PRESIDENTIAL ADDRESS

THE HOST-PARASITE RELATIONSHIP IN FILARIAISIS

by

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Election to the office of President of the Royal Society of Tropical Medicine is a greatly appreciated honour, but six months later the bill arrives, in the form of a call for a Presidential Address, and with it comes the realization that the honour bestowed carries with it certain responsibilities and obligations. To obtain inspiration I have turned, as I suppose all my predecessors have done, to the speeches of previous holders of this office. Some of them, like my immediate forerunner, Dr. Norman White, have spoken of the past, and have conjured up from their long and varied experience vivid pictures of the good old days of great leaders and of great discoveries. For the most part, however, past Presidents have selected, as is only natural, some scientific aspect of tropical medicine in which they were particularly interested, and in so doing they have discussed the habits and pathogenicity of a wide range of creatures that bring affliction to mankind in the tropics. The last two addresses which followed this line of thought were those of Sir Neil Hamilton Fairley, who in 1951 spoke on "Schistosomiasis and some of its Problems," and Sir Rickard Christophers, who in 1939, shortly after the outbreak of war, selected for the subject of his address "Malaria in War." These two addresses, though on very different subjects, had this much in common: they were concerned with subjects to the study of which the speaker had devoted many years of his life, and both speakers emphasized their belief that the knowledge at that time available was insufficient to enable widespread and satisfactory control to be rapidly exercised over the parasites that caused the diseases.

I was present at both these addresses and was particularly interested in the discussion that followed Sir Rickard Christophers', because it soon became clear that some of his audience, malariologists of considerable experience, were, unlike Sir Rickard, confident that the lessons learned in the 1914-18 War and the advances since made in knowledge of the control of malaria were reasonably sufficient to meet any situation that might arise in the unexplored future.

The reason for this difference of opinion was, I think, simple enough: Sir Rickard, as a result of a life-time of study, was able to distinguish clearly between conjecture and existing facts, whereas his critics often failed to do so. If you ask me how one can distinguish between facts and conjectures I can only answer that, whereas many undergraduate conjectures eventually qualify as facts, their graduation can be accepted only after they have been subjected to a very searching examination by those best qualified to judge.

The worker who has really studied his subject, knows his facts, knows the form of the gaps between his facts, and is for ever turning over fresh scientific material in the hope of filling those gaps. Some of that material he uses straightway, but most of it is put on one side for future study or for the use of others. It is the power to recognize such gaps, and the possession of an eye to judge the form of conjecture likely to fill them, that help to make a good
research worker; but the good research worker, although prepared to test any likely conjecture, will not pass the work as satisfactory until he has tested the accuracy of the fit.

Those of us who are fortunate enough to possess a first edition of Manson's "Tropical Diseases" may read for ourselves how that greatest of pioneers in tropical medicine clearly separated the known facts from the conjectures then prevailing concerning malaria; and, as we read what he wrote, we can see how misleading conjectures may be which are based on insufficiently studied facts. The facts regarding malaria as they were known when Manson's classical work was published in 1898 are as follows: the cause of malaria was known to be the plasmodium; its erythrocytic cycle had been well studied, and Ross had proved that, when taken up by the mosquito, it developed to the oocyst stage in the wall of the insect's stomach. In addition, since there was good evidence that man's acquirement of malaria was associated with his proximity to water, it was conjectured that the malaria parasite must reach him, in some unknown way, from this source. Manson's description of the morphology of the parasite, its erythrocytic cycle in the human host, and its development to the oocyst stage in the stomach of the mosquito gives as accurate and as clear-cut a description as can be found in any modern textbook. Having taken the reader so far in established facts, Manson then cautions him that what follows is conjecture, which must not be accepted until it has been subjected to scientific proof. With this warning Manson puts forward his theory of the transmission of malaria, which is summarized in his concluding sentence as follows: "Man, I conjecture, may become infected by drinking water contaminated by the mosquito; or, and much more frequently, by inhaling the dust of the mud of dried-up mosquito-haunted pools; or in some similar way." Then follows the call for further research, coupled with a stringent warning: "I do not maintain that this mosquito hypothesis has as yet been thoroughly proved, but I do maintain that it is so probable, and of a character so important, from both a scientific and practical point of view, that every effort should be made to establish or confute it." Manson then considers the theory of the Italian School in these words: "Bignami conjectures that the plasmodium is conveyed to man by the bite of the mosquito, its proboscis carrying malaria germs acquired from the water or soil of a malaria-infested locality. Experiment has not encouraged this idea." Here we have two theories, both containing the germ of truth and both sufficiently plausible to be postulated by men of outstanding scientific ability and experience; yet neither of them has been found true when subjected to scientific tests — another example of reasonable conjecture slain by plain fact.

