LYMPHATIC FILARIASIS:
THE DISEASE AND
ITS CONTROL

Fifth report of the
WHO Expert Committee on Filariasis

World Health Organization
Geneva 1992
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Acknowledgements

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Summary of the distribution of human lymphatic filariasis and its vectors,
by WHO region
WHO Expert Committee on Filariasis
Geneva, 1–8 October 1991

Members
Dr P.T. Dennis, Chief, Bacterial Zoonoses Branch, Division of Vector-Borne Infectious Diseases, Centers for Disease Control, Fort Collins, CO, USA
Dr G. Dreyer, Aggeu Magalhaes Research Centre, FIOCRUZ, Recife, Brazil
Dr M.M. Ismail, Professor of Parasitology, Faculty of Medicine, University of Colombo, Colombo, Sri Lanka (Co-Rapporteur)
Dr V. Kumaraswami, Assistant Director, Tuberculosis Research Centre, Madras, India
Dr J.W. Mak, Head, Malaria and Filariasis Research Division, Institute for Medical Research, Kuala Lumpur, Malaysia (Co-Rapporteur)
Dr J.U. Mataika, Director, Wellcome Virus Laboratory, Fiji Filariasis Programme, Tamavua Hospital, Suva, Fiji
Dr E.A. Ottesen, Head, Clinical Parasitology Section, Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA (Chairman)
Dr W.F. Piessens, Professor, Department of Tropical Public Health, Harvard School of Public Health, Boston, MA, USA
Dr P.K. Rajagopalan, former Director, Vector Control Research Centre, Pondicherry, India (Vice-Chairman)
Dr B.A. Southgate, Senior Lecturer in Tropical Epidemiology, London School of Hygiene and Tropical Medicine, London, England
Dr Zheng Huijin, Professor and Head, Department of Filariasis, Guizhou Provincial Institute of Parasitic Diseases, Guiyang, Guizhou, China

Secretariat
Dr A.S. Dissanaike, 28 Welikadewatte, Nawala Road, Rajagirinya, Sri Lanka (Consultant)
Dr R. Le Berre, Chief, Filariasis Control, Division of Control of Tropical Diseases, WHO, Geneva, Switzerland (Secretary)
Dr C.P. Ramachandran, Secretary, Steering Committee on Filariasis, UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases, WHO, Geneva, Switzerland
1. **Introduction**

The WHO Expert Committee on Filariasis met in Geneva from 1 to 8 October 1991. Opening the meeting on behalf of the Director-General, Dr P. de Raadt, Associate Director, Division of Control of Tropical Diseases, observed that lymphatic filariasis, like cholera and leprosy, was a disease of the poor that served as an indicator of underdevelopment. Affecting all tropical regions of the world – especially southern and south-eastern Asia, the Pacific and eastern Africa – it was also a debilitating disease with serious economic and social consequences as it affected many young working adults of both sexes and the chronic manifestations, in the form of lymphoedema and elephantiasis, could inflict grave social wounds upon the persons affected. It was encouraging that, in the past few years, knowledge of many aspects of lymphatic filariasis had increased, greatly enhancing the possibility of controlling the disease. The better use of diethylcarbamazine (DEC) and DEC-medicated salt needed further consideration. Ivermectin, which had undergone dose-finding trials for lymphatic filariasis and for which community-based field trials were now planned, might prove to play an important role in control. Bacillus sphaericus, an insecticide of biological origin, showed good potential for the control of the urban vector of lymphatic filariasis. As for many other diseases affecting the poorest of the poor, however, control of lymphatic filariasis faced great difficulties. Not the least of these was the difficulty of accessibility – accessibility of the community to health care, and accessibility of control teams, drugs, and insecticides to the community.

2. **Prevalence, distribution, and the parasites**

2.1 **Prevalence and distribution**

The general geographical distribution of the lymphatic filarial parasites, *Wuchereria bancrofti*, *Brugia malayi* and *B. timori*, was documented with maps and tables in the fourth report of the WHO Expert Committee on Filariasis (*J*). It is difficult to give an accurate estimate of the prevalence of the disease in the different endemic areas, but an attempt has been made to summarize the most recent information available in Table 1 and Fig. 1 and Fig. 2 for the five WHO regions involved. Little information is available for the African Region and, as was emphasized in the fourth report, efforts need to be made to collect more information from all endemic areas, especially in Africa.

On the basis of the information available to the Expert Committee it is estimated that among a total population of 3287 million persons in countries in which the disease is endemic, some 751 million live in areas where transmission is known to occur. Of these, 72.8 million are infected with *W. bancrofti* and 5.8 million with *B. malayi* or *B. timori*. In several countries, control programmes have resulted in a reduction in the rate of
infection – e.g. in China – or even its eradication – as in the Solomon Islands and Jinmen Islands – and in spite of the overall increase in the total population since the fourth report of the Expert Committee (1), there is a decrease in the numbers reported infected.

The parasites and the vectors involved in respect of each country or territory in which the disease is known to be endemic, other than those in the African Region, are summarized in the Annex.

To supplement Table 1, some of the information reported to the Expert Committee is summarized in the following paragraphs.

In the Americas, Brazil reports important re-emergence of transmission of bancroftian filariasis in Greater Recife, with microfilaria rates in communities of low socioeconomic status ranging from 2% to 15%. The

<table>
<thead>
<tr>
<th>WHO region</th>
<th>Total population of endemic countries(^a) (millions)</th>
<th>Population living in endemic areas(^a) (millions)</th>
<th>Filarial infections (microfilaria-positive) and disease (millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Americas(^b)</td>
<td>170</td>
<td>6.5</td>
<td>Wuchereria 0.3</td>
</tr>
<tr>
<td>Eastern Mediterranean(^c)</td>
<td>52</td>
<td>3.7</td>
<td>Brugia 0</td>
</tr>
<tr>
<td>South-East Asia(^d)</td>
<td>1287</td>
<td>493.2</td>
<td>Wuchereria 0.2</td>
</tr>
<tr>
<td>Western Pacific(^e)</td>
<td>1334</td>
<td>135.0</td>
<td>Brugia 4.8</td>
</tr>
<tr>
<td>Total reported to the Expert Committee</td>
<td>2843</td>
<td>638.4</td>
<td>Wuchereria 2.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Brugia 1.0</td>
</tr>
<tr>
<td>Africa(^f) - data from fourth report of WHO Expert Committee on Filariasis (1)</td>
<td>444</td>
<td>113</td>
<td>Wuchereria 25.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Brugia 0</td>
</tr>
<tr>
<td>Total</td>
<td>3287</td>
<td>751.4</td>
<td>Wuchereria 72.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Brugia 5.8</td>
</tr>
</tbody>
</table>

\(^a\) Population figures are taken from World health statistics annual, Geneva, World Health Organization, 1990. The countries and territories included in the endemic areas of the various WHO regions are listed in the following footnotes.

\(^b\) Brazil, Costa Rica, Dominican Republic, Guyana, Haiti, Suriname, Trinidad and Tobago.

\(^c\) Egypt only.

\(^d\) Bangladesh, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand.

\(^e\) American Samoa, Brunei Darussalam, China, Cook Islands, Fiji, French Polynesia, Malaysia, Niue, Papua New Guinea, Philippines, Republic of Korea, Samoa, Tonga, Viet Nam.

\(^f\) In the past 10 years an effective control campaign has greatly reduced the prevalence of *W. bancrofti* and *B. malayi* infections in China. This would account for the marked decrease in the number of infections reported from the Western Pacific Region.

\(^g\) Angola, Benin, Burkina Faso, Burundi, Cameroon, Cape Verde, Central African Republic, Chad, Comoros, Congo, Côte d’Ivoire, Equatorial Guinea, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Liberia, Madagascar, Malawi, Mali, Mauritius, Mozambique, Niger, Nigeria, Réunion, Sao Tome and Principe, Senegal, Seychelles, Sierra Leone, Togo, Uganda, United Republic of Tanzania, Zaire, Zambia, Zimbabwe.
Dominican Republic reports endemic foci in Santo Domingo and other southern areas with microfilaria rates of 7–26%. Haiti reports hyperendemic foci in some areas and lower rates elsewhere. Transmission in Guyana is confined to the coastal area: a microfilaria rate of 6.4% was reported in a survey of Georgetown in 1984. In Costa Rica, Suriname, and Trinidad and Tobago limited foci of continuing low-level transmission probably remain, although no recent surveys have been conducted.

In the Eastern Mediterranean Region, an estimated 171,000 microfilaria-positive individuals are reported from Egypt, with rates of 0–39% in surveyed villages in the Nile Delta. Oman reports no residual transmission. No report was available from the Sudan (where endemic foci of bancroftian filariasis have been known to occur in southern regions in the past) or from Somalia.

In the South-East Asia Region, India reports an estimated 374 million persons living in endemic areas, and 45 million persons infected, an increase over the 18 million estimated in 1983, due mostly to an overall increase in populations living in endemic areas. Brugian filariasis in India is mostly found in Kerala, but scattered foci of low prevalence are reported in Orissa, Assam, Madhya Pradesh, Andhra Pradesh, and Tamil Nadu. A focus of subperiodic bancroftian filariasis has been described in the Nicobar Islands. Indonesia reports an estimated 22 million persons living in endemic areas and 100,000 persons infected. Bancroftian transmission occurs at low levels in the cities of Jakarta and Semarang on the north coast of Java, in interior areas of Sumatra and Kalimantan, along coastal areas of small islands east of Lombok, and in Irian Jaya. Filariasis due to *B. timori*
occurs in scattered lowland areas of small islands surrounding the Savu Sea in eastern Indonesia, and notably in Flores and Timor islands. B. malayi foci remain in Sumatra, Kalimantan, Sulawesi, and Buru. The Maldives, Myanmar, Sri Lanka, and Thailand report transmission of bancroftian filariasis at low levels. There is no recent survey information from Bangladesh and Nepal, but both report continuing endemicity.

In the Western Pacific Region, China reports a dramatic reduction from the estimates of 1983, due to an effective national programme of control. Only some 1.65 million people are believed to have (mostly chronic) filarial disease. Transmission is mostly confined to Anhui Province; in other provinces under long-term surveillance, the microfilaria rates are well under 1%. Viet Nam reports 510,000 infected persons (70,000 W. bancrofti; 440,000 B. malayi) with W. bancrofti rates of 1.6% and B. malayi rates of 0.3-0.6%, but as high as 20-33% in some villages. Peninsular Malaysia has recorded a continuing decrease of filariasis, with only a few scattered foci of low prevalence remaining; moderately endemic foci of bancroftian and brugian filariasis remain in the East Malaysian states of Sabah and Sarawak. In the South Pacific, where subperiodic W. bancrofti infection occurs, daytime-biting Aedes polynesiensis is the main vector in Cook Islands, Fiji, French Polynesia, Samoa, and Tuvalu. Recent surveys in Fiji show microfilaria prevalence rates of 0.9% to 12%.

No information was available from countries in the African Region, although both urban and rural bancroftian filariasis are known to be highly endemic on Zanzibar and along the coastal areas of Kenya, Madagascar, and the United Republic of Tanzania. Scattered foci are also known from
past studies in many areas of central and West Africa in the broad transmission zone delimited on the map.

2.2 The parasites

2.2.1 Human and animal lymphatic parasites

*Wuchereria bancrofti* (Cobbold, 1877) throughout the tropical belt, *Brugia malayi* (Buckley & Edeson, 1956) in Asia and the Pacific and *B. timori* (Partono et al., 1977) in some small islands of Indonesia are the three lymphatic filariae found in humans.

The human parasites have diversified into a large number of strains, as becomes very clear from the different periodicities of the microfilaraemias that they cause. Each strain establishes a particular transmission equilibrium with the natural vector or vectors, which is the outcome of adjustments made at each stage in the cycle – ingestion of microfilariae, crossing of the stomach wall, etc. A reduction in microfilaraemia could in principle therefore act differently on each of these filaria-vector pairs; this point is discussed later under low-density transmission (section 6.4).

The mosquito vectors of some of these filariae also transmit filariae that parasitize animals. The morphology of the infective stage generally indicates the genus concerned; while most of these larvae can be readily distinguished from human parasites, this is not the case for those of the genera *Wuchereria* and *Brugia*.

Up to now 1 *Wuchereria* species and 8 *Brugia* species have been described in animals: *W. kalimantanii*, *B. pahangi*, *B. patei*, *B. buckleyi*, *B. ceylonensis*, *B. beaveri*, *B. guyanensis*, *B. tupaiæ*, and *B. lepori*. (More recently at least 1 species of *Brugia*, as yet undescribed, has been isolated from the coatimundi (*Nasua nasua*) from the Colombian Pacific coast; preliminary studies suggest that it is a new species.) The 10 species of *Brugia* so far described from humans and animals are summarized in Table 2. Of special interest are the species that naturally infect humans (*B. malayi* and *B. timori*) and those that are potential human parasites (*B. pahangi* and perhaps other species).

Five of the species that parasitize animals (*W. kalimantanii*, *B. pahangi*, *B. buckleyi*, *B. ceylonensis*, *B. tupaiæ*) are found in Asia and the Pacific; it is here that the problems of differentiation are most acute, particularly because in this region *B. malayi* is itself a parasite of a wide variety of mammals.

The species diagnosis is made according to the morphology of the microfilariae and adults, and study of the latter has been greatly assisted by the discovery of a very receptive experimental host, the jird, *Meriones unguiculatus*. The stages studied in epidemiological surveys, however, are essentially the microfilaria and the infective-stage larva, and occasionally other stages present in the vector.
Table 2

<table>
<thead>
<tr>
<th>Species</th>
<th>Hosts</th>
<th>Geographical distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>B. malayi</em></td>
<td>Humans, primates, other wild and domestic animals</td>
<td>China, India, Indonesia, Republic of Korea, Malaysia, Philippines, Thailand</td>
</tr>
<tr>
<td><em>B. pahangi</em></td>
<td>Monkeys, cats, dogs, other carnivores</td>
<td>Indonesia, Malaysia</td>
</tr>
<tr>
<td><em>B. patei</em></td>
<td>Cats, dogs, genet cats</td>
<td>Pate island (Kenya)</td>
</tr>
<tr>
<td><em>B. (Brugiaella) buckleyi</em></td>
<td>Wild hare (<em>Lepus nigricollis sinhala</em>)</td>
<td>Sri Lanka</td>
</tr>
<tr>
<td><em>B. ceylonensis</em></td>
<td>Dogs, cats</td>
<td>India, Sri Lanka</td>
</tr>
<tr>
<td><em>B. guyanensis</em></td>
<td>Coati mundi (<em>Nasu nasua vittata</em>)</td>
<td>Guyana</td>
</tr>
<tr>
<td><em>B. beaveri</em></td>
<td>Raccoon (<em>Procyon lotor</em>)</td>
<td>Lousiana (USA)</td>
</tr>
<tr>
<td><em>B. tupaiæ</em></td>
<td>Tree shrew (<em>Tupla glis</em>)</td>
<td>Malaysia, Thailand, Viet Nam Indonesia</td>
</tr>
<tr>
<td><em>B. timori</em></td>
<td>Humans</td>
<td>Lousiana (USA)</td>
</tr>
<tr>
<td><em>B. lepori</em></td>
<td>Wild rabbit (<em>Sylvilagus aquaticus, S. floridans</em>)</td>
<td></td>
</tr>
</tbody>
</table>

Microfilaria. The species can generally be distinguished by reference to the qualitative characters (cephalic space, caudal nuclei, R cells and excretory cells) and the dimensions of specimens when extended full-length with the aid of heat or 2-3% formalin. But in the case of oriental *Brugia*, the microfilariae of three species – namely, *B. tupaiæ*, *B. ceylonensis*, and *B. pahangi* – are liable to be confused with those of *B. malayi*. *B. pahangi* has been distinguished from *B. malayi* by its *innenkörper* length, acid phosphatase activity, and differences in isoenzymes.

Infected stage or *L₃* larva. The *L₃* larvae of *B. tupaiæ* are about 1100 μm in length; those of the other species are longer (1500-2000 μm). The two *Wuchereria* species are distinguished from *Brugia* by large caudal appendages. *B. ceylonensis*, like the very similar African species *B. patei*, has a characteristic caudal extremity (obtuse tip longer than the ventrolateral appendages). It is quite possible that the different morphological descriptions of *B. pahangi* infective larvae reflect differential characters of strains, but in the absence of firm information, the present conclusion is that it is not possible to differentiate reliably between the infective stages of *B. pahangi* and *B. malayi*.

*L₁* and *L₂* larva. The *L₁* larva retains the caudal morphology of the microfilaria, which is sometimes characteristic. Both the *L₁* and *L₂* stages of *B. malayi* can be distinguished from those of *B. pahangi* by the degree of protuberance of the anal plug.

