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The role of the urologist in the treatment and elimination of lymphatic filariasis worldwide

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Introduction

In 1997, the WHO passed a resolution calling for the global elimination of lymphatic filariasis (LF) as a public health problem [1–3]. Currently the disease is thought to affect over 120 million people in over 80 countries in five endemic regions, i.e. South-east Asia, Africa, the Eastern Mediterranean, the Western Pacific, and the Americas, including the Caribbean countries and Central America (Table 1). Most infections worldwide are secondary to *Wuchereria bancrofti*. Although *Brugia malayi* is responsible for 10% of filariasis, only *W. bancrofti* induces the genital pathology, which affects most symptomatic men [3,4]. According to the WHO, filariasis is the second leading cause of disability worldwide. In India, its economic impact has been estimated at $1 billion/year [5]. Although the disfigurement of filariasis is most often seen in adolescents and adults, it is a disease acquired in childhood [6]. In endemic areas, up to 40% of the population may be infected. However, the incidence of hydrocele in infected men approaches 100%, a value that differs substantially from earlier reports. Interestingly, in many urban regions the transmission may be quite focal, restricted even to certain neighbourhoods [6,7]. The Global Programme to Eliminate Filariasis has two main goals; to interrupt the transmission of disease and to alleviate the disability associated with infection [2,3]. The WHO Global Alliance has identified urogenital surgery as critical to the mitigation of the incapacitating effects of this disease in men. These effects include lymphangiectasia of the genitalia including the penis and scrotum, hydrocele, chylocele and chyluria. With medicines and protocols now available to interrupt transmission, LF is one of the diseases, including measles, polio, leprosy and Chagas disease, targeted for elimination by the year 2020 [3]. Until then, LF contributes to sustaining poverty through its crippling physical effects of scrotal elephantiasis and the psychological disability of sexual dysfunction in young men [8,9].

Biology

Lymphatic filariasis is the result of infection by the adult parasites and microfilariae of *W. bancrofti* or *B. malayi*. The adult female *W. bancrofti* is a pale, threadlike nematode 6–10 cm long and 0.2 mm wide. The male is smaller, at 4–6 cm long and 0.1 mm wide [8].

Worldwide, at least 90% of human disease caused by LF can be attributed to *W. bancrofti*; it is this parasite which causes the lymphangiectasia responsible for genital pathology. Transmitted primarily by mosquitoes of the species *Culex*, *Aedes* and *Anopheles*, its range is in the tropical and subtropical zones [3]. Mosquitoes deposit the larvae on the host skin next to the puncture site (the larvae are too large to be transmitted through the mosquito's proboscis), and the third-stage larval parasites migrate through the venous system and lungs to eventually reside in the lymphatics (Fig. 1). In adolescent and adult men, there is a preference for the lymphatics of the spermatic cord. There they form nests occupied by male and female worms, and produce the first-stage larvae or microfilariae by viviparous reproduction (Fig. 2). The microfilariae are 230–300 μm long; they migrate from the lymphatics to the peripheral blood, where mosquitoes then ingest them (Fig. 3). In the vector host, the developing parasite moults to become the infective third-stage larva.

Experience during World War II with American soldiers travelling through endemic areas [10,11] showed that initial infection of a naive host causes an intense inflammatory reaction, particularly in the lymph nodes. The inflammation causes temporary obstruction, which later re-canalizes. The early studies contributed to the misunderstanding of the disease and the thought that lymphoedema was secondary to lymphatic obstruction. In contrast to naive hosts, lifelong inhabitants of endemic areas are thought to develop an immunological tolerance to the parasite. Newer studies show that the damage to lymphatics is not primarily inflammatory but instead secondary to an alteration of

