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FILARIASIS

IN ASSOCIATION WITH INFECTION OF *FILARIA BANCROFTI* *

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The great prevalence of *filariasis* in your country is sufficient reason for my choosing this infection as the subject of my address this evening. But since so much work has been done in connection with the infection, while there are still many problems confronting us, it will not be possible to discuss the whole subject in one lecture. I consider it wiser to limit myself to those particular aspects of filarial infection which I find are at the present time of special interest to the clinicians and laboratory workers on this Island.

It will be well, therefore, for us to consider briefly: I. The microfilariæ in the human body and in the mosquito as well as the clinical phenomena associated with filarial infection in man. II. Certain aspects of infection concerning which we have as yet no definite knowledge. III. Some suggestions that may help in further studies of the infection.

I

In many tropical and subtropical countries microfilariæ of the species *Filaria bancrofti* are found in human blood. The microfilariæ are small embryonic worms measuring about 260m × 7.5–8m which are contained in a membranous sheath. Within this sheath, which they do not completely fill, the small worms wriggle actively. The anterior end of these embryos is rounded while the tail tapers. The cuticle of the parasite is transversely striated. Within the cuticle, in specimens stained with haematoxyline or the Ramonowsky dyes, one can observe a column of nuclei which indicates the preintestinal cells, and this column which approaches nearly to the anterior end, while posteriorly it does not quite reach the tail, is broken at two definite points by clear spaces which are

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called respectively the anterior and posterior V spots. These spots and certain definite cells related to them are actively concerned in the further development of the worm outside the human host. In addition, by using certain stains an internal viscus or "Innenkörper" can be demonstrated. As far as we know no further development of the microfilariæ takes place within the body of man. In some cases, microfilariæ, though absent from peripheral blood may be found in other situations, *e. g.*, in hydrocele fluid or in cystic conditions connected with lymphatic glands, or with the mammary gland, and under these circumstances the patient will often give a history of past attacks of lymphangitis in the parts of the body infected. In certain countries, British Guiana, United States, West Indies, Indies, Southern China. etc., in the northern hemisphere and New Guinea, Australia and other mandated islands of Australia, etc., in the southern hemisphere, the microfilariæ in the blood exhibit a nocturnal periodicity which seems to bear more relation to the hours of sleep than to the hours of darkness. In the large groups of islands extending from the Philippines in the north through the Polynesian groups and to the Solomons, the microfilariæ usually exhibit no such periodicity in the human blood. The most competent helminthologists have hitherto been unable to find morphological differences between the periodic and non-periodic microfilariæ or their parent worms.

Transmission of the parasite from man to man takes place through the agency of mosquitoes, of which many species have now been found to act as suitable insect hosts. Two species are specially notorious in this respect. In parts of the Pacific and especially in the Polynesian groups of islands *Aedes variegatus* is the vector of the non-periodic microfilaria. While in those countries where periodicity of the microfilaria is the rule *Culex fatigans* is most frequently the responsible agent.

In Porto Rico the latter insect has long been suspected of transmitting the microfilaria of *Filaria bancrofti.* On my arrival here, Dr. W. A. Hoffman informed me of the high incidence of microfilariæ which he found in the blood of boys at one of the schools. He and I collected 45 *Culex fatigans* from the boys' dormitory at this school and on dissecting these I found developed larvæ in the heads of three of the mosquitoes, while in another I found half-grown forms in the thorax. This gives a percentage of 8.9 infected. The developed worms found in *Culex fatigans* here differ in no respect that I could determine from those found in *Aedes*

variegatus which I had fed on patients harboring the non-periodic microfilariæ in Samoa.

When a suitable insect ingests human blood containing microfilariæ, the parasites, soon after reaching the insect's stomach, become liberated from their sheaths, and piercing the wall of the viscus, become free in the body cavity. Within 48 hours most of the parasites reach the muscles of the thorax between which they lie, and having become sluggish, they begin to grow in breadth without at first growing in length. Development takes place in the region of the anterior and posterior V spots of the worm and the alimentary canal becomes formed; but no differentiation into sexes has been observed during this phase. Towards the end of the period of development in the mosquito, the parasite increases considerably in length and becomes very active. It finally approaches the head and enters the proboscis. If examined at this time it will be found that the alimentary canal is fully developed, and at the posterior end of the worm there are present small tubercles, the function of which is not definitely determined, but which may possibly be used as a fulcrum and play some part in assisting the parasite to enter the skin of man. When an infected mosquito bites man the parasites reach the skin. They are not injected by the bite of the mosquito but they enter the skin independently and apparently by their own efforts in the vicinity of the wound. The duration of mosquito phase of the parasite shows variation in different countries. In some it takes from 18–21 days. In Samoa it was completed in 9–13 days. This phase of development is also apparently affected by seasonal conditions.

