LYMPHATIC FILARIASIS

A REVIEW 1862-2002

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First published in 2004

Publisher: Warwick Educational Publishing Inc

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National Library of Australia

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Title: Lymphatic Filariasis: A Review 1862-2002.

ISBN 0-9579788-4-7

Date of Publication: 1st Mar 2004 Price: free

Format: WEB Size: 297x210 No. of Pages: 80

Editor: Deon Canyon
Cover design: Deon Canyon
Cover photos: Jamie Carron (Island Beach) & Deon Canyon (Blood Collection)

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Foreword

This review on lymphatic filariasis by Dr Wayne Melrose has come at an opportune time. The Global Program for the Elimination of Lymphatic Filariasis (GPELF) was launched by the World Health Organization in 1997 as a public/private sector partnership organized as a "Global Alliance", the object being to eliminate lymphatic filariasis as a public health problem by the year 2020. The program is in its 5th year of operation and recent advances in the diagnosis of infection, prevention of transmission and treatment of infection has generated considerable expectations of the success of the control program among endemic countries. A good review of any disease should give the reader a comprehensive understanding of the "state of the art" in the subject and discuss areas that need further study and research. Dr Wayne Melrose has accomplished this admirably well as he takes us through the history, biology, epidemiology, immunology, disease pathogenesis, socio-economic impact, diagnosis, control and treatment of this important tropical disease. His wide field experience, particularly in Papua New Guinea, is reflected throughout the book and it brings with it the reality of the situation and the challenges faced when one is dealing with such a complex disease. This review should be compulsory reading for all researchers, students and tropical medicine practitioners and others who are keen to learn more about lymphatic filariasis.

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Introduction

Lymphatic filariasis is a mosquito-borne tropical disease, which afflicts around 120 million people worldwide. The World Health Organization (WHO) ranks it as the second most common cause of long-term disability. In 1997, the WHO identified filariasis as one of six potentially eradicable infectious diseases and initiated a global plan for its elimination as a public health problem by the year 2020 (WHO, 1999).

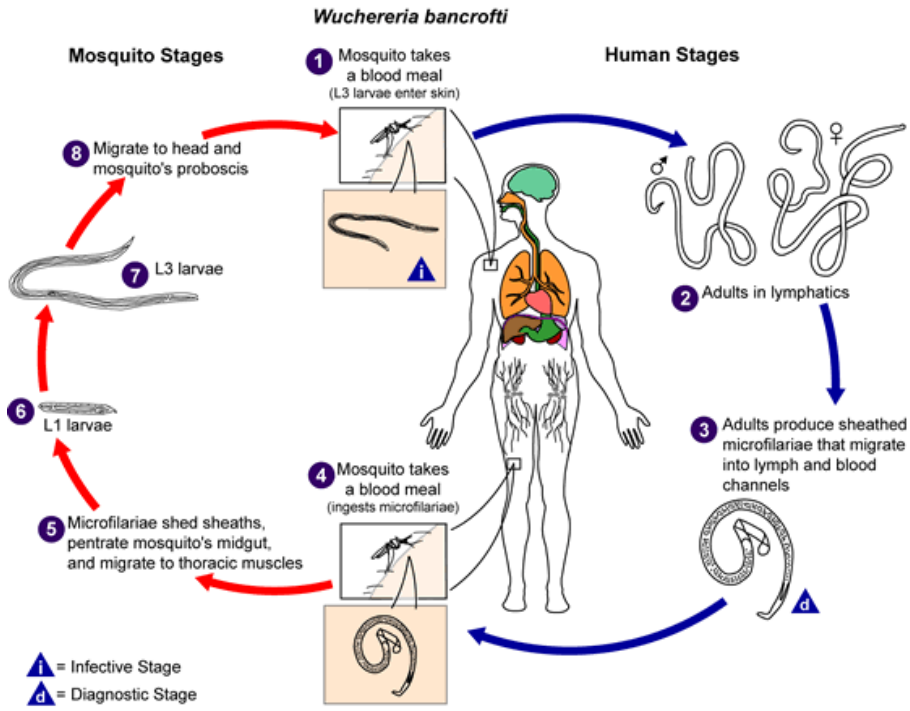
The purpose of this review is three fold: To provide a comprehensive source document which can be used to write educational and health promotional material on lymphatic filariasis; to provide a background for my own original research and to highlight areas which require further investigation in order to stimulate others to carry out further research on this fascinating disease. Extensive use has been made of the reviews by: Sasa, 1976; Ottesen 1980, 1989, 1993, 1994; Piessens and Partono, 1980; Dasgupta, 1984; WHO, 1984, 1987, 1992; 1993, 1994, 1995, 1998, 1999; Partono, 1987; Nanduri and Kazura, 1989; Grove, 1990; Evans *et al.*, 1993; Kazura *et al.*, 1993a; Turner, 1993; McMahon and Simonsen, 1996; Roberts and Janovy, 1996; Ramachandran, 1997; Addiss, 1998; Freedman, 1998; de Almeida and Freedman, 1999; Michael, 1999.

The filariasis literature is voluminous and this review does not purport to cover all available material. An attempt has been made to cover all the most important aspects of filarial parasites and disease, and to include some of the more obscure and often forgotten material, some of which needs to be revisited in the light of modern filariology. Other excellent reviews on the history of filariasis have been written by Manson-Bahr (1959), Grove (1990) and Routh and Bhowmik (1993).

An Overview of Filarial Parasites

Filarial parasites (filaroids) are long hair-like tissue-dwelling nematodes. All except the Guinea worm *Dracunculus medinensis* (which uses a copepod) employ arthropods as intermediate hosts. All filaroids have a similar life cycle that includes an obligatory maturation stage in a blood-sucking insect or copepod, and a reproductive stage in the tissues or blood of a definitive host (Figure 1).

Figure 1. Typical filaroid life cycle



(Source: http://www.dpd.cdc.gov/dpdx/HTML/ImageLibrary/Filariasis_il.asp?body=A-F/Filariasis/body_Filariasis_il_th.htm with permission from CDC)

Adult male and female worms live in the lymphatics, skin, or other tissues (Figure 2). Microfilariae (which are specialised embryos not larvae) are produced by the female worm, circulate in the blood or invade the skin, and are ingested by the vector (Figure 3). Larval development but not multiplication occurs within the muscles of the vector. The infective L3 stage migrates to the proboscis and is transmitted to the new host during feeding (McMahon and Simonsen, 1996). Unlike malaria, the infective stage is not directly injected into the skin of the new host. It is deposited onto the skin whilst the mosquito is feeding and finds its own way through the skin, usually via the puncture made by the mosquito.

Filaroids have been found in all classes of vertebrates except fish and are especially common in birds (Roberts and Janovy 1996). All but one of the species that cause human disease (the Guinea worm) belong to the family Onchocercidae (Roberts and Janovy 1996).

Figure 2. Adult worm in lymphatic vessel. Haematoxylin – eosin stain X400.

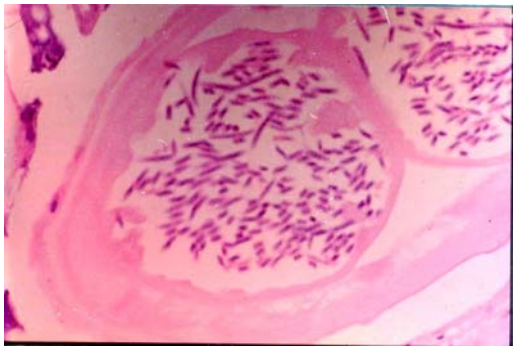


Figure 3. Microfilaria in blood. Giemsa stain X200.

Human diseases caused by filarial parasites

Lymphatic Filariasis

Wuchereria bancrofti, Brugia malayi and Brugia timori are mosquito-borne and cause lymphatic filariasis. In many people's minds lymphatic filariasis is synonymous with "elephantiasis" characterised by the enlargement of scrotum or limbs (Figure 4). In most endemic areas elephantiasis only occurs in a small proportion of the people suffering from lymphatic filariasis.

Bancroftian filariasis, caused by *W. bancrofti* is responsible for 90% of lymphatic filariasis cases and is found throughout the tropics and in some sub-tropical areas. *Brugia malayi* is confined to Southeast and Eastern Asia. *Brugia timori* is found only in Timor and its adjacent islands (McMahon and Simonsen 1996; Roberts and Janovy 1996). In this review "filariasis" always means lymphatic filariasis unless otherwise specified.

Figure 4. Patient with advanced elephantiasis from Papua New Guinea

Onchocerciasis

Onchercerciasis (also called river blindness) is caused by *Oncocerca volvulus* and the vector is the *Simulid* black fly. The largest numbers of cases occur in Africa and it was spread to Central America, Venezuela and Colombia via the slave trade. There is also a small focus on the Arabian Peninsula. Microfilariae invade the skin and give rise to dermatitis premature aging of the skin and skin atrophy. Development of the adult worm leads to nodule formation. Microfilariae invade the eye and cause an inflammatory reaction that can lead to blindness (McMahon and Simonsen 1996; Roberts and Janovy 1996).

Loasis

Loasis is caused by *Loa loa* (sometimes called the African eye worm) and is spread by *Chrysops* flies. It is present in Central and West Africa. Signs and symptoms include fugitive or "Calabar" swellings, itching and joint pains. Sometimes an asymptomatic invasion of the eye surface occurs hence the name "eye worm." (Negesse *et al* 1985; McMahon and Simonsen, 1996; Roberts and Janovy, 1996). It is the most common filaroid infecting travellers from non-endemic

areas (Azimi and Grossman, 1995).

Miscellaneous Filaria Infections

Mansonella perstans (Africa and Central and South America), *Mansonella streptocerca* (Africa) and *Mansonella ozzardi* (Central and South America) are spread by *Culicoid* midges. Most infections are asymptomatic but loiasis-like signs and symptoms can occur (McMahon and Simonsen, 1996).

Zoonotic Filarial Infection

Human infections with various known and unknown animal filarial parasites have regularly been reported throughout the world but especially from the United States (Tobie and Beye, 1962; Beaver and Orihel, 1965; Nelson, 1965; Orihel and Eberhard, 1998). *Dirofilaria immitis* is the cause of heartworm in dogs and occasionally effects humans (for a review see Rodrigues-Silva *et al.,* 1995). Most cases are asymptomatic and the worm becomes calcified in the lung resulting in a "coin lesion" which may be mistaken for carcinoma or tuberculosis. Occasionally asthmatic-like symptoms occur and there may be a marked eosinophilia. Another dog filaroid - *Dirofilaria repens* can cause subcautaneous nodules, peri-orbital lesions, coin lesions in the lungs, and breast lumps in humans and rare cases have been reported throughout the world (Bennett *et al.,* 1989; Pampiglione *et al.,* 1995. High levels of antifilarial IgG, IgE and IgM antibodies are present in patients with dirofilariasis (Simon *et al* 1997) but it should be bourne in mind that there is a high background level of dirofilaria-associated antibody in communities are in close contact with infected dogs and the prevalence of *D. immitis* antibodies in humans in closely related to the number of infected dogs in the community (Welch and Dobson, 1974). At least six cases of human filarial dermatitis have been attributed to *B. beaveri* (Rosenblatt *et al.,* 1962; Grove, 1990), a filarial species whose natural host is the Raccoon (Ash and Little, 1971) and nine cases of lymph node infection by a unidentified *Brugia* species (Baird *et al* 1986) possibly from the domestic cat (Beaver and Wong, 1988). Animal filaroids seldom seen to develop and become sexually mature in man and produce a microfilaraemia but it does occur from time to time (Orihel and Eberhard, 1998). Greene *et al.,* (1978) found circulating microfilariae in a patient from Alabama who was suffering from Lupus erythematosis. Although the species could not be identified with certainty, the most likely species appeared to be Mansonella *interstitium,* a filaroid of squirrels. There is also a report of microfilaraemia and eosinophilia in a 70-year-old Greek man who had never been in an area endemic for human filarial parasites and was presumably infected with an animal species (Petrocheilou *et al.,* 1998).

Cases of encephalopathy due to infection with monkey filarial parasite *Meningonema peruzzi* have been reported from Zimbabwe and the Chimpanzee parasite *Microfilaria rodhaini* has been found in human skin biopsies. Two other *Microfilaria* species believed to be of animal origin have been found in human blood, *M. bolivarensis* in American Indians in Venezuela and *M. semi-clarum* in villagers in North-western Zaire (McMahon and Simonsen, 1996).

Dracunculiasis

Dracunculus medinensis is a large filarial worm that causes Dracunculiasis or Guinea worm disease. Its vector is a fresh water copepod and its life cycle differs from that of a typical Filaroids. Instead of invading the tissues the microfilariae are liberated directly from the uterus of the female worm into water.

The female worm migrates to the lower leg or foot and an ulcer is formed from which the microfilariae are discharged. These ulcers often become infected with bacteria resulting in cellulitis or if in the vicinity of a joint, arthralgia. The worm causes ulcers on the lower leg or foot, which often become infected with bacteria.

Chronic inflammation of the joints can lead to stiffness and permanent disability (McMahon and Simonsen, 1996).

History of Filariasis

Filariasis in Antiquity

Not all cases of elephantiasis are caused by filariasis and elephantiasis is not the most common symptom of lymphatic filariasis, it is however the most visible and has been known since early times. Elephantiasis features in the mythology of several societies (Neisius, 1927; Routh and Bhowmik, 1993). Tales of "skiapodes" mythical beings who could "shade themselves from the sun by the greatness of their leg" occur in the mythology of Greece, Rome and India (Price, 1989; Lawence, 1990). Indian mythology also contains the legend of the "curse of St. Thomas" which states that swollen legs occur in the descendants of those who martyred him (Bowers and Carruba, 1970; Lawence, 1970). Elephantiasis is also depicted in art from ancient times. A statue of Pharaoh Mentuhotep 111 (2000 BC) and the "Queen of Punt" stela (1500 BC) graphically depict the deformities associated with elephantiasis of the limbs (Lawence, 1967; Hoeppli, 1969, 1971; Schacher and Sahyiun, 1967) and scrotal swelling is depicted in art from Nigeria (500-200 BC) and South America (500 AD) (Andrews, 1959; Hoeppli, 1969, 1971).

Mythology and art aside, the disease was well known to physicians and medical writers from very early times. Ancient Hindu medical workers knew of the condition and it is referred to in Sanskrit texts dating back to 600 BC. Included is these is a comment that "the disease is prevalent in areas where stagnant water is found" - a very relevant comment given the link between *Culex* mosquitoes, which like to breed in stagnant water and filariasis transmission (Lawence, 1970; Zimmer, 1979). Between 600 and 250 BC men suffering from elephantiasis were prohibited from becoming Buddhist priests (Lawence 1967). The Roman writer Lucretius Carus (100BC) regarded elephantiasis as a characteristic disease of the Egyptians, which was facilitated by the climate around the Nile (Hoeppli, 1969). Persian physicians of the 10^{th} and 13^{th} centuries AD and medieval European physicians provided very accurate descriptions of elephantiasis and hydroceles (Lawence 1967) but it was not until the 19^{th} century that a firm link was established between elephantiasis, hydroceles and chyluria (Routh and Bhowmik, 1993).

The Discoveries

Wuchereria bancrofti

In 1862 Jean-Nicholas Demarquay, a Cuban surgeon, discovered a worm-like "creature" in hydrocele fluid (Demarquay, 1863). In 1866 Brazilian, Otto Wucherer, found the same organism in chylous urine (Wucherer, 1868) but it was not until 1872 that microfilariae were discovered in blood (Lewis, 1872).

In 1876, Brisbane physician and parasitologist, Joseph Bancroft, discovered a female adult worm in an abscess on the arm of a butcher (Cobbold, 1877) and further examples were found in South America (da Silva Araujo, 1877; dos Santos, 1877) and China (Manson, 1881a,b). In 1888, Sibthorpe and Bourne discovered the adult male (Bourne, 1888; Sibthorpe, 1889). The name *Wuchereria bancrofti* was formally adopted in 1921 (Seurat, 1921).

Brugia Species

In 1927 Lichtenstein and Brug discovered a microfilaria in the Dutch East Indies (now Indonesia) which was morphologically different from *W. bancrofti* and called it *Filaria malayi* (Brug, 1927; Lichtenstein, 1927; Brug, 1928; Brug and de Rook, 1930).

This in fact may not have been the first description of *Brugia*. In 1905 Ashburn and Craig described a case from the Philippines, which had microfilariae that differed from *W. bancrofti*, which they called *Filaria philippinesis* (Ashburn and Craig, 1905). Their material was reviewed by Manson-Bahr in 1941, who believed that the microfilariae were identical to Ashburn and Craig's *F. malayi.* Rao and Maplestone first described the adult worm in 1940 (Rao and Maplestone, 1940). The pioneering work of Brug was acknowledged in 1958 when Buckley proposed the new genus *Brugia* and *F. malayi* was re-named *Brugia malayi* (Buckley, 1958; 1960). The zoonotic feature of *Brugia* was discovered in 1939 when microfilariae, later identified as those of *B. malayi* were discovered in a Kra monkey (Poynton and Hodgkin, 1939). Edeson and Wharton, (1958) and Laing *et al,* (1960) broadened the range of vertebrate host to include other monkey species, domestic cats and dogs.

In the 1960's another filarial species was discovered in Portuguese Timor and given the name *Microfilaria timori* (David and Edeson, 1965). Partono infected Mongolian gerbils with the new species and obtained adult worms. He confirmed that the new species belonged to the genus *Brugia* and called it *B. timori* (Partono *et al.,* 1977).

Mosquito Hosts

On August the 10th, 1887 Patrick Manson fed some mosquitoes on the blood of his microfilaraemic gardener Hin-Lo and was able to demonstrate the development of the larva within the insect (Manson, 1878a, 1878b, 1884). Lewis confirmed his observations in 1872. The mosquitos used by Manson in his initial experiment were later found to *Culex quiquefasciatis* (Manson-Bahr, 1927), which is still regarded as one of the most important vectors of filariasis. By 1976 other species of *Culex* and species of *Anopheles, Aedes* and *Mansonia* had been added and the list had grown to several hundred (Sasa, 1976;

Grove, 1990).

Filarial Nocturnal Periodicity

Patrick Manson had two laboratory assistants. One worked during the day and one during the night. Manson noticed that the night worker found more filaria than his day-working colleague and this led him to set up an experiment whereby serial blood samples were taken on the same patients during the day and night. He found that the microfilariae were present in large numbers during the night but were almost absent during the day (Manson, 1880a, 1880b). Manson's observation was greeted with some disbelief, someone even asking, "whether filaria carried watches" (Grove, 1990). Myers, (1881) and MacKenzie, (1881) subsequently silenced the scoffers by confirming Manson's findings. Mackenzie also successfully reversed the nocturnal periodicity by getting his patient to sleep by day and remain awake at night (MacKenzie, 1881) as did Manson the following year (Manson, 1883) and changes in periodicity have been obtained with as little as a three day reversal in sleeping patterns (Hawking, 1962a). There were a large number of early theories about the mechanism of micro filarial periodicity and they have been given an extensive review by Lane (1948). In 1883 Manson discovered that *D. immitis* microfilariae in a dog hid themselves in the lung when they were absent from the circulation (Manson, 1883; Grove, 1990). Manson confirmed this in a human case in 1897 (Manson, 1899). Thorpe (1896) and Lynch (1905) reported that the microfilariae (subsequently called *W. bancrofti var pacific*) showed no periodicity. Turner and Edeson (1957) demonstrated that there are both nocturnal and sub-periodic forms of *Brugia malayi*.

The Vectors of Filariasis

Unlike malaria whose transmission cycle is dependant on *Anopheles* species, filariasis a wide range of mosquitoes act as vectors for filariasis (Manson-Bahr, 1959; WHO, 1992). By far the most widespread and important species is *Culex quinquefasiatus*. The ability of this mosquito to breed in heavily in collections of heavily polluted water in urban and semi-urban areas he resulted in a prevalence of "urban" filariasis in areas where the rapid growth of urban areas outstrips the growth of sanitation services (figure 5).

It is a night-biting mosquito and filariasis in the areas where it is the major vector shows nocturnal periodicity. Other *Culex* species are also capable of transmitting filariasis and may be important vectors in certain areas. *Aedes polynesiensis* and *Ae. samoanus* are the most important vectors in the pacific area. The former breeds in crab holes and tree holes making it a very difficult mosquito to control with conventional methods (Figure 6).

They are day-biting mosquitoes thus accounting for the diurnal periodicity of filariasis in this region. *Ae. poecilius*, a night-biting mosquito is a major vector in the Philippines. *Mansonia* species are an important vector of B. malayi, and sometimes W. bancrofti, in areas where there are extensive areas of aquatic plants (figure 7).

Anopheles species are important vectors of *W. bancrofti* in parts of Africa and Southern Asia and in Papua New Guinea. *A. barbirostris* breeds in open rice paddies and is the only known vector of *B. timori* (figure 8).

Are any other insects except mosquitoes capable of transmitting lymphatic filariasis? Bed bugs (*Cimex* species) can be naturally and experimentally infected with *Brugia malayi* and *W. bancrofti* (Burton, 1962) and some limited larval development can take place but the mortality of the larvae is extremely high and bed bugs cannot be seriously regarded as a vector of filariasis (Burton, 1963).

Transmission Dynamics in Filariasis

The host-parasite relationship and the transmission dynamics of filariasis have been extensively reviewed by Sasa (1976), Piessens and Partono (1980) and Anderson and May (1991). Two modelling frameworks *lymfasim* (Plaisier *et al.,* 1998) and *Epifil* (Chan *et al.,* 1998) have been developed which also a series of hypotheses can be tested about the life history of the parasite, its transmission, the immuno-regulatory role of the host immune system, the development of disease and the impact of control measures.

In general, the mosquito infection rate, ie the number of mosquitoes that contain microfilariae after a blood meal and the number of microfilariae ingested per mosquito increase with increasing parasitaemia (Piessens and Partono, 1980). Although there is no multiplication in the vector the number of infective larvae is around six times greater than that expected by microfilariae density (Brito *et al.,* 1998). Bockarie (1997) has shown that the annual infective biting rate and the annual transmission potential show a positive correlation with microfilariae rate, microfilariae density and prevalence of leg oedema suggesting that transmission intensity is a major determinant of patent infect and morbidity. Kazura *et al.,* (1997) studied the relationship between annual transmission potential (ATP) and disease status in 1666 individuals from five similar but distinct *W. bancrofti*-infected communities from a highly endemic area of Papua New Guinea. Annual transmission potentials and microfilariae prevalence (MF) in these villages were: 2,344 (MF 94%); 1,338 (MF 82%); 279 (MF 56%); 179 (MF 66%) and 31 (MF 52%) respectively. In all villages the prevalence of leg odema was highly positively related to the ATP (correlation coefficient r=0.89 and probability p=0.04). The incidence of acute filarial attacks is also related to the transmission intensity. Gyapong *et al.,* (1996) found that the incidence of acute filarial attacks we reduced in the dry season when the transmission potential was at its lowest.

The concept of "facilitation" - that the proportion of microfilariae that develop increases as the number of microfilariae ingested increases (WHO, 1992) is an important consideration when the possibility of eradication of filariasis is being considered. In theory, it should be possible to reach a point where there are insufficient circulating microfilariae in the population to support transmission (WHO, 1992). It is important to note however, that persons with microfilariae densities as low as three per ml can still infect mosquitoes and that residual low-density microfilaraemics after mass treatment programs have the potential to cause rapid resurgence of filariasis (Lowrie *et al.,* 1989; Southgate, 1992)**.** Beckett (1973) found that a heavy uptake of microfilariae from the blood can cause life-threatening damage to the internal organs of the mosquito during larval development but this finding is not supported by the recent work of Brito *et al.,* (1998). The feeding of mosquitoes on individuals with medium or low micro filarial densities may therefore enhance transmission potential especially if the main vector is a Culicine rather than an Anopheline (Webber, 1981, 1991). The reasons for this difference, termed "limitation" is discussed by Bryan and Southgate (1988a,b) Bryan *et al.,* 1990; Webber (1981, 1991); Southgate and Bryan (1992) who suggest, that in contrast to Culicines, Anopheline mosquitoes have a well developed pharyngeal armature which damages microfilariae when they are ingested. If the number of ingested microfilariae is low there may be insufficient viable microfilariae to infect the mosquito. Loss of microfilariae also occurs in fluid expelled from the anus of anophelines but not culicines (Bryan and Southgate, 1988a,b). The concepts of facilitation and limitation and their role in filariasis transmission has been critically reviewed by Wada *et al.,* (1995) who concluded that "there was no clear evidence to support the existence of facilitation and limitation-based unstable equilibrium in relation to microfilariae prevalence and density below which filariasis would spontaneously disappear even when the vector was *Anopheles*. Instead, the existence of a critical level of man/mosquito contacts for the disappearance of filariasis was suggested".

Factors that Influence Micro Filarial Prevalence and Density

A spontaneous decrease in microfilaraemia prevalence can occur in the absence of vector control or mass chemotherapy. In a study in Benin the prevalence of microfilaraemia decreased from 9.4% to 0.48% over a 10-year period. The prevalence of people with chronic pathology remained the same. The changes could not be explained by environmental or sociological changes in the region or even by changes in the demographics of the study population (Myung *et al.,* 1998). Microfilariae density is also subject to considerable daily variation (Rouchou, 1954; Nathan *et al.,* 1980) but this is unrelated to lunar phase lactation, or the menstrual cycle (Rachou, 1956; Nathan *et al.,* 1982). Fasting during the month of Ramadan has been shown to reverse nocturnal periodicity (El-Tamami, 1960; Nathan *et al.,* 1982) but solar eclipses have no effect on periodicity (Sahai *et al.,* 1980). The fecund life span of *W. bancrofti* has been calculated by various means and methods and has been variously estimated from 5 to 15 years. A recent study by Vanamail *et al.,* (1996) suggests that the life span is at the lower end of previous estimates - around five years.

