Introduction
Lymphatic filariasis, commonly known as Elephantiasis, has been a health problem of human beings residing in most tropical countries from the dawn of civilization. Its most obvious manifestation - swelling of the legs, has been found to be depicted in the Pharaonic murals of Egypt. The clinical manifestations had been described in the ancient medical texts of India, China, Japan and Persia. However, the disease was first associated with the parasitic filarial worms in late 19th century by French, English and Australian physicians working in Cuba, Brazil, India and China. At the beginning of the 21st century the disease, with its varied clinical manifestations, still remains an enigma for the scientists.

Lymphatic filariasis (LF) is caused due to infection with filarial parasites viz. *Wuchereria bancrofti*, *Brugia malayi* and *Brugia timori*, belonging to the class *Nematoda* and super family *Filarioidea*, which are transmitted from one individual to the other through mosquito bites [1]. In tropical and subtropical areas where lymphatic filariasis is well established, the prevalence of infection is continuing to increase [2]. A primary cause of this increase is the rapid and unplanned growth of cities, which creates numerous breeding sites for the mosquitoes that transmit the disease. Because of its prevalence often in remote rural areas, or in backward semi-urban and urban areas, lymphatic filariasis is primarily a disease of the poor. In recent years, lymphatic filariasis has steadily increased because of the expansion of slum areas and poverty, especially in Africa and the Indian sub-continent [2].
Lymphatic filariasis is a disease with low mortality but high morbidity (Table-1), and it is this morbidity which brings with it the heavy psycho-socio-economic burden among its patients. As many filariasis patients are physically incapacitated, it is also a disease that prevents patients from having a normal working life and hence causes huge loss of man-days in areas where it is endemic. Moreover, the individuals who manifest chronic symptoms i.e. swelling of limbs and genitals are often socially isolated. The psycho-social impact of Lymphatic filariasis is only beginning to be understood and it deserves more attention than it has received [3]. Recent advances in treatment method, in controlling of the disease transmission, simple and successful approaches to disease management along with remarkable improvement in diagnosing the infection, led the WHO sponsored International Task Force for Disease Eradication to identify Lymphatic Filariasis as one of only six diseases it considered to be "eradicable" or "potentially eradicable". The World Health Assembly in 1997 adopted a resolution to eliminate lymphatic filariasis as a global health problem by 2010 [4]. The fight to eliminate lymphatic filariasis is also a fight against poverty

**EPIDEMIOLOGY**

120 million people in at least 80 countries of the world are infected with lymphatic filarial parasites, and it is estimated that 1.2 billion (20% of the world's population) are at risk of acquiring infection. Approximately one third of those infected live in India, another one third live in Africa and most of the remainder live in
<table>
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<th>Helminthic Disease</th>
<th>Number of Infected individuals (in millions)</th>
<th>Morbidity (%)</th>
<th>Mortality (%)</th>
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<td>Onchocerciasis</td>
<td>18</td>
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Table 1: Worldwide morbidity burden of helminthic infections in humans.
Source WHO 2001
Asia, the Pacific and the Americas [5]. 90% of these infections are caused by *Wuchereria bancrofti* parasite, and the remainder by *Brugia malayi* or *Brugia timori* [6]. Bancroftian filariasis is a major cause of clinical morbidity and social handicap in many countries in Asia, East Africa, Latin America, the Middle East, the Pacific Rim, and the Pacific islands. Brugian filariasis is restricted to Asia and parts of the South Pacific [7, 8], it is most highly endemic in India and China (32% and 20%, respectively, of the global burden); it is also prevalent in Indonesia, Thailand, Malaysia, Philippines, Vietnam and Republic of Korea [7]. India accounts for 40% of the global prevalence of lymphatic filarial infection. LF is second only to malaria as the most important vector-borne disease in India. The disease is endemic in 18 states and Union territories, including Andhra Pradesh, Tamilnadu, Kerala, Orissa, Uttar Pradesh and Bihar. Approximately 420 million people reside in endemic areas and about 48 million are infected. Bancroftian filariasis, caused by *Wuchereria bancrofti* and transmitted by the tropical house mosquito *Culex quinquefasciatus*, accounts for 95% of the total lymphatic filariasis cases in India [9].

