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ON THE RELATION

OF THE

PARASITIC PROTOZOA TO EACH OTHER

AND TO

HUMAN DISEASE.

BY

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THE RELATION OF THE PARASITIC PROTOZOA TO EACH OTHER AND TO HUMAN DISEASE.

By E. J. McWEENEY, M.A., M.D., D.P.H., F.R.C.P.I.

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(*Read: Friday, February 17th*, 1905.)

My first duty is to express my sense of the honour conferred on me by the Epidemiological Society in asking me to come forward with a paper on "The Relation of the Protozoa to Disease." This I do most sincerely and heartily. The complexity of the subject, and the energy with which it is being investigated by numerous workers all the world over, make an adequate presentment of our knowledge of it, a task of no little difficulty. In undertaking it, however, there are two circumstances in my favour. In the first place, I selected the "Parasitic Protozoa" as the subject of a Presidential Address delivered about three years ago, when I first took the chair as President of the Pathological Section of the Royal Academy of Medicine (1) in Ireland. In that address I precised, so far as lay in my power, the then state of our knowledge of the subject. This makes it all the easier for me to chronicle on the present occasion the advances that have been made during the three years which have since elapsed. In the second place, the position from which I deal with the subject is not that of an investigator, but rather that of an interested onlooker. The concentration of all the faculties upon some one aspect or department of a subject, necessary as it is for the advancement of science, may in some cases engender a one-sided or distorted view of the relative importance and mutual interrelations of the several branches of that subject. Questions as to priority of new discovery, too, often arise amongst workers, and produce a spirit which is occasionally the reverse of scientific. When a general account of a large subject is required—which I conceive to be the case to-night—the attentive and interested student, with adequate biological training and access to the literature of the subject, is, I believe, in at least as favourable a position for giving it as one who is actually engaged in research. It is from the

standpoint of an onlooker, therefore, that I propose to-night to take a survey of the advances made during the past three years in our knowledge of the disease-producing Protozoa. The outcome of these advances is twofold. They reveal, in the first place, a complexity of reproductive phenomena, quite surprising in such lowly creatures, and constituting a wealth of detail, selection from which is one of the most difficult parts of my task; and, in the second place, an equally surprising parallelism in the developmental cycle of forms which at first sight seem far removed from one another.

It will be remembered that the Protozoa, or One-cell Animals, are divided into four classes: the Rhizopods, the Sporozoa, the Flagellates, and the Infusorians. The Rhizopods are the lowest, comprising mainly Amœbae—shapeless masses of protoplasm. The only one of these which interests us to-night is Amœba Coli.

Many kinds of Amœba occur in the human intestine. Just as the spores of many of the higher fungi, when placed in suitable nutritive conditions, pullulate in the form of yeast-cells, and can only be distinguished from genuine yeast by a study of their development, so it would appear that of the many kinds of Amœbae occuring in the intestine some are *genuine*, viz., the vegetative stage of Rhizopods, whilst others are only Amœboid stages in the development of *higher* forms, such as Trichomonas, Lamblia, and other Infusorians. Genuine Amœbae are divided into those provided with a shell—Thecamœbae, and those that are naked—Gymnamœbae. At least one of the former and two of the latter sort are now known to occur in the intestine. With the representative of the Shell-Amœbae, Chlamydophrys stercorea (Cienkowski), and its complicated life-history,* we need not now concern ourselves, as its habit appears to be purely saprophytic. The two naked forms of Amœbae are genuine parasites. One of them is harmless and the other is one of the most dangerous of pathogenic Protozoa. For reasons based on the laws of zoological nomenclature, the former, which has hitherto been known as *Amœba Coli* (Lösch), has been re-named *Entamœba* by Schaudinn. The second, hitherto called *Amœba dysenteriae* by such authors as admitted its existence (Councilman and Lafleur, Kruse and Pasquale, Koch, Jaeger, and others), has for the same reason been re-named by Schaudinn *Entamœba histolytica*. Schaudinn (2) found out how to distinguish the harmless Amœba from the dangerous one.

* For an account of which see Schaudinn's paper in vol. xix of the *Arbeiten aus dem kaiserl. Gesundheitsamte*, p. 560.

The life-history of these Rhizopods is more complex than was at first suspected. Entamœba Coli occurs very frequently in the fæces of healthy persons, as was first discovered by Grassi. In East Prussia it occurred in half the individuals examined by Schaudinn ; of Berliners he found that only 20 per cent. harboured it, whilst at Rovigno, in Istria, it occurred in two-thirds of the persons examined. It is a shapeless mass of protoplasm, not showing a well-marked distinction into clear ecto- and granular endoplasm, and possessed of a large and distinct nucleus. The obstacle to finding it in the healthy fæces is that its *habitat* being in the upper regions of the colon, its vegetative stages die out as the intestinal contents become firmer on their way down. If, however, their downward course be hurried, then the Amœbae can readily be detected. To Schuberg (3) belongs the credit of showing that saline purgatives, by producing liquid motions, enable the Amœbae to be detected in healthy persons. The Amœbae have two distinct cycles of development: one vegetative or asexual, taking place in the naked state, the other displaying a primitive but unmistakeable form of sexuality, and occurring inside of a capsule resembling an egg-shell and termed a cyst. In the vegetative form, the Amœbae either simply split in two, or their nucleus divides into eight daughter-nuclei, each of which takes a portion of the protoplasm so as to form a characteristic brood of eight young Amœbae, which come apart. In the other, or sexual cycle, the Amœba rounds itself off, comes to rest, contracts, and surrounds itself with a gelatinous coat which becomes the cyst-wall. The two nuclei, after undergoing reconstruction and chromosomic reduction, divide into halves, which copulate, so as to form two fresh nuclei, each containing half of the two parent-nuclei. Each of these copulation-nuclei now divides twice, and the divisions form eight young Amœbae, which, however, cannot leave their cyst until it has been taken in by a new host, and has had its wall softened in the stomach and duodenum. The resemblance in general outline to the developmental process of the Sporozoa will be at once manifest: asexual swarming in the primary host till it is exhausted or conditions become unfavourable; then sexuality with cyst-formation and change of host. The details are different; the underlying idea, so to speak, is the same.

Let us now take a glance at the pathogenic rhizopod Entamœba histolytica. Its vegetative stage differs from that of the non-pathogenic Entamoeba Coli in, firstly,

possessing a clear, tough, outside layer or ectoplasm which enables it to penetrate between the epithelial cells, and, secondly, in not possessing a distinct, well-defined nucleus. Its tough ectoplasm enables it to force its way into the deeper layers of the mucous membrane, where it multiplies and forms the undermined ulcers which are so characteristic of tropical dysentery, and are readily distinguished from the diphtheritic appearance presented by the bacillary form of the disease. Schaudinn (4) has actually observed these Amœbæ in scrapings of the freshly-excised bowel of the experimentally-infected cat, crawling around for hours and pushing in between the epithelial cells. The two sorts of Amœbæ differ also in their reproduction. The pathogenic form, in its vegetative stage, divides into two, or forms new individuals by budding. Brood-formation does not occur. The process of encystment is also quite different. It comes on when the patient is beginning to recover from his attack of dysentery and the fæces are becoming solid. The nucleus gives up most of its chromatin in granular form to the plasma, and its remains are expelled. The plasma now projects from its surface a number of little knobs, each containing a particle of chromatin, and measuring from three to seven micra in diameter. These break off after a while, and each becomes surrounded by a capsule which ultimately becomes quite brown, hard, and opaque. These " spores " are then expelled with the fæces, and serve to infect a fresh host. It will be seen that the indications of a sexual process are much less distinct in this species, owing perhaps to the difficulty of ascertaining precisely what goes on during the maturation of the minute spores.