Endosymbiont Bacteria

In the 1970's intracellular bacteria were discovered in some species of female filarial parasites (reviewed by Taylor and Hoerauf, 1999; Taylor *et al.,* 2000). It was postulated that they were of the genus *Wolbachia* (now

known to be correct) and had a similar role to the symbiont bacteria found in arthropods where they are known to exert an influence upon the growth and reproduction of their host. Symbiont bacteria may be implicated in the pathogenesis of filarial pathology and are a potential target for antifilarial activity (see relevant sections below).

The Global Burden of Lymphatic Filariasis

The total global burden of lymphatic filariasis is not known and mapping of its prevalence is on-going (for review see Michael and Bundy, 1997). The disease is endemic in 76 countries and 1.1 billion people are at risk from infection (Ramachandran, 1997). Statistics for many countries are either old, very sketchy, or non-existent. The most recent estimates (Michael and Bundy, 1997; Michael *et al.,* 1996; Ramachandran, 1997) suggest that filariasis infects 120 million people or 2.0% of the world's population. Of these, 83 million people have lymphatic disability, 23 million men have hydroceles and 15 million people have elephantiasis. Millions more suffer from debilitating acute attacks of filarial fevers and lymphadenitis (Ramachandran, 1997). Over 90% of these cases are caused by *W. bancrofti*.

The estimated country-by-country prevalences in the Asia-Pacific region are given in Table 1.

The true prevalences are probably higher than this because most country surveys done in the past were based on the demonstration of microfilariae. Modern surveys using antigen detection (see "Diagnosis" section below) have shown that surveys of microfilaraemia alone can under-estimate the prevalence of filariasis by as much as 30% (Turner, 1993; Chanteau *et al.,* 1995).

Table 1. Prevalence of filariasis in various countries (Hawking and Denham, 1976; Michael *et al.,* 1996).

COUNTRY	PREVALENCE (%)
China	0.5
Burma	0.1
French Polynesia	12.6
Indonesia	1.8
India	5.3
Laos	0.1
Malaysia	0.4
Nepal	0.8
New Caledonia	18.7
Micronesia	11.1
Papua New Guinea	72.0
Philippines	4.1
Western Samoa	7.7
Seychelles	10.0
Sri Lanka	1.6
Thailand	2.7
Vanuatu	1.9
Vietnam	1.3

Increasing Global Prevalence

There is evidence that the global burden of filariasis is increasing. To quote Piessens and Partono (1980):

> *"Filariasis shares with schistosomiasis the dubious honour of being one of the major diseases whose prevalence and distribution are increasing in the developing world at a time when other tropical diseases are slowly disappearing. This is all the more remarkable in view of the relative inefficience of the filarial transmission, the complexity of the parasite's life cycle and the susceptibility of the worms to the widely available and inexpensive drug diethylcarbamazine, that should render filarial nematodes particularly venerable to effectively applied control measures."*

There are several reasons for this. The main vector mosquitoes thrive in urban slum areas and the increased urbanisation around the world's major tropical cities are putting an increasing number of people at risk (Hunter, 1992; Albuquerque *et al.,* 1995; Dhanda *et al.,* 1996). It has long been recognised that one of the adverse effects of economic development projects is the impact on health. Irrigation projects in Ghana have been associated with an increase in filariasis. Hunter (1992). Found that almost every house in villages bordering a man-made irrigation scheme had a case of filariasis. By contrast, only scattered cases were seen in villages two km or more away from the canals. Dzodzomenyo *et al.,* (1999) observed a similar result.

Rural-urban migration and uncontrolled urbanisation often lead to overburdening of sewerage and wastewater systems. The resulting pools of stagnant, polluted water provide an ideal breeding ground for *Culex quinquefasiatus,* a major vector of filariasis (Mak, 1986). In contrast to anophelines culicines can efficiently transmit filariasis in situations where the microfilariae density is low (Webber, 1991). Adhikari *et al.,* (1994) found a significant difference in filariasis prevalence between colliery areas, where there were opencast pits and other vector breeding sites, and non-colliery areas of the same district in India. A similar study in Egypt (Gad *et al.,* 1994) found that inhabitants of houses facing vacant land (which presumably had more opportunity for water to collect and breed mosquitoes) suffered more from filariasis than their

neighbours from the more closely settled areas nearby. This study demonstrates an important aspect of filariasis - that it is very heterogeneous and very focal in its geographical distribution and its prevalence can vary widely even within a small area.

Pursuit of economic activity can also lead to increased transmission in other ways. Rubber trees are often tapped at dawn in an attempt to increase latex yield. This corresponds with a peak in the biting rate of *Mansonia* mosquitoes (Mak, 1986). In many tropical communities and urban areas people congregate for social activities in the early evening - a prime biting time for many filarial vectors (Mak, 1986). It should also be pointed out that malaria is also on the increase, one of the causes being the winding down of vector control program in many parts of the world and increased mosquito resistance to insecticides. Since malaria and filariasis share some common vectors, failure to control mosquitos also contributes to the increase in filariasis. Population movements are playing an increasing part in the spread of filariasis. Filariasis is generally thought to be under control in Thailand but it is feared that there will be resurgence in the disease caused by infected Myamar migrants (Trieeraprapab *et al.,* 1997). To quote Ramachandran (1997):

> *"Statistics become reality when one takes a walk through the villages and shanty towns in endemic countries and visualise people, both young and old, men women and children walking around with enlarged legs, feet, hands and genitals, in additional to other parts of their bodies. Today the disease still continues to spread unabated in many parts of the world due to continued unplanned urban and semi-urban development; man-made environmental and ecological disasters and habitats which continue to enhance mosquito breeding and consequent transmission of disease."*

Gender Differences

Animal studies have suggested that estrogenic hormones may play a part in reducing filarial infection in females (Reynouard *et al.,* 1984). Several studies have shown that the microfilaraemia density is lower in women of reproductive age compared with age-matched males. This difference cannot be explained by differences in exposure (say by different clothing) is not associated with pregnancy and may be related to hormonal activity (Dutta and Diesfield, 1994; Kaur, 1997; Alexander and Grenfell, 1999b). Mavoungou *et al.,* (1989) suggest a different hypothesis: that the filarial parasites themselves may contribute to reduced steroid and gonadothropin hormone levels in young women and may lead to a delayed menarche.

The Age-Distribution of Filariasis

The age distribution of microfilaraemia is remarkably consistent throughout the parasite's geographic range. Both prevalence and intensity tend to rise with age and peak in the 15 to 25 year age group and decline in adult hood (Sasa, 1976; Day *et al.,* 1991; Chanteau *et al.,* 1995). In a Haitian study, Lammie *et al.,* (1994) found that filarial antigenaemia increased from 24.5% in children aged 1 to 5 years to 70% in adults older than 50 years. More males are infected than females and the incidence of disease is higher in males (Brabin, 1990; Albuqueque *et al.,* 1995; Michael *et al.,* 1996; Kaur, 1997). The prevalence of antigenaemia and microfilaraemia and the density of microfilaraemia are usually closely related to transmission intensity (Day *et al.,* 1991; Chanteau *et al.,* 1995). Transmission intensity is determined by complex interactions between the species of parasite, the microfilariae rate and density and the vector (Southgate, 1984; Bryan and Southgate, 1988a,b; Bryan *et al.,* 1990; Southgate 1992; Southgate and Bryan, 1992). It has also been suggested that the higher microfilariae prevalence in younger individuals is related to the increased vector-biting rate in younger people (Farid *et al.,* 1997).

Classification of Filarial Endemicity

There have several attempts at the classification of filarial endemicity. Most of these used, as well as parasitological data, subjective clinical findings that are difficult to standardise (Iyengar, 1938; Kumar, 1996). It has been shown that the filarial infection rate as evidenced by microfilaraemia closely correlates with other filariometric indices and can be use to set cut off points for various levels of endemicity (Kumar, 1996).

His proposed classification is given in Table 2.

Table 2. Proposed classification of filarial endemicity (Kumar, 1996)

INFECTION RATE	ENDEMICITY
<10%	Low
10-20%	High
20-40%	Hyperendemic
>40%	Holoendemic

Given that microfilaraemia surveys alone underestimates the prevalence of filariasis by as much as 30% (see above) it would be interesting to do a similar study using filarial antigenaemia as the indicator of infection.

CAN FILARIASIS BE TRANSMITTED OUTSIDE ENDEMIC AREAS?

In theory, yes.

Many mosquito species can transmit the parasite the presence of a microfilaraemia person could result in local transmission or a case of "airport filariasis" could occur if an infected mosquito accidentally transported into the country. Rosenblatt *et al.,* (1962) describe a case, which they believe could have been transmitted within the city of New York, possibly because of a visit by the patient to the city's international airport. The species of filaria however could not be identified with certainly and it is possible that it was an animal species rather than a human *Brugia* or *Wuchereria bancrofti.*

Social Attitudes Towards Filariasis

An understanding of the community social attitudes to filariasis (or any other disease) is essential if control is to be achieved. To quote Gyapong (1996):

> *"Disease control programs in developing countries are often unsuccessful or unsustainable because strategies pursued are inappropriate for the community or incompatible with traditional perceptions of aetiology, prevention and control. Feasible interventions to treat and prevent filariasis will require a broad understanding of traditional perceptions of the disease, its cause and consequences and means of prevention. Since perceptions of disease vary from place to place, there is a need to carry out in-depth studies of the social, cultural and economic aspects of the disease before embarking on control measures".*

Although Ramachandran (1997) states that: "It cripples them, demoralises them and makes them social outcasts in their own communities and societies due to social stigma and alienation", the social impact of filariasis varies widely from place to place. In general the degree of stigma seems to be associated with the severity and visibility of the disease (Evans *et al.,* 1993; Mujinja *et al.,* 1997). In the Philippines, men with hydroceles continued to lead normal lives although they are subjected to some teasing. On the other hand, women with labial enlargement were presumed to be promiscuous and the shame associated with the disease lead to poor reporting (Evans *et al.,* 1993). In Thailand filariasis is considered to be a "terrible disease" and some sufferers with elephantiasis are shunned by their family and fellow villagers. People refuse to sit with them, eat with them of marry them. The burden is especially heavy for young women who believe that their marriage prospects are nil and they become reclusive and seldom leave their house (Rauyajin *et al.,* 1995). In Tanzania, having filariasis is considered shameful (Muhondwa, 1983; Evans *et al.,* 1993; Mujinja *et al.,* 1997) and in Polynesia during the 1950's men with elephantiasis of the scrotum were considered to have a social and procreative handicap and women with elephantiasis were not considered desirable as wives (Kessel, 1957; Evans *et al.,* 1993). In Ghana people with mild or moderate elephantiasis are well accepted by the community but those with more advanced disease often stay at home because they feel embarrassed about their disease. Men with hydrocele are often teased behind their backs and those with chronic filariasis cannot be chosen as chiefs. Young women with filariasis usually have problem getting married because prospective husbands consider that the disease will make them unable to work and he will have the cost of paying for her treatment (Hunter, 1992; Gyapong *et al.,* 1996a). In Nigeria, filarial disease seriously hinders a girl's prospect of marriage, or if she is married the stability of the marriage and her prospect for future happiness. The unwillingness of men to marry girls with the disease is compounded by the belief that what happens to the mother will also happen to the child (Amazigo and Obikeze, 1992; WHO, 1995). Women had similar sentiments about marrying men with filariasis but had less of a choice in the matter than men because relatives arranged many of the marriages. Mujinja *et al.,* (1997) in a study in Tanzania, found that stigma, ostracism and discrimination of the filaria-affected, though subtle, have a significant psychological impact. Hunter (1992) records that the marriage situation differs between communities that are filarial-hyperendemic and those where the prevalence of disease is low. Men from the communities where prevalence is low avoid taking girls from the hyperendemic areas as wives. By contrast, there seems to be much less stigma attached to the disease in hyperendemic communities and men will even marry girls who are already showing signs of filariasis. Coreil *et al.,* (1998) however, showed that although young men will take filarial-effected girls as wives, her chances of finding a good husband and marital happiness are diminished. In coastal Ghana suffers are subjected to teasing and considered to unsuitable marriage partners. Those who do marry have a higher than normal divorce rate (Ahorlu *et al.,* 1999).

Because the social stigma associated with filariasis is particular burdensome for women, filariasis as been identified along with schistosomiasis, leishmaniasis, leprosy and onchocerciasis, as diseases which should receive special attention under a "gender and tropical diseases" research program (WHO, 1995). Coreil *et al.,* (1998) showed that Haitian women's lives are heavily burdened both socially and economically by filariasis and collected the following statements:

> *"I can't harvest the garden produce, because you have to stand - I can't stand."*
>
> *"I should be out selling, but I don't get up - my foot is too heavy."*
>
> *"I ask for death because it makes me sick. I've been suffering from this for 33 years."*

Bandyopadhya (1996) has found that the statement that the chronic manifestations of filariasis can cause "grave social wounds" (WHO, 1992, Remme *et al.,* 1993) is especially true for the women of India. Most affected women had very low self-esteem and some

had a fear of being rejected by their husbands because they were "no longer attractive". In a society where arranged marriages are the norm, teenage girls with early chronic pathology consider their chances of being selected as a marriage partner to be seriously diminished and many of those with more advanced disease have given up hope of being married altogether. Dreyer *et al.,* (1997) found that there is a silent burden of sexual disability associated with lymphatic filariasis among men but it is seldom acknowledged because shame and fear caused "a conspiracy of silence" surrounding the man and his partner. They found that a wide range of disease-related problems including marriages devoid of sexual activity, complaints of painful intercourse in women whose partners had lympodema of the penis, recourse to homosexuality by both male and female partners and suicidal thoughts in both sexes.

Children do not escape the social effects of filariasis either due to attacks of ADL interrupting their education or the medical/social effects of chronic pathology. Ramaiah *et al.,* (2000) report the tragic case of a 15-year-old boy with enlarged genitals having to give up his education because of shame, embarrassment and ridicule. Other boys with hydrocele were unable to cycle or walk to school, play, or take part in sport because of scrotal pain.

The Origins of Filariasis

Traditional beliefs about the aetiology of the disease vary widely from place to place. In many developing countries the disease is attributed to sorcery and other supernatural causes. The following examples are cited by Gyapong *et al.,* (1996). In Ghana people believe that elephantiasis of the leg is caused be stepping on "spiritual medicines" thrown on the ground by "juju men" (witch doctors) at funeral dances. Elephantiasis of the arm is believed to be caused by inadvertently picking up an animal tail dropped by a juju man. Others think that it possible to get the disease from walking on ground on which certain herbs have been thrown or removing a thorn from one's own foot rather than standing still and letting a "forest dwarf" remove it for you. Some people in the same community believe that the disease is hereditary and is passed to children *in-utero* via an infected father's semen. Fevers "settling" in the scrotum or breast are blamed for some cases of elephantiasis. Men sometimes blame elephantiasis on their wives use of artificial flavouring agents such as monosodium glutamate or the provision of too much sweet food such as mango and sweet potato. The Duruma of coastal Kenya attribute elephantiasis to witchcraft, sexual intercourse or consumption of burnt food (Wijers, 1977).

Very few people in endemic areas know that mosquitos transmit filariasis or believe that they can help prevent the disease by minimising contact with mosquitoes (Evans *et al.,* 1993). In a Malaysian study only 9 out of 108 respondents associated filariasis with mosquitoes and most people believed that you could catch the disease by walking barefoot on dirty ground or consuming contaminated food or drink (Haliza and Mohd, 1986; Evans *et al.,* 1993). Similar views are held by a population in rural Thailand where only school children knew that mosquitoes transmit filariasis and that the disease could be prevented by protecting one's self from mosquito bites. Most of the older people believed that the disease was hereditary or could be contracted through poor circulation, carrying heavy loads, prolonged standing, bathing in or drinking swampy water, personal contact, or sorcery (Rauyajin *et al.,* 1995). In Tanzania most people knew that mosquitoes spread malaria but very few know that they also spread filariasis (Muhondwa, 1983). Ahorlu *et al.,* (1999) found that many villagers in a coastal Ghanian community rejected mosquito transmission, believing instead in other physical, hereditary and spiritual causes. In Tahiti most people discounted the idea that mosquitoes were involved and filariasis was attributed to immersing an injured ankle in the sea or consuming contaminated food or drink (Kessel, 1957; Carme *et al.,* 1979). In the Philippines (Lu *et al.,* 1988; Schultz, 1988) it was mostly the educated people who knew the connection between mosquitoes and filariasis. Many people believed that coming into contact with cold water caused acute disease after heavy work and elephantiasis by taking long walks or squatting while mending fishing nets. Women were thought to catch the disease by washing whilst menstruating. Despite the lack of knowledge about mosquito transmission many people were able to identify that the people most at risk of developing filariasis were outdoor workers such as farmers, abaca strippers and fishermen. In a study in rural south India only 9.3% of apparently uninfected people and 20% of those with chronic filarial pathology knew that filariasis was contracted through mosquito bites. Other causes listed were occupational activity, bad drinking water and poor nutrition (Ramaiah *et al.,* 1996a). Similar findings were reported in Malaysia (Riji, 1986). This study also found that there was no significant difference in knowledge about filariasis between infected and uninfected persons. In Haiti the traditional view is that filariasis is caused by stepping on a magical powder placed on a footpath, injury to a limb, excessive cold or foreign objects such as glass entering the limb (Eberhard *et al.,* 1996; Coreil *et al.,* 1998). In a study among Indian women, Bandyopadhyay (1996) found that 92% of women interviewed did not know that mosquitoes transmit filariasis. Some believed that disease was hereditary while others blamed pregnancy, a previous injury or "bad spirits". These cultural beliefs are often very deep rooted and may persist long after contact with European culture, religion and medicine and an understanding of them is vital when one is considering a control program. In Tanzania (Muhondwa, 1983) and Tahiti (Kessel, 1957; Carme *et al.,* 1979) for instance, most people steadfastly refused to believe mosquitoes spread filariasis even after an intensive education campaign.

"Where chemotherapy alone is the

main method of control people tend to discount the possibility of mosquito transmission arguing that if mosquitoes were the source of infection, mosquito control measures would have been promoted" (Evans et al., 1993).

Dunn (1976, 1979) and Mak (1986) observed that the impact of human behavioural and socio-economic factors pertinent to the control of filariasis have been largely ignored and there have been few attempts to bridge the gap between modern medical knowledge about filariasis and indigenous perception of the disease. It is also possible that traditional healing methods may influence the course of filarial disease. Ahorlu *et al.,* 1997 in a study from northern Ghana, suggest that scarification (multiple small cuts made on diseased parts of the body to let out "bad blood") may be a risk factor for developing acute adenolymphadenitis and elephantiasis presumably by providing an entry point for secondary bacterial infection, a know risk factor for elephantiasis (see below).

It is of considerable concern to the present writer that even although Papua New Guinea has one of the highest prevalences of filariasis in the world there appear to be no published studies on cultural attitudes to the disease.

Impacts of Cultural Awareness on Filariasis Control Programs

Social class, education, literacy and personality traits can have an influence the outcome of any disease control intervention and a lack of awareness of these issues can affect the success of a filariasis control program (Ramakrishnan 1960; Rao 1982). To quote Sunny *et al.,* (1986):

"An individual's attitude towards filariasis is shaped by the views and awareness of the community of which he/she is a member and may directly or indirectly the acceptance and non-acceptance of the offered control measures."

In the study by Sunny *et al.,* (1986) it was found that there was a marked difference in Diethylcarbamazine (DEC) acceptance between illiterate and literate and non-college educated and college-educated filariasis-infected individuals. Only 30.4% of illiterate suffers accepted the drug whereas 80% who were literate or who had attended school to college level accepted the drug. Interestingly, the incidence of refusal was higher in higher income groups than in low income groups and refusal was more common in females than in males.

The reasons for acceptance and refusal are given in Table 3. These tables provide some very revealing information about while some filarial control programs are successful and some fail. In this study the prime motivators for treatment acceptance was the fact that the medicine was free and it was delivered to their home. The second most important factor was fear of contracting the disease. By far the most important reason for not accepting DEC was the fear of side effects.

Table 3. Reason for acceptance of DEC (Sunny *et al.,* 1986)

Reason	No.	%
Knew it was an effective medicine for	58	17.1
Free medicine supplied at home	154	45.3
Knew that medicine is available to	18	5.3
Afraid that they will get filariasis	80	23.5
Insisted upon by head of household	2	0.5
Persuaded by health worker	24	7.1
No response	4	1.2
Total:	340	

It also highlights the problem of "occult" filariasis - it is difficult for people to accept treatment if they do not believe that they have the disease. This study clearly indicates that active and effectual health promotion is an essential part of any control program and the need to find an effective means of controlling the side effects of DEC without compromising its chemotherapeutic efficacy. Personality traits may also be an important factor in the success of filariasis control programs. In a study in the Philippines by Ventura (1986) 58 acceptors of blood screening and 50 non-acceptors matched for age and sex were given locally-devised personality scales which rated patience, obedience, responsibility, risk-taking, self-control, having an internal or external locus of control, being difficult to talk to and being daring. The study showed that typically, acceptors were those who were responsible, daring, patient, and who had an external locus of control. Being responsible meant that they realised the importance of taking control of their own health, and because they were also daring, they were more likely to have the strength of will to undergo the trauma of a blood test. It was also shown that males tended to comply with a request for a blood test because of a sense of obedience to authority whereas females tended to comply because they were more socially responsible. This study shows that cultural values, sociological attitudes and individual personality traits should be considered when planning a disease control program.

Socio-Economic Impact of Filariasis

> *"It is necessary to understand the social and economic impact of diseases in order to set priorities within the health system. This requires information on the types of symptom that are experienced; their prevalence, frequency and duration; and the nature of the associated social and economic costs. Much of this information is not available for lymphatic filariasis, and in its absence it is not surprising that the disease is not given higher priority in much of the endemic world" (Evans et al., 1993).*

According to Gyapong *et al.,* (1996a, b), a major hurdle for procuring funding for control and research has been the lack of information regarding the social and economic impact of the disease. The estimated socio-economic impact of filariasis varies widely from study to study and documentary evidence of loss of production and income is difficult to find (Andreano and Helminiak, 1988). The current global estimate of the disability associated with lymphatic filariasis is 850 000 disability adjusted life years lost (Gyapong *et al.,* 1996a, c). This is probably a serious under-estimate given the lack of recent prevalence information for many of the endemic countries. The global economic burden of the disease is also difficult to estimate but the annual economic cost to India alone is around US$1,500 million (Addiss, 1998).

There is very strong evidence that late stage chronic disease with its accompanying disability reduces productive capacity (Kessel, 1957; Wijers, 1977; Wegesa *et al.,* 1979; Muhondwa, 1983; Evans *et al.,* 1993), but the economic impact is reduced somewhat by the fact that most people with advanced chronic pathology are beyond their most productive years (Wijers 1977). The impact on some communities can be severe. Gyapong *et al.,* (1996a, b) found that because of chronic filariasis 4.1% of the productive female labour force and 20% of the productive male labour force were disabled by between 10 and 60% and 20% people with advanced chronic disease often had to give up primary - food producing roles and take on a more sedentary occupation such as basket weaving. As a result, the net food production of the community was reduced (Gyapong *et al.,* 1996a, c). Mujinja *et al.,* (1997) have shown that elephantiasis, hydroceles and frequently experienced attacks of adeno-lymphangitis physically incapacitates affected individuals and greatly limits their participation in community economic and social activities. The need to employ labour from outside the family and rises in health care costs have had a negative impact on household income and production. Ramu *et al.,* (1996) found that the productive output of a group of male weavers with chronic filariasis was 27.4% lower than that of uninfected age-matched controls.

As well as the direct economic impact of chronic pathology-induced disability there is the secondary impact derived from the effects of treatment, particularly the cost of surgery and the loss of income during the hospital stay. In one study of hydrocele surgery there was a very high rate of postoperative sepsis and days in hospital varied from 8 to 43 days (Muhondwa, 1983). After discharge, the men were advised to go on "light duties" for 6 months. In the long-term this period of reduced productivity may be balanced by increased productivity because of enhanced physical activity but evidence for this is entirely anecdotal (Muhondwa, 1983).