Efforts to distinguish strains of *W. bancrofti* and *B. malayi* on the basis of patterns of microfilaraemia, numbers of nuclei of microfilariae, shedding of sheaths, ornamentation of the cuticle in the male, stereoscopying, and ultrastructural analysis have not yielded reliable results.
DNA probes developed in recent years (see section 4.1.2) can be used to differentiate between *B. pahangi* and *B. malayi* (microfilariae and infective stages) and therefore can be considered potential epidemiological tools. In field work, however, it must be borne in mind that the vectors may harbour a wide variety of filariae, and even other nematodes (*Mermis*, for example), and that filariae of animals may infect humans (see following section).

### 2.2.2 Zoonotic infections

In recent years it has become clear that several *Brugia* species accidentally infect humans in countries where human infections do not normally occur, particularly on the American continent. Many of the worms identified have no doubt been *Brugia* species of animal origin, identifiable to generic level on the basis of histological appearance and measurement in sections but not to specific level. Nevertheless these case reports emphasize the fact that zoonotic *Brugia* infections do occur in the Americas. The recovery of gravid females suggests that these infections may become patent in immunocompromised individuals.

Similarly, in areas in which human brugian filariasis is endemic, unrecognized zoonotic infections most probably occur, especially with *B. pahangi* and possibly with *B. tupaiæ*, in addition to the known zoonotic forms of *B. malayi* (which include subperiodic forms).

*B. pahangi* has been shown to be capable of infecting humans experimentally and even to lead to microfilaraemia. However, no proven natural human infection has yet been reported, even in Malaysia, where *B. pahangi* commonly infects cats and dogs. A report of nine natural infections of humans with *B. pahangi* in Indonesia has not been confirmed.

### 2.2.3 Cultivation of lymphatic parasites in vitro

In the fourth report of the Expert Committee (1) it was noted that *B. malayi* and *B. pahangi* L₃ larvae had been cultured to L₄ and to juvenile adults, using a system containing a rhesus-monkey kidney cell line (LLC-MK2) with RPMI-1640 medium, 10% inactivated human serum, and incubation at 37 °C in air. Since then, *W. bancrofti* has been cultured to L₄ stage and more recently sexually mature male and female *B. malayi* have been obtained from L₃ larvae after 60 days in an *in vitro* system. After 75-100 days in culture many worms produced living microfilariae (2). This work needs to be extended because of its importance for chemotherapy and immunology.

### 2.3 Suggestions for further study

1. Efforts should be made to collect more information on the distribution and prevalence of the disease and the vectors, especially from the WHO African Region.

2. Attempts should be made to identify and distinguish species and strains of *Wuchereria* and *Brugia* by morphological and biotechnological
approaches. This is particularly important to elucidate a possible geographical basis for known clinical and epidemiological differences. Apart from its obvious application for control, this would also help to recognize true zoonotic infections.

3. **Clinical aspects**

3.1 **Clinical manifestations**

Bancroftian and brugian filariasis are characterized by a wide range of clinical manifestations; the signs and symptoms often differ from one endemic area to another.

3.1.1 **Asymptomatic microfilaraemia**

In all endemic areas a proportion of the population shows no microfilaraemia or clinical manifestation of filarial infection. Some of the population has probably not been exposed sufficiently to become infected at all. Other persons may have been sufficiently exposed but do not have infection (as detectable by current diagnostic techniques); they may be immune or partially immune to infection. Still others in this group may have subclinical infections (without microfilaraemia), as indicated by the presence of filarial antigens in the blood.

3.1.2 **Asymptomatic microfilaraemia**

Certain individuals in the population of an endemic area develop microfilaraemia but with no recognizable clinical manifestation of filariasis. Some remain microfilaraemic but asymptomatic for years (sometimes even for life); others develop clinical disease either after they have spontaneously become microfilaraemic or while remaining microfilaraemic.

3.1.3 **Acute manifestations**

The acute clinical manifestations of lymphatic filariasis are characterized by episodic attacks of adenolymphangitis associated with fever and malaise. In males with bancroftian filariasis this adenolymphangitis may be localized in the genitals and present as acute epididymo-orchitis. It is not certain whether some of these are episodes of adenolymphangitis triggered or accentuated by bacterial infection.

Inflammatory nodules in the breast, scrotum or subcutaneous tissues (presumably reflecting inflammatory reactions around adult or developing adult worms) have also been reported as acute manifestations of infection.

3.1.4 **Chronic manifestations**

Hydrocele, lymphoedema, elephantiasis, and chyluria are the main clinical pathological consequences of chronic bancroftian filariasis. The incidence
and severity of these chronic clinical manifestations tend to increase with age.

**Genital manifestations**
Hydrocele is extremely common in bancroftian filariasis and manifests clinically as a swelling of the peritoneal lining that surrounds each of the testicles. Usually clear, straw-coloured hydrocele fluid accumulates in this closed sac as a result of blockage in the lymphatics draining in the retroperitoneal and subdiaphragmatic areas. Rarely, the fluid has a milky appearance caused by the presence of lymph, a condition known as a chylocele. Hydrocele is a common chronic disease manifestation of *W. bancrofti* infection but has only very rarely been recorded in *Brugia* infections.

Chronic epididymitis, funiculitis (inflammatory swelling of the spermatic cord), and lymphoedematous thickening of the scrotal skin are also genital manifestations of chronic bancroftian filariasis. In female subjects, no homologous lesions have been reported involving the ovary or fallopian tubes, although lymphoedema of the vulva may occur.

**Lymphoedema and elephantiasis of the extremities**
Recurrent episodes of limb lymphoedema, first pitting oedema and then chronic non-pitting oedema with loss of skin elasticity and fibrosis, are the result of anatomical and/or functional blockage of the lymphatics. The legs are more commonly affected than the arms.

In *W. bancrofti*-endemic areas, swelling of the leg often involves the thigh as well as the lower leg, while in *B. malayi* infection usually only the portion of the leg below the knee appears to be swollen. Secondary infections of the skin (bacterial and fungal) are common, particularly in subjects who do not use footwear.

Lymphoedema can be classified as follows:

- **Grade I lymphoedema**: mostly pitting oedema; spontaneously reversible on elevation.
- **Grade II lymphoedema**: mostly non-pitting oedema; not spontaneously reversible on elevation.
- **Grade III lymphoedema (elephantiasis)**: gross increase in volume in a grade II lymphoedema, with dermato sclerosis and papillomatous lesions.

**Chyluria**
Chyluria is defined as the excretion of chyle in the urinary tract. A minority of affected subjects may also have gross haematuria. The basic pathophysiology is related to blockage of the retroperitoneal lymph nodes below the cisterna chyli with consequent reflux and flow of the intestinal lymph directly into the renal lymphatics, which may rupture and permit flow of chyle into the urinary tract. The resultant "milky urine" contains
considerable quantities of lymph originating from the gastrointestinal tract. The condition is usually painless, but large amounts of dietary lipids, proteins, and possibly fat-soluble vitamins are excreted, leading to weight loss or even inanition. Microfilaraemia may or may not be present in these patients.

Renal disease
Scattered reports of glomerulonephritis in patients with bancroftian filariasis exist in the literature. It has recently been shown that haematuria (usually microscopic) occurs in many microfilaraemic persons.

Occult filariasis
Only a very small proportion of individuals in a community where filariasis is endemic develops occult forms of the disease, conditions in which the classical clinical manifestations are not present and where microfilariae are not found in the blood but may be found in the tissues. Tropical pulmonary eosinophilia is the classical example of occult filariasis. Males are affected about twice as often as females, and the disease is rarely seen in children. Extrapulmonary manifestations occur in about 15% of the patients, including mild to moderate splenomegaly, lymphadenopathy, and hepatomegaly. The syndrome is characterized by nocturnal paroxysmal cough, hypereosinophilia, elevated erythrocyte sedimentation rate, radiological evidence of diffuse miliary lesions or increased bronchovascular markings, extremely high titres of filarial antibody (including IgE), and a good therapeutic response to diethylcarbamazine (DEC). Low-grade fever and weight loss may be present.

In most cases lung function is impaired, with a reduction in the vital capacity, total lung capacity, and residual volume. Hypereosinophilia is the most constant feature of this syndrome. Absolute eosinophil counts generally range from 3000 to 50 000 cells per mm³ of blood, but the level of eosinophilia is not related to the severity of the symptoms. If untreated, tropical pulmonary eosinophilia progresses to a condition of chronic pulmonary fibrosis.

Other conditions possibly associated with lymphatic filariasis
A form of monoarthritis, usually involving the knee joint, is quite commonly seen in areas of endemic filariasis. The relationship between filariasis and endomyocardial fibrosis is not clear. Other conditions for which an association with lymphatic filariasis has been suggested include thrombophlebitis, tenosynovitis, nerve palsies, and dermatoses.

3.1.5 Clinical features in previously uninfected individuals entering an endemic area

Persons from non-endemic areas (e.g. expatriate visitors, immigrants, military personnel) have clinical presentations marked by prominent inflammatory reactions to the developing larvae and adult worms. These
include lymphangitis, lymphadenitis, and the clinical pictures of epididymitis or funiculitis, as well as more generalized allergy-like symptoms. These individuals rarely become microfilaraemic unless exposure is prolonged and continuous. Elephantiasis tends to develop more often and sooner in immigrants than it does among the indigenous population; lymphoedema may develop within 6 months and elephantiasis 1-2 years after arrival.

3.2 Problems in differential diagnosis

Differences in the anatomical distribution of the clinical manifestations of brugian and bancroftian filariasis may be due in part to different tropisms of the parasites for particular anatomical locations, which might govern the location of the adult worms in the human lymphatics. However, at present there is insufficient pathological evidence to support such a hypothesis.

3.2.1 Adenolymphangitis

Although fever sometimes precedes adenolymphangitis, fever alone, in the absence of this condition, should not be ascribed to filariasis, even when microfilaraemia is present.

A characteristic feature of filarial adenolymphangitis is the retrograde extension of the lymphangitis from the affected node; this pattern is distinct from that usually found when bacterial infections cause adenolymphangitis.

3.2.2 Lymphoedema and elephantiasis

Persistent lymphoedema and elephantiasis are often difficult to distinguish clinically. 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 following acute or chronic infections, tumours, surgery, or irradiation, obstructive lesions involving a major lymphatic vessel may cause lymphostasis and subsequent elephantiasis.

Another locally important form of elephantiasis in the tropics can be endemic non-filarial elephantiasis, a condition that is particularly common in highland areas in Africa, where alkaline red clay soils of volcanic origin are present and where people go barefoot. This condition is believed to be caused by the irritant effect of mineral particles (aluminium silicates and ferromagnesium compounds) from the volcanic clay that penetrate the skin and damage the vascular endothelium of the lymph nodes draining the lower limbs. The disease progresses slowly and centripetally but may be associated with episodes of acute local inflammation. Elephantiasis supervenes when there are persistent fibrotic changes in the skin and subcutaneous tissue.
3.2.3 Tropical pulmonary eosinophilia

In areas of endemic filariasis other helminthic infections, especially ascariasis and strongyloidiasis, may induce pulmonary syndromes with eosinophilia that must be differentiated from tropical pulmonary eosinophilia of filarial origin. Serological tests and clinical responsiveness to treatment help to distinguish these clinically similar syndromes.

3.3 Natural history of lymphatic filarial disease

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 in human lymphatic filariasis is minimal, 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*, 3.5 months; and with *B. timori*, 3 months. However, as congenital transmission of microfilariae of *W. bancrofti* from mother to child has been reported, these data are difficult to interpret. Studies of primates infected with these parasites have shown prepatent periods 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. These estimates are based on studies of expatriates, and the incubation period may be longer in indigenous inhabitants of endemic areas.

In endemic areas the progression of infection and disease has not been well defined. While microfilaraemia persists in a proportion of patients who remain asymptomatic for long periods, recent studies using lymphoscintigraphy have shown clearly that even in their asymptomatic state these individuals have dilated lymphatics and compromised lymphatic function. This finding represents a major conceptual advance in our understanding of the development of lymphatic pathology and probably reflects the parasite's direct effect on lymphatics (dilatation and proliferation) occurring in the presence of diminished immune responsiveness to the parasite in such individuals (see section 5).

The chronic stage of filariasis usually develops after a variable period of time. Most studies show that patients with hydrocele or elephantiasis are usually microfilaraemic but it is not clear whether microfilaraemia existed in these cases prior to the development of the chronic stage. In some parts of the world (e.g. the island of New Guinea and the United Republic of Tanzania), moreover, microfilaraemia has been reported to coexist with elephantiasis or hydrocele in a high proportion of persons with these manifestations of chronic filariasis. Most often, repeated attacks of adenolymphangitis precede the development of the chronic lymphatic pathology of filariasis and these often continue for many years. In some
individuals, however, the chronic obstructive abnormalities develop without being preceded by recognizable episodes of adenolymphangitis. Treatment of affected patients with DEC has been seen to be effective both in decreasing the frequency of adenolymphangitis attacks and in halting the progression of the lymphatic disease.

The clinical manifestations of tropical pulmonary eosinophilia (both systemic and pulmonary) persist and intensify in the absence of treatment, though their intensity may wax and wane. Restrictive pulmonary functional abnormalities worsen as the lung interstitium thickens in response to continued microfilaria-induced inflammation, and this progression leads to the clinical and pathological picture of chronic interstitial fibrosis with respiratory failure.

Fortunately, treatment can halt or at least dramatically slow the progression of the usual cause of untreated tropical pulmonary eosinophilia. DEC (6 mg/kg of body weight daily) causes dramatic clinical improvement within days of beginning treatment and a sharp fall in the peripheral blood eosinophil count within 1-2 weeks. Earlier studies showed that despite 1-3 weeks of DEC treatment a “relapse” rate (not always distinguishable from “reinfection”) of at least 20% was common. Recent bronchoalveolar lavage studies performed serially in patients with tropical pulmonary eosinophilia have indicated that, although the clinical response is rapid, as many as 50% of patients treated with 3 weeks of DEC maintain a persistent, low-grade eosinophilic alveolitis even 6-12 months after therapy. It is likely that the patients who progress to interstitial fibrosis in spite of receiving DEC therapy come from this subset of patients with incomplete resolution of their tropical pulmonary eosinophilia.

3.4 Suggestions for further study

1. Longitudinal observations should be carried out to yield further insight into the natural history of filarial infection and disease and how it may be altered by treatment.

2. The usefulness should be assessed of noninvasive lymphatic imaging techniques in early diagnosis of cases at risk of developing lymphoedema, in establishing the natural course of lymphatic pathology, including the relationship between acute and chronic filarial disease, and in monitoring the effect of drugs, as an end-point marker of successful treatment.

4. Diagnosis

4.1 Parasitological diagnosis

4.1.1 Detection of parasites

The parasitological methods available for detection of microfilariae, such as the use of the thick blood film, counting chamber, Knott's concentration
technique, membrane filtration techniques and the DEC provocative test are described in detail in the WHO manual *Control of lymphatic filariasis* (3) and in the fourth report of the WHO Expert Committee on Filariasis (7). In addition, a test for detection of microfilariae in preserved blood using membrane filters has recently been developed (4); the preservation of blood samples in a mixture of formalin and anionic detergent makes it possible to utilize the convenience and sensitivity of membrane filtration while eliminating the need to perform tests immediately after blood is collected.

4.1.2 Differentiation of filarial species and stages (5, 6, 7)

New methods have been developed using DNA probes and monoclonal antibodies to identify filarial larvae in body fluids (6) and in mosquito vectors (7), and these can be used to differentiate between larvae of filarial species that infect humans and those that parasitize animals (e.g. between *B. malayi* and *B. pahangi*).

Virtually all species-specific DNA probes developed so far detect DNA sequences that are highly repeated in the filarial genome, and they are theoretically sensitive enough to detect DNA from a single filarial larva. However, the release of sufficient DNA from the larvae and its detection within extracted or crushed mosquitoes have proved difficult, so that an intermediary step to amplify parasite DNA by the polymerase chain reaction (PCR) technique is now being investigated. In the case of *B. malayi, B. pahangi* and *W. bancrofti*, the sensitivity of the species-specific DNA probes compares favourably with microscopic techniques to identify infected mosquitoes. However, the usefulness of DNA probes to monitor infectivity rates in natural vectors remains to be determined, and probes useful for reliable detection of filarial species variants (if these exist) have yet to be developed.

One shortcoming of current DNA probes is that, because they react with all developmental stages of a given filarial species, they cannot discriminate between infected and infective mosquitoes.

A monoclonal antibody that specifically reacts with *B. malayi* L₃ larvae and distinguishes them from other stages and species of filarial larvae in mosquitoes has been developed and successfully field-tested (7). No equivalent stage-specific monoclonal antibody for the identification of *W. bancrofti* L₃ in mosquitoes is available yet.

4.2 Lymphatic imaging

Contrast lymphangiography, while widely used to visualize the morphology of the lymphatic vessels, carries the potential risk of lymphatic damage. The unpredictable consequences of such studies have hampered the early evaluation of the lymphatics of asymptomatic individuals. To overcome these difficulties lymphoscintigraphy using
radiolabelled albumin or dextran has been developed. This technique can be performed and repeated safely so that serial studies of individuals are possible. Preliminary studies with this technique have demonstrated the presence of lymphatic abnormalities in asymptomatic microfilaraemias with no evidence of oedema. With lymphoscintigraphy it should now become possible to make a clear and precise analysis of the lymphatic system function in patients at risk. This technique could be used for the examination of infected but asymptomatic individuals to determine whether they have morphological or functional lymphatic abnormalities and how these alterations could be changed, especially by chemotherapy. It could also provide a new epidemiological tool for detailed studies of morbidity due to endemic filariosis.

