GLOBAL COLLABORATION IS CRUCIAL FOR LYMPHOLOGY AND FILARIOLOGY

David Addiss

'New trial with antibiotics brings hope to elephantiasis sufferers' declared a recent press release from a prominent university in the UK. Researchers reported that lymphoedema stage (but not limb circumference or the incidence of acute inflammatory episodes) had been significantly reduced in eight patients from a filariasis-endemic area of Ghana one year after a six-week course of the antibiotic doxycycline (Debrah et al, 2006). The substantial publicity that surrounded this announcement (BBC, 2006), described as a 'breakthrough' by one of the investigators, reflects how deeply people with lymphoedema and their carers yearn for a definitive 'cure.'

Lymphatic filariasis has long been a source of great interest to lymphologists, lymphoedema therapists, and researchers. Transmitted by mosquitoes, the filarial parasites *Wuchereria bancrofti* and *Brugia malayi* develop into adult worms and reside in the lumen of human lymphatic vessels, resulting in lymphangiectasia and lymphatic dysfunction (Dreyer et al, 2000). The dramatic cases of advanced elephantiasis and the sheer magnitude of the problem — an estimated 15 million people in more than 80 countries (Michael et al, 1996) — serve to sustain this interest. However, despite joint research conferences that have underscored the potential for collaboration (Anon, 1985), the fields of lymphology and filariology remain isolated from each other in practice. Sadly, this insularity contributes to a lack of knowledge about lymphoedema and its treatment worldwide.

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For decades, filariasis research focused on immunologic responses to filarial antigens, which differed among people with and without filariasis-associated disease (Ottesen, 1992). Researchers hypothesised that, in filariasis-endemic areas, lymphoedema was immune-mediated and once oedema appeared, little could be done to arrest its progression (Hawking, 1965). Clinical studies during the early 1990s questioned these assumptions and highlighted the important role of bacteria in acute inflammatory episodes known as dermatolymph-angioadenitis (ADLA) (Olszewski et al, 1997;1999; Suma et al, 1997; Dreyer et al, 1999). They also demonstrated a strong association between ADLA and lymphoedema stage (Pani, 1995; Shenoy et al, 1995, 1999; Dreyer et al, 1999). This work suggested that simple interventions based on hygiene and skin care might prevent these acute episodes and halt the progression of disease (Suma et al, 2002).

Enhanced collaboration between lymphologists and filariasis researchers and between lymphoedema therapists and filariasis programme managers is essential if we are to maximise the return on our limited investment into lymphoedema research and provide real hope to the millions of people who suffer from this disease.

Despite advances in diagnostic tools for infection with *W. bancrofti* and *B. malayi*, no clinical or laboratory test has been developed that can distinguish so-called 'filarial' from 'non-filarial' lymphoedema. Therefore, the concept of 'filarial lymphoedema,' although a convenient epidemiologic shorthand for lymphoedema in filariasis-endemic areas, is of little use at the individual level. The absence of such a diagnostic marker and the recent shift from an immunologic to a clinical model of pathogenesis have helped bring the filariologist's approach to lymphoedema into closer alignment with that of the lymphologist.

Even with this conceptual convergence, standards of lymphoedema care differ dramatically between filariasis-endemic areas of the tropics and the more affluent north. Professionally-fitted compression bandages and garments, which are expensive, form the mainstay of individual lymphoedema therapy in Europe, USA and Australia. In contrast, for filariasis-endemic areas, the World Health Organization recommends a public health approach based on self-care at home (WHO, 2006). This approach relies primarily on hygiene and skin care to reduce the frequency of ADLA, combined with elevation, movement and exercise to mobilise interstitial fluid (Dreyer et al, 2002; Shenoy, 2002; Vagas and Ryan, 2003). Compression garments are not generally recommended because they are too expensive, difficult to keep clean, and uncomfortable in hot humid weather.