Table 1 The regions and countries affected by LF

Americas	*Africa*	*Eastern Mediterranean*	*South-East Asia*	*Western Pacific*
Antigua and Barbuda	**Angola**	Dijbouti	**Bangladesh**	**American Samoa**
Barbados	**Benin**	**Egypt**	**Burma**	**Brunei darussalam**
Brazil	Burkina Faso	Oman	India	Cambodia
Costa Rica	Burundi	Pakistan	Indonesia	China
Cuba	**Cameroon**	Saudi Arabia	**Maldives**	**Cook Islands**
Dominica	**Cape Verde**	Somalia	**Nepal**	Guam
Dominican Republic	Central African Republic	Sudan	Sri Lanka	Micronesia
French Guyana	**Chad**	**Yemen**	**Thailand**	**Fiji**
Guadaloupe	**Comoros**			**French Polynesia**
Guyana	Congo			Kiribati
Haiti	Cote d'Ivoire			Lao Peoples Democratic Republic
Martinique	**Democratic Rep Congo**			**Malaysia**
Panama	**Equatorial guinea**			Marshall Islands
Puerto Rico	**Eritrea**			Nauru
Saint Kitts & Nevis	**Ethiopia**			**New Caledonia**
Saint Lucia	**Gabon**			**Niue**
Suriname	**Gambia**			Northern Marianas
Trinidad & Tobago	**Ghana**			Palau
Venezuela	**Guinea**			**Papua New Guinea**
Virgin Islands	**Guinea Bissau**			**Philippines**
	Kenya			**Samoa**
	Liberia			**Solomon Islands**
	Madagascar			**Republic of Korea**
	Malawi			Tokelau
	Mali			**Tonga**
	Mauritius			Tuvalu
	Mozambique			**Vanuatu**
	Niger			**Vietnam**
	Nigeria			**Wallis & Futuna**
	Reunion			
	Rwanda			
	Saotome & Principe			
	Senegal			
	Seychelles			
	Sierra Leone			
	Togo			
	Uganda			
	United Republic of Tanzania			
	Zambia			
	Zimbabwe			

Bold type signifies endemic and plain type post-endemic.

the microenvironment of the lymphatic vessel resulting, ultimately, in lymphangiectasia [12,13]. This immune tolerance may be acquired *in utero* in children of infected mothers [14,15]. In endemic areas, filariasis is acquired in childhood and can be detected by antigen, a thick smear for microfilaria, or lymph-node ultrasonography in children as young as 2 years [6]. However, male children apparently do not develop hydroceles or significant spermatic cord lymphangiectasia until puberty. Adults harbouring living parasites may be asymptomatic with no microfilaraemia, asymptomatic with microfilaraemia, or symptomatic with acute and chronic disease [16,17]. Currently the antibody test for the adult worm is considered to be the best screening test for its presence [18], although the test is known occasionally to be negative in the presence of adult living worms confirmed with ultrasonography and surgery (G. Dreyer, personal communication). With a lifespan of 5–10 years, adult worms are more resistant to anti-infective agents than are microfilaria. Microfilaria may live up to several months. The diurnal periodicity of the distribution of microfilaria in the blood stream is not related to discharge from the mature female, but instead relies on a circadian rhythm, which is not well understood.