4.3 Immunodiagnosis

Expectations that the availability of monoclonal antibodies selected for stage- and species-specificity and molecularly defined filarial antigens would permit the rapid development of new serodiagnostic assays for lymphatic filariasis have proved too optimistic. A number of these reagents have already shown considerable value in studies on the basic biology of filarial worms and the infections they cause, but their full diagnostic potential remains to be realized.

Some of the factors that have hampered the development of new serodiagnostic tests for lymphatic filariasis have now been partially overcome. The scarcity of parasite materials from species that infect humans has been alleviated somewhat by the ability to maintain complete life cycles of several Brugia species in small rodents and, more recently, by the development of genomic and cDNA libraries from different stages of several filarial species that parasitize humans. In consequence, a number of recombinant filarial antigens have now become available for testing.

The specificity of newer serodiagnostic tests for lymphatic filariasis has been substantially improved, either through the use of excretory-secretory (ES) antigens (which appear to be subsets of whole-worm somatic extracts) or through the use of specific reagents to detect antibody isotypes or subclasses. For example, tests measuring antifilarial IgE or IgG4 antibodies appear to be much more specific than those measuring total antibody responses. Perhaps the most important conceptual advance stems from the realization that much of the cross-reactivity among nematodes is related to the immunodominance of antigenic determinants containing phosphorylcholine (PC), which apparently do not stimulate production of IgG4 antibodies. Thus, assessment of antibody responses to non-PC determinants greatly improves the specificity of serodiagnostic tests for lymphatic filariasis.

Other problems still exist that impede the rational development of serodiagnostic tests for lymphatic filariasis. Foremost is the lack of clear-cut criteria that can be used to define the appropriate “negative”
controls within endemic populations and the significance of a positive test result in an microfilaraemic, asymptomatic resident of an endemic filariasis area. Some of these issues may be resolvable by studies in experimental animal models.

A second problem is the minimal amount of information available on the kinetics of antibody responses to defined filarial antigens during the natural course of infection and on the effect of treatment or other control measures on the rate of acquisition and loss of different types of antibodies to such antigens. This information is essential for the rational development of serodiagnostic tests to confirm, for example, the filarial nature of acute adenolymphangitis. Our ignorance of the relationship between antigen recognition patterns and clinical outcomes of infection is an additional obstacle to the development of diagnostic tests with predictive or prognostic value.

The notion that a single “universal” diagnostic test could provide the factual information needed for the management of individual cases and for population-based control programmes is probably unrealistic and should be abandoned. However, it appears possible to develop a relatively small number of “targeted” serodiagnostic tests that have performance characteristics tailored to provide correct answers to specific clinical and epidemiological questions. Some such tests are available; others are being developed.

Two conceptually different techniques for the diagnosis of lymphatic filariasis have been, and are still being, developed: antigen-detection assays and antibody-detection assays.

4.3.1 **Antigen-detection assays**

Several laboratories have developed monoclonal antibody-based assays to detect and quantify filarial antigens in sera, urine and other body fluids of persons with lymphatic filariasis. While the sensitivity and specificity (for bancroftian or brugian filariasis) of individual tests differ, these tests are generally capable of detecting filarial antigens in the majority of persons with microfilaraemic bancroftian or brugian infections. With some tests, filarial antigens are also detected in variable proportions of sera from microfilaraemic individuals with or without clinical manifestations of infection (8). As seropositivity in these assays presumably reflects the presence of filarial worms, antigen-detection assays should be useful for detecting all persons with “active” infections in an endemic population. Studies in animal models support this concept. It appears that some microfilaraemic and asymptomatic individuals (called “endemic normals” in some reports) are, in fact, not normal but carry subclinical infections that are not detectable by traditional diagnostic techniques.

Though studies in animal models suggest that filarial antigen levels in sera correlate with worm burdens (either adult worms or microfilariae,
depending on the specificity of the monoclonal antibody used to detect the antigen), the assays are not yet precise enough to permit accurate quantification of the worms present in individual animals. Both in animal models and in humans, antigen levels decline after treatment, but antigen clearance appears to be slow. Such antigen assays should be useful to monitor the effect of chemotherapy on filarial worm burdens, but the validity of this concept remains to be confirmed by additional studies in animals and humans.

4.3.2 Antibody-detection assays

Even though suppression of filaria-specific immune responses is a common feature of patent lymphatic filariasis, virtually all adult residents of endemic areas who have been exposed to filarial parasites develop detectable levels of IgG antibodies to crude worm extracts. Seropositivity in this type of assay merely indicates that the individual has been sensitized to parasite antigens and should not be interpreted as evidence of current infection. Such diagnostic tests are of little practical value in endemic areas except for the diagnosis of tropical pulmonary eosinophilia, but they may be useful in expatriates or temporary visitors in endemic areas in whom a positive test result suggests possible filarial infection.

It has been proposed that an IgG4 response to somatic extracts of filarial worms is indicative of active, chronic filarial infection, even in the absence of other clinical or parasitological evidence, and that specific IgG3 responses correlate with the presence of chronic lymphatic pathology (see also section 5.1.3). Both these suggestions need to be confirmed by additional studies.

4.3.3 Role of immunodiagnostic tests in the control of lymphatic filariasis

Most residents of endemic areas give a positive reaction in many serodiagnostic assays that utilize complex mixtures of filarial antigens, such as whole-worm homogenates or crude ES products. These diagnostic tests therefore cannot be used to confirm the filarial origin of clinical conditions that have been associated with but not causally linked to lymphatic filariasis (e.g. acute arthritis). Hence, in the absence of other indications, seropositivity alone is not a sufficient reason to institute antifilarial therapy in residents of endemic areas. Pilot studies suggest that newer diagnostic tests may be useful for diagnosing acute filarial disease, but these are not yet widely available.

Serological tests that would permit the identification of microfilaraemic individuals within populations in endemic areas without the need for night-blood collection, tests that would detect all individuals with current active infections, or tests that could be used to quantify adult worm burdens following chemotherapy would greatly facilitate filariasis surveys and constitute invaluable tools to monitor the impact of control programmes. Such tests are currently being evaluated in multicentre trials.
supported by the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases and may become available in the near future.

4.4 Suggestions for further study

1. Diagnostic assays need to be developed and validated that will:
   (a) detect active infection (both cryptic and microfilaraemic);
   (b) replace night-blood examination for detection of microfilaraemia in areas where nocturnally periodic filariasis exists;
   (c) distinguish filarial from non-filarial adenolymphangitis;
   (d) identify to species (and, where appropriate, to subspecies) parasites in the mosquito vectors; and
   (e) quantify worm burdens in infected persons.
   Such assays will be important for improving the management of individual patients, for providing tools that can be used for epidemiological research, and for monitoring filariasis control programmes.

2. Age-related changes in immunological parameters of the host response to filarial parasites should be determined in areas of different endemicity, as should the effect of treatment on the immune response. This is necessary for the development of diagnostic assays to monitor filariasis control programmes.

5. Pathogenesis, immunopathology, and protective immunity

5.1 Lymphatic pathology

During the past decade several important conceptual advances have been made relating to the pathogenesis of lymphatic lesions in bancroftian and brugian filariasis. These concepts are based primarily on observations in experimental animal models that mimic aspects of filarial disease in human beings (such as *Brugia* infections in ferrets, dogs, cats, and immunodeficient mice) and on the results of studies attempting to correlate antiparasite immune responses in humans with various clinical outcomes of infection.

5.1.1 Distinction between parasite-induced and immune-system-induced pathology

Experimental model systems have provided clear evidence that while much of the pathology resulting from infection with brugian parasites results from the host's immune response to these parasites, a portion is also derived from the direct action on the lymphatic tissue of the parasites themselves or the molecules they release. The most convincing demonstration of this is the finding that immunodeficient mice infected
with brugian parasites develop marked endothelial cell proliferation and lymphatic dilatation, with resultant lymphoedema and elephantiasis, *in the absence* of any appreciable immune response to the parasite. Reconstitution of these immunodeficient mice by immunocompetent cells from filaria-sensitized normal mice results in inflammatory reactions around the parasites, with local granuloma formation and obstruction of the lymphatics, that again leads to lymphoedema and elephantiasis. Thus, there appear to be two distinct forces acting to damage the lymphatic function of such infected animals, one involving the immune system and the other independent of it.

The findings in these animal models parallel those described previously in affected humans (i.e. lymphatic proliferation, dilatation, and oedema formation in the presence of living worms, but obstructive, obliterative reactions in the lymphatics around dead parasites). Furthermore, they are consistent with previous observations that microfilaraemic persons, who appear “hyporesponsive” to parasite antigens (see section 5.4), are often asymptomatic, whereas those with past or amicrofilaraemic infections are the ones with heightened immunological responsiveness and the ones who often have obstructive lymphatic pathology.

### 5.1.2 Lymphatic histopathology reflecting the immune responsiveness of the host

Many of the generalizations about the lymphatic histopathology of bancroftian filariasis have been inferred from tissues removed from soldiers who acquired filariasis after serving in endemic regions of the Pacific during the Second World War. The pathological reactions described were, for the most part, inflammatory, with an abundance of eosinophils and mononuclear cells infiltrating the lymphatic and perilymphatic spaces. It is now recognized, however, that the clinical and pathological responses of such expatriates entering endemic regions and acquiring infection are very different from those of individuals living their whole lives in endemic regions.

A recent study of lymphatic pathology in patients from a region where bancroftian filariasis is endemic (Recife, Brazil) clearly showed, rather than the exuberant inflammatory reactions seen in the expatriate cases, a generally much more subdued condition, with little or no inflammatory activity around adult worms and microfilariae, in asymptomatic patients whose tissue specimens were obtained for reasons other than the suspicion of filariasis (i.e. were not taken because of an acute inflammatory syndrome similar to that described in the infected soldiers) (9). These findings indicate that the immunological “hyporesponsiveness” identified from studies of peripheral blood lymphocytes in such patients is an accurate reflection of the local lymph-node immunopathology (or lack thereof) observed in the majority of infected patients who remain asymptomatic.
5.1.3 **Factors predisposing to the development of lymphatic lesions**

A recent review of the literature indicates that both the prevalence of lymphatic filariasis and the degree of microfilaraemia are lower in women than in men (10). Clinical disease is also less common in women, and pathology has a later age of onset and rise to peak prevalence than in males.

The notion that prenatal conditioning could influence subsequent immunological (and thus, pathogenic) responses to filarial infection has received confirmation from recent studies in Haiti that have shown that maternal microfilaraemia predisposes to microfilaraemia in the offspring, an observation consistent with those made previously in jirds and dogs. This may be very important in explaining the differences in the clinical manifestations of lymphatic filariasis both among residents in endemic areas and between these persons and those who migrate to such endemic areas.

The manner in which an infected individual reacts to (i.e. immunologically “processes”) filarial antigens may determine whether or not lymphatic pathology will develop. Data from humans showing that IgG3 antibody responses to filarial antigens are made almost exclusively by patients who develop lymphatic pathology whereas production of IgG4 antibodies predominates in those who remain asymptomatic but microfilaraemic are compatible with such a hypothesis, though they do not prove it. If the hypothesis is correct, however, it will have profound implications for the development of antifilarial vaccines, as the “right” type of immune response might be protective, whereas the “wrong” type of immune response to the same vaccine might lead to filarial disease. (A different working hypothesis – namely, that resistance and pathology are caused by immune reactions to different antigens – is discussed in section 5.5.)

Though studies in animal models indicate that bacterial infections can aggravate lymphatic pathology caused by filarial worms, and though antibiotics are routinely used in addition to specific antifilarial chemotherapy in many endemic areas, whether or not bacterial (or fungal) infections contribute to the pathogenesis of acute or chronic filarial disease in humans remains a matter of speculation because of insufficient information.

5.2 **Pathogenesis of tropical pulmonary eosinophilia**

The immunological hyperresponsiveness of patients with tropical pulmonary eosinophilia has been well defined previously through studies of eosinophils and filaria-specific antibodies in the blood. Recent investigations employing bronchoalveolar lavage have increased our understanding of the pathogenesis of this syndrome by showing that patients with acute tropical pulmonary eosinophilia have markedly increased numbers of inflammatory cells infiltrating their lungs, the majority of these (60–80%) being eosinophils with the characteristic morphology of activated cells. Also, direct assessments have identified a
preferential accumulation ("compartmentalization") of eosinophils in the lung compared to the blood and similar compartmentalization of filaria-specific IgG, IgM, IgA, and IgE antibodies in the lung. Functionally, the extent of this lung eosinophilia has been recently shown to correlate with the degree of compromise in the lung's ability to oxygenate the blood.

5.3 Pathogenesis of renal lesions

Though the pathogenesis of the recently described renal abnormalities in microfilaraemic individuals with bancroftian filariasis has not yet been investigated, it is probably a form of nephritis related to parasite-antigen-specific immune complexes and their deposition beneath the basement membrane of the renal glomeruli.

5.4 Immunoregulation

5.4.1 Correlation with pathology

It has been recognized for years that, except for individuals with tropical pulmonary eosinophilia, patients with lymphatic filariasis (especially those with microfilaraemia) appear to respond poorly to filarial antigens. This "hyporesponsiveness" is not to be confused with broad-spectrum immunodeficiency but, rather, appears limited almost exclusively to the response to parasite antigens. Recent studies in animal models present direct evidence that the "parasite-specific immunosuppression" induced by filarial infection leads both to decreased pathology in the host and to decreased local immunological responses to filarial antigens. These experimental observations support the correlation madrepeatedly between the finding of little or no pathological response to the parasite and a "diminished" immunological responsiveness to parasite antigen in microfilaraemic patients.

5.4.2 Mechanisms underlying the antigen-specific immunosuppression (11)

It has previously been hypothesized that a variety of suppressive elements (cells and humoral factors) are responsible for the parasite-specific "hyporesponsiveness" identified in infected patients. A major recent advance has been the precise definition of some of the specific molecules involved.

One of these "down-regulating" molecules actually appears to be specific antibody of the IgG4 subclass, which is made in relatively large amounts by microfilaraemic patients (generally considered as the most hypo-responsive of the filariasis patients) and which has been implicated as the "blocking antibody" responsible for controlling IgE-mediated allergic responsiveness to the parasite. Thus, microfilaraemic individuals who have appeared for years to be the least responsive to parasite antigens in conventional assays are now recognized to be, in fact, vigorous responders to such antigens, but their responses involve the production of inhibitory, not stimulatory, molecules (both antibodies and cytokines).
In addition to such host-produced products, molecules derived directly from the parasites themselves have recently been shown to inhibit human lymphocyte function in vitro and, by inference, might play a similar modulating role in vivo, since some of these same molecules have also been found circulating in the blood during active infection.

5.5 Protective immunity (11)

It is generally hypothesized that in an area of endemic filariasis the "endemic normals" (or asymptomatic microfilaraemics; see section 3.1) will include not only a proportion of individuals harbouring subclinical infections (below the threshold of detection) but also individuals with true protective immunity. It is perhaps less widely appreciated that it is possible that those with high microfilaria loads may also possess an effective immune response that protects them from superinfection in the face of continuing transmission of infective larvae. Recent analyses of age-stratified populations in Papua New Guinea and India give support to this proposition. In Papua New Guinea, worm burdens were quantified by a circulating antigen assay performed at 1-year intervals. Parasite loads were seen to increase in children and adolescents, while those in adults (>20 years) remained stable. A similar conclusion was drawn from a large-scale study of infection dynamics in Pondicherry, India, in which the rate of gain of infection, measured by microfilaraemia, levelled off after adulthood was reached.

In the Papua New Guinea study, a further important finding was that the "immune" adults all possessed antibody to the surface of third-stage larvae (L₃), while the "non-immune" children mostly did not. These findings considered together have the following important implications: first, L₃ stage-specific antigens may act as effective targets for a protective immune response in both infected and uninfected individuals; secondly, protective immunity takes many years to develop, a finding in conformity with known epidemiological characteristics; and thirdly, protective immunity may be induced to antigens (on the infective larval stages) that are not involved in the development of immunopathology, thus making the development of safe (i.e. non-pathogenic) vaccines a more feasible prospect. Whether such "natural" immunity can be artificially induced by vaccination strategies remains to be determined. The hypothesis of concomitant immunity, which implies that protective and pathogenic immune responses are directed against distinct life-cycle stages of filarial worms, can be used to guide selection of candidate antigens for potential future vaccines. By analysing differences in antigen recognition patterns between "immune" and non-immune populations, several filarial antigens that might be involved in protective immunity have been identified. Attempts to confirm the protective potential of these antigens in animal models are only just beginning. Thus, it is not likely that a vaccine to prevent lymphatic filariasis in humans will become available in the near future.
5.6 **Suggestions for further study**

1. Studies are needed to define the prenatal and perinatal influences of maternal filarial infection on subsequent outcomes (clinical, parasitological, and immunological) of exposure to filarial infections.