For *W.bancrofti*, humans are the exclusive host, and even though certain strains of *B.malayi* can also infect some feline and monkey species, the life-cycles in humans and in these other animals generally remain epidemiologically distinct, so that little overlap exists. The major vectors for *W.bancrofti* are *Culex* mosquitoes in most urban and semi-urban areas, *Anopheles* in the more rural areas of Africa and elsewhere, and *Aedes* species in many of the endemic Pacific islands. For the Brugian parasites *Mansonina* species
serve as the major vector, but in some areas Anopheles mosquitoes are responsible for transmitting the infection [5].

**THE PARASITES**

Out of the eight species of filarial parasites that infect humans, only three are responsible for causing lymphatic filariasis. They are Wuchereria bancrofti, Brugia malayi and Brugia timori. All the three parasites have a complex life cycle requiring two hosts, the definitive host being human. It is interesting to note that filarial parasites can infect animals of almost all the major orders of vertebrates but the parasite shows remarkable definitive host specificity [10], e.g. W.bancrofti parasite will only establish infection in humans and not in any other animal. The exact cause for this host specificity among filarial parasites remains to be elucidated.

Infection in humans or the definitive host is initiated by deposition of the 3rd stage infective larvae (L3), by a feeding female mosquito. L3 is the only stage in the entire parasite life-cycle that can infect humans. The L3 immediately after deposition migrates into the nearest lymph node and there develop into the adult forms of the parasite through at least two moults (L4 & L5). This transition from the L3 stage to the adult may take anything between 3-15 months. Mature male and female parasites mate within the lymphatics and the females produce an astronomical number of microfilariae (Mf),
which come into peripheral circulation during night time, so that it can be taken up by a feeding mosquito. Once inside the mosquito the Mf migrate to the thoracic muscles and develop, through further two moults, to L3, which can be transmitted to a new susceptible host by the mosquito while taking a blood meal [11, 12]. One of the interesting features of the filarial life cycle (Fig.-1) is the block in development undergone by the Mf in the mammalian host and the L3 in the mosquito vector. For both life cycle stages, the block marks the end of the developmental phase in either mammal (Mf) or mosquito (L3) and is released only upon exposure to the environment of the new host, suggesting the intriguing possibility that filarial nematodes may utilize host-derived signals as a means of regulating development.

Filarial nematodes are obligate parasites, characterized by their ability to persist in the infected host for many years, adult life-span 5-12 years, producing millions of Mf. A striking feature of the filarial infection is the protracted and stable relationship reached between the host and the parasite. This balance serves to limit mortality of the host directly caused by filarial worms but fails to prevent substantial morbidity and disfigurement in many individuals. The parasite survives inside the lymphatics which is at the heart of the immune system for extended periods of time. The persistence of infection is related to the ability of the worm to down regulate the immune response of the infected individual [13].
Fig. - 1: Life Cycle of *Wuchereria bancrofti* and *Brugia malayi* parasites
A close study of the life cycle brings into focus certain important points regarding the disease. First, as the parasite is host specific and cannot develop beyond the Mf stage the disease should, in theory, be eradicable. Continuity in the parasite life-cycle can be broken, either by killing the Mf inside the definitive host by means of chemotherapy and other intervention, or by taking effective vector control measures. Second, because the adult stage of filarial parasite resides within the host lymphatic system for years, it must be having a very effective immune evasion and modulation mechanism where stage-specific molecules of the parasite interacts with the host immune system and hence immunointervention is possible. Third, since L3 is the stage, which establishes the infection in humans and develops into the adult form, which live and mate inside the lymphatics of the host, therefore, these two stages must be responsible for modulating the host immune response. So emphasis should be given in understanding the host – parasite interaction of these two stages. [14]

Much of the information regarding stage-specific antigens of filarial parasites has been obtained through immunological studies. This indicates that different life cycle stages induce distinct immune responses in the infected human. The L3/post-infective L3 stage of the parasite are the likely target of protective immune responses in humans and it has been suggested that while L3-specific antigens are crucial for the development of immunity, the antigens derived from Mf and adult stages are involved in generating profound T-cell hyporesponsiveness and tolerance [11, 15]
THE DISEASE

