This report contains the collective views of an international group of experts and does not necessarily represent the decisions ot the stated policy of the World Health Organization

Lymphatic filariasis

Fourth report of the
WHO Expert Committee on
Filariasis

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Geneva, 31 October–8 November 1983

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LYMPHATIC FILARIASIS

Fourth report of the WHO Expert Committee on Filariasis

CORRIGENDUM

Page 100, lines 1–2:

Delete: The total yearly dosage of DEC for an adult was thus about 4.0 g.

Insert: Treatment was continued for 18 months and the total dosage of DEC for an adult was thus about 4.0 g.

LYMPHATIC FILARIASIS

Fourth report of the WHO Expert Committee on Filariasis

1. INTRODUCTION

A WHO Expert Committee on Filariasis met in Geneva from 31 October to 8 November 1983.

Opening the meeting on behalf of the Director-General, Dr A. Davis, Director, Parasitic Diseases Programme, indicated that lymphatic filariasis in its various forms remains a public health problem of considerable magnitude in many tropical countries. It is a disease affecting people in rural areas as well as an increasing number of those living in urban areas with poor sanitation. Although much progress has been made in the control of lymphatic filariasis, this has been largely as a result of vertically-structured mass treatment and vector control campaigns. It now appears essential to devise methods of control which can be integrated with primary health care systems. A great deal of research into lymphatic filariasis has been sponsored through the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases, and WHO has stimulated a wider interest in the problem by holding biregional meetings in endemic areas of the WHO South-East Asia and Western Pacific Regions. However, there are still many unresolved problems concerning the transmission of the infection as well as the treatment and control of the disease. Much can be achieved with existing tools, but the problems are so formidable that the overall goal of health for all by the year 2000 will not be achieved unless Member States give filariasis control a higher priority in their health programmes.

2. PREVALENCE, DISTRIBUTION, PARASITES, AND RESERVOIR HOSTS

2.1 Estimates of the global prevalence of *Wuchereria bancrofti*, *Brugia malayi*, and *B. timori*

The general geographical distribution of the various types of lymphatic filariasis has been well documented (*1–5*), but it is very difficult to produce reliable data on the number of people infected with the parasite(s) concerned or affected by the disease, and even more difficult to give a realistic estimate of the number of people who are "at risk" of infection. Species of mosquito that are potential vectors of lymphatic filariasis are found throughout the tropics and subtropics, but the endemic areas are limited to those regions where conditions are favourable for transmission. These are predominantly in hot and humid regions of the world but, where filariasis is transmitted by the peridomestic mosquito *Culex quinquefasciatus*, the distribution can extend to drier areas, for example in urban and rural situations throughout much of India. Within the overall endemic area, all persons must be considered to be "at risk" of exposure to infection.

At the present state of diagnostic capability, which depends on demonstrating microfilariae in the blood, the "infection rate", even in the most heavily infected countries, is seldom recorded as more than 50%; this despite the fact that many of the "microfilaria-negative" individuals may have clinical signs of the disease. This last apparent paradox is brought about by the disappearance of microfilariae from the peripheral blood in many people with chronic manifestations of the disease. It is therefore necessary, when estimating the prevalence of lymphatic filariasis, to include both the microfilaria-positive individuals and those with filarial disease, taking into account not only those with chronic lesions, such as elephantiasis and hydrocoele, but also those with the more acute manifestations such as adenolymphangitis and epididymo-orchitis. The estimate for the "number of persons infected" therefore includes both people who are microfilaria-positive and those who are clinically positive but microfilaria-negative. If sensitive immunological diagnostic techniques could be used to supplement parasitological and clinical diagnosis, the figure for the total number of people infected would probably be much higher, for it would include all those infected persons who are asymptomatic and amicrofilaraemic.

In many countries the overall figures for the prevalence of infection have to be estimated by extrapolation from relatively small sample surveys and without an accurate knowledge of the local distribution of the endemic foci. Total figures developed in this way often underestimate the true prevalence because of the inefficient methods used for diagnosis.

In estimating the magnitude of the problem of lymphatic filariasis throughout the world, the Committee has drawn on a variety of information sources ranging from official estimates from ministries of health to those obtained from the literature, and those supplied by individuals with a wide experience of filariasis in their own or other countries.

The figure for the number of people "at risk" represents the number of people living in areas where the vectors still exist and where transmission still occurs irrespective of the level of control achieved. In many parts of the world where there has been no effective control, for example over the greater part of the endemic area of India, the "at risk" figure may be fairly accurate, but in other countries, such as China and Egypt, where the prevalence rate in most of the former endemic area is now less than 2%, the "at risk" figure represents no more than a potential risk in the event of a breakdown in control.

Global estimates for lymphatic filariasis are as follows:

Number of persons living in countries where the disease is endemic:		2677 million
Number of persons living in endemic areas where transmission is known to occur and who are "at risk" of infection		905 million
Number of persons infected with:[1]		
Wuchereria bancrofti	81.6 million	
Brugia malayi and *B. timori*	8.6 million	
Total no. of persons infected		90.2 million

A breakdown of these figures by WHO Region, and the countries included in the endemic areas, are given in Table 1.

The distributions of the endemic areas of the lymphatic filariases are shown in the map (Fig. 1), which also outlines the geographical zones of the vector mosquitos listed in Annex 1.

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[1] Those with microfilaraemia plus those with clinical disease.

Table 1. The total number of persons at risk of infection in endemic areas and the estimated number of persons with overt filariasis

WHO Region	Total population of endemic countries[a] (millions)	Population living in endemic areas ("at risk") (millions)	Filarial infection (Mf +ve & disease) (millions)	
			Wuchereria	*Brugia*
African Region[b]	295	113	25.6	0
Region of the Americas[c]	136	5	1.0	0
South-East Asia Region[d]	1032	399	46.1	4.4
European Region[e]	—	—	—	—
Eastern Mediterranean Region[f]	53	21	2.2	0
Western Pacific Region[g]	1161	367	6.7	4.2
Total	2677	905	81.6	8.6

[a] Population figures have been taken from *World health statistics Annual,* Geneva, World Health Organization, 1982. The countries included in the endemic area are listed in the following footnotes

[b] Angola, Benin, Burundi, Cameroon, Cap Verde, Central African Republic, Chad, Comoros, Congo, Equatorial Guinea, Ethiopia, Gabon, The Gambia, Ghana, Guinea, Guinea-Bissau, Ivory Coast, Kenya, Liberia, Madagascar, Malawi, Mali, Mauritius, Mozambique, Niger, Nigeria, Réunion, Sao Tome and Principe, Senegal, Seychelles, Sierra Leone, Togo, Uganda, United Republic of Tanzania, Upper Volta, Zaire, Zambia, Zimbabwe

[c] Brazil, Costa Rica, Dominican Republic, Guyana, Haiti, Suriname, Trinidad and Tobago, and some other countries or areas in the region

[d] Bangladesh, Burma, India, Indonesia, Maldives, Nepal, Sri Lanka, Thailand

[e] Cases are still being reported from Turkey, but there is no recent evidence of local transmission

[f] Egypt, Oman, Somalia, Sudan

[g] American Samoa, China, Cook Islands, Fiji, French Polynesia, Republic of Korea, Malaysia, Papua New Guinea, Philippines, Samoa, Solomon Islands, Tonga, Vanuatu, Viet Nam, and some other countries or areas in the region.

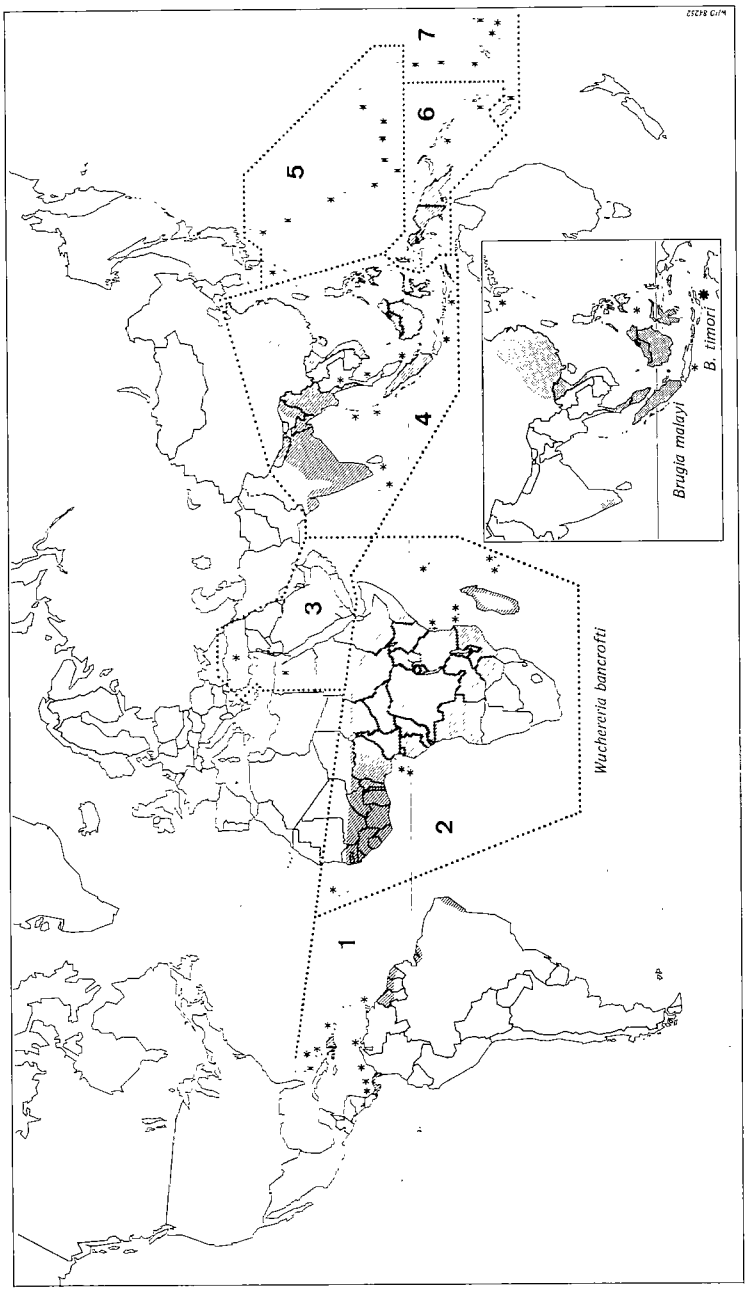
2.1.1 *The current prevalence of filariasis*

Numerically the public health problem of lymphatic filariasis is greatest in China, India, and Indonesia. These three countries account for about two-thirds of the estimated world total of persons infected.

There are extensive endemic areas in many countries of the African Region but detailed epidemiological studies have been confined to a few of those in East and West Africa. There have been no extensive control programmes and the estimate of the number of persons infected in Africa is therefore less reliable than for other regions.

The disease is also a severe problem in many countries with small populations, notably in the Pacific area.

Fig. 1. Distribution of the lymphatic filariases and vector zones[a]



[a] For explanation of the numbered vector zones see Annex 1.

2.1.2 *Increase in prevalence and distribution*

The steady (sometimes rapid) growth of the human population in those endemic areas where control measures are either not effective or non-existent results in a progressive increase in the total number of people "at risk" of developing the disease. The steady increase in urbanization in tropical countries and the resulting increase in *C. quinquefasciatus* populations in areas where mosquito control is ineffective are also major factors in the spread and increase in the prevalence of *W. bancrofti.* There is also the fact that the vector mosquitos often increase as a result of development activities involving water and sanitation.

A special problem has arisen in some resettlement schemes in South-East Asia where, as in Indonesia, migrants from non-endemic areas are becoming infected with *B. malayi* in their new homes. Again, in parts of Sri Lanka, infected migrants have established new foci of infection in areas where it was previously non-existent. Such situations are likely to arise in other areas.

Finally there is the problem of subperiodic *B. malayi* which tends to be maintained, despite control measures, by the presence of a reservoir in monkeys.

2.1.3 *Decrease in prevalence and distribution*

In several countries effective control campaigns have greatly reduced the prevalence of lymphatic filariasis. Of particular note are the decreases in cases due to *W. bancrofti* and *B. malayi* in China, to *B. malayi* in India and Sri Lanka, to *B. malayi* and *W. bancrofti* in Malaysia, and to *W. bancrofti* in Brazil and some of the islands in the Pacific Ocean.

In the more temperate regions of the world, where filariasis transmission was seasonal, there has been considerable success in eliminating the parasites. Notable examples include southern Brazil, northern China, Japan, parts of the Republic of Korea, and Turkey. In some of these areas there has also been a spontaneous decline in prevalence associated with improvements in the economic status of the community and in sanitation and mosquito control.

In acute early clinical filariasis, the increasing use of diethylcarbamazine citrate (DEC) has reduced the proportion of people developing the chronic lesions of elephantiasis or hydrocoele in many endemic areas. This drug is prescribed by practitioners, and

taken by patients as a self-treatment since the drug can be freely purchased.

In areas where anopheline mosquitos are the main vectors of filariasis there has been a decrease in filariasis consequent on malaria control campaigns which make use of vector control methods. This has occurred in Malaysia and in the Solomon Islands in recent years.

2.2 Taxonomy of the parasites

During the past few years, there have been several important advances in knowledge of the speciation and characterization of variants of the filarial parasites infecting man.

The parasite formerly known as the Timor microfilaria has now been characterized, with descriptions of the adult worm, the microfilaria, and the developing stages in the vector. It has been named *Brugia timori.*

A new species of *Wuchereria, W. kalimantani,* has been discovered in the leaf monkey (*Presbytis cristata*) in Indonesia. This parasite has not been recorded in man but the developing larvae in the vector could be confused with those of *W. bancrofti* and *Brugia* spp.

There have not been any recent studies on the various forms of *W. bancrofti* that have been characterized by differences in the nuclear pattern of the microfilariae, and there has been no general acceptance of the species *W. lewisi,* which was designated on the basis of microfilarial nuclear patterns. Likewise, use of the names *W. bancrofti* var. *pacifica* and *W. bancrofti* var. *vauceli* is not endorsed since they do not have valid taxonomic status.

Variants below the species level are of major epidemiological significance in the genera *Wuchereria* and *Brugia.* These variants have been characterized on the basis of differences in the natural host range, microfilarial periodicity, and vector susceptibility, but no clear differences have been demonstrated in either pathogenicity or drug susceptibility.

The variants that are generally recognized as being distinct entities are:

1. *W. bancrofti*
   Nocturnal periodic: The most widespread form; transmitted by *Culex, Anopheles,* and *Aedes.*
   Subperiodic: Mainly in the eastern Pacific; with small foci in Nicobar Islands, Thailand, Viet Nam; transmitted by *Aedes.*

2. *B. malayi*
   Nocturnal periodic: The most prevalent form with interhuman transmission; transmitted mainly by *Anopheles* and *Mansonia*.
   Subperiodic: Less common, with animal reservoir; transmitted by *Mansonia* and *Coquillettidia*.
3. *B. timori*
   Nocturnal periodic: Small foci in Indonesia transmitted by *Anopheles*.

The microfilariae of periodic *B. malayi* in most parts of Malaysia and Indonesia have a marked tendency to shed their sheath on blood slides under normal drying conditions. This is a useful characteristic for distinguishing the periodic and subperiodic variants of *B. malayi*, but this has not been observed in specimens from other endemic areas, such as India and Korea.

2.2.1 *Suggestions for further study*

Attempts should be made to transmit variants of *B. malayi* to jirds, and *W. bancrofti* from different geographical regions to leaf monkeys, with a view to observing differences in the behaviour and morphology of the parasites and to obtaining material for taxonomic, immunological, and biochemical characterization.

2.3 Animal reservoir hosts of human lymphatic filarial infections

A great variety of non-human primates (gibbons, macaques, leaf monkeys, and orangutans) is present in South-East Asia, particularly Indonesia and Malaysia. Of these, the most common are the macaques (*Macaca* spp.) and the leaf monkeys (*Presbytis* spp.). In Indonesia and Malaysia, some members of these genera are important reservoirs of zoonotic filariasis. Recent studies show that they play a significant role in the epidemiology of human filariasis in endemic areas. The contribution of carnivores, domestic cats, and other animals to the zoonotic reservoir is as yet undefined.

2.3.1 *Distribution of monkey reservoir hosts in relation to brugian filariasis*

The three species of leaf monkey and the common macaque are the most widely distributed species in Malaysia and in the three main islands of Indonesia (Sumatra, Kalimantan, and Java). Subperiodic

B. malayi in human populations in Malaysia, west Sumatra, northern and eastern Sumatra, south-east Kalimantan and east Kalimantan is common in localities where leaf monkeys and macaques abound. Conversely, in Sulawesi, where there are no leaf monkeys or long-tailed macaques (*M. fascicularis*), only periodic *B. malayi* has been reported. In general, where leaf monkeys are absent, only periodic *B. malayi* is endemic. However, in Buru, where there are no leaf monkeys, subperiodic *B. malayi* is present. Elsewhere, the distribution of leaf monkeys coincides with that of zoonotic subperiodic *B. malayi*. However, further studies are necessary to determine whether other animal reservoir hosts exist in other endemic areas.

2.3.2 *Domestic animal reservoirs of* B. malayi

Studies in Malaysia have shown that in subperiodic *B. malayi* endemic areas an increase in the microfilarial prevalence rate in man was accompanied by a corresponding increase in the rate in cats. Of 447 cats and 68 dogs examined, 6.9% of the cats but none of the dogs were infected. The cats were probably infected from man and their infection rate is a reflection of the endemicity in the area. Once infected, they could serve to maintain the infection cycle owing to their close association with man.

2.3.3 *Methods for controlling the animal reservoir and further investigations required*

Most monkey species in South-East Asia are protected under the laws of the respective countries in line with the principles enunciated by the International Union for Conservation of Nature and other conservation groups. This has to be borne in mind when planning the control of the reservoir hosts of *B. malayi*. However, certain steps may be taken, in collaboration with the national and international groups involved in non-human primate protection, to prevent transmission of subperiodic *B. malayi* from monkey to man.

Methods should be devised to discourage monkeys from coming into villages; for example, by the creation of a buffer zone without tall trees that might prevent them from moving into settlement areas.

Wherever possible such reservoir control methods should be integrated with vector control and chemotherapy (including chemoprophylaxis) in order to control the infection.

2.3.4 *Suggestions for further study*

(*a*) Further surveys of leaf monkeys should be made to ascertain in which ecological areas subperiodic *B. malayi* is present. It is also important to investigate the presence of monkey infections, and their type, in areas where periodic *B. malayi* is endemic, for other species of monkey can be infected experimentally with this form of the parasite.

(*b*) Epidemiological studies should be undertaken to determine what proportion of subperiodic *B. malayi* infections in man is acquired from the non-human reservoir hosts. Such information would have important implications in the planning of control programmes.

(*c*) Further efforts should be made to determine whether there is a non-human reservoir host of *W. bancrofti.*

3. CLINICAL MANIFESTATIONS

Bancroftian and brugian filariasis are characterized by a wide spectrum of clinical manifestations, the signs and symptoms often differing from one endemic area to another. The disease manifestations can be divided into two distinct clinical types; one caused by juvenile or adult worms in the lymphatic system, normally referred to as lymphatic filariasis; the other, caused by an immune hyperresponsiveness of the human host against microfilariae, resulting in occult filariasis, which includes tropical pulmonary eosinophilia.

3.1 Lymphatic filariasis

The clinical course of lymphatic filariasis is often initially asymptomatic with subsequent episodes of acute adenolymphangitis and finally the development of chronic lymphatic obstruction. In previously unexposed persons who move from non-endemic to endemic areas, this progress is often accelerated with early acute manifestations being followed much more rapidly by the chronic signs.

3.1.1 *Exposure and infection—asymptomatic amicrofilaraemia*

In all endemic areas a proportion of the population does not show microfilaraemia or clinical manifestations of the disease although these individuals have the same degree of exposure to infective larvae

as those who become infected. With presently available diagnostic procedures it is impossible to determine whether persons in this group have undetectable infections, or whether they are free from infection.

3.1.2 *Asymptomatic microfilaraemia*

There is also another group of people, those with microfilaraemia but without clinical manifestations of filariasis. A considerable proportion of these persons remain microfilaraemic and asymptomatic for years—in some instances for life. Some individuals in this group spontaneously become amicrofilaraemic, especially when they move to areas that are not endemic for filariasis.

The microfilaria rate increases with age and then levels off. The more intense the transmission, the lower is this age of levelling off. After a few years at this plateau level, microfilaria rates may decline in middle and old age. In most endemic areas the microfilaria rate is higher in men.

3.1.3 *The prepatent and incubation periods*

The prepatent period is the interval between the entry of infective larvae and the first appearance of detectable microfilaraemia.

Direct information on the duration of the prepatent period of human lymphatic filariasis is lacking, most of the available data being estimated indirectly from epidemiological observations. The youngest infant reported to be microfilaraemic with *W. bancrofti* was 7 months old; with *B. malayi,* 3½ months; and with *B. timori,* 3 months. However, as congenital transmission of microfilariae of *W. bancrofti* from mother to child is known to occur, even these data are difficult to interpret. Studies of primates infected with these parasites have shown a prepatent period of 7–8 months for *W. bancrofti* and 2 months for *B. malayi.*

The duration of the clinical incubation period, i.e., from invasion of infective larvae to the development of clinical manifestations, is variable. The shortest period reported is 4 weeks, but most commonly it is 8–16 months. The incubation period may, however, be of long duration.

3.1.4 *The acute manifestations*

The acute clinical manifestations of lymphatic filariasis are characterized by episodic attacks of lymphadenitis and lymphangitis associated with fever and malaise. There is no evidence to suggest that these are caused or accentuated by bacterial infection. Sometimes the fever precedes the adenolymphangitis by a few days.

Although the fever sometimes precedes adenolymphangitis, fever alone, in the absence of adenolymphangitis, should not be ascribed to filariasis, even when microfilaraemia is present. Painless swelling of lymph nodes in the inguinal region may also be difficult to correlate with filariasis in a barefooted community already prone to infections following trauma of the lower extremities.

Lumps in the breasts, testicles, or subcutaneous tissues, reflecting granulomatous reactions around adult or developing adult worms of human or animal filarial parasites, have been reported. Rarely are microfilariae found in the blood of such patients, and the diagnosis can be established only by histopathological examination.

3.1.4.1 *Bancroftian filariasis.* Acute bancroftian filariasis may commence with malaise and fever, followed by lymphadenitis in the groin or armpit and a typical retrograde lymphangitis. In most endemic areas, such as Africa, India, Indonesia, and the Pacific area, the lymphatics of the male genitalia are frequently affected, leading to funiculitis, epididymitis, and orchitis. The spermatic cord becomes thickened and rope-like, and is painful on palpation. Sometimes it may be confused with a strangulated hernia, but acute inflammatory signs are usually rare. Lymphadenitis affecting the deep abdominal lymph nodes may give rise to an acute abdominal syndrome.

Filarial abscesses in subperiodic *W. bancrofti* infection are often on the medial aspects of the upper thigh and under the rectus fascia of the lower abdomen. Bacteriologically sterile, they develop and resolve slowly and are associated with fever, prostration, and local pain. They usually lie deep to the fascia and do not point to the skin. Incision and drainage reveal communicating pockets.