2. The role of bacterial, viral and fungal infections in the pathogenesis of the lymphatic lesions in patients with filariasis should be determined.

3. Research is required to identify differences in immune responses between individuals and populations with distinct clinical manifestations of lymphatic filariasis in order to develop predictive markers of disease development and to define the mechanisms and dynamics of the disease process. Such information could be used to develop rational strategies for disease control and prevention by immunological interventions.

4. Methods are required by which to generate large numbers of infective larvae of *W. bancrofti* and *B. malayi* for use as an antigen source in differential screening studies to define potential protective immunogens and as source material for making cDNA libraries expressing genes that encode potentially protective protein immunogens and drug targets.

6. **Vector aspects**

6.1 **Entomological techniques**

Techniques such as determination of (a) relative biting densities of vector populations, (b) survival of vector populations, (c) natural infection and infectivity rates, (d) annual infective biting rate (AIBR), and (e) annual transmission potential (ATP) are described in the fourth report of the Expert Committee (1). Other techniques are well documented, such as measurement of mosquito larval populations, which may help in the evaluation of antivector measures, and mosquito blood-meal identification, particularly in areas where zoonotic filarial infections are likely to occur (1, 3).¹

6.2 **Update on distribution and bionomics of vectors**

6.2.1 **Culex vectors**

The *Culex pipiens* complex includes *C. pipiens*, *C. quinquefasciatus*, *C. molestus*, *C. pallens*, *C. australiens* and *C. globocoxitus*. Since many of these coexist and interbreed and entomological surveys often do not pay adequate attention to the complex as a whole, there is a possibility of

overestimating or underestimating the range of distribution of the very widespread *C. quinquefasciatus*.

*C. pipiens* has an extensive distribution in temperate latitudes and is found throughout the Holarctic region and at high altitudes in East and West Africa and lower altitudes in South Africa, North America, northern Europe and Argentina. The distribution of *C. pipiens* is increasing with urbanization, and construction activities have created many new artificial water sources which serve as focal points for the breeding of this opportunistic mosquito. On the other hand, *C. quinquefasciatus* has colonized tropical and subtropical latitudes. In studies of the vertical distribution of mosquito species in four altitudinal zones in India, *C. quinquefasciatus* was recorded only up to 1800 m, its absence above this altitude being due to climatic conditions and the absence of breeding sites and preferred hosts. The distribution of *C. quinquefasciatus* is also increasing with urbanization and human activity, and many rural pockets that were comparatively free from this mosquito are becoming colonized. *C. pallens* occurs widely in China, Japan, and the United States of America. *C. molestus* is mostly distributed in temperate latitudes.

The partly overlapping distribution of species of this complex occurs chiefly in relation to the north and south temperature gradient, as has been confirmed by several observations in the United States of America, where temperature inversions are accompanied by similar inversions in distribution. Since environmental change due to human activities is occurring at such a high speed, it would be difficult to prepare a distribution map of this complex, especially as the taxonomic criteria used by different investigators vary widely.

Studies relating seasonal variation in biting frequency with the transmission pattern of filariasis have shown that in some instances, even in tropical climates, transmission is not perennial and therefore a year-round control strategy may not be necessary. However, a longitudinal study on the population dynamics of *C. quinquefasciatus* in South India showed that, despite the best control efforts, the mosquito population could not be completely eliminated, so that a slight slackness in the control programme resulted in resurgence of the vector population. Studies on the bionomics of this species, in California, USA, showed that it remained gonotrophically active throughout the winter and did not appear to undergo diapause. Dairy cows diverted the normally ornithophagic *C. tarsalis* and *C. quinquefasciatus* females from avian hosts in dairy sheds but not in residential abodes, indicating that, if the human host is available, the presence of cattle does not provide any zooprophylaxis.

*C. quinquefasciatus* breeds in a wide variety of stagnant water habitats. Recently a method of calculating "productivity indices" for different types of *Culex* breeding habitat has been devised (12) that provides an effective method to set control priorities by identifying the most significant breeding sites, which are not necessarily the intuitively most probable ones.
Even though environmental factors are known to regulate the population dynamics of this species, only one study (in Pondicherry, India) has quantitatively examined the effect of environmental variables such as climate in an operational source-reduction programme; the model developed for this study should permit one to make predictions on the effect of future control programmes (13). However, the impact of environmental improvement has yet to be quantified.

6.2.2 *Aedes* vectors

During the past decade, studies on *Aedes* species have been made mainly in Samoa and French Polynesia on *A. polynesiensis* and *A. samoanus* and in the Philippines on *A. poecilius*. The major breeding habitats for *A. polynesiensis* were tree-holes, crab holes, water-storage drums, discarded automobile tyres, cans, bottles, and coconut shells. Tree-holes were the preferred habitat, with year-round breeding. This species was found to have a flight range of 400 m in coconut plantations and coastal villages. *A. samoanus*, on the other hand, breeds in leaf axils; this species is a vector in Samoa and in some other Polynesian islands. *A. poecilius* prefers to breed in axils of banana trees in the Philippines. It is a nocturnally biting mosquito, inactive during the first 3 hours of the night, and its biting activity ceases at early dawn.

6.2.3 *Mansonion* vectors

The genus *Mansonion* is divided into two subgenera: *Mansonion* and *Mansoniotoides*; it is the subgenus *Mansoniotoides* that includes the important vectors of lymphatic filariasis caused by *B. malayi* in southern and south-eastern Asia. Six species of this subgenus occur in the Oriental region and they are vectors of the two types of brugian filariasis, periodic and subperiodic. All six species (*M. bonneae*, *M. dives*, *M. uniformis*, *M. annulifera*, *M. annulata*, and *M. indiana*) are involved in transmission. In the past decade studies on *Mansonion* vectors have been mainly from India, Indonesia, Malaysia, and Thailand.

A large number of aquatic plants in different breeding habitats are associated with *Mansonion*, the larvae of which puncture the submerged parts of the plants to obtain oxygen. Recently several new species of host plants have been found to harbour *Mansonion* larvae. Three species of the family Araceae — *Homalomena cordata*, *H. rostrata*, and *Hydrostemma motleyi* — were reported positive for *M. bonneae* or *M. dives* in Sarawak. In a larval survey in Malaysia, *Setaria geniculata*, a tall grassy plant resembling lalang, was positive for *M. dives*, *M. bonneae*, and *M. uniformis*; and *Hanguana malayanum*, a tall, fleshy plant, was positive for *M. uniformis* and *M. indiana*.

Studies in Sarawak have shown *Mansonion* mosquitos there to be less exophagic than those in Peninsular Malaysia, Sabah, and southern Thailand; this may be related to the construction methods used for
Sarawak's longhouses, whose bamboo flooring has gaps through which mosquitoes can gain access into the houses. The characteristic biting cycle of *Mansoninae* is not related to the age composition of the biting population. The duration of the gonotrophic cycle of *M. uniformis* in the field, as determined by the mark-release-recapture technique, was found to be 3-4 days. A cycle of 4 days was also estimated for *M. bonneae*, *M. dives*, and *M. uniformis*.

6.2.4 *Anopheles* vectors

The genus *Anopheles* is important in the transmission of periodic *W. bancrofti* in Africa, southern Asia and the island of New Guinea. It is also a significant vector of periodic *B. malayi* in southern Asia. New transmission and distribution records include *A. gambiae* from the island of Grande Comore, and *A. flavirostris* from Sabah. No mosquito other than *A. barbirostris* has been identified as a vector of *B. timori*.

6.3 Control of vectors

For filariasis control, several means are now available to reduce vector density and/or human-vector contact, including chemical or biological control, environmental management, individual protection, or combinations of two or more of these methods. Despite insecticide resistance, the present status of chemical insecticides against lymphatic filariasis is such that they continue to play an important role in vector control, especially for *Anopheles* and *Culex* species. New pyrethroid and carbamate compounds as well as new groups such as insect-growth regulators are now in operational use but the number of new active molecules synthesized by the pesticide industry is decreasing, and alternative or complementary means of control have to be improved or perfected.

6.3.1 Chemical control and impregnated materials

In most parts of the world, the use of chemical insecticides becomes more and more problematic, in view of such factors as physiological resistance, negative impact on environment, resting and feeding behaviour of vectors, and replacement of endophilic species with exophilic ones. However, the dependence on chemical compounds remains great since the operational uses of alternatives such as biological and mechanical control methods are still limited.

*Anopheles* vectors

*Anopheles* vectors are generally endophilic mosquitoes and methods for their control are predominantly aimed at the adult stage, through application of residual insecticides inside houses. When filariasis and malaria transmission depend upon the same *Anopheles* species, malaria control operations often result in a satisfactory level of filariasis control, even if malaria transmission continues to be a problem. No large-scale control programme directed specifically against lymphatic filariasis
transmitted by *Anopheles* has been carried out since the malaria eradication era. However, in localized areas where malaria control operations continue, i.e. in epidemic situations, urbanized areas or insular places, lymphatic filariasis transmission has been reduced by house-spraying with insecticides that are still effective, such as malathion in Burundi or fenitrothion in the island of Mayotte. Carbamates and synthetic pyrethroids are effective in total indoor house-spraying, but the cost of these compounds and the occurrence of detoxifying esterases in anophelines may limit their operational application unless they are also used to impregnate mosquito nets (see below).

In some epidemiological situations, it may be appropriate to attack *Anopheles* by larviciding — when they breed, for example, in rice-fields adjoining villages. Organophosphates are widely used and recently new juvenile hormone analogues and chitin-inhibitors, belonging to the insect-growth-regulators group, have given promising results for such control.

**Culex vectors**

Regarding *Culex* species, only recent advances concerning *C. quinquefasciatus* will be reviewed because of its major role in the transmission of bancroftian filariasis. The preimaginal stages develop in tropical urban areas, mainly in habitats containing highly polluted water, and the most appropriate and classical means of control are larviciding and/or environmental management. Like *Anopheles* species, the great majority of female *C. quinquefasciatus* are endophilic and feed at night, thus explaining why *Culex* control benefits from antimalaria campaigns during which house-spraying operations or impregnated nets are applied in urban areas. Filariasis control may, of course, also benefit from antilarval or adulticidal measures directed specifically against *C. quinquefasciatus*.

Since *C. quinquefasciatus* adults are widely resistant to most of the organochlorine compounds, organophosphate larvicides have become the preferred means of control. However, larval resistance to organophosphates has been reported during the past decade, particularly in urban areas where this mosquito is a major filariasis vector. *C. quinquefasciatus* is also becoming locally resistant to other chemical groups such as carbamates or pyrethroids, leading scientists to assess new insecticides and new control methods (for example, expanded polystyrene beads; see section 6.3.2).

**Aedes vectors**

*Aedes* is one of the vector genera of *W. bancrofti* in southern Asia and the exclusive vector genus in Polynesia. The insecticidal control of most adult *Aedes* is very difficult owing to their general exophily and diurnal feeding behaviour. Furthermore, the larvae are not easily amenable to larvicidal control because of the many scattered and inaccessible breeding-sites,
although biological control has given promising results against *A. polynesiensis* in French Polynesia. Consequently, the control of *Aedes* species as vectors of bancroftian filariasis remains problematic, and chemotherapy seems the most appropriate way to reduce transmission. However, in the case of *A. samoanus* application of 5% temephos (emulsion concentrate) sprayed on *Pandanus* (screwpine) plants has provided control for a period of 6 weeks.

In particular situations that render insecticidal control operations feasible, classical insecticides such as organophosphates, carbamates or pyrethroids can be used. However, since resistance is increasing in all parts of the world, new chemical compounds have been tested under laboratory and field conditions; insect-growth regulators have given promising results, but the toxin of *Bacillus thuringiensis* H-14 shows great variability in efficacy according to the formulation used.

*Mansonella* vectors

*Mansonella* mosquitoes are difficult to control with adulticides because of their variability in feeding and resting behaviour. For species that are exophagous and found to bite predominantly at dusk, aerial application can be conducted with chlorinated or organophosphate insecticides. For endophagous species that bite throughout the night, indoor house-spraying and/or prevention of human-vector contacts through the use of residual formulations, household insecticides, repellents or impregnated mosquito nets can be applied with success, particularly as advantage can be taken of the compounds and application methods used for malaria vector control.

The breeding of *Mansonella* vectors is closely associated with aquatic weeds and its control is mainly possible through environmental management, i.e. de-weeding or fish culture. Many compounds are highly toxic to larval *Mansonella* under laboratory conditions but their application in the field is very difficult; the long immature stage and the periodic detachment of larvae from weeds may have serious implications for the use of larvicides. However, good control was obtained in one study in southern Thailand by larviciding with temephos in floating bags containing 24 g of 1% temephos, yielding concentrations of 0.6 mg/l in 10 cm water depth and 0.06 mg/l in 1 m water depth, against a largely isolated population of *M. annulata*, *M. annulifera*, *M. indiana* and *M. uniformis* in a pool with a surface area of 1.2 ha (14).

Anklets and headbands impregnated with deet (*N,N*-diethyl-3-methylbenzamide) as a repellent and a soap-bar impregnated with deet and permethrin have been shown to give good protection against the bites of *Mansonella* species in the field.

Insecticide-impregnated materials

It is now well documented that pyrethroid-impregnated screening devices such as bednets and other materials can significantly reduce morbidity due
to malaria in children (15). One might reasonably expect that these measures could reduce transmission of lymphatic filariasis by vectors that bite indoors and at night (such as *Culex* and some *Anopheles* species), but their value for this purpose remains to be determined.

6.3.2 **Physical control: polystyrene beads**

Unlike many types of aquatic insect larvae, *Culex* and many other mosquito larvae breathe air through the water surface. Hence oil and monomolecular films are used to coat the surface and thereby suffocate the larvae. Being biodegradable, they require repeated applications in pit latrines, cesspits, disused wells, flooded cellars, etc. Floating layers of expanded polystyrene beads, on the other hand, are a non-biodegradable, and therefore permanent, method of controlling breeding of *C. quinquefasciatus* in stagnant water confined within walls. Three years after application to cesspits the layers of beads have been observed to be still in place. This is an order of magnitude greater than the longest persistence ever claimed for any chemical or microbial larvicide.

Killing of larvae and/or prevention of emergence of adults by this means has been demonstrated in individual pits in Belize, Brazil, Egypt, India, Kenya, United Republic of Tanzania, and Zimbabwe. Apart from pit latrines and cesspits, beads have also been successfully applied to cellars of apartment blocks that have long been flooded with sullage water and infested with *C. quinquefasciatus*.

It must be emphasized that polystyrene beads will be effective only in a closed system. In filariasis control programmes the use of beads is recommended in combination with chemotherapy and other control measures.

6.3.3 **Biological control**

Biological control of vectors – a rapidly developing area – provides a very useful alternative control strategy, permitting the exploitation of more ecologically acceptable methods through the use of natural insect pathogens, parasites, and predators. It is not a panacea, but it offers improved methods to supplement other environmental, physical, and chemical techniques, the mixture varying according to species, disease, and local ecological and geographical conditions. Many organisms have been investigated as potential agents for vector control – viruses, fungi, bacteria, protozoa, nematodes, invertebrate predators, and larvivorous fish – but none of these has yet been conclusively shown to be of value in filariasis control.

The most promising candidate is *Bacillus sphaericus*, a spore-forming organism, some strains of which are highly toxic to some species of mosquitoes. In general *Culex* and *Psorophora* mosquitoes are highly susceptible, followed by *Mansonii*, *Anopheles*, and *Aedes* species. The level of susceptibility of *Culex* larvae is very high, being of the same order
as to the currently used synthetic chemical larvicides. *Anopheles* larvae are, as a whole, 10-20 times more tolerant of *B. sphaericus* toxins than *Culex* larvae while *Aedes aegypti* larvae are 1000 times more tolerant. Increasing the dosage of application provides control of *Culex* for longer periods, in some cases for up to 2-3 months.

A particularly attractive feature of *B. sphaericus* is its potential to persist and recycle under field conditions, especially in polluted water. It also has a good safety record and does not affect non-target invertebrates and vertebrates. The bacterium has passed all necessary safety tests and was registered in 1990 by commercial companies for use in the USA and Europe.

By the application of a briquette formulation of *B. sphaericus* to control *Mansonina* mosquitos breeding in ponds in Kerala, India, larval populations were reduced considerably at 15 and 30 kg of active ingredient per hectare. *B. sphaericus* has shown higher residual capability against *M. bonneae* than another spore-forming bacterium, *Bacillus thuringiensis* serotype H-14, also used for biological control of mosquitos. However, both bacterial larvicides sustained suppression of *Mansonina* larvae and of adult emergence for over 4 weeks in the field.

Although effective and possessing a long shelf-life, specific biodegradable bacterial insecticides do have drawbacks. More suitable formulations and more potent strains are now under development and the possibility of improving existing strains by genetic manipulation is being investigated. In 1990, an informal consultation of experts, convened by the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases, prepared a protocol for the operational use of *B. sphaericus*, and a number of large-scale field trials are under way.