There is very little data on the economic impact of acute filariasis but it is obvious that there is potential for a severe economic impact, especially in populations who have a subsistence lifestyle. Kessel (1957) points out that it is very difficult to assess the economic impact of filariasis because most cases occur in rural areas where quantitative measurements of working time lost are seldom made. He states that before filarial control programs were introduced in French Polynesia acute filarial attacks occurred in 27% of the adult population with each individual having 1 to 12 attacks a year and each attack lasting from 1 to 3 days or longer. Fifteen percent of adult males suffered from hydrocele and another 14% had elephantiasis. The work output of those with mild or moderate elephantiasis or hydroceles was reduced and many of those with severe chronic pathology could not work at all and were cared for by their families. Kessel also quotes unpublished reports of a group of 600 Malaysian rubber tappers who reported 150 acute filarial attacks per year with a loss of 450 working days. Gyapong *et al.,* (1996a) found that the average time of incapacitation with Aden-lymphadenitis (ADL) was 3 days per person per year. This may not seem very high but most of the attacks occur during the rainy season - the time of peak agricultural activity. Total incapacitation at this crucial time could mean the family did not produce any food that year. Further evidence for the economic loss inflicted by filariasis comes from India where the estimated cost benefit of filariasis eradication for India in 1971 was said to be in the order of $US133 million per year (Prescott, 1980) It would of course, be much greater, now. Panicker and Sabesan (1990) and Sabesan *et al.,* (1992) estimate that in the city of Pondicherry alone (population 370,000) 323,205 person working days are lost annually at a cost of $US635,000 due to acute filarial attacks. A recent study by Ramaiah *et al.,* (1996b, 1997, 1998, 1999) investigated the impact of acute filariasis in south India and found it to be severe both in terms of the amount of money expended on treatment and the loss of individual and community earning capacity. About 66% of infected persons said that their disease impaired their economic activity and

some had completely given up their employment. Most patients however did not leave work but spent only 4.36 ± hours per day on economic activity compared with 5.25 ± 3.52 hours worked by uninfected controls ($P < 0.01$). Performance of women's domestic chores was impeded and most affected people tried to avoid travel. The disability was worse in those with acute disease. In another Indian study, Sabesan *et al.,* (1992) found that an average of 26.5 man-days per patient were lost annually with a cost per person of around $US20 per person. Bandyopadhyay (1996) in a detailed study of the effect of filariasis on the women of India found that many were unable to work in the house or fields for up to a week at a time, 4 to 5 times per year because of acute filarial attacks. The economic loss per person was estimated at about 24 rupees a day - a small individual sum perhaps, but a large impost on a poor family, and given the large population of India and the high prevalence of filariasis, a large impost upon the country as a whole. Women with chronic pathology, especially those with persisting lymphodema and/or elephantiasis often regarded themselves and were regarded by others as permanently disabled and unable to work. The economic benefits of filariasis programs are well illustrated by a study in China. The cost of the control program in Miaoxi township, Huzhou City was around $US4,000 but the cost saving brought about by the reduction of person-working days lost due to acute filarial attacks and lessened demand for medication was around $US23,000 ie for every $US1 spent on filariasis control there was a net benefit of about $US5.75 (Shi *et al.,* 1995). A study in an urban area of Brazil showed that episodes of acute filarial disease frequently caused interruption of daily activities and kept people away from work from 3 to 15 days at a time. Alexander *et al.,* (1999) reports that is a highly endemic area of Papua New Guinea there are 0.31 episodes of adeno-lymphangitis per person per year in the leg alone and can cause complete incapacitation in the sufferer and curtailment of normal activities.

Nor is the impact of acute filariasis is not confined to the residents of endemic areas. A large number of American troops became infected with filariasis while stationed in the South Pacific during World War II. The socio-economic effects of these cases will be discussed in the section "filariasis in expatriates" below.

The Spectrum of Filarial Disease

Traditionally it has been accepted that five groups of people will be found in a filarial endemic area (Dasgupta, 1984; Partono, 1987; Ottesen, 1989; Evans *et al.,* 1993; Ottesen, 1993; Roberts and Janovy, 1997):

1. Exposed, but with no evidence of disease (so called "endemic normals".
2. Microfilaraemic asymptomatic.
3. Acute filarial disease with or without microfilaraemia.
4. Chronic disease, with or without microfilaraemia.
5. Tropical eosinophilia.

Endemic Normals

In a filarial context "endemic normal" refers to people who, despite constant exposure to filariasis and circulating antifilarial antibodies, are amicrofilaraemic and have no clinical evidence of disease (Ottesen, 1989; Weil *et al.,* 1996). Whether these people are truly immune to filariasis is debatable (Kazura *et al.,* 1993a; Weil *et al.,* 1996) have shown that many of these so called "endemic normals" have a cryptic infection because they have circulating filarial antigen which is identical to that found in people with microfilaraemia and ultrasound examination has also revealed that many men who are classified as "endemic normals have adult worms in their scrotum (Dreyer *et al.,* 1996a,c; Noroes *et al.,* 1996; Simonsen *et al.,* 1997b; Faris *et al.,* 1997; Suresh *et al.,* 1997). This indicates that many "endemic normals" rather than being immune, are harbouring adult worms, and rather than being "normal " or "immune" are in a pre-patent stage of the disease. A conclusion supported by Day (1991) who observed, "if you look carefully enough in any infected population, the endemic normal is a rare individual."

Evidence of Immunity

There is however some evidence, much of it from animal studies, that at least partial immunity to filariasis does occur (Denham, 1977; Oothuman *et al.,* 1979; Weil *et al.,* 1982; Kazura *et al.,* 1986; Hayashi *et al.,* 1984; Kazura and Davis, 1982; Kazura *et al.,* 1986; Nilsen *et al.,* 1988; Nanduri and Kazura, 1989). Work by Steel *et al.,* (1996) supports the concept of filarial immunity and suggests that it is probably T cell mediated. Michael and Bundy (1998) have found conclusive evidence that "herd immunity" does exist in filariasis and is modulated by vector exposure and biting rates. The reduction in microfilariae intensity in older people suggests that some degree of protective immunity may occur with long-term exposure (WHO scientific working group, 1981). Such individuals show high lymphocyte proliferative responses to filarial antigens (Nanduri and Kazura, 1989). Experimental animal models have shown that protective immunity is primarily directed against L3 stages (Oothuman *et al.,* 1979; Denham *et al.,* 1983; Yates and Higashi, 1985, Burkot *et al.,* 1996) and can be produced using radiation-attenuated but not dead L3 larvae (Story and Al-Mukhtar, 1982; Maizels and Lawence, 1991) and that the immunity provides cross protection between different filarial species (Oothuman *et al.,* 1979). Data from Papua New Guinea suggests that protective immunity to infective (L3) larvae is acquired over a number of years of exposure to infected mosquitoes and adults but not children, have high titres of antibody to L3 surface antigens (Day and *et al.,* 1991a,b). This stage-specific immunity may protect the individual from "super-infection" while leaving the resident parasites unharmed in the asymptomatic host (Maizels and Lawence, 1991). When worm burdens from infected individuals of different ages are quantified it can be shown that while childhood-acquired new filarial infections, the worm burden in adults remained the same irrespective of microfilariae density. Thus children with a high worm burden may have an even higher worm burden a year later whereas an adult with a low worm burden did not acquire any new infections (Day *et al.,* 1991b).

Asymptomatic Microfilaraemics

Asymptomatic microfilaraemia is often the most common manifestation of filariasis in many endemic populations and has been reported in children as young as 14 months (Lowman, 1944). It is often regarded as a "non-disease" because the individuals concerned have no inkling that their blood contains large numbers of microfilariae and this situation may persist for decades without any progression to clinical disease (Ottesen, 1992). Recent studies however have shown that asymptomatic microfilaraemia is not a benign phase of filariasis and that considerable lymphatic, tissue and organ damage may be occurring (Freedman *et al.,* 1994; Ottesen, 1994; Dissanayake *et al.,* 1995; Freedman *et al.,* 1995). Ultrasound has shown that approximately half of the men with asymptomatic microfilaraemia have nests of motile adult worms in their scrotal lymphatics: the "filarial dance sign" (Amaral *et al.,* 1994). For several centimetres either side of the worms the lymphatics are abnormally dilated but there is no evidence of an inflammatory response (Amaral *et al.,* 1994; Dreyer *et al.,* 1994). Lymphoscintigraphy has also revealed profound changes in asymptomatic microfilaraemics (Ottesen, 1994). Their lymphatics are markedly dilated with collateral channelling and increased lymph flow. By contrast, patients with elephantiasis (see below) show tortuosity, dermal back-flow, obstruction, stasis and poor regional node visualisation (Witte *et al.,* 1993; Dreyer *et al.,* 1994; Azoubel, 1996; Bernas *et al.,* 1996). The absence of an inflammatory response in the lymphatics near the adult worm in the asymptomatic stage of the disease suggests that the

lymphatic changes are induced by parasite or host-derived molecules acting directly on the lymphatics rather than an inflammatory reaction mounted by the host. Conversely, the changes seen in the tissues of those with chronic pathology are wrought by a mechanism which includes a vigorous inflammatory reaction (Ottesen, 1994). Exactly what triggers the change from one to another is on of the on-going debates in filarial research and will be further addressed in the sections on immunology and pathogenesis (below). People with asymptomatic microfilaraemia frequently show evidence of renal disease (see section on renal disease below).

Acute Filarial Disease

As mentioned in the section above on the socio-economic effects of filariasis, the main focus tends to be on the more spectacular chronic manifestations of filariasis such as elephantiasis. This is a focus that has to be altered if effective control of filariasis is to be achieved because:

(a) In most endemic communities the number of people who have elephantiasis is relatively small compared with those who suffer acute disease and the effects of acute disease on both the individual and the community can be severe.

(b) Health administrations often express the view that "filariasis is not a problem in our area" when what they really mean is that "elephantiasis is not a problem in our area". This distorts the epidemiological pattern of the disease and makes it difficult to convince the administrations in areas where there is very little chronic pathology that they need to undertake a filariasis control program.

(c) Acute filariasis can occur without microfilaraemia and may be mis-diagnosed as malaria or other tropical disease. This leads to the wrong treatment be given and a waste of health care resources.

In endemic areas acute attacks can occur in infants as young as 3 months (Dasgupta, 1984) but they usually start appearing in older children and teenagers and continue throughout life (Nanduri and Kazura, 1989). They can occur in amicrofilaraemics or microfilaraemics and are common in people with chronic diseases (Evans *et al.,* 1993; Roberts and Janovy, 1996). In some cases filarial infection markers such as filarial antigen and antifilarial IgG4 antibody are absent. A possible explanation in these cases is an inflammatory response against injected L3 stages before the adult worm has become established (Addiss *et al.,* 1994) but extensive reviews of acute filariasis in American troops during World War II showed that adult worms were present in up to 30% of cases (Wartman, 1947).

The most common manifestation of acute filariasis is Adeno-lymphadenitis (ADL), which is characterised by intense lymphangitis, lymphadenitis with retrograde extension from the affected node and reddening of the overlying skin. These attacks are usually accompanied by chills and fever (filarial or "elephantoid" fevers. In males there may be orchitis, epididymitis and acute transient hydroceles (Wartman, 1947; Nanduri and Kazura, 1989; Roberts and Janovy, 1996). (For a summary of the diagnostic criteria see the section below on filariasis in expatriates). Each episode lasts approximately a week and resolves spontaneously. Dunyo *et al.,* (1998) have reported that a common finding during the resolution phase is the onset of exfoliation of skin of the affected limb. Das Bidyut *et al.,* (1996) found that circulating Tumour necrosis factor (TNF) is increased during acute filarial episodes suggesting that TNF may play a role in inducing clinical systems and that TNF inhibitors may have a place in its management.

Acute filarial attacks can be extremely debilitating and many people are confined to their houses and unable to take part in productive activity. During a study of 1,300 filariasis patients, Pani and Srividya (1995) found that ADL attacks increased in frequency as the severity of lymphodema increased. In patients with grade 1 lymphodema (mean duration 47.4 days), the mean number of ADL attacks per year was 4.9, while with Grade 2 lymphodema (mean duration 6.2 years), 5.5 per year and Grade 3 lymphodema (mean duration of lymphodema 8.6 years) 10.4 per year. Filarial fevers may occur in the absence of other symptoms and is often treated as "malaria". Health care records which show a high proportion of "antimalarial resistant" fevers is sometimes the first indicator that acute filariasis occurs in a community (personal observation from Papua New Guinea). It has been suggested that the fever is an allergic reaction to excreted worm antigens (Ottesen, 1984; Kar *et al.,* 1993) and studies in ferrets have shown that severe lymphodema is associated with high levels of filarial-specific IgE (Crandall *et al.,* 1993). (See section on humoral immunity below). It has been shown in *in-vivo* studies that disodium cromoglycate selectively inhibits IgE production and enhance the production of IgE-blocking IgG4 antibody by human B cells *in-vitro* (Kimata *et al.,* 1991). It would be interesting to see if the same effects could be demonstrated with lymphocytes stimulated with filarial antigens. Shenoy *et al.,* (1995) found that there was an association between the degree of oedema and the frequency of ADL attacks. They also found that DEC alone or DEC plus antibiotics did not reduce the number of ADL attacks but simple hygienic measures combined with topical antibiotics and antifungal creams were effective in reducing the attacks. Shenoy *et al.,* (1999) have found that care of the feet and local and systemic antibiotic use is an important tool in reducing the frequency and severity of ADL attacks. This suggests that the aetiology of ADL is a complex combination of filarial infection *per sé* and secondary bacterial and or fungal infection (Dreyer *et al.,* 1999c). A important new development has been the finding that the inflammatory responses induced by filaria may be strongly mediated by the lipopolysaccaride-like

substances produced by *Wolbachia* symbiont bacteria carried by the female worms (Taylor *et al.,* 2000). Das *et al.,* (1996) have shown a relationship between Tumour necrosis factor (TNF) and the severity of clinical symptoms of acute disease. Expansion in this area of knowledge would be worthwhile - what happens to phospholipase A_2 (PLA_2) which is modulated by TNF and what is the role of specific TNF and PLA_2) inhibitors in the management of ADL?

Chronic Disease

It has been generally accepted that most people with chronic disease are amicrofilaraemic and that patent infection is negatively related to chronic disease (Jordan, 1955; Nanduri and Kazura, 1989). This basic tenet of filariology has been challenged by metanalysis studies of previously published studies by Michael *et al.,* (1994) who found that, contrary to expectation, that there was an equal prevalence of disease in microfilaraemics and amicrofilaraemics. Indeed, in some studies, especially those involving hydroceles, disease was more prevalent in microfilaraemics than amicrofilaraemics. This demonstrates the need for "traditional filarial dogma" to be re-evaluated in the light of modern diagnostic, immunological and statistical modelling techniques.

Often the first sign of the onset of chronic disease is persistant limb lymphodema or hydroceles after an acute attack (Evans *et al.,* 1993) and the process of development from lymphodema to hydroceles or elephantiasis is a gradual one. The lymphatic dilation, co-channelling and rapid lymph flow seen in asymptomatic microfilaraemic is replaced by tortuosity, dermal back-flow, obstruction, stasis and poor regional node visualisation (Witt *et al.,* 1993; Dreyer *et al.,* 1994). The switch from asymptomatic filariasis to chronic pathology is also accompanied by profound changes in cellular and humoral immunity (see section on immunity below).

There have been several methods devised to try and increase lymph drainage and prevent lymphedema. Hyaluronidase was tried with some success by Jordan (1959) and coumarin, a drug which increases macrophage-associated proteolysis and reduces stasis of protein in the tissues, has been shown to be of benefit in reducing lymphodema and elephantiasis (Jamal *et al.,* 1989a,b, Casley-Smith *et al.,* 1993). Surgical procedures such as the establishment of a shunt between the lymphatic and venous system or the lymphatics and the ometum (Goldsmith *et al.,* 1967; Goel and Misra, 1968; Goldsmith, 1974; Jamal, 1989a; Abalmasov *et al.,* 1994; Binoy, 1998) have been shown to be effective in reducing lymphodema in some patients, and lymphosuction has been proposed as a new treatment modality for chronic lymphedema (Clodius, 1998; Agarwal *et al.,* 1998).

Overall, hydrocele is the most common form of chronic Bancroftian filariasis and in parts of Africa it predominates. Hydrocele is said to have affected up to 70% of males along the Tanzanian coast (Wegesa *et al.,* 1979 and 60% of males in coastal Kenya by the time they reach age 70 years (Wijers, 1977; Estambale *et al.,* 1994a,b). Gyapong (1998) found a very strong positive association between hydrocele and microfilaraemia and only a weak association between elephantiasis and suggests that the pathophysiologies of the two conditions may be different. The strong association between community infection and hydrocele in Ghana, is being used for rapid community assessment of filariasis prevalence (Gyapong *et al.,* 1998a,c)

Elephantiasis is relatively uncommon in Africa and is mostly found in the areas with the most intense transmission (Wijers, 1977; Evans *et al.,* 1993). Hydrocele is also common in India. In Pondicherry, India, 45% of males have a hydrocele by the age of 60 years; Pani *et al.,* 1991) but a whole range of other chronic manifestations ranging from chronic lymphodema to elephantiasis are also seen (Evans *et al.,* 1993). In some populations, despite a high prevalence of microfilaraemia and filarial antigenaemia, filariasis is a mostly a cryptic disease and the number of people with chronic pathology is relatively low. For instance, the prevalence of filarial antigenaemia in many parts of Papua New Guinea is around 80% yet elephantiasis occurs only in scattered foci and is nowhere common (Kazura, 1984)**.** This again draws attention to what I like to call the "elephantiasis only syndrome" whereby we may be tempted to think that because elephantiasis is seldom seen, filariasis in not a community problem.

The first evidence of impending elephantiasis is persisting lymphodema (, which is followed by fibrous infiltration, and thickening of the skin. Granulomatous, fat and fibrous connective tissues are laid down in the subcutaneous tissues (Burri *et al.,* 1996). Fissure and ulcer formation (figures 9 and 10) allows access of bacteria and fungi, which have been shown to play an important role in the pathogenesis of elephantiasis.

Figures 9 and 10: Fissure and ulcer formation.

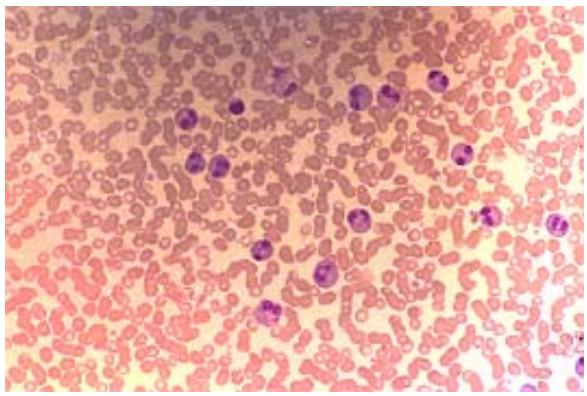
It has been shown that the risk of acquiring chronic filarial disease rises with increasing microfilariae density (Ravindranathan *et al.,* 1980). Chronic manifestation can be graded as follows (Table 4).

Table 4. Grading of lymphedema (Gyapong *et al.,* 1994; Mcmahon *et al.,* 1996)

Manifestation	Grade. Symptoms
Elephantiasis of limb	0. Normal
	1. Loss of contour or lymphodema
	2. Thickened skin and/or loss of elasticity
	3. Evident elephantiasis
Hydrocele	0. Normal
	1. Swelling of spermatic cord
	2. Swelling up to 10 cm in diameter
	3. > 10 cm in diameter
Scrotal elephantiasis	0. Normal
	1. Lymphodema
	2. Thickened skin and/or loss of elasticity
	3. Evident elephantiasis

Tropical Pulmonary Eosinophilia (TPE).

This is the least common manifestation of filariasis and is at the opposite end of the immunological spectrum from asymptomatic microfilaraemia. In TPE there is a severe hypersensitivity response with marked eosinophilia (figure 11), extreme levels of serum IgE and high titres of antifilarial IgG and IgE.



Circulating microfilariae are not usually found (Van der Sar and Hartz, 1945; Ottesen *et al.,* 1982) but adult worms may be detected by ultrasound (Dreyer *et al.,* 1996d). Paranjape *et al.,* (1985) found that although the mean level of anti-filarial IgG antibody is very high, a small number of patients who had clinical TPE had lower than expected antibody titres.

Clinically TPE is characterised by nocturnal coughing and asthma. Pulmonary infiltration gives rise to a characteristic x-ray picture ("snow flake" lung). Accumulation of eosinophils in the lung with the release of cationic proteins and free radicals can lead to fibrosis and permanent lung damage (Pinkston *et al.,* 1987). The culprit is thought to be an IgE-producing allergen derived from microfilariae (Lobos *et al.,* 1992). For some reason the blocking effects of anti-filarial IgG4 do not seem to work in TPE patients. Tropical pulmonary eosinophilia is most common in South India (Ray *et al.,* 1993) and parts of Southeast Asia but is rarely seen in Papua New Guinea (Nanduri and Kazura, 1989) and Africa (Magnussen *et al.,* 1995).

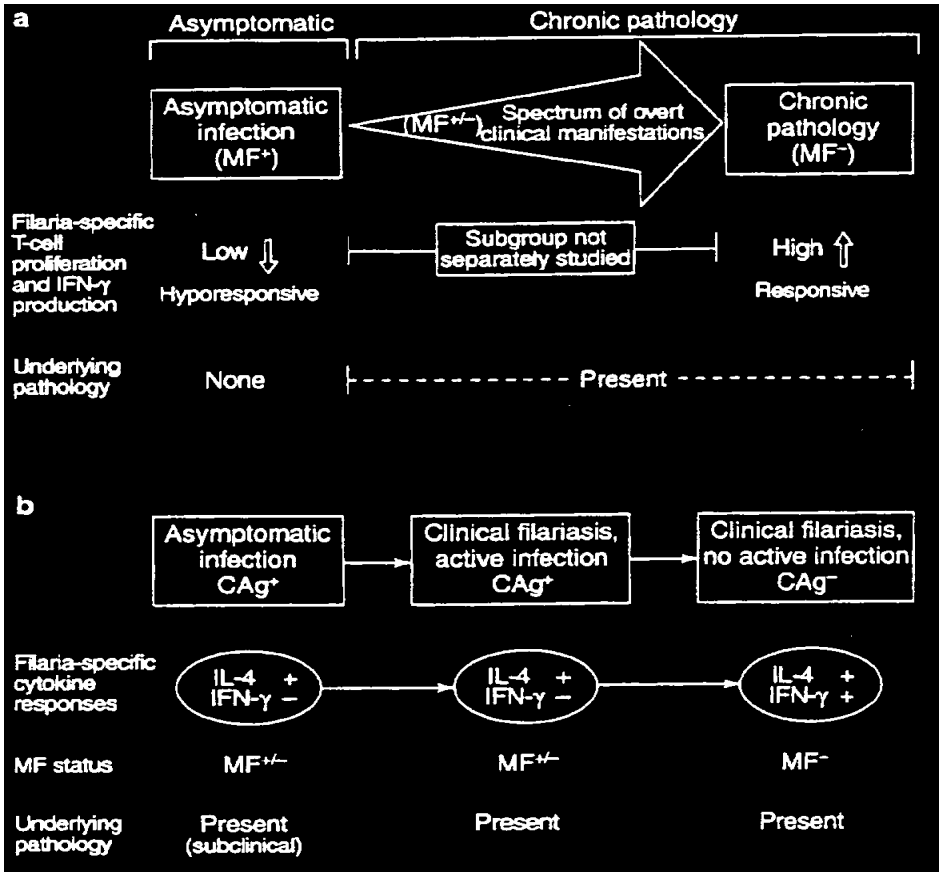
Recent Ideas on the Classification of Disease

The introduction of assays for circulating filarial antigen (More and Copeman, 1990; Weil, 1987; Weil *et al.,* 1987), the discovery of lymphatic pathology in many "asymptomatic microfilaraemics" (see above), a lack of evidence that there is a negative association between microfilaraemia and disease, and the recognition of the role of bacterial infections suggests that the old classification based on the presence or absence of microfilaraemia and/or chronic pathology is outdated. Freedman (1998) proposes a new classification: asymptomatic infected individuals who are antigen negative; individuals who have overt filariasis and active infection (antigen positive) and individuals who have overt filariasis without active infection (antigen negative). Freedman defines overt filariasis as any of the clinical manifestations associated with the known clinical spectrum of filariasis: adenolymphangitis, hydrocele or elephantiasis (Figure 5).

As cytokine responses appear to segregate according to the presence of Cag rather than the results of the clinical examination, patient classification must

account for both factors. Because all filariasis patients have underlying pathology, this term as used in earlier classifications is now unhelpful in segregating patients. Three groups of individuals are proposed as appropriate for detailed immunological study: asymptomatic microfilaraemics; those with clinical filariasis with active infection (Cag+); and those with clinical infection without active infection (Cag-). Microfilariae prevalence status refers to microfilaraemia as detectable by conventional parasitological methods, so that some infected individuals may have microfilaraemia undetectable by these methods. Abbreviations: IFN-γ, interferon γ; IL-4, interleukin 4; MF microfilaraemia (Freedman, 1998, used by permission).

Figure 12. Before the availability of circulating filarial antigen (Cag) assays to sensitively assess current infection status, groupings of humans with filariasis for immunological study have been based on detection of circulating microfilariae (a). Infected individuals with detectable microfilaraemia but without any outwardly discernable manifestations of lymphatic filariasis have been called "asymptomatic microfilaraemic individuals" (top left). Although clinically, filariasis is a spectral disease, those with clinical evidence of lymphatic insufficiency have mostly been grouped together as "chronic pathology" (top right) and have thought to be generally amicrofilaraemic. Separate immunological data on chronic pathology patients who are also microfilaraemic have not been readily available. Infection status as determined by recently available Cag assays permits a different framework for patient classification to be proposed (b).



(With permission of Professor D. Freedman)

Filariasis and Other Illnesses

Filariasis and Asthma

A study from Sri Lanka suggests that filariasis may be a trigger for bronchial asthma (de Sylva *et al.,* 1990). This study of children with cough and wheeze suggests that more than 1/3 had filarial infection. Symptoms improved after DEC therapy probably due both to the elimination of the microfilariae and the anti-inflammatory effects of the DEC. The authors postulate that atrophic individuals have a heightened response to filarial antigen, which may trigger asthma.

Chyluria

The presence of chyle in the urine follows the rupture of dilated lymphatics in the bladder or renal pelvis into the urinary system is a rare but spectacular complication of filariasis (Cahill, 1965; McMahon and Simonsen, 1996).

