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CLINICAL FEATURES, PATHOGENESIS AND MANAGEMENT OF LYMPHATIC FILARIASIS

Lymphatic filariasis of man is due to infection by three lymphatic dwelling filarids, *viz Wuchereria bancrofti, Brugia malayi* and *Brugia timori* transmitted principally by *Culex quinquefasciatus, Mansonia* species and *Anopheles barbirostris* mosquitoes respectively. Infection by *B. timori* does not occur in India.

Although lymphatic filariasis has been identified as eradicable or potentially eradicable among the six infectious diseases by the International Task Force for Disease Eradication[1], it is still a major public health problem in many parts of the world including India[2]. Recent estimates show that there are approximately 119 million persons afflicted with this disease world-wide; 106.19 and 12.91 millions with bancroftian and brugian filariasis respectively[3]. In India, currently 411.65 million people are exposed to the risk of infection, of which only 46 million are protected[2] and there are 31.26 million microfilaria carriers and 48.11 million persons with chronic disease[3]. The current burden of disease globally and that in India is depicted in Table I.

All states and union territories except those of Jammu & Kashmir, Himachal Pradesh, Punjab, Haryana, Chandigarh, Delhi, Rajasthan, Arunachal Pradesh, Meghalaya, Mizoram, Nagaland, Manipur, Tripura and Sikkim are endemic for bancroftian filariasis[2]. About 95% of the total infection is due to *W. bancrofti*[3]. Brugian filariasis is mainly found in Kerala, but scattered foci of low prevalence are reported in Orissa, Assam, Madhya Pradesh, Andhra Pradesh and Tamilnadu. A focus of subperiodic bancroftian filariasis has been described in the Nicobar Islands[4].

Table I. Disease burden of lymphatic filariasis in the world and in India.

Categories of cases	Number of cases in millions					
	W. bancrofti		*B. malayi*		Total	
	World	India	World	India	World	India
Microfilaria carriers	73.27	29.46	10.36	1.80	83.63	31.26 (37.00)
Lymphoedema	13.21	6.58	2.81	0.86	16.02	7.44 (46.40)
Hydrocele	26.79	12.88	–	–	26.79	12.88 (48.00)
Total cases#	106.19	45.53 (42.88)	12.91	2.58	119.10	48.11 (40.30)

Figures in parentheses show contribution of India to the world burden of disease in percentage.

Excludes cases which have both infection and disease

Source: Reference 3

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This disease due to its prolonged course and non fatal nature has attracted little attention of the health planners, thus a low priority has been accorded by the States to the National Filaria Control Programme[5]. The disease, however, has serious socio-economic impact on the society by the significantly lowered productivity and economic loss resulting from its chronicity[6-11]. In addition, there are stigmatizing effects due to the grotesque disfigurements as sequelae of the disease. The number of individuals world-wide with overt physical disabilities resulting from the infection is approximately 43 million, with bancroftian filariasis accounting for about 40 million of these cases[12]. Lymphatic filariasis is the second leading cause of permanent physical disability in humans next to mood disorders[13].

The public health impact of different diseases is compared by using Disability Adjusted Life Years (DALY's) as a standardized metric by the World Bank Development Report (WDR)[14]. By using current estimates of the disease incidence with focus on chronic manifestations only, the global burden of lymphatic filariasis by this measure has been estimated by WDR to be 850,000 DALYs lost representing a mere 0.23% of the total global burden of parasitic and infectious disease. This is seen as a gross underestimate of the disease incidence which ignores the influence of acute disease on DALYs[4,6]. It has been estimated that on an average 23.4 and 26.5 man-days are lost per individual per year due to bancroftian and brugian filariasis respectively and an overall 162.12 million man-days are lost per year in India due to acute filarial attacks[15]. If the cost of treatment including hospitalization and surgical procedures were also to be included, the actual loss would have been manifold. Acute disease is likely to be many times more prevalent than the chronic[16]. In a recent study in an endemic rural area of Tamil Nadu in south India, it was shown that the mean cost incurred on treatment of each episode of the acute disease *ie.* adenolymphangitis (ADL) amounted to Rs. 2.35. It was further estimated, that the cost of treatment of the acute disease (per attack of ADL) was equal to the wages for 2 days for men and for 4 days for women[17]. Presently, filariasis control does not only imply interruption of disease transmission, but also morbidity control by appropriate medical or surgical procedures. In addition, there has of late been a sea change in our understanding of the pathogenesis and progression of the disease process by hitherto unavailable diagnostic tools like ultrasound[18] and lymphangioscintigraphy[19-21]. The definition of the infected person itself has taken a U-turn, since the individual without symptoms or microfilaria in a filaria endemic zone can no longer be considered normal following direct visualization of the parasite by the use of these new diagnostic technologies and by the detection of renal and lymphatic abnormalities in apparently normal individuals. The principles of mass as well as individual chemotherapy have also witnessed a dramatic change. The current review encompasses these recent advances in the understanding of lymphatic filariasis.