THE IMPORTANCE OF FILARIASIS AND THE PAUCITY OF KNOWLEDGE CONCERNING IT

To-day, vast commercial schemes are being undertaken in the tropics for the betterment of mankind, some of them in areas where filariasis is endemic. There is an increasing and well-founded belief that filariasis in general and certain species of filaria in particular are far more injurious to health than has previously been realized, and that the control of such infections must be considered with the same urgency as such other arthropod-borne diseases as malaria, trypanosomiasis and yellow fever. If we agree, then the question arises of whether the knowledge at our disposal is sufficient to enable us to control filariasis with the same measure of success as attends the control of those other arthropod-borne infections.

For myself, I very much doubt it; during the past six years my colleagues and I have been studying certain aspects of loiasis, onchocerciasis and acanthocheilonemiasis in Africa and in the laboratories in this country, and it appears to us that, in so far as these three
Infections are concerned, our knowledge of filariasis is in much the same state as was knowledge of malaria when Manson’s book was published more than 50 years ago. We have a few facts and many conjectures linking them; and some of us are experiencing great difficulty in distinguishing between what is fact and what is conjecture.

During the course of our investigations, we have paid particular attention to the relationship between host and parasite. As a result, we have come to the conclusion both that a proper understanding of the symptomatology, diagnosis and treatment of filariasis is dependent on previous knowledge of the host-parasite relationship between the worm and its vertebrate hosts, and that it is difficult to plan or to judge the effect of control measures without previous knowledge of the host-parasite relationship between the worm and its invertebrate vectors. Since our work has been concentrated on Loa loa and its vectors, it is mainly on the host-parasite relationship in loiasis that I propose to speak this evening.

**AN ATTEMPT TO DEFINE “GOOD AND BAD HOSTS”**

The filariae parasitizing man have no extra-corporeal existence; they pass from the vertebrate host to the invertebrate host and back to the vertebrate host along what one might call a labial pipe-line, so that any reaction excited in either man or fly will effect the life-cycle of the individual parasite and, in consequence, the epidemiology and spread of the disease with which it is associated. It may well be that during this twofold process of development the parasite may pass part of its existence in a congenial or, as it is usually called, a “good host,” and part of its existence in an uncongenial or “bad host.” A good host-parasite relationship is usually defined as one in which the parasite can undergo its normal development, neither parasite nor host unduly interfering with the other’s existence. As Van Beneden wrote nearly 50 years ago, “A parasite is he whose profession it is to live at the expense of his neighbour and whose only employment consists in taking advantage of him, but prudently so as not to endanger his life. He is a pauper who needs help lest he should die on the public highway but who practises the precept not to kill the fowl in order to get the eggs.” Such a definition, however, although generally applicable, cannot always be accepted as accurate. It is true that, although certain parasitic helminths can escape from their hosts only after the host’s death, this does not necessarily imply that the parasite shortens the life-span of its host. On the other hand, a few parasites, such as the larval Multiceps multiceps which occurs in the brains of ruminants, do inevitably shorten the life of what appear to be their normal hosts. We propose as a definition of a good host one which allows a suitable proportion of the introduced parasites to reach that stage of development most propitious for the propagation of the species, such successful propagation generally being dependent on the parasite’s ability to cause no serious injury to its host. It seems appropriate at this point to stress the fact that, just as the term “good host” does not invariably imply lack of pathogenicity on the part of the parasite, so the term “bad host” does not necessarily imply any active resistance on the part of the host. As will be shown later, a proportion of the human population are naturally bad hosts (in the zoological sense of ill-adapted hosts) to L. loa, in that they do not at any time allow microfilariae to appear in the peripheral circulation, in spite of multiple invasions by infective forms. It is possible

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* Our original wording was a “high proportion,” but we substituted “suitable proportion” because many good hosts limit the number of parasites: for example, man tolerates the presence of only a few Taenia saginata in his gut at any one time, but those few individuals are sufficiently prolific to propagate the species.
either that the parasites are destroyed at some stage of their development, as a result of active reaction on the part of the host, or that they perish from inanition either because of the host's lack of some essential requirement for their growth, or because, being in an ill adapted or strange host, the parasites fail to find their way to the organ or tissue necessary for their development.