Renal Disease

There have been several reports of renal abnormalities associated with filarial infections in both humans and animals: hematuria, proteinuria, nephrotic syndrome and glomerulonephritis have all been recorded (Sapico and Baltazar, 1967; Antani and Krishnamurthy, 1971; Casey *et al.,* 1972; Simpson *et al.,* 1972; Crowell *et al.,* 1973; Klei *et al.,* 1974; Mukherjee *et al.,* 1974; Chugh *et al.,* 1978; Dufor and Lepage, 1978; Date *et al.,* 1979; Srivastava *et al.,* 1979; Waugh *et al.,* 1980; Yap *et al.,* 1982; Date *et al.,* 1983; Ormerod *et al.,* 1983; Ngu *et al.,* 1985; Langhammer *et al.,* 1997; Barsoum, 1999). Circulating immune complexes containing filarial antigen have been blamed for the renal damage (Au *et al.,* 1981; Dissanayake *et al.,* 1982; Gajanana *et al.,* 1982; Prasad *et al.,* 1983a,b,c; Das *et al.,*1987; Prasad and Harinath, 1988; Lunde *et al.,* 1988; Lutsch *et al.,* 1988) and filarial antigen has been located in a renal biopsy (Ngu *et al.,* 1985). In a study of 20 patients with asymptomatic microfilaraemia Dreyer *et al.,* (1992) found that 7 had microscopic hematuria and 4 had proteinuria but their creatinine clearances were normal. Ten individuals who had not shown hematuria and 10 who had not shown proteinuria developed it after DEC treatment but all patients in the study had normal urinanalysis 2-3 weeks after therapy. Oliveira (1998) has postulated that one of the causes of membranous nephropathy, an IgG4-mediated disease, are helminths. Amyloidosis also leads to renal disease and filarial infection has been definitely linked to filarial infection in Mongolian gerbils (Crowell *et al.,* 1973) and an association between amyloidosis and human filariasis has been found (see below).

Amyloidosis

Amyloidosis is unusually prevalent in Papua New Guinea (Anders *et al.,* 1976a,b). Cooke and Champness (1970) for instance found amyloid deposits in 7.3% of 1,101 post-mortem material they examined.

Prior to 1978 the tropical diseases known to cause secondary amyloidosis included tuberculosis, leprosy, schistosomiasis, leishmaniasis and chronic suppurative infections (McAdam, 1978). A strong association has been described between filariasis and amyloidosis in a village survey in the Upper Fly region of the Western Province of Papua New Guinea (McAdam, 1978). Six people out of the surveyed population of 224 had evidence of both filariasis and amyloidosis. The level of the amyloidosis-precursor protein SAA (Anders *et al.,* 1976b; Levin *et al.,* 1973) was highest in 2 people who suffered recurrent episodes of filarial adeno-lymphadenitis and in one of these the level of protein SAA rose 10 fold during a acute attack lasting 3 days. Clearly, this is another health threat imposed by filariasis and another reason why filariasis should be eradicated.

Arthritis and Arthralgia

Filariasis can present with rheumatic features (Adebajo, 1996) and mono-arthritis of a knee or ankle joint is common in filarial-endemic areas. Chaturvedi *et al.,* (1993) investigated 19 cases of arthritis of unknown origin in children and found that 16 of them had filariasis. Nine of these cases were treated with DEC and the arthritis resolved. Low *et al.,* (1996) describe a patient with a hot swollen foot and eosinophilia that responded to DEC. Magnetic resonance imaging (MRI) may be a useful tool for diagnosis (Blacksin *et al.,* 1999).

Polymyositis

Poddar *et al.,* (1994) reported two cases of polymyositis, which presented with generalised painful swelling and weakness of the muscles. Serum creatinine kinase was elevated and inflammatory myopathy was present in biopsies. *W. bancrofti* microfilariae were present in the peripheral blood. The patients responded better to DEC and steroids than to steroids alone and clinical improvement was associated with the clearance of the microfilariae. A patient with acute filarial myositis that responded rapidly to DEC therapy was reported by Sundaray *et al.,* (1992).

Central Nervous System (CNS) Disease

Central nervous system involvement has been reported in Loasis (Brunetiere, 1913; Peruzzi, 1928; Tha Mya, 1928; Van Bogaert *et al.,* 1955). Epileptic seizures decreased after Ivermectin therapy for onchoceriasis (Kip *et al.,* 1992) and a similar finding associated with lymphatic filariasis has been reported by Adamolekun *et al.,* (1993). Garg *et al.,* (1996) reported a Pott's paraplegia-like neurological complication in a filariasis patient. Orihel (1973) reviewed cases of neurological disease which were first thought to be due to infection with *D. perstans* but he was of the opinion the morphology of the microfilariae was consistent with *Meningonema peruzzi* a filaroid species usually found in old world monkeys. Psychotic manifestations were also common in United States servicemen who contracted filariasis during the Second World War (see section "filariasis in expatriates" below) and "nervous symptoms" were noted in Ceylonese students with microfilaraemia by Wijetunge (1967a,b) Fonticiella *et al.,* (1995) reported a case of a new born with intra-cranial, partially calcified extra-axial collections, which were shown to be due to filariasis transmitted from the mother. Microfilariae of *B. malayi* have been demonstrated in the brains of experimentally infected animals (Paily *et al.,* 1995).

Ocular Involvement

Gupta *et al.,* (1992) report a case of retinal pigment epithelium inflamation and vasculitis in a microfilaraemic patient which rapidly resolved after anti-filarial treatment and Mathai and David (2000) reported a patient who had and adult *W. bancrofti* removed from his eye.

Guillain-Barre Syndrome

Bhatia and Misra 1993) reported a patient who developed recurrent Guillain-Barre syndrome after acute filariasis.

Filariasis and Leucocytes

Apart from eosinophils (see below), filariasis seems to have little effect on the total or differential leucocyte count. There is one paper by Adhikari *et al.,* (1994) which found that the neutrophil percentage was significantly reduced while lymphocyte and eosinophils were increased in filariasis.

Filariasis and Eosinophilia

Eosinophilia is defined as an increase in the number of peripheral blood eosinophils (Zucker-Franklin, 1983). Eosinophilia can be caused by: Parasite infections, allergic disorders, dermatitis, malignant hyper-eosinophilic syndromes and tumours (Zucker-Franklin, 1983). Eosinophilia is often seen in filariasis and very high eosinophil counts are usually found in tropical eosinophilia syndrome (Van der Sar and Hartz, 1945; McMahon and Simonsen, 1996; Roberts and Janovy, 1996) but many people with filariasis are hosts to other helminth parasites also and it is difficult to measure the direct association between eosinophilia and filariasis. Wong and Guest (1969) found that filarial-associated eosinophilia was present in 11 out of 16 individuals who had strong anti-L3 stage antibodies. By contrast, only 3 out of 14 people with microfilaraemia and 9 out of 16 people with elephantiasis had eosinophilia. Filariasis however, should always be considered when investigating a patient, including returned travellers, for filariasis (Moore and Nutman, 1998).

Cardiac Disease

Tropical endomyocardial fibrosis is common in some tropical areas and is believed to be associated with chronic hyper-eosinophilia caused by helminth infections, including filariasis (Andy *et al.,* 1998). Filarial infection is also a rare cause of pericarditis (Foster, 1956; Chakravarty and Gupta, 1966).

Splenomegaly

Schuurkamp *et al.,* (1987, 1992) have shown that filariasis is an important cause of splenomegaly and that it can be reversed by DEC therapy. Traumatic rupture of a filarial spleen has also been recorded (Behara *et al.,*1995) and Piyaratn and Pradatsundarasar (1961) reported a case of micro filarial granuloma of the spleen. Splenectomy has been shown to increase microfilariae density in animal studies (Hawking, 1962b; Nooruddin and Ahmed, 1967) but there appears to be no information on the effects of splenectomy in the human.

Filariasis and Anaemia

There has been one report of a significant association between filariasis and anaemia. Saxena *et al.,* (1981) found that 70% of symptomatic cases had an Hb <100g/l. None of these had any other helminth infection. By contrast, none of their control cases had an Hb <100g/l.

Filariasis and Platelets

No association between thrombocytopenia and filariasis has been established but there is evidence that circulating microfilaria modify platelet function. A detailed study by Lui and Weller (1992) showed that *Brugia malayi* microfilariae per 104 platelets completely inhibited platelet aggregation with collagen, arachidonic acid and ionophore A231187, thromboxane generation and thromboxane release when incubated with human platelets. Microfilariae also inhibited the aggregation of platelets in platelet rich plasma stimulated by adenosine diphosphate, compound U46619, or platelet-activating factor. The

effect required close proximity but not direct contact between the microfilariae and was mediated by parasite-derived soluble factors of low molecular weight. This phenomenon explains why platelets do not adhere to microfilariae and why filariasis patients do not seem to suffer from thrombo-occlusive events despite having a large number of circulating foreign objects (microfilariae) that could act as a stimulus for such events. Microfilariae also utilise exogenous and endogenous arachidonic acid to generate and release to substances that influence platelet metabolism and function - prostacyclin and prostaglandin E2. The effects on platelet function wrought by microfilariae do raise the question about the possibility of a bleeding tendency in filariasis patients and suggests a study may be worthwhile. Anti-platelet aggregation drugs are widely used to prevent thrombo-occlusion in general medicine and it is possible that if the platelet inhibitor from the filarial parasite could be isolated it could from the basis for a new drug. Paradoxically, infection with the dog heartworm *Dirofilaria immitus* is reported to enhance platelet reactivity (Boudreaux *et al.,* 1989, 1991). Another interaction between microfilariae and platelets has been suggested by the finding by Pancre *et al.,* (1988) that platelets isolated from filariasis patients are cytotoxic to microfilariae *in-vitro* and that this activity is dependant upon the presence of anti-filarial IgE. The cytotoxic effect was strongly inhibited by antigen-stimulated T lymphocyte supernatants from filarial patients - another protective mechanism induced by parasite-induced immune system modulation.

Miscellaneous Complications

Other complications recorded include acute abdomen in pregnancy (Charles, 1976), cystitis with urethral obstruction (Devasia *et al.,* 1998), microfilariae in ascitic fluid (Handa *et al.,* 1996), fibrosing mediastinitis (Gilbert and Hartman, 1996), cases of tropical vaginal hydroceles (Sivam *et al.,* 1995) and bladder pseudotumours (Gourlay *et al.,* 1999). Wijetunge (1967a,b) studied the clinical manifestation of 212 microfilaraemics and suggests that ocular complications, enlargement of the thyroid gland, nocturnal chest pain, buccal ulceration, parotitis, gastrointestinal pain and arthralgia can be caused by filariasis. There is one report of an association between mild Vitamin A deficiency and onchocerciasis (Zambou *et al.,* 1999) but no comparable studies have been done in lymphatic filariasis.

Filariasis in Expatriates

When people from a non filarial-endemic area move to an endemic area two different patterns of disease are seen depending on whether the migrants are visitors who stay only for a short period or migrants who remain permanently in the endemic area.

Filariasis in US World War II Forces

Many thousands of cases of filariasis occurred in the United States forces stationed in filarial-endemic areas during World War II, especially in the Pacific Theatre, Papua New Guinea and the Solomon Islands and filariasis was among the leading causes of medical evacuation in the South Pacific (Swartzwelder, 1963). Coggeshall (1945, 1946) and Wartman (1947) state that about 38,300 naval personnel were exposed to filariasis and of these, 10,421 were diagnosed as having the disease. In one unit alone, stationed in a highly endemic area of Samoa, 70% of the exposed troops became infected (Beaver, 1970).

A list of relevant papers is given in Table 5.

Table 5. Filariasis among United States servicemen in the Second World War: number of cases, places and length of exposure and incubation period (Wartman 1947)

Author and Date	Place of Infection	Exposure Length (mths)	Incubation Period (mths)	Number of Cases
Behm and Hayman, 1946	Tonga-Tabu	12	2-18	532
Burhans et al., 1944	South Pacific	nr	3-21.5	46
Coggeshall 1945	Samoa 96% Solomons 4%	1-27 av 12.5	9	1200+
Coggeshall, 1946	South Pacific	Various	1-12	2288
Dickson et al., 1943	Samoa	nr	1-9.5	251
Englehorn and Wellman, 1945	South Pacific	nr	3-14	127
Flynn, 1944	Samoa	2-22	1-5	125
Fogel and Huntington, 1944	South Pacific	nr	nr	large
Glauser, 1945	Samoa	1-23 (av 9)	2-22	172
Goodman et al., 1945	Samoa	2-23	nr	145
Haviland, 1944	South Pacific 97%	1-18	1-19	228
Hodge et al., 1945	Tonga-Tabu	12	nr	62
Huntington et al., 1944	South Pacific	nr	3.5+	251
Johnson, 1944	Samoa	nr	av 9.5	189
Leede and Josey, 1945	Samoa	16.3	2-22	100
Michael, 1944	Samoa	nr	7-9	120
Rifkin and Thompson, 1945	Samoa	13-30	14-20	30
Saphir, 1945	South Pacific	3-6	4-9	35
Smith, 1945	Samoa 97%	3-17	nr	737
Wartman and King, 1944	Samoa	2-11	3+	268
Wartman, 1944	Samoa	1-5	nr	17

Coggleshall, (1946) made a prospective and retrospective study of 2,288 cases. Wartman and King (1944) record 268 American troops with filariasis and state that one fifth of the troops station on a particular island were admitted to hospital with symptoms of filariasis. Engelhorn and Wellman (1945) reported 127 cases of filariasis at a field hospital in Samoa over a 4-month period. On Tonga-tabu Island in the central Pacific 532 men were diagnosed with filariasis in a single year (Behm and Hayman, 1946). Glauser (1945) reported 72 cases in returning marines during a 6-month period. Two thousand five hundred and ninety five cases of filariasis were admitted to the United States Marine Corps hospital at Klamath Falls, Oregon during a 17-month period (Coggeshall, 1946). Smith (1945) recorded 737 cases which were acquired in Samoa, Wallis Island, New Caledonia and Bougainville and Goodman *et al.,* (1945) studied 145 soldiers with filariasis admitted to Harmon General Hospital who had served in the Cook Islands, Bora Bora Island, Samoa, Woodlark Island (Milne Bay Province, Papua New Guinea) and Ellice Island. Hodge *et al.,* (1945) reported 62 cases at a single field hospital, Flynn (1944) reviewed 125 cases of filariasis admitted to hospital from a single marine battalion that had been stationed in Samoa, Vanuatu and the

Solomon Islands and Dickson *et al.,* (1943) reviewed 251 patients addicted to a Samoan mobile hospital in a single year**.** Two hundred cases were studied by Thompson *et al.,* (1945), 189 cases by Johnson (1944), 268 by King (1944) and unstated numbers by Fogel (1945) and Michael (1944). According to Swartzwelder (1963) filariasis caused a significant loss of manpower and money and seriously compromised the fighting ability of American army units in the South Pacific. He gives the following as an illustration: The 134th Field Artillery Battalion and the 404th Combat Engineer Company were stationed on Tongatabu Island in the Central Pacific from May 1942 until May 1943 and then on Woodlark Island, Milne Bay Province, Papua New Guinea from July 1942 until January 1944. Because of the large number of personnel infected with filariasis the units were withdrawn to Sydney, Australia where the prevalence of filariasis (based on clinical grounds) among the evacuees was found to be 65% in the 134th Battalion and 55% in the 404th Company. The commanding general of the 6th United States Army recommended that the entire units be withdrawn from active service and return to the United States because their fighting efficiency had been seriously impaired and their rehabilitation would extend over an indefinite period of time. There was also a high economic cost to the American forces - estimated by Napier (1947) at around 100 million dollars. When introducing a speaker at the annual meeting of the American Society of Tropical Medicine and Hygiene the moderator remarked "that in World War II filariasis cost the Navy the equivalent of a battalion of marines for 4 years and enough money to run the Naval Medical Research Institute for 25 years." (American Society for Tropical Medicine and Hygiene, 1957). Filariasis is often thought of as a slowly developing disease, which requires a long period of exposure in order to become infected. A notable feature of the above table is the short exposure time, in some cases only 1 month.

Wartman (1947) provides an extensive epidemiological and clinico-pathological review of over 6,678 cases recorded by the authors referenced in Table 6 and other clinico-pathological reviews are provided by Thompson *et al.,* (1945), Fogel and Huntington (1945) and Beaver (1970). One of the most notable features is that microfilaraemia was only detected in about 20 cases (Wartman, 1947; Beaver, 1970). Despite the failure to demonstrate microfilariae in most cases there is little doubt about the diagnosis. The clinical signs and symptoms were typical of acute filariasis and, most telling of all, adult worms were recovered in about 30% of the cases (Wartmann, 1947)**.** There are at least two possible explanations for the lack of circulating microfilariae. In expatriate cases the adult worm induced a marked inflammatory reaction with a dense collection of inflammatory cells. It is possible that the microfilariae get trapped within the lesion and are unable to make their way into the circulation. Another, probably more plausible explanation is that the immune response in previous unexposed expatriates is more vigorous than that seen in "immune tolerate" residents (see below) and the microfilariae are rapidly destroyed. When the rare cases of microfilaraemia did occurred the microfilariae showed the same diurnal periodicity pattern that was usually seen in the native population (Eyles *et al.,* 1947).

Almost all the cases occurring in the American troops the cases could be termed "acute filariasis" and would fall into the modern category of filarial adeno-lymphangitis. It was observed by Huntington *et al.,* (1950) that the signs and symptoms were identical to the syndrome called "mumu" present in Samoan indigenous populations. The attacks commonly lasted from 3 to 5 days with occasional incidences of 2 weeks, or very rarely, one month (Behm and Hayman, 1946). Recurrent attacks were common, occurring at intervals of a few weeks to several months. Hard exercise, fatigue and a hot climate were thought to be precipitating factors (Wartman, 1947). The diagnostic criteria used by Hodge *et al.,* (1945) are provided in Table 6.

Table 6. Diagnostic criteria used for filariasis cases in us forces (Hodge *et al.,* 1945)

A. Involvement of the Genitalia:	**B. Involvement of the Superficial Lymphatics of the Extremities**
1. Episodes frequently follow periods of manual labour	1. Pain in the extremity radiating distally is the usual complaint.
2. Testicular pain was the most common complaint.	2. Pain may be first noticed in the proximal lymph nodes.
3. The pain may radiate up the spermatic cord or may first appear in the lower abdomen and radiate down the spermatic cord to the testicle.	3. The affected extremity becomes edematous.
4. The spermatic cord and epididymis are thickened and indurated but the vas deferens is not involved.	4. A definite "red streak" characteristic of acute lymphangitis appears proximally. The affected lymphatic is palpable and usually only a single vessel is involved.
5. Acute hydrocele is often present.	5. There is increased local heat.
6. Pain in the mesial aspect of the thigh on the affected side may be present.	6. The lesion extends centrifugally.
7. Scrotal edema is often present.	7. Resolution begins proximally and extends centrifugally.
	8. The lymph nodes draining the affected area are enlarged and tender.
	9. Severe constitutional manifestations are usually absent.

The most common presenting signs and symptoms in the American armed forces cases were pain and swelling of the genitalia closely followed by lymphangitis of the arms and legs. Lesions of the genitalia in order of frequency were funiculitis, epididymitis, scrotal oedema and inflamation, lymph scrotum, orchitis, hydrocele and varicocele. Lymphangitis occurred in between 51 and 80% of cases. The most common site was the arm, followed by the leg, groin, buttock and abdomen. An important feature was the tendency for the inflamation to spread in a retrograde direction. Some authors reported skin temperature increases in the effect area but others did not. Lymphodema was occasionally observed but was not common. The prevalence of lymphadenitis varied widely from group to group and ranged from 85% to 7%. Where lymphadenitis was present the most commonly affected nodes were the epitrochlear and the inguinal but other nodes were often involved. Evidence of hypersensitivity was commonplace with many patients suffering urticaria and transient swellings. Some of the latter resembling the "Calabar swellings" or "fugitive swelling" usually associated with *Loa loa* infections. A small number of patients developed a macular erythematous rash. Hypersensitivity-type manifestations were only seen while the patients were an endemic area, which raises the possibility that they were caused by a reaction to mosquito-injected L3 larvae. One study reported a high incidence of conjunctivitis and some incidences of phobophobia. Filarial fevers were very uncommon and only one case of filarial abscess was reported. Systemic symptoms - malaise and fatigue, were very commonly associated with acute attacks.

The most common laboratory finding was eosinophilia and in a few cases there was a very high eosinophil count associated with a chronic cough - a hallmark of tropical eosinophilia syndrome (King, 1944; Hirst and McCann, 1945; Pinkston *et al.,* 1987).

Psychological disturbances were common and are discussed by Dickson *et al.,* (1943), Rome and Fogel, 1943, Coggeshall (1945) Englehorn and Wellman, (1945), Glauser (1945), Goodman *et al.,* (1945), Smith (1945), Zeligs (1945), Behm and Hayman (1946); Coggeshall (1946) and Swartzwelder (1963). Typical manifestations were depression, irritability, concentration difficulty, nervousness, anxiety, sleep disorders and fear. It is possible that filariasis *per sé* does produce some mood swings and depression (Rome and Fogel, 1943) but many of these symptoms may have been precipitated by observing Polynesian and Melanesian nationals with disfiguring diseases such as severe hydrocele and elephantiasis and a fear that they would as one writer puts it "go home with their scrotum in a wheelbarrow" or suffer loss of sexual function. As it turns out however, these fears were unfounded. No cases of chronic pathology occurred. Whilst Behm and Hayman (1946) reported 33 patients who believed their sexual potency had been impaired by filariasis and Smith (1945) reported that many of his patients reported a loss of libido, there is no evidence of long-term effect on sexual function and the prevalence of impotence and sterility was no higher in filariasis patients than in the general population (Wartman 1947). Coggeshall (1946) reported that 107 of 504 marriages among marines with a diagnosis of filariasis resulted in pregnancy within 6 months.

How long do the signs and symptoms of filariasis persist after removal from an endemic area? Behm and Hayman (1946) and Wartman (1947) reported that in most cases, even without treatment, attacks became progressively milder when patients were removed from the endemic area. Most men were free of symptoms after they had been out of the endemic area for 20

months but occasional cases persisted for up to 3 years. By contrast however, Trent (1963a,b) who re-evaluated 25 men who had been diagnosed as having filariasis during the Second World War and found that many of them still had evidence of the disease 15 years after leaving the endemic area. Intermittent genital symptoms - pain, swelling and tenderness precipitated or aggravated by standing or physical exercise was present in 32%. Forty percent had abnormal physical findings such as thickening of the spermatic cord, the presence of a tender nodule near the testis, induration of the testis, varicocele, or thickening of the scrotal skin. Recurrent lymphangitis still occurred in 12% with attacks occurring 1 to 3 times per year and lasting for 1 to 3 days. Symptoms consisted of sudden onset of fever, headache, malaise, swelling of affected lymphatics and swelling of regional lymph nodes. In 68% there were episodes of swelling of the extremities and enlargement of the regional lymph nodes draining the area. These episodes tended to occur most frequently in the summer months and the patients complained that the skin of the affected extremities became "puffy, stiff and tight". Winstead (1978) reported a patient who still complained of symptoms 30 years after contracting the disease during military service in Samoa. At the time of his examination (1972) there was no clinical evidence of active filariasis but he had a positive skin test and a weakly positive haemagglutination test. There is no evidence that any of those infected during WW2 developed chronic hydrocele or elephantiasis but in occasional cases microfilaraemia persisted cases persisted for 15 years (Conn and Greenslit, 1952; Trent, 1963 a, b).

There are several vexing questions to be answered with regard to the American armed forces cases. Why did most of the cases occur in the central Pacific area? Most authors seem to believe that it was because the soldiers were in close contact with infected natives in an area highly endemic for filariasis. Papua New Guinea and the Solomon islands were also highly endemic for filariasis and many American troops were also stationed there. Although some American forces cases did occur in these areas, the numbers seem to be far lower than those that occurred in the Pacific area. Wartman (1947) suggests that the high number of cases in the Central Pacific was due to the fact the vector mosquito is a day time feeder, the microfilariae have diurnal periodicity and since most of the troops activities took place during the day, they were heavily exposed. This does not explain why fewer cases occurred in Papua New Guinea and the Solomon Islands. The vectors there are mainly night feeders but the troops being in an active theatre of war and occupying positions both night and day would be heavily exposed. The other interesting observation is the low number of filariasis cases among Australian troops even although they were stationed in highly endemic areas (Papua new Guinea and the Solomon Islands). Walker (1952) states that there were only 22 cases of filariasis among Australian troops, and as some of these men were Queenslanders (where filariasis was endemic at the time) may have acquired the infection prior to enlisting in the forces. It may have simply been a lack of familiarity with filariasis and the diagnosis was missed but this was unlikely as the Australian forces medical staff were aware of the risk of filariasis and had be extensively briefed on the American experience in the Pacific (Walker 1952). An interesting observation is that most of the filariasis cases occurred in areas that are not endemic for malaria. Is it possible that malaria some how modifies the course of filariasis in naive subjects? Although there is no evidence as yet from human studies, this idea merits further study as there is evidence from animal studies that filariasis modifies the course of *P. falciparum* malaria (Yan *et al.,* 1997). Another possibility is that the commonly used anti-malarial prophylactic in use at the time - atabrin, had an anti-filarial action. Although this appears unlikely, it should not be discounted without exploration**.** Although none of the American servicemen developed elephantiasis, this condition does occur, albeit rarely, in expatriates who have lived in endemic areas for a number of years. One of Patrick Manson's original cases was a French priest from French Polynesia (Manson-Bahr, 1959). Webster reported 15 cases of elephantiasis among white settlers in Samoa. All of these were long-term residents with a mean age of 64.3 years and a mean exposure time of 35.1 years. I, myself discovered an American missionary with severe elephantiasis who had lived on the island of New Britain, Papua New Guinea for over 40 years.

