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Pathogenesis of Lymphatic Disease in Bancroftian Filariasis:
A Clinical Perspective

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The pathogenesis of lymphatic filariasis has been a matter of debate for many decades. Here, Gerusa Dreyer and colleagues propose a dynamic model of bancroftian filariasis, integrating clinical, parasitological, surgical, therapeutic, ultrasonographic and histopathological data. This model has profound implications for filariasis control programs and the management of the individual patient.

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Lymphatic filariasis (LF) caused by *Wuchereria bancrofti* and *Brugia malayi* occurs in individuals of all ages and both sexes, but prevails in those of low socioeconomic level. Early studies recognized lymphangiectasia as a fundamental alteration in the natural history of LF, but had attributed its cause to the downstream obstruction of lymphatic vessels by the adult worms. Furthermore, interstitial fibrosis triggered by diffusible substances released by live or dead worms was thought to have an immunological basis. Traditionally, the natural history of LF has been considered as a wide spectrum of clinical and evolutionary forms in a pre-established sequence – from uninfected individuals at one extreme, through disease-free microfilaria (Mf) carriers, to patients with chronic pathology.

Multidisciplinary studies in bancroftian filariasis

From a multidisciplinary perspective, several problems have hampered studies on the pathogenesis of filarial disease. First, it is difficult to determine whether a given individual is (or was) actively infected, because all existing diagnostic techniques are to some extent

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unsatisfactory[1–4]. Second, it is difficult to establish with absolute certainty the filarial etiology of a given clinical manifestation in an infected individual, because virtually all signs and symptoms of 'filariasis' can also be caused by other conditions. Third, it is possible that more than one pathogenic pathway leads to the same clinical endpoint in different infected individuals. Population surveys provide little insight into the evolution of infection and disease in a given individual. The natural course of filarial infections in native residents cannot be extrapolated from observations in short-term visitors to endemic areas because these populations react differently to the parasite. Fourth, progress has been slowed by uncritical acceptance of hypotheses regarding the pathogenesis of LF. The traditional classification of filarial disease into 'acute inflammatory' and 'chronic obstructive' syndromes has fostered the belief that all acute (or all chronic) manifestations of bancroftian filariasis have the same pathogenesis. Evidence below indicates that this is not true, but only the most recent mathematical model incorporates this fact as a variable[5].

Recent studies, substantiated by clinical examination, ultrasonography, therapeutic trials, surgery and histopathology, have lent support to an alternative model of the natural history of the disease based on lymphangiectasia caused by non-obstructive mechanisms. In these studies, we have attempted to minimize uncertainty in parasitological diagnosis by relying on ultrasonography to detect and locate subclinical lesions that were subsequently biopsied, and to confirm preoperatively the viability of the adult worms present[3]. This has allowed the study of early phase of lymphatic pathology in bancroftian filariasis, and the evolution of lesions following the death of adult worms. We have also used ultrasonography prospectively to monitor and quantify the progression of subclinical lymphangiectasia in a cohort of asymptomatic carriers of adult worms that were not killed by treatment with ivermectin[6] or diethylcarbazine (DEC)[7]. The model of LF we propose is based primarily on our own multidisciplinary studies, but also incorporates several concepts previously formulated by clinical investigators. The focus is on lymphatic pathology and disease caused by adult worms; the pathogenesis of extralymphatic filarial disease manifestations is reviewed elsewhere[8].

Subclinical lymphangiectasia. Lymphangiectasia is present in virtually all adult worm carriers we have examined to date[1,3,4,6,7,9–11]. The adult worm is the only stage of the parasite (ie. no infective larvae or L4 stages) that is consistently present in lymphatic biopsies from patients with lymphangiectasia. Conversely, lymphangiectasia without inflammatory cell infiltration is the only consistent abnormality in biopsies that contain living adult worms with or without free Mf in the vessel lumen[3,12–14]. Lymphatic dilatation with no or a very scant cellular infiltrate is the hallmark of filarial disease in nude or severe combined immunodeficiency (SCID) mice infected with *Brugia* species. The condition can be reversed in nude mice by removing or killing the adult worms[15]. Thus, viable adult worms are capable of causing lymphangiectasia in animals via mechanisms that do not involve lymphatic obstruction and that are independent of specific host antiparasite immune responses.