Phenomena of Filarial Infection in Man.

These may be primarily manifested in one of two ways:

1. By the presence of microfilariæ in the blood.
2. By the onset of acute or subacute symptoms of a more or less definite character.

1. In countries in which filariasis is endemic and especially when the incidence of infection is high, microfilariæ may be found in the blood of persons from the age of four onwards, but it is not commonly found until the age of 7–10. Frequently the presence of microfilariæ in the blood is in no way associated with symptoms, and it may be noticed on the other hand, after symptoms have begun to develop, that microfilariæ may tend to disappear from the blood.

2. It has been observed amongst European visitors to endemic centers of filariasis that within four to six months after arrival, adenitis which may be acute or subacute sometimes develops in the glands of the groin or epitroclear region. These symptoms are frequently mild and may not be associated with noticeable constitutional disturbances. In other cases definite attacks of lymphangitis of one or more limbs may begin and recur at different periods after a few months' residence in such an area. In the early stages of these attacks microfilariæ are generally absent from the blood.

In a country where filariasis is very prevalent the sequence of phenomena is generally as follows: The highest microfilarial incidence is present amongst persons from the ages of ten to thirty. Above the age of sixteen symptoms of lymphangitis, hydrocele, etc., become common, with or without microfilariæ in the blood. With the recurrence of lymphangitis other clinical manifestations such as lymph-scrotum, abscess, chyluria, varicose glands, cystic disease and elephantiasis, etc., become more prevalent, and it is frequently observed that in cases with these severe complications microfilariæ may be absent from the blood. On the other hand, severe symptoms may occur at an early age and microfilariæ may persist in the blood of some cases, but such cases will be discussed later.

The clinical conditions associated with filarial infection may be divided for convenience into (1) Inflammatory and (2) Obstructive.

Inflammatory.

Lymphangitis and adenitis. The lymphangitis may be erysipelatoid in severe cases and in still others may resemble true cellulitis.
Filarial fever
Orchitis and epididymitis
Hydrocele.

Obstructive.

Lymphatic varix
Varicose glands of the groin and elsewhere
Chyluria and chylous conditions of the peritoneum and tunica vaginalis
Lymphatic fistula, and
Elephantiasis of limbs, appendages or limited areas of skin.

Rarer conditions have also been described, such as arthritis and synovitis, gangrene, chylous diarrhea and haemoptysis and temporary swellings, etc. Time does not permit a detailed discussion of these conditions, concerning which, however, ample information may be derived from text books and monographs. I shall therefore limit

myself to some remarks regarding the lymphangitis and elephantiasis, in this and other countries that I have visited, with special relation to the association of clinical signs with the filarial worm.

Filarial Lymphangitis.

The usual history of the patient is that the attacks begin with a chill followed by fever which lasts from a few hours to several days, and which generally ends by sweating. After the onset of the chill red lines appear on the skin along the course of the lymphatics which may often be felt as thickened cords; and then a part of the limb or the whole limb becomes red and swollen. The attacks usually last from three to five days, when the fever abates and disappears. The inflamed condition of the limb lasts one or two days longer. In my Polynesian cases I noticed on inquiry, even without leading questions, that the patient almost always pointed to one spot in the affected area where pain began even before the chill commenced. In the lower limb, for instance, the area indicated was either in the sole of the foot close to the internal or external maleolus, in the calf of the leg, along the line of Hunter's canal, along the course of the superficial femoral vessels, or over one or other of the superficial inguinal glands. In each case examined the patient stated that the pain which preceded the chill always occurred in the same area; further, in those cases subject to lymphangitis who were temporarily relieved of these attacks on return to a cold climate (London or New York) the patients stated that at periods they were conscious of a sensation at the point of the limb where the attacks started when in their own country, although under the changed conditions no such attacks developed. I have been very interested, while observing more than sixty cases with my colleagues in this country, to find that in almost every instance the patient indicated such a definite locality in the limb as being the starting point of his or her filarial attacks, the areas indicated being in order of frequency, in the neighborhood of the ankle joint, the sole of the foot, or one of the superficial inguinal glands.