Filariasis in Other Troops

Alhadeff (1955) reported cases of acute filariasis in Mauritian troops stationed in the filarial-endemic areas of Egypt. It difficult to say however whether these were locally acquired infections or not because filariasis also occurs in Mauritius (Sasa 1976)**.**

Filariasis also occurred in expatriate troops serving in Vietnam where both *W. bancrofti* and *B. malayi* occur (Greenberg, 1969; Colwell *et al.,* 1970; Hembree, 1974; Sasa, 1976). In the 1950's a syndrome consisting of hyper-eosinophilia, bronchial asthma and lymphadenopathy was observed in 151 French and North African troops serving in the Tonkin area of North Vietnam. Microfilariae of *B. malayi* were recovered from the lymph nodes of some cases but there are no reports of circulating microfilariae. Treatment with arsenicals or diethylcarbamazine was followed by rapid clinical improvement (Galliard, 1957). Brown and Armstrong (1968) and Sullivan *et al*. (1969) reported some cases of filariasis in American servicemenBy the use of a soluble-antigen fluorescent antibody test Colwell *et al.,* (1970) were able to show that 11% of United States servicemen who were stationed in filarial-endemic regions of South Vietnam had anti-filarial antibodies. By contrast, only 3% of those stationed in apparently non-endemic areas were positive. Moreover, when the servicemen were characterised according to the degree of potential exposure, the prevalence of sero-positivity in field troops was 3 times higher than in base

personnel. One serviceman was also found to have circulating microfilariae. Sullivan *et al.,* (1970) reported a case of clinical filariasis without microfilaraemia that rapidly resolved following DEC therapy. Again, there appears to be reported cases of filariasis among Australia military personnel. Most of Vietnam is malarious and as far as it can be ascertained, American and Australian service persons were on the same malarial prophylaxis regime.

Other Expatriate Cases

McQuay, (1967) studied a group of furloughed missionaries who had served in filarial-endemic areas. Using haemagglutination and flocculation tests he was able to demonstrate filarial antibodies in 30% of the 1,436% people examined. In some cases microfilariae of *D. perstans, L. loa* and *M. ozzardi* were identified but no cases of *W. bancrofti* or *Brugia* species microfilaraemia were found. Bean *et al.,* (1992) reported a case of acute filariasis in an American traveller. The 45-year-old man had spent a short time trekking in Nepal. En route to Nepal he had stayed overnight in Bangkok. Seven months after his return to the United States he developed fatigue, eosinophilia and lymphodema of the arm and chest wall. There was no lymphangitis, lymphadenitis or pain. The symptoms were aggravated by physical exercise. His indirect haemagglution titre and ELISA assay for filarial antibodies was positive. No circulating microfilariae were detected. Three months after diethylcarbamazine treatment the eosinophilia had fallen and the patient was asymptomatic. During the next 2 years there were several milder episodes followed by complete resolution. Filarial antibodies were present and lymphatic pathology was demonstrated by lymphoscintography. Charters (1981) described a 43-year-old man who had spent 2 years in Papua New Guinea during which he suffered from several bouts of pyrexia of unknown origin. Upon returning to Australia he had several similar episodes accompanied by lymphangitis of the leg. These attacks ceased whilst he was taking phenoxymethylpenicillin but relapsed within a month of him ceasing the medication. Given that penicillin has not been shown to have any antifilarial action but is usually effective against streptococci, it may be possible that these episodes are related to streptococcal infection which has been shown to be implicated in acute filarial attacks (see below). Libman *et al.,* (1993) screened 1,605 expatriates returning from tropical areas and found that 16 (0.995) had positive filarial serology. Turner and Usurup (1997) report a possible case of filariasis in an expatriate miner working in Papua New Guinea and Moore *et al.,* (1996) reported the case of an American Peace Corps worker who developed acute lymphatic dysfunction (proven by lymphoscintigraphy) within 3 months of arriving in a filarial-endemic area. Koya *et al.,* (1998) found a case of filariasis in an Italian woman who developed acute filariasis after staying for a few weeks in a highly endemic area of India and Manfredi *et al.,* (1998) described a case of *B. malayi* infection in another Italian, a HIV-infected drug user which presented four months after returning to from a two month-long journey to India and Southeast Asia. The interesting thing about these two patients is that they were both microfilaraemic, a rare finding in expatriate cases.

From these case descriptions it is obvious that filariasis is a real threat to expatriates living in, working in, or visiting endemic areas and should always be considered in the deferential diagnosis of returning travellers (Doherty *et al.,* 1995). The question of what tests to use in diagnosis is a vexing one and will be discussed in the section on diagnosis below. There is a sharp contrast between expatiates who only visit or work in a filarial-endemic area for short periods of time and expatriates who migrate to filarial endemic areas (or even from one filarial-endemic area to another) permanently. In these people there is an acceleration of the disease progression and they developed chronic pathology such as elephantiasis much faster than the people who are the native inhabitants of the area (Partono *et al.,* 1978).

Cellular Immunity

All parasites induce a degree of immuno-suppression as a means of ensuring their survival in the host (Nussenzweig, 1982). Loss of T lymphocyte proliferation and the emergence of a host response dominated by a Th-2- type profile is characteristic of many nematode infections, especially filaroids (Allen and Macdonald, 1998). The immunology of lymphatic filariasis has been very aptly termed an "immunologic maze" (Piessens, 1981) and all that can be attempted here is a summary of the well-established principles. For comprehensive reviews see: Grove, 1978, 1979; Kwa and Mak, 1980; Ottesen, 1980; Ottesen, 1984; Mistry and Subrahmanyam, 1985; Dasgupta *et al.,* 1987; Kumar *et al.,* 1987; Prasad and Harinath, 1987; Ottesen, 1989; Ottesen, 1992; Maizels, 1995; Freedman, 1998.

In general terms, immunological profile differs between people with microfilaraemia, chronic filarial pathology and tropical eosinophilia syndrome (Ottesen, 1992). Microfilaraemics have reduced cellular immunity to filarial antigens and their lymphocytes stimulation index in lymphocyte proliferation tests is usually below 5.

Weller (1978) followed *in-vitro* lymphocyte blastogenesis in rats infected with *B. phahangi.* Responses to infective larva antigens were detectable only in the first few weeks of infection whereas responses to microfilariae antigens only developed as microfilaraemia waned. Cyclic variation in the response to adult worm antigens occurred throughout the period of infection. Work by Deehan *et al.,* (1998) suggests that a phosphocholine-containing filarial secretion inhibits lymphocyte activation by targeting key lymphocyte proliferative signalling pathways. Allen and Macdonald (1998) found that excretory antigen produced from *Brugia malayi* transplanted into mice induced the formation of adherent peritoneal cells that block T cell proliferation. It has been demonstrated by Pancre *et al.,* (1988) that platelets from filariasis patients are cytotoxic to microfilariae and that this effect is inhibited by supernatants from filarial antigen-stimulated lymphocyte cultures - another immune system-modulated protective effect to enhance the survival of the parasite in the host.

It is a common belief that filarial immuno-suppression is limited to filarial antigens and that response to unrelated parasite antigens and such compounds as purified protein derivative (PPD) is unaffected (Ottesen *et al.,* 1977; Piessens *et al.,* 1980a-d; Haque *et al.,* 1983; Regunathan *et al.,* 1997). Some findings challenge this view. Mistry and Subrahmanyam (1985) found that the lymphocyte proliferative response to PPD was marginally reduced in microfilaraemics but normal in patients with elephantiasis and (Srivastava *et al.,* 1981) found that T cell responses to PPD were normalised after specific antifilarial therapy.

Reports on mitogen response vary. Portaro *et al.,* (1976) Lammie and Katz, 1983; Mistry and Subrahmanyam (1985) and Prasad *et al.,* (1991) report reduced response to mitogen whereas Regunthan *et al.,* 1997 found no difference in mitogen response between groups with microfilaraemia or chronic filarial pathology and endemic normals from the same area. This variation in mitogen response may be due to the timing of the experiments and a variation in responses between subjects. Using a rat model, Weller (1978) demonstrated that the response to phytohaemagglutinin, pokeweed mitogen, and bacterial lipopolysaccharide varied throughout a 1.5-year period of infection with *B. malayi*. Lymphocytes from some animals showed a complete absence of mitogen response between the 16th and 36th week of infection and normal responses at other times. Other animals however, showed no mitogen-elated immuno-suppression throughout the period of infection.

People with elephantiasis usually have normal or increased cellular immunity to filarial antigens with stimulation indexes between 5 and 25 (Ottesen *et al.,* 1977; Weller 1978; Piessens *et al.,* 1980 a, b; Narayanan *et al.,*1986; Nutman *et al.,* 1987a; Ottesen, 1989; Hitch *et al.,* 1991; Ottesen, 1992; Addis *et al.,* 1995). There is a sub-set of elephantiasis patients, however, which demonstrate a hypo-responsiveness to filarial antigens comparable to that seen in microfilaraemics (Yazdanbakhsh *et al.,* 1993a, b). It was demonstrated that circulating phosphocholine-containing antigens from the adult worm, which can be present in levels as high as 5ug per ml, are capable of suppressing mitogen-induced T cell proliferation (Wadee *et al.,* 1987; Lal *et al.,* 1990). Mahanty *et al.,* (1996a, b, 1997) have found evidence that IL-10 induced by parasite antigen plays an important role in down-regulating antigen-specific lymphocyte proliferation in microfilaraemics and they IL-12 can overcome this down-regulation but does so in a non-antigen-specific manner.

The suppression in cellular immunity is not due to the inability of lymphocytes to respond to antigenic stimulation, but to the presence of suppressor cells (Piessens *et al.,* 1982). It has been shown that the degree of immuno-suppression and rapidity of onset is related to the size of the microfilariae burden and that a reduction in microfilariae decreases the immuno-suppressive effect (Piessens *et al.,* 1981b). This concept however has been challenged by Bosshardt *et al.,* (1995) who found using a Gerbil model, that the microfilaria stage alone is not responsible for the maintenance of cellular immuno-suppression and the that the degree of immuno-suppression is related to the total filaria parasite burden. It is interesting to note that Riley *et al.,* (1989) found that the *in-vitro*

immuno-suppression induced by malaria can be partially reversed by indomethacin**.** This effect is thought to be due to the ability of indomethacin, a cyclo-oxidase inhibitor, to block the production of prostaglandin, which are potent inhibitors of blastogenesis. It would be interesting to carry out a similar experiment using mononuclear cells from filariasis patients and filarial antigens.

Filarial Immunity: Lymphocyte Sub-population Profiles

Dasgupta *et al.,* (1986) found that the total number of circulating lymphocytes in elephantiasis patients was lower than normal due to a depletion of T cells but the percentage of null cells and T rosettes was higher in elephantiasis and microfilaraemics than in amicrofilaraemics. Piessens *et al.,* 1982 found that increased numbers of suppressor T cells were present in 15 of 17 patients with microfilaraemia and in 6 of 11 patients with elephantiasis. The increase correlated with the hypo-reactivity to filarial antigens and the removal of suppressor T cells improved the reactivity to filarial antigens. King *et al.,* (1992) demonstrated that the frequency of parasite-specific CD3+ T cells and the proportion of lymphocytes producing parasite-specific IgE or IgE was significantly lower in microfilaraemics than in patients with chronic pathology**.**

Cytokines

Cytokine profiles also differ in various manifestations of filarial disease. In microfilaraemic humans and animals the Th1 arm of the immune response is down regulated and the Th2 arm stimulated. Microfilaraemics produce large amounts of IL-4 and IL-5 (type 2 cytokines) and only small amounts of interferon γ and GM-CSF (type 1 cytokines). The situation is reversed in elephantiasis (Nutman *et al.,* 1987b; Maizels and Lawence, 1991; Ottesen, 1992; Pearlman, 1995; Yazdanbakhsh *et al.,* 1993a,b; Dimock *et al.,* 1996; Mahanty *et al.,* 1996; 1997). The cytokine profile has shown to be influenced by clinical status and age of the patient (de Almeida *et al.,* 1996; Sartono *et al.,* 1997). Interferon γ and IL-5 are suppressed in microfilaraemic carriers but IL-4 was not affected. In microfilaraemics IL-4 production was high in young subjects but decreased with age whereas in microfilaraemics IL-4 increased with age. By contrast, interferon-gamma increases with age in amicrofilaraemics but not in microfilaraemics. IL-5 on the other hand increased with age in both groups (Sartono *et al.,* 1997).

It has also been shown in animal studies that antibodies to inhibitory cytokines have the ability to reverse temporally reverse cellular unresponsiveness and induce a transient increase in microfilariae (Ottesen, 1992. In a human study however by Regunathan *et al.,* (1997) the cellular unresponsiveness was not reversed by the addition of recombinant IL-1a, IL-1b and interferon γ but it was reversed by the addition of serum from endemic normals.

Some studies however have shown that the correlation between Th and cytokine profiles and the manifestation of filarial disease may not be clear cut and that the presence or absence of infection rather than clinical status is most closely associated with cytokine response (Almeida *et al.,* 1996). Pearlman *et al.,* (1995) have shown that T helper cell responses to filarial antigens are modulated by IL-12. Cytokine profiles are also influenced by age (Sartono *et al.,* 1997). Antigen-specific IL-5 and interferon γ are suppressed in microfilaraemics but IL-4 is normal. In asymptomatic amicrofilaraemic cases IL-4 production was increased in young people but decreased with age, whereas in microfilaraemics IL-4 production showed a significant increase with age. By contrast, interferon γ showed an increase with age in asymptomatic amicrofilaraemics but not in microfilaraemics. IL-5 decreased significantly with age in both asymptomatic microfilaraemic and microfilaraemic groups. This indicates that the cytokine profile change with the length of exposure to, and infection with filarial parasites. Manhanty *et al.,* (1996, 1997) have shown that parasite antigen-induced IL-10 plays an important role in down regulating cellular immune responses in microfilaraemic patients.

CD (Cluster of Differentiation) Cells and Molecules

Studies by Yazdanbakhsh *et al.,* (1993) of soluble CD25 (sCD25) and soluble CD27 (sCD27) showed that levels of sCD27 were significantly increased in microfilaraemics and elephantiasis patients compared with endemic normals. By contrast, sCD25 remained low in microfilaraemics and was only slightly raised in elephantiasis.

Cell Adhesion Molecules

The development of chronic inflamation depends upon the migration of peripheral blood mononuclears cells into tissues. Animal models show that this process is facilitated by vascular cell adhesion molecule (VCAM-1) expression on vascular endothelium (Freedman, 1996). *In-vitro* studies by Freedman *et al.,* (1996) and Plier *et al.,* (1997) that cell culture supernatants from filariasis patients stimulated the migration of mononuclear cells and the effects were greater when cell cultures from individuals with clinical filariasis, as opposed to asymptomatic individuals was used. These studies were conducted using the "traditional" classification of disease status and the findings would need to be revised if the proposed new classification of Freedman (1998) is used (see below).

C-reactive Protein and Filariasis

Both serum and lymphocyte-bound C-reactive protein has shown to be significantly increased in patients with filarial pathology compared with asymptomatic microfilaraemics and endemic normals (Lal *et al.,* 1991).

Attempts to Reverse *in-vitro* Immuno-suppression

In an attempt to reverse the *in-vitro* immuno-suppression against filarial antigens Sartono *et al.,* (1995a,b) cultured peripheral blood mononuclear cells in the presence of agents which had been shown to enhance T cell proliferation in other diseases: interleukin 2 (IL-2), anti-interleukin 4 (IL-4), interleukin 7 (IL-7), anti-interleukin 10, anti-CD2, anti-CD27, anti-CD28, indomethacin, phorbol myristate acetate (PMA) and calcium ionophore. Only IL-2, IL-7, indomethacin and PMA produced a result and then only in some of the cases studied. Unresponsiveness in elephantiasis cases was easier to reverse (50% of cases responded) than microfilaraemics (12.5%) and asymptomatic amicrofilaraemics (20%). Their conclusion was that more than one immunological mechanism was involved in filarial immune suppression.

Humoral Immunity

All filarial infections produce an active polyclonal humoral response with the production of IgG, IgM and IgE antibodies (Ottesen, 1984; Kumar *et al.,* 1987; Nutman *et al.,* 1987a,b; Nanduri and Kazura, 1989) but their titres tend to be lower in people with microfilaraemia than in those with elephantiasis and extremely high in cases of tropical eosinophilia syndrome (Wong and Guest, 1969; Ottesen *et al.,* 1982; Ottesen, 1989; Addis *et al.,* 1995; Ottesen, 1992; Estambale *et al.,* 1995). Antibodies against microfilariae are usually absent in microfilaraemia and lymphocytes isolated from microfilaraemics are unable to produce filaria-specific antibodies *in-vitro* either spontaneously or in response to parasite antigen. This is in contrast to patients with chronic obstructive pathology or TPE (a,b). The failure in antibody production cannot be reversed by removal of adherent cells or T^8 lymphocytes suggesting that a state of B unresponsiveness to filarial parasites is present (Nutman *et al.,* 1987a,b).

IgG isotype profile also differs in different manifestations of disease. In microfilaraemics, a large proportion of the IgG consists of IgG4 (up to 90%) and there are low levels of IgG1, IgG2 and IgG3. By contrast, patients with elephantiasis have lower titres of IgG4 antifilarial antibody than microfilaraemics and often have increased levels of IgG2 and IgG3 (Ottesen *et al.,* 1985; Hussain *et al.,* 1987; Kwan-Lim, 1990; Ottesen, 1992; Egwang *et al.,* 1993; Kurniawan *et al.,* 1993; Lammie *et al.,* 1993; Yazdanbakhsh *et al.,* 1993a,b; Rahmah *et al.,* 1994; Addiss *et al.,* 1995; Maizels *et al.,* 1995; Wamae *et al.,* 1995; Yazdanbakhsh *et al.,* 1993a,b; Atmadja *et al.,* 1996; Simonsen *et al.,* 1996; Nicolas *et al.,* 1999). Yazdanbakhsh *et al.,* 1995a have shown that in elephantiasis the IgG3 antibody has a particular affinity with the recombinant antigen Bpa-26, a peptide from the C-terminal region of the filarial heat-shock protein and show a striking association between the elevated levels of IgG3 antibody and chronic obstructive filarial pathology. They postulate that an imbalance of isotypes of antibodies to particular filarial antigens may play a part in the pathogenenesis of chronic disease. Serum antifilarial IgE is lower in asymptomatic microfilaraemics than in individuals with chronic pathology (Marley *et al.,* 1996) and the ratio of IgG4 to IgE is highest in asymptomatic microfilaraemics (Atmadja *et al.,* 1995). Estamble *et al.,* (1994) showed that the mean level of filarial-specific IgG1 was significantly higher in amicrofilaraemic, symptomatic cases than in microfilaraemic cases whereas the mean level of IgG4 was significantly higher in individuals with microfilaraemia. They also found that in most categories of endemic individuals, and for most antibody isotypes, the mean levels of antibodies tended to be higher in younger than in older age groups. It is likely that the elevation of IgG2 and IgG3 contribute to the pathology of elephantiasis by promoting cellular hypersensitivity reactions or immune complex formation (Maizels *et al.,* 1995). IgG3 is a major mediator of type 3 hypersensitivity and is the IgG isotype for which the Fc receptors on mononuclear cells and granulocytes have the highest affinity (van der Winkel and Capel, 1993; Maizels *et al.,* 1995). Immune complexes formed with IgG1, IgG2 and IgG3 isotype antibodies and filarial antigens are large molecules that can become fixed in tissues. By contrast, IgG4 is monovalent and in lymphatic filariasis targets the lower molecular weight antigens. As a result, forms small immune complexes which do not become fixed in tissue and are less damaging than those formed by IgG1, 2, and 3 (Kazura, 1993a)**.** Studies by Prasad *et al.,* (1983) have shown that patients with chronic filarial pathology have significantly higher levels of immune complexes than microfilaraemics or endemic normals. This finding from this study however is at variance from those of Kobayashi *et al.,* (1997) who found that asymptomatic microfilaraemics have high-level filarial antigen-associated immune complexes that corelate with the level of the microfilaraemia. Lutsch *et al.,* (1988) showed that the antibody complexed to antigen is mainly IgM in asymptomatic microfilaraemics and IgG in symptomatic cases.

IgG4 antibody plays an important part in the aetiology of filariasis. Patients with chronic helminth infection, despite being exposed to parasite antigen seldom exhibit any allergic reactions because IgG4 antibodies "block" the action of IgE. In microfilaraemics the ratio of IgG4 to IgE is high (Maizels *et al.,* 1995, effectively

dampening down the allergic response in the host (Hussain *et al.,* 1992), thus ensuring the survival of microfilariae and preserving the potential to transmit the disease (Nanduri and Kazura, 1989). Mahanty *et al.,* (1994) have shown that antifilarial IgG4 is a good index of the intensity and duration of filarial exposure in endemic populations and the level of IgG4 antibody correlate with microfilariae counts (Maizels *et al.,* 1995). This finding however is not true for all filarial species - Akue *et al.,* (1994) found that in *Loa loa* infections there are high levels of parasite-specific IgG4 even in the absence of microfilaraemia. Simonsen *et al.,* (1996) showed that IgG1 and IgG4 antibodies have high specificity for filarial antigens and that their titres have a relationship to micro filarial status. The differences in IgG isotype profile in groups with different manifestations of filariasis have been consistently demonstrated in a number of countries including: Malaysia (Rahmah *et al.,* 1994), Papua New Guinea (Kwan-Lim, 1990), Gabon (Egwang, 1993), India (Ottesen *et al.,* 1985; Hussain *et al.,* 1987), Haiti (Lammie *et al.,* 1993), Tanzania (Simonsen *et al.,* 1996 and the South Pacific Islands (Chanteau *et al.,* 1991; 1995) but there is one report from Haiti where 10% of a group of microfilaraemics did not have an increase in antifilarial IgG4 antibody. These persons had very high levels of filarial antigen and it is suggested that in this situation there may be a down regulation of antibody production, which extends to IgG4 (Marley *et al.,* 1995). Most studies of filarial antibodies have utilised crude antigens prepared from adult *Brugia malayi* or *Brugia phahangi.* There have been some studies using antigens prepared from microfilariae and it has been shown that there is an inverse relationship between the anti-micro filarial antibody titre and the level of microfilaraemia leading to the hypothesis that these antibodies control the number of circulating microfilariae (Piessens *et al.,* 1980b) and there is a correlation between the presence of anti-microfilarial sheath antibodies in serum and the absence of detectable circulating microfilariae (McGreevy *et al.,* 1980; Piessens *et al.,* 1980b). It is believed that the microfilariae contribute to the decline of circulating antibody because antibody is bound onto antigen on the surface of the microfilaria (Piessens *et al.,* 1980b).

Infective (L3) larvae elicit a IgG and IgE response (Das *et al.,* 1992) and Day *et al.,* (1991) have shown that the level of anti L3 antibody correlates with the duration of exposure. Kurniawan-Atmadja *et al.,* (1998) however, found that unlike the response to adult or microfilarial antigens, the immune response to L3 surface antigens dominated by IgG1 and IgM rather than IgG4.

Kar *et al.,* 1993 report some interesting changes in the humoral immune response during filarial fever attacks. Titres of IgG and IgG4 antibody to *W. bancrofti* micro filarial excretory/secretory antigens decreased significantly during fever attacks and remained reduced for up to one month after the fever episode. By contrast, the level of circulating immune complexes rose sharply during the fever episode and in a percentage cases there was also an increase in circulating filarial antigen suggesting a release of filarial antigen into the circulation during fever which bound to antibody and form immune complexes. Total and differential white cell counts and antistreptolysin O titres did not change during or after febrile episodes strongly suggesting that streptococcal infections do not play a part in filarial fevers. It is therefore postulated (Kar *et al.,* 1993) that antigens released from adult worms into the circulation during parturition may evoke an allergic reaction in the host and triggering a febrile episode.

IgM antibodies: Estambale *et al.,* (1994) found that the levels of IgM filarial antibodies rose in individuals from both filarial-endemic and filarial-non-endemic areas. They believed that this was due to the low specificity of IgM antibodies and the subsequent cross-reaction with other parasite and non-parasite antigens.

Filarial Immunity in the BALB/c Mouse Model

In this model, IgG isotype profiles, IgE production and cytokine profiles have been shown to be stage specific (Lawence *et al.,* 1994). Microfilariae induced production of all IgG isotypes but little IgE. By contrast, adult worms stimulated the production of only IgG1 and IgE. When splenocytes from parasite-implanted mice were stimulated *in-vitro* with parasite antigen or con-A cells from microfilariae-infected mice secreted high levels of interferon-γ but IL-4 production did not peak until 28 days after parasite implantation. On the other hand, adult female worms stimulated high levels of IL-4 and very little interferon γ Male worms stimulated lower levels of IL-4 production than female worms. CD4 lymphocytes were primarily responsible for the IL-4 increase. To quote Lawence *et al.,* (1994):

> *"These findings demonstrate that adult filarial parasites, and female parasites in particular, exert a rapid polarisation of the immune response in a TH2-like direction, but this effect may be modulated by the microfilaria stage."*

The Effect of Filariasis on the Humoral Response to Other Antigens

Whilst it is commonly believed that cellular immuno-suppression induced by filariasis is filarial antigen specific (see above), there is evidence that antibody response and delayed skin hypersensitivity to non-filarial antigens is reduced. Grove (1979) found that only 1 out of 35 patients with filariasis responded to tetanus toxoid (3%) compared with 8 out of 31 control subjects (26%)

($p<0.025$). Cooper *et al.,* (1998) studied the response

of oncocerca-infected patients to tetanus toxoid and found that six months after vaccination, antibody levels lymphocyte proliferative responses and levels of interferon γ were significantly higher in non-infected persons when compared to oncocerca patients. Infected subjects produced IL-10 but un-infected controls did not suggesting a role for IL-2 in this process.