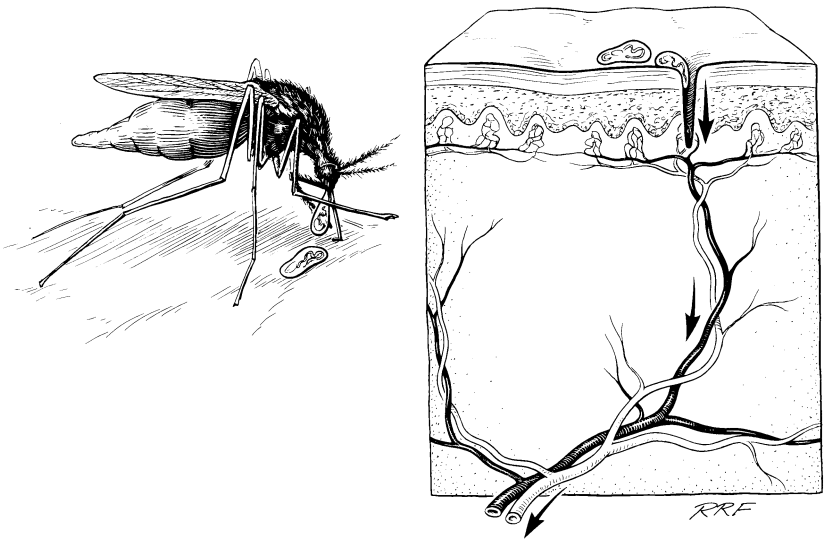

Fig. 1. Mosquito depositing larvae on the surface of the skin. The larvae migrate through the puncture site to the venous system, thence to the lymphatics where they mature and reside as adults.

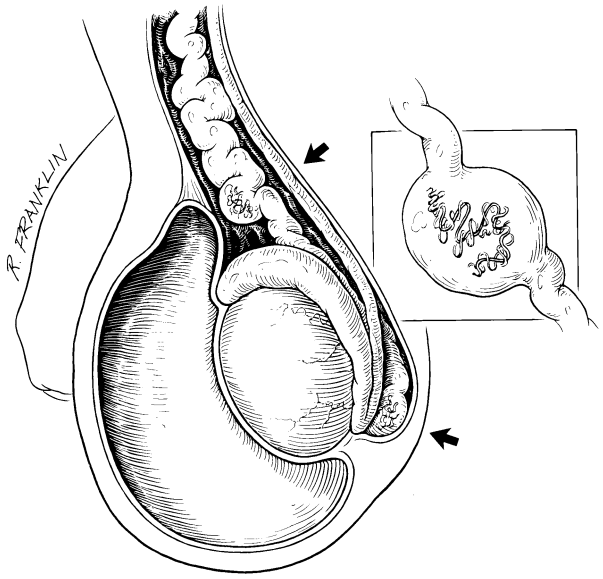

Fig. 2. A nest of adult worms in a dilated lymphatic vessel of the spermatic cord. A larger female worm typically occupies a nest with several smaller males. On ultrasonography these can be seen to move actively within the lymphatic vessels.

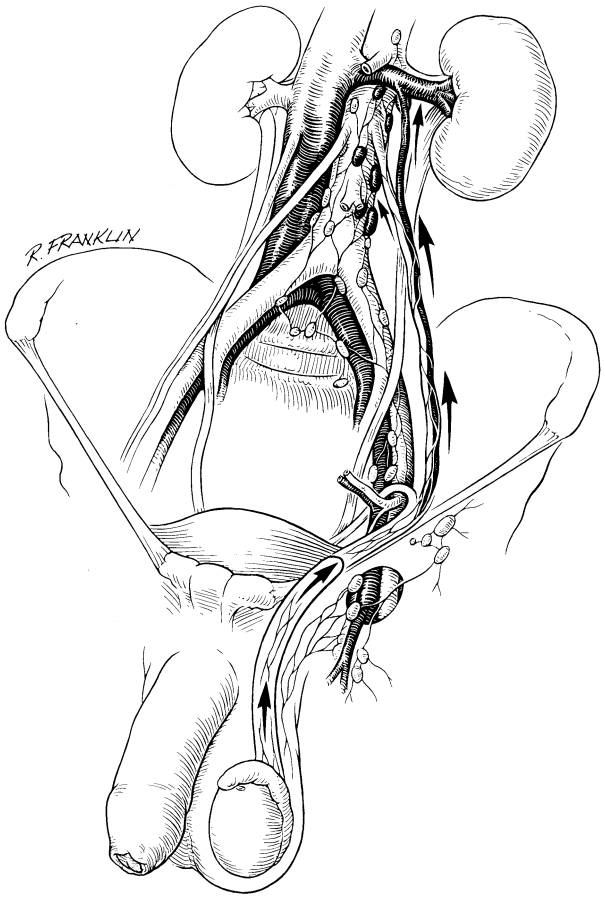

Fig. 3. Microfilariae migrate from the nest through the lymphatics and to the peripheral blood where they become available to mosquitoes ingesting a blood meal.