As in Polynesia, we have been able to observe here that the attacks of lymphangitis show a periodicity for each individual. The usual history is that the attacks occur once a month, but in many cases they occur once a fortnight or more frequently and sometimes patients have attacks only twice a year. Occasionally a patient will state that he sometimes misses an attack. It has also been noticed that patients who suffer from attacks of lymphangitis in both legs will describe those in one leg as occurring once a fortnight,

while in the other leg they may occur once a month, etc. And yet in other cases with recurring lymphangitis of both legs there is a history of alternating attacks in each limb.

Patients are equally definite in their statements as to the duration of the attack, answering without hesitation when interrogated on this point that the condition lasts three days, four days, five, six, or seven days, but each patient finds his or her attacks fairly constant in duration.

Very few patients describe erysipelatoid attacks or attacks resembling cellulitis as being frequent, but they may remember one or more such as occurring during some of the recurrences. These attacks generally last longer than the ordinary ones and the description of each suggests septic complications; the same may be said of abscess; while it may appear as the first evidence of infection, it more commonly develops in the course of one of the recurrences. And it should be noted that though abscess may sometimes be followed by cessation of attacks of lymphangitis, thus suggesting the death of the worm, nevertheless this is not invariably or even most commonly the case. I have seen many cases where patients point to the region of an old abscess scar to indicate the region where subsequent attacks of lymphangitis have continued to occur.

There is considerable variation in the severity of the local and constitutional symptoms in attacks of lymphangitis in countries where filariasis is endemic. In the majority of cases when the attack is well established there is marked swelling, redness and tenderness with severe pain in the limb. The temperature is high and there is headache, nausea, vomiting and a feeling of acute illness. In many cases, however, even with severe local symptoms the constitutional disturbance may be slight or transient. In others there may be only a slight local reaction and the patient may be only conscious of the pain. In each case one notices that the severity of the disease remains fairly constant for each individual except when occasional attacks of those severer complications, erysipilus, cellulitis or abscess intervene during one or more of the recurrences. Some patients may have frequent recurrent attacks of filariasis for many years without developing elephantiasis.

Elephantiasis is most frequently a later manifestation of filariasis, the only essential difference between the attacks of lymphangitis and elephantiasis being that in the latter the affected part does not regain the normal size, and, on the other hand, may continue to increase in size after each new recurrence. It generally develops

after a succession of attacks of lymphangitis and it is usually observed in persons who have passed the adolescent period. But this is by no means invariably the case. In Samoa I saw elephantiasis of the leg in a girl of fourteen. In Porto Rico I have seen two cases of unilateral elephantiasis of the leg in boys of ten and fourteen respectively, and cases may occur from these ages onwards. Although elephantiasis may begin with the very first attack of lymphangitis, in most cases a few recurrences of lymphangitis precede the permanent enlargement.

Elephantiasis may develop in the absence of any constitutional disturbance which is noticeable to the patient, and without any signs in the affected area other than enlargement. In Samoa in one white man there was elephantiasis of both legs, both arms and scrotum, yet this patient had never had pain or redness of the limbs nor had he ever felt feverish. About once a month he noticed painless enlargement of limbs and scrotum. I have seen two cases in Porto Rico with elephantiasis of the leg which gave similar histories.

II

Notwithstanding all the work that has been done on this subject, there are few tropical diseases regarding which there are so many gaps in our knowledge, and as you are especially well situated, in view of abundance of material, skilled workers, and adequate equipment, for investigation of this subject, it may be well to discuss some of the many problems which still confront us.

Although the microfilaria is frequently found in the blood, the method of its access to the blood stream is not certain. In some cases the adult filaria has been found in the thoracic duct with or without microfilaria. In other cases microfilariæ have been present in the blood during life, but on post mortem no parasites have been found in the thoracic duct. In such cases some other means of entry of the microfilariæ to the general circulation may be discovered. We are ignorant as to the longevity of the microfilariæ in the human body; as to how and where they die and how they are eliminated or absorbed. Attention has recently been drawn to the fact that nephritis is common in people with microfilariæ in the blood in some countries. It might be well to study the urines of a large number of cases with microfilariæ in the blood, and to inquire into possible damage to the kidneys by microfilariæ or the toxins of adult worms. Manson showed that during the day the periodic microfilariæ mi-

grated to the lungs and other deeper organs. It would be well to study the degree of their attraction to the kidneys.

It is presumed that the microfilariæ do not develop in the human body. When present in hydrocele fluid and in cystic conditions microfilariæ are often found which have already cast their sheaths. Inquiry might be made to see if such sheathless forms are capable of any, even partial, development in the human body.