In my Address, already referred to, I spoke of the *rôle* of Amœbae in the following terms :—" The general conclusion to which I incline, after a careful survey of the literature, is that the Amœba Coli is, in all probability, either wholly or partially responsible for the causation of one form of dysentery—that which is termed ' tropical,' and is not endemic in this country." Subsequent investigation has borne out this view. One of Schaudinn's experiments seems quite conclusive. He allowed a small fragment of fæces from a case of dysentery, contracted in China, to dry in the air, suspended it in water, made a number of slide and cover-glass preparations, and by searching them systematically throughout on the mechanical stage, he satisfied himself that they contained nothing resembling the cysts of *Entamœba Coli*, but only the small brown spores of *E. his-*

tolytica. Of course there were no free Amœbæ, as these had been destroyed by drying. The cover-glasses were then removed and the fæces washed off with clean water, made up to about 1 cc., and administered with meat and milk to a young, healthy cat, the fæces of which had been proved by careful examination to be free from Amœbæ and their cysts. Three days afterwards, the cat began to pass slimy fæces, streaked with blood. These were found to be swarming with the typical *Entamœba histolytica.* Next day the animal died of dysentery. The autopsy showed characteristic ulceration of the large intestine, with crowds of Amœbæ in all stages of penetration into the intestinal wall. There were, of course, no cysts, the animal having died in the acute stage of the disease. In order to see whether the Amœboid stage could propagate the disease, Schaudinn administered large quantities of this fæcal matter to another cat. It remained quite healthy. Its fæces were examined for four weeks, and no Amœbæ were detected. It was then given a small portion of the same dried-up cyst-containing fæces from the Chinese case that been used in the other experiment. Within six days, Amœbæ appeared in the fæces. This cat, which was older and stronger than the previous one, developed dysentery, and died of it in about a fortnight. From this it would seem that the Amœba-stage introduced by the mou this not capable of producing infection. The older experimenters, from Kruse and Pasquale onwards, had often succeeded in producing infection by introduction of Amœbæ *per rectum:* and Jürgens (5) has again successfully performed the experiment. This rectal transference can, however, hardly be realised under natural conditions; and, accordingly, it is to the dried-up cyst-containing fæces present in dust and water that we must look for the propagation of dysentery. Whether the Amœbæ contained in the fæces from the acute stage will, if gradually dried, become converted into cysts *outside the body,* or whether the Amœbæ that are going on to cyst-formation receive their impetus along that track whilst still in the bowel, does not seem to be quite clear. In any case, the practical importance of these observations is obvious. The cyst-containing fæces of cases of dysentery must be prevented from getting access to drinking-water, or from being conveyed by flies and deposited on food. There would seem, by the way, to be a sort of mutual exclusiveness between *Entamœba histolytica* and the Shiga dysentery-bacillus. Schaudinn failed to find them in the same intestine, and Castellani (6) has recently had the same experience in Ceylon.

The next class is that of the Sporozoa, so called because at one stage of their life-history the individual breaks up into a number of minute reproductive bodies resembling the spores of fungi or mosses, and, like them, often contained within a cyst or thick-walled capsule. Amongst the chief orders of this Class are the *Gregarines*, which mostly live in the intestine of crustaceans and insects; the *Coccidia*, many of which inhabit the digestive tract and its annexes in mammals, birds, and various invertebrates (myriapods, etc.); and the *Hæmosporidia*, or parasites of the blood-corpuscles, which are the cause of malaria, and to which, therefore, a very special interest attaches. All these organisms, however different their vegetative stages, have in common a certain ground-plan of life-history, varying in individual cases, and with regard to matters of detail, but the general features of which pervade the whole Class. This life-history comprises two main features: alternation of generations and change of host. Alternation of generations means that a sexual method of reproduction alternates with an asexual method; whilst the term "change of host" does not, of necessity, imply a change of host-*species*, but in many cases only a change of host-*individual*. The general idea underlying the parasitism of these organisms is that, once the sexually-produced reproductive body, or spore, finds its way into a suitable host, and into a suitable cell of that host—for they are *intra*-cellular parasites—it rapidly attains its full size, and splits up, without the intervention of sexuality, into a number of fragments which fall asunder, and, invading fresh cells of the same host, repeat the process. By this means, the host-animal becomes speedily pervaded by swarms of parasites, and the resultant disturbance of function is the disease. After a time, owing to the production of specific anti-bodies, or the exhaustion of the reproductive power of the parasite under the strain of repeated asexual division, this process gradually ceases, and specially-differentiated male and female forms appear and copulate. The fertilised female forms a cyst containing spores, which have to be transmitted to a fresh host before they can develop. The points at which the greatest variability obtains are, firstly, the place and time of conjugation, and secondly, the arrangements for transfer from one host to another. Where the organism passes its asexual stage in the blood, transfer must necessarily be effected by the only agency whereby blood is at all frequently removed from the vessels, *i.e.*, blood-sucking invertebrates, such as flies and ticks. The intermediate

host of blood-inhabiting parasites is, therefore, an invertebrate blood-sucker. Some of the blood-parasites—those of malaria, for example—avail themselves of the invertebrate host as the scene of their sexual reproduction, and multiply enormously within it. Others, such as the Trypanosomes of the Mammalia, remain, so far as we are at present aware, quite passive within their cold-blooded host, and use it merely as a vehicle.* Others, again (some of the Piroplasmata), in some mysterious way pass on into the eggs of the invertebrate host, and infect its young brood. On the other hand, when the parasite passes its asexual stage in a cavity of the host that is connected with the outer world (the Coccidia), the problem how to escape is comparatively simple, and an intermediate host may be dispensed with.

In order to readily characterise these several stages, and to emphasise homologies, it is necessary to adopt a systematic nomenclature, and I accordingly use that elaborated by Schaudinn and Lühe, according to which

The name Schizont is applied to the mature asexual individual.

„ Merozöites is applied to the pieces into which the Schizont splits up.

„ Gametocytes is applied to the forms which produce or become converted into the sexual individuals, viz. :—

Macrogametocyte	The *asexually-produced* individual which, by chromosomic reduction, becomes converted into a female, and
Microgametocyte	The *asexually-produced* individual, which, by chromosomic reduction and nuclear division, becomes converted into a *number* of males.
Gametes	The sexual individuals, viz. :
Macrogametes	Females (the ova of the Metazoa), and
Microgametes	Males (the Spermatozoa of the Metazoa, Antherozoids of the higher Cryptogams).
Zygote	The fertilised Macrogamete.
Öokinet	The Zygote when capable of locomotion.
Öocyst	The Zygote when it has come to rest, and is surrounded by a thick capsule.
Sporoblasts...	Secondary cysts or spore-bags formed within the öocyst.
Sporozöites	The final products of the act of sexual reproduction—minute bodies formed often in large numbers within the öocyst, and which, on being removed to the new host give rise to the schizonts.

* Since this was written, Schaudinn's former assistant, Prowazek, claims to have observed (*Arb. a. d. kaiserl. Gesundheitsamte*, 1905, p. 376) sexual forms of the rat-Trypanosome (*T. Lewisii*), in its intermediate host the rat-louse (*Hæmatopinus*).

I come now to what has been done on the parasites of human malaria during the last three years. The details of their life-history as established by the labours of Laveran, who discovered them; Golgi, who differentiated them into species; Ross and Manson, who discovered the change of host; MacCallum, who recognised their sexuality; and Grassi, who identified the mosquito, have been more fully worked out, and numerous important details have been added. *Plasmodium vivax*, the cause of tertian ague, has been minutely studied by Schaudinn (7) at an ague-stricken village near Rovigno on the Adriatic, where he had abundant material. Some of his observations regarding the sexual process are of special interest. It starts in from ten minutes to half an hour after the blood has been sucked in by the gnat. The microgametocyte, which is readily recognised by its hyaline plasma, large oval nucleus, and coarsely granular pigment, suddenly shoots forth from four to eight curved filaments, 20 to 25 micra long and 1 micron at thickest. Meanwhile the macrogamete has been preparing itself for fertilisation by ejecting part of its nucleus. This process appears to be homologous with the extrusion of the polar bodies by the Metazoan Ovum. The number of chromosomes is thus reduced by one-half. The extruded matter may possibly, by its disintegration, provide a diffusable substance acting chemotactically on the microgametes and causing them to approach the female, in the same way as the canal-cells of the archegonium of ferns yield malic acid which attracts the Antherozoid. The female then protrudes a "receptive eminence," and as soon as one of the males has adhered to this, it is at once withdrawn carrying the struggling microgamete in with it. In the case of the malarial parasites only the one male obtains admission, but in the Coccidian *Cyclospora caryolytica*, which causes an infective form of enteritis in the Mole (Talpa), what is called *polysperm*y occurs (8). Quite a number of male gametes force an entrance into the macrogamete. Only one of them undergoes the fertilising fusion, whilst the others break down and serve as food for the developing zygote. The presence of superfluous males, however, is apt to disturb the proper relation of male and female pronucleus, and give rise to interesting pathological changes described by Schaudinn. In the Tertian parasite only one favoured microgamete gains access, and no sooner has it done so, than a coat of mucus is secreted by the female, which keeps away the excluded males and

is homologous with the cyst-wall of the Coccidia. The zygote now becomes a motile öokinet, and this becomes an öocyst, which comes to project, as is well known, into the body cavity of the mosquito, and the internal plasma of which splits up into sporoblasts, which in turn split up into sporozöites. Some of the liberated sporozöites, according to Schaudinn, obtain access to the ovary of the gnat and infect the developing ova, so that the young brood next spring harbours the parasite, and the young mosquitoes can confer the disease without having previously sucked blood—a fact of great epidemiological importance, if it be confirmed by subsequent observation. Finally, Schaudinn succeeded in observing the entrance of the sporozöite into his own red corpuscles, and thus completed the developmental cycle.