Pathology

The adult parasites of *W. bancrofti* prefer to occupy the lymphatic vessels of the spermatic cord rather than the lymph nodes in adult men [19]. The reason for this is unknown although there has been speculation about a preference for a localized hormonal environment. In asymptomatic patients, lymphangiectasia and adult worms may be detected by ultrasonography [7]. The mechanism by which the parasite influences

its microenvironment to cause dilatation of the lymphatics is unknown. However, it is not an inflammatory process; while the adult worms are living, the endothelium of the lymphatics shows no sign of inflammation in most cases [20]. The lymphangiectasia is a generalized phenomenon in the lymphatics and not restricted to the local environs of the parasites. This observation has led to the speculation that lymphangiectasia is a response to a diffusible factor affecting the endothelium and eventually the vessel wall [14].

In symptomatic patients 'acute attacks' are the cause of severe focal or generalized pain. They are subcategorized by aetiology. Filarial adenolymphangitis is caused by the death of an adult worm by natural causes or drug treatment, such as diethylcarbamazine (DEC). The characteristics of the attack, either adenitis or lymphadenitis, depend on where the dead parasites lodge. The patient may experience an erythematous, indurated, tender cord accompanied by malaise or a headache. When the parasite dies in the spermatic cord, orchalgia or orchitis, epididymitis or funiculitis may occur. The inflammatory response is characterized by infiltration of the lymphatic walls by neutrophils, eosinophils and macrophages. The degenerating worms may become the focus of micro-abscesses and localized obstruction of the lymphatic channel. There they may become calcified in the later phases of decomposition [21]. However, in most cases the significant pathology caused by LF is not from obstruction of the lymphatics but instead from dysfunction and poor drainage secondary to dilated lymphatics. Acute hydroceles occurring after 'acute attacks' usually resolve spontaneously [8,16].

Acute dermatolymphangioadenitis occurs because of secondary infection in damaged lymphatics, frequently by β-haemolytic streptococci [22]. This occurs in the superficial lymphatics and is a major risk factor for lymph scrotum. Chronic manifestations in the scrotum include a 'puffy' or spongy scrotum, or sometimes an extraordinarily thickened, fibrotic skin and subcutaneous tissue. In these patients, the testis, epididymis, and cord may remain largely intact.

Morbidity does not necessarily correlate with immunological markers for disease. In a study of 121 patients with hydroceles in an endemic area of Haiti, Addiss *et al.* [21] found that only 39% were positive for microfilaria. The circulating filarial antigen (from the adult worm) was identified in 43% of microfilaria-negative men with hydrocele. The hydrocele volume was inversely proportional to blood filarial density. The most important finding of the study was that men with clinical hydroceles show heterogeneity in the immunological expression of filarial burden. Also men with a history of LF may develop hydroceles and lymphangiectasia even after all immunological markers for active infection have resolved spontaneously or as a result of medical treatment. Thus even after eliminating the infection, the clinical disease may persist and progress.

Until 1994, there was no noninvasive way to confirm the presence of living adult worms in the scrotal lymphatics, but recently ultrasonography has been found to reliably identify worms. Ultrasonography has emerged as the primary diagnostic test to confirm the presence of living adult worms in the lymphatics of the spermatic cord in adult men, and in the lymph nodes of children [8,13,23]. Living adult worms are found in nests, including several worms with one female and several males in ectatic lymphatics (G. Dreyer, personal communication). They are identified by their movement within the lymphatics, known as the 'filarial dance sign'. Adult worms are detected by the filarial dance sign in up to 80% of infected men [8]. Aspiration of lymphatic fluid from the nests may be positive for filarial antigen even when the blood is negative (G. Dreyer, personal communication).

