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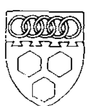

FILARIASIS

A Wiley – Interscience Publication

1987

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FILARIASIS

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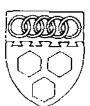

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Participants

D. B. Copeman Graduate School of Tropical Veterinary Science, James Cook University, Townsville, North Queensland, Australia 4811

D. A. Denham London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK

S. Dissanayake Department of Biochemistry, Faculty of Medicine, University of Peradeniya, Peradeniya, Sri Lanka

A. Ewert Department of Microbiology, The University of Texas Medical Branch at Galveston, Galveston, Texas 77550-2782, USA

K. Forsyth Papua New Guinea Institute of Medical Research, PO Box 387, Madang, Papua New Guinea

B. M. Greene Division of Geographic Medicine, Department of Medicine, Case Western Reserve University School of Medicine, University Hospitals, Cleveland, Ohio 44106, USA

B. C. Harinath Department of Biochemistry, Mahatma Gandhi Institute of Medical Sciences, Sevagram, Maharashtra, India 442102

R. E. Howells Department of Parasitology, Liverpool School of Tropical Medicine, Pembroke Place, Liverpool L3 5QA, UK

R. Hussain Department of Microbiology, Aga Khan Hospital and Medical College, Stadium Road, PO Box 3500, Karachi 5, Pakistan

M. M. Ismail Department of Parasitology, Faculty of Medicine, University of Colombo, Kynsey Road, Colombo 8, Sri Lanka

J. J. Jaffe Department of Pharmacology, University of Vermont, College of Medicine, Given Building, Burlington, Vermont 05405, USA

T. R. Klei Department of Veterinary Microbiology and Parasitology, School of Veterinary Medicine, Louisiana State University, Baton Rouge, Louisiana 70803-8416, USA

C. D. Mackenzie Wolfson Tropical Pathology Unit, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK

R. M. Maizels Department of Pure and Applied Biology, Imperial College of Science and Technology, Prince Consort Road, London SW7 2BB, UK

J. W. Mak Institute for Medical Research, Jalan Pahang, 50588 Kuala Lumpur, Malaysia

E. A. Ottesen (*Chairman*) Department of Health and Human Services, Clinical Parasitology Section, Laboratory of Parasitic Diseases and Laboratory of Clinical Investigation, Building 10, Room 11C-108, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20892, USA

R. M. E. Parkhouse Division of Immunology, National Institute for Medical Research, The Ridgeway, Mill Hill, London NW7 1AA, UK

F. Partono Department of Parasitology, University of Indonesia, Jakarta, Indonesia

W. F. Piessens Department of Tropical Public Health, Harvard School of Public Health, 665 Huntington Avenue, Boston, Massachusetts 02115, USA

B. K-L. Sim Department of Immunology, Walter Reed Army Institute of Research, Washington, District of Columbia 20307, USA

B. A. Southgate London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK

D. Subrahmanyam R 1056.3.16, CIBA-GEIGY Ltd, CH 4002 Basle, Switzerland

D. Wakelin Department of Zoology, University of Nottingham, University Park, Nottingham NG7 2RD, UK

N. Weiss Department of Medicine, Swiss Tropical Institute, Socinstrasse 57, CH 4051 Basel, Switzerland

J. F. Williams NIH-SUDAN Medical Parasitology Research Project, A-22 Veterinary Clinical Center, Michigan State University, East Lansing, Michigan 48824, USA

V. Zaman Department of Microbiology, Faculty of Medicine, National University of Singapore, Lower Kent Ridge Road, Singapore 0511

Introduction

Eric A. Ottesen

National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20892, USA

1987 Filariasis. Wiley, Chichester (Ciba Foundation Symposium 127) p 1–4

'Filariasis' is an extremely broad topic for a single symposium, not just because it encompasses eight distinct species of parasites producing disease in humans (*Wuchereria bancrofti*, *Brugia malayi*, *Brugia timori*, *Onchocerca volvulus*, *Loa loa*, *Dipetalonema streptocerca*, *Mansonella ozzardi*, *Mansonella perstans*) but also because its study requires participation by at least an equal number of 'species' of biomedical scientists (biochemists, epidemiologists, human physicians, immunologists, molecular biologists, parasitologists, pharmacologists and veterinary physicians)—all, incidentally, represented at this symposium. This complexity notwithstanding, it is clear that filariasis today is in a phase of rapid acceleration in both our acquisition of knowledge and our increase in understanding. Since this acceleration has not been restricted to any one discipline, it is particularly appropriate now to take stock of these advances so that appropriate goals and priorities for the future can be more effectively visualized.

Borrowing a typical organization from medical textbooks, one can clearly pinpoint some of the major problems that have faced 'filariologists' for decades and on which we must focus during this symposium.

(1) *Aetiology*. Getting to know these parasites has been especially difficult because most (including *W. bancrofti* and *O. volvulus*, the two most important) cannot be maintained in laboratory animals. Thus, only limited amounts of parasite material have been available for study, and techniques for defining and differentiating substrains or even subspecies and species have been slow to develop. Even the lifespans of the different parasites and different stages of each parasite are not well defined. Furthermore, for some of the less common filarial infections it is not even certain where the adult parasites reside, and there is essentially no information on how the parasites migrate and mate during the long prepatent periods of these infections.