I now come to the last part of my subject, namely, the Order of Flagellates, to which belong the Trypanosomes. Three years ago, in the Address already referred to, I gave some account of these parasites in connection with the diseases of animals known as Nagana, due to T. Brucei, and Surra, due to T. Evansi, and I described the *rôle* of the Tsetse fly as carrier of the latter. I also referred to my own experience of these parasites, gained on the only species accessible to me at the time—the Trypanosome of the common sewer-rat, T. Lewisii. During the three years that have since elapsed, the *rôle* of these parasites as disease-producers amongst the lower animals has been greatly enlarged. Dutton and Todd (9) found a disease of horses in Gambia to be due to T. dimorphon. Elmassian, (10) followed by Voges and Lignières, have shown that the disease of horses in South America known as Mal de Caderas, is due to another Trypanosome (T. equinum). The sexual malady of stallions and brood-mares known to the French as Dourine, or Mal de Coït, is due to T. equiperdum, which was first discovered by Rouget in 1896 (11). The so-called Galziekte or Gall-sickness of Bovines in the Transvaal has been shown by Theiler to be caused by a species called after him T. Theileri (12). Other forms have been described in the smaller Mammals, such as, the rabbit, guinea-pig, dormouse, bat, as well as in birds, reptiles, amphibians, and fishes. But the great access of interest in the study of Trypanosomes is due to the fact that they are now known to produce disease in the human race. In December, 1901, Dutton (13) was the first to recognise as a Trypanosome the *vermicule* previously seen by Forde in the blood of a European

patient in the Hospital at Bathurst. He described it accurately, and named it T. Gambiense. In April, 1903, Castellani (14) discovered a Trypanosome in the cerebro-spinal fluid of natives of Uganda affected with sleeping-sickness, and this malady has consequently come to be regarded as one of the manifestations of human Trypanosomiasis. David Bruce (15) with his fellow-workers Nabarro and Greig, brought home the propagation of the disease in Gambia to the fly *Glossina palpalis*. Finally, there is the discovery, so far back as 1900, by Leishman, and, independently in 1903, by Donovan, in smears of spleen-pulp from cases of splenic cachexia in India, of parasites which Rogers (16) has shown to be stages in the development of a Trypanosome. These, shortly summed up, seem to me the most important landmarks in the development of our knowledge as regards Trypanosomes.

The side of the question which I propose to deal with this evening is the relation of Trypanosomes to other Protozoa, more especially to the malarial parasites, and to certain organisms known as Spirochætæ, and hitherto regarded as Bacteria.

A correct idea of the structure of a Trypanosome is essential to an understanding of what follows. Its fish-like body, twice or thrice as long as a red corpuscle, is fringed along one side with the undulating membrane, which is prolonged at the end now generally looked upon as anterior, into the flagellum. In the body is a large nucleus, and there is also, towards the posterior end, a smaller dot-like mass of chromatin close to which originates the margin of the undulating membrane—the edge which is prolonged into the flagellum. The nature and homologies of this smaller mass of nuclear substance have given rise to lively discussion. Some term it a centrosome, others a micro-nucleus. There seems to be no doubt that it gives origin to and presides over the locomotive apparatus—that the edge of the undulating membrane and the flagellum (both of which give the colour-reaction of nuclear substance by the Romanowsky method) are part and parcel of this mass, which I shall therefore term the *blepharoplast* (literally, flagellum-former). Trypanosomes bear a close resemblance to the spermatozoa of some animals (Bombinator), and are constructed on similar lines. They multiply mostly by unequal longitudinal division, more rarely by multiple division (rosette-formation). The first part to divide is always the blepharoplast. They are agglutinable by foreign or immune serum, as was shown by

Laveran and Mesnil. To Professor F. G. Novy, of the University of Michigan (U.S.A.), and his collaborator, Dr. W. J. MacNeal, belongs the great merit of discovering a culture-method applicable to Trypanosomes (17). By its means they have succeeded in growing the Trypanosomes of the rat, of Nagana and of Surra, on an artificial medium (blood-agar), and have recently cultivated several forms from the blood of birds. Until the researches of Schaudinn, which I am now about to detail, Trypanosomes were looked upon as independent organisms, and were not known to possess any trace of a sexual mode of reproduction. It appears to me that the discoveries of this brilliant and industrious worker have not as yet been received in this country the attention to which they are entitled.

In the blood of the barn-owl (*Athene noctua*), Schaudinn (18) found three distinct protozoal parasites. First there was the Proteosoma, the development of which in the mosquito, *Culex nemorosus*, had been so brilliantly discovered by Ross and subsequently studied by Koch. Then there was another plasmodial form of parasite of the red corpuscles *Halteridium*, previously studied by MacCallum and Koch; and finally there was the so-called *Leucocytozöon*, discovered so far back as 1894, by Danilewsky. The two last-named parasites own *Culex pipiens* as their intermediate host.

Previous observers had followed the development of *Halteridium* (called by Schaudinn *Trypanosoma noctuæ*) as far as it goes on in the hanging-drop of blood. Further they could not pursue it, not knowing the species of mosquito which serves as its intermediate host. Schaudinn having ascertained that it is propagated by *Culex pipiens*, found that, as the result of fertilisation, an öokinet is formed which moves along like a slug by the aid of its own mucus towards the front of the mosquito's stomach and there becomes converted into a Trypanosome. Omitting the minuter details, the process is as follows (Fig. 1). The nucleus divides unequally, so as to form a hetero-polar spindle. The larger (left) half enters the resting stage, whilst the smaller (right) half, which is now in the ectoplasm at the periphery, again divides, forming another hetero-polar spindle, with the long axis parallel with that of the öokinet and the smaller pole forwards. The chromatin of this spindle forms the skeleton of the locomotive apparatus of the future Trypanosome, the thickest thread forming the free edge of the membrane, whilst the posterior centro-some becomes the blepharoplast. Thus a Trypanosome is formed, and of these Schaudinn describes three types: the "indifferent," the "female," and the "male."