Clinical Features

The clinical manifestations of lymphatic filariasis tend to vary in different geographical locations[22,23]. The disease spectrum of bancroftian and brugian filariasis varies widely from an asymptomatic state to a severely debilitating chronic condition. Depending upon the infection status of the individuals in endemic areas and the resulting clinical consequences thereof, five main categories of the filarial clinical spectrum have been recognized[4]. These are: (i) asymptomatic amicrofilaraemia; (ii) asymptomatic microfilaraemia; (iii) acute manifestations; (iv) chronic manifestations; and (v) allergic manifestations.

Besides, there are reports of manifestations like glomerulonephritis and monoarthritis in patients with bancroftian filariasis[24-27].

Asymptomatic Amicrofilaraemia

A proportion of individuals in endemic areas neither show any microfilaria (mf) in the blood nor exhibit any symptoms. This may comprise persons who have not been exposed enough to become infected or persons though sufficiently exposed, do not show any detectable infection by current diagnostic techniques[4]. It may be that they have successfully cleared the infection (immune individuals) or are harbouring developing worms of one sex or unfertilized female adult worms. This group may have subclinical infection as evidenced by detectable antigenaemia[28-34].

Asymptomatic Microfilaraemia

Some individuals who develop microfilaraemia do not manifest any clinical disease. Among these, some may remain asymptomatic for years even for life, while others manifest clinical disease with or without losing the microfilaraemic status[4]. Besides, this group of individuals shows lowered parasite specific IgE response but generate large amounts of specific antibody of the IgG_4 class which is considered as a blocking antibody[33,35].

Acute Manifestations

The acute manifestations are characterized by episodic attacks of ADL with constitutional symptoms like fever, chills, malaise, headache, nausea and vomiting[4,36,37]. The ADL attacks usually involve the limbs and the groins and also the male genitals (acute funiculitis or epididymitis or orchitis, most commonly involving all three simultaneously), the female breast and rarely other sites. Acute attacks never occur at more than one site at the same time[36]. In case of the limb, groin or breast, there are local signs of lymphangitis and lymphadenitis (redness, swelling, raised local temperature, pain and tenderness at the local site). These attacks have been described as adenolymphangitis, since the patients usually complain of lymph node involvement followed by retrograde lymphangitis[36,38]. Sometimes infection of deep lymphatics may mimic an acute abdominal emergency as if to require surgical intervention immediately[39,40].

The ADL attacks commonly occur in patients with established chronic filarial disease, more frequently with lymphoedema than with hydrocele[34]. The attacks can also occur in asymptomatic persons, many of whom present with lymphoedema with the first attack itself. Most often, repeated attacks of ADL precede the development of chronic lymphatic pathology of filariasis and these often continue for many years[34,41]. The ADL attacks usually last for about 3 to 5 days, but rarely may be prolonged upto a fortnight[10,16,37,41]. The frequency of these attacks is usually 1 to 3 in a year. However, it can also be more than twice a month in some patients[16]. Each attack of fever and lymphadenitis subsides spontaneously with a crisis. Lymphoedema is frequently present during these episodes, but usually subsides after the acute stage. With time, resolution of the lymphoedema after each attack becomes less complete and the characteristic chronic changes develop[42].

Chronic Manifestations

The common chronic manifestations of lymphatic filariasis affect the male genitals and limbs of both sexes. Most of these patients are amicrofilaraemic[39,43-46]. The incidence and severity of these chronic clinical manifestations tend to increase with age[4,47,48]. These manifestations are the result of structural damage following lymphatic obstruction and fibrosis. In brugian filariasis, genitals are rarely involved.

Hydrocele

Hydrocele is the commonest manifestation of chronic bancroftian filariasis. It has only been very rarely recorded in brugian filariasis. It presents as a swelling of the peritoneal lining that surrounds each of the testicles. A clear straw coloured fluid accumulates in the closed sac (hydrocele) as a result of the blockage in the lymphatics draining the retro-peritoneal and sub-diaphragmatic areas. Rarely the fluid has a milky appearance caused by the presence of chyle, a condition known as chylocele. Sometimes mf can be detected in the hydrocele fluid[4,49]. Besides hydrocele, chronic epididymitis, funiculitis, lymph scrotum (vide infra) are other genital manifestations of chronic bancroftian filariasis in males[4]. Though in an endemic region hydrocele is assumed to be of filarial origin and conventionally used as an absolute indicator of filarial disease in clinical surveys, even in known endemic areas of India, *eg.*, Pondicherry and Orissa, only 69 and 43% of cases of hydrocele respectively could be demonstrated to be of definite filarial etiology[49,50]. Similar findings have been reported from Puerto Rico[51].

Lymphoedema

For both sexes, and independent of age, it has been observed that approximately 11% of the population at risk eventually develop lymphoedema. Lymphoedema commonly affects the lower limbs, rarely upper limbs and genitals in both sexes and female breast. In both forms of lymphatic filariasis, the legs are most commonly involved[52-54]. Lymphoedema can be graded as follows[55]:

Grade I : Oedema spontaneously reversible on elevation.

Grade II : Oedema not spontaneously reversible on elevation, skin normal.

Grade III : Oedema not spontaneously reversible on elevation, skin thickened.

Grade IV : Oedema not spontaneously reversible on elevation, skin thickened with warty/papillomatous growth.

Elephantiasis supervenes following persistent fibrotic changes in the skin and subcutaneous tissue. Elephantiasis can also affect the genitals as stated above (lymph scrotum or penis in males and vulva in females) and the female breast[4,39].