The pathology associated with lymphatic filariasis results from a complex interplay of the pathogenic potential of the parasite, the immune response of the host, and external bacterial and fungal infections. In its most obvious manifestations, lymphatic filariasis causes enlargement of the entire leg, arm or breast and the genitals (vulva or scrotum). In endemic communities, 10-50% of men and up to 10% of women can be affected. Even more common than the overt abnormalities is hidden, internal damage to the kidneys and lymphatic system caused by the adult worms. Adult *Brugia* and *Wuchereria* worms usually reside in afferent lymphatics or in the cortical sinuses of lymph nodes they are in continuous vigorous motion, but remain 'fixed' at these sites. This causes the dilation of the lymphatic vessels followed by hypertrophy of the vessel wall as evident from ultrasonographic and lymphoscintigraphic studies. These lymphatic changes are due to the proliferation of endothelial and connective tissues and is associated with the formation of polyploid protrusions into the vessel lumen. The lymph vessels appear to remain patent as long as the worms remain alive [16, 17]. As a general rule the patient can be cured by proper therapy at this stage. The death of the adult worm contributes to the actual pathology of the disease. An area of necrosis develops around the dead parasite due to the dissolution of the worm and this causes obstruction of the lymph vessel, and hence the lymph flow is shunted via collateral lymph vessels giving rise to the characteristics chronic pathogenesis of the disease [16].
Introduction

Lymphatic filariasis was generally thought to occur only sporadically in children. New, highly sensitive diagnostic tests such as antigen detection and ultrasound examination, now reveal that lymphatic filariasis is primarily acquired in childhood, often before age 5. Numerous community-based epidemiological studies and individual case reports attest both to the existence of lymphatic filariasis infection in children and to the occurrence of clinically evident disease. Microfilaremia prevalence in children from different populations is seen to be significantly related to the level of endemicity seen in their respective adult populations. Initial damage to the lymphatic system by the parasites generally remains hidden ('subclinical') for years or gives rise only to 'non-specific' presentations of adenitis/adenopathy, but especially after puberty the characteristic clinical features of the adult disease syndromes - lymphoedema/elephantiasis and hydrocoele - begin to develop.

The hallmark of lymphatic filariasis is the presence of a clinical spectrum. Residents of an endemic area exposed to the same species of parasites show a broad spectrum of clinical manifestations. It is postulated that the different disease manifestations of filariasis are caused by different types of immune responses mounted by the hosts [18]. The different clinical manifestations of lymphatic filariasis are discussed below:

**Asymptomatic Amicrofilaremic**
This group also known as Endemic Normals (EN), consists of individuals who are resident of a lymphatic filariasis endemic area but do not have any sign or symptom of filariasis. They do not have
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circling Mf in their night blood and also are negative for circulating filarial adult (CFA) parasite antigen as measured by Og4C3 ELISA [19]. The parasite specific IgG4 titres remain low in these individuals. By all probability these individuals are exposed to the L3 stages of the parasite but it is difficult to ascertain whether they have cleared the infection or have cryptic subclinical infections. The fact that they are exposed can be demonstrated by their strong T cell response against the parasite antigens [20]. With the help of longitudinal follow-up studies it has recently been possible to identify truly infection free individuals in endemic regions. Hence there is an emerging consensus that these individuals may be protected.

Asymptomatic Microfilaraemic
The individuals of this group do not show any clinical sign or symptom of lymphatic filariasis but have circulating microfilariae in their blood at night, so this group acts as the parasite reservoir, and hence they are also termed as Carrier or ASM individuals. They also have very high parasite specific IgG4 titres. Their immune response to parasite antigens appears to be suppressed and hence they are regarded as hyporesponsive individuals [21]. Although, they are classically said to be asymptomatic, recent studies have shown that essentially all have hidden damage to their lymphatic vessels, as evidenced by lymphoscintilography and/or renal systems, as evident from microscopic haematuria and/or proteinuria [22].
Introduction

**Acute Cases**
Acute (Ac) bancroftian filariasis may commence with malaise and fever, followed by lymphadenitis in the groin or armpit and a typical retrograde lymphangitis. In most endemic areas, such as: Africa, India, Indonesia, and the Pacific area, the lymphatics of the male genitalia are frequently affected, leading to funiculitis, epididymitis, and orchitis. The spermatic cord becomes thickened and tender. The acute attack may last for 3-15 days, and may occur several times a year in the same individual [23, 24].