(2) *Epidemiology*. It is clear that different populations infected with the 'same' parasite (*W. bancrofti*, *O. volvulus*, *B. malayi* etc.) can have very different clinical manifestations of the infection. Although definition of these regional differences has, for most areas, been reasonably complete, there are still certain areas (particularly in Latin America) where previously unrecognized foci of *O. volvulus*, *M. ozzardi* and other filarial infections need basic clinical epidemiological description. Furthermore, it is not known whether the regional differences seen in clinical expression of these infections result from undetected differences in parasite strains, from differences in host responsiveness among the different populations, or from the time and way in which individuals are exposed to the infection. One of the major obstacles for the epidemiologist of filarial diseases has been the inability to detect many infected individuals because of the poor sensitivity of diagnostic techniques. The lack of sensitive identification techniques has also made speciation of larval filarial parasites in the vector (necessary for determining accurate transmission indices) difficult or impossible.

(3) *Pathology*. The major lesions from these infections are localized to the lymphatics, eye and skin. What determines the development of lymphatic obstruction has largely remained a mystery, as have the pathogenic mechanisms responsible for skin lesions, although the latter have been histologically well characterized. How the eye responds to any immunogen is poorly understood, and how it responds to something as large and complex as a microfilaria is almost totally unknown.

(4) *Clinical manifestations*. For the most important filarial diseases (onchocerciasis and lymphatic filariasis) clinical manifestations can differ markedly among individuals even in a single regional population. For the lymphatic filariases, especially, it is amazing that there are almost no studies of the natural history of the infection. Thus, it is unclear whether the different clinical manifestations seen reflect different pathogenetic 'pathways' different individuals follow or whether all patients progress through a defined sequence of different clinical stages or manifestations before reaching the final stage of lymphatic obstruction. In addition to this lack of understanding about the natural *progression* of disease, there are some filarial infections for which even the clinical manifestations themselves have not been unequivocally defined (e.g. *M. ozzardi* and *M. perstans* infections). One important reason that these uncertainties persist is that the clinician has no definite means of detecting infection in many possibly affected individuals. 'Cryptic' filarial infections, which are well recognized in animals, almost certainly occur in humans as well. These infections, characterized by an absence of detectable microfilariae (the stage usually sought in diagnostic assays), may affect a large but currently undefined and undefinable number of individuals in populations exposed to filarial infection.

(5) *Diagnosis*. The primary diagnostic techniques now available are those in which the microfilarial stage of the parasites is visualized directly. Although this approach is useful for detecting infection in many individuals, its sensitivity is limited not only by the amount of human material (skin or blood) available for examination, but also by the fact that in those patients with cryptic (i.e. amicrofilaraemic or amicrofilardermic) infections and in those during the long prepatent period of infection this approach makes no sense at all. Diagnostic techniques based on the detection of antibody have proved of only limited use, largely because the mere exposure to parasite infection in endemic regions leads to antibody responses which are as yet indistinguishable from those of individuals who actually acquire infection after exposure.

(6) *Treatment*. There is no safe drug that will effectively eradicate filarial infections. In onchocerciasis, most lesions develop in response to microfilariae, and the drugs used to kill these microfilariae have been notorious for causing local inflammatory reactions which can damage the host perhaps even more than the untreated infection itself. Furthermore, only the very toxic drug suramin has been available for killing the adult worms in these infections. For the lymphatic filariases, diethylcarbamazine also effectively kills microfilariae, but with side-effects often unacceptable to large populations under treatment. Furthermore, although this drug is active against adult parasites, its effectiveness against this stage depends on chronic administration over long periods of time. For other filarial infections (e.g. *M. perstans*, *M. ozzardi*) no effective form of treatment has yet been found.

(7) *Prevention*. To date, most efforts to prevent individuals from acquiring filarial infections have focused on vector control to decrease human exposure to infective larvae. The greatest success has been achieved by the Onchocerciasis Control Programme in West Africa, where extraordinary vector control efforts have successfully eradicated *Simulium* fly populations that previously served as vectors for *O. volvulus*. However, both for this programme and for the many mosquito control programmes that have been only partially successful in lymphatic filariasis areas, it has been clear that success can be achieved only when efforts are intense and sustained. Once the control measures have been relaxed, the 'eradicated' parasite has in many instances returned and re-established itself. Efforts to prevent infection by vaccination are only in the dream stage. In fact, it has not been conclusively shown that immunity develops (either naturally or artificially) in humans at all. Studies of animal filarial infections suggest that partial immunity can be achieved through immunization, but very little work has been done in this important area.

The list of problems to be approached in these filarial diseases is indeed a long one. Though the number of workers in this field remains disappointingly small, it is clear that advances in our approaches to many of these problems are currently taking place at an accelerating and exciting pace. I anticipate that,

during the course of this symposium, much of our effort will focus on examining these advances and identifying those areas where greater immediate attention might lead rapidly to practical results. Such results are necessary if we are to diminish significantly the spread and impact of filarial disease among the enormous populations living in the world's filarial endemic regions.