In hydrocele in the Polynesian Islands microfilariæ are not infrequently found and sometimes occur, as in the specimen I have shown you, in enormous numbers. In specimens of hydrocele fluid examined after centrifugalization from fourteen cases of hydrocele taken during the day in Porto Rico, I failed to find microfilariæ. As the microfilariæ in this country shows a nocturnal periodicity in the blood, it might be well to examine hydrocele fluid taken from cases at night in case the parasites, if present, show any tendency to migrate to the deeper tissues of the scrotum and inguinal canal during the day.

Mosquito Phase of the Parasite.

More light is required on the selection by the parasite of its arthropod host. It develops easily in some species of mosquito and not at all in others, but even more remarkable is the fact that it undergoes partial development in some mosquitoes and then dies. We do not know the function of the papillæ at the posterior end of the larvæ at the end of development in the insect host. The question of the method of the parasite's exit from the mosquito to the skin of man is again raised by the research work of the Japanese who describe its emergence from the tip of the labella. Low, has shown that the larvæ enter the proboscis in pairs. In one of my Porto Rican mosquitoes there was a single parasite in the proboscis and two in the head. It is important to ascertain if, when at least two larvæ are present in the head of the mosquito, they are liberated from the proboscis in pairs, and if, as is suggested, this is concerned with subsequent pairing of the sexes. The time that the parasite requires for development in *Culex fatigans* in Porto Rico must be worked out at different seasons, and also the possibility of other possible carriers of the microfilariæ of man in this Island. We as yet know nothing about the causes of periodicity. Several interesting theories have been advanced, but nothing has been proven. If the filaria of this country and that of Polynesia are of the same species, it is remarkable that the microfilariæ of one should show a nightly periodicity while the other shows no periodicity whatever.

The Filaria in Man.

A veil covers the subsequent development of the filaria larva after it enters man and we wish to know when sexual differentiation occurs and when sexual maturity is reached. Analogy with other worms strongly suggests the existence of a toxin formed by the filariæ. The early onset of symptoms of a nature suggesting local toxaemia suggests that this toxin may be formed soon after the parasite enters man. What are the actual factors concerned in the death of the adult in the human body? Is there a definite period to the adult worm's life in the human host? Further work is required on the migrations of the adult in the definitive host.

III

The Relationship Between the Filarial Worm and the Clinical Manifestation of Filariasis Including Elephantiasis.

Some medical men question the relationship between the presence of the filarial worm in man and the clinical phenomena described as filarial, and base their objections to the validity of such a relationship principally on the facts that cases with filarial symptoms often have no microfilariæ in the blood, and further that in cases of lymphangitis as well as in other infections in countries where filariasis is endemic that bacteria and especially streptococci have frequently been found in cultures made from fluids drawn from the inflamed tissues during the acute attacks. In the first place I also believe that in those severe cases resembling erysipelas, cellulitis and often in cases of abscess, that secondary infection by the pathogenic bacteria are responsible for the severity of the cases. On the other hand, there is good evidence for believing that in most cases of clinical filariasis and elephantiasis the causative agent is the filarial worm, by means of its toxins. Epidemiological evidence strongly supports the relationship between the worm and filarial disease. But we shall at present confine ourselves to a consideration of the clinical phenomena themselves.

(1) When a patient begins to have clinical filariasis, all further attacks usually occur in the same limb and the same part of the limb.

(2) Each recurrence usually shows a remarkable similarity as regards period, duration, and intensity of the local and constitutional signs.

(3) In many patients the severity of the local symptoms is out of all proportion to the mildness of the constitutional disturbance.

(4) Examination of cultures of lymph from inflamed tissues in

many cases has failed to reveal pathogenic bacteria, and frequently the cultures have been sterile.

(5) The onset of elephantiasis usually (though not always) is insidious and with the exception of the enlargement shows the same tendency to periodicity of recurrence, duration of attack, and nature of local inflammation. and general illness.

(6) Elephantiasis may develop with periodic enlargements without any noticeable constitutional symptoms whatever.

(7) Elephantiasis may develop without any local signs of inflammation.

(8) The adult worm, alive or dead, has been found in filarial abscess, and several reports are on record of the pus of such abscesses being sterile, although this is not always the case.

(9) In some cases of elephantiasis the opening of a lymphatic fistula has been followed by a cessation of the elephantoid attacks, which have recommenced when the fistula closed.