Acute filarial lymphangitis (AFL). Death of the adult worms, whether or not as a result of DEC treatment, ends the non-inflammatory phase of lymphatic dilatation. In many persons, this event merely results in the subclinical formation of granulomatous nodules that are detected incidentally during physical examination. In other patients, the death of adult worms is represented as an episode of AFL. Biopsies confirm that the cessation of adult worm movement detected by ultrasonography and the formation of lymphatic nodules in the scrotal area after DEC treatment reflect damage to the parasite[7,16]. Thus, lymphangiectasia and inflammatory reactions are two independent components of lymphatic pathology that are triggered by 'toxins' of living adult worms and by host reactions to damaged or dead worms, respectively.

Syndromes of lymphatic dysfunction: hydrocele and lymphedema. No available evidence contradicts the notion that filarial worms *per se* cause hydroceles. Sequential ultrasonographic observations indicate that some patients who harbor living adult worms in intrascrotal lymphatics, which are not sensitive to several courses of DEC, develop chronic hydroceles. However, most of our clinic patients have developed acute hydroceles shortly after the 'spontaneous' or DEC-triggered death of adult worms[7]. In most of these cases, the hydrocele disappears within 30 days, whereas some will become chronic. The acute hydrocele, as well as the acute lymphedema following an AFL episode, probably result from the temporary clogging of lymphatics by the inflammatory reaction to disintegrating worms[17]. Unless the obstruction is extensive and collateralization is scant, the initial impediment to the flow of interstitial fluid is offset. Thus, an uncomplicated AFL episode, as is common in endemic areas, rarely causes chronic lymphedema[17].

Chyluria, chyloceles and lymph scrotum. Rupture of a dilated lymphatic causes extravasated lymph to accumulate in the affected body site (such as chyloceles), or to drain via a fistula with a pre-existing channel, such as the urinary tract (chyluria). In endemic areas, these syndromes are strongly associated with bancroftian filarial infection. Superficial scrotal lymphangiomatosis, not a rare condition and known as lymph scrotum in filariasis-endemic areas, is unique among the clinical manifestations of chronic LF; its pathogenesis remains unknown. Acton and Rao[18], from India, were the first to associate this syndrome with previous surgery for the treatment of hydroceles. In our region, however, almost a third of the patients have no history of scrotal surgery. This condition can progress to lymphedema and elephantiasis of the scrotal wall when bacterial infections occur (Box 1).

Cofactors predisposing to chronic filarial disease

Permissive and non-permissive factors. Factors that permit filarial worms to survive or cause them to die play a pivotal role in the pathogenesis of bancroftian filariasis. No direct evidence exists that the immune system kills adult *W. bancrofti in vivo* in long-term residents of endemic areas. However, irrespective of whether it caused or was caused by the death of adult worms, the inflammatory host response seen in biopsies of AFL sites is a risk factor for the development of some types of chronic LF syndromes, such as hydrocele, chylocele and chyluria. The demise of the worms is

Box 1. Bancroftian Filariasis: Pathogenesis of Lymphatic Disease in the Adult Population

In permissive hosts, lymphangiectasia is present in all individuals who harbor living adult worms. It can remain subclinical for undetermined periods of time, or evolve into chronic disease (Fig. I, below). Hydrocele, chyluria, chylocele and, possibly, lymph scrotum, will develop depending on cofactors such as adult worm burden, degree and extent of lymphangiectasia, location of adult worm nests (for instance, in the spermatic cord or the infratesticular area), and the chronology of sequential adult worm death. The death of adult worms can cause episodes of acute filarial lymphangitis (AFL) or may result in no clinical complaints by the patient (subclinical). However, lymphangiectasia in the skin (upper and lower limbs, breast, scrotum and penis) further impairs lymphatic function and predisposes to secondary bacterial infections. Recurrent bacterial infections are an essential cofactor in the development of lymphedema and its progression to elephantiasis. Recurrent bacterial infections promote the progression of lymph scrotum to scrotal lymphedema and elephantiasis.