Principles of surgical care

Personal hygiene is critical to the care of patients with clinical manifestations of lymphatic filariasis, whether it be elephantiasis of an extremity or of the genitalia. As the most serious morbidity relates to bacterial and fungal infections, secondary infections, regular bathing, antibiotics when necessary and local care are critical to the outcome of any medical treatment. Experience has shown that in this disease, which is most commonly seen in humid tropical and subtropical countries in regions with poor public sanitation, personal hygiene is the cornerstone of effective management (J. Noroes and G. Dreyer, personal communications) [2,8].

Hydrocele

Current Western textbooks give minimal attention to the prevalence and morbidity associated with filarial-related hydroceles. On physical examination, a hydrocele associated with scrotal lymphangiectasia or nodules of the cord in a patient in an endemic area is highly suggestive. Strictly speaking, the hydrocele contains a clear or yellowish fluid with no leukocytes, in contradistinction to a chylocele, which contains milky chylous fluid. On aspiration, this fluid will not usually contain microfilariae unless contaminated by blood during the procedure [8]. Although some have recommended partial excision of the sac by 'bottle neck' inversion of the tunica vaginalis or the Lord-type plication, current thinking based on experience at the filarial disease centre in Recife, Brazil, is that complete excision with meticulous attention to cauterization of the edges, and oversuturing

of the edges, offers the best cosmetic and functional result with less risk of the later complication of lymph scrotum (J. Noroes, personal communication). The orientation of the scrotal incision also appears to be important. Whereas many urologists in temperate climates may use a transverse incision in the scrotal folds for better cosmetic effect, in this disease it is important to make a vertical incision to preserve the already damaged superficial lymphatics of the skin and subcutaneous tissues, to prevent secondary obstruction from scarring of the incision. It is highly discouraging to a patient or a surgeon if, once the hydrocele is repaired, the patient later develops a devastating lymph scrotum. Before surgery for a presumed hydrocele, it is necessary to ensure that all superficial skin inflammation, bacterial and fungal infection has resolved, and that the scrotum is aspirated to document whether a hydrocele or a chylocele will be encountered. As a treatment modality, aspiration and drainage is not often effective, and recurrence is expected.

Chylocele

Chylocele is most often associated with long-standing disease characterized by acute and chronic inflammation, thought to be secondary to the original lymphatic pathology. The lymphatics draining the tunica vaginalis are damaged and chylous fluid leaks into the sac. Aspiration of a chylocele most often reveals leukocytes characteristic of acute and chronic inflammation. Frequently, the testis and epididymis are severely inflamed and necrotic. For patients with chylocele, orchidectomy and removal of the cord is occasionally necessary, although, as in Fournier's gangrene, the superficial tissues may be affected with the testis and cord remaining intact. Surgery for chylocele, especially when carried out by an inexperienced surgeon, is a major risk factor for the disfiguring and functionally devastating lymph scrotum. Freedom from infection at the time of surgery is critical to effective management (J. Noroes, personal communication).

Lymph scrotum and penile dermatolymphangiopathy

Lymph scrotum is perhaps the most crippling complication of lymphatic filariasis in men; it is almost always apparent in patients who have a history of many acute attacks because of bacterial and/or fungal superinfection and who have chronic lymphangiectasia [8,22]. The condition may be seen after surgery for chylocele or hydrocele, and represents the dermatological manifestation of pathological lymphatic drainage. Patients experience continuous dripping of milky lymphatic fluid from 'blisters' on the surface of the scrotal skin. Some patients wear cloth coverings with plastic backing to blot the fluid. Others fashion cups and other contrivances to catch it. In these patients the skin of the penis is often also involved in the process, including the entire shaft but limited by the corona of the glans. The principles of effective surgery for lymph scrotum and lymphangiectasia of the penis include complete scrotectomy and removal of the shaft skin and subcutaneous tissue. The scrotum may be covered by a mesh skin graft and the penile shaft with a full-thickness skin graft after the patient has received effective antibiotic treatment and has stabilized the inflammatory process.

