

Review

Epidemiology and immunopathology of bancroftian filariasis

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ABSTRACT – Human lymphatic filariasis affects 120 million people worldwide. Although the disease is considered to be potentially eradicable by the World Health Organization, comprehensive studies on epidemiological aspects as well as mechanisms of pathology development are still premature. The following review summarizes currently available data on these topics and ends by discussing the latest control strategies. © 1999 Éditions scientifiques et médicales Elsevier SAS

bancroftian filariasis / disease control / immunopathology / epidemiology / diagnosis

1. Introduction

Human lymphatic filariasis, which is caused by the helminths *Wuchereria bancrofti* (90% of cases) and *Brugia malayi* (10% of cases), affects approximately 120 million people, with one billion people considered to be at risk of becoming infected [1]. It is found in 76 countries through regions of South and Central America, Central Africa, Eastern Mediterranean, Southeast Asia and Western Pacific.

Infection with *W. bancrofti*, which will be the focus of this review, occurs with the bite of a mosquito (i.e., *Culex*, *Aedes*, or *Anopheles*) carrying the infective third-stage larvae (L3). The larvae mature over a period of months into lymphatic-dwelling adult worms which mate and release microfilariae into the host's blood stream, ready to be passed by a blood meal to the mosquito.

In the mosquito, infective larvae range from 0.8 to 1.5 mm. Due to their significant size, it carries only a limited number of larval parasites while feeding on a prospective host [2]. Therefore, exposure to infective larvae must be intense and prolonged for infection to occur [3].

One peculiar characteristic of these lymphatic-dwelling parasites in most of the world is their nocturnal periodicity. During the day, the microfilariae sequester in the lungs, and at night they spread through the blood circulation, peaking between the hours of 11:00 p.m. and 1:00 a.m. [4]. In certain areas of the world, though, microfilariae of either *W. bancrofti* or *B. malayi* can be found during the day, being considered subperiodic.

Bancroftian infections are characterized by a wide range of clinical manifestations. The majority of individu-

als develop microfilaremia but remain clinically asymptomatic for years. In all endemic areas, a proportion of those individuals may never become symptomatic. When individuals go on to develop clinical disease, it ranges from episodic attacks of adenolymphangitis associated with fever to largely irreversible manifestations such as hydrocele, lymphedema, elephantiasis, and chyluria. In rare instances, infected individuals may develop tropical pulmonary eosinophilia, which is characterized by nocturnal cough and wheezing, low-grade fever, adenopathy, and high-grade eosinophilia [5]. Although mortality is not associated with the disease, morbidity due to these clinical manifestations is highly significant [6]. In addition to time and wages lost from work, the resulting deformities have severe psychosocial impact [7].

2. Epidemiology of bancroftian filariasis

2.1. Global prevalence

Lymphatic filariasis is considered one of only six potentially eradicable diseases by the World Health Organization (WHO). In order to achieve this goal, reliable information on the prevalence and intensity of transmission in all areas where the disease is present is fundamental, but not always available.

Based on data derived from published community-based studies, and using a careful methodology which extrapolated individual study prevalences to larger populations, Michael et al. recently estimated the total number of *W. bancrofti* infections to be 73 million, with the total number of cases (infection and chronic disease combined) to be approximately 106 million [1]. When separated according to regions defined by the Global Burden of Disease (GBD), the larger number of cases were, expectedly, found to occur in India (45.5 million) and sub-