Using this definition as a guide, let us see to what extent the invertebrate and vertebrate hosts of *L. loa* allow the parasite to develop to the stage most propitious for the propagation of its species, and what injuries, if any, the parasite inflicts on its hosts during the development.

**THE HOST-PARASITE RELATIONSHIP BETWEEN *Loa loa* AND ITS INVERTEBRATE HOSTS.**

In the past it was accepted as fact that all filarial infections found in captured flies belonging to the genus *Chrysops* had been acquired from a human source, and that in West Africa only two very closely allied species of *Chrysops* were concerned in the transmission of loiasis. We now know that both these beliefs were founded on insufficient evidence, that many species of *Chrysops* are concerned in the transmission of loiasis, and that the parasites develop in monkeys as well as in man. It is certain that, in addition to any potential physiological differences in the habitat afforded to the parasite by different species of vertebrate and invertebrate hosts, the habits of the vertebrate and invertebrate hosts must also affect to a greater or lesser extent the host-parasite relationship. In so far as the invertebrate host is concerned, most of the evidence we possess concerning both these aspects is derived from studies of the development of *L. loa* in *Chrysops silacea*; and we shall therefore use this species as our type.

*C. silacea* bites man freely between sunrise and sunset, with its biting peak during the middle of the day, so that, so far as its feeding habits are concerned, it appears to be a good host for the parasite. Although we know that *C. silacea* feeds freely on man and probably on monkey, and although we have reason to believe that it seldom, if ever, attacks birds or reptiles, nevertheless it is possible that in nature, as in laboratory conditions, the fly may feed on a wider variety of hosts, a point which cannot be settled until precipitin tests have been made.

The next stage in the host-parasite relationship is the taking up of the parasite; and here again, although we possess certain facts, the picture we have drawn is mainly conjectural, for we lack the precise information that we have of the taking up of microfilariae by the mosquito. In the case of the mosquito we know that, according to whether the insect indulges in intercapillary or in pool feeding, the microfilariae are ingested either from the lumen of a blood-vessel or from the extravasated blood. In the case of *Simulium* feeding on the onchocerciasis patient, it seems proved that the majority of the microfilariae are taken up during the probing process and are, so to speak, washed down with a "chaser" of blood. In the case of *Chrysops* it seems almost certain that intercapillary feeding is impossible, and that the microfilariae found in the fly are taken up from a blood-pool charged with anticoagulant. This belief is founded mainly on the study of the histology of the bitten area as observed in laboratory animals, studies which we are now endeavouring to supplement by direct observations, by means of a modification of the apparatus used for watching the feeding mosquito. It is possible that the results may modify our opinions, and may explain the remarkable differences observed between the intake of the microfilariae of *Acanthocheilonema perstans* and the intake of *L. loa*. Whatever the result, however, the fact remains that *C. silacea*, when feeding on man, usually takes up a concentration of microfilariae of *L. loa*.
similar to that in the patient's peripheral blood; hence, in respect of the taking up of the parasite, we can again classify *C. silacea* as a good host.

The development of *L. loa* in its host *C. silacea* must next be considered. Our definition stated that the good host allows a suitable proportion of the introduced parasites to reach the stage of development most propitious to the propagation of the species. This definition, of course, implies that, not only must the worms reach the infective stage, but they must be allowed access to the next host, for it is obvious that an infective fly which does not partake of another blood-meal or which deposits its load of infective filariae in an unpropitious host, is no more a good host than is the innkeeper who misdirects his parting guests.