6.3.4 **Integrated vector control**

Integrated vector control involves the combination of two or more of the methods or techniques mentioned above. As indicated in the report *Integrated vector control* of the WHO Expert Committee on Vector Biology and Control (16), it should be envisaged in the context of community participation (see section 9).

6.4 **Low-density microfilaremia and transmission**

6.4.1 **Low-density microfilaremia**

Low-density microfilaremia is a density of circulating microfilariae that cannot be detected in a significant number of instances when commonly used blood sampling techniques are applied. As a consequence a significant number of persons recorded as microfilaria-negative are in fact microfilaria-positive, and the true rate of infection in a community is underestimated.

Detection of low-density microfilaremia depends on a number of
variables: volume of blood examined (usually 20 μl, 30 μl, 60 μl, 100 μl, or 1.0 ml); source of blood sampled (usually venous or capillary); technique of microfilaria detection adopted (usually stained thick blood film, counting chamber, membrane filtration, or centrifugation-concentration). Increasing the volume of blood sampled will reduce the proportion of microfilaria-negatives reported and will do so to a much greater extent than will increasing the efficiency of microfilaria detection. Higher microfilaria counts are observed for equal volume samples in capillary than in venous blood. These considerations have been shown to be of importance in a substantial part of the geographical range of lymphatic filariasis – South Pacific, Western Pacific, India, Egypt, East Africa, West Africa, and the Caribbean.

The commonest technique for microfilaria detection in public health practice remains the examination of stained 20-μl finger-prick blood films. For working purposes it is proposed that low-density microfilaraemia should be defined as a microfilaria (mf) count of <4 mf/20 μl (= 200 mf/ml) when capillary blood is examined, or of <30 mf/ml, when venous blood is sampled, regardless of the volume of blood sampled or the method of microfilaria detection employed. This definition has the incidental advantage that it corresponds closely to the estimate of 3.64 mf/20 μl, calculated as the density of microfilariae in finger-prick blood produced by one mated adult female W. bancrofti.

6.4.2 The infection of mosquitoes from low-density microfilaraemia

The capacity of mosquitoes to ingest and develop microfilariae at low or even ultra-low blood densities has been frequently demonstrated – for instance, with Aedes-transmitted W. bancrofti in Fiji, Samoa, and Tahiti. In experimental subperiodic B. malayi infections, 17.2% of Aedes togoi became infected after feeding on a cat with a microfilarial density of 18 mf/ml blood, and a mean of 1.4 infective larvae developed per mosquito.

In Culex vectors, there is also abundant evidence (from Egypt, Haiti, India, Sri Lanka, and the United Republic of Tanzania) of the ability of mosquitoes to sustain development of infective larvae after feeding on low-density carriers.

Studies on the uptake of low-density microfilariae from areas where Anopheles species are the natural vectors are much less numerous. However, recent experimental studies in the Gambia showed that more than 10% of A. gambiae and A. arabiensis ingested microfilariae when fed on human volunteers with weighted mean densities between 8 and 11 mf/ml of venous blood. In spite of the fact that between 40% and 60% of microfilariae were damaged at the time of ingestion by the pharyngeal

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1 A density of 4 mf/20 μl in capillary blood corresponds to a density of about 33 mf/ml in venous blood, calculated using an exponential function.
armatures, just under 1% of mosquitos yielded normally developing larvae on dissection 7 days after the infective blood-meal. In an earlier study in the United Republic of Tanzania, 17% of *A. gambiae* fed on a volunteer with a mean count of 2.25 mf/20μl of finger-prick blood developed infective larvae.

Also in earlier studies, humans with *B. malayi* microfilaraemia of 25 mf/ml yielded infective larva infection rates of 7.8% in *M. longipalpis* (= *M. dives*).

### 6.4.3 Mosquito-parasite relationships

Three epidemiologically important categories of relationship between filarial parasites and their mosquito vectors are recognized – proportionality, limitation, and facilitation. Proportionality implies that the proportion of microfilariae developing to infective larvae is constant and independent of the number of microfilariae ingested; limitation is the situation where this proportion is reduced as microfilarial intake increases; facilitation occurs when the proportion of ingested microfilariae developing to infective larvae is increased as microfilarial intake increases. As examples, proportionality has been demonstrated for subperiodic *B. malayi* in *M. dives* in Malaysia; limitation for subperiodic *W. bancrofti* in *Aedes polynesiensis* in Samoa and Tahiti, for periodic *W. bancrofti* in *C. quinquefasciatus* in Sri Lanka and the United Republic of Tanzania, and for periodic *W. bancrofti* in *C. molestus* in Egypt; and facilitation for periodic *W. bancrofti* in *Anopheles gambiae* and *A. arabiensis* in the Gambia.

The importance of these distinctly different host-parasite relationships lies in the predicted importance of low-density microfilaraemia in sustaining transmission in various endemic areas with different genera of mosquito vectors. Theoretically low-level proportionality and limitation will increase the probability of transmission and of building up the parasite reservoir when most infected human hosts have low microfilaria densities. Situations of well-marked proportionality or facilitation will give rise to transmission thresholds that could lead to the ultimate extinction of lymphatic parasites from the human population.

Vector control aimed at malaria eradication has eradicated *Anopheles*-transmitted *W. bancrofti* in the Solomon Islands and Togo. In China, efficient mass drug administration with diethylcarbamazine (DEC) appears to have interrupted transmission of *B. malayi* by *A. sinensis*. In all these examples, facilitation was the local vector-parasite relationship.

On the other hand, two campaigns of mass drug administration with DEC in Samoa had reduced the prevalence rate of *W. bancrofti* microfilariae from 19.1% in 1965 to 0.19% in 1972; in early 1973, 24.7% of persons known to have had normal-density microfilaria counts in 1965 were found to have persisting low-level microfilaraemia, mostly with counts of less than 10 mf/ml of venous blood. In this situation, with *Aedes polynesiensis* and *A. samoanus* as uncontrolled vectors, the phenomenon of limitation
allowed transmission to resume. Prevalence rates and densities of microfilaraemia and the reappearance of acute clinical disease manifestations forced the reintroduction of annual mass drug administration with DEC.

The control situation in areas of *Culex* transmission is less clear and requires further research. Experimental studies show clearly that with *Culex* species the phenomenon of limitation occurs. Studies in China indicate that prolonged and continuous control measures, aimed at both parasite and vectors, can over many years lead to the virtual elimination of filariasis. Other work, in Sri Lanka, suggests that *Culex* is capable of sustaining transmission with very low prevalence rates of low-density microfilaraemia.

6.4.4 **Indicators of interruption of transmission**

Recent studies in China indicate that long-term surveillance of microfilaria prevalence rates and intensities after control leads to the recognition of critical levels indicating that the interruption of transmission may have occurred, and hence the possibility of relaxing or ceasing active control operations (17). The critical levels vary with the epidemiological situation and the vector-parasite combination. Clearly, use of such indicators is of great potential importance to the rest of the world, and it is strongly recommended that the subject be the topic of future research programmes in areas with different vector-parasite combinations.

6.5 **Suggestions for further study**

1. Standardized protocols should be developed for detailed entomological studies on vector distribution, ecology, bionomics, and transmission. These studies would be particularly useful for control strategies.
2. It would be desirable to conduct large-scale studies to evaluate the respective efficacies of larvivorous fish, impregnated materials, and *B. sphaericus* in filariasis vector control and reduction of transmission.
3. Studies are necessary, for all vector-parasite combinations, to determine critical prevalence and intensity levels at which active control could be stopped.
4. In view of the implications of the facilitation phenomenon in *Anopheles* vectors, it is recommended that careful trials using DEC should be carried out to determine whether theoretical predictions of parasite disappearance are fulfilled when low prevalence rates and intensities of microfilaraemia have been attained.

7. **Epidemiological aspects**

7.1 **Epidemiological studies for filariasis control**

Epidemiological studies for the control of lymphatic filariasis can be placed into five categories: (1) determining the geographical distribution of
filariasis and the parasite burden in populations at risk; (2) assessing the impact of filariasis on the health of the individual and the community; (3) determining the “force” of filarial infection (see section 7.1.3) by quantifying vector and parasite exposure factors; (4) designing control strategies and implementing, monitoring, and evaluating control activities, both experimental and applied; (5) measuring the impact of the interventions and establishing a system of long-term filariasis surveillance.

7.1.1 Determining the distribution of filariasis and the parasite burden in populations at risk

Epidemiological surveillance is a means of determining the distribution and trends of incidence of disease through the continued and systematic collection, analysis, and interpretation of health data. Although filariasis is detectable in most endemic areas, infection is largely undetected and often misdiagnosed and underreported. This is due partly to the large proportion of persons in endemic communities who are infected but both asymptomatic and microfilaraemic, or who are symptomatic but without detectable microfilaraemia. Further, symptoms may be non-specific or overlooked. Even when filariasis is diagnosed, there may be little motivation to report cases of a disease for which containment of infection and interruption of transmission are not readily achieved. Under optimal conditions, information of use in planning filariasis control programmes is collected in systematic surveys, using appropriate population sampling methods and standardized techniques for compiling demographic, health history, physical examination, environmental, parasitological, and vector-related information. Mapping and census of the population identify logistic needs, define sampling frames, provide denominators for the computation of rates of infection, morbidity and other health-related events, and identify baseline, parasite and vector population characteristics that shape the intervention strategy and determine its impact. Optimal conditions do not often occur, however, and the development of simpler methods of performing surveys should be a high priority. Practical methods of community sampling and examination have been outlined elsewhere (3).

Information collected in surveys may suggest certain factors which put some persons at greater risk of infection and disease than others; once identified, putative risk factors can then be examined in an analytical framework, using either a retrospective case-control approach or a prospective cohort design for determining relative risks. Recent studies in Haiti show that maternal infection may be a risk factor for filarial infection and altered parasite-specific immune reactivity in the offspring.

7.1.2 Assessing the parasite burden and the disease impact in the target population

The examination of measured quantities of peripheral blood in stained thick films continues to be the most widely used method for determining
the prevalence of patent infection and the density distribution of microfilaraemias. Membrane filtration of larger volumes of venous blood is a more sensitive method, which allows a more accurate determination of prevalence and parasite density. Filtration is especially useful in evaluating post-treatment parasitaemias and in monitoring the long-term effects of control programmes because of its ability to detect microfilaraemias of very low density, which may provide an important reservoir for continuing reinfection in a community (see section 6.4). Parasite densities in a population are not normally distributed and data are most informative when examined as geometric means or as cumulative frequencies in a log-probit analysis (18).

Important recent advances have been made in methods for detecting specific filarial antigens and antibodies (see section 4.3). The first priority is the development of tests that will, with ease and accuracy, allow the determination of prevalence and incidence of filarial infection in communities. Species-specific and quantitative antigen-detection methods have been described that are especially promising as epidemiological tools to detect patent infections. There is a further need to identify prepatent and other amicrofilaraemic states of infection, and to assess the impact of control programmes using drugs that suppress microfilaraemia but have limited adulticidal properties. The ability to measure exposure to larvae and quantify adult worm burdens would greatly increase the understanding of the relation of infection and disease to parasite dynamics. Similarly, immunodiagnostic methods that discriminate between past and current infection are needed to monitor trends of infection.

Considerable attention has recently been directed to developing epidemiological models to describe lymphatic filarial infection and disease in communities, and there is an increasing interest in developing statistical techniques to describe quantitative aspects of infection (see section 7.2).

For community assessment purposes, lymphatic filariasis morbidity is divided into acute adenolymphangitis and chronic (lymphostatic) categories; the former is usually determined in surveys by medical history and the latter by physical examination. Case classifications have, however, been poorly defined and non-uniform. Standardized criteria for defining clinical status have been developed and are being tested within the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases. There is a considerable need to correlate the incidence of adenolymphangitis with the intensity and force of infection, and with the subsequent development of chronic, obstructive disease manifestations.

7.1.3 Determining the force of infection

Measurement of the intensity of transmission of human filarial infections is complex, and none of the available methods used to measure it is ideal. The force of filarial infection to which persons are exposed may, however, be
crudely determined by measuring and combining the annual transmission potentials (ATP) of each vector species of mosquito present in the community under study. The ATP is the estimated number of infective larvae to which a person is exposed over a 1-year period. It is derived from the annual biting rate (ABR) of each vector species and its infectivity rate (the annual infective biting rate; AIBR), and the mean density of infective larvae per biting mosquito \( I, \) pp. 86-90. It does not take into account the efficiency of transmission of infective larvae from vector to human host, the attrition of larvae within the human host, or the success of surviving larvae in becoming mated pairs. Monitoring changes in the ATP can be useful in assessing the impact of control programmes on transmission.

7.1.4 The design, implementation, monitoring, and evaluation of control programmes

Methods of filariasis control include chemotherapy (both selective and mass administration), vector suppression, and protective measures and behaviours that reduce vector-human contact. The control programme planners select the type and emphasis of control methods based on public health objectives for reducing existing disease, preventing future morbidity, and interrupting transmission. Although interruption of transmission and elimination of detectable microfilaraemia have been achieved by various means in some populations, the goal of most programmes is to lower morbidity and transmission to sustainable, low levels. Epidemiological studies and methods can be used to determine the best design for control in the individual situation; the control programme must consider the size and demographic features of the populations at risk, their parasitological and disease profiles, vector dynamics, and the sociocultural and political characteristics that determine levels of cooperation and support of the planned intervention. Increasing attention is being given to integration of control with primary health care services and to strategies that incorporate community participation in personal protection, environmental sanitation, and drug delivery.

Recently, specific guidelines have been developed within the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases for clinical and field trials of ivermectin and diethylcarbamazine for lymphatic filariasis. These guidelines address drug effects on microfilaraemia, on acute clinical disease, and on the reduction of transmission in communities, and provide a basis for uniform comparisons of results between different sites, between infections caused by different parasite species and strains, and between varying endemities and disease patterns. Similarly, as mentioned in section 6.3.3, a protocol has recently been developed for vector control using Bacillus sphaericus. These guidelines and protocols set the ground for developing standardized, epidemiologically comparable control activities.

Epidemiological study of the implementation phases of filariasis control
programmes involves analysis of the organization of the programme, its personnel requirements and productivity, and its cost; of the uniformity and proficiency of testing methods (precision, sensitivity, specificity, and predictive values of clinical, parasitological and entomological assays); and of levels of coverage and compliance of the population with the various interventions and test procedures applied. Validation of new testing methods requires carefully designed studies to determine precision, accuracy, and field utility. Quality control, especially of microscopical procedures, is essential. Epidemiological monitoring employs the continuous collection and analysis of data and should provide feedback in a timely fashion so that control activities can be guided by the findings in a dynamic manner. Continuous monitoring also promotes managerial efficiency. The following are useful measures of programme outcome: frequency and severity of adverse events (e.g. reactions to drug treatment); standard parasitological and entomological parameters, including transmission potential; frequency and severity of new and recurring acute filarial disease episodes, and long-term variations in the prevalence and severity of chronic manifestations. Children and migrants from non-endemic areas may serve as special indicator groups for measuring continuing parasite transmission.

7.1.5 Measuring the impact of interventions

The impact of filariasis control programmes on the health of a community can be measured in terms of the reduction of morbidity, disability and interference with normal productive activities, and by the psychosocial and economic consequences. Determination of the effects of control is based on historical comparisons within the intervention cohort, which are subject to serious confounding, and to comparisons between intervention and control cohorts, which frequently present problems of incomparability and bias, as well as confounding. Some standard methods of analysis for such comparisons, discussion of the limitations of study design, and ways to control for confounding variables are given in a recent manual, on trials of interventions against tropical diseases, of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (19).

Long-term surveillance is required to assess the impact of control on transmission. In the past, this has usually entailed the examination of large numbers of mosquitoes for infection with larvae and/or repeated human blood surveys, using concentration techniques as appropriate. It is expected that advances in practical applications of DNA probes for identifying larvae in mosquitoes and immunodiagnostic tests will replace these methods in the future. There is a need to develop and test models to predict parasite extinction or re-emergence in populations with low residual parasite burdens, so that thresholds of sustained disease control can be established as targets for control programmes.
7.2 Epidemiological modelling

Modelling is a way of organizing information so that the interrelationships of such variables as transmission, infection, and disease can be readily appreciated, and so that the information lacking for complete understanding of the problem can be identified easily. Quantitative models developed from epidemiological data put numbers on these relationships and give the research investigator and epidemiologist tools for:

- steering research, by pointing to the key relationships in the system and identifying the additional information needed to understand them fully;
- planning control strategies, by preliminary assessment of control options to identify the most effective approaches;
- evaluating control programmes, by providing a framework for data collection and for gauging the changes to be expected during the course of programmes.

Epidemiological modelling has proved a useful tool both for understanding disease transmission and for formulating control strategies for diseases other than lymphatic filariasis.

