from place to place by winds or rivers or floods.

BIOLOGICAL OBJECTIONS.

I have already alluded to the position taken up by certain zoologists with regard to the nature of the flagellated organism of malaria. They say that it is merely a degeneration form similar to what may be seen sometimes in scorched blood corpuscles, or to such as is exhibited by certain of the protozoa as death approaches.

The degenerationists, as I stated in my first lecture, in arguing against the vital nature of the process, make much of the rapidity with which the final steps of the evolution of the flagellated body are effected. This suddenness and the tumbling, boiling-like movements of the pigment particles in the rapidly transforming plasmodium Labbé likens to, and evidently regards as, an active chemical perturbation—a decomposition process. We are, however, not without evidence that sudden exflagellation is in certain organisms a regular and an unquestionably vital occurrence. Lister, in the introduction to his monograph on Mycetozoa, published in 1894, describes such a process. He points out that when the spores of these protozoa are placed in water they give exit to amoeboid bodies which, after creeping about for a while as amoebæ, put out each a single flagellum and then for a long time go on lashing this flagellum and feeding on bacteria and other appropriate nutriment. At length they draw in the flagellum, assume a spherical form, and then divide, each division behaving like the original body; first, creeping about as an amoeba and then as a flagellated organism. Sir Joseph Lister informs me that when watching these bodies, which his brother has so successfully studied, he has seen the flagellum protruded quite suddenly from the protoplasmic mass, and that he regards this exflagellation as being undoubtedly, though thus suddenly brought about, a vital process.

Most of the facts these degenerationists adduce can, as I have shown in my first lecture, be used as arguments in favour of, rather than as arguments against, the process of exflagellation being regarded as a vital process. Grassi and Feletti, however, advance a statement which, if well founded, would, I admit, be fatal to my hypothesis. They say that the nucleus of the plasmodium takes no part in the development of the flagella. Labbé, too, makes a similar assertion; but other zoologists who have studied this point tell quite a different story. Sacharow, who is also a degenerationist, but on somewhat different grounds, and who has made very careful studies of the flagellated forms, says, "the process of formation of the flagellate bodies consists in a perversion of the karyokinetic nuclear division, in a breaking up of the nucleus into chromatin filaments, and in the escape of these from the parasite; these filaments, which are in lively motion, represent the flagella." Whose statement are we to believe—that of Grassi or that of Sacharow? Both cannot be right.

Labbé calls attention to the fact that, whereas all the known species of gymnosporidia in birds and man—the malaria organisms of birds and man—produce flagella, those of frogs

and lizards—*dactylosoma* and *cytamœba*—do not. He uses this as an argument against regarding exflagellation as a necessary and vital process in the malaria parasite of man. I regard it, on the contrary, as an argument in favour of my hypothesis. Mosquitos do not prey on frogs and lizards; therefore the *gymnosporidia* of these cold-blooded reptiles must find some other way of continuing their species than that applying to the *gymnosporidia* of man and birds; and if it be so, why not by a different adaptation of the parasite concerned?

MOSQUITOS ATTACK BIRDS.

It has also been advanced that although the malaria parasites of birds flagellate, this flagellation cannot be a vital process adapted to such conditions as the mosquito supplies, seeing, it is said, that mosquitos do not attack birds. As a matter of fact, I know that mosquitos do prey on birds in China, and Lewis has had a similar experience in India.

THE MOST SERIOUS OBJECTION TO THE MOSQUITO THEORY.

To my way of thinking the most serious objection to the mosquito theory lies in 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 always possible that I 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 simply coincidence. 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?

CONFIRMATION OF THE THEORY ANTICIPATED.

While acknowledging that these are points requiring further investigation, I do not recognise in them grave arguments against the validity of my theory. I do not hold that the theory is established, but I do hold that Ross's investigations have rendered it so probable that it is in a fair way of being established; and 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.

SCIENTIFIC AND PRACTICAL DEVELOPMENTS LIKELY TO ACCRUE.