In respect to the first of these two requirements, i.e., that a suitable proportion of the ingested parasites must reach the infective stage, *C. silacea* can be regarded as a most accommodating host, who is prepared to provide food and lodging for an almost unlimited number of guests, for both field and laboratory observations confirm that a very high proportion, quite possibly 80 per cent., of the microfilariae ingested are allowed to reach the infective stage so long as the fly survives the incubation period.

The second requirement— that the infective forms must be allowed access to a new host—implies that the fly must survive beyond the time necessary for the parasite to reach the infective stage, and that it subsequently partakes of another blood-meal on a propitious host. Most of our established facts concerning these aspects of the host-parasite relationship are founded on laboratory observations, and it may well be that the life span and habits of the parasitized fly in nature are very different from those recorded in the laboratory. Let us first consider the laboratory results, which are founded on observations made on large numbers of wild flies and on a limited number of bred flies fed on persons with the microfilariae of *L. loa* in their peripheral circulation. The results may be summarized as follows.

The fly, if not interfered with, feeds to repletion, taking up some 30-50 c.mm. of blood, which passes directly into the midgut; having completed its meal, the gorged fly rests amongst the vegetation available in the cage until such time as the egg mass is laid, usually at the 7th to the 9th day after the full blood-meal. During that period the resting fly generally refuses all offers of a further blood-meal, although on very rare occasions it may feed again, usually just before the egg mass is deposited. Although the fed fly refuses blood, it will, however, at any time avidly take up sugar water, which passes directly into the crop; and we have reasonably good evidence that this food prolongs the life-span of captive flies. Immediately after oviposition the fly is ready to take up a second full blood-meal; and from that point our knowledge ceases, for we have not succeeded in keeping flies alive for more than 17 days under laboratory conditions, and on only one occasion have we observed the deposition of a second egg mass. These results have been compared with those obtained when uninfected flies have been maintained under similar laboratory conditions, and no significant differences have been recorded.

So much for the behaviour of the parasitized fly; the next point to be considered is whether any injury is caused to the fly by the developing filariae and, if such injury does occur, whether it shortens the fly's life or seriously interferes with its activity. In the laboratory we have obtained no statistically significant evidence that even the most intense infections shorten the life-span of the vector. On the other hand, certain observations have given rise to the suggestion, which is now being more fully investigated, that flies which have discharged their load of infective larvae into a fresh host, survive for a shorter period than uninfected flies or parasitized flies which have not yet parted with their filarial infection.
The histological evidence so far available supports the biological observations already mentioned. Workers on loiasis have examined a large amount of material obtained by dissecting and sectioning both naturally infected and laboratory infected flies, the latter including flies infected from monkeys. The work is not yet complete, but it can be stated with some certainty that the paths of migration pursued by the filariae during the course of their development in the fly are not mere indiscriminate tunnellings through the fly’s tissues, but are predestinate, not those of a bus but a tram! All available evidence suggests that the paths pursued are such that the parasite never or, at any rate, very rarely has cause to penetrate an air sac or nervous tissue, the only obvious damage being associated with the invasion of the fat-body, the thoracic muscles and the eye, and the stripping of the membrane at the base of the labium. These laboratory findings on the absence of biological or histological evidence of any obvious damage inflicted on the host by the developing parasite, are very different from those recorded in certain other filarial infections.

In the laboratory conditions just described it is quite certain that *C. silacea* is a good host, indeed one might call it an exceptionally good host; but to what extent does the host-parasite relationship in nature correspond with the artificial conditions we have imposed on the fly during the course of our laboratory investigations? So far as the form of development, the paths of migration, and the lesions produced are concerned, there appear to be no obvious differences between those which occur in naturally infected flies and those which occur in flies infected and kept in the laboratory. We have, however, very little factual knowledge regarding the extent to which the habits and life-span of the parasitized fly differ in nature from what we have observed in the laboratory. In the laboratory the undisturbed fly, once it begins to suck blood, continues its meal until it is completely gorged; in nature we have seen flies similarly completing their blood-meal on both African and European hosts, the victims’ attention not being aroused until the jerk which accompanies the withdrawal of the mouthparts. On the other hand, it would appear that the majority of flies feeding in nature are disturbed by their human hosts before feeding to repletion; and, since similar observations have been recorded with monkeys, it appears that *Chrysops* can be classed with other Tabanidae as an “interrupted feeder.” What happens to these interrupted feeders? Do they immediately renew their attacks, or do they obtain their full meal over a period of perhaps several days? The vast majority of flies captured when coming in to feed have undeveloped ovaries, and a few have undeveloped ovaries and one or more eggs retained from a previous oviposition. These findings suggest that the fly, once it seeks a blood-meal, persists in its search until it has obtained sufficient blood for oviposition, and that, as in laboratory conditions, it seeks no further blood-meal until after oviposition, when it returns for a further supply. On the other hand, the finding of half-grown filariae in flies with undeveloped ovaries suggests that the blood-meal may occasionally be distributed over longer periods. We are now trying to acquire more exact information concerning the amount of blood required for oviposition, the hosts from which it is obtained, and the number of meals usually taken.