The acute attacks of adenolymphangitis, etc. in bancroftian filariasis may last for 3–15 days, and may occur several times a year in the same individual. In Tahiti, these symptoms commence around the age of 6 years, and are most intense at about 25 years. Acute

disease incidence rates have been reported as being 1–2% per half-year in a highly endemic area of India.

3.1.4.2 *Brugian filariasis*. Lymphadenitis occurs at intervals, with fever, chills, and other constitutional symptoms. The attacks are often precipitated by work in the fields, but sometimes they occur without any apparent cause. The patient may be incapacitated for a few days or may remain ambulatory. With rest the symptoms often subside spontaneously. At times, lymphadenitis is followed by a characteristic retrograde lymphangitis. There is an induration around the affected lymphatics, which may spread to the surrounding tissues and occasionally involves the whole thigh or the entire lower limb. The affected lymph vessel feels cord-like and tender. At this stage, there is often lymphoedema of the foot and ankle.

In most cases the lymphadenitis occurs in the inguinal region on one side, and there is lymphangitis on the medial side of the limb and foot on the same side. Occasionally the axillary lymph nodes are involved, and the lymphangitis may spread through the medial aspect of the arm to the hand. Infrequently lymphadenitis occurs at atypical sites such as the breasts, the popliteal lymph nodes, or elsewhere. Lymphadenitis rarely occurs at more than one site simultaneously.

The frequency of episodic lymphadenitis varies from 1–2 attacks per year to several attacks per month. At times a person may cease to experience episodic lymphadenitis in spite of continuing to reside in an infected village. Attacks of adenolymphangitis may start as early as 2 years of age. Lymphoedema is frequently present during these attacks, but usually subsides completely after the acute stage. With time, resolution of the lymphoedema becomes less complete after each attack and the chronic stage then gradually develops.

In Indonesia, and to some extent in Malaysia and Thailand, the infected lymph nodes may suppurate and form abscesses, usually superficial in position, which burst leaving an ulcer. In time the ulcers heal, often with cicatrization, and the scar tissue thus formed remains recognizable for a long period and provides an objective sign of past lymphadenitis. The acute clinical course, including complications, may last from 3 weeks to 3 months. Abscess formation is rarely encountered in India or in the other countries where *B. malayi* is endemic.

3.1.5 *The chronic manifestations*

The chronic stage of filariasis usually develops 10–15 years from the onset of the first acute attack. The incidence and severity of chronic clinical manifestations tend to increase with age.

3.1.5.1 *Bancroftian filariasis.* Hydrocoele, elephantiasis, and chyluria are the main characteristic features of chronic bancroftian filariasis. In a highly endemic area in India the annual incidence rate of chronic filarial pathology was about 0.5%.

(*a*) *Hydrocoele.* In most endemic areas, such as east and west tropical Africa, Egypt, the northern states of Uttar Pradesh and Bihar in India, and Indonesia a hydrocoele is the most common sign of filariasis. In other parts of India, elephantiasis is more common than hydrocoele; in the Pacific islands, the prevalence of the two conditions is similar.

Formation of a hydrocoele is usually preceded by episodes of funiculitis or orchitis, although sometimes one may develop without any preceding acute attack. Most hydrocoeles remain comparatively small, but some may become very large. An increase in size often coincides with a decrease in the number of attacks of funiculitis. Sometimes haemorrhage may occur in a hydrocoele and occasionally a hydrocoele becomes a hard fibrotic mass, especially when the patient has been treated by a "traditional healer" or when he has tried to tap his hydrocoele himself. Only rarely does a hydrocoele become an abscess. Small hydrocoeles that develop during the acute stage of orchitis may sometimes regress spontaneously, but most are irreversible. Microfilariae may be found in hydrocoele fluid even if they are not detectable in the blood. There seems to be no association between hydrocoele and infertility, but reproductive capacity may be reduced in persons with very big hydrocoeles.

(*b*) *Lymphoedema and elephantiasis.* Elephantiasis begins as lymphoedema. The leg(s), scrotum, arm(s), penis, vulva, and breast(s), are affected usually in that order of decreasing frequency. In most countries males are more often affected than females. In some endemic areas, such as Indonesia and the Pacific area, the whole leg or arm is affected. However, in Africa, India, and Sri Lanka the swelling may remain below the knee. In the initial stage the swelling can best be observed around the ankle(s), from which it gradually

spreads to the back of the foot, the leg, and the thigh. The affected limb may increase to more than three times its original size. Elephantiasis is usually preceded by periodic attacks of adenolymphangitis, although occasionally it develops without any such episodes.

(*c*) *Chyluria.* The prevalence of chyluria is usually very low. It often occurs intermittently and is more pronounced after a heavy meal. It is usually symptomless but sometimes it is associated with haematuria. More advanced cases may develop weakness and loss of weight resulting from the loss of fat and protein from the body. Microfilariae may be found in the urine in some cases.

3.1.5.2 *Brugian filariasis.* In brugian filariasis the characteristic sites for elephantiasis are the leg(s) below the knee(s) or, less frequently, the arm(s) below the elbow(s), although the lymph nodes affected during the acute stage are usually located in the inguinal or axillary regions. In most cases only the foot and the distal part of the lower leg are affected and, as the swelling usually occurs only below the knee, the contour of the affected knee is more or less normal. The affected leg is usually less than twice its original size.

Genital involvement and chyluria have not been reported, except in areas where brugian filariasis occurs together with bancroftian filariasis.

3.1.5.3 *The chronic stage and its relationship to microfilaraemia and acute adenolymphangitis.* Most studies show that patients with a hydrocoele or elephantiasis are usually amicrofilaraemic, and that persons with acute clinical manifestations are more likely to have microfilaraemia than those with chronic manifestations. However in the Pacific area, and Irian Jaya in Indonesia, there have been reports that approximately 40% of persons with elephantiasis have microfilaraemia. Persons with chronic manifestations of filariasis often continue to suffer intermittent attacks of adenolymphangitis for many years, although these attacks often become less frequent and less severe as time goes by.

3.1.5.4 *Problems in differential diagnosis of lymphoedema and elephantiasis.* Persistent lymphoedema and elephantiasis are often difficult to distinguish clinically. The diagnosis of lymphoedema can be made with confidence only when the swelling proves to be transient. Between advanced lymphoedema and early elephantiasis (the

latter characterized by hyperplasia and fibrosis of the subcutaneous tissues) there is a wide range of intermediate stages. However, it should be stressed that both are caused by the same pathological process and should be regarded as different stages of one clinical entity. Not all elephantiasis is caused by lymphatic filarial infection. Even in endemic areas a small proportion of cases may be due to other causes. Any obstructive lesion involving a major lymphatic vessel may cause lymphostasis distal to the obstruction, which will lead to elephantiasis. Such obstructions may follow infections, acute or chronic (such as tuberculosis), tumours, surgery, or irradiation.

Another important cause of elephantiasis in the tropics is endemic non-filarial elephantiasis which is particularly common in highland areas in Africa, where alkaline red clay soils of volcanic origin are present, and where people go barefoot (*6*).

This condition is believed to be caused by the irritant effect of mineral particles (aluminium silicates and ferro-magnesium compounds) from the volcanic clay, that penetrate the skin and damage the vascular endothelium of the lymph nodes draining the lower limbs. Clinically it starts with a burning sensation and swelling of the toes, which become thickened with hyperkeratosis. This is followed by lymphatic blockage, including plantar oedema and splaying of the anterior part of the foot. The disease progresses indolently and centripetally but may be interrupted by acute attacks. These include sudden swellings and tenderness of the affected leg, with painful femoral lymph nodes and fever, often with rigors, all of which may incapacitate the patient. Elephantiasis supervenes when there are persistent fibrotic changes in the skin and subcutaneous tissue.

3.1.5.5 *Physical deformities and psychological reactions to chronic manifestations of filariasis.* The chronic stage of lymphatic filariasis is painless as long as there are no acute episodes of adenolymphangitis. However, the psychological effects of the deformities produced cannot be fully appreciated except by those who are personally afflicted. Persons with elephantiasis or hydrocoele have a tendency to hide or retreat into the background Women with elephantiasis, and men with obvious hydrocoele, have reduced chances of getting married. Men with huge hydrocoeles or scrotal elephantiasis are sexually incapacitated. Sufferers from the most severe forms of elephantiasis or hydrocoele are often confined to their homes and

require full-time care. They become a burden to the family and to the community unless surgical relief can be obtained.

3.1.6 *The clinical course of filariasis among previously uninfected individuals entering an endemic area*

The clinical course of filariasis among previously uninfected individuals follows a characteristic pattern. A few months after arriving in the endemic area, the affected newcomer experiences periodic attacks of fever and adenolymphangitis, although microfilariae may never appear in the blood. Some 12 000 American soldiers suffered from such attacks following a relatively short exposure on Pacific islands during the Second World War. Where the exposure of the newcomer is more prolonged and continuous, microfilaraemia occurs; elephantiasis tends to develop more often and sooner among immigrants, than it does among the indigenous population of an endemic area. Lymphoedema may develop within 6 months, and elephantiasis 1–2 years after arrival.

3.2 Occult filariasis

The term occult filariasis refers to filarial infections in which the classical clinical manifestations are not present and microfilariae are not found in the blood, although they may occur in the internal organs or tissues (see sections 4.2.5 and 4.3.2.1). Occult filariasis is believed to result from a hypersensitivity reaction to filarial antigens derived from microfilariae. The best known example is tropical pulmonary eosinophilia (TPE) but it is possible that in endemic areas occult or cryptic forms of filarial infection account for several other clinical entities. Only a very small proportion of individuals in a community where filariasis is endemic develop occult forms of the disease. In a 5-year longitudinal study carried out in a rural community with endemic bancroftian filariasis in India, the annual incidence rate of TPE was found to be 10 cases per 100 000 individuals.

3.2.1 *Tropical pulmonary eosinophilia*

Tropical pulmonary eosinophilia is a syndrome that occurs in both adults and children and is more common in males. It is found particularly in those areas of the Indian subcontinent and South-East Asia that are endemic for lymphatic filariasis. The syndrome

is characterized by nocturnal paroxysmal cough, hypereosinophilia, elevated erythrocyte sedimentation rate, radiological evidence of diffuse miliary lesions or increased bronchovascular markings (especially at the bases of the lungs), extremely high titres of filarial antibody (including IgE), and a good therapeutic response to diethylcarbamazine (DEC). Low-grade fever and muscle tenderness may be present.

As the name suggests, the clinical features mainly affect the respiratory system. In many cases lung function is impaired with a reduction in the vital capacity, total lung capacity, and residual volume. Hepatosplenomegaly and lymphadenopathy have been observed. Hypereosinophilia is the most constant feature of this syndrome. Absolute eosinophil counts generally range from 3000 to 50 000 cells per mm^3 of blood but the level of eosinophilia is not related to the severity of the symptoms. Although spontaneous remissions occur, TPE, if untreated, tends to relapse and progress to a condition of chronic pulmonary fibrosis.

3.2.2 *Other conditions possibly associated with lymphatic filariasis*

A form of monoarthritis is quite commonly seen in filarial endemic areas. Clinically it is often indistinguishable from other forms of arthritis. The condition runs a benign course of short duration. The majority of patients are afebrile with a painless swelling of a single joint. Sometimes the affected joint may be painful, warm, and tender, with limitation of movement. The knee joint is most frequently affected, followed by the ankle; small joints are generally not involved and the reason why the knee joint is so often affected remains unexplained. Although microfilariae are not present in the circulation, filarial antibodies can be demonstrated in the blood and/or synovial fluid. However, a filarial etiology has not been conclusively established.

The relationship between filariasis and endomyocardial fibrosis (EMF) is not clear. There is, however, an apparent geographical correlation between the incidence of EMF and a variety of filarial infections.

Occasionally, the occurrence of glomerulonephritis has been associated with human lymphatic filariasis; other conditions, such as thrombophlebitis, tenosynovitis, nerve palsies, and dermatoses, are also found in filarial endemic areas, sometimes coexisting with filariasis. A filarial origin for these conditions has sometimes been

postulated, but so far there is no convincing evidence to support these claims. Some of the syndromes attributed to filariasis may be atypical manifestations of other diseases conditioned by pre-existing lymphatic filarial infection.

3.3 Suggestions for further study

(*a*) Long-term studies should be undertaken in areas where control programmes are operating to determine the relationship between carefully measured residual transmission and the incidence of clinical manifestations, and thus to provide a better basis for defining targets for parasite and vector control.

(*b*) In view of the gaps that still exist in knowledge of the natural history of lymphatic filariasis, and recognizing the impossibility of conducting long-term prospective cohort studies of a controllable disease, case-control studies should be carried out to elucidate the relationship between infection, microfilaraemia, and the development of clinical manifestations, including "occult" forms of the disease such as monoarthritis.

4. PATHOLOGY, IMMUNOPATHOGENESIS, IMMUNODIAGNOSIS, AND PROTECTIVE IMMUNITY

4.1 Pathology[1]

Invasion of man by the infective-stage larvae (L_3) of *W. bancrofti, B. malayi,* and *B. timori* usually occurs without causing any symptoms. Only after moulting to fourth-stage larvae and young adults (1–3 months later) do these lymphatic-dwelling filariae begin to induce local inflammatory reactions. While most of the pathology associated with infection occurs around adult worms in the lymph nodes and afferent lymphatic vessels, some pathology may develop elsewhere, either around microfilariae cleared from the blood or around adults located in ectopic sites. Such pathological changes have cell-mediated, humoral, and foreign-body components, but little is known about the factors that modulate the sequence and intensity of these reactions since very few direct observations have

[1] See also reference 7.

been made on human tissue.[1] In general, the pathology for all three species in man is similar except that genital and renal lymphatic involvement is limited almost exclusively to *W. bancrofti* infections.

4.2 Specific pathological lesions

4.2.1 *Lymphadenopathy*

Epitrochlear, cervical, supraclavicular, axillary, antecubital, inguinal, pelvic, and abdominal lymph nodes may be involved. Unusual sites include mediastinal, midhumeral, intercostal, popliteal, back, wrist, iliac crest, and pectoral nodes. The nodes enlarge, become tender or painful and are discrete or matted, but not attached to the skin. When examined they have bulging, moist, grey-pink cut surfaces with intact capsules.

In man the earliest stages of infection have not been studied, but in cats following inoculation, it has been shown that infective larvae penetrate a lymphatic vessel, migrate to the nearest node, and provoke both cell-mediated and humoral responses. The larvae then descend through afferent lymphatic vessels where they mature to adults and produce microfilariae. In man the earliest lymph-node changes are both inflammatory and reactive, but none is specific. When well developed, however, the combination is so characteristic that a diagnosis of filariasis is strongly suggested.

Nodes with or without worms have distended sinuses containing histiocytes and eosinophils, septal fibrosis, thickened capsules traversed by dilated lymphatics, hyperplasia of follicles, and increased numbers of paracortical lymphocytes. Sinuses may be enlarged to the point of forming "lake-like" expansions containing proteinaceous fluid. In long-standing cases, follicular atrophy has been noted. Some nodes also have focal collections of histiocytes, epithelioid cells, and giant cells, and these may also be found in connective tissue adjacent to the node. Nodes containing worms have similar changes around the worms. Adult worms, male or female, dead or alive, lie in sinuses and in dilated lymphatics of the capsule. The worms are coiled and sometimes centred in granulomas. There is a matrix of degenerating histiocytes immediately

[1] Many of these tissues can be found in the repository of the WHO Collaborating Centre for the Histopathology of the Filarial Infections of Man, at the Armed Forces Institute of Pathology, Washington, DC, USA.

around the worm and this central portion is surrounded by viable histiocytes, a layer of epithelioid and giant cells, and finally scar tissue at the perimeter. The epithelioid cells are palisaded and supported by granulation tissue. Varying numbers of eosinophils, lymphocytes, and giant cells of both foreign-body and Langhans-type populate the outer portions of the lesion. Degeneration and calcification begin within the worm and later extend to the cuticle. Eosinophils cluster in sinuses, in lymphoid cords, and in connective tissues of the hilum. Eosinophils are especially prominent near and around adult worms and are usually the most conspicuous inflammatory cell. The inflammation may extend to adjacent tissue especially when the degenerating worm is in the capsule. The lesions resolve as compact scars. Similar changes can be induced and studied in the nodes of dogs, cats, monkeys, and jirds infected with either *B. pahangi* or *B. malayi.*

4.2.2 *Lymphangitis*

Inflamed, dilated, and varicose lymphatics have long been recognized as a feature of filariasis, but much of the tissue available for histological study has come from patients who have developed acute filarial lymphangitis and lymphadenitis after only a few months residence in an endemic area.

Microscopically the lymphatic vessel dilates and its wall thickens with oedema and inflammatory cells that are mainly lymphocytes, histiocytes, and eosinophils; but neutrophils, plasma cells, and giant cells may also be present in the wall and in adjacent tissue. The endothelium thickens and may become heaped up in folds or polypoid masses. Segments of adult worm may be free or enclosed in lymphatic thrombi, which organize and recanalize. Splendore-Hoeppli substance has also been identified in the inflamed tissue around the worm. Haemorrhage into lymphatics may also occur. Degenerating worms in the lymphatics provoke a necrotizing granulomatous response identical to that in lymph nodes. The pathological picture of filarial lymphangitis in animals is similar to that in man.

4.2.3 *Genital lesions (funiculitis, epididymo-orchitis, hydrocoele)*

Filarial funiculitis is filarial lymphangitis of the spermatic cord with surrounding inflammation of adjacent connective tissue.

Microscopically the changes in the cord lymphatics are identical to those of the peripheral lymphatics and surrounding tissues. Varicocoeles commonly develop after attacks of funiculitis. A similar predisposition to inflammation in spermatic cord lymphatics is also seen in experimental filariasis.

Epididymitis usually accompanies funiculitis and is also primarily a lymphangitis. The epididymis becomes large, smooth, soft, and tender. Microscopically there is interstitial oedema and infiltrates of lymphocytes, plasma cells, eosinophils, and histiocytes surround the lymphatics. Degenerating worms are common in the fibromuscular tissue of the cord and in the lymphatics of the tunica vaginalis. The lymphangitis and focal granulomas provoked by the worms are identical to those described above.

Filarial orchitis is characterized by a boggy oedematous testis —probably from oedema and inflammation of the tunica and adventitia rather than inflammation of the testis itself—but interstitial orchitis has been noted with oedema and an increase in leukocytes (mostly eosinophils) with "little damage" to the germinal tubules.

Hydrocoele is the most common genital manifestation of chronic bancroftian filariasis. Pathologically it is characterized by a distended, generally thickened tunica vaginalis with hyalinization and fibrosis of the subserosal layer, disorganization of the muscle layers, lymphoid and foreign-body giant cell infiltration, and, in extreme cases, calcification. The hydrocoele fluid itself is amber in colour and the sediment shows a characteristic predominance of vacuolated mesothelial cells, fibrin, old blood clots, cholesterol clefts, and calcium dust. Such findings, when associated with epididymal changes, are highly suggestive of a filarial etiology for the hydrocoele even without the recovery of *W. bancrofti* microfilariae from the fluid or adult worms from the cord and epididymal tissues.

4.2.4 *Lymphoedema and elephantiasis*

As a result of the associated lymphatic obstruction, lymphoedema (which initially is usually transient) and elephantiasis develop progressively. Affected tissues first become oedematous and then characteristically develop proliferative dermal changes with subsequent dermal and subcutaneous fibrosis. Increased numbers of mast cells have also been described in these elephantiasis tissues. The

external genitalia may be affected and may have verrucous changes of the epidermis.

4.2.5 *Tropical pulmonary eosinophilia*

Tropical pulmonary eosinophilia is a rare manifestation of filariasis and is characterized by clinical and immunological hyperresponsiveness. Histopathological findings during the early weeks of clinical symptoms show histiocytic infiltration of the alveolar spaces and interstitium, followed by bronchopneumonia and eosinophilic abscesses. After several months, the infiltrates, characterized by eosinophils, histiocytes, and lymphocytes, often organize into nodular granulomatous responses and fibrosis develops. The final, irreversible phase of the pulmonary pathology in this condition is a chronic interstitial fibrosis without tissue eosinophilia. Rarely, microfilariae surrounded by eosinophilic granulomatous reactions have been found in biopsies of lung, liver, or lymph nodes from affected individuals.

4.2.6 *Other pathology*

Chyluria may develop in patients with bancroftian filariasis following obstruction of renal or abdominal lymphatic vessels. Such blockage results in the drainage of lymph into the urinary collecting system usually at the level of the renal pelvis or bladder.

Filarial granulomas of the female breast are firm solitary inflammatory masses provoked by adult worms in the lymphatics of the breast or axillary tail. Microscopically the lesions resemble those already described in lymph nodes.

At autopsy, granulomas are also found in the spleen and occasionally at other sites. They are discrete and consist of eosinophils, histiocytes, and giant cells around degenerating microfilariae. Similar findings have been seen in a variety of animals with filariasis, including leaf monkeys.

Glomerulonephritis and interstitial nephritis have also been reported rarely, but it is unclear whether these renal conditions are truly a manifestation of filariasis or simply coincident with it. Lesions typical of glomerulonephritis have been observed in cats infected with *B. pahangi*.

Rare ocular manifestations described in patients with filariasis include adult *W. bancrofti* in the anterior chamber, adult *Brugia* spp. in the conjunctiva, and microfilarial uveitis caused by *B. malayi.*

Amyloid has been observed in natives of Papua New Guinea with chronic filariasis

4.3 Immunopathology and immunopathogenesis

4.3.1 *Immunosuppression and its effects*

Patients with all forms of lymphatic filariasis (except tropical pulmonary eosinophilia) are in general poorly responsive to filarial antigens. This hyporesponsiveness appears limited almost exclusively to parasite antigens, and is most prominent in patients with microfilaraemia. Its existence is presumably important for the successful persistence of the parasite within the host and its effects extend clearly to both cellular and humoral immune mechanisms.

4.3.1.1 *Suppression of cell-mediated immune (CMI) responses.*[1] Lymphocytes studied *in vitro* show little or no response to filarial antigens in patients with microfilaraemia and only modest responses in amicrofilaraemic individuals, despite the fact that reactivity to non-filarial antigens and to mitogens is normal. Such unresponsiveness occurs not because the patients fail to become sensitized to filarial antigens but because various modulating mechanisms develop that can specifically suppress responses to these antigens. The mechanisms described include serum suppressor factors that are still incompletely defined, T-lymphocyte suppressor cells, and suppressive adherent cells that are probably monocytes. The number of suppressor T cells and the ratio of these cells to helper T cells are abnormally high in most affected patients. Both abnormalities have been found to revert to normal after microfilaraemic patients are successfully treated with diethylcarbamazine (DEC).

Similar studies of lymphocyte reactivity in several animal model systems have generally substantiated the finding of antigen-specific cell-mediated immunity suppression during chronic filariasis and have further indicated that these suppressive mechanisms develop following a transient, initial phase of normal vigorous responsiveness to parasite antigens, which occurs early in infection. Further-

[1] See also reference *8*.

more, *in vivo* (skin test) studies of cell-mediated immunity modulation in animal models have confirmed the existence of immunosuppression that is antigen specific. Similar studies in man have been less conclusive.

4.3.1.2 *Suppression of humoral immune responses* (*9*). Hyperglobulinaemia with elevated levels of specific antibody has long been recognized in filariasis, with only the microfilaraemic patients having relatively deficient antibody responses. It may be that these lower antibody titres when there is an obvious infection reflect an element of specific humoral immunosuppression, but this possibility remains to be confirmed.