In acute brugian filariasis, lymphadenitis occurs at intervals, with fever, chills, and other constitutional symptoms. The symptoms often subside spontaneously with rest. There is an induration around the affected lymphatics, which may spread to the surrounding tissues and occasionally involves the whole thigh or the entire lower limb. The affected lymph vessel becomes swollen and tender. At this stage, there is often lymphoedema of the foot and ankle. In most cases the lymphadenitis occurs in the inguinal region on one side, and there is lymphangitis on the medial side of the limb and foot on the same side. The frequency of episodic lymphadenitis varies from 1-2 attacks per year to several attacks per month [25].

**Chronic Cases**
The chronic (CH) stage of filariasis usually develops in 10-15 years from the onset of the first acute attack. Hydrocoele, elephantiasis, and chyluria are the main characteristic features of the chronic bancroftian filariasis. Elephantiasis begins as lymphoedema. The leg(s), scrotum, arm(s), penis, vulva, and breast(s) are affected
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usually in that order of decreasing frequency. In most countries males are more often affected than the females. In brugian filariasis the characteristic sites for elephantiasis are the leg(s) below the knee(s), or less frequently the arm(s) below the elbow(s), although the lymph nodes affected during the acute stage are usually located in the inguinal or axillary regions. In most cases only the foot and the distal part of the lower leg are affected. Genital involvement and chyluria have not been reported, except in areas where brugian filariasis occurs together with bancroftian filariasis [26].

Tropical Pulmonary Eosinophilia

Tropical Pulmonary Eosinophilia (TPE) is a syndrome that occurs in both adults and children and is more common in males. This syndrome is characterized by nocturnal paroxysmal cough, hyper-eosinophilia, elevated erythrocyte sedimentation rate (ESR), radiological evidence of diffuse miliary lesions or increased bronchovascular abnormalities especially at the bases of the lungs, and extremely high parasite specific IgE. These individuals usually respond well to DEC therapy. In many cases the lung function is impaired with a reduction in the vital capacity, total lung capacity, and residual volume. Although spontaneous remission occurs, TPE if untreated tends to relapse and progress to a condition of chronic pulmonary fibrosis [27].

Recently, a new filarial syndrome (Expatriate Syndrome) has been described as one of clinical and immunologic hyper-responsiveness found in expatriate visitors to endemic regions. Originally this
syndrome was observed with loasis but recent findings suggest that it is present in patients with onchocerciasis, lymphatic filariasis, and other filarial infections. Instead of developing the commonly described chronic clinical manifestations of their filarial infections, individuals who have grown up outside of the endemic regions and then moved to these regions and acquired a filarial infection manifest prominent signs and symptoms of inflammatory (including allergic) reactions to the mature or maturing parasites. In loasis, these manifestations have included primarily Calabar swellings, hives, rashes and occasionally asthma; and in bancroftian filariasis (when military personnel or other migrants to endemic areas have acquired these infections), they have usually been lymphangitis, lymphadenitis, genital pain (from inflammation of the associated lymphatics), along with hives, rashes and other 'allergic-like' manifestations, including blood eosinophilia. The reason for these different clinical presentations lies almost certainly in the different immunoregulatory responses to filarial antigens between those with long (including prenatal) exposure to these antigens and those meeting them for the first time [5].

A variety of syndromes co-existing with filariasis are found in filarial endemic regions, and because they show some evidence of therapeutic response to DEC, they have been suggested as possible manifestations of lymphatic filariasis. These include arthritis (typically monoarticular), endomyocardial fibrosis, tenosynovitis, thrombophlebitis, glomerulonephritis, lateral popliteal nerve palsy, and others. While future studies may strengthen the relationships,
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such syndromes at present cannot confidently be attributed to filarial infection.