Epidemiology of lymphatic filariasis

J. W. Mak

Institute for Medical Research, Jalan Pahang, 50588 Kuala Lumpur, Malaysia

Abstract. Human lymphatic filariasis is caused mainly by *Wuchereria bancrofti*, *Brugia malayi* and *Brugia timori*. Of the estimated 90.2 million people infected, more than 90% have bancroftian and less than 10% brugian filariasis. The distribution and transmission of the disease are closely associated with socioeconomic and behavioural factors in endemic populations. Urban *W. bancrofti* infection, as seen in South-East Asia, is related to poor urban sanitation, which leads to intense breeding of *Culex quiquefasciatus*, the principal vector. Rural strains of *W. bancrofti* are transmitted primarily by *Anopheles* spp. and *Aedes* spp. mosquitoes. Brugian filariasis is mainly a rural disease transmitted by *Mansonia*, *Anopheles* and *Aedes* spp. mosquitoes. The periodic form of *B. malayi* is principally a human parasite, whereas the subperiodic form is zoonotically transmitted in some countries. The control of filariasis has relied on chemotherapy, vector control and reduction of human–vector contact. Although eradication of *W. bancrofti* and periodic *B. malayi* can be achieved, it is possible only to reduce transmission of zoonotic subperiodic *B. malayi* in some areas. A rational approach to control should consider ecological, socioeconomic and behavioural factors and, where feasible, integrate control programmes into the delivery system for primary health care.

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Lymphatic filariasis in humans is caused by the developing and adult forms of filarial parasites present in the lymphatic system. Three parasites belonging to two genera are responsible: *Wuchereria bancrofti*, *Brugia malayi* and *Brugia timori*. As there are several recent reviews on the distribution of filariasis (World Health Organization 1984, Mak & Dennis 1985), it is sufficient to note here that the infection is most common in subtropical and tropical regions of the world and that there are no reliable observations on the actual numbers of people infected. Of the estimated 90.2 million persons infected, more than 90% (81.6 million) have *W. bancrofti* and less than 10% (8.6 million) *B. malayi* and *B. timori* infections (World Health Organization 1984). Most infected persons are in Asian and African countries, with the highest numbers in China, India and Indonesia.

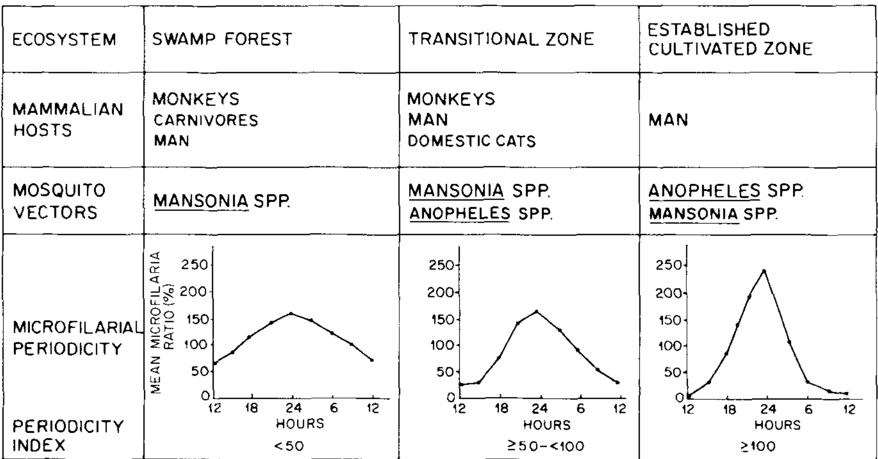

FIG. 1. Characteristics of different variants of *Brugia malayi*. Mean microfilarial ratio = ratio of microfilarial count to average count over 24 h. Periodicity index = standard deviation of microfilarial ratios (Sasa & Tanaka 1972, Tanaka 1981).

Parasite species and strains

Traditionally, the parasites that infect humans have been classified on the basis of their microfilarial periodicity into periodic and subperiodic forms. These variants have minor morphological differences but can be distinguished through their vector and mammalian host ranges and distribution. Thus, the nocturnally periodic form of *W. bancrofti*, the predominant infection, is an urban parasite and is transmitted very efficiently by *Culex quinquefasciatus*, the mosquito associated with poor urban sanitation, whereas the rural forms are transmitted by *Anopheles* and *Aedes* mosquitoes. The subperiodic form mainly seen in the eastern Pacific islands, is transmitted by *Aedes* spp. No animal reservoirs are known for *W. bancrofti*.

