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COMMENTARY

LYMPHATIC FILARIASIS AND THE INTERNATIONAL SOCIETY OF LYMPHOLOGY

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The International Society of Lymphology (ISL) has long recognized that Lymphatic Filariasis (LF) is the numerically most important cause of lymphedema. Some of the leaders of the ISL have studied how the lymphedema is induced, and several have involved affected patients in their studies of the management of lymphedema with surgery, physical methods, or with coumarins. By contrast, the ISL has not focused on breaking the transmission to the mosquito and all the issues relating to population surveys, vector control and the mass distribution of drugs.

A global Alliance for the Elimination of Lymphatic Filariasis has come into being stimulated by the gifts of the drugs albendazole and ivermectin by, respectively, GlaxoSmithKline and Merck & Co., Inc. The World Health Organization (WHO) procured 58 million diethylcarbamazine tablets, and The Bill and Melinda Gates Foundation has been a significant player.

This Alliance has stated that its first objective is to break transmission. Its second is morbidity control. The first is an overwhelmingly ambitious project. It is very expensive, requires the survey of populations and the supervision of the delivery to and the taking by those populations of two out of three of these drugs once yearly for five years. The Annual Report on Lymphatic Filariasis 2002 from WHO describes the huge achievement of the ingestion of drugs by 60 million persons. This is not strictly lymphology, and it is not surprising that the ISL has given little publicity to this massive program.

I have attended some of the Alliance's meetings by invitation because for several years I have championed taking Dermatology into general health services expecting it to be helpful in the management of diseases such as leprosy and lymphatic filariasis. In spite of the fact there is much there of common interest, I am surprised by how little overlap there is between the "membership" of the two organizations. Few leaders of either organization can be met at the other's meetings. On the other hand, I recognize there are interests which do not overlap and in my case how to fund a vector control program, or the implications of the genome and molecular makeup of parasites, are not a high priority.

At the end of 2003, I attended a "Lymphatic Filariasis Research Forum" in Philadelphia and the following is a personal interpretation of what went on focusing on areas that are clearly of interest to the ISL as well as to myself.

A striking point is that the LF community is not familiar with basic lymphology and is at risk of reinventing the wheel using precious funds to do so. The lymphology literature also suggests that LF is not well understood by most lymphologists as having its own

specific pathogenic factors differing from other causes of lymphedema. Definitions and standardization of terminology are needed and as these are the subject of endless and ongoing debate at ISL meetings, it is a waste of LF energy to separately create their own.

This Alliance for the Elimination of Lymphatic Filariasis is the greatest patient-focused happening in our field. All the other great advances in our understanding of the lymphatic system cannot claim to have eliminated the cause of lymphedema in so many millions. As a dermatologist examining the taking of skin care into the developing world, I believe one of the best things to have come out of the observations of the last two decades is the role of skin care to which both our Society and The Alliance have contributed.

FILARIASIS RESEARCH SUMMIT (DEC 7th – 10th 2003) PHILADELPHIA

This intensive discussion about all aspects of lymphatic filariasis was a wonderful and informative update.

The meeting started on Sunday, December 7th, with a symposium on Filarial Genomics, which was an eye opener to anyone normally on the fringe of such! The advances are staggering, but the costs versus the practical value of it all when so much more immediately practical expenditures are needed was bemusing. It was difficult to keep in view that "no worm leads to no LF" and for this to be achieved without harm or for the general good requires that fully understanding the worm is a priority for funding. Lymphologists should be aware that parasite infection of domestic animals drives the economics underlying much of this rather than human disease. I was eventually convinced that it was critical knowledge to have if only to develop the diagnostic tools we lack for tracing the whole story of the life of the parasite in LF in both populations and in individuals. Genomics, bioinformatics, applications of transfection methods in helminths, microarrays and gene expression analysis in *Brugia malayi,* RNA interference pathways in parasitic nematodes all pointed to ways to still further knowledge, more costs, and uncertain application.

Monday, December 8th, began with an appeal for yet more funding. From 1975-1996 there were1,213 new drugs but only 11 were for tropical diseases. Drug resistance in nematodes and filarial worms is a serious threat, and identification and validation of new anti-nematode drugs is urgently needed. It was emphasized that least was known about DEC for which there were non-responders and possible resistance has been described in Sri Lanka. For maximum effectiveness, DEC needs a functioning immune system. Albendazole (which inhibits microtubule formation) and ivermectin (acting on chloride channels) are widely inducing resistance through genetic mutations in animal nematodes, especially in small rodents. Genomics is clearly helpful in identifying new approaches to efficacy, less resistance and less toxicity. Paucity of microfilaria in the laboratory is a barrier to progress much in need of a "MF bank."

Much attention was given to the rickettsial bacteria *Wolbachia,* which lives in the filaria and is the basis for embryogenesis of the filaria and its role in pathogenesis. Death of the worm from DEC releases *Wolbachia* and thus may contribute to inflammation and dilatation of the lymphatics. TNF and various interleukins and their receptors are involved and exactly how it plays its roles depends on various possible cofactors. Doxycycline is prescribed (but not in children) to knock out the worm but some recover and *Wolbachia* resistance may be an explanation.