7.2.1 Modelling of lymphatic filariasis

Recent years have seen a growing interest in the development and application of epidemiological modelling of lymphatic filariasis for epidemiological research and for the planning and evaluation of filariasis control. This is encouraging as modelling is of particular relevance to filariasis for two main reasons. First, lymphatic filariasis has unusually complex and dynamic relationships that are difficult to grasp. This complexity occurs because three populations – the human host, the vectors, and the parasites – are involved, and because the interaction between host infection levels, vector infectivity, and disease expression changes over time. Moreover, the exceptionally long time scales of filarial infection make empirical study difficult and expensive. The duration of life of the adult worms, the progression to lymphatic disease, and the evaluation of the effects of control all involve time-spans of several years or even decades.

Basic analytical models for filariasis were developed in the 1960s and 1970s and have been important in guiding subsequent epidemiological approaches to filariasis research. Analyses of epidemiological data using these models have revealed remarkable differences between brugian and bancroftian filariasis in the age distributions of microfilaraemia and disease and have made it possible to arrive at preliminary estimates of the duration of microfilaraemia, the average worm burden, and important

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1 Informal consultation on epidemiological modelling for research and control of lymphatic filariasis (unpublished document TDR/FIL/EPI-MOD/90.3; available on request from the UNDP/World Bank/WHO Special Programme on Research and Training in Tropical Diseases, World Health Organization, 1211 Geneva 27, Switzerland).
variables of worm fecundity. Most of this resulted from early studies, which also highlighted the important discrepancy between extremely high levels of exposure to filarial infection and relatively low levels of detectable infection in endemic areas.

More recently, the extensive data set assembled by the Vector Control Research Centre in Pondicherry, India, has been analysed using dynamic methods related to earlier catalytic models. This unique data set has permitted estimates of the age-specific rates of acquisition and loss of microfilaraemia (a measure of “fecund infection”), of the relationship between microfilaraemia and the development of chronic lymphatic obstructive disease, and of geographical variations in disease patterns.

There are as yet no epidemiological models for lymphatic filariasis that can be used in the planning and evaluation of control. This would require comprehensive models of the transmission cycle, the disease process, and available methods of control. However, the positive experience of the Onchocerciasis Control Programme in West Africa, in which a comprehensive epidemiological simulation model has become an important operational tool for both planning and evaluation, provides an example of this approach.

7.2.2 Information required for the development of quantitative models for lymphatic filariasis

The construction of quantitative models for lymphatic filariasis requires numerical estimates of the various parameters associated with infection, transmission, disease, and control. The availability of such estimates has been limited mainly by the lack of adequate longitudinal data sets and the lack of sensitive diagnostic tests for filariasis infection. In filarial infections the only feasible measure of intensity of infection is counts of microfilariae in the blood or skin, since adult worms are difficult or impossible to detect and are not accurately quantifiable. In lymphatic filariasis it is unclear whether the pathology in the lymphatics is caused by adult worms only or by a combination of adult worms, developing larvae, and microfilariae. Since there is no way of confidently determining the number of adult worms infecting a patient, it is not possible to know whether, in a given individual, there is a direct relationship between the degree of microfilaraemia at any time and the number of adult worms. Furthermore, those who manifest chronic disease are usually not the heavily microfilaraemic but individuals with little or no microfilaraemia.

Virtually no information is available from longitudinal studies on whether heavy microfilaria loads are a prelude to chronic disease manifestations. The discrepancy between intensity of infection (as defined by microfilaraemia) and disease consequence is often presumed to result from a host immune response, which has been described in qualitative and semi-quantitative terms but is not sufficiently understood or quantified for confident use in epidemiological models.
Studies to date have attempted to correlate current immune status with current disease and/or infection. Since the exposure to infection, the immunological status, the level of microfilaraemia, and the development of disease in an individual all appear to change over time, it is necessary to adopt a dynamic approach to clarifying the relationship between infection, immunity, and disease.

There are many other parameters of the vector/host/parasite/environment interaction that need quantification in order to formulate useful epidemiological models. Fig. 3 is a schematic representation of the transmission cycle, disease process, and available options for controlling lymphatic filariasis. The important epidemiological factors and relationships are listed in Table 3, specifying the information needed to formulate quantitative models, and the current availability of that information.

It is recommended that more information should be obtained from existing data sets or specific experimental and field studies. These questions may be addressed by all investigators who are conducting field trials. In this connection there is particular need for methods to detect circulating adult

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**Figure 3**

Schematic representation of the transmission cycle, disease process, and available options for control of lymphatic filariasis

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* Dotted lines represent the possible influence of the host’s immunological status on the transmission cycle and disease process; broken lines indicate control options.
Table 3

Information needs and availability for quantitative models for lymphatic filariasis

<table>
<thead>
<tr>
<th>Modelling parameter</th>
<th>Information availability</th>
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<tbody>
<tr>
<td></td>
<td>Some available</td>
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<tr>
<td><strong>Dynamics of uninfected mosquito population</strong></td>
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<td>Mosquito reproductive potential</td>
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<tr>
<td>Longevity/mortality</td>
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<td>Immigration/emigration</td>
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<tr>
<td>Spatial dispersion (environmental factors)</td>
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<td><strong>Dynamics of human-to-vector transmission</strong></td>
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<tr>
<td>Infection rate of vector</td>
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<tr>
<td>Relation with microfilaria density</td>
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<tr>
<td>Relation with microfilaria frequency</td>
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<tr>
<td>distribution in humans</td>
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<tr>
<td>Relation of human and vector population densities</td>
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<td>Zoophily of vector</td>
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<td><strong>Dynamics of infection in the vector</strong></td>
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<td>Rate of successful development of infection to L₃</td>
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<td>Time period for development to L₃</td>
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<td>Gonotrophic cycle</td>
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<td>Vector mortality</td>
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<td>Relation with larval density</td>
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<td>Relation with larval stage</td>
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<td><strong>Dynamics of vector-to-human transmission</strong></td>
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<td>Vector biting patterns in relation to host factors</td>
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<td>Period for larval development</td>
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<td>Rate of larval development to maturity</td>
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<td>Mating probability of adult female worms</td>
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<td>Lifespan of adult worms</td>
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<td>Microfilaria production</td>
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<td>Survival of microfilariae</td>
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<td>Relationship of microfilaraemia to adult worm burden</td>
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<tr>
<td><strong>Dynamics of pathogenesis in humans</strong></td>
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<tr>
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<tr>
<td>Relation to age/sex</td>
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<tr>
<td>Relation to host immune response</td>
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<tr>
<td>Mortality</td>
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parasite antigen. Longitudinal studies that help to elucidate the relationships between the level of parasite antigen, the level of microfilaremia, the changing immune status, and the progression of disease should be specifically encouraged. Whenever possible, these and other relevant field studies should be incorporated in community intervention studies.

Further development, testing, and application of epidemiological models for lymphatic filariasis are encouraged. The current analytical models should be further elaborated and used in the analysis of longitudinal data on infection and disease in order to test alternative hypotheses on the development of lymphatic pathology. Epidemiological simulation models, similar to those for onchocerciasis – e.g. ONCHOSIM (20) – are being developed for lymphatic filariasis and will be tested in multidisciplinary field-research projects and filariasis control programmes.

7.3 Suggestions for further study

1. There is a need to develop highly sensitive, long-term surveillance techniques capable of detecting continued parasite decline or parasite recrudescence after control programmes have produced low microfilaria prevalence rates and densities. DNA probes and immunological techniques for detecting mosquito infections and serodiagnostic tests in humans should be subjected to controlled field trials for this purpose as soon as they can be made widely available.

2. Further development, testing and application of epidemiological models for lymphatic filariasis should be pursued; current analytical models and epidemiological simulation models should be elaborated and used to analyse longitudinal data on infection and disease, including existing data sets.

8. Treatment

8.1 Diethylcarbamazine citrate (DEC)

For more than 40 years diethylcarbamazine citrate (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 wide experience with DEC has shown it to have low toxicity and to be safe for large-scale use in lymphatic filariasis, even in circumstances of limited medical supervision. Attempts have been made to find favourable alternatives to DEC for treating lymphatic filariasis, 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 (21).
8.1.1 **Action on lymphatic filarial parasites**

**Action on microfilariae**
It has been shown that, *in vitro*, 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. 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 hydrocele fluid are not affected by DEC. The precise mechanism of action of DEC remains a subject of debate.

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

**Action on third- and fourth-stage larvae**
DEC has no effect on developing third- and fourth-stage larvae of *W. bancrofti* or *B. malayi* *in vitro*, but it has prophylactic action on *B. malayi* in cats and *Presbytis* monkeys and on *W. bancrofti* in humans (see section 8.3.4).

**Action on adult worms**
In humans, 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. However, sometimes not all the adult worms are killed, even after repeated courses of DEC. A proportion of patients so treated continue to have microfilaraemia and experience periodic attacks of adenolymphangitis, a sign of active infection. The mechanism by which DEC kills adult worms is unknown.

8.1.2 **Effect on disease manifestations**

While the value of using DEC to treat filarial infection is undeniable, there is controversy as to whether treatment during the acute phase will shorten the attack.

**Effect on recurrence of acute clinical manifestations**
The prevalence and incidence of adenolymphangitis decrease significantly after treatment with DEC. The drug also reduces the frequency of attacks of funiculitis and epididymitis. Longitudinal studies show that repeated DEC therapy (either during the acute adenolymphangitis or chronic
asymptomatic phases) reduces the likelihood of developing chronic obstructive lesions.

**Effect on chronic clinical manifestations**

Patients with transient lymphoedema, small developing hydrocele, haematuria, or chyluria usually respond well to treatment with DEC, although repeated courses are often necessary to eliminate all the adult worms. Patients with grade I lymphoedema are often favourably affected by treatment. In some cases, elephantiasis of several years’ duration can be reduced partially by DEC treatment alone. However, patients with a large hydrocele and/or elephantiasis with deformities often do not show any improvement after DEC treatment.

**Effect on tropical pulmonary eosinophilia**

DEC is the drug of choice for tropical pulmonary eosinophilia. Marked clinical and haematological improvement occurs within a few days of treatment with 6 mg/kg of body weight daily for 21 days, but relapses may occur in as many as 20% of patients, who then require treatment with higher doses (6-12 mg/kg daily for 21-30 days). Pulmonary 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 (see also section 3.3).

8.1.3 **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 uninfected 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.

**Pharmacological toxicity**

Direct effects of the drug in persons who have no filarial infection are dose-dependent. At the recommended dose of 6 mg/kg of body weight per day, there are rarely any side-effects at all. At higher dosages there may be anorexia, nausea, abdominal pain, weakness, dizziness, or lethargy. 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.

**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 than in brugian filariasis. There are two groups of reactions, systemic and local, both with and without fever.

*Systemic reactions* include headache, aches in other parts of the body, pain in the joints, dizziness, anorexia, malaise, transient haematuria, allergic reactions, vomiting, and sometimes attacks of bronchial asthma. These reactions 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 more than 3 days. Fever and systemic reactions tend to be commoner and more severe in those with higher microfilarial density in the blood. If the drug is given in spaced doses, systemic reactions are much less frequent and less intense after the second dose and 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. The systemic reactions to DEC eventually cease spontaneously and interruption of treatment is rarely necessary. Symptomatic treatment of the reactions with antipyretics or analgesics may be helpful.

*Local reactions* include lymphadenitis, abscess, ulceration, transient lymphoedema, and hydrocele, which occur with decreasing frequency in that order and in varying combinations. In bancroftian filariasis, local reactions also include funiculitis and epididymitis. These reactions tend to occur later in the course of treatment and to last longer. They also disappear spontaneously and interruption of treatment is not necessary. In some cases lymphoedema andhydrocele 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; they are probably related to the presence of adult or immature worms or fourth-stage larvae in the tissues.

### 8.2 Treatment with DEC of individual cases of lymphatic filariasis

The object of treatment of individual cases is to destroy the parasite and to eliminate, reduce, or prevent morbidity. DEC is the only drug now available that is effective, safe, and relatively cheap for the treatment of lymphatic filariasis. The dose most generally accepted for the treatment of bancroftian filariasis is 6 mg of DEC per kg of body weight per day orally for 12 days, given preferably in divided doses after meals. For brugian filariasis, various dosage schedules have been used in different countries, but current recommended doses range from 3 mg to 6 mg of DEC per kg of body weight per day, up to a total dose of 36–72 mg of DEC per kg of body weight. This recommended course will clear microfilariae of most patients but complete parasite cure may require repeated courses of treatment.

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 life-threatening adverse reactions.

### 8.3 Chemotherapeutic control of filariasis in the community with DEC

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, and persons with obvious debilitating disorders are normally excluded. Successful results quite often become apparent within a relatively short time and the occurrence of true resistance has not been established.

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 the efficacy and speed of control measures being great enough to prevent the parasite from becoming 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 mosquito vector, and the infective larvae do not multiply in the human host. Therefore, the parasite never causes epidemics.

#### 8.3.1 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. In an area of high endemicity, everyone may be considered to be more or less equally exposed to the infective bites of the vector, and current methods are not sufficiently sensitive to diagnose subpatent or subclinical infections.

The advantages of mass treatment are that:

- it avoids the cost of a mass blood-examination programme before treatment, and no carriers with false-negative results on blood survey escape treatment; and
- all members of the community receive treatment, nobody feels left out, and compliance is therefore enhanced.

In *selective treatment*, only microfilaria-positive persons and/or persons with clinical manifestations of filarial disease are treated, after having been
selected by large-scale screening of the community, which involves a blood
survey. The advantage of selective treatment is that 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 very 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 (22).

8.3.2 *Spaced single dose of DEC*

Results of recent therapeutic trials in Fiji and French Polynesia (23) have
indicated that a single dose of DEC of 3 mg or 6 mg per kg of body weight
reduces microfilaria density by 80-90% whether given twice a year or
yearly. Adverse reactions reported appeared to be related to the
pretreatment microfilaria load and not to the dosage of the drug. Regarding
compliance, these recent trials indicate that a control strategy based on
administration of spaced doses of 3 mg or 6 mg/kg should be better
accepted than repeated 12-day regimens.

8.3.3 *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 of salt has been used for control in several areas in which
*W. bancrofti* or *B. malayi* filariasis is endemic.

The large-scale distribution of DEC salt to a population of 26,000 in
Lakshadweep Islands, India, eliminated 90% of circulating microfilariae in
80% of the initial carriers and the disease rate was reduced by 20%. A
larger trial in Karaikal, Pondicherry, India, covered a population of nearly
130,000. Initially, 0.15% DEC salt was distributed for 8 months and 0.2%
for the subsequent 38 months; the 46-month regimen produced a decline
of 98% in the microfilaria rate and 72% in the disease rate. Similar trials
were done in India in Kerala and in Andhra Pradesh. All these trials were
in bancroftian filariasis areas. A trial of DEC salt at a concentration of
0.4% was also undertaken in three hill settlements in a *B. malayi*-endemic
area in Kerala with a tribal population of 1380 for a period of one year. The
total intake was 7.2 g of DEC and an excellent result was achieved, with
the microfilaria rate reduced to zero. None of these regimens in India
precipitated any untoward side-effects and the community acceptance was
good.

From 1970 to 1982 a programme was conducted to eradicate bancroftian
filariasis from Little Jinmen Island. A precontrol survey had revealed a
microfilaria rate of 9.6% and a clinical disease rate of 26.2%. DEC-mediated salt (0.33% w/w) was supplied free and was used exclusively by the whole population during the 6-month period July-December 1974. Strict quarantine was enforced throughout this time. Most of the clinical manifestations of filariasis among the precontrol carriers disappeared or were greatly improved after completion of the course of medicated salt.

Elsewhere in China salt medicated with DEC at 0.1-0.3% for 3-6 months has been distributed to more than 18 million people, resulting in significant decrease of transmission.

Administration of DEC-mediated salt is simple, rapid, safe, inexpensive, efficient, prophylactic, and practical for filariasis control or, in some circumstances, eradication. However, a prerequisite for success is motivation of the community through the mass media to accept the medicated salt. Political commitment and appropriate legislation and government policy decisions will greatly smooth the running of medicated-salt campaigns, for which preventive and curative services must, of course, be made available. Such campaigns should cover only large geographical areas, or sharply circumscribed ones, in which filariasis is highly endemic. In small endemic countries the national governments, and in larger countries provincial or state governments that have responsibility for health, could directly implement campaigns through committed workers. Careful preparation of the infrastructure and logistics for a campaign is also essential. Among the elements to be taken into account are salt and DEC manufacture and procurement in the quantities required, the supply line, the places and methods of distribution, and the stoppage of supplies of unmedicated salt. Commercial channels similar to those used for iodized salt in goitre control could be used. The concurrent medication of salt with DEC and iodate or iodide in India has not shown any adverse effects.