B. malayi, mainly seen in South-East Asia, is a much more complex parasite. In Malaysia, Thailand and at least some areas in Indonesia, it is inadvisable to classify *B. malayi* rigidly into subperiodic and periodic variants because this will not accurately reflect the range of variants in the field. There appears to be a close relationship between the type of ecosystem in a particular locality and the parasite variant associated with it (Fig. 1). In this respect the microfilarial periodicity reflects the adaptation of the parasite to changing environmental conditions, such as the presence, type, and biting characteristics of mosquito vectors and the availability of animal reservoirs. Indeed, the various forms of *B. malayi* probably arose through adaptation of the original aperiodic or subperiodic swamp-forest strain seen in carnivores to new combinations of invertebrate and vertebrate hosts (Wharton 1963, Mak 1983).

The periodic form probably represents the most highly evolved variant, adapted mainly to *Anopheles* spp. vectors and humans. This variant is normally seen in established agricultural areas such as rice fields, where *Anopheles* vector mosquitoes predominate. Between this variant and subperiodic *B. malayi* are several transitional forms which share features with parasites at both extremes of periodicity. Thus *Anopheles* spp. and *Mansonia* spp. mosquitoes can serve as their vectors and the range of animal reservoir hosts is much wider. Unlike the subperiodic and the periodic variants, which have periodicity indices (Sasa & Tanaka 1972, Tanaka 1981) of < 50 and ≥ 100 respectively, the transitional forms have indices ranging from 50 to 100.

In spite of epidemiological differences between these variants, they are morphologically very similar. In Malaysia and southern Thailand, the periodic can be distinguished from the subperiodic form on the basis of microfilarial sheath casting, a feature first described by Wilson et al (1958). More than 50% of periodic *B. malayi* microfilariae shed their sheaths, but less than 10% of the subperiodic form do so (Sivanandam & Dondero 1972). The transitional forms of *B. malayi* have sheath-casting characteristics similar to those of subperiodic forms (Mak 1983). In Malaysia and Thailand, this sheath-casting characteristic is fairly consistent but in such areas as Bengkulu, Indonesia, it is not (Sudomo et al 1982). Thus this feature is reliable for strain classification only in Malaysia and Thailand.

B. timori, essentially a human parasite and transmitted by *Anopheles barbirostris*, has been detected only in the Indonesian Islands of Timor, Flores, Rote and Alor (Oemijati & Lim 1966, Kurihara & Oemijati 1975). It has not been found in neighbouring countries.

Animal reservoirs and zoonotic lymphatic filariasis

Several wild and domestic animals have been shown to be naturally infected with subperiodic *B. malayi* (Laing et al 1960, Mak et al 1982, Mak 1984). In some endemic areas, for example in Malaysia, infection rates in these animals, especially leaf monkeys (*Presbytis* spp.), can be very high (> 55%, Table 1). Infection rates in monkeys are similarly high in certain parts of Indonesia (Masbar et al 1981, Lim et al 1984). Domestic cats have infection rates for subperiodic *B. malayi* similar to those in humans. Of 447 cats examined from various areas of Malaysia, 31 (6.9%) were infected; the infected animals were found only in areas where subperiodic and not periodic *B. malayi* infection is endemic. Although it is believed that zoonotic transmission by *Mansonia* vectors from *Presbytis* spp. monkeys can be intense enough to reduce the effectiveness of control measures (Mak et al 1982), available evidence indicates that the domestic cat is probably infected from the same source as humans (Mak et al 1980b). However, because of their close association, transmission of the infection from cats to humans is a distinct possibility.

TABLE 1 Brugia spp. infections in some common wild and domestic animals in Malaysia[a]

Animal host	No. examined	Positive (%) *B. malayi*	*B. pahangi*	*B. tupaiae*	Other *Brugia* spp.
Presbytis melalophos	92	62 (67.4)	0	0	0
Presbytis obscura	150	107 (71.3)	4 (2.7)	0	0
Presbytis cristata	13	7 (53.8)	0	0	0
Macaca fascicularis	150	4 (2.7)	0	0	0
Tupaia glis	285	0	0	9 (3.2)	17 (6.0)
Nycticebus concang	199	0	10 (5.0)	0	0
Cat	447	31 (6.9)	59 (13.2)	0	0
Dog	68	0	7 (10.3)	0	0

[a] Data compiled from Lim & Mak (1978) and Mak et al (1980a, b, 1982).

B. pahangi, a common filarial parasite of wild and domestic animals in South-East Asia (Laing et al 1960, Mak et al 1980b, Mak 1984, Lim et al 1984, Palmieri et al 1985), has been experimentally transmitted to humans (Edeson et al 1960) and natural human infections have been reported from South Kalimantan, Indonesia (Palmieri et al 1985). Although numerous searches have been made in Malaysia for human *B. pahangi* infection, they have not been successful. It is regrettable that the infections in the eight persons reported to have *B. pahangi* microfilaraemia were not passaged to animals, and that the parasite species were not confirmed by detailed analysis of adult morphological features but identified mainly by the staining characteristics of the acid phosphatase activity of the microfilariae. Nevertheless, zoonotic *B. pahangi* infection should be considered a real possibility, especially in areas where animals reservoirs are present.