(10) Even in the absence of microfilariæ in the blood, patients suffering from filariasis symptoms who have been examined before the filarial attacks started remembered having seen or been informed that they had had microfilariæ in their blood previous to the onset of symptoms. I have seen two such cases here in Porto Rico. I saw many in Polynesia.

(11) The duration and nature of the filarial attacks in different individuals strongly suggests a local toxic disturbance.

While in the present state of our ignorance of this infection, it would be most unwise to dogmatize regarding either the causation of either filarial symptoms or elephantiasis, I may make some suggestions regarding the sequence of filarial phenomena in man, my object being only to suggest a line of investigation which you are in an admirable position to study.

As we have evidence that the adult filaria worm is capable of migrations (based on the remote situations from the possible points of infection where the worm may be found, as well as on analogy with other species, *e. g., Loa Loa*) I feel that it is possible for the female during her wanderings in the human tissues to come into relation directly with the capillaries or smaller vessels, and to discharge therein her microfilariæ and toxins—that if this is the case and while it is so, the microfilariæ appear in the blood and the toxins, diluted in the great quantity of blood in the body, are eliminated through the kidneys or elsewhere without obvious hurt to the human host. That subsequently, either by migration or by

being shut off by inflammation due to local injury, etc., from the capillaries, the adult comes to lie in the connective tissues where at periods she will continue to discharge her embryos and toxins into a more confined space from which they cannot easily be eliminated. This might explain the disappearance of microfilariæ from the blood, and the onset of symptoms produced by concentration of toxins in limited areas, as well as the enlargement of lymphatic glands even when adult filariæ are not present in the glands themselves. It would further explain those cases in which. amongst others, new residents show signs of filariasis without ever having had microfilariæ in the blood, and it would also explain cases in which persons have been known to harbor microfilariæ for a considerable number of years without having experienced any clinical symptoms of filariasis. In the course of time by a recurrence of attacks of inflammation followed by fibrosis, sufficient obstruction to the whole or greater part of the lymphatic system of the limb may take place and occasion the condition known as elephantiasis. Or elephantiasis might be caused or accelerated by "hyperfilaration" due to frequent reinfection with a large number of new filariæ. The presence of microfilariæ in cases showing filarial symptoms might possibly be explained by the presence of independent parent female worms other than those causing symptoms, which may have access as in the first instance to the general circulation. If the foregoing surmise is correct it may have a very important bearing on treatment. Finally I shall repeat that I consider in the majority of cases in which marked inflammatory complications develop during one or more of the recurrent attacks that secondary bacterial invasion is probably responsible for the severity of the condition.

Treatment.

This has hitherto been most unsatisfactory, for while local treatment may help to modify the severity of any individual attack of lymphangitis or elephantiasis, all our efforts to prevent recurrences have been unavailing. Numerous drugs have been tried, including tartar emetic, stibenyl, quinine, preparations of salvarsan, emetin, various collosols, etc., etc., but though many of these have been given intravenously as well as intramuscularly and subcutaneously, the results have not been encouraging. By rest in bed preliminary to treatment in some cases, clinical symptoms have improved or have been temporarily absent, and this fact should be taken into account before determining the results of any kind of treatment.

In view of what has been said, I feel that the following suggestions for further studies in treatment might be considered:

(1) Since the clinical condition suggests a localized position of the adult filariæ in the affected limb or area, I believe that subcutaneous or deep injections of drugs might be undertaken immediately below those areas where attacks of lymphangitis are known to begin, and if those areas are not clearly defined, then the injections might be made well below the inflammatory area. Treatment should be undertaken preferably during the absence of attacks. It is possible that tartar emetic which has failed to effect a cure when given intravenously might be more efficacious if given as suggested, and the other drugs which have failed by the intravenous route might also be tried.

(2) In cases where local symptoms definitely suggest the position of the filarial worm. I am inclined to believe that careful exploration by the surgeon in well selected cases might give promissing results. While much dissection might be necessary in some cases, the operation if conducted with proper aseptic precautions could be performed with a minimum of risk.

It has been noted frequently that patients who are subject to filarial lymphangitis and elephantiasis frequently improve and that sometimes the recurrences cease entirely after their return to a cold climate. One case in this Island at present reports that her frequent attacks of lymphangitis ceased during nine months' residence at an altitude of 2,000 feet in the Island. In practice I have found that cold applications give more relief during attacks than other forms of treatment and that sometimes combined with rest they tend to cut short the fever and inflammation. It might be well therefore to study the effects of cold therapy in the distressing conditions included under the name of filariasis.