8.3.4 DEC as a prophylactic agent

The possible prophylactic effect of DEC in W. bancrofti infections was recently investigated in the area of Varanasi in Uttar Pradesh, India (24). The results showed convincingly that in a population of 3055 persons inhabiting three rural villages, with microfilarial and disease rates of 10.1 and 7.0%, respectively, there was a prophylactic effect throughout the 18 months of administration of DEC at a dosage of 500 mg on each of two consecutive days each month, and for an additional 12 months after the cessation of prophylactic DEC dosage. Active transmission in the area was confirmed by the finding of vector mosquitoes (C. quinquefasciatus) with infective larvae, and by the incidence of new cases of microfilaraemia in the control groups not given prophylactic DEC.
8.4 Ivermectin

Ivermectin is a semisynthetic macrolide antibiotic with a broad spectrum of activity against a variety of nematodes and ectoparasites. Because a single oral dose of 150 μg/kg of body weight rapidly clears microfilariae from the skin of patients with onchocerciasis without inducing the severe side-reactions seen following DEC treatment of such patients, and because its therapeutic effect lasts for a year or more after treatment, ivermectin has entirely transformed strategies for the treatment and control of onchocerciasis.

8.4.1 Single oral doses

Studies have been carried out in eight trial sites around the world for *W. bancrofti* filariasis and in three trial sites for *B. malayi* filariasis. These studies have evaluated the anti-microfilarial effects of single oral doses of ivermectin ranging from 20 to 400 μg/kg of body weight and have compared these effects with both "full-course" DEC (i.e. 6 mg/kg of body weight per day for 12 days) and single doses of DEC. Preliminary studies have also looked at the effectiveness of single doses of ivermectin repeated yearly or twice-yearly in comparison with similar DEC regimens in decreasing microfilarial levels in individuals.

**Efficacy**

For *W. bancrofti*, trials at the eight sites in Brazil, French Polynesia, Haiti, India (two sites), Kenya, Papua New Guinea, and Sri Lanka showed that single oral doses of 20-400 μg/kg of body weight were effective in completely clearing blood microfilariae in all treated patients within weeks; by 3 months microfilaraemia recurred in most patients and by 6 months reached geometric mean levels of approximately 5-40% of pretreatment values. The variability in results at 6 months generally occurred at the lower doses of ivermectin, the doses of 200 and 400 μg/kg of body weight appearing to be maximally effective.

For *B. malayi*, trials at the three sites in India, Indonesia, and Malaysia indicated that the microfilaricidal response to ivermectin was qualitatively different from that in *W. bancrofti* infections. Rather than causing rapid and complete clearance of blood microfilariae in patients with brugian filariasis, ivermectin caused a gradual decrease in blood microfilaria levels over 2-4 weeks to approximately 15-20% of the pretreatment values. These low levels were sustained, however, for at least 6 months after treatment. While the patterns of response were generally similar at all doses tested (20-400 μg/kg of body weight), maximal effectiveness, as in the case of *W. bancrofti* infections, was seen at the higher dosages 200 and 400 μg/kg.

**Drug tolerance**

When ivermectin is given to individuals with no microfilaraemia (either normal volunteers or infected patients with amicrofilaraemic clinical
syndromes) at dosages between 20 and 400 μg/kg of body weight, absolutely no side-effects are seen (i.e. no drug toxicity). However, when it is administered to microfilaraemic patients there may be a variety of reactions as a result of inflammatory responses triggered by the cleared and dying microfilariae. Thus, the reactions to ivermectin treatment have essentially the same pathogenesis as those following DEC treatment and do not reflect specific drug toxicity.

At all study sites the frequency, character, and time course of the reactions were very similar. They occurred in approximately 90% of all treated patients but appear to be milder in patients with *B. malayi* than in those with *W. bancrofti* infections at the above-mentioned doses. Systemic reactions such as fever and malaise were transient, generally beginning 12-24 hours after treatment and lasting for 36-48 hours. Localized reactions, such as lymphangitis and the formation of nodules, were also observed, beginning later and lasting longer than systemic reactions. Both types of reaction were easily managed with antipyretics or analgesics. Even the most severe reactions (occasional postural hypotension, bronchoconstriction, haematuria) were transient and required only symptomatic management.

8.4.2 *Comparison between ivermectin and DEC treatment in lymphatic filariasis*

*Single-dose ivermectin versus “full-course” DEC*

Two studies were carried out to test the relative efficacy and tolerability of single doses of ivermectin – 20 or 120 μg/kg of body weight in India (25) and 100 μg/kg of body weight in China (26) – by comparison with 12-day courses of DEC (6 mg/kg of body weight per day) in patients with bancroftian filariasis. It was found that the single doses of ivermectin cleared microfilariae from the blood more rapidly than did the 12-day course of DEC and that ivermectin was essentially equivalent to DEC in its ability to maintain this effect for up to 3 months after treatment. In lightly infected patients living in an area where transmission had been stopped (China) the 12-day course of DEC and the single dose of ivermectin were equally capable of keeping microfilaraemia from returning to levels greater than 1% of the pretreatment values for at least 12 months. In heavily infected patients living in a region of persistent transmission in India, however, ivermectin was found not to have maintained the clearance of microfilariae from the blood as well as DEC at 6 months after treatment.

In both trials the ivermectin and DEC treatment regimens induced similar reactions. No similar comparative studies between single-dose ivermectin and “full-course” DEC have been carried out in patients with brugian filariasis.

*Single-dose ivermectin versus single-dose DEC*

Treatment of patients with nocturnally periodic bancroftian filariasis with single oral doses of either ivermectin (220 μg/kg of body weight) or DEC
(6 mg/kg of body weight) have been carried out at two study sites, in Haiti and Papua New Guinea. In both trials ivermectin was the more effective drug both in the initial clearance of microfilariae from the blood and then in sustaining this clearance during the first 3 months after treatment. Six months after treatment, the superiority of ivermectin over single-dose DEC was still statistically significant in the Haitian population, but the effect of the two drugs had become equivalent (a return to approximately 20% of pretreatment microfilaraemia levels) in Papua New Guinea.

In the only study comparing single-dose ivermectin with single-dose DEC in patients with subperiodic bancroftian filariasis (Raiatea, French Polynesia), results similar to those in the periodic bancroftian filariasis studies were obtained over the first 30 days after treatment, i.e. clearance after ivermectin being significantly greater than that after DEC. However, at 3, 9, and 12 months after treatment the microfilarial clearance induced by the two drugs did not differ significantly. The reason for this poorer response to ivermectin than that seen in the Haiti and Papua New Guinea studies may, of course, lie in differences in the parasites or human populations studied, but it may also be the result of the different ivermectin dosages used in the two studies (220 µg/kg of body weight in Haiti and Papua New Guinea but only 100 µg/kg of body weight in French Polynesia).

For *B. malayi*, single-dose ivermectin at the three trial sites mentioned above did not induce complete clearance of blood microfilariae, whereas DEC (6 mg/kg of body weight) induced rapid and almost complete clearance within the first two days of treatment. Thereafter (10 days to 6 months), microfilaraemia levels after DEC or ivermectin (220 µg/kg) treatment were not statistically different.

Adverse reactions following treatment were generally comparable for the ivermectin-treated and DEC-treated patients at all study sites for both *W. bancrofti* and *B. malayi*.

8.4.3 **Annual and semi-annual single-dose treatments with ivermectin or DEC**

To date, studies to look at annually or semi-annually repeated treatment with single doses of either ivermectin (100 µg/kg of body weight) or DEC (3 mg/kg of body weight) have been reported only from French Polynesia. For both drugs two treatments (at 6-month intervals) were more effective than one in sustaining a reduced microfilaraemia (at 1 year). Once-yearly treatment with ivermectin at 200 µg/kg of body weight was shown to be effective in sustaining decreased microfilarial counts to levels of 5% of pretreatment values when assessment was made 1 year after the second yearly dose was given.

8.4.4 **Effects of ivermectin on filarial parasites and their vectors**

Two recent studies have examined the effect of feeding mosquitoes on patients treated with ivermectin at various stages after administration of
the drug. In one study there were effects on the vector and the parasite; in the other there were effects on the intake of microfilariae and output of infective larvae only. Further studies are needed.

8.5 Trials with other therapeutic agents

8.5.1 Albendazole

This benzimidazole derivative with broad-spectrum anthelminthic activity has been shown to have filaricidal activity against Brugia pahangi in jirds and B. malayi in leaf-monkeys (Presbytis spp). A recent open trial to compare albendazole at 400 mg twice daily for 21 days with DEC showed that albendazole had less microfilaricidal effect but appeared to have a macrofilaricidal effect.

8.5.2 Coumarin

Oral treatment with coumarin of patients with bancroftian filariasis caused significant reductions both in quantified oedema and in the symptoms and complications of elephantiasis in clinical trials carried out in China and India. The reductions were still apparent one year after treatment. Side-effects were few and minor, and occurred in the early stages of treatment. If these results are confirmed by further trials, coumarin may be a useful addition to the treatment regimens for filarial lymphoedema.

8.6 Compounds under development

8.6.1 CGI 18041

CGI 18041 (a benzothiazole) has been evaluated as an antifilarial agent in rodents and also against B. malayi and W. kalimantani in leaf-monkeys. In monkeys given a single oral dose of 25 mg/kg of body weight or more, there was almost complete reduction in blood microfilarial counts, for at least 6–10 weeks, with both filarial species. The compound was also completely macrofilaricidal against both species at a single oral dose of 50 mg/kg and had significant activity at a single dose of 25 mg/kg. CGI 18041 is now undergoing further development. Preclinical toxicological studies are being completed by the parent company, and human clinical trials will be undertaken if efficacy and toxicological results are satisfactory.

8.6.2 UMF 078

A benzimidazole, UMF 078 (or its soluble salt form UMF 289) shows activity against B. pahangi in the dog when administered intramuscularly or orally. This seems a promising compound, which is being developed by the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases and the Onchocerciasis Control Programme in West Africa as a potential macrofilaricide for lymphatic filariasis or onchocerciasis.
8.7 Surgical management of elephantiasis

Earlier surgical techniques, consisting primarily of the excision of redundant tissue from severely affected limbs, generally led to unsatisfactory long-term results. Much more beneficial responses have been obtained recently with lymphnodovenous and lymphvenous shunt procedures, followed by the removal of excess subcutaneous fatty and fibrous issue from the affected extremities and adequate postural drainage and physiotherapy.

Significant improvement is evident for months or years after such shunt operations, but the duration of patency of the shunt and the subsequent course of the disease several years after surgery are not known since few patients have yet been followed up over long periods of time.

8.8 Suggestions for further study

1. Studies should be pursued to determine whether ivermectin:
   (a) has the potential to be macrofilaricidal against bancroftian or brugian parasites;
   (b) is effective in interrupting transmission by repeated administration at 6- or 12-month intervals and how this compares with single-dose administration in the different parasite-vector combinations;
   (c) has an effect on the clinical course and manifestations of lymphatic filariasis (adenolphangitis, elephantiasis, hydrocele, haematuria, tropical pulmonary eosinophilia); and
   (d) has an effect on parasites and vectors that might reduce transmission.

2. Better chemotherapeutic agents that have macrofilaricidal effects need to be developed.

3. Since nodovenous shunt surgery has been reported as a valuable form of treatment for established chronic lymphoedema and elephantiasis, its long-term efficacy should be carefully evaluated.

9. Human behavioural and socioeconomic aspects

9.1 General considerations

The observed and potential impact of human behaviour on the vectors of lymphatic filariasis can usefully be considered under the heads of primarily individual impacts and primarily community impacts, although the distinction is not always clear-cut. Examples of the effect of human behaviour on vector control are given in Table 4.

As well as providing a valuable conceptual framework, this classification provides an element of predictive capability, in suggesting situations where human behaviour is likely to be of potential importance in control.
A factor of great importance which must be stressed when considering individual or community impacts on filariasis control is the sustainability of the impact. Interest and long-term activity understandably decline sharply when successful control operations make clinical manifestations of an infection uncommon. Similarly, programmes may come to depend on the enthusiasm and drive of one or two individuals, and their departure can lead to the rapid decline of community involvement in control measures. These two aspects of sustainability are likely to become of increasing importance in the coming years and should be made the subject of research by behavioural scientists.

### 9.2 Individual behaviour

In all endemic areas of lymphatic filariasis, a useful individual contribution to control is the prompt seeking of drug treatment by patients at the earliest stages of noticeable symptoms and signs, in areas where organized drug administration programmes do not exist. The process is greatly facilitated by education campaigns to increase individual awareness of filariasis, and by ensuring that primary health care workers recognize the disease and have adequate supplies of drugs to treat it. Examples of individual vector control action are given in Table 4.

#### 9.2.1 *Anopheles* transmission areas

A potentially valuable individual control activity in *Anopheles*
transmission areas is the use of impregnated bednets, curtains, screens, etc. in areas where there are no organized community-wide programmes of bednet use for malaria control. The Anopheles vectors of both W. bancrofti and B. malayi are largely endophilic and endophagic, and mainly nocturnal, and hence conscientious use of impregnated bednets or impregnated curtains and screens could be a valuable method of personal protection from infection. However, it must be stressed that the value of these individual interventions is purely theoretical at present, and careful, controlled trials of the method are urgently needed.

9.2.2 Culex transmission areas

Again, the use of impregnated bednets could be a powerful tool for personal protection, particularly since the perceived biting nuisance of C. quinquefasciatus is greater than that of Anopheles species. Individual contributions to breeding-source reduction in the peridomestic environment are potentially valuable.

9.2.3 Aedes transmission areas

Aedes vectors of lymphatic filariasis bite mainly by day and out of doors; the nocturnal, endophilic and endophagic accessory vectors, A. fijiensis and A. samoanus play only a minor role in transmission in localized foci in the Pacific, and impregnated bednets, curtains and screens would only be of possible value in areas where these two species are highly prevalent. Covering domestic water tanks and water-storage containers, removing discarded tins, jars, tyres, and coconut shells, and general peridomestic cleanliness could contribute to source reduction.

9.2.4 Mansonia transmission areas

Although most biting is daytime and outdoor, impregnated bednets would be a useful auxiliary tool in vector control. The wearing of appropriate protective clothing and the weed-free maintenance of domestic ponds are other examples of useful individual control behaviour.

9.3 Community behaviour

Community participation in its broadest sense may be defined as a dynamic process in which people are consciously engaged in planning, implementing, monitoring and evaluating activities which affect their lives; in a narrow sense community participation in disease control may be defined as the process by which individuals and families assume responsibility for their own health and welfare and for those of the community.

The degree of participation achieved in a control programme could be grouped into four major classes:

1. *Active participation*, where the community recognizes the problem,
designs the programme with or without the help of an expert group, and plays an active role in implementation and evaluation of the programme.

2. *Passive participation or acceptance*, where the community simply cooperates with the programme. The extent of such participation depends on the awareness of the problem, the beneficial effects of the programme, the methods used for achieving participation, the literacy rate and the economic conditions of the people.

3. *Passive resistance*, where people, being afraid of open defiance, passively resist by non-cooperation. It has been observed that when survey teams visit an area for night-blood surveys many residents lock their houses, accept tablets but do not consume them, refuse to provide blood specimens for surveillance, etc.

4. *Active resistance*, where people perceive some deleterious effect of the programme and vehemently oppose it. Fear of AIDS has drastically reduced cooperation of the population when blood-taking is involved. In some cases, people refuse to swallow tablets given by health workers owing to the mistaken idea that they are meant for birth control.

Community participation has considerable potential to contribute to vector-borne disease control, especially to source reduction in urban areas and reduction of human-vector contact by adoption of personal protection measures or acceptance of antiparasitic or antivector measures. This can happen only when centralized programmes are willing to share their authority with the people.

True sustainable participation is possible only when the present trend of “top-down” planning is reversed to “bottom-up” planning and when decision-making power is handed over to the community. The basic requirement of community participation is that the people should be involved in conceiving, planning, implementing, and evaluating all developmental programmes.

### 9.3.1 *Anopheles transmission areas*

Community participation in filariasis control in areas of *Anopheles* transmission seems to be confined to well-documented studies of drug administration on a community basis, using volunteer village workers, from the Coast Province of Kenya and from the island of Flores, Indonesia. The latter programme was based on the distribution of drug by motivated villagers to heads of households weekly for 18 months, as well as prompt treatment by these motivated persons of all newcomers and of villagers who, in the consolidation phase, developed signs of acute filariasis. With this programme, microfilaria rates and densities were brought to a very low level, and important reductions in both acute disease episodes and signs of obstructive disease were achieved.

Impregnated materials and residual house-spraying, as employed in malaria control, may also be valuable in *Anopheles* transmission areas.
9.3.2 *Culex transmission areas*

Most *Culex* transmission of *W. bancrofti* occurs in cities, towns, or very large villages. Most of the vectors’ breeding habitats are man-made. Examples are given from Africa, China, and India.

*Africa.* Lymphatic filariasis has not been identified as a major public health problem by many countries of the African Region. The disease is, however, recognized as a priority problem in parts of countries such as the Comoros, Kenya, Madagascar, and the United Republic of Tanzania. In some of these countries district management teams have organized and coordinated successful vector control activities. Such programmes as the Makunduchi project in Zanzibar for control of *Culex* breeding with polystyrene beads have enjoyed the enthusiastic support of the community. The integration of such control programmes into other disease-control activities (e.g. malaria) has been successful, but a more comprehensive integration into the general health services has been limited by lack of resources. The Makunduchi project has also given rise to the phenomenon of “auto-surveillance”, whereby a local breakdown of control due to construction of new latrines or flooding is recognized at once by the community as a result of the immediately noticeable dramatic increase in mosquito biting.