Despite differences in standards and approaches to care, a strong case can be made for expanding the fledgling collaboration between clinicians, lymphologists and lymphoedema therapists in the north (i.e. non-filariasis-endemic areas) and clinicians and public health officials in the south (filariasis-endemic areas). First, it is increasingly

clear that the underlying physiology, pathogenesis, and factors involved in progression of lymphoedema are similar, irrespective of aetiology (Dreyer et al, 2000; Vagas and Ryan, 2003). Thus, basic research is likely to have relevance for both endemic and non-endemic areas.

Second, although compression therapy is emphasised more in the north, many of the core features of lymphoedema care are the same in both areas: protecting the barrier function of the skin to avoid ADLA; prompt administration of antibiotics when ADLA is suspected; and mobilising interstitial fluid through movement and exercise. Advances in the application of these core components of care could have global significance.

Third, an increasing number of studies indicate that the experience of lymphoedema — in particular, the adverse psychological and social effects, and issues of stigma and disfigurement — are remarkably similar, regardless of economic and geographic differences (Coreil et al, 1998; Suma et al, 2003; Kumari et al, 2005; Morgan et al, 2005; Richard et al, 2007). Thus, allowing for cultural differences, similar interventions may be used to address these issues. For example, patient support groups, which have proved critically important in the north, have also been adopted in filariasis-endemic areas with major success (Coreil et al, 2002).

Profound neglect is another feature that is shared by people with lymphoedema worldwide. Although lymphoedema management is considered an important part of the *Global Programme to Eliminate Lymphatic Filariasis* (WHO, 2006), few if any filariasis-endemic countries provide comprehensive access to even basic lymphoedema care. Sadly, this is also true for many countries in the north, where, with a population prevalence of 1.3 per 1,000, lymphoedema remains a significant public health problem (Moffatt et al, 2003). Despite this, major public health agencies such as the US Center for Disease Control, allocate no resources for lymphoedema research, treatment, or prevention.

Given these similarities, there are clear opportunities for a productive global collaboration. First, the public health perspective and the practical approaches that are needed in filariasis-endemic countries can also benefit patients in the north. Studies in filariasis-endemic areas to identify and evaluate simple, low-cost interventions (e.g. locally available topical agents for interdigital lesions) are highly relevant for the north, where insurance coverage or access to treatment for lymphoedema is often limited. In addition, the filarial worms themselves may yield clues to understanding the molecular signals responsible for endothelial regulation and lymphangiectasia. Research to explore the complex relationship between filarial worms and human lymphatic endothelial cells is now under way.

It is time for investigators worldwide to adopt standardised terminology, case definitions, diagnostic criteria and outcome measures to enhance the comparability and global relevance of their research into lymphoedema. Such standardisation would greatly facilitate our capacity to interpret the significance of research findings...

Filariasis-endemic countries could also benefit from increased collaboration with the north. WHO recognises the need to train healthcare workers to properly manage severe lymphoedema and ADLA, but such training has often been overlooked in the push to establish basic services at the community level. If coordinated with a strategy to eliminate filariasis, experienced lymphoedema therapists and physicians from the north could provide training and assistance in equipping national-level lymphoedema reference centres.

Finally, in both settings, much remains unknown about the pathogenesis, optimal treatment, and prevention of lymphatic disease. There is little consensus even on the classification and staging of lymphoedema (Ryan, 2004). Several important issues remain unresolved in all geographic areas, such as the aetiology of ADLA (Bonnetblanc and Bedane, 2003), the effectiveness of antibiotic treatment (Badger et al, 2004), and the microbial contributions to interdigital skin lesions (Aste et al, 2001; McPherson et al, 2006). It is time for investigators worldwide to adopt standardised terminology, case definitions, diagnostic criteria and outcome measures to enhance the comparability and global relevance of their research into lymphoedema. Such standardisation would greatly facilitate our capacity to interpret the significance of research findings, such as those reported at the beginning of this editorial. Enhanced collaboration between lymphologists and filariasis researchers and between lymphoedema therapists and filariasis programme managers is essential if we are to maximise the return on our limited investment into lymphoedema research and provide real hope to the millions of people who suffer from this disease. JL

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