Control strategies

Control programmes have relied heavily on chemotherapy with diethylcarbamazine citrate (DEC) and to a lesser extent on vector control. DEC has been administered by mass chemotherapy at daily, weekly or monthly intervals or as a medicated salt. It is probably immaterial to the final outcome whether DEC is given daily, weekly or monthy as long as treatment is sustained to give a final total dose of 36 mg/kg for *Brugia* infections and 72 mg/kg for *W. bancrofti* infections. Even at these dosages some patients will remain microfilaraemic with low densities of microfilariae for a few months.

Weekly DEC administration at low doses (25 mg for those under 10 years old and 50 mg for those over 10) for 18 months (Partono et al 1984) and

administration of DEC-medicated salt at 0.26% formulation (giving an estimated daily dose of 65 mg DEC) for 11 weeks (Sen et al 1974) or at 0.1%–0.15% formulation (Sharma et al 1982) for 27 months can reduce microfilarial counts by more than 90%.

Theoretically, *W. bancrofti* and periodic *B. malayi* transmission can be reduced to extremely low levels or even interrupted completely through a combination of drug administration and vector control, as in many areas of Malaysia. In contrast, in areas where a sizeable animal reservoir exists, interruption of transmission can be extremely difficult if not impossible (Mak et al 1982). In such areas, a combination of control measures, including the possible chemoprophylactic use of either DEC (Mak & Lim 1983) or a more easily administered drug, may be needed to reduce transmission and prevent new cases of clinical disease.

Environmental management, such as the filling of swamps to create agriculturally productive land, which indirectly drives non-human primates deeper into the jungle, will not only decrease the number of breeding sites for vector mosquitoes but also reduce zoonotic transmission.

Control programmes should as far as possible consider all the above factors and target for control or eradication according to the filarial species and variant endemic in the locality. Even in the same country, programme objectives may differ in different endemic areas.

Behavioural and socioeconomic factors are recognized as important determinants of filarial transmission, e.g. the wearing of clothing that exposes limbs to mosquito bites, the social congregation of people outside houses at night, work schedules (such as tapping rubber trees at dawn) that expose workers to peak biting periods of vectors, and activities that increase the number of breeding places for mosquitoes. These behavioural factors are well known, but the tools and methods for behavioural changes are on the whole rather ineffective and seldom applied. Often too, economic necessities have placed many people in endemic areas and have forced them to work where the risk of infection is high, e.g. rubber estate populations in Malaysia and transmigrants in Indonesia.

Finally, it is stressed that, to maximize the returns from limited resources in endemic countries, the filarial control programme should enlist the participation of the community and utilize the delivery system for primary health care, as in Indonesia (Partono et al 1984).

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DISCUSSION

Jaffe: How often do you see cats naturally doubly infected with *B. pahangi* and *B. malayi*? It would be interesting to find out whether infection of such animals with one species influences their subsequent susceptibility to the other.

Mak: In nature we sometimes see cats that are doubly infected, and we can also produce double infection experimentally. The types of infection seen depend on various factors. *Armigerus* is one of the principal vectors of *B. pahangi*, and if you have *Armigerus* in an endemic locality then the animals will be infected with *B. pahangi*. If *Mansonia* mosquitoes are present as well, the animals will also be exposed to *B. malayi* infection.

Subrahmanyam: In India, both *Wuchereria* and *Brugia* have been observed simultaneously in humans.

Mak: Yes. We have also found double infections in humans in Malaysia.

Subrahmanyam: You mentioned that periodic and subperiodic *B. malayi* differ in their ability to cast their sheaths. Do such differences also exist between the periodic form of *W. bancrofti* and the subperiodic form?

Mak: I don't think sheath-casting characteristics have been described for the various forms of *W. bancrofti*.

Klei: Is sheath casting just an artifact of the staining procedure, or do microfilariae lose their sheaths spontaneously?

Mak: I don't think it is simply an artifact. The difference between periodic and subperiodic *B. malayi* is very consistent in Malaysia and Thailand. We use the ordinary blood smears that we make for epidemiological studies, and if we dry them under standard conditions before staining, we get the same result again and again.

Ottesen: Does sheath casting have any physiological significance?

Mak: The conventional view is that microfilariae need to cast their sheaths before they can penetrate the mid-gut of the mosquito into the haemocoele. McGreevy et al (1978) have shown that certain mosquitoes have cibarial and pharyngeal armatures that are able to tear the sheath, and I would like to suggest that the pharyngeal armatures might help the microfilariae to cast their

sheaths when they are passing through the pharynx of the insect into the mid-gut.

Ewert: I had always assumed that, after microfilariae are taken into a mosquito with a blood meal, those that are going to develop further cast their sheaths in the gut of the mosquito. But Dr C.C. Chen (National Defence Medical Centre, Taipei, Taiwan) tells me that some microfilariae do not cast their sheaths until they reach the haemocoele of the mosquito.

Denham: That's right. You do occasionally get sheathed microfilariae in the haemocoele, but it is a rare event.

Piessens: We find by scanning electron microscopy that about half the microfilariae lose their sheaths after they penetrate the mosquito mid-gut.