Chyluria

Chyluria is the excretion of milky urine due to admixture of chyle with urine. A minority of the affected subjects complain of gross haematuria. The condition is due to the blockage of the retro-peritoneal lymph nodes below the cisterna chyli, with consequent reflux and flow

of the intestinal lymph directly into the renal lymphatics which may rupture and permit flow of chyle into the urinary tract. Microfilaraemia may or may not be present in these patients. The urinary sediment may contain microfilaria and red cells but seldom leucocytes. Chyluria is often symptomless, but some patients complain of fatigue and weight loss due to loss of fat and protein[4,39,56].

Allergic Manifestations

Tropical pulmonary eosinophilia (TPE) is a form of occult filariasis developing in a small proportion of individuals in areas endemic for filariasis. It is considered as an allergic manifestation of the disease with extremely high titres of anti-filarial antibodies[4]. A majority of these antibodies is of IgE class and is directed against microfilaria[57]. Hypereosinophilia is the most common feature with absolute eosinophil counts ranging from 3,000-50,000 cells/mm^3 of blood. Here the classical clinical manifestations are not present, with absence of circulating mf in the blood, but probably present in the tissues particularly the lung. The commonest presentation is nocturnal paroxysmal cough with radiological evidence of diffuse miliary lesions or increased broncho-vascular markings and elevated erythrocyte sedimentation rate[4]. There is impaired lung function in most cases with a reduction in the vital capacity, total lung capacity and residual volume[58]. Males are affected twice as often as females and the disease is rarely reported in children[4]. The therapeutic response to diethylcarbamazine (DEC) is generally good. If untreated (even in some treated cases) TPE may progress to chronic pulmonary fibrosis[58].

Differences between Bancroftian and Brugian Filariasis

In India, bancroftian and brugian filariasis are characterized by a wide range of clinical manifestations presented by only a small proportion of infected individuals.

Although, it has been reported that in bancroftian filariasis genital involvement is more in the north Indian states when compared to states in south India[22], subsequent studies have shown that the disease distribution is more or less uniform[44,59]. The reported discrepancy was attributable to the difference in methods of clinical examination and improper survey design[48]. In periodic brugian filariasis in Kerala, the clinical spectrum of the disease though found to be generally similar to that reported elsewhere in the world,[6,36,60] the progress of oedema to elephantiasis was observed to be a slow process extending even upto a period of 20 years probably related to the frequency of ADL attacks[53], and abscess formation in the inguinal lymph nodes and along the main lymphatic channel was found to be rare[53] though reported to be common in similar infection in Indonesia[52] and Sri Lanka[6]. This is in contrast to bancroftian infection in south India where elephantoid changes and dermatosclerosis appear more rapidly[53]. In brugian filariasis, involvement of the male genitals was found to be much less common as compared to bancroftian filariasis in Kerala[53] as found elsewhere[6,36]. A comparison between the clinical aspects of the two forms of lymphatic filariasis is shown in Table II.

Table II. Comparison of clinical aspects of bancroftian and brugian filariasis.

Parameter	Bancroftian filariasis	Brugian filariasis
Progression of the disease[53]	Fast	Relatively slow
Relation with gender[39,48,53]	Occurrence in males more than in females	No difference between genders
Frequency of acute attacks per year in patients with lymphoedema[34]		
Grade I	4.9±1.70	0.9±0.22
Grade II	5.5±1.01	2.5±0.29
Grade III	10.4±3.20	5.1±1.08
Mean duration (yr) of lymphoedema[34]		
Grade I	0.1±0.02	0.1±0.01
Grade II	5.8±0.56	13.6±1.17
Grade III	8.6±0.92	28.7±2.66
Involvement of male genitals[39,53]	Common	Rare
Extent of elephantiasis[39]	Above kneee	Below kneee

Superscript numbers refer to sl.nos. in the reference list.

Filarial arthritis which may manifest in endemic regions is monoarthritic usually affecting the knee joint. Other conditions suggested to be associated with lymphatic filariasis include endomyocardial fibrosis, glomerulonephritis, thrombophlebitis, tenosynovitis, nerve palsies, dermatoses, *etc.* Lymphoedema has also been considered to predispose to lymphosarcoma[61].

Pathogenesis

Observations on studies undertaken in Pondicherry and Calcutta suggest that filariasis endemic populations consist of individuals who remain amicrofilaraemic and

asymptomatic and those who progress through the sequence : uninfected, microfilaraemic and amicrofilaraemic to develop irreversible lymphatic pathology[62].