The öokinet, which is to develop into a "female" Trypanosome, has darker protoplasm and a smaller nucleus than the form which he calls "indifferent." It goes through the same nuclear processes, the result being the formation of a larger Trypanosome, which is provided with a relatively small flagellum, and is, therefore, less active in its movements. These become limited to slight bending and twisting. The "female" Trypanosome ultimately comes to resemble a mature Gregarine, and possesses a marked power of resisting external unfavourable influences. If, for instance, the mosquito is starved and then kept on ice, all the parasitic forms within it die out save the "female" Trypanosomes, which lie buried between the epithelial

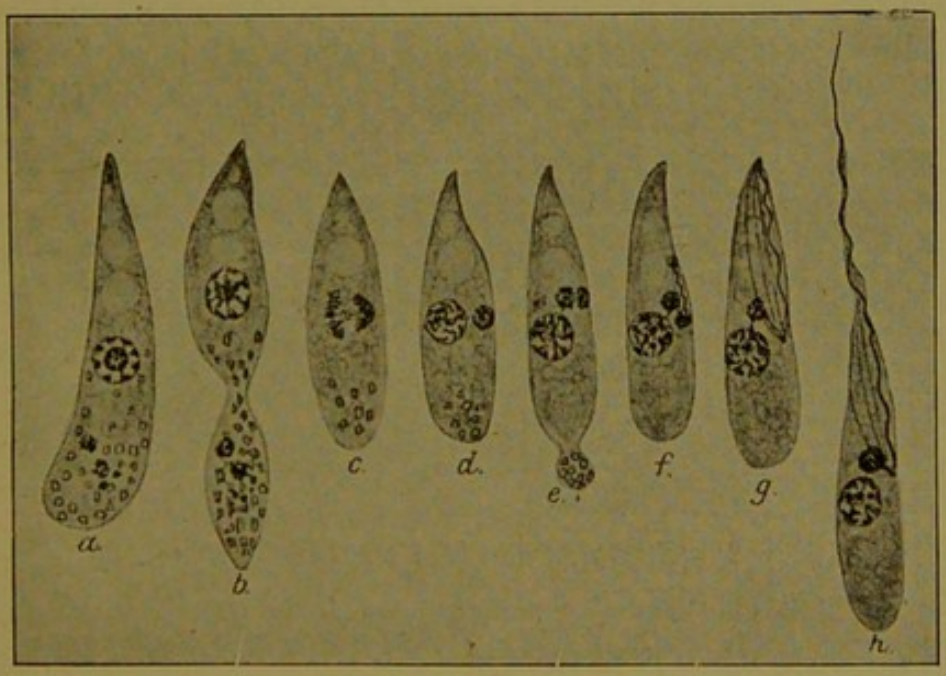

Fig. 1.—*Trypanosoma (Halteridium) noctuæ* (Schaudinn).

Stages in the development of the Öokinet into the "indifferent" type of Trypanosome (after Schaudinn): *a*, the slug-like öokinet, showing its complex conjugation-nucleus (synkaryon), near the middle, whilst in its lower part are seen the remains of the reduction-nuclei, and pigment-granules, the protoplasm containing which is being removed in *b* by abstriction; *c* and *d*, the first unequal (heteropolar) nuclear division; *e*, the second ditto; *f*, the third ditto, and first appearance of edge of undulating membrane; *g*, *h*, further development of undulating membrane and flagellum. (All highly magnified.)

and elastico-muscular coat of the intestine, last through the winter, and infect the brood of eggs laid next spring. Multiplication of this Gregarinoid stage takes place by a process termed by Schaudinn "parthenogenesis," and which he homologises with the re-infection of the warm-blooded host in Malaria, the so-called "relapses." The forms which persist in the blood of old-standing cases of malaria are,

according to him, old females (macrogametes) [? macrogametocytes]. After a time these "sink" to the level of schizonts; in other words, produce a brood without having been fertilised. This mode of reproduction—the skipping of the sexual generation—appears to me to be homologous with the phenomenon amongst ferns, first described by De Bary under the name of "apogamy."

The öokinet which is to form the "male" Trypanosomes, is distinguished *ab initio* by its small size, large nucleus and absence of reserve material in its protoplasm (Fig. 2.) By a process of reduction it gets rid of one half of its nucleus—the half which is preserved in the female—and the remainder splits up so as to form eight minute Trypanosomes. These he regards as microgametes which, however, are unable to perform their physiological function of fertilisation. This act is only performed at one period of the life-

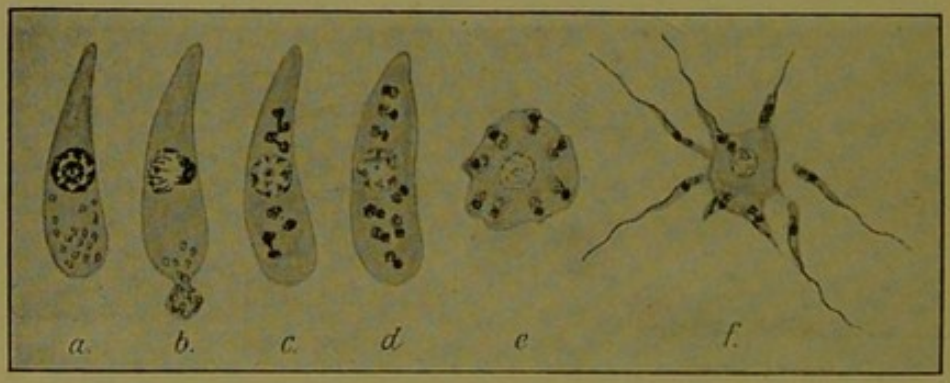

Fig. 2.—*Trypanosoma* (*Halteridium*) *noctuæ*.

Development of "male" Trypanosomes from the Öokinet (after Schaudinn); *c*, *d*, gradual disappearance of larger half of nucleus, whilst from the smaller half the microgametes are developed (*e* and *f*).

history of the parasite, viz., within a few minutes of its arrival within the stomach of the mosquito.

As the result of these processes, the intestinal canal of the mosquito becomes inundated with "Trypanosomes" of all three kinds. Sometimes they are produced in such swarms that their resting-stages occupy all the epithelium, and the mosquito dies of the disease. Ordinarily, the insect feeds three times, and it is during these three periods of digestion that the parasites make their way down the bowel, through the wall of the colon, and so into the blood-stream, whereby some get carried to the ovaries, where they infect the young brood; most, however, are carried to the front of the body-cavity into the head, where they accumulate round the pharynx, and ultimately rupture into it, and so obtain access to the lumen of the proboscis. The

mechanism of transference to the warm-blooded host is extremely interesting, and as the parasites of human malaria may possibly be transferred in the same way, it seems worth while to mention the details. *Culex pipiens* possesses œsophageal diverticula which become distended with gas, and may therefore be termed, for brevity's sake, "gas-bags." The gas is carbon dioxide, which is evolved by a sort of yeast-like fungus always present in the insect's stomach, from traces of glucose present in blood, or—much more abundantly—from glucose present in the plant-juices which the insect occasionally sucks. At the commencement of the act of suction, when the insect has its proboscis buried in the skin of its victim, its body undergoes one or more violent contractions, which eject the contents of its fore-gut and gas-bags into the skin. These contents comprise gas, saliva, and whatever particulate matter is present, viz., yeast-cells and sporozöites. Schaudinn looks upon this contraction as a sort of dyspnœal effort due to the entrance of the CO_2-laden air, which immediately bathes the skin, into the tracheæ of the insect. He succeeded in producing the contraction artificially by placing an infected *Culex* on a cupped-slide, with its proboscis in a drop of glycerine under a cover-glass, and its body projecting over the hollow. In this he evolved some CO_2 from a fragment of chalk and a droplet of acid; and he observed that the gnat's body underwent a violent contraction, which had the effect of expelling into the glycerine its contained gas, yeast-cells, and sporozöites. Viewed teleologically, the effect of the CO_2 would be to paralyse the thrombocytes, and in other ways to delay the coagulation of the blood. The hyperæmia and pain caused by the bite he considers to be due to the enzyme of the yeast-cells. He dissected out the "gas-bags," and pushed them into a fine puncture in his own skin, with the result that the typical swelling, redness, and itching came on at once. The salivary glands he found quite inoperative in this respect. The irritating effect of the "gas-bags" appears to depend on the quantity of yeast-cells contained in them, for it was much more marked when the yeast had been allowed to proliferate actively as the result of feeding the gnat on plant juice. The fungus is not a true yeast, but a yeast-like stage in the life-history of one of the *Entomophthoreæ*—fungi with which we are all acquainted in the shape of the well-known *Empusa muscae*, which kills flies in the fall of the year, and causes their bodies to adhere to the window-pane, surrounded by a white cloud of ejected conidia.