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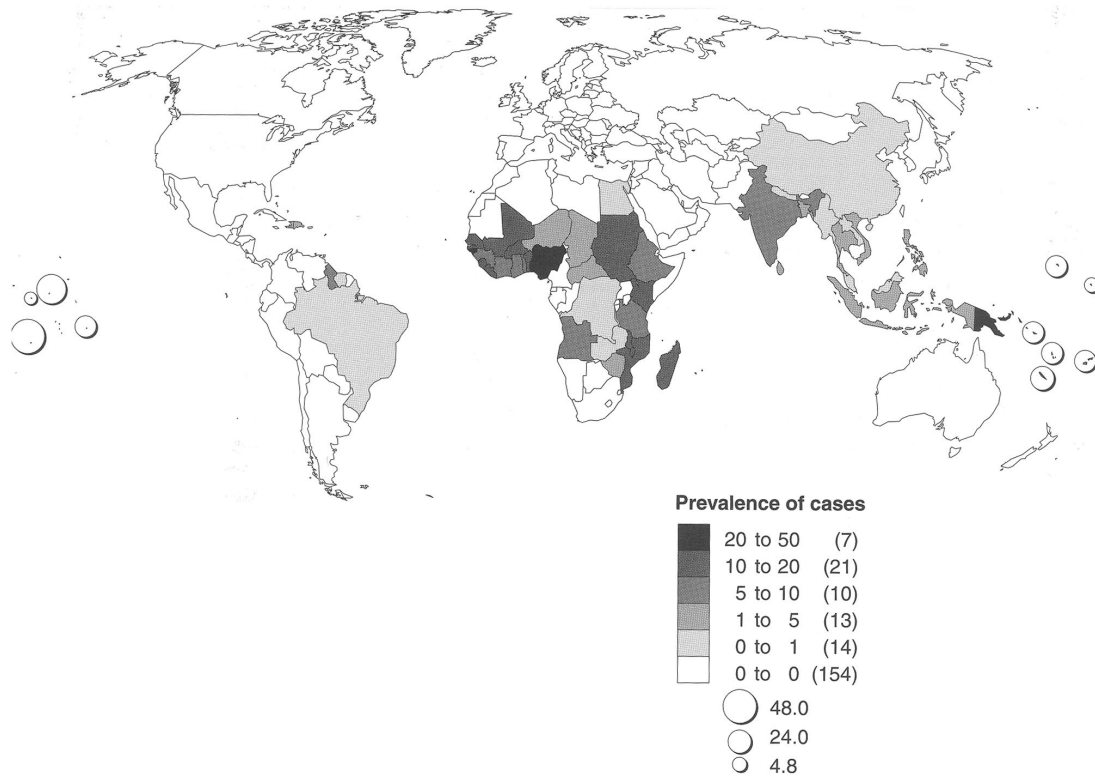


Figure 1. Geographical distribution of bancroftian filariasis case prevalences (%) based on the crude global burden of disease estimates. Different sized circles denote the corresponding prevalences estimated for various Pacific islands. The numbers in brackets indicate the number of countries. Reprinted from *Parasitology Today*, 13, Michael E., Bundy D.A.P., Global mapping of lymphatic filariasis, 472-476, 1997, with permission from Elsevier Science.

Saharan Africa (40 million), with prevalences of 5 and 8%, respectively [1] (*figure 1*). With the largest numbers of countries with moderate to high prevalence, and a potential underestimation of these prevalences due to the current lack of data on the incidence of disease in several countries, sub-Saharan Africa poses as the region where the disease is of greatest public health significance [1]. These findings contrast the previous estimate from WHO which suggested that a significant majority of filarial infections and disease cases occurred in India [8]. Another important region in number of cases is the 'Other Asia and Islands', defined by the GBD as Asia, excluding China, India, and Pakistan, including the Pacific Islands. This region has the largest variation in prevalence with the highest prevalences of the disease occurring in Papua New Guinea (72%) and the Republic of Togo (48%). In contrast, Latin America and Egypt have the lowest prevalences. With access to this information, a global mapping of the disease has provided better assessment of spatial patterns in the infection and disease distribution [1].

2.2. Intensity and efficiency of transmission

In order to accurately assess intensity of transmission in lymphatic filariasis, one would ideally measure the rate of acquisition by an individual, of sexually mature adult worms, regardless of whether or not these worms were mated or fecund [9]. One approach to this goal would be the development of highly sensitive probes to detect spe-

cies and stage-specific circulating antigen. Such a technique has been recently made available by detection of adult circulating antigens in serum or whole blood (discussed below), but no large-scale epidemiological studies have been performed yet. Therefore, available data on intensity of transmission relies primarily on the appearance of new cases of microfilaremia, which implies the presence of mated, fecund female worms [9].

Based on formulas created by Walsh and colleagues to express entomological parameters of infection in onchocerciasis, the terms 'annual biting rate', 'annual infective biting rate', and 'annual transmission potential' have been adopted by the WHO to also describe these parameters in lymphatic filariasis [10]. Based on these assessments, high transmission generally correlates with severity of disease [9, 11]. Important issues should be considered when using these parameters: for instance, transmission efficiency is known to be higher in Africa when compared with Asia and Oceania, and this difference is generally correlated with the different vectors responsible for disease spread in these distinct geographical locations. In general, *Anopheles* spp. transmit disease much more efficiently than *Culex* spp., although there are exceptions to the rule [9].