Conventionally, it had been the view that the pathogenesis of the lymphatic abnormalities in this disease is essentially mediated by the immune system of the host[33] but the advent of recent techniques such as ultrasound[18] and lymphangioscintigraphy[19-21] has shown that factors other than immunological, such as the parasite itself may play a role in the pathogenesis. The presence of the adult worms in the lymphatics causes early lymphatic dysfunction and dilatation *etc* due to factors released by the parasite as described in other systems[63] or elaborated directly by the host. The primary role of the immune system in this early lympathic dysfunction appears to be the production of down-regulatory molecules which contain or inhibit inflammatory responses[64]; this hypothesis being supported by recent findings that cytokine responsiveness in microfilaraemics is of the Th-2 type *ie.* heightened production of interleukins -4, -5 and -10 which are contra-inflammatory [65,66]. Th-2 type down regulating suppressive cytokines in asymptomatic microfilaraemics facilitate persistence of the parasite in the host while inducing little or no inflammatory clinical disease. IL-4 stimulates B cells proliferation resulting in IgG_4 and IgE production where IgG_4 acts as blocking antibody with consequent reduction of the inflammatory activity of IgE[29]. This contrasts with the relatively pro-inflammatory Th-1 response seen in amicrofilaraemic patients with chronic lymphatic pathology following breakdown of this tolerance. This is associated with a high level of IgE, IgG_1 and IgG_2 and low level of IgG_4. Elephantiasis may result by IgE mediated mechanisms or a passive reaction to naturally dying adult worm evoking IgG_1 and IgG_2 antibody response mediating inflammatory reactions. This immunological hyper-responsiveness may remove the parasite from circulation as in developing lymphoedema[67].

Though microfilaraemics remain asymptomatic for long periods, they cannot be considered to be truly free from any abnormalities. The asymptomatic state earlier thought to be benign is no longer so; it has been demonstrated that most of the so called asymptomatic microfilaraemics have lymphatic abnormalities as detected by lymphangioscintigraphy and also renal abnormalities as evidenced by microscopic haematuria and/or proteinuria. Renal abnormalities are generally reversible after treatment[27]. Prenatal tolerance to filarial antigens has been shown to determine immune responsiveness to the parasite and thereby the development of lymphatic pathology *ie.* children born of microfilaraemic mothers are much less capable of responding to filarial antigens than those born of non-infected mothers[68,69]. However, recent studies on bancroftian microfilaraemia in children in relation to parental infection have shown that there is hardly any role of intrauterine sensitization, since the microfilaraemic status of the father has also been seen to influence microfilaraemia in bancroftian infection of the children[70]. This only highlights the influence of household exposure on all family members.

The findings in animal models parallel those in the affected humans, *ie.* lymphatic proliferation, dilatation and oedema formation due to the presence of living adults and obstructive, obliterative reactions in the lymphatics around dead parasites. The earliest changes occur four weeks after infection and involve the regional lymph nodes. Within four days of the infecting larvae reaching the lymphatics, there is a marked cell mediated response in the regional lymph nodes followed by an antibody mediated response in the afferent lymphatics. The local lymph node is enlarged followed by an increase in diameter and formation of tortuosities of the lymphatics through which the infective larvae migrate. These changes may revert if the worms are killed by microfilaricidal drugs[71]. Following appearance of antimicrofilarial antibodies, resistance to reinfection develops causing obstruction to the lymph flow resulting in lymphoedema. Initially there is an acute inflammatory response characterized by infiltration of polymorphs, histiocytes, eosinophils and lymphocytes around the lymphatics. This is followed by formation of epitheloid granuloma and foreign body giant cells after the death of the adult worms, which may calcify, become lysed and surrounded by fibrosis. Lymphatic abscesses may form at the site of dead and degenerating worms. Finally, the lymphatics are obliterated by fibrosis with the disappearance of microfilariae from the blood[71]. Lymph stasis results in increased susceptibility to secondary bacterial infection particularly with group A streptococci resulting in episodic attacks of ADL. Each attack of ADL results in the progression of chronicity of disease and increased lymph stasis, thereby, again increasing susceptibility to ADL attacks[16]. This culminates in fibrosis with the formation of solid oedema and probable decline in ADL attacks.

The pathogenesis of late stage abnormalities (lymphoedema and elephantiasis) includes an inflammatory component comprising significant cellular infiltration in the epidermis and hypodermis as revealed by examination of biopsy specimens of skin from patients of filarial lymphoedema. In comparison, similar examinations in individuals with non-filarial lymphoedema showed far

fewer changes[72]. Alternatively, in a compromised state of lymphatic function, superinfection of tissue with micro-organisms may be largely responsible for local inflammation[67] and eventual elephantiasis as the clinical outcome of this disease[73].

Management

The management of lymphatic filariasis varies according to the stage of infection, disease manifestations and its complications. The overall management comprises mainly medical measures and surgical intervention is only called for if indicated. Medical measures include physiotherapy and chemotherapy for the acute and chronic forms of the disease. The principles of management accordingly are enunciated below:

Asymptomatic Infected

Chemotherapy is the mainstay of treatment of mf carriers and antigen positive individuals. The following drug or combination of drugs are in use currently : diethylcarbamazine citrate (DEC) is the drug of choice. It is used singly or in combination with other anthelmintics *eg.* ivermectin or albendazole. One of the following schedules is advocated. (i) DEC: 6 mg/kg body weight (b w) in three divided doses per day after meals for 12 days *[W.bancrofti]* or for 6 days *[B. malayi]* - standard regimen[12], or (ii) DEC: 6 mg/kg b w in single dose at monthly intervals for 12 months, or (iii) Ivermectin: 400 µg/kg b w repeated at three monthly intervals for 12 months (not marketed currently in India for human use), or (iv) DEC and ivermectin: a single dose of DEC 6 mg/kg b w and ivermectin 200 µg/kg b w repeated after 6 months, or (v) DEC and albendazole: DEC 6 mg/kg b w and albendazole 600 mg for adults to be repeated after one year if required[74].