Despite high levels of total and specific IgE antibodies in almost all patients with filariasis, as well as normal or increased numbers of basophils and mast cells and an often constant exposure to parasite antigen, patients with chronic infection rarely show allergic reactivity to their parasites. This paradox may be explained by the finding that, during the course of natural infection, patients with lymphatic filariasis develop high levels of IgG "blocking antibodies", that can suppress or modulate IgE-mediated allergic reactivity to parasite antigens. As with the cell-mediated immunosuppressive mechanisms, this modulation of allergic reactivity is filarial-antigen specific (since the blocking antibodies are themselves antigen specific).

4.3.1.3 *Suggestions for further study.*

(*a*) While several distinct immunosuppressive mechanisms have been described in lymphatic filariasis, the complexity of the immune system in its interaction with these parasites is such that many more probably exist. It is, therefore, important to continue efforts to define the immunological effector and suppressor elements that are active during chronic infection.

(*b*) The biological implications of these immunosuppressive mechanisms need to be defined.

(*i*) Are they beneficial or harmful to the host?
(*ii*) Are they important in determining the clinical manifestations of filarial disease?
(*iii*) Do they play an role in natural immunity?
(*iv*) Will they complicate efforts to induce immunity by vaccines?

(*c*) The temporal development of these suppressive mechanisms should be characterized and their determinants studied. The possibility that they are established prenatally (*in utero*) or early in childhood must be explored.

4.3.2 *Immunological determinants of clinical filariasis*

4.3.2.1 *Clinical and immunological correlates* (*10*). Although the determinants of each of the clinical manifestations of filarial infection cannot yet be defined, it is possible to recognize characteristic clusters of immune responses in different groups of patients.

(*a*) *Tropical pulmonary eosinophilia.* The most unequivocal clustering is that found among patients with tropical pulmonary eosinophilia. These individuals make up fewer than 1% of all patients with filariasis and clinically they appear to be entirely distinct from the other groups of patients. Immunologically they are extremely hyperresponsive to all filarial antigens but especially to those derived from microfilariae. Antifilarial antibodies of all classes are markedly elevated, and the IgE and eosinophil levels are as high in this condition as in any non-neoplastic disorder; lymphocyte responses, too, are uncharacteristically elevated. This clinical syndrome is now generally regarded as a form of occult filariasis, in which the absence of circulating microfilariae reflects an immunological hyperresponsiveness on the part of the host that leads to very effective clearance of these parasites from the blood. Most of this clearance is probably mediated by IgG antibodies and is effected preferentially by the lungs, with the asthmatic symptoms resulting from allergic responses mediated through specific IgE antibodies bound to lung mast cells. While the acute phase thus appears to develop in relation to antibody-dependent mechanisms, the chronic phase of the syndrome, which is marked by pulmonary fibrosis and restrictive lung disease, may result more from tissue damage induced by the heightened or inadequately suppressed lymphocyte or by eosinophil responsiveness.

(*b*) *Asymptomatic microfilaraemia.* Individuals with microfilaraemia who are asymptomatic and without acute or chronic lymphatic involvement are the least immunologically reactive group. Their lymphocytes generally fail to respond to filarial antigens *in vitro* and their levels of serum antibodies to both adult and

microfilarial antigens are minimal or absent. This hyporesponsiveness is probably a manifestation of hyperreactive suppressor mechanisms limiting responsiveness to the parasite; it is likely that the clinical hyporeactivity of the host is a direct consequence of this concomitant immunological hyporesponsiveness.

(*c*) *Lymphatic pathology*. While some microfilaraemic patients remain asymptomatic for decades, others develop intermittent episodes of adenolymphangitis. It is unclear which immune mechanisms initiate these episodes, but the importance of this inflammation in the development of the lymphatic damage and pathology that characterize chronic filariasis cannot be overestimated. These patients with recurrent adenolymphangitis have been little studied as a group, partly because they blend almost imperceptibly into the larger group of symptomatic patients who have overt elephantiasis or hydrocoele. In both groups however, it is reasonably clear that immune responsiveness to filarial antigens, both cellular and humoral, is greater than in patients with asymptomatic microfilaraemia. It may be that the same increased immunological recognition of the parasite (or less effective immunosuppression), which can result in microfilariae being cleared from the blood, also induces increased local inflammatory responses that lead to the subsequent lymphatic damage and characteristic obstructive pathology. Indeed, there is confirmatory evidence from animal experiments that amicrofilaraemia depends on the production of anti-microfilarial antibodies and that there is direct correlation between the severity of lymphatic lesions and the intensity with which the host responds to parasite antigens.

(*d*) *Asymptomatic and amicrofilaraemic inhabitants of endemic areas ("endemic negatives")*. Individuals living in endemic regions who have no clinical or parasitological evidence of infection make up a particularly important group for study. As a group, their immune responsiveness to filarial antigens may be quite high, regardless of whether lymphocyte or antibody responses are evaluated, but it is unclear why this is so. It is probable that this group is very heterogenous, with some individuals being immune to the parasite and others harbouring the "post-patent" or other occult infections described in numerous animal models but not yet in man. Until this group can be more precisely defined clinically and parasitologically, it will be impossible to determine which types of

immune response in man are associated with naturally developing protective immunity and which with other manifestations of infection.

4.3.2.2 *Predisposing host factors affecting the response to infection* (*11*). If the different clinical manifestations of filarial infection result from different types of immunological response among infected individuals, then it is important to know why different individuals do not respond in the same way to parasite infection. Two types of experimental approach have been used, one looking at genetic and the other at prenatal predisposing factors.

When a large Polynesian population living in an area endemic for bancroftian filariasis was studied, there was significant familial clustering of patients with filariasis, and this clustering suggested genetic inheritance of susceptibility to infection. The alternative hypothesis that susceptibility was environmentally (i.e., not genetically) determined was also compatible with the data but was estimated to be 1.9 times less likely to account for the observed findings than was the genetic hypothesis. Extensive evaluation of HLA-A and HLA-B locus specificities failed to detect any significant linkage between HLA antigens and either the clinical manifestations of filariasis or the predisposition to filarial disease.

Before approaching the question of how prenatal conditioning (i.e., being born of a parasitized or non-parasitized mother) might affect the way in which an individual would subsequently respond to infection, it has first been necessary to determine whether or not prenatal sensitization actually occurs. Two recent immunological studies support the earlier isolated reports of congenital microfilaraemia and suggest that prenatal sensitization does occur. The first study reported IgM antifilarial antibodies in the cord sera of a small number of babies born in a region endemic for *W. bancrofti,* and the second showed that at least half of the babies born to infected mothers produced specific IgE antibodies directed against the parasite. These findings are significant because neither IgM nor IgE antibody crosses the placenta. Long-term follow-up of these prenatally sensitized children is not available.

4.3.2.3 *Suggestions for further study.*

(*a*) The more that is known about the immune responses of different clinical groups, the more likely it is that an understanding

of the pathogenesis of filarial disease will be reached. Therefore it is necessary to continue analysing these responses in increasingly greater detail. The following are examples.

(*i*) Can the use of better-defined and more highly purified antigen preparations lead to a greater understanding of the clinically important host responses?
(*ii*) Can newer immunological techniques of T- and B-cell cloning lead to a better definition of the regulatory mechanisms involved in the host's response to infection?
(*iii*) How can "harmful" host responses be distinguished from "helpful" ones so that such responses can be selectively manipulated?
(*iv*) What role do immune complexes or autoimmune reactions play in the regulation of host responsiveness or the determination of pathology?
(*v*) What initiates the adenolymphangitis that is so critical in the development of lymphatic pathology?
(*vi*) How do immune responses localized in the lung or lymphatics differ from those studied in the blood in patients with localized disease?

(*b*) Antigen detection assays must be developed and used to define which individuals in that heterogenous group of "endemic negatives" actually have occult infection, and which have developed immunity.

(*c*) The issue of differential susceptibility to infection or disease should be examined using recently available and increasingly more precise genetic markers. Populations with patients having the hyperresponsive tropical pulmonary eosinophilia syndrome should be studied with particular care.

(*d*) Studies of cord blood and of infants born to infected and noninfected mothers should be expanded to define more of the cellular and humoral alterations in these children, which might have a bearing on their subsequent susceptibility to infection or disease.

4.4 Filarial antigens, immunodiagnosis, and protective immunity

4.4.1 *The antigens*

The antigens of greatest importance in lymphatic filariasis are those related to immunodiagnosis, protective immunity, and im-

munopathology. Ideally, such antigens should be specific for each filarial species and for each developmental stage. Since these are molecules that are defined functionally (i.e., by eliciting an immune response), their analysis should be closely integrated with functional studies. Thus, immunochemical techniques (such as affinity chromatography, immunoprecipitation, etc.) are especially useful for purifying antigens and are valuable additions to the more traditional biochemical techniques for antigen purification.

4.4.1.1 *Antigens derived from* Wuchereria *or* Brugia *species* (*12, 13*). One of the most significant advances in the study of antigens from filarial parasites of man has been the development of techniques for increasing the availability of parasite material. *Brugia* spp. can be reared intraperitoneally in jirds, allowing the collection of adult filarial parasites, as well as microfilariae, in quantities sufficient for ready antigenic analysis. The collection of microfilariae from the blood of patients with *W. bancrofti* as well as *Brugia* infections has been possible for some time, but the development of techniques for the successful cryopreservation of microfilariae simplifies the task of studying these parasites in convenient laboratory settings.

While intact parasites and crude somatic extracts continue to be used in diagnostic and clinical studies, many recent studies have focused on the analysis of either surface or excretory-secretory (E-S) antigens, since these appear to have a greater stage and species specificity. Experiments to radiolabel surface proteins of certain non-filarial parasites have suggested that nematode surfaces may be very simple and distinct antigenically, but studies with *B. timori* and *B. malayi* have been less encouraging. In these species, there is not only appreciable surface protein antigenic complexity but also cross-reactive or shared antigens, both among the different life-cycle stages (adult, microfilaria, L_3) of each species and among the different species themselves. These antigens range in apparent relative molecular mass from 15 to 160 by SDS-PAGE analysis.[1] Most are derived from the parasites themselves, but some are clearly identifiable as being of host origin.

In contrast to this protein antigen complexity of the parasite surface, studies with lectins to analyse carbohydrate and glyco-

[1] Sodium dodecyl sulfate–polyacrylamide gel electrophoresis.

protein moieties have indicated no appreciable carbohydrate exposed on the surfaces of either adult or L_3 forms of *B. malayi*. In contrast, *B. malayi* microfilariae collected from the peritoneal cavity of jirds readily bound wheat-germ agglutinin, indicating the presence of exposed residues of *N*-acetyl-D-glucosamine; microfilariae derived *in vitro* directly from the uterus bound not only wheat-germ agglutinin but also a second lectin, concanavalin A, whose specificity is for glucose and/or mannose residues. Such observations show that there is stage specificity of the carbohydrate-containing antigens on the parasite surface and also a changing or dynamic aspect of these surface molecules that reflect either masking by host proteins or actual loss of surface antigens as microfilariae mature *in vivo*.

Stimulated by the marked stage and species specificity found in the E-S antigens of other species, studies have been undertaken to characterize and define the potential usefulness of E-S antigens derived from *B. malayi* adult worms maintained *in vitro*. Such antigens are less complex than the somatic extracts from adults but they account for most of the immunoreactivity of these somatic antigen preparations. They appear to be a subset of the antigens found in the crude somatic preparations; they have molecular weights in the range of 10–70 and they can be shown to contain certain of the surface antigens that can be identified by protein radiolabelling techniques.

4.4.1.2 *Antigens derived from non-human filarial parasites.* Analyses of surface and somatic antigens using biochemical, immunochemical, and radiolabelling techniques have also been carried out on a variety of other filarial parasites, including *Setaria* spp., *Dipetalonema viteae, Onchocerca* spp., *Litomosoides carinii, B. pahangi,* and *Dirofilaria immitis*. In general, the conclusions were similar to those made in studies with *B. malayi* and *B. timori*. There is extensive stage and species cross-reactivity among crude somatic extracts, while certain fractions of these extracts show greater stage and species specificity than others. Surface antigens also show appreciable stage and species cross-reactivity, and there appears to be surface-antigen loss or masking as microfilariae mature from *in utero* to *in vivo* forms. The potential usefulness of these "heterologous" antigens in immunodiagnosis and protective immunity is discussed below.

4.4.1.3 *Suggestions for further study.*

(*a*) Filarial parasite material remains in extremely limited supply. Efforts should be made to increase the production of those filarial parasites of man that can be maintained either *in vitro* or in an animal model and to ensure that this material is available to competent individuals who have no direct access to the parasites themselves.

(*b*) Much of the problem of antigen supply could be overcome by the use of recombinant DNA technology if the appropriate parasite genes could be cloned to produce antigen. Accordingly, particular emphasis should be given to developing gene libraries of parasite DNA and to encourage the production of monoclonal antibodies with the unique specificities necessary to identify important parasite antigens.

(*c*) Efforts to define and isolate the antigens that are *functionally important* for immunodiagnosis, immunopathology, and protective immunity should continue, using the array of new immunochemical techniques available.

(*d*) Standardized protocols for the preparation and preservation of these "useful" antigens should be made available and adhered to by the various investigating groups. Maintenance and distribution of reference standards for antigens that prove especially useful should be coordinated by WHO.

4.4.2 *Immunodiagnosis*

Good immunodiagnostic tests would be of value for many aspects of lymphatic filariasis, including the following.

(*a*) Clinical situations such as:
- (*i*) diagnosis of amicrofilaraemic states, i.e., prepatent infections, chronic infections without microfilaraemia, tropical pulmonary eosinophilia, and filarial granulomas;
- (*ii*) quantifying the worm burdens of infected patients;
- (*iii*) defining the etiology of potentially filaria-related syndromes, such as arthritis, cardiomyopathy, tenosynovitis, etc.;
- (*iv*) assessing the effectiveness of treatment in individuals.

(*b*) Epidemiological situations, such as:
- (*i*) definition of critical factors necessary for epidemiological evaluation, e.g., intensity of infection, evidence for past

infection or recent exposure to infective larvae, distinction between states of resistance or susceptibility to infection;

(*ii*) indication of exposure to non-human filarial parasites;

(*iii*) evaluation of control measures.

Reliable immunological methods would also be useful for identifying the human and animal filarial parasites present in vector or reservoir hosts.

Traditionally, immunodiagnostic tests have been serological or skin-test determinations of antibodies generated by the host and, while there have been dramatic recent advances in development of the techniques used to detect these antibodies (e.g., the enzyme-linked immunosorbent assay, ELISA), there has been little progress in the use of such techniques for the diagnosis of filarial infections. In part this is because the antigens used have not been specific enough to overcome the persistent problem of cross-reactivity among the filariae and other helminths. As all such assays share the major drawback of being unable to discriminate between past exposure and current infection, recent interest has focused instead on the direct detection of parasite antigens in patients' blood or urine, an approach that yields a "parasitological" diagnosis by employing techniques with sensitivities dramatically increased by immunological means.

4.4.2.1 *Antibody assays.* Immunodiagnostic techniques with "low or moderate sensitivity", such as complement fixation, gel diffusion, latex agglutination, indirect haemagglutination, and indirect immunofluorescence, have largely been replaced by those of "high sensitivity", such as the labelled-reagent assays (radioimmunoassay, fluorescence immunoassay, enzyme immunoassay, luminescence immunoassay, etc.) for immunodiagnostic purposes. However, the dramatically increased sensitivity of these assays (detection of femtogram or attogram[1] levels of antibody), means that assay reagents of equally enhanced specificity must be developed before these sensitive diagnostic techniques will be more useful than the less sensitive tests employed previously.

Recent efforts to define highly specific antigen and antibody preparations that can be used in these assays have led to the following conclusions.

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[1] 1 femtogram = 1×10^{-15} gram; 1 attogram = 1×10^{-18} gram.

(*a*) It is likely that homologous (*Wuchereria* or *Brugia* spp.) antigens are preferable to heterologous ones for developing specific immunodiagnostic tests. Successful maintenance of *Brugia* infections in jirds has permitted the use of *B. malayi* and *B. timori* parasites to develop antigens for diagnosing filarial infections, but the general unavailability of *W. bancrofti* parasites has led to attempts to purify, from heterologous filariae, antigen fractions that show "specificity" for these human parasites. Such studies have included the use of antigens of *Setaria digitata, Dipetalonema viteae, Onchocerca gibsoni, Litomosoides carinii,* and *Dirofilaria immitis* and, although fractionation of the crude antigens does diminish cross-reactivity, it can be said that no antigens from these heterologous parasites have yet been isolated with clear stage or species specificity for the human lymphatic filariae.

(*b*) E-S or surface antigens of homologous parasites are simpler and almost certainly more specific antigen preparations than the whole worm somatic extracts of which they appear to be subsets. For neither type of antigen, however, have stage- or species-specific components yet been isolated.

(*c*) The isotype or subclass of host antibody may be important in conferring greater or lesser specificity on immunodiagnostic tests. For example, IgE antibody responses have greater specificity than IgG responses in human filarial infection. Qualitative analysis of these IgE antibodies has only recently begun, and the implications of the findings for immunodiagnosis are still uncertain.

(*d*) Skin tests are also assays of high sensitivity used to detect specific IgE antibodies. However, since they are currently used with antigens of inadequate specificity, they are of little help in immunodiagnosis.

(*e*) Monoclonal antibodies of high stage- and species-specificity have been produced and are currently being evaluated for their usefulness as immunodiagnostic reagents in a number of different assay systems. Their use should be of enormous value in increasing both the specificity and sensitivity of future immunodiagnostic techniques.

4.4.2.2 *Antigen assays.*[1] The major shortcoming of immunodiagnostic techniques based on the detection of antibody in the infected host is their inability to distinguish past exposure from

[1] See also reference *14*.

current infection. Detection of parasite material (antigens or other products) in blood or urine should be much more effective in assessing an individual's infection status.

Circulating parasite antigen in patients with bancroftian filariasis has already been demonstrated using techniques of moderate sensitivity such as counter-current immunoelectrophoresis and indirect haemagglutination, but positive results have been confined almost exclusively to sera from microfilaraemic individuals. Increasing the sensitivity of the techniques used, e.g., by radioimmuno-polyethylene–glycol assay (RIPEGA), immunoradiometric assay (IRMA), or the two-site radioimmunoassay, has permitted the detection of increased numbers of patients infected with *W. bancrofti,* and this approach promises to be of considerable diagnostic help in the future.

However, detection of circulating antigens can be complicated by the binding of antigen into immune-complexes. Such complexes are common in sera from patients with filariasis although the antigens they contain are largely undefined. The potential for binding individual antigens depends on the relative concentrations of specific antigen and antibody in the serum. Variability in the amount of serum antigen in the free or bound state certainly makes it difficult to develop a *single* assay for detecting circulating antigens in all situations, and may make it impossible to quantify accurately the intensity of infection based on this type of assay.

4.4.2.3 *Cellular assays.* Cell-mediated immune responses of patients have been evaluated by delayed hypersensitivity skin tests and *in vitro* lymphocyte responses to parasite antigens. Neither assay has yet been shown to have the necessary sensitivity or specificity (much less the ease of performance) to be used as an immunodiagnostic test. Similarly, although specific antibody-dependent cellular adherence and cytotoxicity responses have been described in affected patients, there is as yet no practical way to exploit these reactions in immunodiagnosis.

4.4.2.4 *Suggestions for further study.*

(*a*) Immunodiagnostic techniques based on the detection of antigen or other parasite products must be developed to diagnose active infection, prepatent infection, and the intensity of infection (i.e., worm burden). Development of such assays will necessitate the

production of monoclonal antibodies to provide reagents of high and reproducible specificities.

(*b*) Analysis of antibody responses should continue with special emphasis on potential differences in the specificity of the various antibody isotypes and subclasses that have to date received little attention.

(*c*) Longitudinal studies of antibody and/or antigen levels in individuals undergoing treatment should be initiated to determine the value of these immunodiagnostic techniques in assessing the effects of treatment programmes.

(*d*) Antigens found to be particularly useful in immunodiagnosis should be produced by DNA cloning techniques if possible, to ensure an adequate supply and to obviate the need for extraction from the parasites themselves.

(*e*) Specific immunodiagnostic probes should be developed to distinguish the different species and stages of developing filarial larvae in mosquito vectors.

(*f*) Reagents for immunodiagnostic tests (both antigens and antibodies) should be standardized in a reference bank and made available to interested investigators to ensure reproducibility and equivalence among different diagnostic laboratories. This goal has already been partly achieved with the establishment of a reference bank[1] of species-specific sera from patients infected with each of the different filarial infections.

(*g*) When appropriate antigens are recognized, efforts should be made to develop a skin test or other simple immunodiagnostic test that can be easily carried out in epidemiological field studies.

4.4.3 *Protective immunity and potential for developing vaccines*

4.4.3.1 *Current status* (*15, 16*). Information about protective immunity in man is scanty. The general shapes of age-prevalence (microfilarial) and age-density (microfilarial) curves indicate that protective immune responses do occur, but only after many years of exposure. Thus, the mechanisms involved in this protective immunity in man are difficult to study and to date remain undefined. In certain animal models, protective immune resistance to challenge with infective larvae has been described, but the mechanisms under-

[1] Supported by the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases.

lying this immunity are also poorly characterized, largely because the model systems employed are expensive or cumbersome to study. In the absence of significant knowledge regarding the mechanisms of protective immunity, there has been little direct effort towards the development of vaccines.

The most efficient form of protective immunity would be that directed against the infective or early developing larval stages of the parasite. Successful vaccination against these stages has, indeed, been achieved using live, radiation-attenuated infective third-stage larvae of several filarial species in dogs, cats, jirds, and monkeys. In general, the effective doses of irradiation are those sufficient to inhibit or arrest development of the third- and fourth-stage larvae, but which do not kill the parasites. Such immunizations have been up to 80–100% effective, with the effects lasting at least a year. The antigens responsible for stimulating these protective responses and the types of immune mechanism involved have not been defined. It is clear, however, that such protection can be both stage- and species-specific and that killed parasites or parasite extracts are greatly inferior to living, attenuated parasites in inducing this protective immunity. While the use of irradiated larvae for immunization could not be considered for human populations, it is hoped that the mechanisms underlying the immunity induced by this technique can provide ideas for new approaches to vaccine development.

Much more is known about "immunity" to the microfilarial stage of the parasite. Animals specifically immunized or spontaneously developing anti-microfilarial antibodies rapidly clear microfilariae from the blood and remain amicrofilaraemic. Similar observations have been made in man. Such "immunity", however, appears not to affect the viability of adult worms. Therefore, while obviously inhibiting transmission of the parasite (and therefore of potential value to community control efforts), it would probably be of limited benefit for the individual.

Studies of parasite killing by host effector cells and molecules are readily carried out *in vitro* and may provide clues to the mechanisms of protective immunity *in vivo*. Both infective larvae and microfilariae of several different species have been used as targets, and although details sometimes differ among studies, evidence has been presented that complement alone, specific antibody alone (IgG, IgM, or IgE directed against the parasite surface), or antibody and complement together, can result in the adherence of eosinophils, neutrophils, and/or macrophages to the parasites. This subsequently

kills the parasite as these cells degranulate their lysosomal contents onto its surface. Which of these mechanisms for parasite cytotoxicity is most important to the human host, either for protective immunity or for the clearance of parasitaemia *in vivo*, is not clear.