Let us now follow the Trypanosomes into the blood of the owl, whither they are carried by the bite of the *Culex*. Such "males" as are conveyed in the fully-differentiated state die off. The mature "females" are usually too large to pass the gnat's proboscis. It is the "indifferent" forms and young "females" that thrive in their new surroundings. Adhering by their flagellum to the red corpuscles, they bore their way in, withdraw their flagellum, and grow larger in the plasmodial form described by MacCallum, Koch, and other observers. They do *not* proceed to form asexual rosettes (schizonts), a fact expressly drawn attention to by Koch, who could not find in the blood of his artificially-infected sparrows and pigeons any trace of this form of multiplication, which is so abundantly met with in

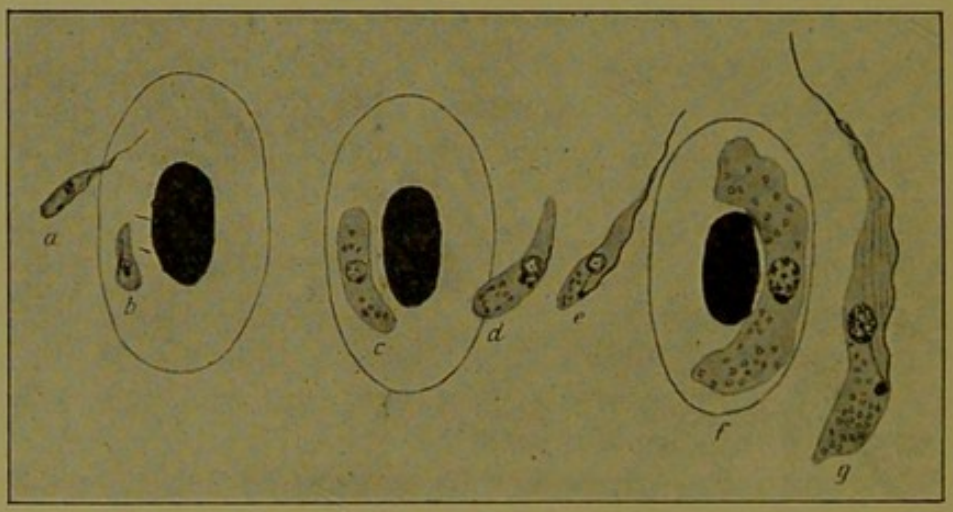

Fig. 3.—*Trypanosoma* (*Halteridium*) *noctuæ*.

a, attachment of "indifferent" Trypanosome to a blood-corpuscle of the owl, by its flagellum. Another individual, *b*, has completely penetrated into the corpuscle and has lost its flagellum; *c*, increase in size, and *d*, escape of the intra-corpuscular parasite; *e*, *f*, *g*, further stages of growth. (After Schaudinn.)

human malaria. What actually happens is this. The intra-corpuscular parasites leave their host-cells only during the night, and in the deepest recesses of the circulation—the spleen and bone-marrow. There they swim about for a while as free Trypanosomes (of all three varieties above described) (Fig. 3). During the day they mostly go back to the corpuscles. Thus they change about at intervals, for six days, by the end of which time they have attained their full size. Finally emerging, the full-grown parasite now multiplies by repeated acts of longitudinal fission till the products have attained their minimal size. The excessively minute flagellates so formed penetrate into fresh red

corpuscles, till the blood become fairly inundated. Then they die down, and only a small number of "indifferent" forms survive, which become gradually evolved into macro- and micro-gametocytes, and can only complete their evolution in the body of the gnat. In concluding the *resumé* of the remarkable life-history of Trypanosoma (*Halteridium*) noctuæ, as observed by Schaudinn, I would point that of previous observers only Danilewsky seems to have come across the Trypanosome. Koch, in his careful study of the parasite, does not seem to have observed this stage; at any rate, he makes no mention of having seen Trypanosomes in the blood of his birds infected with *Halteridium*.

I have dwelt thus at length upon the history of this parasite on account of the light it throws upon the nature of the Leishman-Donovan body. These parasitic bodies are contained in large endothelial cells of the spleen and marrow: so, for a time, are the *Halteridium*-parasites The Leishman-Donovan bodies possess two nuclei—a large oval and a small rod-shaped one,; so do the involuted intra-corpuscular Trypanosomes of *Halteridium*. Finally, we have the brilliant discovery, by Rogers, that blood containing Leishman-Donovan bodies gives rise to Trypanosomes. The details given by Rogers tend to support the supposition that the life-history of the parasite of cachexial fever runs on the same lines as those of owl-malaria. For example: "the splitting-up of the parasite into two, the separation usually beginning at one end," suggests the longitudinal division of the Trypanosomes; and "the presence of smaller pear-shaped flagellated bodies like those described by Plimmer in Tsetse fly disease," which are evidently involution, or immature forms, also described by Laveran and Mesnil in their recently-published text-book (19), under the name of *mises en boule*, and figured on p. 156. Finally, there is the fact that the Trypanosomes were only developed in Major Rogers' cultures at a low temperature (22 deg.), which would point to their being naturally produced outside the warm-blooded host in a blood-sucking Invertebrate, such as a bug or mosquito. There can be little doubt that the original opinion of Major Leishman with regard to these bodies is correct, and that Kala-azar and cachexial fever will prove to be a form of human Trypanosomiasis. The same opinion doubtless holds good of the bodies found in the granulation tissue of Delhi-boil and Tropical ulcer, by Cunningham, Wright, James, Christophers and others.

Remarkable as is the connection so established between

the malarial parasite and the Trypanosome, it is, at any rate, a connection between one Protozöon and another. But the developmental cycle which I am now about to recount will, if established by further investigation, effect a still more surprising connection, viz., between a malarial parasite and an organism hitherto looked upon as a Bacterium, Spirochæte.

The malarial parasite in question was discovered so far back as 1891, by Danilewsky, of Charkow (20), in the blood of *Athene noctua*, and called by him the Leucocytozöon, from its dwelling in the white corpuscles. It was afterwards seen and depicted by Ziemann, (21) in his well-known work on blood-parasites. Both its warm-blooded and cold-blooded host (*Culex pipiens*), as well as its general aspect, are identical with those of *Halteridium*. In the mosquito's

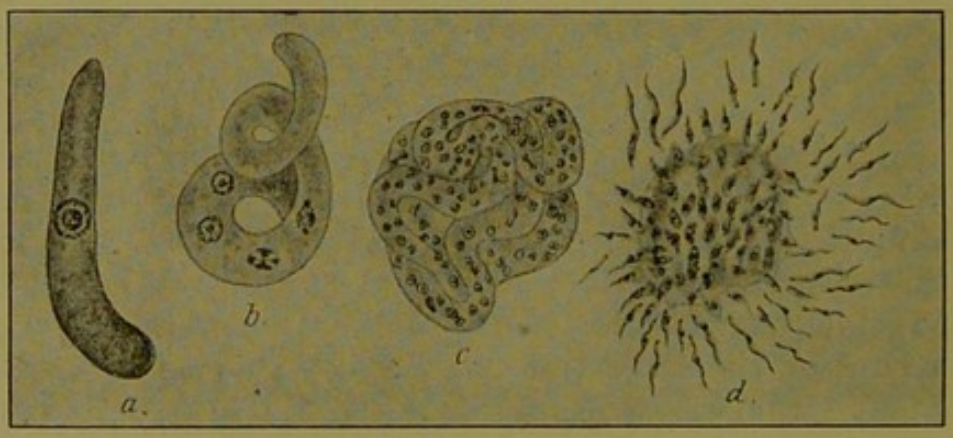

Fig. 4.—*Spirochæte Ziemanni*. (After Schaudinn.)