It is also important to consider that, in certain endemic areas, the dynamics of transmission efficiency can be drastically changed when communities implement mass treat-

ment as a means of disease control. In this situation, reduction in transmission will diminish peak intensity of the disease. However, it has been suggested by Anderson and May that it could also delay the onset of immunity and move the peak intensity into an older age class [12]. By means of mathematical models, Michael and Bundy conclusively showed that infection patterns in bancroftian filariasis correlate with the occurrence of an effective herd immunity in endemic communities, and that the effect of this immunity is greater and occurs earlier in areas of higher mosquito biting rates [13]. These findings have great implications in the implementation of appropriate strategies of disease control and will be discussed below (see 'Treatment and control of bancroftian filariasis' below).

2.3. Infection and disease

A recently developed mathematical model (EPFIL) by Chan and colleagues has been designed to quantify the relationship between adult worm population dynamics and morbidity [14]. The model is derived from the simple assumption that worms cause damage to the lymphatic system and thus progression to disease. Prevalence of both lymphedema and hydrocele is suggested to be related to past experience of worms and the damage they cause. Due to anatomical differences, the prevalence of lymphedema was shown to increase very slowly with age, while that of hydrocele was shown to appear earlier in life and increase at a much higher rate [14]. Their analysis suggests the presence of a partially protective acquired immunity, resulting in a reduced rate of establishment of new infections, but fails to show involvement of the immune system in the development of disease pathology, which would argue against the involvement of CD8⁺ T cells and specific T-cell receptors in development of pathology, as has been recently found (see 'Immunopathology of lymphatic filariasis' below).

2.4. Age and sex

In general, the mean prevalence of filarial infection is lower in females when compared with males. The question of whether this difference is related to lower exposure to the parasite or to immunological differences has divided the opinions of many investigators, but the available data appears to support the latter idea. A review of 53 epidemiologic studies from different parts of the world in which gender susceptibility was examined showed that this difference is only apparent in the women's reproductive years, suggesting a pregnancy-associated mechanism [15]. In these studies, chronic disease has also been found to be higher in males, but mostly due to the high numbers of hydrocele, which, as mentioned above, is likely to be related solely to anatomical size of the organ being affected [14]. Peak microfilaria rates are usually found in teenagers and young adults, with the reduction of those rates in older individuals likely to be correlated with acquisition of immunity. However, when levels of adult circulating antigenemia were measured in an endemic population in Haiti, they seemed to slowly but steadily rise with age, suggesting a slow, but significant acquisition of infection in adults [16].

2.5. New tools for diagnostics

An accurate diagnosis of lymphatic filariasis and therefore an accurate estimate of disease prevalence is of extreme importance in the implementation of control programs at the community level.

The most widely used diagnostic technique has been the detection of microfilariae in peripheral blood by microscopic examination of thick smear, due to its relative simplicity and low cost. However, with the nocturnal periodicity of the nematode in most parts of the world, which requires late night examination for best results, and the very small amount of blood usually collected, this technique commonly fails to detect low levels of microfilariaemia. Membrane filtration of venous blood is usually a more sensitive technique. However, it is more time consuming, usually requiring well-trained personnel to perform the filtration and read the results, and still poses an inconvenience to communities where the disease has a nocturnal periodicity. Aside from these parasitological techniques, clinical diagnosis is also routinely used, but is often times insensitive, nonspecific and cannot distinguish between active and past infection.

In the past few years, the challenge to find a diagnostic test which would be simple, more sensitive, and cost effective resulted in new methods for diagnosis of bancroftian filariasis, a few of them, very promising. With the advent of PCR, development of species-specific primers for detection of parasite DNA in blood samples as well as in infected mosquitoes has shown conflicting results. Sirdewa and colleagues showed a slight increase in sensitivity when the PCR method was compared with routine microscopic examination (thick smear) of individuals from an endemic area [17], with the finding that a few endemic individuals, negative by thick smears, were positive by PCR and later on confirmed to be positive by night blood filtration. A decrease in sensitivity was reported by Williams and colleagues, with their primers being unable to detect *W. bancrofti* DNA in 14 out of 17 individuals whose microfilaria counts by membrane filtrations were lower than 10 mf/mL [18].