Partono: When Wilson first described sheath casting and identified the two strains of *B. malayi* (Wilson et al 1958), he made his classification on the basis of several biological features of the parasites. He chose periodicity as the distinguishing feature, so it is important to know how exactly the periodic and subperiodic forms are defined. In your studies, Dr Mak, is the definition based on the curves you showed us (Fig. 1) or on mathematical methods? Are the criteria used by different investigators the same? If they are not, the issue may be very complicated, as I can show by describing the kinds of studies we have been doing for the last few years in Indonesia.

For the periodic form of *W. bancrofti* from Irian Jaya, we have been able to compare different methods of determining microfilarial periodicity. In addition to the peak hours we calculated the periodicity index as defined by Sasa & Tanaka (1972), who take 80 as the lowest point for the periodic form and 30 for the subperiodic form. We also worked out the index by the criteria of Aikat & Das (1977), who use a cut-off point of 50, and finally by our own method, using the ratio between the counts of microfilariae in night blood samples and the counts in day-time samples. We found empirically that the differentiating values were 80, 100 and 4 respectively for the three methods. In nocturnally periodic *B. malayi* from south and central Sulawesi the periodicity values were > 80, > 100 and > 10 respectively. This form casts its sheath as a fairly consistent biological feature, which it surprisingly retains even after the parasite is passed through an animal. The Bengkulu strain that you mentioned is also undoubtedly nocturnally periodic: its periodicity index is > 80, the Aikat & Das index is > 100 and our method gives a value > 8. But it has all the other biological features of a subperiodic strain, including non-casting of its sheath in thick blood smears. Therefore to distinguish a parasite just by using a periodicity index is very difficult; other features of the strain must also be taken into consideration.

Mak: I cannot agree with you more. The periodicity index can only help us in describing a parasite; we must also consider other features, such as animal reservoir range and vector range. But the periodicity index can be useful. In Malaysia, we have devised a quick method for determining whether strains in a

particular endemic locality are periodic or subperiodic, and that is to examine the cats whenever we go there—if we find infections we are dealing with a subperiodic form of the parasite, whereas if the cats are not infected the form is periodic. These observations have always correlated very well with our periodicity indices for human populations in such areas.

You mentioned that some of the nocturnally periodic strains of *B. malayi* from Indonesia retain their morphological characteristics in an animal host. This has been shown again and again in passage experiments from humans to animals in Malaysia. A periodic form from a human on being passaged to a cat will always retain its microfiliarial sheath-casting characteristics, and a subperiodic form will always retain its property of not casting its sheath.

Harinath: After giving human carriers a full course of DEC treatment, we found persistent microfilaraemia in 2–3%. After seven years with no further treatment, about 30% of the 78 patients became microfilaraemic, i.e. some of the patients who became negative after treatment, as assessed by parasite examination, were later found to be positive again. What factors do you think are responsible for this? Are we seeing reinfection or lack of immunity or do persisting adult parasites start releasing microfilariae into the circulation again for some reason? In what percentage of patients do you see persistent microfilaraemia even after repeated treatment?

Mak: The persistence of microfilariae in low densities despite treatment is common in endemic areas. We really do not know whether it is due to inability of the drug to get rid of the parasite completely, or whether inadequate dosage or poor bioavailability of the drug is responsible. The surprising thing is that even patients given multiple doses of DEC can show very low grade microfilaraemia. Or microfilaraemia can reappear a few years after treatment. Unfortunately we cannot as yet say whether this is due to inadequate treatment or to reinfection. Immunity after treatment is an interesting question, but I don't think anybody has studied it.

Southgate: There is some strong evidence that the adult females of another filarial parasite, *Onchocerca volvulus*, produce their microfilariae in short bursts and then go for long periods without giving rise to any microfilariae (H. Schulz-Key, unpublished work). They may have up to four cycles of production of microfilariae each year as young worms, but as they become older, perhaps after 10 or 15 years, they produce microfilariae only once or twice a year for relatively short periods of time.

Partono: The issue of persistent microfilaraemia was raised in the late 1950s when control measures had been implemented in the western Pacific. At that time, however, the filtration method was not widely used. Subsequently, in Indonesia, we have never encountered persistent microfilaraemia. If we keep giving the carriers DEC, the microfilariae disappear. So I think it is just a question of how much DEC you give, how long you observe the patients and how high the sensitivity of your method for picking up microfilariae is.

Ottesen: Our experience is different. We have seen patients in hospital with *W. bancrofti* infection who show persistent low level microfilaraemia despite daily administration of DEC.

Partono: You should not examine patients only during their hospital stay, because they will tend to have persistent microfilaraemia for up to six months. You need to keep observing them for several years, and then you will see the microfilariae disappear.

Denham: We have used DEC against experimental *B. pahangi* infection in cats, and agree with the view that it is a macrofilaricide. But we had one cat that we could not cure with DEC. We thought we might have established a resistant strain, but when we passaged it to other cats they were totally susceptible. We next treated the original cat with an arsenical to kill the worms for sure, and when we reinfected it the new infection was completely susceptible to DEC. I felt that with the first infection in this cat the worm had somehow got into an anatomically peculiar site, where the drug couldn't reach it. This probably happens in some of the people who cannot be treated. Last week, for example, I met an eight-year-old boy who had been given a total of 210mg DEC/kg and was still full of microfilariae, and I suspect that he had worms in a site somewhere in his body that excluded DEC.