Acute Manifestations

Antibiotic therapy has recently gained importance following recent studies that have demonstrated the role of bacteria especially beta haemolytic streptococci in the causation of ADL episodes[67]. Penicillin, the drug of choice, is given as Benzathine penicillin G 1,200,000 units by injection every 4 weeks or penicillin G potassium salt 250,000 units or 250 mg penicillin V orally 3 to 4 times a day till the symptoms subside[75]. Synthetic penicillin analogues like amoxycillin can also be given. If allergic to penicillin, erythromycin or other macrolides may be used. Antipyretics *eg.* paracetamol; non-steroidal anti-inflammatory drugs (NSAID) *eg.* diclofenac sodium and antihistaminics may be used if indicated. Symptomatic treatment for nausea and vomiting if necessary can be given. Immobilization and elevation of the affected limb should be carried out to ameliorate suffering during the acute attack. In case of abscess formation, surgical drainage is to be done with necessary follow up.

Standard regimen of DEC is to be administered after the acute attack of ADL has subsided to avoid severe allergic reactions during the acute attack.

Chronic Manifestations

Hydrocele

Most hydroceles of small size may not require any treatment. For moderate to large hydroceles, the treatment of choice is surgical. Monthly courses of DEC (10 mg/kg b w per day for three weeks) for a period of 6 months have been reported to be beneficial[76]. However, further evaluation in this regard is required.

Lymphoedema

Management of lymphoedema calls for both prophylactic and therapeutic measures. Therapeutic measures comprise the following :

(i) *Medical*

(a) Physiotherapy: It is useful in the early stages of lymphoedema and includes the use of pressure bandage, manual massage, thermotherapy, pneumatic compression and interferential current therapy.

Pressure bandage: Crepe bandages and elasto-crepe stockings are commonly used and the latter are preferred for simplicity, but they have to be tailor made for individual patients. Care has to be taken to educate the patients in the proper use of these, since these are often used inadequately and improperly.

Manual massage: The principle is to mobilize the oedema fluid away from the affected part milking it upwards along the cutaneous and subcutaneous networks to the abdomen. Though the experience in filarial lymphoedema is limited, it has the potential for domiciliary management since the patients and relatives could be educated and trained in this therapy for daily application. It is a technique where gentle pressure is applied on the skin to reduce the pain and oedema of the affected region by promoting lymph circulation from the periphery to the centre. The massage needs to be done daily and requires a lot of patience and motivation on the part of the patient as

well as total involvement of the therapist. The massage needs to be done daily and evaluated regularly at monthly intervals. The details of the procedure are given elsewhere[74].

Thermotherapy: It is useful both for the reduction of oedema and the associated pain. Wet heat therapy by immersing the affected limb in a bucket of warm water for about 10 to 15 min daily in the evenings when the size of the swelling is increased due to the day's activities, is recommended to facilitate circulation. After this, the patient could massage the limb and lie flat with the foot being kept elevated. In addition, hot ovens (modified Chinese therapy) have also been found to be useful.

Pneumatic compression: Single and multi-cell jackets are used for pneumatic compression of affected parts either by intermittent low pressure or continuous high pressure generated by electrically operated machines. Reduction occurs immediately after therapy, but the results are not sustained in course of time particularly in ambulatory patients. Hence, elastic bandaging as an adjunct after compression is essential.

Interferential current therapy: Low frequency interferential current stimulation is given to the affected part using two electrodes placed diametrically opposite on the skin, with one having a fixed stimulation (4000 Hz) and the other variable (3850 to 4000 Hz). This creates an interferential beat frequency equivalent to the difference between the two through the tissue. This therapy though tried on a limited scale has been found to be useful in the reduction of pain and oedema particularly in patients with grades II and III lymphoedema (VCRC data).

(b) Chemotherapy: Standard regimen of DEC as for mf carriers can be given every month for 12 months. Apart from this coumarin 200 mg twice a day has been reported to be helpful in the reduction of filarial oedema in the long run. However, the role of coumarin needs further evaluation.

(ii) *Surgical interventions*

In lymphoedema, surgery is resorted to only in cases who do not respond to aggressive medical management or have impaired functions particularly in cases with physical and occupational disabilities or for social reasons. The surgical procedures include lymphatic drainage and/or excisional surgery.

(a) Drainage procedures: These include lymphangioplasty, omentoplasty, flaps, lymph-vein anastomosis, lymph-lymph anastomosis, lympho-nodo-venous (LNV) shunt, *etc.* LNV shunt shows immediate good response epecially in patients with moderate to high oedema *ie.* grade III with oedema volume more than 2 litres and duration of about 5 years. There is a rapid reduction in oedema volume (about 40%). The gains are not sustained and in most of the patients the oedema volume gets gradually increased. Post-surgery ADL attacks are the most important cause for the failure of the viability of the shunt. However, LNV shunt may have a role as a pre-excisional surgical procedure in filarial lymphoedema

(b) Excisional procedures: These procedures are resorted to only in patients with gross physical deformities or occupational disabilities. Reliable objective assessment of excisional procedures are not available for long-term results.