4.4.3.2 *Suggestions for further study.*

(*a*) Careful descriptions of the host immune mechanisms associated with protective immunity should be undertaken. In man this would mean:

(*i*) more precise definition of the apparently non-infected individuals of endemic regions and their division into those with true immunity and those harbouring occult infections;

(*ii*) analysis of factors potentially affecting host responsiveness to the parasite, such as genetic influences (including HLA or other IR gene associations), prenatal induced tolerance or sensitization, and infant or early childhood exposure to filariae and other infections.

In animals such descriptions would mean:

(*iii*) definition of the immune mechanisms that determine experimentally-induced protective immunity, including correlation between the parasite killing mechanisms, defined *in vitro* and the protective immunity seen *in vivo*.

(*iv*) evaluation of the reasons why different host species vary in their susceptibility to filarial infections, why animals within a single species or strain but of different sex show similar variability, and why even different individuals of the same sex in inbred strains differ in their response to infection. Such analyses should provide clues to the mechanisms that are important in determining protective immunity.

(*b*) New models for protective immunity that are less cumbersome than those currently available must be developed. These could include "proxy hosts" for isolating single stages of the parasite life-cycle but should preferably involve natural host-parasite systems in which responses would be similar to the situation found in man. Work with the leaf monkey, (*Presbytis* spp.) experimentally infected with *W. bancrofti* or *B. malayi* should be especially encouraged.

(*c*) Potential problems with vaccines should be analysed; for example:

(*i*) their effectiveness in presence of the antigen-specific immunosuppression found in infected individuals;
(*ii*) their potential for inducing immunopathology in both previously sensitized and non-sensitized hosts.

(*d*) The role of different adjuvant systems to enhance desired immune responses should be evaluated.

5. EXPERIMENTAL FILARIASIS

Two major areas of research have yielded valuable and important results since the last meeting of the WHO Expert Committee on Filariasis. These are:

(*a*) successful transmission of *W. bancrofti* to monkeys;
(*b*) partial success with the *in vitro* culture of both the arthropod and mammalian stages of human and related filarial parasites.

5.1 Transmission studies

5.1.1 *Transmission of* Wuchereria *spp. to monkeys*

The establishment of the life cycle of *W. bancrofti* in the laboratory has required experimentation with a large variety and number of laboratory animals. The development of adult worms and microfilaraemia was first demonstrated in experiments with the Taiwan monkey (*Macaca cyclopis*) (*17*). A total of 78 monkeys (some immunosuppressed) were exposed to infection with strains of the parasite from China and Indonesia; worms were recovered from 29 animals and circulating microfilariae were found in 9. The earliest prepatent period was 8 months; microfilarial densities in all of these monkeys were low. In other studies, with a Malaysian strain of rural *W. bancrofti,* gravid females were found to develop in *M. fascicularis* but did not produce microfilaraemia. In India, attempts to infect *M. radiata, M. mulatta,* and the slow loris (*Loris tardigradus*) were unsuccessful.

Recently, leaf monkeys were reported to be easily infected with *W. bancrofti,* often resulting in the development of microfilaraemia (*18, 19*). In Thailand, *Presbytis melalophos* and *P. cristata* were infected with the Thai rural strains; significant numbers of worms were recovered (as many as 79) and the microfilarial densities ranged

from 11 to 619 per mm^3 of blood. The best results were obtained in monkeys given cortisone as an immunosuppressant. In other studies in Indonesia, an urban strain of the parasite was reported to develop, with patent infections in 4 out of 7 *P. cristata.* From each monkey 2–5 worms were recovered and the microfilarial densities varied from 1 to 26 per ml of blood.

A new species of *Wuchereria, W. kalimantani,* has been obtained from *P. cristata* trapped in South Kalimantan, Indonesia. The parasite was located in the inguinal lymph nodes and testes, and microfilariae were found in the blood of 22 out of 64 animals examined. Third-stage larvae have been recovered from experimentally exposed *Anopheles subpictus* and *A. balabacensis* so that the establishment of the life cycle can now be accomplished in the laboratory; in addition to having a natural host for wuchererian filariasis, it may be possible to transmit the parasite to other animals.

5.1.2 *Attempts to transmit* Wuchereria *spp. to rodents*

Although *Wuchereria* species have been established in monkeys, a small laboratory animal model needs to be established for *W. bancrofti* and *W. kalimantani* in order to have a practical, inexpensive system in which to carry out a variety of immunological and chemotherapeutic studies. Attempts have been made to find such a laboratory animal model with variable results. Partial development of *W. bancrofti* is reported in jirds, hamsters, and multimammate rats; in more recent studies, an adult male worm was recovered from a jird after 92 days, and advanced fourth-stage larvae or young adults were recovered from hamsters after 60 days.

5.1.3 *Suggestions for further study*

Attempts to adapt strains of *W. bancrofti* by serial passage through *Presbytis* species should be encouraged. At the same time the strains should be introduced into available inexpensive species of monkeys and laboratory rodents such as jirds, hamsters, and multimammate rats in an attempt to adapt the strains into more easily workable animal models. Strains of parasite from various geographical areas should also be used. Similar experiments should be carried out with *W. kalimantani.*

5.2 *In vitro* maintenance and culture of filarial parasites

5.2.1 *Maintenance*

Filarial parasites can be maintained alive in certain *in vitro* culture media for various periods of time, and both the microfilariae and infective larvae can be successfully cryopreserved. Such parasites have been used in biochemical and metabolic studies, which have led to an enhanced understanding of the feeding and uptake mechanisms of the worm, and to the identification of biochemical pathways, unique to these parasites, that might serve as targets for specific antifilarial chemotherapy.

5.2.2 *Culture*

A clear definition of the different stages of filarial parasites must be kept in mind when assessing studies of *in vitro* parasite culture:

microfilaria	—the unique pre-larval form characteristic of filarial parasites
first-stage (L_1)	—from microfilaria to the first moult in the arthropod vector
second-stage (L_2)	—from the first to the second moult in the arthropod vector
third- or infective-stage (L_3)	—from the second moult in the arthropod vector to the first moult in the mammalian host
fourth-stage (L_4)	—from the first to the second moult in the mammalian host
juvenile adult	—from the second moult in the mammalian host to sexual maturity
adult	sexually mature parasite.

Advances have recently been achieved with the *in vitro* culture of both the arthropod and mammalian stages of filarial parasites. Prior exsheathment of sheathed microfilariae appears obligatory for *in vitro* culture to the first-stage (L_1) and this can be artificially induced. Mosquito cell lines have allowed more than 14% of exsheathed *B. pahangi* microfilariae to develop to the late sausage-stage (L_1) by days 7–8 and these survive for over 30 days. However, 80–90% of *W. bancrofti* microfilariae exsheathed and 30% developed to L_1 after 8 days in Medium 199 supplemented with organic acid, sugars of Grace's insect medium, and 10% inactivated human serum at pH 7.4 and 28 °C. To date there has been no *in vitro* development of microfilariae to infective-stage larvae in any of the lymphatic filarial parasites studied.

Significant advances have recently been achieved in the cultivation of the mammalian stages of lymphatic filarial parasites (*20*). After 3 days of *in vivo* priming in jirds, the majority of *B. pahangi* L_3 moulted to L_4 after 5 days incubation in Medium 199 with a dog sarcoma cell line as a feeder layer. This prior *in vivo* priming also allowed *Dipetalonema viteae* L_3 to moult to L_4 in a system with a hamster kidney cell line (BHK) feeder layer, BHK-21 medium, 10% tryptose-phosphate-broth, and 15% fresh jird serum. The presence of an irradiated BHK feeder layer was able to replace the *in vivo* trigger and induce moulting. Complete moulting of *B. pahangi* and *Dirofilaria immitis* L_3 and L_4 has been obtained in culture systems using bovine embryonic kidney (BEK) and dog skeletal muscle (DSM) with Minimum Essential Medium, supplemented with 10% fetal calf serum. *B. malayi* and *B. pahangi* L_3 have been cultured to L_4 and juvenile adults in a system using rhesus monkey kidney cell line (LLC-MK_2) with RPMI-1640 medium, 10% inactivated human serum, and incubation at 37 °C in air. The larvae survived for more than 7 weeks. Similar success has recently been achieved with *in vitro* culture of *D. immitis* larvae. Systems such as these are now being used for the screening of potential antifilarial drugs (*21*).

5.2.3 *Suggestions for further study*

(*a*) Further development of *in vitro* culture techniques for the production of infective larvae and sexually mature adults.

(*b*) Development of continuous filarial cell lines from various stages of filarial parasites.

(*c*) Adaptation of maintenance and culture techniques for the *in vitro* screening of drugs against various stages of the parasites.

6. CHEMOTHERAPY

6.1 Diethylcarbamazine

Over the past 35 years diethylcarbamazine (DEC) has been the drug of choice for treating lymphatic filariasis. As the mainstay of treatment, both of the individual case and of infected communities, it has been administered to millions of persons throughout the world under widely varying conditions of endemicity and in various doses. This widespread experience with DEC has shown it to have a low toxicity and to be safe for large-scale use in lymphatic filariasis, even under circumstances of limited medical supervision. Attempts to

find favourable alternatives to DEC have been made, but none has so far been found. An important goal for the immediate future is, therefore, to determine the most acceptable dosage schedules of DEC within the limits of toxicity, efficacy, and feasibility.

6.1.1 *Chemistry and physical properties*

The chemical name of diethylcarbamazine is 1-diethylcarbamyl-4-methylpiperazine.

DEC was first used as the chloride, but it is now produced as the dihydrogen citrate which contains only half its weight as base. For convenience, and because the chloride is no longer in use, the abbreviation DEC is used in this report for diethylcarbamazine citrate as well as for the base. In reporting doses it is important to indicate whether they refer to a specific salt or to the base; unless otherwise stated, it can generally be assumed that the dose refers to the citrate.

DEC is a white powder, freely soluble in water, with a slightly unpleasant sweetish taste. It is stable under all ordinary laboratory conditions including autoclaving and cooking when used in medicated salt.

Estimation of DEC in blood, body fluids, and urine can usually be made by a simple colorimetric method in the field. More accurate estimation in the laboratory can be made by gas–liquid chromatography.

6.1.2 *Absorption, excretion, distribution, and metabolism*

The drug is rapidly absorbed after oral (as well as cutaneous or ocular) administration with peak blood levels of about 100 ng/ml 1–2 hours after an oral dose of 50 mg of DEC. Higher doses (800 mg) generally result in peak blood levels of 4–5 ug/ml.

DEC rapidly equilibrates with all tissues (including hydrocoele fluid and presumably other body fluids) and it is not concentrated either by specific organs in the host or by adult or microfilarial stages of filarial parasites when these have been studied in animal models.

Excretion in man is primarily renal with the blood half-life depending on the urine pH. In acid urine, the blood half-life of DEC is only 2–3 hours but in alkaline urine it is about 10–12 hours. In acid urine, 60–80% of DEC is excreted unchanged in the urine within 48 hours, with 10% appearing as DEC-*N*-oxide; 4–5% of the DEC dose is excreted in the faeces.

6.1.3 *Action of lymphatic filarial parasites*

6.1.3.1 *Action on microfilariae. In vitro* studies have shown that therapeutic concentrations of DEC have no significant effect on the microfilariae of any species. *In vivo,* however, DEC causes a rapid disappearance of microfilariae from the circulation. It has been shown that its microfilaricidal action depends upon the proper function of the humoral and cellular immune mechanism of the host. Most of the microfilariae from the blood are destroyed by the reticuloendothelial cells of the liver; but some of them may not be affected, even after repeated courses of DEC. The microfilariae of *W. bancrofti* in hydrocoele fluid are not affected by DEC. The precise mechanism of action of DEC remains a subject of debate.

6.1.3.2 *Action on the development of microfilariae in the mosquito.* DEC may not achieve a complete clearing of microfilariae in all individuals. Surviving microfilariae are able to develop in the insect host even after exposure to repeated courses of DEC.

6.1.3.3 *Action on third- and fourth-stage larvae.* DEC has no effect on third-stage larvae of *W. bancrofti in vitro,* but it has a prophylactic action on *B. malayi* in cats and *Presbytis* monkeys. It is reported that DEC given orally at 5 mg/kg body weight to *Presbytis* 2 days before, and up to 7 days after infection, was lethal to the infective larvae. The same dosage given 29–35 days after infection killed fourth-stage larvae and protected the monkeys from developing a patent infection. Its possible chemoprophylactic action against *W. bancrofti* and *B. malayi* in man is currently under investigation.

6.1.3.4 *Action on adult worms.* In man, DEC has a considerable macrofilaricidal action against the lymphatic filarial parasites. Direct evidence of this macrofilaricidal action was obtained from patients who, after treatment with DEC, developed local nodular reactions in the lymphatics. When these nodules were excised, they were found to contain dying or dead adult worms surrounded by degenerated cells. Indirect evidence of an action on adult worms can be obtained from microfilaraemic persons treated with DEC. After adequate treatment, the microfilariae disappear quickly and, in most cases, the microfilariae do not reappear, even after a period of 4–6 years, by which time any surviving adult worms could presumably have recovered from any temporary damage. However, sometimes not all

the adult worms are killed, even after repeated courses of DEC. A proportion of patients so treated continue to experience periodic attacks of adenolymphangitis, a sign of active infection with adult worms. The mechanism by which DEC kills adult worms is not clear.

6.1.4 *Action on disease manifestations*

While the value of using DEC to treat filarial infection is undeniable, none of the results at present available shows that treatment during the acute clinical phase is any more beneficial than simply waiting until the acute reactions subside spontaneously. However, there may be advantages in giving treatment during the acute phase since the side-effects of treatment will be masked by the acute clinical manifestations already present.

6.1.4.1 *Action of DEC on the recurrence of acute clinical manifestations.* The prevalence and incidence of adenolymphangitis decrease significantly after treatment with DEC. The frequency of attacks of funiculitis, epididymitis, and orchitis is also reduced by DEC. Longitudinal studies show that DEC therapy (either during the acute adenolymphangitis or chronic asymptomatic phases) reduces the likelihood of developing chronic obstructive lesions. There is no evidence that DEC treatment provokes the development of elephantiasis.

6.1.4.2 *Action on chronic clinical manifestations.* Patients with transient lymphoedema, small developing hydrocoele, or chyluria usually respond well to treatment with DEC, although repeated courses are often necessary to eliminate all the adult worms. The treatment of microfilaria carriers with DEC reduces the incidence of chronic disease. Patients with early elephantiasis, who also have pitting oedema, are often favourably affected by treatment. In some cases, elephantiasis of several years' duration can be reduced partially or completely by DEC treatment alone. However, patients with a large hydrocoele and/or elephantiasis with deformities often do not show any improvement after DEC treatment.

6.1.4.3 *Action on occult filariasis.* DEC is the drug of choice for tropical pulmonary eosinophilia. Marked clinical and haematological improvement occurs within a few days but relapses may occur in as many as 20% of patients, who then require retreatment. Pul-

monary function returns to normal only if damage to the lungs is not extensive. In other forms of occult filariasis DEC has also been used, often with beneficial effects.

6.1.5 *Drug resistance*

Although resistance to anthelminthic drugs is known to have developed in some non-filarial nematodes, no experimental or clinical evidence of resistance to DEC has yet been reported for any human filarial parasite. Persistent microfilaraemia after treatment with DEC is probably not due to resistance to the drug. Factors such as malabsorption of the drug or deficiency of the host immune system, may be responsible for this phenomenon. Additional courses of DEC usually eliminate the residual microfilaraemia.

6.1.6 *Pharmacological toxicity and side-reactions*

The reactions that occur with DEC treatment of lymphatic filariasis are basically of two types. The first is a pharmacological dose-dependent response to the chemical properties of the drug itself, which occurs equally frequently in infected and non-infected recipients. The second is a response of the infected host to the destruction and death of parasites, which is, within limits, independent of dose but directly related to the parasite burden.

6.1.6.1 *Pharmacological toxicity.* Direct effects of the drug in persons who have no filarial infection are dose-dependent and include the following: weakness, dizziness, lethargy and sleepiness, anorexia, nausea, and vomiting. These symptoms begin within 1–2 hours of taking the drug, and persist for a few hours.

There is no accumulation of the drug following prolonged administration and chronic toxicity does not occur. There are no known abortifacient or teratogenic effects.

6.1.6.2 *Effects attributable to filaricidal action.* Certain reactions to treatment with DEC occur in persons infected with bancroftian and brugian filariasis. These are thought to be immunological reactions to the disintegrating microfilariae and dead adult worms. It is generally agreed that such reactions are less likely to occur and are less severe in bancroftian filariasis than in brugian filariasis. There

are 2 groups of reactions, systemic and local, both with and without fever.

(*a*) *Systemic reactions* include headache, aches in other parts of the body, pain in the joints, dizziness, anorexia, malaise, urticaria, vomiting, and sometimes attacks of bronchial asthma in asthmatic patients. These side-effects occur more or less in decreasing frequency in the order given above, and in varying combinations. They may occur a few hours after the first oral dose of DEC and generally do not last for more than 3 days. Fever and systemic reactions are positively associated with microfilaraemia and with the density of microfilariae in the blood. If the drug is given in spaced doses, systemic reactions are much less frequent and less intense after the second dose of DEC and are rare after subsequent doses. A similar reduction in reaction can be achieved by giving repeated small doses, the ultimate example being the use of DEC-medicated salt. These reactions to DEC eventually cease spontaneously and an interruption of treatment is rarely necessary. Symptomatic treatment of the reactions with antipyretics or analgesics may be helpful.

(*b*) *Local reactions* include lymphadenitis, lymphangitis, abscess, ulceration, and transient lymphoedema, which occur with decreasing frequency in that order and in varying combinations. In bancroftian filariasis, local reactions also include funiculitis, epididymitis, and orchitis. These reactions tend to occur later in the course of treatment, beginning 3–5 days up to 3–4 weeks after the first oral dose, and they last longer. They also disappear spontaneously and interruption of treatment is not necessary. Lymphoedema may persist for several months after treatment with DEC, but development to elephantiasis has not been observed in well-documented, follow-up studies.

Local reactions are more likely to occur in patients with a history of filarial adenolymphangitis, and they are probably related to the presence of adult or immature worms or fourth-stage larvae in the tissues.

6.2 Treatment of individual cases of lymphatic filariasis

6.2.1 *Treatment with DEC*

The object of treatment of individual cases is to destroy the parasite and to eliminate, reduce, or prevent morbidity. DEC is the

only presently available drug that is effective, safe, and relatively cheap for the treatment of lymphatic filariasis.

The dose of DEC that is most generally accepted for the treatment of bancroftian filariasis is 6 mg of DEC/kg body weight per day orally for 12 days, given preferably in divided doses after meals. For brugian filariasis, various dosage schedules are used in different countries, ranging from 3 to 6 mg of DEC/kg body weight per day up to a total dose of 18–72 mg of DEC/kg body weight. Repeated courses of treatment are usually necessary to ensure complete parasitological cure.

In Africa, a patient requiring treatment with DEC for bancroftian filariasis may sometimes also be infected with *Onchocerca volvulus* and/or *Loa loa*. Special care must then be taken since the action of DEC on these parasites may cause a serious reaction.

6.2.2 *Surgical treatment*

Elephantiasis, chyluria, and hydrocoele associated with filariasis can be treated surgically.

Usually for advanced elephantiasis of the leg or genitalia, with considerable induration of the subcutaneous tissues and marked thickening of the skin, the fundamental operation is excision of the diseased tissue, followed by plastic surgery for the reconstruction of severely affected limbs. Mild cases, which may be classified as lymphoedema, can be treated by lymphovenous anastomosis distal to the site of lymphatic obstruction. Anastomosis of lymph nodes with the veins does not require as much microsurgical equipment and technique, but the results are not as good.

Chyluria is often intermittent and it is therefore difficult to be certain that any particular surgical treatment has resulted in a cure. No treatment is necessary in mild cases where there is only an occasional spell of chyluria. In addition to the usual urological examinations, lymphangiography has proved to be quite useful in locating the site of lymphatic leakage into the urinary system. Usually chyluria is due to a leak in the pelvis and/or calyces of one or both kidneys. Surgical treatment involves the ligation and stripping of the lymphatics of the pedicle of the affected kidney. The use of sclerosing solutions, such as 20% sodium iodide and 1–2% silver nitrate, has given only transient improvement.

Hydrocoeles can be treated by inversion or resection of the tunica vaginalis; in voluminous cases resection is especially useful, and

often excess skin needs to be excised. Small hydrocoeles (50–500 ml) can be treated by drainage followed by the injection of a sclerosing agent.

6.3 Chemotherapeutic control of filariasis in the community

The objective of chemotherapeutic control, at present based on the use of DEC, may be one of the following:

(*a*) to reduce morbidity by treating clinical cases of filariasis;
(*b*) to reduce transmission by treating people with microfilaraemia;
(*c*) to interrupt transmission.

In most endemic areas, the general approach to the control of filariasis is by reducing morbidity and transmission. However, there are no objective criteria to suggest a level to which the morbidity or the microfilaria rate and density should be decreased, in order that filariasis no longer constitutes a public health problem.

The interruption of transmission is the ultimate objective. However, given the longevity of the adult worms and the limited resources in most endemic countries, in terms of manpower and finance, it may be unrealistic to aim for the total elimination of filariasis. Only a few countries have achieved this goal, but once it is reached, and provided there is no risk of reimportation, there is no further need to continue costly evaluation of the control programme or to reinstitute control measures.

There is a basic difference between individual and community treatment of filariasis. In the first case, it is usually the patient who is in need of help and therefore he or she is more likely to comply with treatment. In a community, on the other hand, only a small proportion of the population is suffering from acute clinical filariasis at any one time and therefore few people feel the need for help.

During a large-scale treatment programme the key to success is the ability of the control team to communicate effectively with the community. Once mutual understanding has been established, the treatment objectives and the nature of possible reactions should be explained. Apart from this, success depends on establishing a positive balance between the speed of control measures and the ability of the parasite to become re-established within a given period of time. In filariasis, the life-cycle of the parasite is relatively long. In contrast to the malaria parasite, it does not multiply in the mos-

quito vector, and the infective larvae do not multiply in the human host. Therefore the parasite never causes explosive epidemics. These factors favour the success of filariasis control programmes.

Parasite control with DEC is often relatively cheap when compared with vector control. The drug is safe and effective for human lymphatic filariasis, but in DEC control programmes (apart from those based on DEC-medicated salt) infants, pregnant women, or persons with obvious debilitating disorders are normally excluded. Successful results quite often become apparent within a relatively short time and resistance has not been reported.

6.3.1 *Mass versus selective treatment*

In *mass treatment,* DEC is given to almost everyone in the community irrespective of whether they have microfilaraemia, disease manifestations or no signs of infection. Conceptually, in an area of high endemicity, everyone is more or less equally exposed to the infective bites of the vector, and presently available methods are not sufficiently sensitive to diagnose subpatent or subclinical infections.

The advantages of mass treatment are:

(*a*) it avoids the cost of a mass blood examination programme before treatment, and no carriers giving false negative results on blood survey escape treatment;

(*b*) all members of the community receive treatment and nobody feels left out.

In *selective treatment,* microfilaria carriers and/or persons with clinical manifestations of filarial disease are first selected by large-scale screening of the community by means of a blood survey and, subsequently, DEC is given only to those who are microfilaria-positive.