*China.* In order to improve environmental sanitation and control of mosquito vectors, a Patriotic Health Movement Committee has been organized from national to county level to reduce mosquito breeding sites by improving environmental sanitation and to promote people’s participation through health education. Village leaders, primary health care workers, and villagers have worked together not only in the elimination of mosquito breeding sites but also in organizing the distribution of DEC tablets and DEC-medicated salt.

*India.* A filariasis control programme was launched in Pondicherry in 1981, placing emphasis on community participation and intersectoral collaboration. Individuals were asked to refrain from throwing garbage into drains or from building any structure over the drains, to seal hermetically septic tanks, water tanks and unused wells, to drain any water that collected in containers, and to get town planners’ approval for the construction of houses. The impact of the integrated vector control programme on prevalence of disease as well as on vector density was remarkable.

9.3.3 *Aedes transmission areas*

In Fiji, community participation is part of traditional village life and hence an essential element of a mass DEC-administration programme currently being carried out in the country. The success of the programme hinges upon public health education at the local community level in relation to filarial infection and its transmission and treatment, and on the selection by village committees of the villagers who are responsible for drug distribution.
9.3.4 *Mansonía transmission areas*

Though *Mansonía*-transmitted *B. malayi* infection is on the decline in India, it still continues in a few pockets in the country, particularly in the Shertallai area of Kerala State. This area, sandwiched between a large natural lake and the Arabian Sea, is highly waterlogged, with numerous canals and ponds in which weeds such as *Pistia*, *Eichhornia* and *Salvinia* proliferate. These weeds, which support the breeding of *Mansonía* mosquitoes, are periodically cut and used as green manure for coconut trees, the major local crop. Attempts to mobilize the people to remove the weeds were unenthusiastically received, since the population did not wish to lose its source of fertilizer. To provide an acceptable incentive for weed removal, fish culture was introduced into the area. Fingerlings of fast-growing edible fish were distributed free of cost to those who de-weeded their ponds. The obvious economic gains to be made motivated the community to undertake fish culture in private ponds, thereby making these water bodies free from vector breeding. To sustain the programme many commercial banks were approached to provide loans for the inland fisheries. To provide an alternative source of green manure, *Crotalaria juncea* (sunn hemp) and *Sesbania aculeata*, two leguminous plants well known for their nitrogen-fixing ability, were popularized in the area. To make the programme sustainable without external agencies, various organizations such as the Filariasis Patients' Association, and a filaria control (FILCO) movement were started among volunteers in the community. FILCO volunteers collect night-blood smears and distribute DEC tablets.

9.4 *Socioeconomic aspects*

The full spectrum of social and economic effects of lymphatic filariasis has not been systematically assessed or quantified. It is clear, however, that filariasis is almost entirely a disease of poor communities. Slum dwellers with inadequate housing and no basic sanitation are at highest risk of infection with *W. bancrofti* transmitted by *C. quinquefasciatus*, and it is the rural poor who are affected by filariasis transmitted by other species. Despite this association with poverty, there is only one study, in the Philippines, which has successfully linked an income or "wealth" variable inversely with prevalence.

Some economic activities such as the processing of coconut fibres in ponds and the accumulation of discarded coconut shells are known to provide important vector breeding sites and to facilitate transmission of *W. bancrofti* in India. Conversely, the spread of rice-farming into marshy land in Indonesia reduced the breeding sites available to *M. uniformis*, leading to reduced transmission of brugian filariasis. Rural-urban migration and uncontrolled urbanization resulting in crowded living conditions and inadequate water and sanitation facilities also favour the spread of *W. bancrofti* infection in areas where *C. quinquefasciatus* is a vector.
Studies in endemic communities in French Polynesia, Malaysia, the Philippines, and the United Republic of Tanzania have shown that people are aware of the chronic manifestations of lymphatic filariasis but that the association between mosquitoes and the disease is very poorly understood. In the Philippines there was an awareness that certain tasks, such as farming, abaca stripping, and fishing, were associated with risk of developing chronic signs of disease but the role of mosquitoes or vectors was not known.

Acute filarial attacks account for a significant loss of productive days of work. Attempts to quantify their impact on productivity have been made in India and in Flores, Indonesia; the data from India are shown in Table 5. There is inadequate understanding of the social stigma and psychological effects resulting from chronic disease, but more severely affected people are probably socially restricted as well as physically burdened. Indirect economic losses result from social or physical confinement of people with large hydroceles and advanced elephantiasis, and from working-days lost when hydrocele operations are performed. Information from the Philippines and the United Republic of Tanzania indicates that individuals may incur significant costs relating to treatment for hydrocele and that this can be a disincentive to seeking medical care. The costs incurred by the health care system can also be substantial; in 1976, 15% of all major operations in one district hospital in the United Republic of Tanzania were for hydrocele.

The levels of coverage and compliance by communities over a number of rounds of mass or selective DEC chemotherapy have varied widely between programmes and may depend on a range of factors related to the social and economic environment, including people's knowledge and

Table 5

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<th>Bancroftian filariasis</th>
<th>Brugian filariasis</th>
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<td>(a) Total population</td>
<td>372 000</td>
<td>435 000</td>
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| (b) Number of working population (20–58 years only)
  | 161 076                | 188 355            |
| (c) Disease rate in working population
  | 11.51%                 | 9.57%              |
| (d) Total number of diseased persons of working age
  | 18 540                 | 18 025             |
| (e) Frequency per year of acute attacks resulting in loss
  | 4.47                   | 2.20               |
| (f) Duration of each attack in days
  | 3.90                   | 4.05               |
| (g) Number of working-days lost per case (e x f)
  | 17.43                  | 8.91               |
| (h) Total working-days lost per year (d x g)
  | 323 205                | 160 603            |
| (i) Official minimum daily wage (in rupees)
  | 24.00                  | 24.00              |
| (j) Economic loss in a year (in rupees) (h x i)
  | 7 756 913              | 3 854 466          |

*a Reproduced (with the original figures) from: Proceedings of a seminar on future research needs in lymphatic filariasis, 8–10 October 1990. Pondicherry, Vector Control Research Centre, 1990: 47.

*b Calculated from age distribution data of Registrar-General of India.
experience of the disease and of its prevention and treatment; social and economic characteristics of the population; views regarding its severity, including fears and stigma associated with the disease; and side-effects resulting from administration of the drug. Several of these factors also apply to vector-control measures. Further study is needed to ascertain which social determinants are important for the development of the most appropriate treatment regimens.

Since DEC is relatively cheap, drug administration costs and, in the case of targeted programmes, the costs of blood-sample collections and examination make up the bulk of the expenditure of an active chemotherapy programme, and the level of compliance will to some extent affect the costs of control by influencing the need for repeat cycles of mass or selective treatment. Trials are needed to determine the cost-effectiveness of different treatment regimens and to compare those of a traditional nature with alternatives such as the distribution of DEC-medicated salt, single-dose regimens, and community participation.

9.5 Suggestions for further study

1. Studies should be conducted to identify the psychological and social impact of evident chronic filarial disease on individuals and on knowledge, attitudes, and practices within endemic communities and to assess the priority given to filariasis by the community.

2. The public health significance of lymphatic filariasis should be quantified, including loss of income due to acute attacks and chronic disease as well as the direct costs of medical care to individuals and health care systems.

10. Organization of control programmes

Successful programmes for the control of lymphatic filariasis are based on a thorough understanding of the distribution and dynamics of the disease in the targeted populations. The diverse demographic, environmental, and socioeconomic characteristics of communities in endemic foci of lymphatic filariasis, as well as differences in vector, parasite and disease parameters, do not permit a simple, uniform approach to control that is applicable in all or most situations. Each control programme must be tailored to the unique circumstances of the particular affected population and its environment and ecology.

10.1 Administrative structure

Except in countries in which lymphatic filariasis is endemic in only one or two administrative areas, a national programme for control is required. The head of this programme is responsible for developing a national strategy for control, establishing a budget to support the required control activities, maintaining the administrative structure, and facilitating the
integration of activities at the national level, including links with other sectors (medical services, environmental agencies, public works, etc.) and with representatives of the public and international agencies. Filariasis control programmes are usually located within the national services for the prevention and control of communicable diseases and thus operate within a structure that reaches down to provincial, state, and local government levels. Specialized field survey and control teams are used to implement control-programme activities at the community level.

10.2 Control programme elements

10.2.1 Situation analysis

A thorough review and analysis of existing information on the distribution and determinants of filariasis, supplemented by information gathered in special surveys, is needed as a baseline (a) to establish the magnitude of the problem and its public health importance, including the socioeconomic impact; (b) to establish the environmental, vector, parasite, and human factors contributing to the dynamics of the disease; and (c) to identify populations of high priority and determine the crucial risk factors.

10.2.2 Resources inventory

The programme coordinator must inventory personnel, facilities, equipment, and supplies; evaluate surveillance and epidemiological, laboratory, and health care (especially primary health care) support services; and identify sources and amounts of budgetary allocations.

10.2.3 Control strategy development

This is based on the situation analysis and resources inventory and involves a decision on the major programme objective – i.e. whether it is (a) the control of morbidity or (b) the elimination of the parasite reservoir. Reduction of morbidity is directly achieved by chemotherapy and indirectly by reducing transmission and protecting persons from infective exposures; elimination of the parasite reservoir may be achieved (except in areas where the infection is a zoonosis) by a prolonged mass chemotherapy campaign or, in certain circumstances, by interruption of transmission through vector control.

In most endemic areas, the objective is to reduce morbidity and to control filariasis as a public health problem. However, no objective criteria have yet been defined to suggest a level to which the morbidity or the microfilaria rate and density should be decreased so that filariasis no longer constitutes a problem of public health importance.

The elimination of the parasite reservoir is the ultimate objective of some control programmes. However, given the longevity of the adult worms and the limited human and financial resources in most endemic countries, it may be unrealistic in many situations 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.

Methods of control include chemotherapy (see section 8.3), vector control (see section 6.3), and protective measures that reduce human-vector contact (see section 9.2). The best approach in many situations is a programme of integrated control that employs two or more methods and fully utilizes community participation (see section 9.3).

10.2.4 Control implementation

Once communities have been selected for control activities, and strategies have been selected appropriate to these communities, the implementation phase is initiated. The organizational structure of the programme is worked out in detail, personnel and logistic requirements are identified, and detailed cost estimates are made. Clear operational targets, such as percentage treatment coverage of the target population within a given period of time, need to be set for all intervention activities. Organization of filariasis control often involves the use of teams or team supervisors from the central filariasis control programme working with and through the primary health care system, and with the support and active participation of the community, to undertake such activities as health education, drug administration, environmental sanitation, and vector suppression (see also section 7.1.4).

10.2.5 Monitoring, evaluation, and surveillance

Monitoring involves the continuous collection and analysis of routine data to provide feedback for the management of programme activities. For instance, regular accounts of the number of DEC tablets used may be helpful in indicating sudden changes in programme performance. However, even when the control operations are running smoothly, a programme may not necessarily be achieving its objectives and special efforts may be needed to evaluate the epidemiological impact of control. This may involve longitudinal parasitological surveys in selected indicator populations to measure changes in levels of parasitaemia and morbidity or entomological evaluation of the decline in transmission levels (see section 7.1.4). When the parasite reservoir has been so drastically reduced as to allow the cessation of control activities, a programme of surveillance will have to be instituted to ensure that the decision to stop control was correct and that there will be no recrudescence of the disease thereafter. Long-term surveillance of treated communities is costly and problematic at present, since it is not known for how long such surveillance needs to be maintained (see also section 6.4.4).
10.3 **Suggestions for further study**

1. The component costs of existing filariasis control programmes, including their various vector control and chemotherapeutic elements, should be measured and used for determining the relative costs of alternative strategies.
2. Simple and cost-effective control strategies should be developed and tested that are appropriate for, and can be sustained by, the health services of different endemic countries.

11. **Coordination at the intercountry, regional, and global levels**

Technical cooperation between countries with endemic filariasis provides a means of initiating, designing, organizing, and supporting control programmes. Exchange and sharing of information and knowledge through this mechanism can be of mutual benefit. Where filariasis foci overlap national boundaries or where there is regular migration between countries, the countries concerned should coordinate their control programmes. In certain cases, intercountry organizations such as the South Pacific Commission offer a mechanism for coordinating control activities between neighbouring countries. Liaison between individual countries and between groups of countries is needed for exchange of technical data and for ensuring that control methods and principles are up to date.

At the regional and interregional levels, organization of meetings and other training activities, research, and exchange of scientists should be promoted. There is a need at the global level for international standardization of control criteria and of technical methods for comparative evaluation of different control methods. Specific mention has been made in the report of standardized research protocols for evaluation of the use of *B. sphaericus* for vector control and of the need for standardized clinical and field trials of chemotherapeutic agents against filariasis.

12. **Training and human resource development**

Although the strategies and methods used in filariasis control operations vary from country to country, any such control programme will need to deploy a large number of field and laboratory workers. Proper training to develop job skills at different levels is therefore a prerequisite; it should be given by trainers with practical field experience. The training activities described below are needed to ensure the availability of human resources and the success of control programmes.

1. **Physicians and other medical personnel**: in endemic areas, physicians should be trained to recognize the clinical features of the disease and to
treat patients. The subject of filariasis control should be included in the curricula of medical schools and paramedical teaching institutions in endemic countries. Refresher courses, with special reference to diagnosis and treatment of filariasis, should be organized periodically for physicians.

2. **Community health workers** should be trained to identify suspect cases and to refer them to a physician, who can arrange for laboratory diagnosis and provide treatment.

3. **Laboratory technicians** require specific training in filariasis microscopy.

4. **Entomologists** assigned to collaborate in the filariasis control programme need special training courses to become familiar with the programme's activities.

5. **Field workers**, including vector control personnel, should be trained in appropriate control activities.

6. **Epidemiologists and statisticians** in control programmes need to be trained in monitoring and evaluation methods and in advanced epidemiological techniques such as computer simulation modelling.

7. **Sociologists** should be trained in educating and motivating the community to ensure the successful implementation of programmes.

National training courses are particularly recommended since local circumstances are recognized by both the participants and the trainers, large groups of staff can be reached, and the courses can usually be organized at relatively low cost. Assistance to national courses may be available through bilateral and international collaboration. WHO is in a good position to identify countries, or small groups of countries, interested in such collaboration.

International training courses on filariasis, held in endemic areas, should also be encouraged to provide a greater focus on global problems of filariasis.

The WHO publication *Control of lymphatic filariasis: a manual for health personnel* (3), which describes the planning, management, and conduct of control programmes, is recommended for use by workers at all levels.

13. **Recommendations**

1. There is an urgent need for studies that will help to determine the public health importance of lymphatic filariasis in different endemic countries. These should include investigations of the psychological and social impact of the disease as well as of its economic consequences.

2. Efforts should be made to collect more information — especially from Africa — on the distribution and prevalence of lymphatic filariasis and its vectors.

3. Longitudinal observations need to be made that will yield further
insight into the natural history of filarial infection and disease and how these may be altered by treatment.

4. Efforts should be made to identify differences in immune responses between individuals and populations with distinct clinical manifestations of lymphatic filariasis in order to develop predictive markers of disease development and to define the mechanisms and dynamics of the disease process. Such information could be used to develop rational strategies for disease control and prevention by immunological interventions.

5. Studies should be carried out for all vector-parasite combinations in order to determine the critical prevalence and intensity levels at which active control could be stopped.

6. It is important to develop and test simple and cost-effective control strategies that are appropriate for, and can be sustained by, the health services of different endemic countries.

7. The use of DEC-medicated salt as a control strategy should be considered in many endemic areas, and methods to increase its availability (for instance, by commercial manufacture and distribution) and evaluate its acceptance should be encouraged.

8. Continued support is recommended for research and training activities carried out by or through WHO, including those of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases.

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References


Annex

Summary of the distribution of human lymphatic filariasis and its vectors, by WHO region

Key to abbreviations:
- B.m.p. = *Brugia malayi*, periodic
- B.m.sp. = *B. malayi*, subperiodic
- B.t. = *Brugia timori*

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1 For the African Region, there is no detailed information available on the relative importance of the various vectors of the only known parasite, *W. bancrofti*. *Culex quinquefasciatus* is known to be the only vector in the Seychelles, and in the cities, towns and large villages of East Africa and the islands off the East African coast. Over the rest of the region, *Anopheles* spp transmit *W. bancrofti*. In most areas, *A. gambiae* and *A. funestus* are the most important vectors, but locally *A. arabiensis* is the principal vector. In limited brackish water areas on the West African coast, and in tidal reaches of rivers such as those of the River Gambia, *A. melas* is locally important. In the region of Tanga on the coast of the United Republic of Tanzania, the brackish-water breeder *A. merus* has been shown experimentally to be an efficient vector and to play a significant role in transmission in a number of villages.
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