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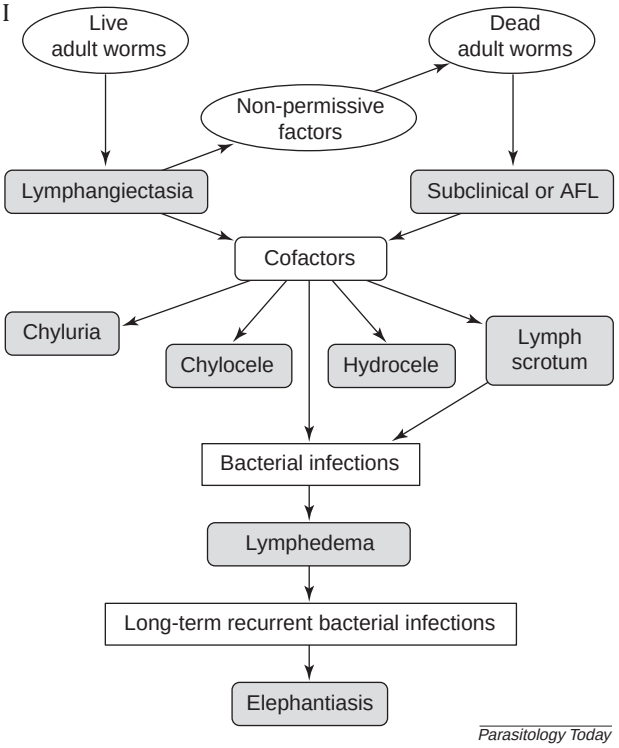

likely to result from a localized rather than a systemic process. Indeed, treatment with DEC often triggers a new AFL episode, either at the same site of a previous spontaneous AFL attack or at a different body site[17]. These clinical observations indicate that adult worms can remain viable for many months after other worms located at the same or a different site have died. This hypothesis has been repeatedly confirmed by serial ultrasonography and histopathology[7,16,19]. These findings suggest that the host response is a reaction to, and not the cause of, the death of adult worms.

Heavy infection. The notion that infection with large numbers of worms *per se* can cause LF was proposed by Manson in 1898. It is easy to imagine that the greater the parasite population, the greater the lymphatic damage produced by living or dying adult worms at different intervals of time. So far, the relative weight of this factor has not been assessed accurately, owing to the lack of suitable tools to determine adult worm burden. However, our findings suggest that pre-existing lymphangiectasia and collateral lymphatic channels can compensate for the acute loss of function that follows the death of adult worms, and that recanalization can restore at least some flow in occluded parasitized vessels. This was also observed in animal models[20]. Thus, the death of adult filariae, as an isolated fact, is not ordinarily likely to cause chronic clinical disease in the absence of other factors; otherwise, it would be difficult to explain why subclinical lymphatic damage is so common, whereas chronic lymphatic disease is comparatively rare, and why the simultaneous death of many adult worms after DEC treatment seldom leads to chronic disease in endemic populations. Adult worm burden could be considered a very important cofactor in the pathogenesis of hydrocele because its prevalence in endemic populations correlates with intensity of infection; Mf and antigenemia rates are consistently higher in patients with hydroceles[21]. On the contrary, comparable groups of people with chronic lymphedema do not show this parasitological pattern[22].

Host responses. It is likely that host immune and inflammatory reactions contribute to the development of filarial disease, but the predicted causal relationship between changes in antifilarial immune responses and clinical status of infected individuals has yet to be documented in untreated persons. Our observations strongly indicate that systemic immune responses in LF, which form the basis of current pathogenesis models, do not adequately represent immune effector mechanisms that are active locally or compartmentalized in infected lymphatic tissues. Indeed, the same pattern and extent of subclinical lymphangiectasia is present in two different groups of patients who consistently show contrasting systemic immune reactions to filarial antigens: a subset of infected persons without Mf and virtually all microfilaremic individuals. Those without Mf characteristically have strong T helper cell type 1 (Th1)-like antiparasite immune responses, while microfilaremic individuals typically mount vigorous Th-2-like responses to filarial antigens[23]. Both groups exhibit the same clinical and ultrasonographic features: the presence of living adult worms in dilated lymphatics and absence of inflammation[1,3].