Greene: It is not uncommmon to see people with onchocerciasis who do not respond to DEC, and the presumption is that in this disease the response depends, at least in part, on the host immune response.

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The spectrum of disease in lymphatic filariasis

Felix Partono

Department of Parasitology, University of Indonesia, Jakarta, Indonesia

Abstract. Lymphatic filariasis affects predominantly the poorer sector of a community, who can least afford to have the disease. According to an estimate by the World Health Organization in 1984, more than 90 million people are currently infected. It is postulated that the different disease manifestations of filariasis are caused by different host immune responses. An understanding of the clinical spectrum of lymphatic filariasis is essential for the effective treatment and control of the disease, and for correctly correlating clinical status with host immune responses. The disease should be divided into lymphatic filariasis caused by adult worms and occult filariasis due to hyper-responsiveness of the host against microfilariae. The acute stage of filariasis is characterized by episodic adenolymphangitis, followed by obstructive lesions one or more decades later. In brugian filariasis, adenolymphangitis is most commonly observed at the inguinal region, and elephantiasis predominantly involves the leg below the knee. In bancroftian filariasis, the lymphatics of the male genitalia are frequently affected, leading to epididymo-orchitis and hydrocele. Lymphatic filariasis runs an accelerated clinical course in previously unexposed adult migrants. Occult filariasis is not a disease of public health importance. It is characterized by lymphadenopathy, asthmatic bronchitis, hypereosinophilia, and an increase in the production of antibodies, especially immunoglobulin, against microfilarial antigens.

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Lymphatic filariasis caused by *Wuchereria bancrofti*, *Brugia malayi* and *Brugia timori* is prevalent in the rural and slum areas of many tropical countries, predominantly affecting the poorer sector of the community. It is more prevalent among the young and active working population, who can least afford to have the disease, than in children and in old age. Worldwide, there are 905 million people at risk of acquiring the parasitoses, and 90 million are currently infected (World Health Organization 1984). About two-thirds of those infected live in China, India and Indonesia. An understanding of the clinical spectrum of lymphatic filariasis is essential for the effective treatment and control of the disease, and for correctly correlating clinical status with host immune responses. Pathophysiologically, the disease should be divided

into two distinct clinical syndromes. One is caused by adult or developing adult worms, and is commonly referred to as lymphatic filariasis. The other is caused by immune hyper-responsiveness of the human host against microfilariae, producing occult filariasis, including tropical pulmonary eosinophilia (Lie 1962, Ottesen 1980).

Lymphatic filariasis

The course of lymphatic filariasis in individuals is highly variable and often unpredictable. But when the different subclinical and clinical statuses of persons in an infected community are analysed as a whole, a general pattern is discernable. The sequence of events following an infection runs: prepatent period, asymptomatic microfilaraemia, acute and chronic clinical filariasis. The acute stage is characterized by episodic lymphadenitis and lymphangitis, with or without fever, followed by obstructive lesions one or more decades later. During the chronic stage, episodic adenolymphangitis indicates active infection.

The prepatent period is the interval between the entry of infective larvae and the appearance of detectable microfilaraemia, and has been presumed to be seven months for *W. bancrofti*, three and a half months for *B. malayi* and three months for *B. timori*, identical with the age of the youngest infant with microfilaraemia. These estimates are similar to the prepatent periods in experimental animals and in an experimentally infected man (Dondero et al 1972).

The clinical incubation period is the interval between the invasion of infective larvae and the development of clinical filariasis. In an endemic community, this interval may vary from two to more than ten years; some microfilaraemic individuals remain asymptomatic for life. In people migrating from non-endemic to endemic filarial areas, the incubation period has been observed to be as short as two months for brugian filariasis (Partono et al 1977), and three and a half months for bancroftian filariasis (Huntington et al 1944). The shortest interval observed in men experimentally infected with *B. malayi* was four and a half weeks (Dondero et al 1972).

The clinical manifestations of Malayan and Timorian filariasis are similar, but they differ from those of bancroftian filariasis.

Brugian filariasis

The clinical manifestations of brugian filariasis are usually more distinct than those of bancroftian filariasis. Lymphadenitis occurs most frequently in the inguinal region (Poynton & Hodgekin 1938, Turner 1959, Dondero et al 1971, Dennis et al 1976, Partono et al 1978), generally affecting one superficial node at a time. The attacks occur episodically, and are often said to be precipitated

by hard labour in the fields. The patient may be unable to work for several days, but may remain ambulatory. Lymphadenitis usually resolves spontaneously without treatment. Sometimes, lymphadenitis is followed by a characteristic retrograde lymphangitis, although on rare occasions the infection has been observed to progress centripetally (Turner 1959). The infected lymph vessel appears as a red streak, feels cord-like and is often painful on palpation. The infection may spread to the surrounding tissues, producing cellulitis, which may affect the whole thigh or even the entire limb. At this stage, the patient is