Recently, detection of circulating filarial antigens has been making the transition from the laboratory to the field with great success [19]. Two commercially available tests, with distinct methodology, have proven to be very sensitive and species-specific. They have the advantage of using finger-prick blood or serum collected at any time of day and of detecting adult filarial antigens, exposing a population who had been previously considered to be uninfected, but who in fact harbor either single sex or infertile mature filariae. The *W. bancrofti* antigen test based on the monoclonal antibody Og4C3 (TropBio), is an antigen-capture ELISA which has been well received in field studies. The majority of the field studies comparing the Og4C3 ELISA with the commonly used parasitological diagnostics have shown the sensitivity of the former to be of 94–100% when compared with the latter [20, 22]. More importantly, these studies showed that i) a much larger percent of individuals in an endemic community currently harbor active infection, despite the fact that they are amicrofilaraemic; ii) it dispelled the long-held concept that individuals with clini-

cal disease are no longer infected, since some of these studies show that 15–60% of these individuals in Brazil, Tahiti and Haiti are in fact actively infected. Only one study has reported that, although the test can be 100% sensitive when individuals have > 30 microfilariae per mL, the sensitivity goes down in individuals with ultra-low microfilaria densities (< 1mf/mL) [23].

Another diagnostic method which also detects adult antigen in serum or whole blood is the ICT filariasis card test. It uses reverse chromatography technique to trap the free antigen and antigen-antibody complexes to a monoclonal filarial antibody (AD12) which is bound to nitrocellulose. A colorimetric detection shows a pink line when the test is positive. The method was first evaluated independently by three laboratories with frozen serum from various locations. Similarly to the results obtained with the Og4C3 ELISA, the card test gave positive results (96–100%) when compared with sera from microfilaremic individuals. When tested in the field in Recife, Brazil, the test presented 100% sensitivity when compared with parasitological tests, and 95% sensitivity when compared with the Og4C3 ELISA [24]. The advantage of the ICT card test over the Og4C3 ELISA is the fact that samples can be read almost immediately, with no technical difficulty, which may enhance control community compliance where implementation of control strategies is needed.

3. Immunopathogenesis of bancroftian filariasis

Human lymphatic filariasis is clinically a spectral disease. The pathogenesis of the characteristic lymphatic damage is thought to involve three components: mechanical damage by motile parasites [25, 26]; bacterial superinfection in previously damaged vessels [27]; and local immunological responses to parasite antigen [28]. The relative contribution of each of these components is poorly defined, but the literature on the immunological aspects of the disease is by far the best characterized and will be discussed below.

Up until recently, when researchers have studied the immunopathogenesis of the disease, only individuals at the two opposite clinical poles have been carefully examined. These individuals have usually been grouped as follows: at one pole, there have been those with asymptomatic microfilaremia, who manifest relative *in vitro* immunologic hyporesponsiveness to filarial antigen [29], and at the other pole, those with chronic pathology, characterized by hydrocele or chronic lymphedema, who have either been assumed to be amicrofilaremic or specifically chosen for being no longer infected. These latter individuals have relatively increased filarial antigen-specific lymphocyte blastogenesis, T- and B-lymphocyte precursor frequency, and serum IgG levels compared with asymptomatic microfilaremic individuals [30, 32].

3.1. Redefining patient classification

The concept that chronic pathology is uniformly associated with amicrofilaremia has been dispelled by a recent metaanalysis of 25 studies done between 1945 and 1982, which shows that, in fact, individuals with lymphatic

filariasis, with or without microfilaremia, are equally likely to have clinical manifestations of disease [33]. Moreover, recently developed CAg assays, which detect the presence of viable adult *W. bancrofti* parasites, and are more sensitive determinants of active infection [19], have helped define a more precise classification of patients with chronic disease. For instance, with the use of these techniques, it has been possible to determine in studies in Haiti, Tahiti, and Brazil, that 15–60% of individuals classified as having chronic pathology are actively infected [20, 22]. Therefore, these individuals form a heterogeneous group based on their infection status, so a new patient classification which takes into account both infection status and clinical status has been suggested.