Where does the parasitized fly rest during the period of gestation (which corresponds to the development to the infective stages of the filariae), and are the fly’s movements in any way hampered by the developing parasite? Our laboratory observations give little help as regards what may happen in the field, and so far we have almost entirely failed to follow the movements of parasitized flies, in nature. Our knowledge is confined to the visits which the fly pays when, like Van Beneden’s metaphor of the poor relation, it is hungry for a meal.
We know that immediately after obtaining its blood-meal the fly directs its flight towards the nearest high vegetation, and such flies as we have been able to follow have been found resting on twigs or leaves. We do not know whether the flies remain in such sites during the whole period of gestation, or whether, if they do move about, they partake of food other than blood; nor do we know to what extent these movements and the length of life of the flies are, in nature, different in parasitized and in unparasitized Chrysops. We have referred to the fact that in the laboratory the damage sometimes produced by the larvae in the muscles of the thorax and in the eye do not appear to affect the life of the fly; it by no means follows that this is so in nature. In the laboratory the fly has no need to seek its food; but in nature it is possible that the parasitized fly is at a disadvantage, and that its chances of survival and length of life are shortened.

Clearly all these points concerning the host-parasite relationship require investigation; but, whatever the results may be, it is unlikely to alter the broad principle that up to this point Chrysops must be regarded as an exceptionally good host for L. loa. Before we pass the final verdict, however, one last stage must be considered: the guests are, so to speak, gathered in the hall; it remains for the host to speed them on their new journey, when host and parasite must part at the next blood-meal. In the case of mosquito-transmitted filariasis, the infective forms escape from the labium by penetrating Dutton's membrane; but in the case of Chrysops the filariae almost certainly escape from the head at the base of the labium, after which they can be seen with the naked eye, like minute eels, writhing down the relatively massive pillar of the fascicle. As in mosquito-borne infections, the filariae which fail to enter the bore-hole made by the proboscis perish rapidly, though direct observations and the examination of sections cut from the bitten area produce convincing evidence that at any rate a considerable number of escaping forms succeed in reaching the deeper tissues of their new host.

C. silacea is indeed a good host to L. loa; and if, as has been suggested, its life is cut short as a result of thus speeding its parting guests, the final assessment remains unaltered.