Medical management of lymphoedema is of primary importance since it can be undertaken at domiciliary, PHC or referral levels. Surgery is advocated in selected cases as a last resort since it can be accomplished in referral centres only. Though the long-term value of any procedure is still not certain, the cases need to be followed up by objective limb circumference measurement at fixed points.

Allergic Manifestations

Tropical pulmonary eosinophilia, a form of occult filariasis considered as the most important allergic manifestation of this disease, responds fairly well to standard regimen of DEC. If neglected, it may lead to an irreversible condition of chronic pulmonary fibrosis. However, relapses may occur in 20% of patients who may require higher doses of the drug *ie.* 6-12 mg/kg b w daily for 21-30 days. Beneficial effects of DEC have also been observed in other forms of occult filariasis.

Management of Adverse Reactions to Antifilarial Drugs

The adverse reactions to antifilarial drugs may result in two ways. The first is a pharmacological dose dependent response to the chemical properties of the drug itself. This may occur in infected as well as in uninfected recipients of the drug with equal frequency. The second is due to the response of the infected host to the destruction and death of the parasite and is independent of the dose but is related to the pre-therapy parasite load[77-79]. Usually, there is hardly any adverse effect due to pharmacological toxicity of the standard dose of DEC in the uninfected person. At higher dosage only, there may be

anorexia, nausea, abdominal pain, weakness, dizziness or lethargy which may begin 1-2 hours after ingestion of the drug on an empty stomach and persist for a few hours. There is no accumulation of the drug following prolonged administration and chronic toxicity does not occur. The second type of reactions is attributed to the filaricidal action of DEC. These reactions are the result of immunological response to the disintegrating microfilariae and dead adult parasites. They are usually less severe in bancroftian than in brugian filariasis. These reactions may be systemic or local, both with and without fever.

Systemic reactions include malaise, headache, body ache, joint pain, dizziness, anorexia, vomiting, transient haematuria, allergic reactions and rarely bronchial asthma. They usually occur a few hours after the first dose of DEC and last for about 3 days. Fever may be present. The systemic reactions cease spontaneously and symptomatic treatment with antipyretics and analgesics is given.

Local reactions usually comprise lymphadenitis, abscess, ulceration, transient lymphoedema and hydrocele occurring in decreasing frequency. In bancroftian filariasis, there may be funiculitis and epididymitis. Though they appear later in the course of the disease and last longer, they also disappear spontaneously and interruption of treatment may not be necessary. In cases where lymphoedema and hydrocele have persisted for several months after DEC therapy, elephantiasis has not been observed. Local reactions tend to occur more often in patients with history of ADL being probably related to the presence of adult or immature worms or fourth stage larvae in the tissues.

Prophylaxis of Filariasis

For prevention and management of the acute disease, foot hygiene is of prime importance[74]. This consists of the following : (i) cleaning feet with soap containing 2% glycerine, (ii) regular application of Whitfield ointment on the webs of toes to prevent fungi infection and to smoothen the skin, (iii) regular clipping of toe and finger nails. Clipping of finger nails is important to prevent injuring the skin of the affected limb by scratching on itching, and (iv) prompt and appropriate attention to all injuries in the body specially the feet.

Other measures of prevention include (i) treatment of any other focus of infection *eg.* caries tooth, CSOM *etc.*; and (ii) for patients who get frequent attacks of ADL, long acting penicillin (benzathine penicillin 12 lakhs units) intra-muscular once every 3 weeks after carrying out mandatory sensitivity skin test or oral penicillin V 100 00 IU, 65 mg tablet can be given daily (VCRC unpubished data).

As stated above, in endemic areas, individuals termed endemic normals may not be so, since the absence of symptoms or microfilaraemia does not necessarily mean that they are uninfected. In a proportion of this population, infection may be evidenced only by the demonstration of antigenaemia, whereas in the rest, the presence of infection or otherwise cannot be ascertained by the currently available means. This justifies the institution of mass chemotherapy for the infected and individual prophylaxis for the supposedly uninfected by antifilarial drugs.

In endemic areas, preventive measures against mosquito bites *eg.* bednet and mosquito proofing of the house should be taken. In addition, DEC 300 mg as a single dose after dinner per day for 2 days every month acts as prophylaxis against filariasis for people from non-endemic regions visiting endemic regions immediately on arrival. In an area with cofirmed active transmission of filariasis, DEC at a dosage of 500 mg on each of two consecutive days each month for 18 months has been shown to be prophylactic throughout and also for further 12 months after the cessation of DEC administration[80].

Conclusions

Although lymphatic filariasis continues to be a major public health problem in many parts of the world particularly India, it has of late been identified as a potentially eradicable disease. The clinical features of lymphatic filariasis present a highly variable spectrum and recent advances in diagnostic techniques have led to questioning of the earlier concept of endemic normals, since lymphatic and renal abnormalities have been directly visualized in otherwise apparently normal individuals in endemic regions. In such cases as also in arthritis associated with this disease, the exact etiopathogenesis is not fully understood. Control of acute attacks of ADL by antibiotics and simple measures like foot hygiene *etc.* have been shown to prevent the progression of the disease to its chronic from with the resultant disability. Though DEC continues to be the mainstay of individual as well as mass chemotherapy, newer antifilarials like ivermectin and anthelmintics like albendazole are being added to the arsenal of antifilarial treatment. The earlier sense of hopelessness in morbidity management has also given way to a new sense of optimism and hope both to the clinician and the patient who can be given simple training of self support.