The high level of resistance and lack of new drugs was not good news. There is ignorance about optimum prescribing of currently available drugs such as frequency, coverage, or for how long. All this pointed to the importance of focusing on "cofactors"and alternative approaches to LF elimination. There was awareness of the long term effects of an elimination program on population

immunity and the development of a vaccine of uncertain effect and complicated by cofactors such as a high prevalence of HIV. Cofactors discussed throughout the 4 days included: other diseases — malaria, HIV, other helminths or *Loa loa*; nutrition — too little or too much; as well as innate and adaptive immunity. At risk soil types causing severe lymphedema (podioconiosis) also needs re-examining.

On December 9th, Eric Ottesen began with a reminder that the program for the elimination of LF was bigger and more expensive than expected in a climate of great competition for funds and that the group needed to come forward with innovative, prioritized, and attractive (to donors) proposals for research.

We were divided into working groups with the following headings: chemotherapy, infection and drug trials, disease and drug trials, pathogenesis, diagnostics, epidemiology and parasite biology, programmatics, protective immunity, vector biology and control. There was an opportunity to hear overviews and proposals for each of these.

I spent an interesting 4-5 hrs in the pathogenesis group and an even more enjoyable time in a 4-6 hr session with the disease control group including David Addiss, Gerusa Dreyer, Joaquim Noroes, Charles Mackenzie, Krishna Shenoy.

Some general points I picked up:

Epidemiologists and program managers are inhibited by the fact there is no test to identify the endemic normal or the completely recovered and disease negative; that is a person who is certainly microfilaria /worm/ antigen/antibody negative in all age groups

In addition to the fact that albendazole and ivermectin do not kill the worm, DEC does not kill all the worms with certainty.

Previous infection and consequent immunity affects population responses. Migrating peoples moving into endemic areas may respond differently. Host immunity has to explain how infection and antibody responses correlate poorly with disease. Some populations and some individuals, although microfilaemic, do not get the disease. Reinfection or relapse is difficult to identify.

Advocacy so that communities take the eliminating drugs does depend on having a concurrent program for morbidity control. It may benefit from integration with other programs such as Dermatology, Leprosy, HIV/AIDS.

The viability of the worm is central to the understanding of this disease. Is it even necessary to kill it? Ultrasound is currently the best tool to measure it, and improved equipment for the field would be of great value.

Drug interaction such as albendazole with HAART needs an early warning system.

Unless we learn how to deal with *Loa loa*, the long term aim of complete elimination will be difficult.

ADIPOSE TISSUE

I have traveled to a number of countries advocating morbidity control. It was in Guyana that I finally concluded that obesity inhibits effective management not just in individuals but in populations. The knowledge that obesity is a rising epidemic draws attention to its role as a cofactor in LF. There are clinical facts that an obese person with lymphedema suffers from greater immobility, rarely takes a deep breath, cannot elevate, and has a body posture that aggravates lymph drainage. In obesity, the tissues are less responsive to massage and to compression, there is considerable additional venous loading, and the skin's barrier function is more easily breached.

Attention must be drawn to the studies of Caroline Pond (1,2) for the special requirements of lymph nodes to be fed by a specific type of adipose tissue in order to meet energy requirements.

Discussion of parasite needs at the LF Workshop reminded me of the fact that

perinodal adipose tissue has a cytokine behavioral profile that involves TNF and IL-4. It is reminiscent of the needs of the parasite that inhabits the same nodal environment. The release of TNFα by *Wolbachia* is clearly important, and the way gram negative bacteria stimulate lipolysis in adipocytes by secreting TNFα is of interest.

During the LF discussions we heard of receptors and needs for lipopolysaccharide of both filaria and *Wolbachia*. The gene studies could inform us of biochemical needs that are fulfilled by the relationship of the worm to both the bacteria and its perinodal environment. Its offspring induce IL-4 and have a great need for a phospholipid coat unlikely to be met by normal lymph, while the bacteria's (the only gram negative bacteria lacking LPS) preferred location is close to the lymph nodes. There is currently increasing evidence for a role of intracellular lipid droplets containing adipose differentiation related protein (ADRP) in wound repair and barrier function, and the same is likely for other components of wound healing such as inflammation and immunosurveillance.

Hills (3) emphasized the lubricating properties of surface active phospholipid and the special role this played in the lymphatics. The ISL has heard at its meetings of the role of free fatty acids derived from adipocytes as a source of energy and the manner they are transported in lymphedema (4).

ENTRY POINTS AND SKIN BARRIER FUNCTION

While the story of recurrent inflammatory episodes (adenodermatolympangitis ADL) has permeated the literature from the earliest of times, it received a great boost from the observations of Shenoy and Dreyer as the ISL has heard at its meetings in India and Brazil. Their demonstration that entry points through the skin for bacteria could be managed by simple washing and skin care procedures was important to the field of LF. Dermatologists have long used such procedures to control skin disorders such as eczema and psoriasis. I have reinterpreted entry points as barrier breakdown and discussed the latest views on the effect of such breakdown on epidermal responses. Thus breakdown immediately stimulates immunosurveillance and the production of cytokines needed to effect a response in blood supply and lymphatic drainage. Furthermore, this same response effects repair of the barrier. I have discussed some of the fine tuning underlying the management of barrier breakdown in the Filaria Journal online (5).