Chyluria and haematuria

Chyluria in patients with LF is often intermittent and related to diet and other factors; it is caused by rupture of the small lymphatics of the collecting system, and is possibly related to secondary infection. Haematuria often accompanies chyluria, but must be evaluated separately to exclude other common pathology associated with haematuria in adults. Chyluria frequently responds to a high-protein and low-fat diet. Haematuria and proteinuria are seen in up to 40% of microfilaraemic men [8,16] but not in infected men with no microfilaraemia. Gross and microscopic haematuria from LF responds to medical treatment with DEC within 2 weeks of treatment.

Medical treatment

The core strategy for the global elimination of filariasis is the interruption of transmission of the disease. Successful programmes to disrupt transmission depend on reducing the burden of microfilariae in hosts. Reducing the microfilariae also reduces the rate of morbidity such as haematuria. Some medications also kill the adult form of the parasite or render the females less fertile. The early treatment of patients with LF might also reduce the later sequelae of infection, including the genital pathologies. Pre-treatment education and active participation of the community is critical for the success of these community-wide medication programmes. DEC given as a single 6 mg/kg dose once per year is currently the drug of choice for WHO-coordinated treatment programmes; it effectively kills microfilariae and at least some adult worms, as detected by the 'filarial dance sign'. The findings corroborate with other studies in that 45% of men treated with DEC develop scrotal nodules secondary to the death of adult worms [16,24]. The microfilariae burden is reduced to $\approx$ 60% after a single dose. DEC does not appear to have any effect on established hydroceles. DEC is contraindicated in sites (Africa) where co-infection with onchocirciasis or river blindness is a possibility.

Ivermectin, a macrolide antibiotic, is highly effective against microfilariae and is the drug of choice for sites where DEC cannot be used; it may also play a role in communities that will not accept the possibility of 'acute attacks' secondary to DEC and that thus limit the use of the latter. For the WHO Programme, ivermectin is donated by Merck & Co, Inc. as an extension of its commitment to the treatment of onchocerciasis.

Albendazole: co-administration of albendazole with either ivermectin or DEC seems to confer a longer duration of suppression of microfilaremia than can be achieved with either drug alone. The current WHO recommendation is for annual co-administration of albendazole with either DEC or ivermectin, depending on local conditions. Glaxo SmithKline has embarked on a remarkable collaboration as a private partner of the Global Alliance to provide sufficient albendazole to treat all patients until the disease is eliminated.

Conclusion: the urologist's role

The ambitious programme devised by the WHO for eliminating LF worldwide depends on an educated medical community and an educated public. In endemic areas, partners in the Global Alliance are initiating local village and urban programmes for education, e.g. 'Hope Clubs'. Patients learn not just from healthcare providers, but also from each other.

Surgeons both from temperate climates and tropical regions must become educated about the pathophysiology of the disease so that they can care for their patients and prevent harm from foreseeable complications of surgery. Patients with LF must be considered to have a life-long disease requiring management even after all evidence of active infection has resolved. Therefore, there is no 'simple hydrocele' in a patient living in an endemic region. Before consideration for surgery, the patient should be evaluated for LF by antigen and smear testing, and for adult worms by ultrasonography. Meticulous attention to local skin care and preventing superinfection is essential, and should be considered with stringent counselling and follow-up for all patients. This is even more important for patients with chylocele or lymph scrotum. Protocols for skin care, antibiotic prophylaxis and management are currently being developed. With an educated community of health professionals and patients, lymphatic filariasis may indeed be eliminated by the year 2020.

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Abbreviations: **LF**, lymphatic filariasis; **DEC**, diethylcarbamazine.