The advantage of selective treatment is that acceptance of the drug is better because infected individuals can be told that they are infected and forewarned about the possible side-effects of treatment.

It is generally accepted that mass treatment is preferable in highly endemic areas and that selective treatment may be more suitable in areas of low endemicity. Other factors influencing the choice of method will be the health resources available and the size of the population at risk.

The decision as to the minimum level of endemicity that justifies a selective as opposed to a mass treatment campaign has to be an

empirical one, based on the degree of perfection aimed at and the cost of the operation.

6.3.2 *Regimens of DEC administration for large-scale campaigns*

6.3.2.1 *Administration of DEC tablets.*

(*a*) *Bancroftian filariasis.* The generally accepted dosage schedule for DEC is 6 mg/kg body weight per day for 12 days. Repeated courses may be necessary to lower the microfilaria prevalence and density to the desired level. The drug has also been given weekly, monthly, or even yearly with successful results.

(*b*) *Brugian filariasis.* The regimen employed varies from country to country and from time to time within a country. It ranges from 3 to 6 mg of DEC/kg body weight per day with a total dose of 18–72 mg of DEC/kg body weight. Again repeated courses may be necessary.

6.3.2.2 *DEC-medicated salt.* The use of DEC in salt is a special form of mass treatment using very low doses of the drug over a long period.

Common salt medicated with 1–4 g of DEC per kg has been used for filariasis control in some endemic areas of *W. bancrofti* and *B. malayi,* particularly after an initial reduction in prevalence has been achieved by mass or selective treatment of microfilaria carriers. This form of treatment is only feasible in areas where adequate control of the salt supply can be achieved and where the people will accept medicated salt. Treatment should be continued for at least 6–9 months. In the Lakshadweep Islands and on Quemoy Island this regimen has been shown to be safe, cheap, and effective. In China, DEC-medicated salt has been distributed to more than 18 million people with no observed adverse side-effects and with satisfactory results.

6.4 Experience and difficulties encountered when using DEC in the control of lymphatic filariasis in India

Mass treatment, selective treatment, and DEC-medicated salt regimens have all been tried in India. Treatment programmes were preceded by blood surveys, subsampling total populations to obtain baseline data. It was found that the total dose of DEC, and not the

size or spacing of individual doses, is most important in terms of reducing microfilaria rates and densities.

Both mass and selective treatment were well accepted and equally effective when preceded by a mass blood survey. After selective treatment 80% of microfilariae carriers showed mild reactions to DEC as against 50% of persons in the mass treatment programme. On the other hand, mass treatment preceded by only a small-sample blood survey was poorly accepted and gave disappointing results. The people did not understand why they were being asked to take the drug.

It follows that for DEC treatment to be accepted a good rapport must be established with the community before the treatment begins, and there must also be health education. The use of fewer and larger tablets, each containing 100 mg or 200 mg of DEC, instead of the usual 50-mg tablets, also improves acceptability.

Unfortunately, the resources allocated to the National Filariasis Control Programme in India can provide coverage with DEC and/or larviciding for only about 10% of the total population living in the endemic areas. It would appear, therefore, that the present vertical programme of filariasis control is insufficient to deal with the problem on a national scale, and a new horizontal strategy making use of the existing health infrastructure may have to be considered (see section 9).

6.5 Experience in the control of lymphatic filariasis using DEC in Tahiti

Regular large-scale DEC treatment of the community carried out over the past 25 years reduced the microfilaria rates to such low levels that mass screening and selective treatment were no longer cost-effective. However, when the DEC treatment was stopped there was an annual increase of 1% in the prevalence rate. This problem has been dealt with successfully during the past 4 years by giving a single dose (6 mg/kg body weight) mass DEC treatment once a year. This annual regimen has resulted in a further steady fall in the microfilaraemia rate.

6.6 Newer filaricides in the treatment of lymphatic filarial infections

Several drugs have shown antifilarial activity during animal screens and of these, levamisole, mebendazole, and centperazine have already undergone trials in man.

6.6.1 *Levamisole*

Levamisole has been tested in man at a dose of 100 mg twice a day for 10 days. By comparison with DEC, it was a less effective filaricide and produced more severe reactions, as well as producing its own toxic side-effects; in addition, it is more expensive. For these reasons it is not recommended for use either alone or in combination with DEC or mebendazole.

6.6.2 *Mebendazole*

Using 500 mg t.i.d. for 21 days this drug did not produce any adverse reactions in patients suffering from *B. malayi* and *W. bancrofti* infections. Follow-up of the few patients treated so far suggests a macrofilaricidal action. However, the use of this drug at the high doses required for filariasis treatment is not recommended for the following reasons: (*i*) the absorption of the drug is erratic; (*ii*) it has a teratogenic effect in some animals and cannot therefore be safely used in women; (*iii*) it can be toxic in large doses; and (*iv*) it is expensive.

6.6.3 *Centperazine*[1]

This is an analogue of DEC which has been developed by the Central Drug Research Institute, Lucknow, India. It has undergone toxicity studies in India and has been shown to be an effective microfilaricide and possibly also acts on adult worms. It is reported to be undergoing phase II clinical trials and to be safe and well-tolerated. Detailed results of these studies are not yet available.

6.6.4 *Other drugs*

Limited studies with amoscanate (at a total dosage of 500 mg/kg body weight for several days), amodiaquine (at 600 mg daily for 15 days), primaquine (at 15 mg daily for 5 days), and furazolidone (at 600 mg daily for 5 days) did not show any filaricidal effect in man. Metrifonate (10 mg/kg body weight per month for 3 months) was

[1] 3-Ethyl-8-methyl-1,3,8-triazabicyclo[4.4.0]decan-2-one.

also ineffective. A new drug, furapyrimidone,[1] is currently undergoing clinical trials in China.

6.6.5 *Drugs for future trials*

Two drugs that have recently been shown to act against *O. volvulus*, should undergo clinical trials in the near future. These are flubendazole and ivermectin.

6.7 Suggestions for further study

(*a*) Long-term studies of prolonged treatment with DEC-medicated salt should be undertaken to determine the effect of this regimen on adult filarial worms and on the prevention of clinical manifestations.

(*b*) Studies should be designed and carried out to determine the usefulness of prophylactic treatment with DEC in preventing lymphatic filarial infection by killing or damaging developing L_3 and L_4 larvae in man.

6.8 Experimental chemotherapy

6.8.1 *Criteria for the choice of models*

The essential elements in choosing appropriate laboratory models are as follows:

(*i*) detailed knowledge of the basic biological features (qualitatively and quantitatively) of the life-cycle of the filaria species in both the vector and the final host.

(*ii*) the ability to rear, infect, and maintain the proper vector in sufficient quantities and harvest from it large numbers of infective larvae (L_3) at little cost.

(*iii*) ability to rear or otherwise obtain economically the final host in sufficient numbers and at a constant rate. This host should permit the infective agent to mature and produce microfilaraemia in a

[1] *N*-(5-nitro-2-furfurylidene)aminotetrahydro-2(1*H*)pyrimidinone.

reasonable period of time, ideally in all of the inoculated animals. Levels of microfilaraemia should be sufficiently high to infect the vectors efficiently, or at least adequate for the type of studies envisaged.

(*iv*) experimental variables must be definable as regards the various stages of the parasite and vector as well as the final host.

6.8.2 *Pharmacological studies in filariasis*

6.8.2.1 *General considerations.* In the development of filaricidal drugs the following types of drug action must be considered to be of potential value for use in control programmes or individual treatment.

(*a*) *Chemotherapy* of filariasis refers to the treatment of established infections using macrofilaricidal and/or microfilaricidal drugs.

(*b*) *Suppressive treatment* is the reduction of the microfilariae and/or of the clinical manifestations without killing all the adult worms. It could include drugs with a prolonged or permanent sterilizing effect on adult female worms.

(*c*) *Chemoprophylaxis* of filariasis implies the protection from, or prevention of, disease. This may be achieved by *causal prophylaxis,* or by *clinical prophylaxis.*

(*i*) *Causal prophylaxis* implies the complete prevention of filarial infection by the early elimination of the invading or migrating infective third-stage larvae.

(*ii*) *Clinical prophylaxis* implies the prevention of clinical symptoms and the appearance of microfilariae by early damage to or destruction of the developing immature parasite, or by killing or damaging the young mature parasite before it becomes pathogenic. Clinical prophylaxis does not necessarily mean elimination of a filarial infection.

Experimental models and methods for the evaluation of antifilarial chemical compounds must investigate not only the different organ sites of the parasites in the experimental and human hosts, but also the migration and time course of development of the filarial larvae through the various stages to mature worms. Furthermore, marked differences in the susceptibility to drugs of male and female filariae may occur and reflect qualitative and/or quantitative dif-

ferences in metabolism. Similar metabolic differences may also exist between the adult and microfilarial stages of the parasite.

6.8.2.2 *Objectives of pharmacological studies in filariasis.* Essentially, the objectives of experimental pharmacological studies in the field of lymphatic filariasis may be defined as follows.

(*a*) To find and develop new antimacrofilarial compounds, the most pressing need is for a safe drug that will eliminate the adults but will not at the same time cause tissue damage as a result of the rapid elimination of macro- and/or microfilariae.

(*b*) To find new antimicrofilarial compounds that will eliminate microfilariae without causing serious reactions.

(*c*) To develop dosage schedules for new drugs that are applicable to large-scale control programmes.

(*d*) To find means of reducing the inflammatory reactions that occur in the human host in response to the presence and death of filarial parasites.

(*e*) To find and develop prophylactic drugs.

6.8.2.3 *Steps in antifilarial drug development.* Evaluation and development of antifilarial drugs involves the following consecutive steps:

(*a*) *Lead finding* is the random screening of chemicals or natural products to identify new active principles displaying antifilarial effects. It is usually carried out in small animal models.

(*b*) *Lead optimization* is the most complex step, normally linked to a lead-directed synthesis programme. It may ideally be supported by biochemical studies to elucidate the modes of action and facilitate a rational approach to structural modification of the bioactive molecule. This testing has to confirm the efficacy of a drug against micro- and/or macrofilariae by using a greater number of infected animals of the same test system and a variety of dosages and routes of administration. It should also provide information on the spectrum of activities in other models of filariasis. Preliminary studies on toxicity should provide, in comparison to other well-known antifilarial drugs, a basis for a first judgement of the antifilarial capacity and the therapeutic index (i.e., safety margin) of the most interesting substance. This will facilitate the selection of the most promising compound(s) for the next step—preclinical standardization. Preliminary data on blood- and tissue-levels of the

compound in its active form are highly desirable at this stage to determine the therapeutic index with greater precision.

(*c*) *Final characterization* or preclinical standardization of the most interesting compound is intended to confirm its antifilarial efficacy in higher mammals. Ideally this final characterization should take place in the host species routinely used or foreseen for use in the preclinical studies of toxicity, mutagenicity, teratogenicity, and carcinogenicity. Such studies should include the use of the primate models for lymphatic filariasis.

6.8.3 *Animal models for chemotherapy studies in lymphatic filariasis*

In view of the fact that *Brugia* spp. have been established in both small and large animal models, most chemotherapy screening and development programmes are encouraged to focus on models involving these parasites instead of those using *Litomosoides carinii, Dipetalonema viteae, Breinlia sergenti,* and *Dirofilaria immitis.* While these parasites may be useful for studying certain aspects of chemotherapy or side-reactions to new drugs, the use of *Brugia* spp. in the following drug development scheme for agents active in lymphatic filariasis has been adopted by the most recent Scientific Working Group on filaricide screening:[1]

In vitro
B. pahangi
↓
Rodent species
transplanted *B. pahangi* L_3-induced *B. pahangi*
↓
Cat/Dog
B. pahangi
↓
Monkeys (Presbytis)
B. malayi
↓
Man
Brugia spp.
W. bancrofti

[1] Report of the 7th meeting of the Scientific Working Group on Filariasis: filaricide screeners. Unpublished WHO document TDR/FIL-SWG(7)/82.3 (1982).

6.8.3.1 Brugia *spp. in small animals.* Despite numerous efforts to transmit to animals the various filarial parasites causing disease in man, *B. malayi* remains the only species pathogenic for man that readily infects small laboratory animals and leads to long-lasting patency of microfilariae in the blood. The relative ease of establishing patent infections in the laboratory with one of the two most common lymphatic parasites of man has prompted numerous studies on pathogenicity, pathophysiological dynamics, immune response, and immunopathology, as well as on development in the mosquito and on experimental transmission. Although a susceptible strain of *Aedes aegypti* was selected as a vector for *B. malayi,* transmission is relatively inefficient when compared with *B. pahangi.* In addition, the prepatent period of *B. malayi* in small rodents is relatively long (average from 91 to 136 days, depending on the host species) and shows enormous inter-individual variation. The same applies to the recovery rate of adult parasites that are normally located in the lungs, the heart, carotid and pulmonary arteries, and the testes. Thus, there is no site-analogy with the human lymphatic filariases. Because of these shortcomings, *B. malayi* in small rodents should not be considered as a model for finding new leads for chemotherapy. It may, however, be of interest for finding leads for chemoprophylaxis and for improving suppressive chemotherapy.

B. pahangi readily infects various rodent species (*Meriones unguiculatus, Mastomys natalensis, Saccostomus campestris,* and *Mesocricetus auratus*). The prepatent period is relatively short (66–84 days) and reasonably constant. Of the infective larvae inoculated, 40% are recovered as adult parasites. In contrast to *B. malayi, B. pahangi* invades the lymphatics in small rodents in significant numbers. When infective larvae are inoculated subcutaneously into the groin of jirds, hamsters, or multimammate rats, up to 79%, 50%, and 50%, respectively, of the adults are found in the lymphatics of the lower half of the body. L_3-induced *B. pahangi* infection in jirds thus has several advantages as a screening model for lead-finding and lead-optimizing in chemotherapy and chemoprophylaxis.

Upon intraperitoneal injection the majority of the infective larvae of *B. pahangi* develop to the adult stage free in the peritoneal cavity, providing a rich source of developing larvae or adults. These macrofilariae may be collected from highly infected animals and transplanted (5 males and 5 females per animal) into the peritoneum of naive jirds, where they survive well. These jirds can then be treated

with potential antimacrofilarial test compounds almost immediately. This test system offers the advantage of well-defined "infections" and is highly economic with respect to time, animal-room space, and numbers of animals to be kept over any period of time. All these advantages are, however, offset by a few disadvantages. Antimicrofilarial effects cannot be tested in this system. The macrofilariae are "ectopically" located and this is not the case in the human disease. Potential antifilarials with certain pharmacokinetic features (low volume of distribution and rapid excretion pattern) may never reach these "ectopically" located parasites in sufficient concentrations or for a sufficient length of time and they may thus be mistakenly dropped as inactive.

Additional use of *B. pahangi* has been made to study the prophylactic activity of various antifilarial drugs by maintaining third-stage larvae in diffusion chambers implanted into the peritoneal cavities of jirds. Development of the larvae can be assessed over a 2-week period in the presence or absence of antifilarial treatment of the jird hosts.

6.8.3.2 Brugia *spp. in higher mammals including primates.* In contrast to *B. malayi, B. pahangi* is found in a much more limited range of primate hosts. In carnivores the situation is reversed. *B. pahangi* more readily infects carnivores than does *B. malayi. B. pahangi* in cats, dogs, and ferrets is analogous to human lymphatic filariases in a number of ways. Similarities between the ferret and cat model on one hand and clinical observations in man on the other are very striking with respect to the progressing pathophysiological lymphatic sequelae, the interrelationship of immune response and pathology, and the predominant lymphatic localization of the adult parasites. *B. pahangi* infections in rodents and carnivores used in combination as chemotherapeutic models should play a more important role in the future in the successful development of improved lymphatic antifilarial drugs.

Various leaf monkey species (*Presbytis* spp.) are easily infected with subperiodic *B. malayi.* However, practical experience with this primate model is relatively limited as regards optimal inoculum size, injection site, average recovery rate, and inter-individual variation in macrofilarial counts. As the supply of animals has to depend on monkeys of natural origin, the two latter parameters could be influenced by undetected earlier natural infections. Both host-parasite combinations, *B. pahangi* in carnivores and subperiodic *B. malayi* in

leaf monkeys, are naturally established relationships and thus reflect ontogenetically and phylogenetically the situation in human lymphatic filariases. Both systems should be used for the final characterization of promising antifilarials (prophylactics and therapeutics).

6.8.3.3 Wuchereria *spp. in primates.* The subject of *W. bancrofti* and *W. kalimantani* in primates has been discussed in section 5.1. To date, neither of these models has been used for chemotherapy studies though the potential value of such models is great.

7. VECTOR BIOLOGY AND CONTROL

7.1 Identification and incrimination

During the last 10 years, the names of several vectors have been changed and some additional mosquitos have been incriminated as vectors of *W. bancrofti, B. malayi,* and *B. timori.* A list of all the known principal and subsidiary vector mosquitos, and the zones in which they occur, is given in Annex 1, which should be studied together with the map shown in Fig. 1 (page 11).

7.1.1 *Vectors of periodic* W. bancrofti

Culex quinquefasciatus has been recognized as the valid name for the urban tropical mosquito which was previously known as *C. pipiens fatigans.* Within the *C. pipiens* group of mosquitos, which includes *C. quinquefasciatus,* the differentiation of several crossing types is based on cytoplasmic incompatibility.

In the African region, the two freshwater-breeding vectors of the *Anopheles gambiae* complex are now known as *A. gambiae* and *A. arabiensis* instead of *A. gambiae A* and *A. gambiae B,* respectively. Two new vectors have been identified from Liberia, *A. nili* and *A. hancocki.* In the Western Pacific region vector species are recognized in the *A. punctulatus* group namely, *A. farauti, A. koliensis,* and *A. punctulatus.* In South-East Asia *A. balabacensis* has been incriminated from Borneo and *A. aconitus, A. vagus,* and the *A. subpictus* complex from Flores.

7.1.2 *Vectors of subperiodic* W. bancrofti

In Thailand a vector in the *Aedes niveus* group has been named *A. harinasutai.* In the bicol area of the Philippines, *Aedes poicilius,* incriminated in the past as the main vector of *W. bancrofti,* has proved to be less common than *Aedes ananae,* the dominant breeder in abaca axils. The latter deserves further study to determine whether it plays a role in parasite transmission. In the Tonga archipelago, a vector of the *Aedes scutellaris* group has been named *Aedes kesseli.*

7.1.3 *Vectors of* B. malayi

Coquillettidia crassipes has been incriminated as a vector of subperiodic *B. malayi* in Malaysia. It has been confirmed that *Anopheles sinensis* is a vector of periodic *B. malayi* in peninsular Korea.

7.1.4 *Vectors of* B. timori

The recognition of *B. timori* as a distinct parasite of man in one area of Indonesia has been followed by the incrimination of *Anopheles barbirostris* as a vector.

7.1.5 *Identification methods*

Morphological recognition of mosquito species (by examination of eggs, larvae, pupae, or adult males or females) remains the main method of vector identification, but increasing attention is being focused on the use of other identification methods such as cytotaxonomy, zymotaxonomy, and experimental techniques. The methods of chromosomal identification are particularly appropriate for *Anopheles* spp., which have giant polytene chromosomes that can readily be spread and stained for study and show specific banding patterns. This cytotaxonomic method is useful for the identification and separation of *A. gambiae* complex sibling species in Africa and can also be applied to other anophelines. The specific identification of each member of the *A. punctulatus* complex and the *A. gambiae* complex is also facilitated by the use of biochemical keys. Difficulties in making microscopical preparations prevent the cytotaxonomic technique being used for culicine mosquitos (*Aedes, Culex, Mansonia,* etc.). Mosquitos belonging to the *C. pipiens* complex, can be distinguished by male mosquito morphology and the behaviour of both sexes, but the taxonomic status of some populations remains unclear.

A general account of the mosquitos of Polynesia, with keys to the *Aedes kochi* group and pictorial keys to larvae and adults of the *Aedes scutellaris* group, has been published (*22*).

The ecological features of the *A. scutellaris* group are relatively homogeneous and the absence of taxonomy need not be an obstacle to planning epidemiological studies or control programmes.

Interspecific and intraspecific enzyme differences within the *A. scutellaris* group have been recorded. There can be differences in esterases, and differences in alcohol dehydrogenase can be used to separate *Aedes polynesiensis* and *Aedes kesseli;* other enzymes may be used to distinguish between closely related populations in the future. There are constant isozyme differences between western (non-vector) and eastern (vector) members of the group, but an attempt to detect constant biochemical characteristics among different island populations of *A. polynesiensis* was unsuccessful.

7.2 Ecology and bionomics

7.2.1 *Preimaginal stages (factors favouring an increase in vectors)*

Man-made ecological changes tend to increase the multiplication of *C. quinquefasciatus*. Urbanization with poor sanitation is the main reason for the multiplication of this mosquito, which displaces other species of mosquito because it is more often resistant to insecticides and is better able to tolerate domestic detergents (*23*).

In villages, towns, and cities the availability of breeding-sites, particularly of *C. quinquefasciatus* is related to the size of human settlements, the standards of living, the level of education of the inhabitants, and other socioeconomic factors. Unfortunately, some of the trends favouring the multiplication of this species are expected to continue. Moreover, the extra water supplies provided during the water and sanitation decade may have tended to increase the number of breeding-sites or to extend the production period of those already existing. In most endemic areas water storage is on the increase, and in the southern Pacific area this is favouring the breeding of the local vector *A. polynesiensis*.

Dam building and irrigation, especially for rice cultivation, are resulting in an increase in vector populations, such as the species of the *A. gambiae* complex in Africa and *Anopheles barbirostris* in Indonesia.

Development activities and deforestation projects have increased breeding opportunities and have put local populations in close con-

tact with some important vectors such as *A. balabacensis* in Malaysia and Indonesia and some species of the *A. gambiae* complex in Africa. For instance, *A. arabiensis* has been able to colonize new environments including urban areas in West Africa.

7.2.2 *Adult stages (observations concerning transmission)*

New information on adult mosquito ecology can help provide a better understanding of the epidemiology of filariasis and improve the planning of control operations. For example, vector longevity, which is an important parameter in disease epidemiology since it reflects the transmission potential, tends to be greater in endophilic species of the *A. gambiae* complex than in those that are largely exophilic. Studies on *Anopheles merus* in East Africa and on *Anopheles melas* in West Africa (*24*) have shown that these salt water-breeding members of the *A. gambiae* complex have lower survival rates than the fresh water-breeding vectors *A. arabiensis* and *A. gambiae*. Such observations help to explain the higher transmission rates of *W. bancrofti* in areas where *A. gambiae* or *A. arabiensis* are the dominant vectors.

The longevity of *C. quinquefasciatus* is usually less than that of the anophelines although it can sometimes equal that of the *A. gambiae* complex. In other areas where, for environmental reasons, *C. quinquefasciatus* has reduced longevity, this could be partially responsible for the low filarial infectivity rates that have been observed. However, vector longevity can vary greatly from season to season and from place to place; this emphasizes the importance of selecting different sampling sites to get accurate values for this parameter.

Early observations on the flight range of *C. quinquefasciatus* in an urban environment suggested that this was usually less than 1 km. More recently, in a village in India, many marked adults were recaptured at 1 km from the release point and there were indications of natural dispersal up to 11 km away. Although *C. quinquefasciatus* does not usually fly more than a few hundred metres, these observations indicate that it is quite capable of flying much further under favourable conditions. Where control operations are restricted to small areas, the importance of reinvasion must be recognized. In an area in Malaysia endemic for subperiodic *B. malayi*, where both leaf monkeys and the human population were infected, individual *Mansonia bonneae, M. dives, M. uniformis, M. annulifera,* and *M. indiana*

were found to have travelled widely within an area of 4 km^2. Dispersal can also occur in vehicles, trains, and aircraft.