With the recent advances in the use of radionuclide lymphoscintigraphy to examine the lymphatic vessels in individuals with lymphatic filariasis, it has been demonstrated, as expected, that patients with clinical manifestations of the disease have abnormalities in both deep and superficial vessels, as manifested by dermal reflux [22]. With this technique, it was also, and surprisingly shown that, in asymptomatic microfilaremic individuals, abnormal lymphatics are present in 69% of limbs by static lymphoscintigraphy and in 100% of limbs by dynamic flow lymphoscintigraphy. Another technique which is becoming an important tool to visualize adult *W. bancrofti* in the scrotal area of infected individuals is the ultrasound [34]. Observations that abnormal scrotal lymphatic dilation is found in all men who have adult worms, independent of whether they have clinical symptoms or not, along with the lymphoscintigraphic findings have prompted us to re-evaluate the use of the term chronic pathology to characterize individuals with clinical signs of the disease. The term 'pathology' can be defined as the structural and functional changes that result from a disease process, regardless of whether these changes are clinically apparent or not. Therefore, all individuals with lymphatic filariasis have underlying pathology in different degrees of expression. It would be more appropriate, then, to refer to those previously said to have 'chronic pathology' as having 'clinical filariasis', with or without active infection [35].

3.2. Cytokine patterns in filarial patients

By using the bipolar classification, the earliest studies of antigen-specific cytokine production showed that, in general, patients with asymptomatic microfilaremia were unable to produce either IFN- γ or IL-2 and suggested a state of T-cell tolerance to the parasite in this particular patient group [31]. Yasdanbakhsh and colleagues demonstrated that filarial infection was associated with an expansion in IL-4-secreting T cells [36]. She found that peripheral blood mononuclear cells (PBMCs) from nonendemic controls released low levels of IL-4 compared with patients with asymptomatic microfilaremia or clinical filariasis when stimulated with anti-CD2 plus either anti-CD28 or recombinant IL-2. King and colleagues also demonstrated that individuals with asymptomatic microfilaremia showed a predominant type 2 response based on the ratio of the frequency of Ag-specific lymphocytes secreting either IL-4 (type 2) or IFN- γ (type 1) [32]. These findings were discordant with the earlier notion that individuals with asymp-

omatic microfilaremia were hyporesponsive to parasite antigen and showed that these individuals responded by producing a set of suppressive cytokines that could facilitate persistence of the parasite within humans while producing little disease. When individuals with chronic pathology were segregated into those with active infection and those no longer infected, and compared with the microfilaremic individuals, the kinetics of cytokine production by PBMCs upon antigen stimulation segregated with infection status, rather than clinical status [37]. Sustained production of IL-4 and IL-5 beyond the first 24 hours of stimulation was seen only in the individuals with clinical disease who were no longer infected. Moreover, when the frequency of cytokine-producing cells upon mitogen stimulation were examined in individuals classified according to infection status, the authors showed that the frequencies of both IFN- γ - and IL-4-producing cells are significantly lower in actively infected individuals than in those who were no longer infected [38].

Several hypotheses have arisen in attempts to explain this downregulation of the type 1 cytokine response in individuals with microfilaremia. These include differences in host genotype, intensity of infection, and prenatal exposure to specific antigens [39, 40]. Type 2 cytokines, particularly IL-10, have also been implicated in the suppression of both IL-2 and IFN- γ responses, most likely through the ability of this cytokine to inhibit expression of MHC class II molecules on antigen-presenting cells or by inhibiting the expression of certain costimulatory molecules necessary for T-cell activation and proliferation [41, 42].

3.3. Immunopathogenesis at the site of disease

Development of chronic immune-mediated inflammation in humans occurs around the adult worm and is dependent upon infiltration of circulating PBMCs across the endothelial cell lining of postcapillary venules into affected inflamed tissues [35]. However, literature on the role of this immune response at the site of disease is scarce. In one study, immunohistologic examination of local tissue inflammatory responses revealed an abnormal CD3⁺ perivascular infiltrate in 73% of the individuals with clinical disease and in 55% of the asymptomatic microfilaremic individuals [43]. This CD3⁺ infiltrate was composed of predominantly CD8 T cells in the limbs of patients with clinical disease and predominantly CD4 T cells in the limbs of the asymptomatic microfilaremic individuals. Individuals with clinical disease have also been found to have elevated levels of soluble CD8 molecules and of CD8⁺ HLA-DR⁺ T cells in their circulation [44, 45], so this T-cell subset may be important in the pathogenesis of the disease. In another study, Freedman and colleagues found that in sections of skin punch biopsies from filarial patients, vascular cell adhesion molecule-1 (VCAM-1) staining was present on the vascular endothelial surface in individuals with clinical disease, but not in asymptomatic microfilaremic individuals [46]. It was hypothesized that VCAM-1 may preferentially increase transmigration of CD8 T cells which, in turn, could be important sources of local cytokine production. More recently, Freedman and colleagues have found that individuals with lymphatic filariasis, regardless of disease status, have distinct and

limited T-cell populations concentrated in affected tissue, when compared with tissue of normal subjects, with no difference in cytokine expression [47].