THE HOST-PARASITE RELATIONSHIP BETWEEN L. loa AND ITS VERTEBRATE HOSTS

To what extent does man, as a vertebrate host of L. loa qualify as a good host under our definition of "one which allows a suitable proportion of the ingested parasites to reach a stage most propitious to the propagation of the species (in this case, the microfilariae, in the peripheral circulation) while not seriously interfering with the normal life of the host"? I think we can give an immediate, if modified, answer to the first half of the question by saying that a proportion of the population exposed to the infective forms of L. loa are bad hosts, in that, although constantly exposed to infection, they fail to allow microfilariae to appear in their blood at any time. It may be argued that this failure is due to the development of immunity, for clearly it would be absurd to say that man is a bad host for Salmonella typhi if the statement were based only on the examination of recovered typhoid patients. We have, however, some more convincing evidence, acquired from a limited number of individuals who have been under close observation from the time of their first exposure to infection with L. loa. Members of the European staff of the Helminthiasis Research Scheme who have been working in the British Cameroons for a prolonged period have all shown the presence of microfilariae of A. perstans in their peripheral blood in a fairly high con-
centration, at any rate for some time; and, since these individuals show no observable ill effects from the presence of the adult worms and their larvae, we can regard them as good vertebrate hosts for this species of filariae. Now, these persons have been similarly exposed to infection with *L. loa*, but with very different results. One of them shows the presence of large numbers of microfilariae of *L. loa* in every 50 c.mm. of his peripheral blood, and adult worms have frequently been seen below the skin and conjunctiva; but at no time has he suffered any such obvious ill effects as Calabar swellings. This individual must therefore be considered as a good host for *L. loa*. A second member of the team has repeatedly shown the presence of adult *L. loa* beneath the skin and conjunctiva, and one removed female worm was found to have the uterus full of active microfilariae. This individual has now been treated, and both before and after treatment has suffered from Calabar swellings, accompanied by a persistent high eosinophilia. A third member of the team has been in the Cameroons, with intermissions for leave, since 1948; for the past six years he has suffered from severe, and sometimes incapacitating, Calabar swellings accompanied by a high eosinophilia; yet, in spite of long-continued blood examinations, no microfilariae have ever been seen in his blood, and adult worms have not been recorded. These two members of the team must consequently be regarded as bad hosts for *L. loa*. So much for the European members of the team who have been kept under more or less constant observations from the time of their first exposure to infection. There are also many well-authenticated instances of both Europeans and Africans, similarly kept under observation since their arrival in the endemic area, in whose blood microfilariae have either not been observed or have been observed in numbers so scanty as to render them unlikely reservoirs from which *Chrysops* could take up the infection.

You will observe that, in the limited number of instances I have quoted, the individuals concerned have at no time acted as good hosts, that is to say, they are naturally bad hosts, or, as the zoologists would put it, ill-adapted hosts; and it seems essential to distinguish such individuals from those who at first act as good hosts and allow the development of microfilariae, but later develop resistance which either prevents the development of *L. loa* to the adult form or allows the development but suppresses the appearance of microfilariae in the peripheral blood. We know that only a small proportion of the population of the Cameroons, who are constantly exposed to infection, allow the microfilariae to appear in their peripheral blood in numbers sufficient to carry on the infection, and we know that a proportion of such persons have always possessed this power of resistance, i.e., that they are bad hosts, in the zoological sense of ill-adapted hosts. It has recently been shown that whereas only some 25 per cent. of the indigenous population examined in the Cameroons show the presence of one or more microfilariae of *L. loa* in every 50 c.mm. of their peripheral blood; this figure can be increased to 45-50 per cent. if the concentrate from some 5-10 c.c. of their blood is examined. It seems probable that the examination of still larger amounts would raise the percentages of positives still higher, and that it would be found that the vast majority of the population harbour microfilariae in their peripheral circulation but that only a relatively small proportion of these people harbour them in numbers sufficient to render infection of the vector likely. The question at once arises whether all these persons who partially or completely suppress the appearance of microfilariae are naturally ill-adapted hosts, or whether the suppression is due in some instances to acquired immunity. If we are to understand the host-parasite relationship in loiasis properly, it seems essential to seek an answer to these two questions.
At the present time we have insufficient knowledge to answer them, but we have reason to believe that the naturally ill-adapted host may increase his resistance as a result of repeated invasion by the infective forms of *L. loa*, and that the originally susceptible human host may develop resistance which either destroys the adult form or interferes with its reproductive cycle. This conjecture, and it is little more than a conjecture, is based on the fact that there is a falling off in the concentration of the microfilariae in the peripheral blood in the older age-groups of the indigenous population, and that a similar falling-off has been observed in Europeans who have been kept under observation while working for long periods in intensely infected areas.