Observations on resting habits made in Burma and India indicate that adult *C. quinquefasciatus* show a marked tendency to exophily which most workers view as one of the reasons why indoor residual sprayings fail to reduce populations of this species.

Other observations relevant to control operations include the recognition that *Anopheles aconitus* and *A. barbirostris* rest low down on the walls of houses, so that it might be possible to apply selective spraying indoors, thus saving time and money. On the other hand, because of house spraying, *A. farauti* has become more exophilic and is now an earlier biter, promoting extradomiciliary transmission.

7.3 Vector-parasite relationships and transmission

7.3.1 *Intrinsic factors affecting mosquito susceptibility to infection*

Mosquitos possess several mechanisms that minimize the intensity and pathogenicity of filarial infection in the vector. The cibarial and pharyngeal armatures, protruding into the foregut lumen inflict lethal damage on microfilariae; these armatures are most elaborate in some anophelines. In all the genera of filaria vector mosquitos, the pharyngeal armature is developed as a cluster of 30 or more strong teeth near the posterior passage from the pharynx. The cibarial armature is not developed in *Aedes, Mansonia,* or *Anopheles* subgenus *Anopheles,* whereas the *Anopheles* subgenera *Cellia, Kerteszia,* and *Nyssorhynchus* have very well-developed cibarial teeth. The subgenus *Cellia* is characterized by armatures, forming rows of sharply pointed and serrated teeth differentiated as so-called rods and cones. By contrast, typical *Culex* have a single moderately developed row of 20–30 short, spoon-shaped teeth facing a shagreened area on the roof of the buccal cavity.

Variations of the cibarial armature result in different degrees of damage to microfilariae, *Brugia* being more vulnerable than *Wuchereria.* The majority of microfilariae remain undamaged when ingested by *Aedes, Culex, Mansonia,* or *Anopheles* subgenus *Anopheles,* whereas the majority of microfilariae are killed by the armatures when ingested by *Anopheles* of the subgenus *Cellia.*

The phenomenon of "facilitation" (see section 7.3.2) could be due to some microfilariae shielding others from the armatures during ingestion. Conversely, this implies that *Anopheles farauti, A. gam-*

biae, and other species with strong armatures are vectors of reduced efficiency for lower densities of microfilaraemia. *A. gambiae* seldom develops infections with *W. bancrofti* after feeding on carriers with less than 10 mf/ml, but *Aedes aegypti* and *C. quinquefasciatus* do. Hence, transmission of bancroftian filariasis may die out where both the microfilaria rates and anopheline densities are depressed, as in the Solomon Islands where *Anopheles farauti* was the vector.

Within the mosquito stomach, the blood-meal coagulates and microfilariae are thus prevented from moving towards the gut wall and through it to the haemocoele of the vector. Coagulation of the blood-meal is more rapid and complete in *Aedes, Culex,* and *Mansonia* than in anopheline mosquitos.

Host responses of the vector may cause encapsulation or melanization of the stage-I filarial larva in the haemocoele or of the stage-I–II larvae in thoracic flight muscles, but encapsulation is unusual in most of the normal vector species.

For species, strains, and individual genotypes of mosquitos that are inherently refractory to *Brugia* or *Wuchereria,* stage-I larvae simply fail to develop after reaching the thoracic muscles. The physiological basis of this phenomenon remains obscure.

7.3.2 *Experimental infections*

Experiments carried out in East Africa indicate that *Anopheles merus,* the salt-water breeder of the *A. gambiae* complex, is a poorer vector than the 2 freshwater breeders *A. gambiae* and *A. arabiensis.* This difference is mainly explained by a shorter life expectancy of the former as already mentioned in section 7.2.2.

Laboratory experiments have shown that *C. quinquefasciatus* from Liberia has a low susceptibility to local *W. bancrofti.* This was considered of potential value in manipulating strains that might have been used to replace those responsible for the transmission of the parasite in East Africa. However, the Liberian strain of *C. quinquefasciatus* proved to be susceptible to East African strains of *W. bancrofti.*

It is surprising to find that *C. quinquefasciatus* is abundant in many other regions of West Africa where *W. bancrofti* is highly endemic, and yet the transmission is carried out entirely by anophelines. This is despite the fact that laboratory experiments show that several other strains of *C. quinquefasciatus* from West Africa are susceptible to West African strains of *W. bancrofti.*

It has been shown with *Aedes polynesiensis* and *W. bancrofti* that, as the number of microfilariae ingested increases, there is a decrease in the proportion passing through the wall of the mosquito stomach and developing further. This phenomenon has been termed "limitation". On the other hand, *A. polynesiensis* has the capacity to concentrate microfilariae during the course of a blood-meal; this concentrating effect increases as microfilarial densities in the human host decline. Several workers have now shown that relatively high infection rates can be attained in *A. polynesiensis* that are fed on carriers with very low densities of microfilariae. The reverse situation, termed "facilitation", when the proportion of microfilariae that develops increases as the numbers of ingested microfilariae increase, is exhibited by anophelines (see section 7.3.1). Mathematical formulae have been refined to describe these phenomena, also taking into account the mosquito mortality that is related to the numbers of microfilariae passing through the stomach wall. Such studies have more than a theoretical interest if, in control programmes, the microfilarial reservoir in the human population is lowered by chemotherapy. Experience with DEC shows that a proportion of carriers in a community continue to circulate microfilariae at low levels after treatment, and these can infect the local vectors.

7.3.3 *Transmission studies*

In initial surveys where the vectors are still unidentified, or where their relative importance requires clarification, the following methods may lead to a rapid determination of potential vectors of filariasis. As a first step, any anthropophilic mosquitos should be sampled and identified. Some laboratory-reared examples of each suspected vector species should be fed on a microfilaria carrier, and kept until the infective larvae can be retrieved by dissection, thus proving which species have vector potential. Large numbers of these particular species should then be collected and dissected by mass methods in order to determine whether they are vectors under natural conditions.

The methods for determining transmission potentials are dealt with in section 8.2.3.

In East Africa and the neighbouring islands of the Indian Ocean, the number of bites per person per year seem to be related to microfilarial endemicity but the correlation with disease prevalence rates is less pronunced. For instance, in one village on Mayotte,

where the microfilaraemia rate was 45% in adults, the rate of exposure to transmission was over 400 infective bites/person per year. Lower rates of exposure and infection have been recorded in Tanzanian villages where the annual infective biting rate was 189 in the most highly-infected village (microfilaraemia rate 28.5%) and 24 in the least affected village (microfilaraemia rate 15.6%). In two villages in Andhra Pradesh (India), 32 infective bites/man per year maintained a microfilaria rate of 16.7%, while in a fishing community in Trinidad a small number of infective bites, 14/man per year, was enough to maintain a microfilaria rate of 15%. In Japan, a quadratic relationship was demonstrated between microfilaria prevalence rates and infection rates in the main vector, *Culex pipiens pallens*.

Contrasting results have been obtained from big urban settlements in South-East Asia where the breeding of *C. quinquefasciatus* is more intense than in any rural area of the world. The infectivity rate of the mosquito is usually low (0.3%) but, owing to the enormous number of biting females, the number of infective bites/person per year is always very high. Estimates include 1106 in Pondicherry, 350 and 1850 in Calcutta, and 647 in Jakarta. Nevertheless *C. quinquefasciatus* is able to maintain microfilaria rates that are similar to or lower than those recorded in rural areas (14.8% in Calcutta, 6% in Jakarta). The factors responsible for these differences between rural and urban settlements have not been identified.

7.4 Mosquito control

For vector-borne diseases in general, it is important to reduce the rates of transmission and incidence of disease by means of vector control. Wherever possible, this should be done in conjunction with chemotherapy for reduction of disease prevalence. The feasibility and value of vector control as one of the components of filariasis control depend upon the identity, ecology, and behaviour of local vectors and other epidemiological conditions. In the many areas where endophilic mosquitos transmit filariasis, house-spraying with residual insecticides may result in satisfactory levels of vector control. This is particularly beneficial where malaria as well as filariasis transmission depend upon the same *Anopheles* species or vectors with similar bionomics. In urban areas where *C. quinquefasciatus* is the vector, control by such means as larviciding, source reduction, screening, and trapping has the additional advan-

tage of reducing the nuisance effects of this pest mosquito and thus helps to encourage community participation.

7.4.1 *Methods of control*

7.4.1.1 *Chemical control.* Where the vectors are anopheline mosquitos it is appropriate to use the same methods of adult mosquito control as are employed in anti-malaria campaigns (see section 7.4.2.1). House-spraying with DDT or other residual insecticides has thus reduced the transmission rates of periodic *B. malayi* by *Anopheles sinensis, A. barbirostris,* and other endophilic populations of mosquitos in South-East Asian countries. Likewise, where malaria control operations have been maintained at an adequate level, *W. bancrofti* transmission has been reduced in parts of central America where *A. darlingi* is the vector; in Melanesia, where the vectors belong to the *A. punctulatus* complex; in the Maldives where *A. tessellatus* was a minor vector; and in some African areas involving *A. funestus* and the *A. gambiae* complex. The development of insecticide resistance in some of these species was reviewed by the Expert Committee on Vector Biology and Control at its fifth meeting in 1980 (*25*).

Although it is seldom easy or economical to use chemical insecticides against anopheline larvae in their breeding-places, it may be appropriate in the environs of a village to attempt larvicidal control of those anopheline vectors that breed abundantly in rice-fields, e.g., *A. barbirostris, A. nigerrimus, A. sinensis, A. lestri anthropophagus, A. whartoni,* and perhaps *A. arabiensis,* and *A. aconitus.*

The insecticidal control of most adult culicine mosquitos is impractical due to their general tolerance of insecticides and the general exophily of *Aedes, Culex,* and *Mansonia.* Fogs or aerosols of fenitrothion, malathion, or pyrethroid insecticides can be effective against adult vector culicines, but are usually uneconomical and may give only short-term control. For example, in Sarawak a small-scale field trial of thermal fogging with 3% malathion reduced the numbers of *Mansonia bonneae* and *M. dives* for about 2 weeks.

During the past decade, larval control of *C. quinquefasciatus* has been based on the use of organophosphorous insecticides which gave excellent results in some tropical cities, such as Dar es Salaam and Rangoon. However, resistance to chlorpyrifos, fenthion, and temephos is found in larval vector populations from urban areas of Brazil, Burma, Kenya, Liberia, Sri Lanka, and the United Republic

of Tanzania. Thus, since insecticides have been used on a wide scale, *C. quinquefasciatus* has developed resistance to many of these chemicals. New insecticides are becoming available but they are expensive. New synthetic pyrethroids such as cypermethrin, deltamethrin, and permethrin have proved to be very effective against strains resistant to organophosphorus compounds. For detection and monitoring of resistance to organophosphorus compounds in *C. quinquefasciatus,* it is generally possible to employ a test for the presence of high intensity esterase, the commonest detoxifying enzyme, in addition to bioassay tests.

Mosquito larvicidal oils have also been used in some countries. They are active against all preimaginal stages. However, they have proved to be less efficient under field conditions, and more expensive, than insecticides.

Insect growth regulators might be good substitutes for insecticides. One, methoprene inhibits adult emergence, the other, diflubenzuron is a chitin inhibitor. Slow-release formulations of these have a residual effect of about 2–4 weeks when used against *C. quinquefasciatus.*

Crab-hole breeding *Aedes* vectors of subperiodic bancroftian filariasis are not easily amenable to larvicidal control because of the many scattered and inaccessible breeding-places. The *Mansonia* larvae are best controlled by the destruction of the host plants either by drainage, physical removal, or herbicides.

Laboratory tests on the susceptibility of *Mansonia* to insecticides have shown that the larvae are susceptible to chlorpyrifos and temephos, gamma-HCH, fenthion, DDT, fenitrothion, and malathion in declining order. There appear to be no recent susceptibility tests on adult *Mansonia.* In general, the rapidly increasing costs of insecticides during the past decade, together with increasing problems of insecticide resistance make it more necessary to adopt alternative methods of vector control involving environmental management, biological control agents, programmes of integrated vector control, and improved sanitation.

7.4.1.2 *Biological control.* The larvivorous fish, *Poecilia reticulata* is able to adapt itself to polluted breeding-sites but it does not reduce *C. quinquefasciatus* densities significantly. Better results have been obtained with *Poecilia* and two other species of larvivorous fish (*Molliensia spherops* and *Kuhlia taeniurus*) when the target mosquito develops in non-polluted or moderately-polluted water. For

the control of vectors breeding in rice-fields or wells, locally indigenous fish or introduced species such as *Gambusia affinis* can be quite effective biological agents of control. The use of larvivorous fish is relatively simple and can be exploited at the village level.

In some rural areas of the East African coast, *C. quinquefasciatus* can be displaced by *C. cinereus,* a mosquito that does not bite man. The reverse situation has been observed in Nigeria, where *C. quinquefasciatus* displaced the non-vector *C. nebulosus* from latrine breeding-sites after application of chemical larvicides. Further studies are needed to assess the potential of these and other species of mosquitos as biological competitors of *C. quinquefasciatus.*

Laboratory experiments have shown that nematodes of the genus *Romanomermis* can infest a high proportion of *C. quinquefasciatus* larvae. Nevertheless, under field conditions this percentage was insufficient to reduce mosquito densities significantly. *R. culicivorax* was able to establish itself in man-made tree holes for long periods (several years) and to parasitize *Aedes polynesiensis.*

A larvicidal bacterium, *Bacillus sphaericus* (strain 1593) has also given good results against *C. quinquefasciatus,* and there is some evidence that *B. sphaericus* can multiply naturally in sewage, thus maintaining its activity against *C. quinquefasciatus* larvae over a prolonged period. The potential for this type of persistent biological control agent should be fully explored and exploited.

A spore-forming bacterium, *Bacillus thuringiensis* serotype H-14 produces a crystal of toxic protein that is a stomach poison for mosquito larvae. In the field this toxin is capable of drastically reducing the preimaginal populations but it loses activity within a few days. Moreover this bacterium does not maintain itself at sufficient levels to kill larvae for more than a few days.

7.4.1.3 *Environmental management.* Efficient drainage and sewage systems that remove unwanted water and solid waste help to eliminate mosquito breeding. When properly maintained they are the most efficient approach to the problem of mosquito breeding, especially for *C. quinquefasciatus* control. Unfortunately, there are many places where mains drainage cannot be installed because of high construction costs or water shortage, so the building of cesspools and latrines has to be considered. Cesspools have to be built in such a way that gravid female *Culex* mosquitos are denied access to the contaminated water. They must be hermetically covered with soil or cement and a mosquito screen has to be fixed onto the pipe

draining used water. Pit latrines have to be replaced by systems that do not use water and do not reach down to the water table. Several types of traps can be used to collect adult mosquitos leaving latrines. The supply of piped water should lead to the elimination of the various containers used to store water and others that have been discarded. *Aedes polynesiensis* and sometimes *C. quinquefasciatus* breed in these containers.

7.4.1.4 *Reduction of man–vector contact.* This is achieved by house-screening and the use of mosquito nets. Screening of house windows and eaves with plasticized mesh is very efficient, as are bed-nets, provided they are correctly used and kept in good repair.

In order to kill mosquitos that land on the outside of a bed-net the material should be treated with a pyrethroid insecticide (e.g., permethrin, decamethin, cypermethrin). Impregnated bed-nets can thus reduce the transmission efficiency of the whole vector population in addition to protecting the individual. The use of cheap methods of personal protection that are well accepted by the community should be encouraged.

7.4.1.5 *Integrated control.* For various reasons, such as high cost, insecticide resistance problems, and the difficulty of adaptation of some biological agents to polluted waters, none of the methods described above results in satisfactory control of filariasis vectors in all situations. The aim of integrated control is to combine two or more of these methods so that they act in a complementary way to achieve a high degree of control. The choice of methods depends upon the type of area to be controlled (urban or rural). Vector control activities can be implemented by individuals, the community, or centrally-organized programmes.

7.4.2 *Control programmes*

7.4.2.1 *Effects of malaria control programmes on filariasis.* As previously noted, reductions of microfilaria rates have occurred as a by-product of malaria vector control based on residual DDT house-spraying in areas where both diseases are transmitted by the same vectors, such as *Anopheles darlingi* in Guyana, *A. gambiae* in Togo, and *A. farauti* in the Solomon Islands. In the last of these areas, *W. bancrofti* has been almost eliminated as a result. This indicates that filariasis control or eradication can be achieved by

such programmes even though malaria transmission continues to be a problem.

7.4.2.2 *Specific filariasis campaigns.* The following examples illustrate situations where the control of mosquitos may have helped to reduce the transmission of filariasis.

(*a*) *C. quinquefasciatus control.* This is mainly carried out in urban areas, some of which are endemic for filariasis, although the main objective might be the reduction of the biting nuisance. The following are examples of control programmes where an evaluation of filariasis has also been included.

(*i*) *India.* A National Filaria Control Programme (NCFP) was started during 1955–56. At the beginning of the eighties there were 176 control units protecting about 30 million people in urban areas. The current control strategy is based on antilarval measures in collaboration with malaria schemes, in addition to the detection and treatment of microfilaria carriers. Mosquito larviciding oil has been the main chemical used to control *C. quinquefasciatus* for some time, but it is being replaced by temephos, pyrethrum oil, and fenthion. Larvicidal treatments are also complemented by minor engineering operations. About 70% of the units established for more than 5 years have reported reductions of over 50% in microfilaria rates, and 80% of the units established for more than 10 years show a 50% reduction in the disease rate.

A special 5-year project to control urban filariasis by controlling the vector *C. quinquefasciatus* was started at Pondicherry in 1981. It is mainly based on environmental management together with community participation. Environmental measures are complemented by the release of larvivorous fish (*Gambusia affinis*), and where no other method works, larviciding of all breeding sites with fenthion and phentoate. Unfortunately, the control methods used in urban areas have not proved acceptable either economically or operationally in rural areas, so that new initiatives are necessary to integrate filariasis control with primary health care programmes.

(*ii*) *Sri Lanka.* Bancroftian filariasis is restricted to a coastal belt in the south-west of the country with a population of about 2.7 million (1981 estimate). An antifilariasis campaign based on antilarval measures and the detection and treatment of microfilaria carriers was started in 1952. In 1972–73 the microfilaria rate was around

0.6% and fell to below 0.26% by 1982. Meanwhile, the prevalence of filariasis in Colombo city remained high in comparison with other areas and there was a risk of a spread of the infection. In 1978 the vector control programme of Colombo was modified. Larviciding operations were restricted to permanent sites; action was taken to eliminate temporary and semi-permanent sites; and the control of *Aedes* mosquitos, which are vectors of dengue and dengue haemorrhagic fever, was included in the project. Comparison surveys carried out in 1982 in 17 wards of Colombo showed a decline of the microfilaria rate in 16 of them. The highest rate in 1982 was 3.5%, the lowest 0.14%. Infective mosquitos were found in only 11 out of 29 wards surveyed in 1980–81.

(*iii*) *Mayotte.* In Mayotte, where *C. quinquefasciatus* is the main vector, the average microfilaria rate was around 51% in 1971 and control based on DEC chemotherapy and vector control was started in 1976. Malathion at a rate of 2 g/m^2 was initially aimed against anophelines but, subsequently, larviciding with temephos, environmental management, and biological control with larvivorous fishes have all been used. The overall microfilaria rate had declined to 20.6% in 1980.

(*b*) Mansonia *control.* In India there has been a natural reduction of *B. malayi* filariasis in some areas thought to be due to the elimination of the indigenous *Pistia* by *Salvinia* and the conversion of ponds to fish or lotus culture. In the South Kerala Hill settlements there has also been a reduction in transmission; the microfilaria rate fell from 25.9% in 1957 to 6.0% in 1979. This fall may be the result of several factors including an extensive DDT indoor-spraying programme and aerial applications of insecticides for forestry and agricultural purposes, together with the general availability of DEC.

Elsewhere in Kerala, where *Mansonia annulifera* and *M. uniformis* are vectors, there has been a successful reduction in transmission following several alternative control strategies. In one area the microfilaria rate fell from 10.6% in 1966 to 2.6% in 1975 following 36 rounds of HCH residual spraying at a concentration of 0.2 g/m^2. In a second area, in addition to 36 rounds of spraying, one course of DEC was given to the population (in 1972–73). The microfilaria rate then fell from 13.3% in 1966 to 5.4% in 1972 and to 1.2% in 1975. In a third area treated with insecticide at the same frequency, DEC was given in 1973 only to microfilaria carriers. The microfilaria rate fell from 7.7% in 1966 to 4.1% in 1972 and to 0.9% in 1975.

DEC treatment without vector control measures also led to a reduction in the microfilaria rates. In all areas under residual house-spraying diazinon was added to HCH from the 25th spraying round to increase the effect of the treatments on other domestic-pest insects.

The Kerala experiments demonstrated that transmission of *B. malayi* could be greatly reduced by vector control with or without chemotherapy. However, vector control was much more expensive than treatment with DEC.

It is worth noting that although *B. malayi* has disappeared from some Indian villages, e.g., in Madhya Pradesh, Orissa, and Tamil Nadu, new foci of *W. bancrofti* have become established in these areas.

In southern Thailand, as in Kerala, there has been a reduction in *B. malayi* infections. In Chumphon province the microfilaria rate fell from 10.8% in 1970 to 0.9% in 1979; there was also a fall in the elephantiasis rate from 3.3% to 1.0%. The improved situation is probably a result of household spraying with DDT which forms part of the malaria eradication programme.

7.5 Suggestions for further study

(*a*) Present vector identification methods should be refined and new methods developed.

(*b*) Because insecticides are still expected to be a major weapon for the control of vectors, all new insecticides that become available should be evaluated against filariasis vectors.

(*c*) The search for new and more cost-effective methods of vector control should be intensified in order to overcome the limitations of the methods currently employed.

8. METHODS USED IN THE ASSESSMENT OF FILARIASIS CONTROL PROGRAMMES

The effect of filariasis control can be assessed using clinical, parasitological, and entomological methods. The clinical parameters measured are the incidence of acute manifestations (adenolymphangitis, epididymo-orchitis, etc.) and the incidence and prevalence of chronic manifestations (lymphoedema, elephantiasis, hydrocoele, chyluria, etc.). Parasitological assessment is made chiefly on the basis of changes in the prevalence and intensity of microfilaraemia. After

successful control, changes in the incidence and prevalence of clinical and parasitological manifestations will be seen first in the younger age-groups. Assessment of transmission depends on measuring the annual biting rate of the vector and the numbers of infective larvae that they are carrying.

8.1 Parasitological methods

8.1.1 *Microfilarial studies in epidemiological assessment*

The ideal parasitological diagnostic technique for use in the epidemiological assessment of infection and its control should be sufficiently sensitive to detect low-density microfilaraemia, accurate in counting the number of microfilariae, easy to handle, economical, and should meet prevailing local requirements (e.g., acceptability of the technique to local people; and species identification of microfilariae).

Several different parasitological techniques have been employed. Among these, the thick blood-film, the counting-chamber, and membrane filter concentration (MFC) methods are most commonly used in epidemiological studies on lymphatic filariasis. Each of them has advantages and disadvantages, and none of them can simultaneously fulfil all the ideal requirements.