Grove (1979) found that the response to *Salmonella typhi* vaccine is effected with only 15 of 26 patients with filariasis (58%) having an antibody titre of 1:40 2 weeks after immunization compared to 25 of 31 in controls (81%) ($p < 0.05$). Delayed skin hypersensitivity reactions to Candida, mumps or streptococcal antigens were significantly reduced in filariasis patients compared with controls ($p < 0.01$). Srivastava *et al.,* (1981) showed that filariasis patients have a significantly impaired antibody response to the H and O antigens of TAB vaccine and reduced skin hypersensitivity to PPD and chlorodinitrobenzine. This immuno-suppression may contribute to secondary cutaneous infections (Grove, 1979). Streptococcal infection has been strongly implicated in the clinical manifestation of filarial disease and the question could be asked, "Does filariasis suppress immunity to streptococci." Lal *et al.,* (1991) however demonstrated *increased* rather than *decreased* streptococcal antibody levels in patients with filariasis and King *et al.,* (1992) found no difference in streptolysin O-induced lymphocyte proliferation between filariasis patients with various manifestations of disease and normal controls.

Srivastava *et al.,* (1981) demonstrated a reduced antibody response to TAB vaccine in filariasis. Antibody titres to *S. typhi* H and O antigens were significantly reduced in asymptomatic microfilaraemics and patients with chronic filaria pathology when compared with normal controls.

Malhotra *et al.,* (1997; 1999) have shown that 2 to 10 year old children born to mothers who did not have filariasis produced a 10-fold increase the production of interferon γ when challenged with PPD than those children born from filarial-infected mothers. This raises two serious questions: is the efficacy of BCG vaccine impaired by filarial infection and does filarial infection influence the course of TB infection? The effect of filarial immuno suppression on the response to other vaccines should be investigated. If filariasis does reduce the efficacy of vaccination it is another reason why the control of filariasis is important.

Does Filarial Immunosuppression Impact Upon Other Tropical Diseases?

It is also possible that filariasis may decrease the immunity to other tropical diseases and that hypothesis should be actively explored using modern immunological techniques. Sidkey *et al.,* (1987) reported a patient with filariasis who presented with a disseminated *Hymenolepis nana* infection and they postulated that the filarial immuno-suppression many have contributed to the spread of the other parasite. The situation is somewhat clouded however by the fact that the patients had been treated in the past with corticosteroids. Younis *et al.,* 1997 studied the relationship between filariasis and intestinal parasites in a filarial-endemic area of Egypt. The overall prevalence of parasites was 81% in non-filarial-infected people and 92.4% in filariasis patients. On the basis of this data they concluded they suggest that the immune suppression caused by filariasis may increase the host's susceptibility to other parasitic infections. Mohamed *et al.,* (1983) could find no evidence of interaction between filariasis and schistosomiasis in an area endemic for both parasites. This is an area that warrants further study.

Piessens *et al.,* (1983) have shown that malaria and filariasis have opposing effects on human immuno regulatory T lymphocytes and a study by Schmidt and Esslinger (1981) found that *P. falciparum* infections in Owl monkeys (*Aotus tri-virgatus griseimembra)* infected with the filarial parasite *Tetrapetalonema barbascalensis* followed a more benign course than in monkeys who were not infected with the filaroid. Yan *et al.,* (1997) showed a down-regulation of murine susceptibility to cerebral malaria by inoculation with third-stage larva of B. pahangi. There is no evidence at this time however that filariasis influences the course of human malarial infections. Ravindran *et al.,* (1998) studied patients with both filariasis and malaria and found that there was no evidence to suggest that either of these two diseases impacted upon the other. This subject does warrant further investigation however, as it would not be helpful if the eradication of filariasis led to an upsurge in malaria!

Work by Fiennes (1969) suggested that filarial infection might aid in the pathogenic activation of latent viruses in new world non-human primates. In a Japanese study by Tajima *et al.,* (1983) it was found that the positive rate of antibodies to HTLV-1 virus among people with a high antibody titre to filariasis antigen was high than in those with a low filarial antibody titre and postulated that filariasis may promote the effects of HTLV-1 infection but no correlation could be found by Linhares *et al.,* (1995) in Brazil.

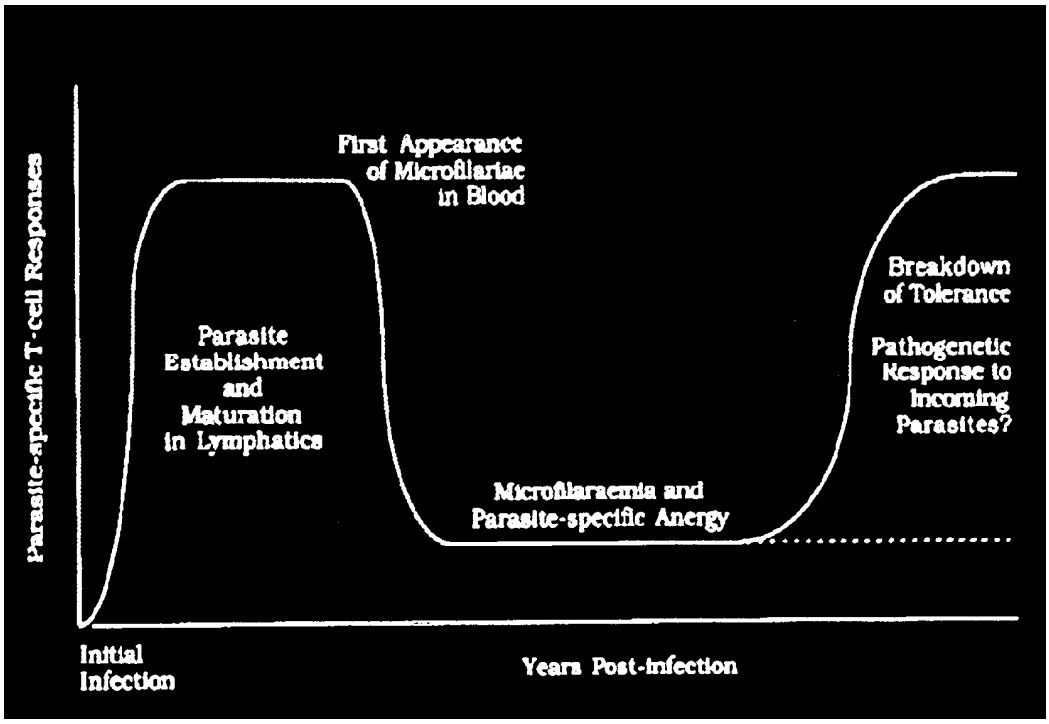
Another important question could be asked in the light of the experimental evidence above. Does filarial infection in children reduce the efficacy of vaccination?

Unravelling the Pathogenesis of Chronic Pathology

Although much progress has been made many questions are yet to be resolved. What causes one individual to progress from asymptomatic microfilaraemia to elephantiasis yet his next door neighbour, or even their spouse who shares the same house (Hunter, 1992) remains asymptomatic or even avoid the disease altogether? What factors cause the "re-awakening" of the suppressed immunity? How is it that microfilaraemia and chronic pathology can co-exist in some people? Why is it that some communities have exceedingly high prevalence of filarial antigenaemia and microfilaraemia and very little chronic pathology? Is it a just a matter of duration and intensity of exposure? Would everyone who has microfilaraemia progress to chronic pathology if the time frame is long enough? Piessens and Partono (1980) hypothesise that the *chances* of developing clinical manifestations of filarial disease increase with increasing worm burdens and the *differences* in the clinical course of filariasis are due to the individual's immune response to filarial antigens. There is however evidence from animal models which suggests that individuals which are subjected to repeated infections with L3 infective larvae are especially at risk for developing chronic pathology. Repeated infection of cats and ferrets with infective larvae produced increased oedema (Rogers and Denham, 1975; Hines *et al.,* 1985; Maizels and Lawence, 1991) and lymphatic damage is more severe in cats after repeated infection. Lymphatic pathology is more severe in cats that have the immunological capacity to kill adult worms and microfilariae than it cats who are microfilaraemic (Maizels and Lawence, 1991).

A good working model is that proposed by Maizels and Lawence (1991). It is based on the idea that microfilaraemia is dependent upon immune tolerance to filarial antigens developing in the host and that chronic pathology arises when the immune tolerance breaks down (Figure 6).

Figure 13 Maizels and Lawence (1991) working tolerance model (with permission of the authors)



In accepting that model however it needs to be recognised that filariasis is an extremely complex disease and the old classification which separated patients in the basis of microfilaraemia and the presence or absence of chronic pathology have been seriously challenged in recent years (Michael *et al.,* 1994; Freedman, 1998). What Ottesen (1992) likes to call "overlap" syndromes do exist and other mechanisms besides immunological ones may play a part in the induction of pathology.

In an immuno deficient mouse (nude mouse) model it has been shown that there are pathological mechanisms that lead to lymphodema and elephantiasis. If these immuno deficient mice are infected with Brugia the parasite itself will, even in the absence of an immunological reaction in the host, induce lymphatic damage and ultimately elephantiasis. If infected nude mice are rendered immuno-competent by transplantation of cells from an animal previously sensitised to filarial antigens, inflammatory reactions around the parasites again lead to lymphatic damage and elephantiasis (Suswillo *et al.,* 1981; Vincent *et al.,* 1984; Vickery *et al.,* 1991. Here two different pathways to chronic filarial pathology are demonstrated; one dependent on the parasite alone and one dependant on the reaction of the host. Whether or not a comparable situation occurs in humans remains to be seen, but there is histological evidence that supports the hypothesis. Tissues removed from filariasis cases showed two different patterns of pathological response. Around living parasites the process was that of lymphatic dilation, around dead parasites there was a granulomatous inflammatory reaction (Von Lichtenburg, 1987). Patients with "overlap syndromes" could be explained on the basis that pockets of local immuno-suppression could be developed around adult worms even if the inflammatory process was occurring elsewhere.

Genetic Influences

It is possible that there are genetic variations in antigen processing and immunologic response and there have been a number of attempts to find linkages between genetics and filariasis. Any evidence of such a linkage so far has been weak and sometimes contradictory. Ottesen *et al.,* (1981) noted a family clustering of microfilaraemia but was unable to demonstrate a linkage with human leucocyte antigen (HA) but an association between elephantiasis and HA-B1 has been noted in India and Sri Lanka (Chan *et al.,* 1984; Dasgupta, 1985) and filarial antigens have been shown to be processed with HA-DR (Nutman *et al.,* 1984). Mohamed *et al.,* (1987, 1992) found a significant association between HLA-B7, the susceptibility of retaining circulating microfilariae and the development of clinical filariasis. A study by Yazdanbakhsh *et al.,* (1995b) suggested that HLA class II genes may influence the course of Brugian filariasis by influencing the T-cell dependent antibody repertoire but a later study by the same authors concluded that this evidence is very weak (Yazdanbakhsh *et al.,* 1997). Studies of ABO group linkages have shown varying results (Gyorkos *et al.,* 1983; Srividya and Pani, 1993). Ayers *et al.,* (1976) found a higher incidence of group B in filarial patients, a lack of group A_2 and a higher frequency of non-secretors, Suresh *et al.,* (1982) an increase in A and AB groups and Srikumari Srisailapathy *et al.,* (1990) showed excess of group B and a deficiency of group AB in filariasis patients compared to controls. This difference however was only statistically significant in males. A positive association between filarial hydrocele and group B (Rh) negative was also noted by Dutta and Diesfeld (1987). Srividya and Pani (1993) tested 1,444 people in south India and found no association between ABO blood groups and filariasis. Mohamed et *al.,* (1987, 1989) could find no statistical correlation between filariasis and the ABO, Rh and MN blood group systems in 520 Egyptians. There was no association between haemoglobin variants and filariasis in the only published study found to date (Ayers *et al.,* 1976). Because if its rarity, its geographical distribution and distinctive clinical and laboratory features tropical pulmonary eosinophilia would be a likely candidate for a genetic basis but nothing has been found so far (Ottesen, 1992).

The Influence of Maternal Sensitisation

Prenatal experience with filarial antigen determines the subsequent character of the immune response to post natal infection (Ottesen, 1992) and it is believed that neonates exposed to parasite antigens in utero may developed altered foetal immune responses that influence the development of disease in later life (Malhotra *et al.,* 1997). It is now generally accepted that *in vivo* exposure of the foetus to filarial antigens and the development of immune tolerance plays an important role in determining infection status in later *life*. Animal studies have shown that the offspring of an amicrofilaraemic mother are more likely to develop filarial pathology than the off spring of microfilaraemic mothers (Schrater *et al.,* 1983; Klei *et al.,* 1986; Krishnarao *et al.,* 1989; Miller *et al.,* 1990). In humans, a child born to (or tolerized by) a microfilaraemic mother is more likely to develop microfilaraemia than a child born to an amicrofilaraemic mother and children born of microfilaraemic mothers are less capable of mounting an immune response to filarial antigens than those child born of amicrofilaraemic mothers. This effect may persist into adulthood (Lammie *et al.,* 1991; Hightower *et al.,* 1993; Steel *et al.,* 1994; Roberts and Janovy 1996). There are probably several mechanisms by which the foetal exposure to filarial antigens occur. There is evidence of transplacental passage of microfilariae in both animals (Mantovani, 1966; Sucharit and Rongsriyam, 1980) and humans (Neves and Scaff, 1952, 1954; Raghavan, 1958; Bloomfield, 1978; Ramalingeswararao *et al.,* 1984; Pires, 1991; Campbello *et al.,* 1993; Eberhard, 1993) and microfilariae are occasionally seen in the neonatal circulation Bloomfield *et al.,* 1978). Animal studies have shown that transplacental transfer of microfilariae induces immune tolerance in the resulting offspring (Haque *et al.,* 1982, 1988). Antifilarial IgM antibodies

have been detected in cord blood (Dissanayake and de Silva, 1980) and the level of antibody was found to be higher in cord blood from infants of amicrofilaraemic mothers compared to microfilaraemic mothers (Agarwal *et al.,* 1986). Weil *et al.,* (1983) have demonstrated antifilarial IgE in the cord blood of microfilaraemic mothers. IgE does not cross the placenta (Carlier and Truyens, 1995) and there was a quantitative difference between the level of cord blood and maternal antibody which suggests that it was derived from the foetus rather than being the result of the transfer of maternal blood at birth. Not all studies however support the idea of that maternal infection influences subsequent microfilaraemia. Hitch *et al.,* 1997 found that cord blood mononuclear cells showed very little evidence of *in-vivo* sensitisation to filarial antigens. Filaria-specific IgM levels in half the infants were no greater than the background level of pooled cord blood samples from a non-endemic area and the anti-filarial IgM levels did not correlate with the filarial antigen state of the mothers. Seventy one percent of the cord blood samples showed no anti-filarial IgE and there was no correlation between cord blood anti-filarial IgE and maternal filarial infection status. Only 14% of the cord blood mononuclear cells tested responded to filarial antigens in utero. The oral route via breast milk is another possible mechanism for sensitisation in infancy. *Onchocerca volvulus* antigen has been found in breast milk (Petralanda *et al.,* 1988) but there have been no comparable studies in lymphatic filariasis.

Support for the role of maternal sensitisation in influencing the course of filariasis also comes from studies of filariasis in expatriates. As discussed above, exposure to filarial antigens in expatriates produces an inflammatory reaction which is often more severe than that see in long-term residents of the same endemic area (Ottesen, 1992) and Indonesian studies have shown that newly settled immigrants from an area where filariasis endemicity was low have a greater chance of developing elephantiasis when they re-settle in a highly endemic area than those who had lived there all their lives (Partono *et al.,* 1978). Although the evidence for *in-utero* conditioning as a risk factor for microfilaraemia appears strong, there is also evidence that the intensity of local transmission can influence the outcome. Alexander *et al.,* have shown that local transmission intensity is a confounding variable in determining the propensity of children to develop a patent filarial infection.

The Role of Super-added Bacterial and Fungal Infections

Lymph stasis provides an ideal medium for the growth of microorganisms and skin lesions allow bacteria and fungi to invade and set up chronic infection (Olszewski et *al.,* 1993, 1994, 1997, 1999; Olszewski and Jamal, 1994; Burri *et al.,* 1996; Roberts and Janovy, 1996). The link between filariasis and bacterial infection, especially streptococci, has been established for a long time (Grace et *al.,* 1932). While some investigators have recovered streptococci directly from patients with acute filarial disease (Grace, 1932, 1934, 1943; Castellani, 1969) others have failed to do so (McKinley, 1931; O'Connor, 1932). Vincent *et al.,* (1998) found strong evidence that the streptococcal disease erysipelas is a significant factor in triggering or amplifying lymphodema or elephantiasis. Anti streptolysin O tires have suggested a relationship between streptococci and filarial pathology in both human (Otero and Lebron, 1936; Rose *et al.,* 1945; Liu *et al.,* 1964; Suma *et al.,* 1997) and animal studies. Bosworth and Ewert (1977) demonstrated that streptococcal infections in cats experimentally infected with *B. malayi* contribute to causation of elephantiasis and developing worms were adversely affected by streptococcal infection of the worm-infected lymphatics. It has been shown that delayed skin hypersensitivity to streptococcal antigens is reduced in filariasis (Grove, 1979) and it would seem that the application of modern methods of immunological research to the interaction of filarial parasites and streptococci might be an area for fruitful research.

It has been shown that careful attention to hygiene, the use of antibiotics and anti-fungals, and the use of physiotherapy and pressure bandages, will modify disease progression and lead to resolution in some cases (Olszewski *et al.,* 1993; Ottesen, 1994; Addiss and Louis-Charles, 1997; Shenoy *et al.,* 1998a, 1999). National inhabitants of the Finschhafen district of Papua New Guinea use the bark of the Lawang tree (*Cinnamomum culilawan)*, which contains the essential oils euenol and safrole, as a poultice to relieve the pain of acute adeno-lymphangitis (McMillan, 1968) and such local treatments warrant more detailed investigation. A fitting closure to this section would be to quote the words of Ottesen (1994).

> *"No clear cut evidence exists to demonstrate an inevitable progression from one clinical form of lymphatic filariasis to another. Instead there appears to be a definite element of plasticity in the response to the parasite the reflects the balance among a variety of factors including prior sensitisation to parasite antigens and present influence of parasite- and host-derived immuno-modulating molecules, as well as the current nature of exposure to infection by the parasite."*

Diagnosis of Lymphatic Filariasis

Lymphatic filariasis may be diagnosed by:

1. Demonstration of microfilariae. This can be subdivided into:
   - Direct techniques, and
   - Concentration techniques
2. Detection of filarial antigens
3. Detection of filarial antibodies
4. Detection of parasite DNA by DNA probes or the polymerase chain reaction (PCR)
5. Detection of adult worms
6. Skin tests with filarial antigen

(WHO, 1984, 1987, 1992, 1993, 1994; Eberhard and Lammie, 1991a; Wame, 1994).

Methods for Direct Detection of Microfilariae

In areas where microfilariae exhibit nocturnal periodicity blood should be taken within two hours either side of midnight when the highest density of microfilariae is expected to occur. Where they show diurnal periodicity blood should be taken two hours either side of midday. Simonsen *et al.,* (1997a) have devised a method to adjust for the effect of sampling time on microfilariae density. Using their technique it is possible to predict what the microfilariae density would be at midnight in blood collected at say, 2200 hours. The simplest technique for direct diagnosis of microfilaraemia is a giemsa-stained thick blood film of capillary blood collected by finger-prick (Khamboonruang *et al.,* 1987; Schultz, 1988; Schuurkamp *et al.,* 1990; Sabry, 1992. If a measured amount of blood is used (say 40 to 60 ul^3 the number of microfilariae per ml can be calculated (Moulia-Pelat, 1992). A modification (Sasa, 1967), which allows easier counting of microfilariae, is to expel 60µl of blood onto the slide so it forms three even linear strips. The dried films are de-haemoglobinised in buffered water before staining with Giemsa stain. The disadvantage of thick films, like other direct methods, is that they underestimate the prevalence of microfilaraemia if microfilariae densities are low because theoretical detection limit for such procedures is between 15 and 50 microfilariae per ml (Panicker *et al.,* 1991; Turner 1993; Turner *et al.,* 1996; Faris *et al.,* 1997). Even if 60µl of blood is used subjects with less than 60 microfilariae per ml will not be reliably detected. Another problem is loss of microfilariae from the film during processing especially if anticoagulated blood is used. Southgate (1973) observed a loss of up to 51% and Denham *et al.,* (1971) a loss of between 10% and 40%. Loss of microfilariae is minimised if un-anticoagulated blood is used and the films are dried over night at room temperature (Goldsmid and Rogers, 1976a,b; Partono and Idris (1977). Youssef *et al.,* (1995) have shown that applying a thin film of agar to the thick film before staining greatly reduces the loss of microfilariae. The thick film does lack sensitivity when microfilariae density is low but is still a useful and cheap technique for survey work were other more sensitive techniques are too expensive (Moulia-Pelat, 1992) or when it is difficult for cultural or other reasons to obtain to obtain venous blood. It has also been suggested that more microfilariae are present in capillary blood than venous blood and that the use of capillary blood may be an advantage when microfilariae densities are low (Eberhard *et al.,* 1988).

There is no question, however, that direct techniques often fail to identify patients with low parasite densities and concentration techniques should be used wherever possible (Southgate and Hamilton, 1974; Weller *et al.,* 1982). Acridine orange staining and fluorescence microscopy has been used as an alternative to Giemsa staining (Goldsmid and Rogers, 1976a,b; Goldsmid *et al.,* 1976) and various combinations of stains can be used to demonstrate the internal structure of microfilariae (Laurence and Simpson, 1969). Counting chamber techniques using various diluents have been used for counting microfilariae by several investigators (Denham, 1971, 1979; Southgate, 1973; Sucharit and Vutikes (1975) and, although not as sensitive as concentration techniques, are a reasonable compromise if 0.1ml of blood is used (McMahon *el al* 1979).

Concentration Methods for Microfilariae

The most widely used is the method of Knott (1935). One ml of blood is added to 9ml of a 1% formalin solution in normal saline. After red cell lysis is complete the mixture is centrifuged and the deposit examined for microfilariae. Because the formalin preserves the microfilariae, Knott's tests can be set up in the field and processed when the field worker returns to base. The theoretical detection limit is 1 microfilaria per ml. The accuracy of the Knott's test and its ease of use is compromised when blood is processes from individuals with excessive amounts of plasma gamma globulins, a common finding in tropical populations. The formalin precipitates the protein and makes the examination of the deposit very difficult. The method has been improved by Melrose *et al.,* (2000) who added a small of Triton X-100 to the diluent which dissolves most of the proteingenous deposit and enhances the visibility of the microfilariae. If a citrate-saponin solution is substituted for the 1% formalin used in the Knott's method, viable microfilariae can be obtained (McQuay, 1970). Another widely used concentration method is the membrane filter technique whereby 1ml of blood that has been diluted in water is passed through a cellulose filter and the microfilariae are trapped on the cellulose (Bell, 1967; Chulerek and Desowitz, 1970; Desowitz *et al.,* 1973a,b; Nathan *et al.,* 1982; Moulia-Pelat

1992). Viable microfilariae can be recovered from the filter for further experimentation or the filter can be fixed and stained and the microfilariae counted. Again, the theoretical detection level is 1 microfilaria per ml but there are some disadvantages of the method. Blood must be processed at once, the filter apparatus and filters are relatively expensive and it may be difficult to count the microfilariae if large numbers are present. Dennis *et al.,* (1976) conclude that if the volume of blood is increased from 1ml to 5ml the technique is sufficiently sensitive to allow day time blood to be screened for microfilariae in areas where there is nocturnal periodicity alleviating the necessity of night surveys. Moulia-Pelat *et al.,* (1992) found that less periodicity-induced variation in microfilariae counts was obtained with membrane filtration than with capillary blood films but the microfilariae density at the peak of the microfilaraemia was lower in the membrane filter technique than with capillary blood films.

Other concentration methods include: the examination of the buffy coat in a centrifuged microhaematocrit tube (Goldsmid *et al.,* 1972); buffy coat samples prepared from a cytocentrifuge (Goldsmid and Rogers, 1975); and the Becton Dickinson QBC method (Long *et al.,* 1990; Wang, 1998; El Serougi, 1999). The Shandon cytoconcentration technique ordinarily used to detect malignant cells in cerebral-spinal fluid and organisms in broncho-alveolar lavage fluid can be used to detect microfilariae and other blood parasites in diluted, saponin-lysed blood and it is claimed to 7.5 times more sensitive than a thick film (Petithory *et al.,* 1997).

The Diethylcarbamazine (DEC) Provocation Test

If 1.5 to 2 mg of DEC per kg of body weight is giving during the daytime microfilariae are "provoked" into leaving the lungs and entering the peripheral circulation where they can be detected by any of the techniques above (WHO, 1987). The use of this test should be discouraged as it has a lower sensitivity than night blood collection and runs the risk of also provoking a severe reaction (see below) especially in areas where *W. bancrofti* occurs with *O. volvulus* or *L. loa* (WHO, 1987). The other antifilarial drugs ivermectin and albendazole do not induce microfilariae to enter the blood during the day (Dunyo *et al.,* 1999).