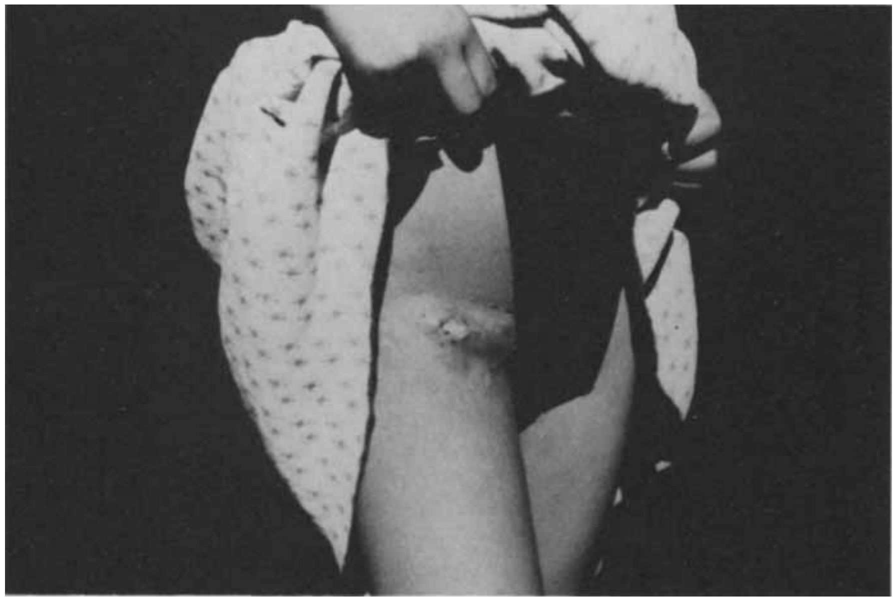

FIG. 1. An ulcer formed by suppuration of an inguinal lymph node in brugian filariasis. Typically, the ulcer is relatively clean, in contrast to those caused by bacterial infections.

usually bedridden with constitutional symptoms, and there is frequently slight lymphoedema of the foot and ankle.

If the infected lymph node becomes an abscess, it may suppurate to form an ulcer (Fig. 1). Constitutional symptoms usually resolve by rapid lysis or crisis once the abscess suppurates. Typically, the ulcer is relatively clean, in contrast to those caused by bacterial infection, and heals spontaneously within a few days. The resulting scar tissues may serve as objective signs of past lymphadenitis. The appearance of these scar tissues is closely related to the severity of infection of the affected node and the time between ulceration and examination.

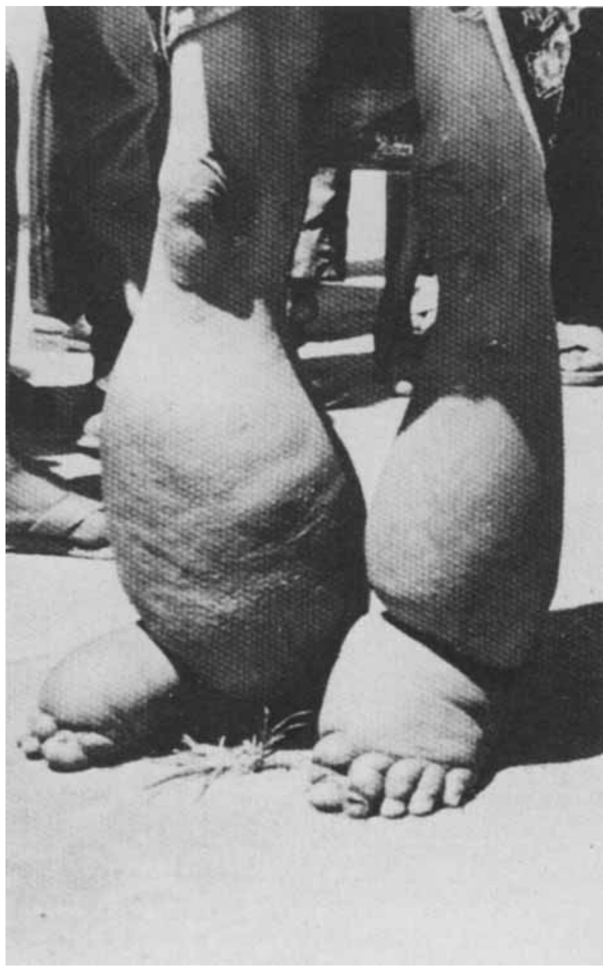

FIG. 2. In chronic brugian filariasis the legs below the knees are characteristically affected, and the normal contours of the knees are more or less preserved.

The acute clinical phase with its complications may evolve completely and last from several weeks to as long as three months. There may also be spontaneous healing at different stages of the clinical course. Lymphadenitis may also occur at the medial aspect of the leg and foot, at the axilla, at medial sites on the arm and hand and, occasionally, at atypical sites, such as the breast. In Timorian filariasis, the inguinal node may be initially affected, but as it heals, nodes at lower sites are in turn affected, so that the disease simulates a hot stone rolling down from the inguinal area to the foot. This