If it is established, as I believe that ere long it will be, that the plasmodium is a parasite of the mosquito, that malaria is a disease of insects, we may look for some strange scientific and practical developments. The discovery will spread before us a vast field for future study. The real science of malaria will only be begun. We may find that the special forms of the plasmodium—the quartan, the tertian, and the malignant—each requires a special species of mosquito host. We know that special localities have special clinical types of malaria. May not this depend on local peculiarities as regards species of mosquito? The different species of mosquito will require to be determined, their special habits ascertained, and the action of each as regards the plasmodium studied. We may thus be enabled to ascertain one reason why some tropical regions are malarious whilst others are not. We may even find a way of controlling malaria by introducing the natural enemies of the malaria germ into malarious localities—cats to keep down rats. We will be able to settle the long-vexed question as to the possibility of contracting malaria from drinking water, the exact physical conditions that favour and regulate the diffusion of the malaria germ in the atmosphere, and many other points of important practical bearing.

Precision, too, will in time be given by such studies to our efforts at prophylaxis in malaria and malarial disease,

efforts which at present are but vaguely directed. The hygiene of malarious localities will become a matter of science instead of, as at present, mere haphazard empiricism founded on what is little better than tradition.

A SUGGESTION.

I understand that extensive drainage works are about to be undertaken in India with the object of mitigating the insalubrity of certain pestiferous districts, and that the schemes entail an enormous expenditure of the public money. This money will be expended simply to fight the plasmodium. Would it not be well to know a little more about the enemy before attacking him? Would it not be a wise, a businesslike thing, before proceeding to expend powder and shot, first to find out something about his habits, and so learn when, and where, and how he may be most easily, most effectually, and most economically attacked? I think the Indian Government would do well to do this, and to encourage men like Ross in their efforts to lay a scientific foundation on which a truly scientific prophylaxis might subsequently be built.

TEN CASES OF OPERATION FOR EXTRA-UTERINE FETATION.

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It has not yet been established that extrauterine foetation commences anywhere except in some portion of the Fallopian tube. By bearing in mind the relation of this structure to the broad ligament it will be understood how different the conditions will be according as to whether the foetal sac as it grows protrudes upwards or downwards. If upwards, it will protrude like a sacculated aneurysm into the abdominal cavity; if downwards, it will extend between the layers of the broad ligament, separating them widely. When rupture takes place through the free surface of the sac there is nothing to arrest the hæmorrhage, and a large number of cases bleed to death in a few hours. On the other hand, when the blood is poured downwards between the layers of the broad ligament it will spontaneously cease, as these can only be detached to a limited extent. In a large number of these latter cases the extravasated blood ultimately becomes absorbed and the patient recovers. There is, however, a third condition, and which is probably more common than either of the other two (see Cases III and V), in which a ruptured tube pours out blood in such a way that it becomes encysted in Douglas's pouch. In these cases a mass of coagulated blood forms a tumour the size of a cocoanut, bounded below and at the sides by Douglas's pouch, and above by the dilated tube, small intestine, and free end of the omentum bound together by inflammation and plastered over the roof of the pelvis. The probable explanation of these intraperitoneal circumscribed collections is that some localised peritonitis is set up in the first place by a slight oozing or irritation, and thus the general cavity of the peritoneum is shut off before any extensive pouring out of blood occurs.

Without recapitulating all the well-known symptoms which are so diagnostic of ruptured extrauterine pregnancies, it may be worth while to mention some of the chief points in the differential diagnosis between rupture occurring free into the peritoneal cavity, or when it occurs between the layers of the broad ligament, or when circumscribed in Douglas's pouch, for the whole question of operative treatment depends upon the position of the rupture.

When the sac bursts into the peritoneum, pain, though severe, is not so intense as when the bleeding is into the broad ligament. On the other hand, the general symptoms are graver, doubtless due to a larger amount of blood being lost. Indeed, the hæmorrhage may be so profuse, that within an hour or two of the accident the patient may be pulseless, and almost moribund, but as a rule she will rally to a certain extent from the immediate effects of the first loss of blood, thus affording time for surgical interference, which, to be effective, must be prompt, the cases being almost invariably fatal if the bleeding is not arrested by abdominal section.