**DIAGNOSIS**

It had never been an easy task to study lymphatic filariasis because the accurate diagnosis of active infection could be made essentially only by detecting microfilariae in the blood of infected individuals; and in most parts of the world the nocturnal periodicity of the parasite meant that such blood examinations had to be carried out between 22:00hrs. and 02:00hrs., a time period evoking little enthusiasm from either the affected population or the responsible health worker. Thus, the development of assays to detect circulating antigen released by living adult parasites and remaining at stable levels in the circulation both day and night [28, 29] has opened up many avenues related to surveillance and monitoring that were almost completely closed before. There are two monoclonal antibody-based assays for detecting circulating filarial antigen (CFA) now available, one in an ELISA format, especially suitable for laboratory analysis of samples collected in the field [30] and the other in a card-test format, suitable for evaluation either in the laboratory or in the field [31]. Both of the currently available assays can use small samples of serum in their test, but recent adaptations have made the card test suitable for testing finger prick-specimens of whole blood as well. Since these CFA assays detect not only microfilaremic individuals but many with amicrofilaremic, 'cryptic' infections [28, 29], their diagnostic
sensitivity is greater than anything available previously, and, indeed, they have become the new ‘Gold Standard’ for diagnosing lymphatic filariasis caused by *Wuchereria bancrofti* infection. Furthermore, specificity of the test is so high (no recognizable cross-reactivities yet identified) that even *Brugia* infections, unfortunately, are not detected. Thus, while we have a superb (and commercially available) tool available for diagnosing and monitoring *Wuchereria bancrofti* infections, important research efforts are still required to develop a similar assay for detecting *Brugia* infections. In addition to their high sensitivity, specificity and usefulness both day and night, the CFA assays also have the ability to define when infection has been cured; i.e., CFA assays convert from ‘positive’ to ‘negative’ generally within 12 months after the infections have been cured [32]. This important observation implies that these tests can play important roles in monitoring the success of large-scale programs to eliminate lymphatic filariasis, but only now is data on the changing levels of circulating antigen becoming available from control programs based on single-dose, once-yearly treatment [33].

Conventional X-rays are rarely helpful in diagnosing lymphatic filarial infection, except in the case of tropical eosinophilia where the picture can be variable but characteristically includes interstitial thickening and diffuse nodular mottling in the lung fields. Ultrasound examination of the lymphatics (especially scrotal lymphatics in men, and the breast and retro-peritoneal lymphatics in women) can reveal rapidly moving (“dancing”) adult worms [34], and lymphoscintigraphy, though not diagnostic of filarial infection,
can identify lymphatic functional and gross anatomical abnormalities. In situations of lymphadenopathy with or without accompanying inflammation of the nodes or lymphatic vessels, biopsy can often detect adult worms, but this approach is rarely used as a diagnostic procedure [5].

**TREATMENT**

In human lymphatic filariasis the drug of choice is Diethylcarbamazine (DEC). For human use, DEC is manufactured primarily as the dihydrogen citrate salt. The drug is rapidly absorbed from the gastrointestinal tract and reaches peak levels in the blood 1-2 hours after an oral dose of 50mg. The time required for the kidneys to excrete DEC increases with the pH of the urine, but even when the urine is alkaline, the half-life of DEC in the blood is only 10-12 hours [35]. The mechanisms of action of DEC are not well understood. In addition to its antifilarial properties, the drug appears to have complex and somewhat paradoxical effects on the immune system, cellular adherence, complement activation, and arachidonic acid metabolism. It is unknown whether any of these properties of DEC are related to its antifilarial action [36-38].

When given in conventional doses, DEC is active against both the microfilariae and the adult worms of *W. bancrofti* and *B. malayi* [35]. The microfilaricidal effectiveness of DEC has been extensively documented. Microfilariae are usually rapidly cleared from the peripheral blood, but in a small percentage of infected persons,
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particularly those with high microfilarial densities, clearance of microfilariae is incomplete. The degree to which DEC kills adult *W.bancrofti* or *B.malayi* has long been a matter of debate because direct methods of monitoring the adult worm have not been available [35, 39]. Recently, investigators in Brazil have used ultrasound to directly monitor the effect of DEC on the adult worm *in vivo*. In the study, 31 men examined before treatment had 53 individual adult worm nests detected by ultrasound. After treatment with DEC, the "filaria dance" sign became undetectable in 22 (42%) of these nests. Twelve (39%) of the 31 men had cessation of the filaria dance sign in all adult worm nests that were previously detectable by ultrasound [40].