Bacterial infections. Aggravation of pre-existing filarial pathology by bacterial infections is well documented in animal models[24], and it is almost certain that lymphatic dysfunction caused by filarial worms predisposes to secondary infections in humans[25,26]. High protein lymphedema of any cause triggers an inflammatory reaction that can lead to progressive sclerosis of the skin and pachyderma elephantiasis in residents of non-endemic areas[27], but recurrent secondary infections are certainly the most common cofactor in the development of lymphedema and elephantiasis of the extremities in patients living in LF-endemic areas[17,26].

Other cofactors. In some parts of Africa, silicate toxicity is a major cause of non-filarial elephantiasis[28]; it might be a risk cofactor for filarial lymphedema wherever people walk barefoot on sandy soils. Also, it has long been suspected that differences in the

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Fig. 1. Clinical presentation of bancroftian filariasis in adult populations living in filariasis-endemic areas are shown here. Lymphangiectasia: dilation of lymphatic vessels (*); in this context, it is not caused by obstruction but by 'toxins' released by living filarial adult worms (arrows). No inflammatory reaction is found in the lymphatic vessel wall(**). Hematocyclin and eosin stained; (a). Chylocele: collection of white lymph fluid (rich in fat) in the cavity of the Tunica vaginalis testis caused by a ruptured dilated lymphatic vessel (b). Hydrocele: collection of serous fluid in the cavity of the Tunica vaginalis testis caused by lymphatic dysfunction (c). Acute skin bacterial episode: a reticular lymphangitis(*) caused by bacterial infection, currently named acute dermatolymphangioadenitis (ADLA) (d). Acute filarial lumphangitis (AFL) (arrows): caused by the death of adult worms (e). Chyluria: milky fluid caused by the presence of white lymph fluid (rich in fat) resulting from a ruptured dilated lymphatic vessel in the excretory urinary tract (f). Lymph scrotum (superficial lymphangiomatosis of the scrotal skin): superficial dilated lymphatic vessels of the scrotal skin with intermittent discharge of white or straw-coloured lymph fluid (g). Lymphedema: swelling of the skin, as a result of accumulation of interstitial fluid after recurrent bacterial infections, predisposed in its turn by lymphatic dysfunction (h,i). Elephantiasis: disfiguring clinical presentation of lymphedema with hypertrophy and fibrosis of the skin and subcutaneous tissues as a result of long-term lymphedema after recurrent skin bacterial episodes (j,k).

pathogenicity or virulence of filarial subspecies contribute to the variable clinical outcome of infection with these parasites. This possibility is suggested by animal models and by findings in brugian filariasis[29], but it has not been formally evaluated in bancroftian filariasis.

Natural evolution of lymphatic filarial disease: a dynamic model

The dynamic model of lymphatic filarial disease proposed (Box 1) has three basic tenets: (1) lymphangiectasia constitutes a major risk factor for the development of chronic lymphatic disease because it can cause lymphatic dysfunction; (2) clinical syndromes of chronic lymphatic disease (Fig. 1) do not ordinarily develop in bancroftian filariasis unless at least one other cofactor superimposes the filaria-induced lymphangiectasia, and thereby overwhelms the compensatory capabilities of the lymphatic system; and (3) distinction between the pathogenesis of chronic hydroceles and chronic lymphedema: worms alone are sufficient to induce hydroceles, but chronic lymphedema develops only when the lymphatic system is damaged by two factors acting in concert: filarial worms and secondary bacterial infections.

The broad outline of the model is based on sound clinical research data, but many more years of follow-up studies will be needed to document completely the natural course of infection and disease in bancroftian filariasis.

Morbidity control in bancroftian filariasis

The current emphasis of worldwide filariasis transmission control programs is on mass treatment with combinations of DEC, ivermectin and albendazole[30]. Although these drugs may protect future generations from the ravages of LF, they are not adequate for morbidity control in those who are currently at risk of developing a wide range of clinical disease, irrespective of past or current infection. Bacterial infections are an essential cofactor in the development of filarial lymphedema and its progression to elephantiasis. Thus, optimal disease prevention at the community level will require the development of simple, reliable and effective strategies to control secondary infections. Morbidity control programs will also need to include hydrocele repair to prevent or reduce an important silent burden of sexual disability associated with bancroftian filariasis[31].

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