8.1.2 *Comparison of techniques*

There has been much discussion on the sensitivity of techniques in detecting microfilariae. Many of the conflicting results reported arise because a given technique employed by a particular individual researcher may not always be used by other workers in exactly the same way. Without doubt, the use of a larger volume of blood is advantageous in detecting low-density microfilaraemia, and the use of measured volumes with quantitative assessment of the parasitaemia is a prerequisite for careful epidemiological studies. In this sense, the finger-prick method, which provides a maximum volume of blood of 100 mm^3 is inferior to venepuncture, from which 1–5 ml of blood can be obtained. However, venepuncture involves several difficulties; it will not be accepted by people in many areas, and it is impractical for most small children.

(*a*) *The thick film* made from capillary blood is still the most commonly used method for epidemiological assessment. Wherever

possible it is advantageous to take measured quantities of blood so that changes in both prevalence and density of microfilariae can be determined. It is essential to use sterile lancets, non-heparinized pipettes, and very clean slides, otherwise microfilariae may be lost. Stained blood films are better than the counting-chamber and filtration methods because they can be used in integrated control programmes where malaria and filariasis coexist. This can result in an enormous saving in cost and personnel. It is also easier to distinguish the microfilariae in stained films when several species of filarial parasite occur in the same geographical area.

(*b*) *The counting-chamber* method is sensitive, easy, less costly, and provides rapid results. The live microfilariae can also be exhibited to local people, and this may result in improved population cooperation. The listed disadvantages of the method in field use are: (i) species identification is difficult or impossible; (ii) the preparation is not permanent; (iii) counting is difficult at night; (iv) bad weather conditions may disturb an observation. Most of these disadvantages can be overcome by transferring blood samples to a heparinized capillary tube or to a small container with 0.5 ml of 3% acetic acid. These samples can be taken to the laboratory and counted at leisure. However, the counting of dead microfilariae in acetic acid needs more care than counting live ones.

(*c*) *Membrane filter concentration (MFC) methods* include the use of Nuclepore membrane filters or Millipore membrane filters. No difference in sensitivity is reported between the two. For routine use, Nuclepore filtration is more convenient in that a large volume of blood (even 10 ml) can be filtered easily without haemolysis so that the same blood can later be used for immunological or other tests. It also has the advantage that the membrane is transparent and parasites can be easily stained for species differentiation. One of the disadvantages is the high cost; another is the potential for cross-contamination between specimens unless great care is taken.

Although MFC is the most sensitive method available at present for the detection of microfilaraemia, some very low-density carriers will still not be detected. In Samoa, 9% of the total number of positives detected by Nuclepore filtration were estimated to have been falsely diagnosed as negative by conventional blood films. For the most effective application of MFC (i.e., minimizing the number of false negatives) it is advisable to collect blood samples around the peak of microfilarial periodicity, even in regions where parasites are subperiodic.

(*d*) *DEC provocation.* In areas where night-blood collection is difficult or unacceptable to the population and where the only microfilariae present are nocturnal periodic *W. bancrofti,* the provocative day-test with DEC has been employed with some success. Nocturnal periodic brugian filariasis has also been "provoked" in this way but side-reactions were experienced in 15% of those who took the provocative dose of DEC.

On most occasions, DEC at a dose of 2–8 mg/kg body weight has been administered and the blood examined 20–60 min later. It has been shown in the United Republic of Tanzania, where nocturnal periodic bancroftian filariasis is endemic, that higher doses of DEC result in an earlier appearance of microfilariae (but for a shorter time) in the peripheral blood when compared with lower doses. The best time intervals for examination after an oral dose of DEC of 6, 4, or 2 mg/kg body weight were 15, 30, and 50 minutes respectively.

With finger-prick blood, the provocative DEC test by day was nearly as sensitive as night-blood examination for detecting positives except in areas of low endemicity where more positives were missed. Even in individuals with high-density microfilaraemia, "provoked" microfilarial densities were considerably lower than those found in night-blood.

In areas where *O. volvulus* or *L. loa* infections overlap with *W. bancrofti,* the provocative test should not be used.

8.1.3 *Identification of infective larvae in epidemiological studies*

It is a fundamental principle in epidemiology that there can be no confidence in the analysis of data on the transmission of insect-borne diseases in the absence of positive identification of the infective organisms isolated from suspected vectors. Failure to identify the infective larvae in mosquitos will result in the wrong mosquitos being incriminated as vectors with the result that transmission studies and control programmes could be based on false premises.

Several hundred species of filarial worms have been described. The life-cycles of most of them are unknown, but at least 30 complete their development in mosquitos. They all undergo three stages of development in the mosquito. The first is from microfilariae to the short sausage or first-stage larva. There is then a moult to the long sausage or second-stage larva; and a final moult to the third-stage (L_3), which is the infective larva. Development is always tissue

specific, e.g., *Wuchereria, Brugia, Setaria,* and *Cardiofilaria* in the thoracic flight muscles, *Dirofilaria immitis* in the malpighian tubules, and *D. corynoides* in the fat-body cells. The third-stage larvae should be regarded as infective irrespective of their position in the mosquito because they move freely throughout the haemocoele.

8.1.3.1 *The importance of larval identification.* The following are some of the reasons why it is necessary to identify filarial larvae in mosquitos:

(*a*) to discover the vector responsible for the transmission of lymphatic filarial parasites to man in any particular area;
(*b*) to provide accurate data for epidemiological studies on the dynamics of transmission;
(*c*) to help monitor control programmes;
(*d*) to indicate the possibility that false positive immunological tests may be due to heterologous infections of animal origin;
(*e*) to identify the source of transmission of zoonotic infections that produce abortive infections in man, e.g., *Dirofilaria* from cats and dogs;
(*f*) to identify animal filarial parasites that might produce hypersensitivity reactions in human hosts or those that might result in some degree of cross-protection;
(*g*) to provide new animal models;
(*h*) to indicate the source of blood-meals in mosquitos that feed on both man and animals;
(*i*) to establish the identity of "unknown" larvae which are frequently seen in the routine dissection of mosquitos caught in the wild.

8.1.3.2 *Methods for collecting and preserving larvae.* In preliminary surveys, where the vectors are still unidentified, large samples of all man-biting mosquitos should be collected and separated into their different species and either examined immediately in the field or transported to the laboratory, preferably on ice. If there is to be a long delay before dissection, the identified mosquitos can be preserved in 80% ethanol and subsequently stained and dissected. In initial studies it is not necessary to dissect individual mosquitos and the mass dissection technique can be used. This simple procedure involves crushing the mosquitos by rolling a heavy glass rod over the specimens on a thick glass plate and then extracting the

larvae from the debris by filtration in normal saline through a sieve of 50 μm pore size. In this way large numbers of infective larvae can be obtained and examined to determine the variety of filarial species in the different man-biting mosquitos. This is a rapid method for identifying the most likely vectors in any particular area.

In situations where the vectors are already known and where detailed epidemiological studies are in progress, it is usual for a proportion of the mosquitos to be dissected individually to determine their stage of parity and to find all stages of the filarial parasites in the vector. If the mosquitos are examined individually and both developing and infective larvae are found, the site of development of the first and second stages in the mosquito may help to indicate the likely species of infective larvae; but although the parasites infecting man all develop in the flight muscles of the mosquito, this is also the site of development of numerous species of *Setaria* and *Cardiofilaria* commonly seen in man-biting mosquitos. As it is difficult to identify the species of first- and second-stage larvae, it is usually necessary to examine the third-stage larvae for differential diagnosis.

Although under field conditions experienced scientists and laboratory technicians can distinguish the infective larvae of *W. bancrofti* and *Brugia* from other species, it is always preferable to preserve the larvae for subsequent detailed examination in the laboratory. This requires the careful removal of the delicate larvae into a preservation medium, either formalin, glycerol, or glycerine alcohol. If only temporary mounts are required, the larvae can be immobilized in saline either by heat or in the refrigerator and they can be examined directly under a coverslip. Whichever method is used it is necessary to mount the larvae so that they can be examined using the high magnification of an oil-immersion lens.

In situations where there are problems in distinguishing infective larvae of different species in the same genus, e.g., *B. malayi* and *B. pahangi,* it may be necessary to infect laboratory animals and recover the characteristic adult worms.

8.1.3.3 *Methods for distinguishing infective filarial larvae.* The criteria that can be used to distinguish *Wuchereria* and *Brugia* from other genera have been illustrated, and keys have been produced for use in East Africa and Malaysia.

The main morphological criteria for distinguishing the larvae are size, caudal morphology, anal ratio, internal anatomy, and oral

morphology; but as a general rule it is difficult or even impossible to distinguish the infective larvae of species in the same genus using morphological criteria. Even the scanning electron microscope has not revealed morphological features that are of value in field studies.

In any particular area where epidemiological studies require reliable data on infectivity rates in mosquitos, it is necessary to collect known species of infective larvae as reference material. This may require feeding mosquitos on infected animals, and a key should be produced to help with the routine identification of the larvae.

In the genus *Brugia,* where morphological criteria are of little value in distinguishing the infective larvae of animal parasites from those of man, it is necessary to develop other methods; and the same may be true for areas where *W. kalimantani* occurs.

8.2 Entomological methods

The parameters for analysis of the dynamics of transmission were listed in the third report of the WHO Expert Committee on Filariasis (*26*). Those used in the assessment of control measures are discussed here.

8.2.1 *Relative biting density of vector populations*

Vector control operations are usually evaluated by changes in the biting density of the vector population. The most important index of relative density is the number of bites received by one man per year, the annual biting rate (ABR), which is estimated from direct 24-hour human bait landing-catches carried out once a fortnight or once a month for a year. Other surveillance methods, either less tedious or with a shorter catch period are used more frequently to measure relative abundance as catch per man per hour or catch per house.

The methods used for the standard 24-hour catch should be related to human behaviour. Thus, if the catch is made on selected members of a household by following them while they engage in their daily routine, e.g., sitting out in the compound or indoors at dusk, going out to the stream or well to bathe or fetch water, engaging in indoor activities before retiring to sleep, leaving home at sunrise to work in plantations, a more realistic value for the parameter can be obtained.

Another practical and productive surveillance method is to make human bait landing-catches lasting 2–3 hours at the peak activity period of a species. Thus in Malaysia, catches on the bare legs of collectors from 19 h 00 to 21 h 00, are routinely used to collect *Mansonia*. In the south Pacific area human bait catches are made indoors from 18 h 30 to 21 h 30 for *Aedes samoanus*, and simultaneously indoors and outdoors from 07 h 00 to 09 h 00 and from 16 h 00 to 18 h 00 for *Aedes polynesiensis*.

Some vector species, that reach peak activity after midnight and remain inside houses after feeding, may be taken while resting to provide an indirect estimate of biting densities. Thus *C. quinquefasciatus* in India and Sri Lanka are collected resting indoors using mouth aspirators and flashlights, 5–10 min per hour, in 15–20 houses from 07 h 00 to 09 h 00. The use of handnets increased the efficiency of collection in a study in India.

The double bed-net trap provides a good method for catching mosquitos coming to feed on man. With this trap the insects are caught before they can bite; thus the human bait is not exposed and the mosquitos caught still contain their full load of infective larvae. Essentially the individual (bait) sleeps inside a normal mosquito net covering his bed. Outside this is hung a larger net that can be lowered every hour from outside to collect the mosquitos that have landed on the inner net and are trying to get through it to bite.

It must be emphasized that the above methods only provide an estimate of the relative biting density of a vector population in an area. Changes in the absolute density in an area may be estimated by mark-release-recapture experiments using the modified Lincoln Index. Such estimates of absolute densities are essential for calculating critical vector densities (see section 8.2.2).

8.2.2 *Estimation of critical vector densities*

By analogy with the mathematical model for malaria transmission, it is possible to express the dynamics of filaria transmission in the following terms:

- m = the adult female mosquito density in relation to man;
- r = the proportion of microfilaraemic people who revert to negative in one day, considered as the reciprocal of the patent period of microfilaraemia taken as approximately 10 years, i.e., 1/3650 = 0.000274;
- p = the probability of a mosquito surviving through one day;
- a = the average number of people bitten by one mosquito each day;

b = the proportion of mosquito females with infective larvae that successfully induce a patent infection;

n = the number of days to produce infective L_3 filarial larvae in the vector (often about 12 days).

It is thus possible to estimate the critical density of filariasis vectors from the formula:

$$m = \frac{-r \ln p}{a^2 b p^n}$$

The critical density of filariasis vectors can be defined as "the greatest density of vectors with standard longevity that can exist while the rate of filarial transmission declines". The critical density estimated theoretically for *Anopheles farauti* in Guadalcanal was approximately 20 which represented 8 mosquito bites/person per night, and this rate was confirmed by observation.

Since anti-vector measures involving residual insecticides aim to reduce the life expectancy of vectors of malaria and filariasis, it is more likely to be informative to estimate the vectorial capacity (C), thus:

$$C = \frac{m a^2 P^n}{-\ln p}$$

Use of this approach should be encouraged as a means of early monitoring of the control measures and deciding whether they need to be intensified or not. The epidemiological incentive for introducing this type of filariasis vectorial capacity monitoring is that it should not be difficult to reduce the transmission potential to a safe level. Since the transmission of filariasis is so much less efficient than that of malaria, the former may be interrupted while the latter continues, as has been observed in Guadalcanal, where the same anopheline vector was transmitting both diseases.

8.2.2.1 *Survival or the vector population.* Daily survival is determined by two methods: from parous rates obtained by the tracheolar coiling method, or from age composition data obtained by study of ovariole dilatations. Survival is estimated from the regression of the number of females in each age-group (y) on the age of the females

in days at the midpoint of each group (x). The duration of the gonotrophic cycle of a vector in nature is best estimated from mark-release-recapture experiments and is a prerequisite for the estimation of survival.

8.2.2.2 *Natural infection in the vector population.* The intensity of transmission in an endemic area is evaluated by examination of the vector population over a period of time for the percentage of mosquitos with developing and infective third-stage larvae (infection rate), the percentage of mosquitos with infective third-stage larvae only (infective rate), and the number of infective larvae (worm load) per infective mosquito. These parameters are obtained by the dissection of individual mosquitos from samples taken in density studies.

The worm load in individual mosquitos is expressed as a frequency distribution of specimens with different numbers of larvae, and the intensity of transmission is measured by the median density of infective larvae estimated by regression of probit cumulative percentage of mosquitos (y) containing (x) number of larvae.

Intensity of transmission may also be measured by the number of infective larvae separated out by the mass dissection of a large number of mosquitos. Recovery rates of infective larvae of over 98% can be obtained in this way.

8.2.3 *The annual infective biting rate and the annual transmission potential*

For onchocerciasis, another filarial infection, it has been demonstrated that there is a correlation between the level of exposure to infective larvae and the prevalence and severity of the disease. It would be helpful if such a correlation could be demonstrated for lymphatic filariasis transmitted by mosquitos. This could then be used to evaluate the effectiveness of control operations.

Dissection of individual mosquitos from a 24-hour catch will give the number of infective mosquitos biting one man and hence the number of infective larvae one man is exposed to in each catch. The product of the infective rate in each catch and the estimated fortnightly or monthly biting rate gives the infective biting rate for that period. The annual infective biting rate (AIBR) is obtained by the summation of this parameter for 26 fortnights or 12 months.

The product of the mean number of infective larvae per infective mosquito in a catch and the estimated fortnightly or monthly infective biting rate gives the transmission potential for the period. This parameter summed up for the year estimates the annual transmission potential (ATP). Changes in transmission based on the ATP have recently been evaluated in the United Republic of Tanzania (see section 7.3.3). Clearly, meaningful estimates of the AIBR and ATP are extremely difficult to make as infective mosquitos are very few and larvae may be missed during dissection. A comparison of these parameters before and after control operations is valid when carried out by the same staff using the same methods. It is therefore necessary to standardize the procedures and catching methods for the determination of the ABR as well as the methods for dissection of material for infective larvae to assess the ATP.

8.3 Suggestions for further study

(*a*) Immunologists should be encouraged to provide species-specific reagents, either with monoclonal antibodies or with DNA probes, for the identification of larvae in vectors.

(*b*) Further studies are necessary to standardize the methods used for correlating the ABR, AIBR, and ATP with the levels of endemicity and disease of lymphatic filariasis resulting from infection with different species and variants of parasites in different regions.

9. THE PRIMARY HEALTH CARE SYSTEM AND COMMUNITY PARTICIPATION IN THE CONTROL OF LYMPHATIC FILARIASIS

Following the Declaration of Alma-Ata, and in the context of the World Health Organization's goal of health for all by the year 2000, it is now widely recognized that it is essential to incorporate the control of lymphatic filariasis into the primary health care (PHC) system. Participation of the community is already an accepted strategy in control programmes.

Community participation ranges from active involvement of the community in all stages of a control programme to acceptance of

those control measures that satisfy the community's needs. It also includes the delivery of control measures via health workers from the community.

This section discusses the basic concepts and principles involved in the integrated approach to filariasis control, and describes the relevant experience of a few selected countries.

Lymphatic filariasis is often closely associated with malnutrition, illiteracy, poor environmental sanitation, inferior housing, and poverty. It is, therefore, important that communities living under these unsatisfactory socioeconomic conditions should be approached in the right manner and informed of the steps they can take to prevent and control filariasis. Communities are usually able to deal with their own problems, and if they want change they usually have the capacity to put it into effect. They must be involved in any filariasis control activities from the beginning—from the process of understanding the problem to the planning and implementation of countermeasures. However, it is recognized that for some communities, filariasis control may not be a high priority and therefore careful preparatory work may be necessary to ensure their participation.

9.1 Concepts and principles of primary health care in relation to filariasis control

Important concepts of PHC in relation to filariasis include:

(*a*) the use of methods and technology that are acceptable to, and can be carried out by, individuals and families in the community, and which permit their full participation at an acceptable cost;

(*b*) the development, through appropriate education, of the desire and ability of communities to participate;

(*c*) the involvement, in addition to the health sector, of all related sectors and aspects of community development;

(*d*) the provision of essential drugs;

(*e*) the application of relevant results of social, biomedical, and health services research and of public health experience.

Different countries are at various stages of implementing primary health care systems and each may have its own definition of what this involves. Whatever the definition, it is important that when filariasis control is integrated with PHC, it should include the entire population and involve the active participation of the community.

9.1.1 *Community participation*

Community participation is the key to the success of any health programme that is integrated with the primary health care system. In filariasis control programmes, the community members can be motivated to take part because the disease causes a significant loss of working hours, thereby decreasing productivity. Furthermore the disease can lead to gross physical deformities and mental stress. There is also the added nuisance of high densities of biting vectors.

To ensure community participation, a preparatory phase is necessary, during which time community leaders and other motivated persons should be identified and approached to cooperate in the programme. During this phase adequate education should be given on the nature of the disease, on the role of the vector and means for its control, and on the effectiveness of DEC in reducing morbidity and transmission. The safety of the drug should be emphasized, as well as the possibility of reactions occuring during treatment.

An initiative to start the process of community participation may come from the community itself or from outside the community, from the health service, the government, or private agencies. The underlying message of WHO in the PHC approach is that the health services should take the initiative. However, a prerequisite is that the community should always recognize the need and be made to feel that the programme is theirs.

The felt needs of the community can provide the entry-point for integration of filariasis control into the PHC system. If filariasis control is not popular, but is considered important from the point of view of the community's health status, it may have to be packaged with other activities that are attractive to the people, such as the provision of water supplies and food supplements, or the control of malaria. Where filariasis overlaps with malaria, control of the two diseases should be integrated.

9.1.2 *Health education*

The aim of health education in support of filariasis control should be to motivate the people in the following respects:

(*a*) awareness of the early signs and symptoms of the disease;
(*b*) willingness to take treatment to prevent the development of a chronic disability;
(*c*) acceptance of DEC in mass or selective treatment;
(*d*) acceptance of diagnostic procedures;
(*e*) self-protection of each individual from mosquito bites; and
(*f*) environmental sanitation to reduce mosquito breeding-sites.

Until now, health education efforts and medical campaigns in many countries have endeavoured to encourage community acceptance of selected vertical programmes carried out in isolation from other health and development needs. Only limited efforts have been made to develop an integrated approach. Suitable programmes for integration with filariasis control need to be identified and may include malaria control or other components of PHC.

Increasing efforts are being made in a number of countries to use the information and broadcasting services in support of health programmes in order to keep the public well informed and to create a favourable social climate. As an example, radio programmes have been used to promote the acceptance of mass DEC campaigns for filariasis control in Tonga and Samoa.

Acute infectious diseases that cause mortality, often provide an immediate stimulus to community action for health. Filariasis, on the other hand, is a chronic disease with a prolonged incubation period and an insidious onset, and does not have such a dramatic impact. By the time an afflicted individual does seek care, serious lesions may have developed. Health education thus has an important role to play in preventing the development of the chronic debilitating forms of filariasis.

There is a need for more instruction in schools on general parasitic disease control, including filariasis. Health education should be developed as an integral part of the school curricula, particularly in primary schools and teacher training-institutions; health education on filariasis may be given in an informal or formal way, but there must be dynamic interaction between schools and communities for health promotion.

Although the process of changing human behaviour may be difficult, any progress in this direction will be long lasting. Any success the community may have in solving its own problems, however small it may be, will increase its self-confidence and encourage the acceptance of further challenges, thus leading to greater success.

Community leaders and other motivated persons who have received health education in the preparatory phase, will be needed as future educators and supporters of the programme.

9.1.3 *Appropriate technology for integration of DEC chemotherapy with the primary health care system*

The primary health worker should be involved in the control of lymphatic filariasis with DEC at the village level in one or more of the following ways. The choice of approach depends on the level of sophistication in filariasis control that has been achieved in the country concerned. DEC should be available for use by health workers in all endemic areas, except in those areas where onchocerciasis or loiasis coexist with lymphatic filariasis.

(*a*) *Treatment of individuals with acute clinical filariasis.* The primary health worker must be trained to recognize the signs and symptoms of the various forms of this malady, and these are usually well known in affected communities. Such cases must be treated when they present themselves. The health worker should explain the prognosis and the causes of filariasis and the means for its control among the community. This explanation should be simple, such as: the worms in the blood (which can be demonstrated) or in the glands, cause the disease; the DEC medicine will kill the worms; the death of the worms may be accompanied by fever or painful glands lasting for a few days. The primary health worker may also give a routine course of DEC to all newcomers to the village when they first arrive.

(*b*) *Mass treatment.* The primary health worker may undertake mass DEC treatment in the community using a predetermined regimen. He will have to explain the cause of the disease and the reasons why everyone needs to be treated; he will also have to forewarn the people about the possibility of reactions to treatment.

(*c*) *Selective treatment.* For selective treatment the same considerations apply as for mass treatment, but it will be necessary to explain the need for blood-film examination (especially if it is done at night) in the selection of persons to be treated, and to convince symptomless carriers that they should be treated for the good of the community to prevent them spreading the worms or the disease to others. Usually the blood survey will be conducted by a filariasis survey team from outside the village.

(*d*) *DEC-medicated salt campaign.* The health worker can help promote acceptance of DEC-medicated salt programmes.