If man is a badly adapted host for *L. loa*, does a better host exist? Again, we can give no definite answer. We know that *C. silacea* acts as a good host to both the human and the monkey strains of *L. loa*, in so far as the development of the parasite to the infective form is concerned. We also know that it transmits the monkey strain from monkey to monkey, and the human strain to the monkey, though we have as yet no evidence whether or not it transmits the monkey strain to man. In addition, we are in possession of certain facts which we regard as strong presumptive evidence that the monkey is a better vertebrate host than man. During the past three years the Helminthiasis Research Scheme at Kumba has employed native hunters to capture or kill monkeys, and of every animal taken the skin and skull have been preserved for identification, the whole carcass has been examined for the presence of filariae, and the blood has been examined for the presence of microfilariae. The examination of the material obtained at autopsies is not yet complete, but amongst the first 200 monkeys examined there were 14 short-tailed drills (*Mandrillus leucophaeus*), of which 11 harboured adult *L. loa*, and in all these animals microfilariae were found in every 50 c.mm. of blood taken from the deep vessels. Of course, it is by no means certain that the examination of the peripheral blood of these animals would have revealed a similar high association between the presence of adult worms and the occurrence of microfilariae in the blood. Finally, in only one instance (the occurrence of a single Calabar swelling in a drill) have any ill effects been observed in captive monkeys infected in nature, or in the laboratory with human or simian strains of *Loa*; nor have pathological lesions attributable to the presence of *L. loa* been observed at autopsies made on shot monkeys.

**SUMMARIZATION OF OUR KNOWLEDGE OF THE HOST-PARASITE RELATIONSHIP IN LOIASIS**

I began my address by saying that I proposed to consider the facts and conjectures regarding the host-parasite relationship in filariasis, with special reference to loiasis. May I now try to summarize these facts and conjectures, in order to substantiate my original statement that, in so far as the host-parasite relationship in loiasis is concerned, our knowledge is in much the same state as that concerning malaria when Manson’s book appeared in 1898. The facts would appear to be that *C. silacea*, when observed under laboratory conditions, is an almost ideal host for the developmental stage of *L. loa*, and that strong presumptive evidence exists that it is similarly so in nature. It has been proved that a proportion of human beings are naturally ill-adapted hosts, and there is good presumptive evidence that a proportion of human beings can acquire some degree of resistance or immunity, which results in preventing the appearance of microfilariae in the peripheral blood in sufficient numbers for the propagation of the species. Finally we have evidence which suggests that the fly
*Chrysops* and certain species of monkeys are both good hosts for *L. loa* and we conjecture that this association represents the normal and well-established cycle of development, whereas the cycle of the human strain of *L. loa*, although well established in the fly, is badly established in man.

I have dealt with one species of filaria, *L. loa*, with one species of its vectors, *C. silacea*, and with its two known vertebrate hosts, man and monkey; and I have tried to indicate the extent of our factual knowledge concerning their host-parasite relationship and the extent and nature of the gaps in our knowledge. I have made no reference to other and more important species of filariae which parasitize man, but I have no doubt that a similar analysis would show a similar dearth of factual knowledge, coupled with a vast amount of conjecture.

**THE NEED FOR FURTHER RESEARCH IN FILARIASIS**

If my summarization of our existing knowledge of the host-parasite relationship in filariasis is not a gross underestimate, then you will agree that it is very scanty in comparison with our knowledge of the same subject in other arthropod-borne infections. Does that really matter however? How much truth is there in our previous contention that a proper understanding of the symptomatology, diagnosis and treatment of filariasis is dependent on such knowledge, and that without it great difficulties will arise both when planning control measures and when subsequently judging their effects? Let us consider these points in sequence.

As regards symptomatology, is it sensible to enter into discussion of the signs and symptoms of filariasis when we know so little about the parasite from the time when it disappears beneath the surface of the skin until, some nine months later, it announces its survival by the production of microfilariae? What value could be attached to conjectures regarding the signs and symptoms of ancylostomiasis if we had no knowledge of the life-cycle habits and wanderings of the parasitic larvae and adults?

With regard to diagnosis, it appears that the only generally available method of establishing a diagnosis of filariasis is by the finding of the microfilariae, many months after the acquirement of infection. This belated method has the added disadvantage that, according to the available evidence, it is the very persons who suffer most severely from filariasis who are least likely to show the presence of microfilariae. At one time it was thought that — in loiasis, at any rate — the disappearance of the microfilariae was indicative of the death of the adult worms: but this generalization is misleading, and it appears unlikely that better methods of diagnosis will be evolved until we have a clearer understanding of the host-parasite relationship which is responsible for suppressing the larvae while still allowing the adult worms to survive.