Detection of Filarial Antigen

Filarial antigenaemia is associated with active filarial infection (Hamilton, 1985) and several investigators have developed assays for filarial antigen using both polyclonal and monoclonal antibodies raised against various antigens (Dasgupta *et al.,* 1984; Hamilton *et al.,* 1984; Reddy *et al.,* 1984; Forsyth *et al.,* 1985; Hamilton, 1985; Harinath, 1986; Lal *et al.,* 1987; Weil and Liftis, 1987; Weil *et al.,* 1987; Zheng *et al.,* 1987; Santhanam *et al.,* 1989; Cheirmaraj *et al.,* 1990). The first commercial assay (Trop Bio Og4C3 Antigen Test, produced by Trop Bio Pty Ltd, Townsville, Australia) is based on the assay developed by More and Copeman (1990; 1991). The monoclonal antibody is raised against *Onchocerca gibsoni* antigen and shows very strong specificity for *W. bancrofti* antigen. Since it detects antigen from both adult worms and microfilariae the Og4C3 assay will detect amicrofilaraemic and microfilaraemic infections (More and Copeman, 1990; Turner, 1993) and is a very good marker of active filarial infection with adult worms (Chanteau *et al.,* 1994a,b). Unlike microfilaraemia, antigen levels show no significant nocturnal or diurnal variation and blood can be taken at any time of day or night (Moulia-Pelat *et al.,* 1993b). Blood samples taken onto filter paper strips can be used for the Og4C3 assay and Lalitha *et al.,* (1998) and Itoh *et al.,* 1998 found that the capillary blood collected on filter paper and serum gave comparable results. By contrast, Gyapong *et al.,* (1998b) found that the sensitivity of the filter paper test to be significantly inferior with only 50.3% positive with both tests. More and Copeman (1990) showed no cross-reaction in the Og4C3 test with Brugia species or other helminths but there is a recent report by Rocha *et al.,* (1996) of a person from a "non endemic" filarial area who tested positive with the Og4C3 test. This individual was found to be parasitised by *Hymenolepsis nana.* Whether this represents a true cross-reaction or not is debatable as she also showed a positive immunoblot with crude *B. malayi* antigen. The reported diagnostic sensitivity of the Og4C3 assay for *W. bancrofti* varies from 73% (Chanteau *et al.,* 1994a) to 100% (Lammie *et al.,* 1994). The variation in sensitivity might be partially explained by the variation in the amount of blood used for the detection of microfilariae, which varied from 20µl to 1ml. A more recent study by Rocha *et al.,* (1996) suggests that the sensitivity of the OG4C3 assay may be reduced when microfilariae density is very low. At micro filarial densities of <1, 1 to 30, and >30 the sensitivity was 72.2, 97.6 and 100% respectively and the log OD of the assay was strongly associated with microfilariae density.

The ICT antigen test (ICT Diagnostics, Sydney, Australia) is rapid immuno-chromatographic technique using specific monoclonal and polyclonal antibodies It utilises capillary or venous blood and is simple enough for field use by people with a minimum amount of training (Weil *et al.,* 1997). The efficacy of filarial antigen tests has been reviewed by Simonsen and Dunyo (1993), Nguyen *et al.,* (1999) and Phantana *et al.,* (1999). Phantana *et al.,* (1999) compared the ICT to thick blood films and membrane filtration and obtained the following results: Sensitivity 100%, specificity 96.3%, predictive value positive 70.7%, predictive value negative 100%. Pani *et al.,* (2000) however, found it less sensitive than the filtration test for detecting low-level microfilaraemia citing an 88.3% positive predictive value when compared with the latter test.

Detection of Filarial Antigen in Body Fluids Other Than Blood

It has been shown by Needham *et al.,* 1996 that there is potential for parasite diagnosis through the detection of antibodies in saliva. A novel, yet untried approach to filariasis diagnosis would be to develop an antigen detection method similar to that used for blood, which could be used on saliva. This would be a much less invasive test than blood collection and would not expose health workers to the danger of blood-borne pathogens such as HIV and hepatitis B and C. Filarial antigen is also present in urine and may demonstrated there even when it is cannot be detected in serum (Das *et al.,* 1987). This anomaly is thought to be caused by the formation of antigen - antibody complexes in the circulation (Das *et al.,* 1987). These immune complexes should not interfere with detection of filarial antigen by the Trop Bio test however as that assay includes a procedure to disassociate antigen - antibody complexes (More and Copeman, 1991).

Detection of Filarial-specific Enzymes

Filarial-specific enzymes have been characterised and show diagnostic potential either as antigens for antibody assays or by the detection of the enzyme itself. Filarial acetylcholinesterase has been identified in the serum of infected people (Misra *et al.,* 1993), and in *in-vitro* culture fluid (Rathaur *et al.,* 1987) and has inter-species cross-reactivity (Sharma *et al.,* 1998). Filarial Glutathione binding proteins, Glutathione-s-transferase, proteinases and superoxide dismutase have been detected in the serum of filarial-infected cattle and humans (Bal and Das, 1995, 1996; Beuria *et al.,* 1995) and the latter has been shown to be strongly antigenic.

Filarial Antibody Assays

There has already been some discussion about filarial antibody in the section on humoral immunity (above). Lack of readily obtainable adult worms makes has made it very difficult to prepare *W. bancrofti* antigen for immuno-diagnosis but the recent introduction of ultrasonic detect (Amaral *et al.,* 1994; Suresh *et al.,* 1997) should make the task easier. The only animals that can be infected with *W. bancrofti* are the leaf monkeys *Presbytis cristata* (Palmieri *et al.,* 1982; Rajasekariah *et al.,* 1986) and *P. melalophos* (Sucharit *et al.,* 1982) and Taiwan monkeys *Macaca cyclopis* (Cross *et al.,* 1979) and these animals are expensive and difficult to maintain in captivity (Franke *et al.,* 1987). *Wuchereri bancrofti* microfilariae can be maintained in culture (Chen and Howells, 1979; Devaney and Howells, 1979; Kharat *et al.,* 1980) or isolated from blood (Jones *et al.,* 1975; Chandrashekar *et al.,* 1984; Van Hoegaerden and Ivanoff, 1986; Franke *et al.,* 1987; El Bassiouny *et al.,* 1993) and used to prepare antigen for antibody studies. The viability of separated or cultured microfilariae can be ascertained by means of a tetrazolium formazan assay (Comley and Turner, 1990; Mukherjee *et al.,* 1997).

Fortunately, there is marked cross reactivity between filaroid species (Tandon *et al.,* 1981) and wide range of other crude filarial parasites antigens have been utilised for filarial antibody detection: *Dirofilaria immitis* (Amboise-Thomas, 1980; Ata *et al.,* 1993; Turner, 1993; Turner *et al.,* 1993); *Litomosoides carinii* (Hamilton *et al.,* 1981, 1985; Tandon *et al.,* 1981; Rajasekariah *et al.,* 1986); *Setaria cervi* (Tandon *et al.,* 1981, Almeida *et al.,* 1990); *Setaria digitata* (Dissanayake and Ismail, 1980); *B. malayi* (Hamilton *et al.,* 1981; Ottesen *et al.,*1985; Paranjape *et al.,* 1985; Rajasekariah *et al.,*1986; Hussain *et al.,* 1987; 1992; Kwan-Lim *et al.,* 1990; Chanteau *et al.,* 1991, 1994, 1995; Hitch *et al.,* 1991; Kurniawan *et al.,* 1993; Murthy *et al.,* 1993; Yazdanbakhsh *et al.,* 1993a,b; Lawence *et al.,* 1994; Mahanty *et al.,* 1994; Terhell *et al.,* 1996); *B. Phahangi* (Weller, 1978; Maizels *et al.,* 1985; Rajasekariah *et al.,* 1986; Hitch *et al.,* 1991; Lammie *et al.,* 1993; Estambale *et al.,* 1994; Addiss *et al.,* 1995; Marley *et al.,* 1995; Wamae *et al.,* 1995; Simonsen *et al.,* 1996) and *Dipetalonema viteae* (Rajasekariah *et al.,* 1986). There is a down side to this cross reactivity - antifilarial antibodies cannot be used to distinguish between filaroid species (Rajasekariah *et al.,* 1986).

Other antigens under evaluation for filarial antibody detection include a chitinase-like recombinant antigen from *W. bancrofti* (Dissanayake *et al.,* 1994, 1995; Raghavan *et al.,* 1994), a cloned antigen with IgG4 specificity (Dissanayake *et al.,* 1992), recombinant *B. malayi* antigen (Kumari *et al.,* 1994; Ramzy *et al.,* 1995), a highly specific antigen from *W. bancrofti* 3rd stage larvae (Burkot *et al.,* 1996), fractionated urinary antigen (Ramaprasad and Harinath, 1995), fractionated circulating filarial antigen (Cheirmaraj *et al.,* 1992). Antibodies to recombinant paramysin from *B. malayi* can be used as a marker for adult worms of that species (Langy *et al.,* 1998).

Antifilarial IgG antibody reacts with a wide range of other helminths and protozoa due to shared phosphocholine antigens (Ambroise-Thomas 1974; Voller and de Savigny 1981; Taylor and Denham 1985; Lal and Ottesen 1989; Chanteau *et al.,* 1995). Species shown to cross react include *Ascaris suum* (Betschart *et al.,* 1990; Willenbucher *et al.,* 1993), *Ascaris lumbricoides* (Kagan *et al.,* 1963; Paranjape *et al.,* 1985; Gam *et al.,* 1987; Murthy *et al.,* 1993; Rahmah *et al.,* 1994), *Trichuris trichiura* (Rahmah *et al.,* 1994) and hook worm (Gam *et al.,* 1987), Strongyloides (Gam *et al.,* 1987, Rahmah *et al.,* 1994), Fasicola *hepatica* and *Shistosoma mansoni (*Rahmah *et al.,* 1994) and *Trichinella spiralis* (Kagar *et al.,* 1963). The degree of cross-reactivity between filaroids and other parasites vary between different species of filaroids. Saxcena *et al* (1981) showed no cross reactivity between *L. carinii* and *Ancylostoma, Ascaris, Taenia* or amoeba (species not specified).

Various methods can be used to detect filarial antibody: Complement fixation, indirect haemagglutination, gel diffusion, immunoelectrophoresis, counter current immunoelectrophoresis, indirect immunofluorescence and enzyme-linked immunosorbent assay (ELISA) have all be used (Kagan, 1963; Ambroise-Thomas, 1980). Currently, almost all filarial antibody studies use ELISA and the following discussion deals with that method of detection unless otherwise indicated. Cross reactivity limits the usefulness of IgG antibody in filariasis diagnosis but they may be of some value in communities where parasites other than *W. bancrofti* are absent or rare (Chanteau *et al.,* 1991) and have been used to diagnose occult filariasis in Indian children (Chaturvedi *et al.,* 1995). Because humans are not able to synthesise anti-phosphocholine or anti-carbohydrate antigen IgG4 (Maizels *et al.,* 1987; Scott *et al.,* 1987; Lal *et al.,* 1991) the assay of filarial IgG4 antibodies greatly increases specificity and enhances the diagnostic ability of the test (Lal and Ottesen, 1988; Kwan-Lim, 1990; Rahmah *et al.,* 1994; Haarbrink *et al.,* 1995, Chanteau *et al.,* 1995; Terhell *et al.,* 1996) and Mahanty *et al.,* (1994) have shown that antifilarial IgG4 is a good index of the intensity and duration of filarial exposure in endemic populations, and (Maizels *et al.,* 1995) found that the level of IgG4 antibody correlates with microfilariae counts. Filter paper collection techniques can be used to detect filarial IgG4 antibody (Chanteau *et al.,* 1991; Terhill *et al.,* 1996). IgG4 antibodies are extremely useful for the detection of *Brugia* species because they will not be detected by the current antigen tests because they are specific for *W. bancrofti* (Rahmah *et al.,* 1998; Haarbrink *et al.,* 1999a). There appears to be very little literature on the usefulness of anti-filarial IgM antibody for filariasis diagnosis but Ata *et al.,* (1993) found it to be more specific than IgG. Chanteau *et al.,* (1992) trialed an IgA antibody test but found it unhelpful. It should be bourne in mind that sero-positivity does not always indicate active filarial infection. The antibody may have been raised by exposure to infective larvae without an adult worm being present or the antibody may persist after parasites have been cleared and although the sensitivity of antibody tests is high, the specificity, and hence the predicative value, is low (Chanteau *et al.,* 1991).

Demonstration of Parasite DNA by DNA Probes or the Polymerase Chain Reaction (PCR)

Polymerase chain reaction methods have been successfully used in the detection of *W. bancrofti* DNA in sputum (Abbasi *et al.,* 1996, 1999), *B. malayi* DNA in blood (Lizotte *et al.,* 1994; Rahmah *et al.,* 1998). *W. bancrofti* in blood, plasma and paraffin-embedded tissue sections (McCarthy *et al.,* 1996), urine (Lucena *et al.,* 1998) and *W. bancrofti* larvae in infected mosquitoes (Chanteau *et al.,* 1994c; Nicolas *et al.,* 1996; Furtado *et al.,* 1997). A combination PCR-ELISA method for detection of filarial DNA has been devised by Fischer *et al.,* (1999).

The Demonstration of Adult Worms

The use of ultrasonography to detect adult worms in the scrotum (Amaral *et al.,* 1994; Simonsen *et al.,* 1997a; Faris *et al.,* 1997; Suresh *et al.,* 1997, Dreyer *et al.,* 1999) has already been dealt with above. The same technique can be used to detect adult worms in the breast (Dreyer *et al.,* 1996a,b) and has detected viable worms in children (Dreyer *et al.,* 1999). The need for specialised technology means that this diagnostic tool is not available to most of the at-risk population.

Skin Testing

Skin tests using filarial antigens which were usually prepared from *D. immitis* (Bozicevich and Hutter, 1944; Franks *et al.,* 1947; Sawada *et al.,* 1965) were widely used for filariasis diagnosis from the 1940's to the 1970's and the subject has been extensively reviewed by Kagan (1963) Desowitz *et al.,* (1966) and Ambroise-Thomas (1980). The Sawada antigen skin test was evaluated by Smith *et al.,* (1971). They obtained 22% false positives in non-exposed controls, 53 to 85% false negatives and there was much cross-reaction with other helminth species. Because of this lack of sensitivity and specificity, the skin test has been largely abandoned although it may have a part to play in the monitoring of filarial control programs (Desowitz, 1966; Amboise-Thomas, 1980; Tada *et al.,* 1982).

Which Test is the Best One to Detect Filarial Infection?

To quote Southgate and Hamilton (1974):

> *"Clearly, the unexpected prevalence rates determined by the newer techniques will change our ideas on filariasis control; even in areas where it has been recognised as highly prevalent for years, the amount of filariasis obviously been under estimated. Apparently rather small changes in the techniques of epidemiological measurement in estimating the prevalence and densities of microfilaraemia in a human population can produce quite remarkable changes in our views of the epidemiology of the disease. Clearly our changing understanding of epidemiology has very serious implications for control programs."*

These comments were made during a study of the value of concentration methods to estimate the prevalence of microfilaraemia but they stress the necessity of utilising the very best test available. The question "which is the best test available" can be best answered by quoting Chanteau *et al.,* (1994). "The detection of microfilariae is very specific but insensitive, the antibody tests are very sensitive but not specific enough, and finally the Og4C3 antigen test seems to be a good compromise of specificity and sensitivity for the diagnosis of Bancroftian filariasis". This sentiment is echoed by Simonsen and Dunyo (1999). The other commercially available antigen test, the ICT rapid card test is now widely accepted as the tool of choice for survey work because of its simplicity and its ability to provide “on the spot” data. While it has been more or less decided what the most appropriate tests for filariasis in patients from endemic areas are, the situation with acute expatriate cases is more difficult. IgG anti-filarial antibodies can be demonstrated in most exposed expatriates but this is not a useful marker of active infection as is could just be the result immunological stimuli of injected L3 larvae, infection or contact with an animal filaroid, or could be due to cross reactions with other helminth parasites. IgG4 antibodies are slow to develop and this limits their usefulness. IgM antibodies are too non-specific to be of any value. Expatriates do not seem to become antigen positive (why that is so would be an interesting topic for further research) and microfilaraemia is extremely rare. It has been suggested that testing for low levels of antifilarial IgE may be of value (Nutman 1997, *pers. comm.*) and this should be explored. Currently, he resolution in symptoms and the reduction in eosinophils after a diethylcarbamazine therapy is often the best indicator of infection.

Control of Lymphatic Filariasis

There are several approaches to controlling vector-borne parasitic diseases: vaccination, vector control, breaking of vector-host contact by use of repellents and bed nets, and chemotherapy.

Vaccines

Despite some promising research, a vaccine for any filarial parasite (and indeed any parasite) is not yet a reality (Philip *et al.,* 1988; Selkirk *et al.,* 1992; Chenthamarakshan *et al.,* 1995; Dissanayake *et al.,* 1995; Grieve *et al.,* 1995). There has recently been some progress in this area with cloned filarial antigens, a recombinant chitinase and a protective epitome SXP1, an antigen found in multiple worm stages showing promise as vaccine candidates (Cryz 1991; Wang *et al.,* 1997) and Zang *et al.,* (1999) suggests that a serine protease inhibitor expressed by *B. malayi* microfilariae that inhibits neutrophil serine protease and aids the parasite to evade the immune system, may be a target for vaccine development.

Vector Control

Vector control does have a part to play and can be very successful when malaria and filariasis have common vectors. In the Solomon Islands for instance, where both malaria and filariasis are transmitted by *Anopheles farauti* and *Anopheles koliensis*, the prevalence of microfilaraemia was reduced from around 15% to <2% by vector control carried out during a malaria campaign (Webber, 1977, 1991). Vector control however does take a long time to become effective. For instance, Schuurkamp *et al.,* (1987) estimated that it would take 11 years to reduce the prevalence of microfilaraemia to <2% in the Tabubil area of the Western Province of Papua New Guinea by vector control alone. Such prolonged campaigns are very labour intensive and costly and the development of insecticide resistance makes them become less and less effective. Data collected during a 5-year vector control program in Pondicherry, India, found that vector control alone might have little impact on the overall age-prevalence of infection even when sustained for long periods (Srividya *et al.,* 1996). Toilet pits and the like are prime breeding grounds for *Culex quinquefasiattus* (Nwoke *et al.,* 1993) and the use of polystyrene beads can be a very effective control mechanism for this and other *Culex* species. By use of this method Maxwell *et al.,* (1989) reduced the numbers of mosquitoes entering houses by about 97% Webber and Southgate (1981) have shown that in the Solomon Islands approximately 8 mosquito bites per person per night are required for reliable transmission of filariasis. Maxwell *et al.,* (1999) found that although the treatment of cesspools and pit toilets with polystyrene beads reduced the mosquito population in houses the cost of achieving this could not be justified by its impact on filariasis alone, but the reduction in nuisance biting may increase the community support for other control programs

Insecticide-treated Bed Nets

Insecticide-treated bed nets have the potential to reduce filariasis transmission (Charlwood and Dagoro, 1987) but they are of only limited effectiveness because there are a large number of mosquito species that transmit filariasis and some of these bite during the time of when people are not under bed nets.

Chemotherapy

There are essentially two regimes used to control filarial infections using chemotherapy: selective and mass treatment. In selective therapy individuals are examined for the presence of disease and those who are found to be infected are treated. There are major problems associated with that approach. If microfilaraemia is used as the indicator of infection many infected people will be overlooked, as not all those who have the disease are microfilaraemic. People with very low micro filarial densities may not be detected and it has been shown that such people are capable of infecting mosquitoes and causing a resurgence of disease (Lowrie *et al.,* 1989). The use of antigen testing will overcome these problems but you are still left with the logistical problem of screening all members of the community. If selective chemotherapy is used the lost infections are balanced by new infections to produce a dynamic equilibrium and there needs to be continual reassessment of the filarial status of the community to identify the newly infected. By studying the transmission potential of a number of diseases, including helminth parasites, Woolhouse *et al.,* (1997) found that, typically, 20% of the infected host population contributes at least 80% of the net transmission potential and that control programs which fail to reach all of that core group, a problem with selective treatment programs, will be less effective in reducing levels of infection in the group as a whole. Using mass chemotherapy regardless of parasite status excludes the problems of selective therapy. Mass treatment aims to treat all members of the endemic community at the same time and will therefore treat pre-patent as well as patent infections. In other words the community becomes the focus of the control program rather than the individual. Originally antimony and arsenic based drugs and naphthalene sulfonic acid (Suromin) were used to treat filariasis but with limited success (James and Gillies, 1985; Campbell and Rew, 1986). These compounds had a moderate amount of anti-filarial activity but were very toxic. Suramin has been shown to be moderately active against adult *W. bancrofti* and *Brugia phahangi* (Howells *et al.,* 1983) but it has no effect on microfilariae and will therefore not interrupt the transmission cycle in the short term. It is also more

toxic than other antifilarial drugs and is not widely used today (James and Gillies, 1985). Levamisole has been shown to have limited activity against filarial parasites (Duke 1974; O'Holohan and Zaman 1974; Rogers and Denham 1976; McMahon 1979).

The Use of Diethylcarbamazine (DEC)

For the last 50 years the piperazine derivative diethylcarbamizine (DEC, proprietary names: Hetrazan, Banocide and Notezine) has been, and still is, the most widely used drug for the treatment of lymphatic filariasis (James and Gillies, 1985; MacKenzie and Kron, 1985; Campbell and Rew, 1986). Diethylcarbamazine was discovered by Hewitt *et al.,* in 1947 and used to treat human filariasis in the same year (Santiago-Stevenson *et al.,* 1947). The pharmacology of DEC has been extensively investigated (for reviews see: Hawking, 1950b; Hawking *et al.,* 1950a; MacKenzie and Kron, 1985; Maizels and Denham, 1992) and the following summary is taken from those publications unless otherwise indicted. Diethylcarbamazine is given orally and is rapidly absorbed reaching peak blood levels one to hours after ingestion. It reaches all parts of the body within 25 minutes after the dose is given. Accurate blood levels of DEC can be determined by ELISA (Mitsui and Aoki, 1998). The plasma half life varies from 6.1 to 8.1 hours. Excretion is mainly renal and the blood concentration reaches zero within 48 hours. Diethylcarbamazine, albeit in high concentrations and in *in-vitro* experiments, has been shown to affect several systems of the body. It can have a depressive effect on myocardial activity, stimulate the production of hepatic enzymes and produce relaxation of intestinal tissue (MacKenzie and Kron, 1985). Joseph and Dixon (1984) found that DEC enhances the ability of oxytocin and acetylcholine to induce contractions of uterine tissue and that led Subbu and Biswas (1971) to recommend that DEC should not be given to pregnant women, but in practice however, there have been no reports of abortifacial or tetrogenic effects. Diethylcarbamazine does not have any effect on the white cells of non-filarial infected patients but it does cause a rapid fall in eosinophils which often show loss of granulation and vacuolation suggesting that these cells have a role in the destruction of microfilariae. Diethylcarbamazine causes the release of serotonin from platelets and stimulates the production of platelet adhesion factor and thromboxane. Paradoxically it also appears to inhibit platelet aggregation induced by adenosine diphosphate and collagen.

Hawking *et al.,* (1950a) suggested that DEC acted as an opsonin and enhanced phagocytosis of microfilariae but the exact mechanism by which DEC destroys microfilariae is still a matter of debate (see the comprehensive review by MacKenzie and Kron (1985). Mukhopadhyay and Ravindran (1997) have found evidence that antibodies formed against the drug itself potentiate the action of antifilarial antibodies but this finding is disputed by Cesbron *et al.,* (1987) whose study suggests that blood platelets play a role in DEC-mediated microfilariae killing possibly involving a free radical process.

In summary, the main modes of action thus far identified are focussed in two main areas: the effect of the drug itself upon the parasite and the facilitation of host-parasite interactions. Diethylcarbamazine has been shown to overstimulate parasite neuromuscular systems and increase motility, to inhibit vital parasite metabolic enzymes, activate complement on the parasite's surface membrane, activate eosinophils and stimulate them to produce eosinophil-derived cationic proteins, enhance eosinophil-dependant antibody-mediated destruction of parasites and increase the adhesion of parasites to phagocytic and antibody-producing cells. It has been demonstrated by Bhattacharya *et al.,* (1997) that one of the ways that filarial parasites ensure their survival in the host is to secrete acetylcholesterase into the circulation of the host, which degrades circulating acetylcholine. Since acetylcholine stimulates the release of lysosomal enzymes such as β-glucuronidase and acid phosphatase, which are involved in phagocytosis, is depressed during filarial infections. After DEC treatment the level of plasma beta-glucuronidase and acid phosphate rose and this is believed to be due to DEC inhibiting the production of parasite acetylcholinesterase. Another focus in recent years has been the role of nitric oxide in microfilariae clearance. *In-vitro* tests have shown that Microfilariae are killed by exposure to nitric oxide (Taylor *et al.,* 1996) and Winkler *et al.,* (1998) has shown that high levels of nitrite and nitrate were released into the serum during microfilariae killing.

Another contentious issue is whether DEC is macrofilaricidal as well as microfilaricidal. MacKenzie and Kron (1985) concluded that it had a limited amount of macrofilariacidal activity and their opinion is supported by Weil *et al.,* (1988). The degree of activity however, is still questionable (Ottesen, 1985, Weil *et al.,* 1988). There is also histological evidence - Figueredo-Silva *et al.,* (1996) removed nodules after DEC treatment and found almost all contained degenerating adult worms. Experiments by Ismail *et al.,* (1996) suggest that fortnightly 10mg/kg doses of DEC suggested that there was some macrofilaricidal activity but the outcomes were inconsistent and the finding by Weil *et al.,* (1988) that filarial antigenaemia persists for up to 12 months after DEC therapy has eliminated circulating microfilariae suggests that DEC is only partly effective against adult filarial parasites. Eberhard *et al.,* (1997) reported that although filarial antigen fell after treatment, in no case did it fall to zero, even in individuals who remained amicrofilaraemic for several years after treatment. This they suggest was evidence that adult worms were persisting. The absence of microfilariae would suggest however, that if the adult females are still living they are prevented from

producing microfilariae or that DEC in some way, facilitates the rapid removal of microfilariae from the circulation. In any case, the lack of microfilariae means that the transmission cycle has been interrupted. There is no doubt however that DEC is a highly effective microfilaricidal drug for *W. bancrofti*. Jing-Yuan *et al.,* (1991; 1992) when assessing DEC treatment and residual spraying in China, found that Bancroftian filariasis had been eliminated and that subsequent surveillance showed no signs of resurgence. The question of parasite resistance to DEC has been raised since the early days of its use. Hawking (1950a,b) and Otto *et al.,* (1953) both noted that small numbers of microfilariae persisted in some patients after treatment. Zhong-Xing and Zhong-Jun (1989) found that in former filariasis endemic areas where the disease has been largely controlled, a few cases of low-density microfilaraemia remained and could possibly be related to parasite tolerance to DEC.