3.4. Animal models of the disease

A good understanding of the host/parasite interactions and the exact mechanisms involved in the pathological process have been hampered by the lack of an appropriate animal model in which to study the disease, since the parasite is incapable of completing the life cycle outside the human host. Although the role of the immune response in induction of pathology cannot be assessed in intact mice, studies with athymic (nude) and SCID mice, however, suggest that a large component of the pathological process may not be immune mediated. Studies by Vincent and colleagues using *Brugia pahangi* subcutaneous L3 infection of nude C3H/HeN mice showed that these mice developed adult worms which induced histological changes such as lymphatic fibrosis, lymphangiectasis, and accumulation of macrophages, which were potentially thymus independent [48]. This study was further confirmed and extended in an identical animal model using a subperiodic strain of *B. malayi*, where adult worm infections in these animals caused lymphatic dilation, progressive lymphedema, lymphangitis, and lymphadenitis [49]. Removal of the adult worms caused shrinkage of the affected vessels and, therefore, in the absence of T-cell-mediated responses, the pathological process was reversible. Immune reconstitution of these nude mice with primed spleen cells 21 days after they were exposed to *B. malayi* L3 and developed dilated lymphatics resulted in a progressive buildup of massive lymph thrombi and interstitial infiltrates. Development of these lesions was associated with concurrent destruction of both adult worms and microfilariae, which suggests that the obstructive disease seen in these mice is caused by host cell-mediated and parasitocidal immune response against living worms [50]. Although in these studies pathology was also associated with immune responses toward the microfilaria, the same has never been found in humans.

4. Treatment and control of bancroftian filariasis

It is well documented that the best strategy for reducing both prevalence and microfilarial density in an endemic population is by mass treatment of at least 80% of the population, as opposed to selective treatment of recorded cases. Therefore, for a control strategy to be successful, a number of questions should be carefully considered: How large is the area to be controlled? Does the control plan have political as well as community support? Are individuals from the community involved with the control plan? Is the drug regimen to be applied likely to have high compliance?

Ever since its first synthesis 50 years ago, diethylcarbamazine (DEC) has been the drug of choice and still the only registered drug for treating lymphatic filariasis [51]. It is a potent microfilaricidal drug, which has also been shown to have a moderate macrofilaricidal effect [51]. For decades, the standard drug regimen consisted of a 12-day course of 6 mg of DEC/kg of body weight. Although this

treatment regimen has been efficacious in individual treatments, its long duration and the frequent occurrence of side effects such as fever, malaise, and gastrointestinal problems causes great reduction in treatment compliance, being unsuitable for mass treatment.

More recently, studies carried in the Pacific Islands and Indonesia have found that a single dose of DEC given monthly, semi-annually, or annually can be very effective in reducing both microfilarial density and prevalence, with the advantage of sharply reducing the occurrence of side effects [52]. In Tanzania, a study comparing the standard 12-day treatment with a semi-annual single-dose treatment for a period of one year actually showed a slightly better reduction of microfilaria rates in the community that was given the standard treatment when compared with the rates for the semi-annual dose (81 vs. 70%). However, considering that the semi-annual regimen was much easier to administer, continuation of that treatment for another year would likely reduce the microfilaria rates to equivalent levels of the standard treatment, and therefore, be the treatment of choice (Simonsen et al. *Am. J. Trop. Mest. Hyg.* 53 (1995) 267–272).

Another attractive alternative for mass treatment is the use of 0.1–0.4% DEC-fortified salt. The idea was first introduced in Brazil in 1967, when Hawking and Marques determined that the compound was stable even after cooking [53]. Since then, it has been tried with success in various parts of China, Taiwan, and India [51]. For example, in Shandong, China, the use of 0.24% DEC-fortified salt started in one county where the microfilaria rate was thought to be 9% by thick smear. After six months of treatment and an estimated intake of 7.2 g of DEC, the microfilaria rate decreased to less than 1% [51]. The success of this treatment was an incentive to spread the treatment to other counties and similar results were found in most of them. One important point to be considered in the success of this strategy in these countries is the strict control by health authorities of the salt supplies.