For years the WHO has recommended that patients with bancroftian filariasis be treated with a total dose of 72mg/kg of DEC (6mg/kg for 12 consecutive days) [5]. The rationale for this regimen has "largely been forgotten", although early experience suggested that such high total doses resulted in more prolonged and profound reductions in microfilaremia [41, 42]. Treatment for 12 days has proven impractical for community-based control programs. Therefore, investigators have recently questioned the necessity of giving DEC for 12 consecutive days and have begun to systematically compare its efficacy to that of other treatment regimens. Studies have shown that microfilarial suppression is both enhanced and prolonged when the 12 doses of 6mg/kg are given once a week rather than on 12 consecutive days [43]. The standard 12-day DEC treatment produces a more rapid reduction in microfilaremia than does single-dose DEC, but microfilaria levels
are similar 6–12 months after treatment. Studies have shown that a single 3–6mg/kg dose of DEC can reduce microfilarial density by about 90% when measured 6–12 months after treatment [39, 42]. This figure is comparable to that generally reported for a 12-day course of DEC, although some investigators report greater reductions in microfilariaemia with 12 days of treatment. In summary, the currently recommended 12-day, 72mg/kg course of DEC treatment, or variations thereof, have remained the standard for many years; however, recent data indicate that single-dose treatment with 6mg/kg of DEC has comparable macrofilaricidal and long-term microfilaricidal efficacy. The 12-day course provides more rapid short-term microfilarial suppression, but when other factors are considered, including cost, convenience, and patient compliance, it now seems reasonable to recommend single-dose treatment for individual patients with \textit{W.bancrofti} or \textit{B.malayi} infection. Single-dose treatment can be repeated every 6–12 months for persons who remain infected. For patients with TPE or haematuria, current data are insufficient to recommend single-dose treatment [44].

Side effects of DEC are mild or absent when the drug is given in daily doses of 6mg/kg [45]. Symptoms of drowsiness, nausea, and gastrointestinal disorder are observed more frequently as the dosage of the drug increases [35, 45]. Adverse reactions of DEC in persons with filarial infections can be either localized (associated with death of the adult worm) or systemic (associated with death of microfilariae). Local adverse reactions, which usually begin 2–4 days after the first dose of DEC, may include localized pain and
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inflammation, tender nodules, adenitis, and retrograde lymphangitis [46]. In a small percentage of patients, these reactions are accompanied by acute lymphoedema or hydrocoele. Most, but not all, of the hydrocoele are transient. Systemic adverse reactions following treatment with DEC include fever, headache, malaise, myalgias, and haematuria [46]. These reactions generally begin a few to 48 hours after beginning treatment with DEC and last 1–3 days.

Because DEC is only partially effective against the adult worm, intense interest persists in identifying a macrofilaricidal drug for treatment of lymphatic filariasis. Thus far, no single drug has been shown to have both greater macrofilaricidal activity and fewer adverse reactions than DEC. Several recent studies have explored the effectiveness of co-administration of two drugs for lymphatic filariasis. When given sequentially or in combination, DEC and ivermectin tend to produce more prolonged suppression of microfilaremia than either drug alone; however, ultrasonographic and clinical findings suggest that the macrofilaricidal efficacy of DEC may be reduced when the drug is given simultaneously with ivermectin [47-49]. It has been reported that repeat high-dose albendazole may have a macrofilaricidal effect against W.bancrofti. Single doses of albendazole appear to have no significant short-term effect on microfilaremia, but they may result in long-term reduction of microfilaremia. Simultaneous administration of albendazole (400mg/kg) and ivermectin (200–400mg/kg) appears to result in greater microfilarial suppression than does ivermectin alone [50, 51]
While it is important to try to cure the infection itself, management of the consequences of that infection (particularly the lymphoedema, elephantiasis and hydroceles) is what is often of greatest concern to the patient. Interestingly, with respect to hydroceles it has now been shown repeatedly that treatment of infection in communities with either intermittent (monthly, 6-monthly, yearly) drug administration or the steady use of DEC fortified table/cooking salt, leads to clinical improvement with decreases in both hydrocele size and prevalence. Similarly, it is not uncommon to find early lymphoedema regressing completely after treatment of an affected patient with DEC. Personal hygiene, like regular cleaning and drying of the oedematous limbs also help a lot in reducing the size as well as the burden of secondary infections to the chronic patients [5].