Kimura *et al.,* (1985) reported that annual low dose treatment with DEC did not reduce microfilariae densities in subjects with high pre-treatment micro filarial levels. Eberhard *et al.,* (1991b) found that there appeared to be evidence for non-susceptibility to DEC in Bancroftian filariasis. They found that treatment with DEC does not always result in total clearance of microfilariae and suggested that filarial parasites may develop partial resistance. The standard DEC treatment regime is 6 mg per Kg body weight per day over a 10 to 20 day period (James and Gillies, 1985; WHO, 1992; 1994). This is suitable for treated isolated cases but it is not a suitable regime for community-wide mass treatment programs because it is labour-intensive and incurs high costs (Michael *et al.,* 1996). Other regimes for mass treatment are: monthly doses, 6 monthly doses and annual doses. All these methods are effective but not all are equal when assessed on a cost-effective basis (Michael *et al.,* 1996)

DEC Medicated Salt

Common cooking salt medicated with DEC in concentrations ranging from 0.1% to 0.6% (Gelbrand 1994; WHO, 1992; 1994) has been effectively used in mass treatment programs for Bancroftian filariasis in China (Jing-yuan *et al.,* 1991; 1992; Liu *et al.,* 1992; Shaoquing *et al.,* 1994), India (Rao *et al.,* 1981; Chandrasekharan *et al.,* 1984; Narasimham *et al.,* 1989; Krishnarao *et al.,* 1991) and Tanzania (Meyrowitsch *et al.,* 1996; Michael *et al.,* 1996) and has shown to be effective in brugian filariasis (Chandrasekharin *et al.,* 1984; Shenoy *et al.,* 1998b, 1999), but it is logistically difficult to organise due to the bulky nature of the salt, and only slightly less expensive than using the standard dose regime.

Mass Drug Treatment with DEC

Current practice is a single annual dose of 300 mg of DEC for adults and 150 mg for children (often combined with Ivermectin, and sometimes Albendazole - see below). This simplifies the treatment, increases compliance and can be easily accommodate into existing primary health care networks without over-burdening them (Wijers, 1984; Kimura and Mataika, 1996; Taylor and Turner, 1997).

Low dose DEC has been shown to significantly reduce the prevalence and density of microfilariae in treated communities and reduce the prevalence of chronic pathology (Forsyth, 1987; Partono *et al.,* 1984, 1989). Panicker *et al.,* (1991) found that there was a reduction in microfilariae prevalence of 74.9% in the annual treatments and 90% in the biannual treatments.

He also found that attacks of filarial fever and incidence of recent oedema cases were also significantly reduced after DEC treatment. A trial in Tanzania achieved microfilariae clearance rates of 92% (Meyrowitsch *et al.,* 1996). Meyrowitsch *el al* (1998) have shown that the beneficial effects of DEC treatment persist for at least 4 years and although microfilaraemia does recur in some patients, especially those who had high microfilaria densities before treatment, the level of microfilaraemia does not reach the pretreatment levels. Khan *et al.,* (1998) found that 5 years after a dose of 72 mg/kg of DEC given over a 21 day period, 51% of subjects were still amicrofilaraemic, 36.4% had densities less than pre-treatment levels and 11.8% had increased microfilariae counts. In Samoa, 3 annual treatments of DEC 6 mg/kg, achieved an estimated 80% reduction of microfilaria in the population and lowered the annual transmission potential from 2.18 to 0.67 (Kimura *et al.,* (1992). Mataika *et al.,* (1998) obtained similar results with a five-year annual treatment program in Fiji.

Other Benefits of DEC Therapy

There are several other benefits apart from parasite killing in the treatment of filariasis with DEC. Schuurkamp *et al.,* (1992) found that a significant reduction in splenomegaly within the communities around the Ok Tedi Mine after a successful control programme with DEC. Piessens *et al.,* (1981) stated that *in vitro* lymphocyte proliferative responses to microfilariae antigens increased in patients who became amicrofilaraemic after treatment with DEC. Piessens' group also showed that no changes were observed in amicrofilaraemic individuals who were given DEC or in those who remained microfilariae positive after treatment. Partono *et al.,* (1981) showed that the total number of working days lost due to filariasis was substantially reduced after treatment with DEC in Indonesia with the lymphadenitis rate falling from 46% and the prevalence of elephantiasis falling from 17% to 4%.

There is strong evidence that DEC has some activity against a range of non-filarial infectious agents (Mejia *et al.,* 1996) - probably due to its opsonic activity and enhancement of phagocytosis (Hawking *et al.,* 1950a,b; Mejia *et al.,* 1996). It has been shown to enhance blood microbicidal activity (Kitchen *et al.,* 1995a,b; 1998), to be effective in the treatment of chronic bacterial osteomyelitis (Kitchen *el al.,* 1995b),

and to influence the course of bacterial and fungal infections in mice (Kitchen *et al.,* 1992; 1993) and humans (Mejia *et al.,* 1996). It has been shown that bacterial and fungal infection play a pivotal role in the development of filarial elephantiasis (Addiss *et al.,* 1995) and it has been suggested that DEC's antibacterial and antifungal effects may supplement its antifilarial action when it is given to treat filarial disease (Mejia *et al.,* 1996. It has been known for some time that DEC therapy improves T cell responses to purified protein derivative of *Mycobacterium tuberculosis* (PPD) in filariasis and onchocerciasis patients (Green *et al.,* 1985; Sartono *et al.,* 1995b) but there is also a recent suggestion by Kitchen (1995a, 1998) that the anti-mycobacterial effects of DEC may not be limited to the filarial-infected. If this is proved to be the case it is possible that a major side benefit of mass DEC therapy for filariasis control could be reduction in tuberculosis, leprosy and atypical mycobacterial infections in filarial-endemic areas. Diethylcarbamazine has also been shown to have therapeutic potential in feline and murine leukaemia virus infections (Kitchen *et al.,* 1990; Nelson *et al.,* 1995) and has been shown to increase antibody levels in feline oncornavirus-associated cell membrane antigen (Kitchen and Cotter, 1998).

Use of Ivermectin

Ivermectin has been used very successfully for the treatment of oncocerciasis for a number of years (for reviews see Goa *et al.,* 1991: Townson *et al.,* 1994) and a single annual dose of 400 µg/kg, either alone of in combination with Diethylcarbamazine, has proved to be very effective producing long-term suppression of microfilaraemia in Bancroftian lymphatic filariasis in a number of countries (Diallo *et al.,* 1987; Kumaraswami *et al.,* 1988; Ottesen *et al.,* 1990; Campbell 1991; Ismail *et al.,* 1991; Zheng *et al.,* 1991 a,b; Cartel *et al.,* 1992; Eberhard *et al.,* 1992; Addiss *et al.,* 1993; Kazura, 1993b; Moulia-Pelat *et al.,* 1993a, 1994a,b, Coutinho *et al.,* 1994; Nguyen *et al.,*1994; Ottesen and Campbell, 1994; Chodakewitz 1995; Dreyer *et al.,* 1995a; Moulia-Pelat *et al.,* 1995; Ottesen and Ramachandran 1995; Nguyen *et al.,* 1996; Cao *et al.,* 1997) and is equally effective against brugian filariasis (Shenoy *et al.,* 1993). Nquyen *et al.,* (1996) found that twice yearly doses of 100 µg/kg of Ivermectin did not reduce the prevalence of microfilaraemia, but when the dose was increased to 400 µg/kg the prevalence dropped from 21% to 7% and the microfilariae density to 0.5% of its initial value. Plaisier *et al.,* (1999) found that Ivermectin removes 100% of microfilariae regardless of dose and at a does of 400 µg/kg a single treatment irreversibly reduces the microfilariae of the adult parasite by at least 65%. Zheng *et al.,* (1991a,b) found that Ivermectin was especially useful in the treatment of filarial relapses after DEC treatment. Like DEC, Ivermectin treatment does give rise to adverse side effects. Cao *et al.,* (1997) describe them as mild and "flu like", generally mild, and well tolerated by patients. Mild reactions were also noted by Zheng *et al.,* (1991) who also found that local flare-up of acute filariasis was less likely with Ivermectin than with DEC. The severity of the reaction was strongly associated with the pre-treatment microfilariae density but independent of the dose (Cao *et al.,* 1997). Weil *et al.,* (1991) states that local adverse reactions such as nodule formation, lymphangitis and epididymitis are not seen with Ivermectin therapy because these reactions are caused by the death of adult filarial worms and Ivermectin is not a macrofilaricide. An ELISA for blood levels of Ivermectin is available (Mitsui *et al.,* 1996).

As with DEC, the macrofilariacidal action of Ivermectin is debatable. Ismail *et al.,* (1996) found that multiple, high dose Ivermectin treatment (12 fortnightly doses of 400 µg/kg) does have macrofilaricidal activity but the results are neither predictable nor consistent. Eberhard *et al.,* (1997) reported that although filarial antigen fell after treatment, in no case did it fall to zero, even in individuals who remained amicrofilaraemic for several years after treatment suggesting that some adult worms survived. By contrast however, Dreyer *et al.,* (1995b; 1996) could find no evidence of macrofilariacidal activity. In their study 15 men who had living, adult *W. bancrofti* detected by ultrasound were treated with 400 µg/kg body weight of Ivermectin at 2 week intervals for 6 months (total dose 4.8 mg/kg). Microfilaraemia was rapidly suppressed but no changes in the motility or location of the adult worm were detected. In another study Dreyer *et al.,* (1995a,b) removed live adult worms from several patients 8 months after being treated with 400 µg/kg of Ivermectin.

Effect of Ivermectin on Mosquito Survival

There is strong evidence that Ivermectin ingested from a treated person during a blood meal decreases mosquito survival and fertility (Tesh and Guzman, 1990; Nasr *et al.,* 1996; Bockarie *et al.,* 1999).

Use of Albendazole

Albendazole has been used for the treatment of intestinal helminths for a number of years but it has only recently been trialed as an anti-filarial. Addiss *et al.,* 1997a,b have shown that at a stated dose of 400 mg per person it is an effective microfilaricide. It is even more effective when combined with DEC or Ivermectin (see) below. The problem of adverse reactions with Albendazole is no better or worse than with DEC or Ivermectin (Addiss *et al.,* 1997a,b). The potential for Albendazole to be used as a macrofilaricide for the treatment of individual patients is regarded by Ottesen *et al.,* (1999) as one of the most important questions in filarial research.

Combination Therapy

A combination of DEC and Ivermectin has shown to be very effective in providing rapid and long-term clearance of microfilariae (Moulia-Pelat *et al.,* (1994a,b, 1996). Nicolas *et al.,* 1997 found that DEC and Ivermectin was much more effective than either drug alone for clearing circulating filarial antigen in both amicrofilaraemic and microfilaraemic subjects. Addiss *et al.,* (1997) have shown that a combination of 200-400 μg/kg of Ivermectin plus 400 mg of albendazole is more effective in clearing microfilariae than either drug alone. Ishmail *et al.,* 1998 studied the effects of Albendazole, DEC, and Ivermectin alone an in combination and showed that although all were well tolerated and effective macrofilaricide, a single dose of a combination of 600 mg of albendazole and 400 μg/kg of Ivermectin was the most effective. Decreasing levels of filarial antigens after treatment suggested that all four regimes have significant macrofilaricidal activity. The most effective, however, was a combination of 600 mg of Albendazole with 6 mg/kg of DEC. With this combination, filarial antigen levels decreased by 77% 15 months after therapy.

Other Advantages of Combination Therapy

Another advantage of antifilarial therapy using Albendazole and/or Ivermectin is the potent broad spectrum effects against intestinal helminths (Ismail *et al.,* 1998). Another possibility, if Ivermectin is used, is controlling scabies as well. Beach *et al.,* (1999) have shown in a randomised, placebo-controlled study that a 6 monthly combined treatment with Albendazole and Ivermectin was effective in controlling *W. bancrofti, A. lumbricoides, T. trichuria* and hook work in Haitian primary school children with an obvious benefit to their height and weight. The cost effectiveness of controlling more than one parasite with an annual program is obvious and studies to confirm these possibilities are urgently needed.

The Search for New Antifilarial Agents

There is a very active global search for new antifilarial compounds, the ultimate goal being the production of a safe effective macrofilaricide (Lazdins and Kron, 1999). *In-vito* effects of potential anti-filarial can be studied by use of the colorimetric viability test derived by Comley *et al.,* (1989).

Extracts of a wild Indian herb, *Andrographis paniculata* and the ginger plant *Zingiber officinale* have been shown to have activity against canine filariasis (*D. immitis)* both *in-vitro* and *in-vivo* (Dutta and Sukul, 1982, 1987) and a major search for new natural anti-parasite drugs is being carried out in the Philippines (Monzon, 1995). Animal trials of three promising new agents were reviewed by Mak *et al.,* (1991). CGP 30376, a derivative of Benzothiazole and has been shown to be both micro and macrofilaricidal but there is concern about its hepatic toxicity. The methyl-piperazine compound 6140 CGP has significant macrofilaricidal activity and CGI 18041 (its chemistry is not revealed) kills both microfilariae and adult worms. Gayral *et al.,* (1995) have identified a group of ethynesulphonamides, epoxyethanesulfonamides and their carboxamide analogues that show some promise as antifilarial agents. Phenoxycyclohexane definitives are showing promise in *in-vitro* studies, as are thiosemicarbazones in animal studies (Loiseau and Depreux, 1993). Beta-carbolines (Srivastava *et al.,* 1999), bis-cationic hetero-aromatics (Sundberg *et al.,* 1998) and beta-amino substituted 4-amino-3-nitropropiophenones (Varma Rajendra *et al.,* 1992) have shown promise as micro and macrofilaricides in *in-vitro* and animal experiments. An analogue of ubiquinone, 2,3-Dimethoxy-5-methyl-1,4-benzoquinone (QO) has been shown to irreversibly paralyse adults and microfilaria of *S. digitata* and the microfilariae of *W. bancrofti* suggesting that this class of drugs has the potential for anti-filarial therapy (Sivan and Kaleysa, Raj 1999).

Another exciting approach to therapy is to use the lymphatic system rather than the blood for delivery of antifilarial drugs. Adult filarial worms, living as they do in the lymph nodes, are in intimate contact with lymph and this approach may lead to the discovery of a potent macrofilaricide. Derivatives from to drugs used in tumour therapy - Closantel and chlorambucil showed some promise in *in-vitro* experiments but no activity could be detected *in-vivo* (Loiseau *et al.,* 1997).

The search for new antifilarial drugs has moved to the marine environment and the antifilarial activity of a synthetic marine alkaloid, aplysinopsin (CDRI compound 92/138) derived from Australian reef sponges shows *in-vitro* activity (Singh *et al.,* 1997).

Another novel approach suggested by Hoerauf *et al.,* (1999, 2000) is to target the endosymbiont bacteria that live within filaroids and may have a beneficial effect on microfilarial growth and survival. Treatment of onchcerciasis patients with tetracycline resulted in the sterilisation of the female worms.

Adverse Reactions to Anti-Filarial Drugs

Post-treatment reactions are common in lymphatic filariasis and onchocerciasis (where it is called the Mazzotti reaction) and although most cases are relatively mild, they can cause communities to be wary of treatment (Sunny *et al.,* (1986) and lead to failure of control programs (Ottesen, 1980; Forsyth, 1987; Schuurkamp, 1992; Schuurkamp *et al.,* 1990, 1992; Fan, 1992; Turner *et al.,* 1994). Fever is the most common manifestation, but lymphadenitis, arthralgia, chills, drowsiness, headaches, hypotension and urticaria are also common. The reaction is not caused by the drug itself but by an inflammatory reaction induced by dying microfilariae and severity tends to increase with increasing numbers of circulating microfilariae (Piessens *et al.,* 1981b; Francis *et al.,* 1984; Haarbrink *et al.,* 1999b). Laigret (1983) found that reactions to DEC were less frequent as the number of treatments increased. The exact cause of the treatment reaction is still unknown but it has been shown that cytokines such as Interleukin 6 (IL-6) and tumour necrosis factor (TNF) are implicated (Turner *et al.,* 1994). Anti-inflammatory drugs and steroids can be used to lessen the reaction (Ottesen, 1987; Stingl *et al.,* 1988) but the effects are not consistent and concern has been raised that the use of these drugs may reduce the killing efficacy of antifilarial drugs (Schofield and Rowley, 1961; Adwadzi *et al.,* 1982) and Dreyer and de Andrade (1989) are of the opinion that the mild nature of most reactions means that such drugs are seldom warranted. As well as the systemic effects mentioned above, localised reactions such as nodule formation, lymphadenitis and epididymitis are sometimes seen near sites occupied by dying adult worms. This type of reaction is more common when DEC is used because of its at least partial, macrofilaricidal action (Weil *et al.,* 1991).

Effect of Therapy on Microfilaraemia and Immunological Responses

All authors report a rapid decrease in microfilariae levels following therapy. Typically, results are seen within 24 hours and in most cases microfilariae are cleared from the blood within 7 days. There is considerable variation in the length of time that patients remain amicrofilaramic after treatment, varying in different studies from 1 to 12 years (WHO, 1987).

Usually, filarial antibody levels against whole parasite antigen rise immediately after therapy peaking at about 30 days, they fall during the next 12 months to below treatment levels but can remain positive for up to 10 years (Gao *et al.,* 1994). Bal and Das (1999) found that DEC therapy increased the level of IgG and IgM antibodies. Antibodies of different IgG sub-classes and IgE antibody behave differently. After therapy IgG4 antibody levels decreased sharply and were down to 65-78% of the pre-treatment levels within 12 months. IgG1 levels declined in a less predictable manner and IgG2 and IgG3 only declined in elephantiasis patients who have an elevation of these antibodies to start with. IgE showed only a mild reduction (7-28%) over 12 months and 56% over 2 years (Atmadja *et al.,* 1995; Kurniawan *et al.,* 1995. Wamae *et al.,* (1992) found that IgG4 antibody rose markedly after treatment with DEC or Ivermectin to peak at 30 days and then began to decrease. Post treatment microfilariae density was inversely correlated with the decrease in IgG4 antibody and gave a good indication of the success of treatment. Murthy *et al.,* (1997) also found that treatment elevated IgG4 antibody and a reduction in IgG1 antibody. IgG2 and IgG3 antibodies remained unaffected. A rather different pattern is seen if antigen from microfilariae is used. Antibodies to microfilariae are usually absent from the blood of microfilaraemics or present only in low titre. Anti-filarial treatment and the clearance of microfilariae are followed by a rapid rise in antibodies against microfilariae (Grove, 1981).

Sartono *et* (1995b) studied a group of patients one year after therapy and found that cellular immune responses to filarial antigens had increased significantly but the response to PPD remained low. Similar results were obtained by (Gopinath *et al.,* 1999). These studies confirm the earlier work of Piessens *et al.,* (1981). Lammie *et al.,* (1992) found that interferon production from filarial-antigen-stimulated mononuclear cells increases but there is no significant change in IL-4 production. Zheng *et al.,* (1991a,b) reported a sustained increase in serum levels of IL-1, TNF and IL-6 in patients treated with either DEC or Ivermectin.

Antigen levels usually rise immediately during, and immediately after treatment peaking but there is considerable individual variation (Ramaprasad *et al.,* 1988; Eberhard *et al.,* 1997). Most authors record a fall in antigen levels in the months following treatment. For instance Weil *et al.,* (1988) found that filarial antigen fell to 72%, 58% 53% and 48% at 1, 3, 6 and 12 months after treatment respectively. A rise in filarial antigen levels is associated with the re-appearance of microfilariae in the patient's blood (Ramaprasad *et al.,* (1988). Nicolas *et al.,* (1997) observed that there was a difference in the clearance of antigen and resurgence of antigenaemia between amicrofilaraemic and filaraemic subjects when they were treated with an annual single-dose treatment of DEC, Ivermectin or a combination of both. Their results are summarised in Table 7.

Ramaprasad *et al.,* (1988) found that like filarial antigen, filarial antigen associated immune complexes initially increased then fell, reaching a steady state by about day 60 after treatment.

Table 7. Effects of Diethylcarbamazine (DEC) and Ivermectin (IVR) alone and in combination on filarial antigen in microfilaraemic (mf+) and microfilaraemic (mf-) subjects (from Nicolas *et al.,* 1997)

	DEC 6 mg/kg	IVR 400 µg/kg	DEC 6 mg/kg IVR 400 µg/kg	DEC 3 mg/kg IVR 400µg/kg
% residual antigen level at 12 mths	55.5 mf+ 21.4 mf-	70.0 mf+ 0.0 mf-	60.0 mf+ 19.2 mf-	52.3 mf+ 7.1 mf-
% residual antigen level at 24 mths	37.6 mf+ 25.0 mf-	63.3 mf + 0.0 mf -	41.0 mf+ 44.4 mf-	27.0 mf+ 17.8 mf-

Conclusion

The last few years has seen a virtual explosion in both basic and applied filariasis research. We now have a better understanding of the immunological basis of infection and the pathogenesis of filarial disease. We now know that opportunistic bacterial and fungal infections play an active part in the progression to chronic obstructive filarial disease and that attention to basic hygiene, the use of antibiotics and antifungals and local physiotherapy can slow, prevent, or in some cases, reverse elephantiasis.

The diagnosis of bancroftian filariasis has been revolutionised by the introduction of filarial antigen tests that are not dependent on the presence of microfilariae, removing the need to take night bloods. The ICT test can be done by finger-stick in the field and results are rapidly available. Ultra-sound is proving to be a valuable tool for identifying adult worms *in-situ.* Annual mass treatment with Diethylcarbamizine (DEC) either alone or in combination with Ivermectin and Albendazole has been proven to be very effective in destroying microfilariae and interrupting transmission. With this knowledge and armed with these tools, the WHO goal of elimination lymphatic filariasis as a health threat by the year 2020 is achievable. Despite these advances there is still work to be done and many questions to be answered. There is still a lot of "traditional dogma" about filariasis that needs to be re-evaluated by modern research methods

A fundamental question is, "What is the burden of disease?". A conservative estimate is around 160 million cases, but no one really knows because a large part of filarial-endemic areas remain un-surveyed. Geographic Information Systems (GIS) and other spacial analysis tools need to be employed so that the geographic distribution of filariasis can be accurately determined. Ultrasound and antigen tests have shown that many "endemic normals" have low-grade patent infection and many of those with asymptomatic microfilaraemia have lymphatic damage, varying degrees of renal impairment and immuno depression. It makes good sense to define a filariasis case as all those who have evidence of active infection (i.e. those with a positive filarial antigen test regardless of microfilaraemia status or presence or absence of chronic pathology). Clinical diagnosis of acute filariasis is often difficult and can be confused with other febrile inflammatory illnesses. There is thus a need to develop and trial clinical checklist that will improve diagnosis. The role of the filarial parasite *per sé* and the contribution of other infectious agents, in particular streptococci, to acute filarial attacks need to be investigated and treatment regimes devised.

There are many other questions. Most filarial research has neglected children. What level of disease and pathology can be expected in children of different ages? What effect does filarial-induced immuno suppression have on the efficacy of vaccinations? What part does filarial-induced immuno suppression play in host susceptibility to other parasites and other infectious agents especially tuberculosis? There is some anecdotal and some limited experimental evidence of renal disease in filariasis, but there needs to be a detailed assessment of the contribution that filariasis makes to the burden of renal disease in tropical populations and the amount of long-term kidney damage that is prevented by filariasis control programs. There have been some studies on the social effects of disfiguring filarial disease in Africa and India, but very little has been done in other endemic areas. There is an urgent need to develop simple, effective health promotion materials to inform people about the disease and its prevention. Given the link between secondary infection and the development of chronic pathology special education materials on basic limb hygiene must be made available to those who are at risk of developing such complications.

Filarial control can only be achieved if the majority of the population takes the drugs. In many endemic areas the health system is already struggling to cope with programs already in place and are unable to cope with the extra impost of a filariasis control program. There must be research into innovative, cost-effective means of drug delivery. How can non-governmental organisations such as religious organisations and missions, schools and industry be actively involved in filariasis control? In a country like Papua New Guinea, for example, where a large percentage of the population attend church, it would be possible for the church eldership, with local health authority support, to distribute anti-filarial drugs at major church festivals and obtain excellent population coverage. The use of Albendazole raises the possibility of not only controlling filariasis, but a range of intestinal parasites as well, making such a control project attractive to health authorities. Pregnant and lactating women have been excluded from drug treatment because of safety concerns, but hard evidence of risk is lacking and the matter requires investigation. Although the drugs presently available appear to be very effective, there is still a great need to discover other anti-filarial drugs, especially effective macrofilaricides. Although there is at present, no real hard evidence of drug resistance, that does not mean that it will not occur in the future, and techniques to monitor the emergence of drug resistance need to be developed and trialed. As can be seen in the foregoing, much progress has been made in filariasis research and control, but a large amount of work remains before the scourge of filariasis is finally eliminated.

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