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This article has been contributed by Dr; S. P. Pani, Dy. Director and Dr. R. Lall, Asstt. Director, Vector Control Research Centre, Pondicherry.

ABSTRACTS

Some Research Projects Completed Recently

Over expression of p 53 and cell proliferation indices in non-Hodgkin's lymphoma.

The study was carried out to assess the morphological classification of non-Hodgkin's lymphoma (NHL) on H&E stained sections and the over expression of p53, argyrophilic nucleolar organiser regions (AgNORs) and proliferating cell nuclear antigen (PCNA) in immunohistochemistry of formalin-fixed, paraffin embedded sections.

According to the NCI Working Formulations for Clinical Usage, 1982 the 50 NHLs were classified as small lymphocytic lymphoma-17; follicular, small cleaved lymphoma-6; follicular, mixed small and large lymphoma-2; diffuse small cleaved lymphoma-11; diffuse, mixed small and large lymphoma-7; diffuse, small non-cleaved lymphoma-4; immunoblastic lymphoma-2; and lymphoblastic lymphoma-1. Out of 50, 25 were low grade lymphomas, 18 intermediate and 7 high grade.

Six (12%) NHLs (1/25 low grade, 2/18 intermediate and 3/7 high grade lymphomas) were positive for p53 (>10% of tumour cells showing positivity).

PCNA labelling index was >1% in 4(16%) of the low grade lymphomas, 6 (33%) of the intermediate and 5 (71.5%) of the high grade lymphomas. It was found that all the p53 positive lymphomas had a PCNA labelling index of >30%. The range of AGNORs was 2.0 to 7.0 in all but one low grade lymphomas, whereas the intermediate grade lymphomas showed a range of 7.0 to 9.2 and high grade lymphomas a range of 8.0 to 14.4.

It was found that PCNA showed a higher labelling index in high grade cases, indicating the presence of higher proportion of proliferating cells. AGNOR scores showed a direct relationship to PCNA lebelling index in that both were increased in high grade lymphomas. p53 and PCNA immunoreactivity showed a relationship in that PCNA labelling index was high in tumours with p53 positivity.

Findings of this study indicate that p53 expression in malignant lymphomas is related to the grade of lymphomas and that p53 positivity may also be a marker for cell proliferation.

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Role of peptide M, uveitopathogenic fragment of 45 kDa retinal S-antigen in human uveitis.

The study was carried out in patients of uveitis (38), diabetic retinopathy (27) and systemic connective tissue disease (CTD, 30) and 30 healthy volunteers to investigate the role of retinal S-antigen and its uveitopathogenic peptides (M and G) and uveitopathogenic fragment of interphotoreceptor retinoid binding protein (IRBP) in idiopathic human uveitis. Lymphoproliferative responses were tested *in vitro* against native S-antigen, peptides M and G, yeast histone H3 peptide and IRBP:R 16 to establish their role in pathogenesis of human uveitis.

Seven of 38 (18.4%) patients with uveitis, and none among the diabetic retinopathy and CTD patients and healthy volunteers responded (stimulation index >3) to at least one antigen used. One uveitis patient showed response to native S-antigen, peptide M and yeast histone H3. One responded to both S-antigen and peptide M and another to

responded to both S-antigen and peptide M and another to both peptide G and R-16 peptide. Two responded to S-antigen only, one to peptide M and one to peptide G. In addition, one uveitis patient and two patients of diabetic retinopathy responded to histone H3 only.

These findings thus suggest that retinal antigens may play a role in the etiopathogenesis of a subset of idiopathic human uveitis.

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Medical Sciences, Lucknow

Publications:

1. Nityanand, S., Singh, V.K., Shinohara, T., Paul, A.K., Singh, V., Agarwal, P.K. and Agarwal, S.S. Cellular immune response of patients with uveitis to peptide M, a retinal S-antigen. *J Clin Immunol 13* : 352, 1993.

2. Rajasingh, J., Singh, V.K., Singh, V., Sharma, K. and Agarwal, S.S. Cellular immune response to retinal S-antigen and interphotoreceptor retinoid binding protein fragments in idiopathic human uveitis. *Indian J Med Res 103* : 222, 1996.

3. Singh, V.K. and Nagaraju, K. Experimental antiimmune uveitis. Molecular mimicry and oral tolerance. *Immunol Res 15* : 323, 1996.

ICMR NEWS

The X meeting of the Directors of the ICMR Institutes/Centres located in different parts of India was held at New Delhi on May 6 and 7, 1998.

*** *** ***

Meetings of the Project Review Committee (PRC)/Task Force (TF) held at New Delhi:

PRC for Projects in Non-Communicable Diseases	April 16, 1998
TF on Management of Glaucoma under Indian Conditions	May 8, 1998

Participation of ICMR Scientists in Scientific Events:

Dr. N.K. Ganguly, Director-General, ICMR, participated in the I Joint Session of the South-East Asia Advisory Committee on Health Research and Directors of Medical Research Councils at Colombo (April 22-24, 1998).