As regards treatment, it seems reasonable to believe that what has been said about symptomatology and diagnosis applies also to treatment, for how can the efficacy of any form of therapy be estimated when there exists no certain means of deciding (except after a waiting-period of weeks or months) whether the adult worms have or have not survived? We know that, even when the adult worms have been destroyed, the manifestations of filariasis may persist. How can we prescribe relief for these persistent signs and symptoms when we are
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My colleagues are now considering whether the ill effects encountered in loiasis can be explained on the hypothesis that they result from a previous sensitization of the patient to the worm or its products, and whether, if this proves to be the case, desensitization can usefully be employed. At present this is a mere speculation, and even if it proves true in loiasis the explanation may not be applicable to other forms of filariasis.

It is when we come to the planning of control measures against filariasis, and later seek to estimate the success or failure of such plans, that the necessity for further knowledge of host-parasite relationship becomes most evident. How can we confidently plan control measures directed against any particular form of filariasis while we lack knowledge of the presence or absence of an animal reservoir? At the present time, plans for the control of onchocerciasis and wuchereriasis are based on the assumption that there is no animal reservoir for either infection. Until very recently a similar view was held regarding loiasis but we now know that that assumption was false. May it not also be false in the case of wuchereriasis and onchocerciasis?

Quite apart, however, from whether there are, or are not, animal reservoirs for human infections, there remains the problem of whether those species of vectors that are responsible for transmitting filariasis to man are in nature also found infected with other species of filariae. It is remarkable that most experienced workers on filariasis, while recognizing the fallacy of interpreting the extent of parasitization in the human population by the results of examining the peripheral blood for microfilariae, nevertheless are prepared to deduce the risk of infection from a previous survey of the numbers and infection rate found in the vectors coming to bite man. But what good evidence, morphological or biological, have we that all the forms encountered in these vector surveys are developmental stages of a species capable of infecting man? Already there is evidence that some insect vectors of wuchereriasis and onchocerciasis are capable of infection in the laboratory with species of filaria which cannot develop in man. It remains to be seen if a similar state of affairs occurs in nature.

Even if satisfactory answers are found to these questions regarding the presence or absence of animal reservoirs of infection, and the identity of the filariae found in the insect vector, there still remains the problem of estimating the extent of control necessary to protect the human population from serious ill effects. When planning measures for the control of filariasis what should be our Plimsoll Line? Should it be similar to that generally accepted for the control of protozoal diseases such as malaria? In malaria the number of sporozoites inoculated is immaterial, provided that infection results. Nor does it matter whether the person exposed receives an infective bite once a day or once a week; the result is the same, because the individual parasite is capable of reproducing itself, until saturation of the vertebrate host has been reached. In filariasis, however, the situation is different: the parasite, although it can produce microfilariae cannot reproduce itself, and each infective form introduced by the vector can result in the production of only one adult, male or female. Recent work by one of my colleagues has shown that in onchocerciasis the host-parasite relationship is seriously interfered with only after long-continued series of infective bites have been received by the human host. It appears possible, although it can by no means be regarded as proved, that in onchocerciasis even a small reduction in the infective density of the vector may lead to a reduction in the incidence of blindness, or even to its complete elimination. If further research confirms this opinion, methods for the control of onchocerciasis may have to be planned on a new basis. Until we have settled these questions, all of which are directly or indirectly concerned with the host-parasite relationship, what reliance
can we place on deductions drawn from previous surveys, or how can we plan future surveys to be undertaken both before and after the instigation of control measures?

It is to be hoped that no one will interpret these remarks as in any way belittling the value of the recent advances which have been made in our knowledge of filariasis. The very reverse is the case, and I know that, so far as my own colleagues are concerned, they will agree with me when I say that the most valuable amongst their many contributions has been their exposure of certain previous misconceptions, because they have thereby opened up new lines of research.

It would be equally wrong to suppose that anything which I have said tonight implies that I believe efforts to control filariasis will be of little value until we have acquired more knowledge, or that we should withhold aid from those vast commercial schemes already referred to which are now envisaged in the tropics. Nothing could be farther from the truth. In war, the statesmen of an ill-prepared country send what aid they can to the point of attack; they do so to avoid immediate disaster, but for final victory they rely on long-sustained study of the enemy’s strength and weakness, and on never-failing attention to the improvement of their own weapons of offence and defence. I sincerely believe that a similar policy is the one most likely to bring us success in a campaign directed against filariasis.