**IMMUNO-PATHOGENESIS**

The immune response of the human host to the infecting filarial parasite plays a significant role in determining the pathological manifestations of the disease. The broad clinical spectrum seen in lymphatic filariasis, both Bancroftian and Brugian is mostly attributed to the differences in immune responsiveness of hosts, although other mechanisms underlying the pathology are likely to play some role [52]. Thus, in lymphatic filariasis the range of immune responses found in infected individuals is wide i.e. the immune reactivity to parasite antigens vary considerably. Generally
speaking, the severity of pathology correlates with \textit{in vitro} immune reactivity to parasite antigens. The ASM individuals who are clinically asymptomatic and have high parasite burden mount little or no parasite specific cell mediated responses, at least by the standard measures of T cell proliferation and IL-2 secretion, but mount a prominent antibody mediated response characterized by high parasite specific IgG4 titres. In contrast Chronic patients, who are typically amicrofilaremic, mount a more vigorous T cell response to the same parasite antigens. The EN individuals also mount a cell-mediated response against parasite antigens but usually the response is less intense than the chronic patients. The TPE patients mount a typical allergic response with high eosinophilia and high parasite antigen specific IgE titre \cite{53, 54}.

Further analysis of the immune response in the different clinical groups have shown that ASM individuals secrete significantly higher levels of IL-4 in response to filarial antigens than the EN or chronic individuals. Moreover, the ASM individuals exhibit an apparent inability to secrete IFN-\(\gamma\) in response to filarial antigens. This inability on the part of the ASM individuals is thought to represent a state of parasite induced anergy that provides a strategy for parasite survival while protecting the host from disease. Similarly, an IFN-\(\gamma\) response is attributed to the presence of protective immunity in filariasis, as this type of response is found mostly in amicrofilaremic individuals \cite{55}. Recent studies have shown that the IL-4 secretion bias correlates more closely to the presence of adult worms than presence of microfilaria \cite{56}. Dissecting the possible immunoregulatory mechanisms operating in humans is
complicated by a number of factors, including intensity of infection, exposure to different life-cycle stages, individual host genotype, presence of other infections and prenatal tolerance [57].

Most of the immunological studies have employed microfilarial or adult antigens, although L3 is the stage in the parasite life-cycle that establishes the infection in a human host and develop into the adult form, which has an average life-span of 8-10 years. Thus, it becomes apparent that, in order to survive inside the host it is the L3 and the adult stages, which must bring about the required immunomodulation in the host, rather than Mf stage as previously thought. It is quite possible that the Mf appears in an environment, which has been rendered permissive by the L3 and/or the adult, and the Mf may be responsible for the maintenance of that host permissive state. Moreover, the majority of the studies in lymphatic filariasis in humans employed either purified, or fractionated, or excretory-secretory, or complex soluble antigens of different stages of the parasite. The responses to these antigens in isolation may be quite different than that mounted by the host in the presence of live parasites. Studies using live parasites in permissive and non-permissive animal models also suggest this apprehension. Further, most of the studies on human lymphatic filariasis have mostly used individuals living in an endemic area as subjects. Although these studies are of paramount importance in dissecting the host-parasite response in the different clinical conditions, they throw little light on the nature of the primary response of the human host towards the invading parasite. However, this information is essential for a complete understanding of the mechanism of immunomodulation.
brought about by the parasite. Therefore, in the present study live L3 and adult stages of *Brugia malayi* parasites were used *in vitro* to stimulate PBMCs of EN, ASM and Non-endemic normal (NEN) individuals. The NEN individuals were selected from a resident population in a high altitude area (more than 10,000ft above sea level), where transmission of the parasite does not take place because of the lack of vector, which cannot survive at such high altitude. Thus, these individuals were never exposed to the L3 stage of the parasite and are hence, expected to mount a primary immune response when exposed to L3 or adult stages of the parasite *in vitro*. 