Development of minute Trypanosomes (*Spirochætæ*) from Öokinet (see text).

stomach its stationary macrogametes are fertilised by the motile microgametes. An öokinet (*a*) is thus formed, which becomes spirally coiled, so as to form a sort of corkscrew (*b*), the coils of which coalesce (*c*) (Fig. 4). To my mind, this process is remarkably like what occurs in the development of the sexual fructification of the cleistocarpous Ascomycetes, such as Eurotium. The original nucleus divides into a vast number, each of which presides over a territory of protoplasm, which gradually becomes differentiated into a Trypanosome-like body, with blepharoplast, undulating membrane, and flagellum (Fig. 4, *c*, *d*). Of these, as in *Halteridium*, there are three sorts—"indifferent," "female," and "male"—and all are very minute. As the result of repeated division, the individuals may become so small as to become not only incapable of measurement, but even of being perceived individually with the highest magnifications. It is

only when agglutinated in rosette form that they can be well seen; and Schaudinn, who describes these remarkable appearances, has no doubt that they would constitute a *filtrable* virus: that is, one capable of passing the pores of a porcelain filter, and therefore in the same category as those of pleuro-pneumonia, foot-and-mouth disease, and perhaps of small-pox. These minute Trypanosomes increase greatly in length, and become spirally twisted round their long axis, so as to constitute what have hitherto been termed Spirochætes. Now the leading pathogenic Spirochæte hitherto known is S. Obermeieri, the cause of Relapsing Fever. It has been observed to move equally well in either direction, "forwards" or "backwards." But Trypanosomes always move forwards, *i.e.*, flagellum first, and this would seem to be a serious difference between them and Spirochæte.* Schaudinn states, however, that these long, thin Trypanosomes divide longitudinally, and that the two new individuals *remain coherent by their hinder ends*, and can accordingly move in *either* direction. They continue to cohere until each individual has again divided in the same way. These Spirochæte-Trypanosomes agree with the Trypanosomes of the Mammalia, and differ from those of birds (*Halteridium*), in becoming agglutinated by their *hinder* ends. It is at the end of the first digestive period of the mosquito that these Spirochæte-like Trypanosomes are developed from the öokinet, inundate the body-cavity, and infect the ova. On re-introduction, natural or experimental, into the owl, they begin by multiplying enormously in the Spirochæte form before proceeding to the formation of sexual individuals. It is surprising to me that neither Danilewsky nor the other workers who observed the intra-corpuscular stage of this parasite should have seen the Spirochæte. Possibly, their birds were old cases, in which all the parasites had passed on into the intra-corpuscular resting stage. The cell preferred by this parasite is not the mature red corpuscle, nor yet the mature leucocyte, but the hæmoglobin-free precursor of the former—the erythroblast. This accounts for its presence mainly in the spleen and marrow (*cf.* the behaviour of the Leishman-Donovan body). In human relapsing fever, Metschnikoff observed that when the Spirochæte disappears from the blood at crisis, it accumulates in the spleen. It would be interesting to know whether Metschnikoff observed any flagellated or plasmodial forms amongst the spleen-cells. If the development of human

* Prowazek (*loc. cit.*) now holds that this is not always the case.

relapsing fever really proceeds on the same lines as *Spirochæte Ziemanni* of the owl, so accurate an observer as Metschnikoff could hardly have avoided seeing them, more especially as Schaudinn describes the sexual forms as relatively very large: so large as to be unable to find entrance into their host-cell, but rather drawing it into themselves, and provided with a distinct undulating membrane. Ziemann also in his figures misses the flagellated form, though his figure of the peculiar way in which the erythroblast-nucleus is flattened out exactly agrees with that of Schaudinn. The parasites undergo successive stages of intra- and extra-corpuscular existence in the blood

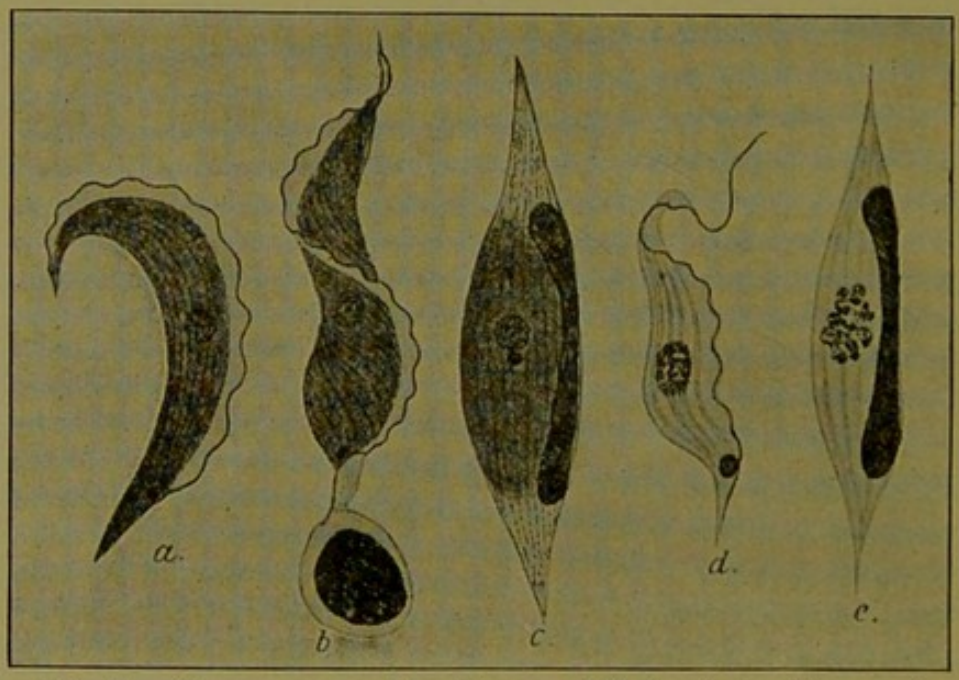

Fig. 5.—Trypanosome-like Stages of Spirochæte Ziemanni in the Blood of the Owl (after Schaudinn).

a, motile stage of full-grown female (the female forms possess the undulating membrane, but not the flagellum); *b*, the same, showing spiral twisting during motion, and an erythroblast of the owl adherent to the *hinder* end of the parasite; *c*, resting stage with transparent outer sheath (periplast), the dark structure to the right is the nucleus of a digested erythroblast; *d*, active stage of the microgametocyte; *e*, resting stage of same, showing its nucleus already divided up, and the nucleus of a digested erythroblast to the right.

of the owl (Fig. 5), and on removal from it by *Culex pipiens*, at once proceed to the formation of large rounded macrogametes with dense protoplasm, and small active microgametes which look like a minute Trypanosome or a Spirochæte. Fertilisation gives rise to the öokinet from which we started.

Should this developmental cycle be confirmed by other observers, then it follows that Trypanosoma and Spiro-

chæte are really only different names for the same thing. The following features about relapsing fever would then be accounted for: the non-cultivability of the Spirochæte on ordinary substrata, and the persistence of the parasite in the spleen after its disappearance from the general circulation. It would also appear probable that its propagation would be effected by some blood-sucking parasite. This has actually been found to be the case with the "Spirillosis of fowls," recently described by Marchoux and Salimbeni (22). They found that the Spirilla were conveyed by the bird-tick, *Argas miniatus*. Unfortunately, they give no details as to what happens to the parasite inside of the tick; and although they describe the spleen as enlarged to three times its size, they give no account of its minute appearances.

I am not aware that the intermediate host of the Spirillosis of ducks described by Sakharoff, nor of that of oxen quite recently described by Laveran (23), has been ascertained.

In the case of human relapsing fever, it seems most probable that bed-bugs carry the infection. Karlinski (24) found abundant Spirilla in the bugs captured in Bosnian houses where the inmates suffered from the fever, whilst he could find none in bugs obtained from houses where there was no fever. He found that the Spirilla persisted for 20 days in the bugs. Marchoux and Salimbeni say that their Spirilla persist in *Argas* for 100 days.

As I pen these lines, another Spirillosis of the human subject has been discovered. Major Ross, F.R.S., announces in the current number of the *British Medical Journal* (Feb. 4th, 1905) that human "tick" fever in the Congo has been found by Dutton and Todd to be caused by Spirilla which are conveyed by the tick *Ornithodorus*.

The question is, of course, still open whether the Spirilla of these diseases are really built on the same lines as the Spirochæte Ziemanni of Schaudinn. So much would thus be explained that it is certainly a very tempting hypothesis.*

This Paper, already far too long, would be swollen to inordinate dimensions were I to attempt to refer in detail to the *Piroplasma* parasites. I am, however, absolved

* As I correct these lines for the Press, the interesting announcement has just reached me of the discovery by Schaudinn, in various syphilitic lesions, of extremely delicate, actively motile Spirochætæ, which he is inclined to look upon as the cause of the disease. The paper appears in the *Arb. a. d. k. Gesundheitsamte*, Bd. xxii, p. 527, and is dated April 10th, 1905. I have since confirmed this discovery.

from the task by the fact that this Society has already been this season the recipient of a very admirable communication from Prof. G. H. F. Nuttall, F.R.S., on the subject of Ticks and Tick-transmitted Diseases, which practically covers the ground. I will merely mention that Kossel and Weber (25), of the German Imperial Health Office, have found Trypanosome-like stages in the blood of cows affected with haemoglobinuric fever, and also in the intestines of ticks that had sucked the blood of such cows. Furthermore, Theiler, and quite recently Bowhill (26), have found both Trypanosome and Spirochæte forms in the blood of oxen and dogs affected with Piroplasmosis.