9.1.4 *Appropriate vector control technology for community participation*

9.1.4.1 *Personal protection.* The WHO Expert Committee on Vector Biology and Control, in its seventh report (*27*), underlined the importance of individual measures in preventing man–vector contact. Motivated individuals and families may contribute towards filariasis control by various methods of protecting houses or sleeping rooms. These range from screening or using mosquito bed-nets (which must be kept in good repair) to spraying aerosol insecticides or even simply closing the doors and windows of sleeping quarters before sunset. Burning "mosquito coils" or local herbs that produce repellent smoke also help to deter mosquito biting.

9.1.4.2 *Environmental management.* Insecticide resistance, increasing concern for the environment, and escalating recurrent costs have recently focused attention once again on environmental management as a major strategy in mosquito control. The fourth report of the WHO Expert Committee on Vector Biology and Control (*28*) has dealt with this problem and WHO has issued a manual on environmental management for mosquito control (*29*). Many of the simple measures recommended in this report apply equally to the control of filariasis vectors. For the control of the major groups of filariasis vector mosquitos, communities should undertake the following simple measures.

(*a*) *Control of* C. quinquefasciatus. Most of the breeding-sites are man-made and communities should therefore:

(*i*) avoid building pit latrines where the ground water-table is high;
(*ii*) repair faulty septic tanks and soak pits and dispose properly of all sewage and waste water;
(*iii*) cover sanitary and latrine ventilation pipes with appropriate mosquito gauze.

(*b*) *Control of anophelines.*

(*i*) *Species breeding in permanent water.* Species such as *A. funestus, A. sinensis, A. barbirostris.* May be controlled by draining or filling in pools, canalizing marshes and swamps, and the use of larvivorous fish. The introduction of *Eucalyptus* trees may help with the drainage of permanent breeding-sites.

(*ii*) *Species breeding in temporary pools.* Species such as *A. arabiensis, A. gambiae, A. farauti, A. ponctulatus.* These species that breed in temporary pools, such as roadside ditches and drains, borrow-pits, hoof-prints, wheel-ruts, puddles, may be controlled to some extent by in-filling, grading, and drainage.

(*c*) *Control of* Mansonia *spp.* In addition to drainage and in-filling the physical removal of *Pistia* and other host plants has led to the elimination of *Mansonia* in certain localities.

(*d*) *Control of* Aedes *spp.* Measures for the control of *Aedes* breeding-sites include the destruction of discarded containers, removal of worn-out tyres, filling up small breeding-sites, removal of plants which provide breeding-sites in the axils of their leaves, and preventing the creation of new breeding-sites.

9.1.4.3 *Integrated control.* None of these control measures applied alone is likely to bring about sustained control of filariasis vectors. A properly run community-based vector control programme should use all the appropriate methods in optimum combinations. At a later stage in development, communities may be able to support or even take over vector control activities promoted by the health authorities. Integrated vector control was dealt with by a WHO Expert Committee in 1982 (*27*).

9.1.5 *The role of community health workers*

The role of community health workers in filariasis control should be clearly defined. They may be assigned one or more of the following responsibilities:

(*a*) DEC treatment of acute cases of filariasis in the community;
(*b*) distribution of DEC to the community in mass treatment;
(*c*) provision of DEC treatment to all newcomers arriving from potential endemic areas;
(*d*) provision of advice on self-protection from mosquito bites;
(*e*) promoting environmental sanitation measures to reduce mosquito breeding-sites;
(*f*) carrying out larviciding and residual insecticide spraying in conjunction with malaria control;
(*g*) taking blood samples;
(*h*) staining and examining blood-films for microfilaraemia.

The decision as to which tasks they should undertake must be an empirical one, based on the number of other responsibilities that the health worker has to cope with, the degree of perfection in filariasis control that is sought, and the financial resources of the community concerned. Each health worker should undergo a training period for his specific role in the control programme. It must be stressed that the various responsibilities need not necessarily be taken on by a single individual. It is also important to introduce the various tasks of the community health worker into the control programme in a phased manner.

In endemic areas, where the disease rate is high and the resources are inadequate to cope with the problem satisfactorily, control of filariasis should be based on the distribution of DEC by the community health worker to those with acute clinical manifestations of filariasis. If resources for control are increased, then some form of mass DEC distribution may be initiated.

Where the disease rate is low, people may be less motivated to receive treatment. Screening for microfilaraemia may then play a vital role provided technical and financial resources are available. Vector control may be used to supplement chemotherapy. Again the level of activity will vary according to resources, but personal protection against mosquito bites, and efforts to reduce breeding sites should always be components of any filariasis control programme.

9.2 The experiences of individual countries

9.2.1 *India*

The number of cases of lymphatic filarial disease (mostly caused by *W. bancrofti*) in India is greater than in any other country. Over 300 million people live in zones where lymphatic filariasis is endemic. There are estimated to be at least 6 million attacks of acute filarial disease per year and at least 15 million persons currently have one or more chronic filarial lesions.

The vertical approach to the control of lymphatic filariasis has had very limited success in India in terms of coverage of the population at risk, except in the relatively small areas where brugian filariasis occurs.

The reasons for this lack of success appear to be as follows.

(*a*) Treatment with DEC in mass or selective campaigns has not been well accepted owing to the severe reactions that occur in many symptomless infected persons, particularly microfilaraemics.

(*b*) House-spraying against indoor-resting mosquitos has been poorly accepted.

(*c*) Mosquito larviciding, although acceptable, is considered to be the responsibility of the government (which cannot cover the whole endemic area), as well as being of limited efficacity.

(*d*) The population in the endemic areas is so vast that with current financial and manpower resources it has not been possible to cover more than a small proportion of those "at risk" of infection.

Vertical filariasis control programmes aim at eliminating infection and interrupting transmission, but in India it appears that such goals cannot be achieved in the foreseeable future. Instead, public health efforts should concentrate on controlling lymphatic filarial disease and, by early treatment of acute attacks of clinical filariasis, preventing the development of chronic lesions (elephantiasis, hydrocoele, chyluria, etc.).

To do this it is essential to adopt a horizontal approach and make use of the primary health care system for the distribution of the DEC. Such an approach has proved very successful in parts of Indonesia.

If treatment of acute filarial disease is to be included in the primary health care system the village health guides (VHGs) or their equivalent must not be overloaded with work as each is often responsible for the primary health care of about 1000 people. This can be done by training the village health guides to recognize the acute clinical manifestations of lymphatic filariasis and by issuing them with DEC so that they can treat these conditions, without making any blood examination for microfilariae. DEC can be safely used in this way by local health workers at the current standard regimen of 6 mg/kg body weight daily for 12 days, but even shorter courses than this would probably be beneficial to the sufferers.

To support this campaign, efforts have to be made to devise simple methods for educating vilagers in the primary health care approach to the control of filarial disease, especially via the schools and the village health guides. In addition, some consideration must be given to the most acceptable size of DEC tablets to be used. A 200-mg tablet might be more convenient than the 50-mg or 100-mg

pills used at present. The smaller tablets could be reserved for children.

9.2.2 *China*

Lymphatic filariasis has been successfully controlled over large areas of China. Active participation of the community is reported to have been an important factor contributing to this success. A 95% coverage by blood-smear collection, a high acceptance of DEC treatment, including its use in medicated salt, and improvement of environmental sanitation have all contributed to the reduction in the parasite reservoir and in mosquito sources. This reduction has been achieved largely through the people's "Patriotic Movement". Health education on the transmission and prevention of filariasis uses all the available media of communication, and political will has motivated the people to participate actively in control efforts. Trained brigade leaders, barefoot doctors, and part-time health aids (the latter two categories being commune members) have collected and examined blood smears and have given DEC treatment under supervision.

9.2.3 *Indonesia*

The vertical approach to filariasis control using DEC has achieved significant success in certain areas of Indonesia, but reactions following administration of the drug were found to be a major obstacle to the control programme. In addition, the costs of drug delivery and travel of the blood survey and control teams far exceeded the cost of the DEC.

A low-dose DEC administration scheme was developed in 1977 in West Flores, an island highly endemic for *B. timori,* with health education and community participation as an integral part of the control programme. Health education included knowledge of the parasite as a causative agent, the role of mosquitos as transmitters, recognition of the acute and chronic clinical manifestations of filariasis, the efficacy of DEC, and the reactions to treatment. Motivated persons in the community, such as the village chief, schoolteachers, and especially including people with elephantiasis, were identified and assigned the responsibility for distributing DEC on a weekly basis to all heads of family in the village. Each family head was in turn responsible for treating his family members. The weekly dose of DEC was 25 mg for those below 10 years of age, and

50 mg for those aged 10 years and above. The total yearly dosage of DEC for an adult was thus about 4.0 g.

After mass treatment with DEC was stopped, all acute cases of clinical filariasis that occurred subsequently in the community were immediately treated by the same people with 3 × 100 mg of DEC for 10 days, or with half this dose for children below 10 years. With this regimen the microfilaria rates decreased dramatically to very low levels (confirmed by Nuclepore filtration) and they have remained low for 3–4 years (the longest observation period so far). The adenolymphangitis rates and the total loss of working days also decreased significantly. As an unexpected bonus, a considerable proportion of people with lymphoedema and long-standing elephantiasis have also gradually become normal again. Encouraged by the favourable results obtained, the same schedule was tried in a *W. bancrofti* area, using a total dose of 6.0 g DEC with similarly good results.

Subsequently the 4.0 g DEC total-dose schedule was tried in a subperiodic *B. malayi* area where the literacy rate of the population was lower than in Flores. Again very good results were obtained. Finally, a trial was then conducted in Buru, an island highly endemic for subperiodic *B. malayi,* where the people were illiterate and seminomadic. After one year of treatment the microfilaria and adenolymphangitis rates decreased to a level similar to those observed in West Flores.

On the basis of these results it was felt that this regimen could be applicable in many other parts of Indonesia. The results of low-dose DEC treatment regimens, given "by-the-people-for-the-people", were therefore presented to the Indonesian Ministry of Health early in 1983, for consideration as a national filariasis control programme, to be integrated with the existing primary health care system of the country.

9.2.4 *Samoa*

Samoa is a relatively small country which has put a high priority on filariasis control because of the high endemicity of the disease. The women's committees are a most important mechanism for mobilizing community resources for health activities, including the control of lymphatic filariasis which is a big problem in the country.

Health education has been extensively used to promote community cooperation and participation in mass DEC campaigns against

filariasis. District nurses have been the vital links between filariasis control staff and the rural village community. Collaboration has even extended to schoolteachers, who have registered schoolchildren and assisted in their treatment; voluntary workers, such as student nurses and high-school students have also distributed DEC tablets to persons at hospitals, markets, and community gatherings. A teaching guide on filariasis control has been useful in obtaining the participation of nurses and schoolteachers in these activities, which have also involved simple environmental measures for reducing the densities of the *Aedes* vector mosquitos. After the dates of mass drug administration have been set, radio announcements are repeatedly used to inform the public. An annual single-dose mass treatment regimen at 6 mg/kg of DEC body weight is now being used.

9.2.5 *Egypt*

In Egypt, there is a focus of bancroftian filariasis in the Nile delta, particularly in the eastern region. Filariasis control was implemented from the beginning through integration with the primary heath care system.

A well-developed primary health care network exists in the form of 2500 rural health centres and units. More than half of these have an outreach programme of regular home visiting carried out by nurses and motivators recruited from local communities. In such a relatively advanced setting, integration of an antifilarial control programme met with no difficulties. The programme components include blood sampling and microscopy at village unit level, in addition to selective treatment and vector control. A high degree of acceptance of late-night blood sampling and DEC treatment has been observed. This can be attributed to thorough implementation by the resident health teams, to the heavy involvement of the community through health education, and to the role of the village councils, which represent the administrative authority supervising the village services. At present the microfilaraemia rate is less than 1% in the population of the endemic areas.

9.2.6 *Viet Nam*

Use of mosquito nets is encouraged to prevent bites by brugian filariasis vectors. The nets are purchased by, or made in, the commune, which also arranges repairs to keep them effective.

9.3 Suggestions for further study

(*a*) Identification of factors that:

(*i*) influence community participation in vector control;
(*ii*) hinder epidemiological surveys, e.g., reluctance to contribute blood samples;
(*iii*) limit participation in chemotherapeutic control.

(*b*) Assessment of the cost-effectiveness of different control strategies, including comparison between the primary health care approach and specialized filariasis control programmes.

10. HUMAN BEHAVIOURAL AND SOCIOECONOMIC ASPECTS

10.1 Behavioural aspects

Human behavioural factors have an important influence on the exposure of man to filariasis and other vector-borne diseases (*30*). Although this was recognized in the third report of the WHO Expert Committee on Filariasis (*26*) there is still a lack of knowledge in almost every endemic area about the influence of human behaviour on filariasis transmission and control. There are also considerable differences between modern medical knowledge and the existing indigenous perceptions of the disease, and these differences may hamper control programmes. Information on sociocultural concepts can be used in control programmes to provide an understanding of the mode of transmission and development of the disease and a knowledge of the parasite, the vector, and methods of prevention and treatment. Of particular interest in relation to control programmes is the attitude of people to such things as the side-effects of DEC treatment or house-spraying, and the social customs of the people in relation to vector breeding-sites. These aspects are of relevance to the development of health education programmes aimed at community participation in the control of the disease.

10.2 Socioeconomic aspects

While it appears that filarial disease may result in direct and indirect economic losses, such costs are difficult to assess. A substantial review of the economics of malaria, filariasis, and trypano-

somiasis cites a few qualitative judgements about the impact of filariasis on production, but notes that supporting empirical data are scarce.[1]

An example of such an economic study on lymphatic filariasis was conducted in the province of Sorsogon, Luzon, Philippines. In the course of epidemiological surveys, direct and indirect costs were estimated in an attempt to determine the economic losses due to the disease. Direct costs included physicians' fees, laboratory examinations, and treatment by drugs or surgery. Indirect costs included loss of working-time due to the effects of acute or chronic filarial disease. The results of this study showed that the economic losses estimated for filariasis were potentiated by the social attitudes towards the disease.

The cost and effectiveness of control measures differ considerably between different specific situations. Recognizing the limited financial and manpower resources available, it is important to analyse the cost and effectiveness of alternative control strategies. Such analyses may enable a control programme to define the most cost-effective strategy to reach its target as, for example, in the reduction of microfilaria rates to a certain level. In countries where *Anopheles* vectors transmit both malaria and filariasis, an integrated control programme directed towards both diseases may be more cost-effective.

10.3 Suggestions for further study

Research on human behavioural and socioeconomic aspects of filariasis should be closely related to the needs and priorities of the control programme so that the results can be put to practical use. This type of research would benefit from a collaborative approach involving control programme staff, social scientists, economists, epidemiologists, and entomologists, including those concerned with other vector-borne diseases.

The following lines should be followed:

(*a*) identification of traditional beliefs and practices concerning causation of filariasis, traditional therapy, management of symptomatic filariasis, and reduction of transmission;

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[1] Prescott, N.M. *The economics of malaria, filariasis and human trypanosomiasis.* — Unpublished WHO document WHO/TDR/SER(SC-1)/80.4 (1980).

(*b*) study of environmental change, especially man-made modifications, that affect the transmission and endemicity of filariasis; and of human behavioural factors that contribute to the creation of mosquito breeding-sites;

(*c*) study of the direct and indirect consequences of filariasis on economic production, through analyses of work-time lost, productivity reduced, and related costs of medical care.

11. TRAINING AND MANPOWER DEVELOPMENT

The strategies and methods used in filariasis control operations vary from country to country and require a detailed knowledge of the biology of the parasite and vector, and of the factors affecting transmission. Therefore, there is a need for training programmes both in countries within the endemic areas and in specialized institutions elsewhere. The role played by WHO in improving the research and training ability of local institutions has had a major impact on filariasis control.

Training courses at different levels are necessary for the successful implementation of a control programme and these are available in some endemic countries. However, even in countries where filariasis control operations have been in existence for a long time, such as India and Sri Lanka, there is a real need for refresher training courses.

In some countries, training programmes have either failed to attract trainees or there has been a high turnover of trained personnel. An important factor contributing to this has been the lack of incentives offered to the field worker, and equally important is the fact that the type of work involved is often unattractive, involving night-blood surveys or repetitive antilarval measures in unattractive environments.

In many affected countries, filariasis control is not given special status so that training at the highest level (postgraduate) has to be considered on a broad base, i.e., medical parasitologists, entomologists, and epidemiologists able to cope with a variety of communicable diseases, especially those that are vector-borne.

At the time of the third report of the WHO Expert Committee on Filariasis (*26*), most of the training at postgraduate level was given in institutions located in non-endemic countries. Since the late 1970s, several universities and institutions located in countries where

filariasis is endemic have, with WHO support, developed specialized courses at the Master's degree level involving medical entomology, medical parasitology, and the epidemiology of tropical diseases. This trend should be encouraged and further supported.

Training of medical assistants and technicians should be organized on a more specific basis. Lower-level workers should continue to be trained locally.

It is emphasized that the subject of filariasis control should be included in the curricula of medical schools and paramedical teaching institutions. Where lymphatic filariasis is a problem of public health importance it will also be appropriate to include relevant aspects of its control in the on-going training programmes for primary health workers; training aids, manuals, brochures, films, slides, and posters should be provided for these programmes.

Bridges between applied research and control (planning, implementation, and evaluation) should be developed. Training centres should be associated with both applied research and control projects.

12. CONCLUSIONS

(1) Although there have been several successful programmes to control lymphatic filariasis, the disease continues to be one of considerable public health and socioeconomic importance in many tropical countries. It affects large numbers of people in some Asian countries (notably China, India, and Indonesia), and it is still a major problem, at least focally, in some countries in the Western Pacific and African Regions.

(2) The control of lymphatic filarial disease can be achieved using the primary health care system and by community participation, as well as by vertical disease-oriented programmes, but the strategy selected must be adapted to local conditions. Assiduous application of present control techniques could result in a rapid reduction of the disease, and even to the disappearance of the infection from many endemic areas.

(3) The activities stimulated and carried out by WHO, including those of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases, have made a major contribution to the knowledge and control of lymphatic filariasis.

13. RECOMMENDATIONS

(1) Efforts should be made to collect more information on the distribution and prevalence of lymphatic filariasis in all endemic areas, especially Africa.

(2) Every effort should be made to integrate the treatment of lymphatic filarial disease into the primary health care system, to enlist the participation of the community in the control of the infection, and to provide adequate health education to support these activities. Problems in implementing this approach should be solved by research.

(3) The role of the primary health worker in filariasis control programmes should be identified, and appropriate training courses, including health education, should be developed to support this role.

(4) The search for better regimens for administering DEC for filariasis control should continue, with special emphasis on: (*i*) short courses of treatment that will control acute clinical manifestations, prevent their recurrence, and stop the development of chronic lesions; and (*ii*) single-dose widely-spaced regimens that will prevent the development of chronic lesions, control microfilaraemia, and reduce transmission.

(5) Research should continue to find more effective, low-cost filaricidal drugs that can be easily administered.

(6) Because the clinical, parasitological, and immunological techniques currently available are cumbersome and inadequate for diagnosing all cases of filarial infection, efforts should be made to develop immunodiagnostic or other sensitive techniques capable of accurately detecting infection.

(7) In view of the domestic habits of many filariasis vectors, the community should be involved in vector control by preventing the production of new breeding-sites, by controlling breeding in existing sites, and by personal protection against mosquitos.

(8) Urban and rural development programmes, especially those concerned with water management, should from the beginning include measures to prevent the multiplication of filariasis vectors.

(9) Ministries of health should provide technical support (training, evaluation, research) for any filariasis control programme, particularly those integrated with the primary health care system.

(10) The development, especially in tropical countries, of specialized postgraduate courses in applied parasitology, medical entomology, and epidemiology of tropical diseases should continue

to be encouraged and supported, since this will provide the high calibre personnel essential for the successful implementation of filariasis control programmes.

(11) Since there are still many unsolved problems in relation to the disease and its control, it is essential that WHO should continue to sponsor research and training in this field if the overall goal of health for all by the year 2000 is to be reached.

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ANNEX 1

NAMES OF THE PRINCIPAL (AND SUBSIDIARY) MOSQUITO VECTORS OF HUMAN LYMPHATIC FILARIAL PARASITES IN THE MAJOR ENDEMIC ZONES OF THE WORLD[a]

Filaria species and type	Endemic area	Principal vector (subsidiary vectors)
Wuchereria bancrofti – periodic		
Zone 1	Tropical America	*Culex quinquefasciatus* *Anopheles darlingi* *(Aedes scapularis)* *(Aedes taeniorhynchus)* *(Anopheles albimanus)* *(Anopheles aquasalis)* *(Mansonia titillans)*
Zone 2	Tropical Africa	*Culex quinquefasciatus* *Anopheles arabiensis* *Anopheles funestus* *Anopheles gambiae* *Anopheles melas* *Anopheles merus* *(Anopheles hancocki)* *(Anopheles nili)* *(Anopheles pauliani)* *(Anopheles wellcomei)* *(Culex antennatus)*
Zone 3	Middle East	*Culex molestus* *Culex quinquefasciatus* *(Culex antennatus)*
Zone 4	South Asia	*Culex quinquefasciatus* *Aedes poicilius* *Anopheles balabacensis* *Anopheles dirus* *Anopheles donaldi* *Anopheles flavirostris* *Anopheles candidiensis* *Anopheles anthropophagus* *Anopheles letifer* *Anopheles leucosphyrus* *Anopheles maculatus* *Anopheles minimus* *Anopheles sinensis* *Anopheles subpictus* *Anopheles vagus* *Anopheles whartoni* *(Aedes togoi)* *(Anopheles aconitus)* *(Anopheles barbirostris)* *(Anopheles kweiyangensis)* *(Anopheles nigerrimus)* *(Anopheles philippinensis)* *(Anopheles tessellatus)* *(Culex bitaeniorhynchus)* *(Culex sitiens)*

[a] See Map in Fig. 1 for outline of zones 1–7.

Filaria species and type	Endemic area	Principal vector (subsidiary vectors)
Zone 5	Far East	*Culex pipiens pallens* *Culex quinquefasciatus*
Zone 6	New Guinea	*Anopheles farauti* *Anopheles koliensis* *Anopheles punctulatus* *Culex quinquefasciatus* *(Aedes kochi)* *(Anopheles bancrofti)* *(Culex annulirostris)* *(Culex bitaeniorhynchus)* *(Mansonia uniformis)*
Wuchereria bancrofti – subperiodic		
Zone 4	South Asia	*Aedes harinasutai* *Aedes niveus*
Zone 7	Polynesia	*Aedes cooki* *Aedes fijiensis* *Aedes kesseli* *Aedes oceanicus* *Aedes polynesiensis* *Aedes pseudoscutellaris* *Aedes samoanus* *Aedes tutuilae* *Aedes upolensis* *Aedes vigilax*
Brugia malayi – periodic	South Asia	*Anopheles anthropophagus* *Anopheles barbirostris* *Anopheles campestris* *Anopheles donaldi* *Anopheles kweiyangensis* *Anopheles sinensis* *Mansonia annulata* *Mansonia annulifera* *Mansonia uniformis* *(Anopheles nigerrimus)* *(Aedes kiangensis)* *(Aedes togoi)* *(Mansonia bonneae)* *(Mansonia dives)* *(Mansonia indiana)*
Brugia malayi – subperiodic	South Asia	*Mansonia annulata* *Mansonia bonneae* *Mansonia dives* *Mansonia uniformis* *(Coquillettidia crassipes)*
Brugia timori – periodoc	Flores, Timor	*Anopheles barbirostris*