Dr. Manjula Datta, Dy. Director, Tuberculosis Research Centre (TRC), Chennai, participated in the meeting of the WHO Steering Committee on the Immunology of Mycobacteria at Geneva (April 22-24, 1998).

Dr. Soumya Swaminathan, Asstt. Director, TRC, Chennai, participated in the International Conference of the American Thoracic Society at Chicago (April 24-29, 1998).

Dr. Sajid Hussain, Senior Research Officer, Central JALMA Institute for Leprosy, Agra, participated in the Conference of Orthopaedic Surgeons from SAARC Countries at Kathmandu (April 28-May 1, 1998).

Dr. L. Singotam, Dy. Director, National Institute of Nutrition (NIN), Hyderabad, participated in the X Annual International Scientific Meeting on Scanning Microscopies "Scanning 98" at Baltimore, Maryland (May 9-12, 1998).

Dr. D.K. Das, Officer-in-Charge, Institute of Cytology and Preventive Oncology, New Delhi, participated in the XIII International Congress of Cytology at Tokyo (May 10-14, 1998).

Dr. Ganguly participated in the VIII meeting of the Indo-Russian Joint Council for Integrated Long-term Programme (ILTP) of Cooperation in Science and Technology at Moscow (May 14-15, 1998).

*** *** ***

Dr. V.P. Sharma, Addl. Director-General, ICMR and Director, Malaria Research Centre, Delhi, retired on April 30, 1998.

*** *** ***

Dr. Padam Singh, Director, Institute for Research in Medical Statistics, New Delhi, took over as Additional Director-General of ICMR w.e.f. May 1, 1998.

ICMR AIDED SYMPOSIA/SEMINARS/WORKSHOPS/COURSES/CONFERENCES

Symposium/Seminar/Workshop/ Course/Conference	Date & Place	Contact Address
Symposium on Tribal Medicines of North-East India	May 25-27, 1998; (at Tezpur)	Dr. M.P. Chacharkar, Director, Defence Research Laboratory, Tezpur-784001.
National Workshop of Medical Editors and Reviewers in Medical Communication: Peer Review, Ethics and Internet	June 16-18, 1998; (at Pondicherry)	Dr. C. Adithan, Organising Secretary of the Workshop, Department of Pharmacology, Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry-605006.
International Symposium on Frontiers of Genetics and Development	July 7-8, 1998; (at Bangalore)	Dr. U. Vijayaraghavan, Convenor of the Symposium, Department of Microbiology and Cell Biology, Indian Institute of Science, Bangalore-560012.
International Symposium on Temporomandibular Joint Disorders and Chronic Orofacial Pain	October 30-31, 1998; (at Mangalore)	Prof. P.K. Dayal, Organising Secretary of the Symposium, KMC College of Dental Surgery, Mangalore-575001.

COUNCIL'S TRAINING PROGRAMMES FOR 1998-99

Leprosy

At the Central JALMA Institute for Leprosy, Agra: -

- Multidrug Therapy Orientation Course in Leprosy for Medical Officers (August 17-28, October 26-November 6, and December 7-18, 1998).

Virology

At the National Institute of Virology, Pune:

- Diploma in Medical Virology (July 1998-May 1999).

Reproductive Biology

At the Institute for Research in Reproduction, Mumbai:

- Workshop on Andrology for Clinicians (November 16-30, 1998)

Endocrinology

At the National Institute of Nutrition, Hyderabad:

- Annual Certificate Course on Endocrinological Techniques and their Applications (August 1-September 15, 1998).

Nutrition

At the National Institute of Nutrition, Hyderabad:

- M.Sc. in Applied Nutrition (June 1, 1998-February 28, 1999).
- Postgraduate Certificate Course in Nutrition (December 1, 1998-February 28, 1999).

Laboratory Animal Technology

At the National Centre for Laboratory Animal Science, National Institute of Nutrition, Hyderabad:

- Training Course for Laboratory Animal Technicians (June 16-July 31, 1998).

Occupational Health

At the National Institute of Occupational Health, Ahmedabad:

- Training Course on Environmental Hygiene Practice (November 16-20, 1998).

Biomedical Statistics

At the Institute for Research in Medical Statistics, Chennai:

- Basic Course in Statistics for Postgraduate Medical Students (July 1998).
- Basic Course in Statistics for Medical Officers (November 1998).

Haematology

At the Institute of Immunohaematology, Mumbai:

- Training Course in Transfusion Medicine for Blood Bank Medical Officers (August 11-October 9, 1998).
- Training Course in Blood Group Serology and Blood Bank Methodology for Blood Bank Technicians (August 11-September 10, 1998).
- Training Course in Advanced Haematology and Immunohaematology (September 21-October 9, 1998).

INDIAN COUNCIL OF MEDICAL RESEARCH

Grant-in-aid for organising Seminars/Symposia/Workshops

The Council provides partial financial assistance for organising Seminars/Symposia/Workshops. Applications for grant of financial assistance (complete in all respects in the prescribed proforma), will be considered only if furnished **at least four months before the date of commencement of the Seminar/Symposium/ Workshop,** *etc.*

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