With the finding that ivermectin, a drug which has been used for treatment of onchocerciasis, is also a potent microfilaricidal for bancroftian and brugian infections, new possibilities of more efficacious treatments for lymphatic filariasis have arisen. Importantly, single-dose ivermectin has the advantage of being the only alternative drug for use in communities where DEC is contraindicated. These are areas where bancroftian filariasis coexists with onchocerciasis or loiasis, because DEC can have severe adverse effects when administered to individuals with these diseases. Of clinical importance, ivermectin can also cause adverse effects in individuals with loiasis with high microfilariaemia [54]. Various dosages of ivermectin, ranging from 20 µg/kg to 400 µg/kg have been tested, and it is now accepted that the high dose of 400 µg/kg yields superior results, matching those of DEC treatment.

4.1. Combination therapy

It was recently discovered that although treatments with DEC or ivermectin were efficacious in reducing microfilarial rates, combinations of these drugs have been found to be significantly more effective than each drug alone. Moreover, albendazole, a drug currently used for

the treatment of intestinal helminths, has also recently been found to be an efficient microfilaricidal drug when used in combination with ivermectin or DEC [55]. Experience in community-based settings is so far very limited. In Papua New Guinea, Bockarie and colleagues found that in communities that received a single-dose combination treatment of DEC and ivermectin, there was a reduction in microfilaria density of over 90% after one year of treatment [56]. In communities where only single-dose DEC treatment was given, microfilaria density was decreased by only 70% [56]. Other reports of combination treatment come from small trials at individual levels. In Brazil studies showed that on 12 infected individuals, ivermectin treatment (20 µg/kg), followed by DEC treatment (6 mg/kg) four days later reduced microfilariaemia to 2.4% of pretreatment levels after two years [57]. In Haiti, a similar treatment regimen yielded comparable results [58]. In Tahiti, a study on early microfilarial clearance with the use of ivermectin and DEC suggested an additive effect, with microfilaria clearance occurring between eight and 96 hours after administration of the drugs [59]. In a recent study comparing the effects of single-dose treatment with albendazole, ivermectin, or a combination of the two in Haitian children, the combination treatment proved to be significantly more efficacious than either drug alone, with no increase in severity of adverse effects [60]. Moreover, another study showed that a combination of albendazole and ivermectin gave the best microfilaricidal effect, while albendazole in combination with DEC was the best regimen to decrease antigen levels, although antigen clearance was not achieved [55].

In what appears to be a step forward towards bancroftian filariasis control, Smith Kline Beecham, Inc. has generously agreed to donate large amounts of albendazole to control programs established by individual governments, mirroring Merck's program of ivermectin donation for treatment of onchocerciasis. The good news, however, must be taken with caution, since no mass treatment with this drug has ever been reported.

Free access to drugs such as albendazole is only one amongst a wide range of issues to be overcome when implementing a control program. Control strategies constantly need to be revised in order to incorporate an ever-growing body of information on epidemiological as well as clinical data, and also make use of technological advances in diagnostics. For instance, recently available mathematical models now constitute powerful epidemiological tools for prediction and evaluation of a program's success. These models take into account both human and vector hosts and their complex interrelationship, and can predict the effect of long-term control measures [13, 14, 61]. New diagnostic tools will also have an impact in evaluating the effect and success of control measures. The recent use of circulating antigenemia as a more reliable determinant of active infection has demonstrated that available epidemiological data on infection rates are grossly underestimated [19, 24]. More sensitive techniques will likely show higher infection rates in endemic populations, and more strict implementation of control programs should occur. Moreover, recent findings that clinically asymptomatic individuals who have microfila-

remia actually have compromised lymphatics only accentuates the need for implementation of mass control programs, which would reduce the likelihood of those individuals to develop clinical symptoms [62, 63]. Unfortunately, the complex, multiple-stage life cycle of the organism, along with its ability to downregulate the immune system, suggests that development of a vaccine is improbable, if not impossible.

5. Concluding remarks

A better understanding of the epidemiological and pathological dynamics of the disease can greatly contribute to better control strategies in the fight against lymphatic filariasis. Ultimately, it is likely that every community will implement a strategy which can be adapted to their financial resources and to the degree of community involvement in achieving this goal.

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