Judging by analogy, it seems not improbable that the hitherto unseen parasite of Yellow Fever may prove to be a Spirochæte too small to be seen with the highest powers of the microscope.

[Dr. Dutton has since succeeded in conveying spirillum-fever to the monkey by means of the tick, and further, in proving that young ticks reared from naturally-infected parents can convey the disease at their first feed—an observation of the very highest significance, in view of the fact that the tick fever or infectious hæmoglobinuria of cattle ("bovine malaria," as it is sometimes called) is propagated, not by the naturally-infected tick, but by its progeny. That Dutton's brilliant career, already so rich in achievement, should have been brought to an untimely end by infection received during his investigations, is an announcement which will cause profound regret, more especially to those engaged in the study of Tropical Medicine.] (Note made during correction of the proof-sheets.)

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Discussion on Dr. E. J. McWeeney's Paper.

The President: I think the most fitting way of proceeding, after listening to Professor McWeeney's most interesting Paper, which I am sure we have all heard with the greatest pleasure, is to ask Sir Patrick Manson to open a discussion upon it. The Paper deals with points which are highly technical and extremely interesting, but not all of us have had an opportunity of pursuing such studies as would place us in a position to open a discussion of such questions. I will therefore call upon Sir Patrick Manson.

Sir Patrick Manson: Sir, I have no doubt you will agree with me in thinking that Prof. McWeeney has conferred a great boon not only upon this Society, but upon all who are interested in questions bearing upon this particular subject of Protozoa in relation to disease. Schaudinn's Paper we have looked at, but, I fear, very few of us have read it. The subject is abstruse and difficult, and the German in which it is discussed is more abstruse and difficult still. I have read one or two translations, but the translations themselves require to be translated before they are intelligible; but now, with Professor McWeeney's able disquisition in our hands, no one has any longer an excuse to remain ignorant on this subject.

These observations of Schaudinn are exceedingly important, and I presume they are correct; but they are not without opponents. Only lately McNeal and Novy, two American protozöologists who have given a great deal of time and attention to the study of Trypanosomes, have ventured to criticise Schaudinn's conclusions, particularly as regards the connection of Trypanosomes with Halteridium and similar parasites. They say distinctly that

Schaudinn has made a mistake. I do not say so; it is they who say so. They say that he has been working with mixed infections, and not with pure Trypanosoma infections. They say that in certain birds in America—or at all events in a large proportion of them—they can by a process of cultivation, demonstrate the presence of Trypanosoma in the blood, whereas in only a small proportion they can detect anything in the nature of Endocorpuscular Protozoa. They contend that Schaudinn has been working with birds in which a Trypanosoma infection was superadded to another and independent infection by Endocorpuscular Protozoa. That is their criticism, and not mine.

We have had a great deal of information from Professor McWeeny this evening: I should like a little more. Schaudinn tells us he divides the öokinets into three kinds; an "indifferent," a "male," and a "female." I should like to know why he calls them indifferent, male, and female. These öokinets are themselves the result of a sexual process: the microgamete and the macrogamete are the male and female, and the result of the union is the öokinet, which shows no evidence of possessing sexual qualities. Why, then, class them male and female? I have no doubt there is an explanation of the use of these terms, and I should be grateful if Professor McWeeney would supply it.

As regards the important communication on the subject of the Amoeba of Dysentery —*Amoeba histolytica*— I would utter a word of caution as to concluding that this matter is completely settled. The modern doctrine which divides the dysenteries into two categories, those produced by the Bacillus of Shiga and those produced by the *Entamoeba histolytica*, is very complete and fascinating, but it does not square at every point, at all events in my experience, with clinical observation. Nor does it seem to logically fit in with the facts of the case. For example, Schaudinn states that the cause of tropical Dysentery is this *Entamoeba histolytica*, which, in its vegetative form, exists and is active in the bowel of dysenterics during the acute and active phases of disease, but which, when the disease begins to subside, forms spores which become encysted; and, he contends, it is by these spores that the disease is propagated and spread from one person to another. Now, why should this be if the disease is a tropical disease only? Why should these spores not be capable of existence outside the human body, and produce disease in non-tropical countries as well as tropical countries? In view of the resistive

properties of an encysted spore, one would be inclined to think that the disease it gave rise to would, as regards its geographical distribution, behave like bacterial diseases and not as those of a Protozoal origin. Any disease that is limited geographically, like tropical Dysentery, depends for its spread upon a medium which conveys the infective agent from the sufferer to the hitherto non-infected person; and this medium or transmitting agent is the factor that determines the geographical limitations of the disease. But in this instance of Amoebic Dysentery, there is no limitation as regards the transmitting agent: the spore falls on the ground and is directly communicated, unaffected by temperature, to another person. Why, therefore, should not that disease be a pandemic disease as well as a tropical disease? Schaudinn's views, to my mind, do not get over this difficulty.

There is another point I should like to say a word or two about, that is: Schaudinn (or Professor McWeeney) assumes in the case of Leishman's body that the transmitting agent should be, or must be, an anthropophagous insect—a blood-sucker of some sort. I do not quite see why there should be an insect or other kind of blood-sucker. For we now know as a fact that the Leishman body is extruded from the human body by ulcerated surfaces. Patients who suffer from Leishman's disease die, as a rule, from some form of ulceration of the intestine, and from these ulcerated surfaces the Leishman body escapes into the outer world; so that it is more likely that a non-blood-sucking insect conveys the parasite from the fæces or ulcerated surfaces to an uninfected individual. I think this idea is borne out by another circumstance in connection with the bodies referred to. An exactly similar, or possibly the same, body is found to be at the root of the disease known as Oriental Sore, in which case the parasite must escape from the ulcer on the surface of the body, and not by the blood.

Some time ago, possessed with the idea that Leishman's body was possibly a blood parasite, I tried in one case to see if the usual absence of the parasite from the blood might depend on some circumstance connected with light or darkness, day or night; and I instituted a series of observations upon a patient suffering from the disease, to see whether the blood might not, at some period of the 24 hours, contain Leishman's body. My observations were negative: I never saw any bodies during the day or night in the blood. These observations were confirmed by Dr. Low, of the Tropical School. So far, we have no

evidence to show that Leishman's body is in any circumstances a blood parasite.

The idea that Syphilis may be one of these Protozoal diseases is an exceedingly fascinating one; and I think that there is some ground to hope that in these Leishman's bodies we have a clue to that mysterious infection.* Some years ago, a medical man who had practised in Persia and Arabia was invalided home in consequence of a severe attack of Oriental Sore. He came to England, and whilst still suffering from the Sore, he developed what was believed to be tubercular disease of one testicle. The testicle was excised, with the idea of preventing general tuberculosis. The disease appeared, however, in the other testicle, which was also excised. I saw the patient about that time, and the idea that presented itself to my mind was that the Oriental Sore was a sort of Chancre, the point of entrance of a poison which became diffused, and afterwards produced secondary or tertiary effects, one of which was a specific infection of the testicle. Whether the idea is a correct one or not, I cannot pretend to say. It is, at all events, one that suggests a fresh field for observation.

Dr. Copeman: I am obliged to you for calling upon me, for the reason that it gives me the opportunity of adding my thanks to those of Sir Patrick Manson for this admirable and interesting address; but I think it will be generally admitted that it is impossible for anyone who has not done original work on the subject of Protozoa to adequately discuss the Paper. It is, however, as far as I am able to judge of it, a most interesting and most judicial Paper. It sets out, in a delightful way, the work of other observers, and more particularly of Schaudinn. It affords those who have been unable either to work at the subject or to see the original Papers an opportunity of learning what has been done on the subject, and perhaps, in course of time, after carefully reading through the Paper again, of criticising to some extent the points brought forward.

Professor McWeeney states that the Paper contains no original research of his own; but, at any rate, it contains several most interesting suggestions which I take to be his own. There was one that particularly appealed to me because for some years in my leisure time I have worked

* [See footnote on p. 103. Schaudinn's discovery of Spirochætæ in Syphilis was not made at the time when Sir P. Manson used these remarkable words.]

on the subject of sex; and that was the suggestion as to the part played, on the one hand, by the additional Spermatozoa, and by the "polar" bodies on the other hand. I have often wondered what was the reason for the enormous number of Spermatozoa which are always produced in mammalia, when we know that, as a general rule, only one can be utilised in fertilisation; and I have often wondered also what becomes of the "polar" bodies, which are always extruded previous to fertilisation. No suggestion, so far as I am aware, has previously been put forward as to what part may be played by these bodies, or by the excessive amount of material which is cast off from the cells of the seminiferous tubules and other parts of the genital track. One knows that Nature is always prolific; but I agree that it is highly probable that this excess of male and female elements, as well as the fluid portion of the secretion, do play some particular part in the process. I think Professor McWeeney's explanation is a very ingenious one, and one which I think may not improbably turn out to be correct.

I am glad also to see that Professor McWeeney, in his historical statement as to the investigation of the Trypanosomes connected with diseases in man, gives a special place to Castellani: because, I think, it has of late been the custom hardly to give him a fair position in the matter of discovery. One knows that perhaps he did not at first attach a large amount of importance to the presence of Trypanosoma in the cerebro-spinal fluid; still, he did demonstrate its presence, and it is quite possible that unless he had made his examination of the cerebro-spinal fluid, the actual discovery of the Trypanosoma of sleeping-sickness might have been considerably delayed. Whilst others, like Bruce and his colleagues, really brought the discovery to a definite conclusion, I think—as I have said—that had it not been for Castellani's previous work, that of other investigators might not have been so fruitful as it has been.

As regards Professor McWeeney's suggestion of the ultra-microscopic and so possible *filtrable* nature of the specific organism of small-pox and vaccinia, I think that this is definitely disproved by my experimental work (an extension of that of Chauveau and Burdon Sanderson), published in the *Transactions* of the London Congress of Hygiene and Demography in 1891.

I desire once more to thank Professor McWeeney for his Paper, which I shall hope to read again at my leisure, as it is hardly possible to follow such a multitude of new facts in the space of time occupied in reading the Paper.

SIR PATRICK MANSON: I should like to add a few more words. In one paragraph, towards the end of the Paper, Professor McWeeney says that a new form of Spirillosis in the human subject has been discovered by Dutton and Todd on the Congo. That disease has already been discovered by the bacteriologist of the Uganda Government, Dr. Ross, and had been linked up with the Ornithodorus a considerable time before.

There is another question I should like to ask. Did Koch succeed in infecting his birds with Halteridium by injection of Halteridium blood, or was it in a more indirect way? I always understood that other Trypanosomes could be inoculated directly, but that Halteridium could could not be directly inoculated.

THE PRESIDENT: Before calling upon Professor McWeeney to reply, I want to offer him, on behalf of the Society, our most cordial thanks for his admirable Paper and demonstration. We are, indeed, very grateful to him for coming so far to teach us so much.

PROFESSOR MCWEENEY: The observations which have been made, Sir, by yourself and other speakers have been a source of great pleasure to me. It is true that I have come a considerable distance to read this Paper; but the occasions on which an Irish worker has been asked to read a Paper before a London Scientific Society have been few and far between; and accordingly I regard it as a great compliment and a very great honour to be asked to come here and deliver this Paper, and the way in which it has been received has been a source of still greater pleasure to me.

The remarks made by Sir Patrick Manson, whose researches and discoveries in this field of observation have gained a wide-world reputation, and give him a special authority to speak on the subject—what he has said in confirmation of the general views which I venture in accordance with Schaudinn to express, has been eminently satisfactory to me. Eminently satisfactory is it to learn from him that in the main the criticisms, apart from those of Novy and McNeal (which, by the way, had escaped me when I was reading up for this Paper—had I seen them I would have dealt with them in the Paper) are favourable to Schaudinn. It is highly satisfactory to find this, because I am bound to say that, after very careful perusal of Schaudinn's papers (I have read all that he has written upon the subject), they give me the idea of having the true

ring of genuine accuracy and research, and of being very full and accurate. He has written another Paper on the Tertian parasite, which is full of the most beautiful drawings; and the whole work gives one the idea of completeness and painstaking accuracy. At the same time, it should have been remarked that I did not give in an absolute adhesion to all his conclusions. I have but pointed out what appear to me to be some of the more important inferences from his discoveries.

The question which Sir Patrick Manson has asked me undoubtedly draws attention to what appears to me an unjustifiable part of Schaudinn's nomenclature. He speaks of the three kinds of Trypanosomes as "indifferent," "male," and "female." It is quite true they cannot be so regarded, since they are themselves the immediate result of a sexual process. Schaudinn has not exactly stated, so far as my recollection goes, why he selected these terms. His general view is that the "male" Trypanosome is in its mode of formation and morphology precisely similar to the microgamete, and that what he calls the "female" Trypanosome resembles the macrogamete in having dull protoplasm and a relatively small nucleus. That, I think, is the current of thought which has suggested this nomenclature to Schaudinn; but whether it is justifiable or not is a point on which I should be inclined to follow Sir Patrick Manson, who is in a better position than I am to form an opinion on such a point.

With regard to the question of the *Amoeba histolytica*, so far as I have been able to gather, Sir Patrick Manson's difficulty is this: if the parasite is not limited to tropical countries, neither ought the disease to be so confined.* As to this I can only offer a suggestion of my own: might not the ripening of the cysts be a question of temperature? Would not that account for the non-appearance of the disease in some climates? They might require a high temperature to mature in, and such a temperature might only occur where this type of disease is endemic.

In connection with what Sir Patrick says as to the Leishman body not being conveyed by a parasite—that is just the value of discussions like these—the value for me as a man removed from the actual field of observation. I figured to myself a parasite in the liver or the spleen, etc., and I

* Neither the parasite nor the disease is, as a matter of fact, so limited. In addition to the cases of Amœbic Dysentery reported by Jäger (*Berl. klin. Wochenschr.*, 1901), Albu, quite recently, records a similar case that ended fatally. The disease was contracted in Breslau (*Ztschr. f. Klin. Med.*, Bd. lxv, p. 433).

did not know it was excreted from the sores, and therefore capable of being conveyed by other than blood-sucking parasites.

With regard to the disease described three or four months ago under the name of Human Tick Fever, the point of interest appeared to me to be the announcement made by Major Ross, in the *British Medical Journal* last Saturday, that it was due to a Spirillum, and was propagated by the bird-tick, Ornithodorus. That, of course, brings it at once into close connection with the Piroplasmic diseases, which are always produced by ticks.

The last question of Sir Patrick Manson was whether Koch succeeded in producing Halteridium by direct inoculation. I am under the impression that he did. His Paper on the subject, which is contained in the *Zeitschrift für Hygiene* of 1899, describes the results of his study of Halteridium and Proteosoma in the blood of birds. It is a very curious thing that he should never have come across the Trypanosome stage. [My recollection was at fault here. On referring to Koch's Paper, I find that, although he succeeded with Proteosoma, he failed to communicate Halteridium by direct inoculation.]

I am extremely grateful to Dr. Copeman for all he was good enough to say of the Paper. It is quite true that it would require to be read over several times in order that it might be criticised, because I was obliged to compress a great deal of matter into as few words as possible. Coming from one who has done such good original work as Dr. Copeman has upon the virus of Small-pox, such commendation is very agreeable; and it would be extremely interesting if Dr. Copeman could carry out some Small-pox work on the lines indicated. The virus might possibly prove to be a filtrable one, and of Protozoal nature.

I was very glad to be able to lay stress on the work of Castellani, whose application of the centrifuge to the examination of the cerebro-spinal fluid seems to be the critical point in the whole pathology of Sleeping Sickness: demonstrating as it did the constant presence of the Trypanosome at a period when the researches of the Portuguese Commission tended to ascribe to a Coccus the leading *rôle* in the ætiology of the disease.

I think nothing now remains for me but once more to thank the Society for the patience with which they have listened to me.