Barrier breakdown is susceptible to irritants and allergens as well as to infective organisms, the only difference being that the latter thrive on the changes in the epithelial environment when repair is activated. Because the epithelial barrier can be restored by emollients, their role has been the subject of great investigation by both dermatologists and the cosmetic and pharmaceutical industries. Some topicals can have additional effects suppressing infective organisms, being anti-histaminic and anti-oxidant. All of this may point to the fact that repair of the barrier is of greater significance therapeutically than destroying bacteria and fungi. Indeed, contemporary evidence-based studies of infections repeatedly show that the bases of topical applications are nearly as effective as the active principle. Those who, like ballet dancers, make a habit of oiling their feet immediately see a benefit, and this has become a war cry of the fight against recurrent inflammatory episodes in sufferers from lymphedema. A search for an infective cause of ADL-like fungal infections between the toes in Guyana demonstrated at this meeting, is more likely to find clear evidence of barrier breakdown (maceration or cracks) than they are to find organisms.

Our group hardly discussed this topic since their was no disagreement.

HYDROCELE

The Advocacy literature of The Global

Alliance for the Elimination of LF simply and clearly states that the treatment for hydrocele is surgical (6). In the small region of the coast of Tanzania where morbidity control has been activated, 3000 or so hydroceles have been recently operated upon. In the discussion of the disease/treatment subgroup, I put forward the view that this is a disaster because it not indicated, it is expensive and there are risks involved. Dr Shenoy indicated concern that surgery was so firmly Alliance policy. The others were at first reticent but subsequently after very lengthy discourse, we came to share a common view about what is known, needs further research, or should be policy. Many examples can be given of surveys of communities or of individuals in which genital swelling resolves spontaneously or after DEC. A case report by Young and Kinmonth (7) was an observation during the operation on a patient for a hernia in which megalymphatics filled with motile worms were observed. Scrotal swelling responded completely to a course of DEC. The recent Papua, New Guinea study (8) described a whole population responding without surgery.

At the LF workshop, Gerusa Dreyer and Joaquim Noroes required first of all a distinction between lymphedema of the scrotum, hydrocele, lymphocele, hematocele, chylocele, and the presence of megadilations with or without live or dead worms. In the Brazilian experience, pure lymphedema can resolve completely using the same conservative regimen as for the legs. Pure hydrocele is rare and has the same prevalence and capacity to resolve spontaneously as that in the non-filarial population. Their concern was that dilated filarial filled or megalymphatics can rupture, and the spilled contents are inflammatory. This inflammation can provoke lymphedema or if the rupture is into the tunica vaginalis it creates a lymphocele. The normally fine wall of the tunica becomes inflamed and fibrosed. The testis is either directly, or through impairment of its blood supply, severely damaged and may be destroyed. Megalymphatics in communication with and draining the mesentery can fill the tunica vaginalis with chyle. Dr. Noroes had with him superb illustrative material. Based on this information, a scheme of best practice could be proposed.

1) Ultrasound should identify the status and location of worms. These are destroyed by DEC but some surviving worms can and should be identified. It is common to find and palpate nests on clinical examination, and this is commonly unaccompanied by any lymphedema. Ultrasound can distinguish between hydrocele fluid and lymph or chyle. Ultrasound will also identify tumors. These are not rare and require planned management not accidental partial removal at surgery.

2) Aspiration of fluid to identify and distinguish between the clear yellow hydrocele and a similar yellow but slightly contaminated lymph with cell debris and microfilaria or chyle is also necessary in order to plan treatment. Surgery on an inflamed tunica vaginalis can be difficult sometimes involving more bleeding, infection, or incomplete removal and later recurrence.

3) Where worms have survived DEC, they should be removed surgically. It is a very simple operation.

All of this is an argument for surgery in a specialized center. Sclerotherapy, which is widely used in Africa and which is appropriate for the uncommon true hydrocele, is completely contraindicated for lymphocele.

It is recommended that the term hydrocele should be replaced by filariacele where hydrocele is clearly the wrong diagnosis.

As a consequence of this discussion, I propose that careful clinical surveys of scrotal swelling should clarify what pathology we are dealing with. After DEC some swellings will resolve. Conservative therapy is appropriate for lymphedema. Specialist centers are required for surgery.

Megalymphatics and reflux of chyle are not unique to LF; chylocele may be. Every nation should have a center to manage such cases especially considering that in any

population non-filarial causes of genital swelling are not rare.

Megalymphatics are seemingly a dilation with preserved contractions and thickened walls. Obstruction to outflow and loss of function of valves have not been studied. In a symposium on elephantiasis I organized in Oxford 1988 (9), M Witte described a report of inducing such dilatation in a normal animal by infusing lymph from an infected animal. Dilatation occurs early (within days of infection) before obvious inflammation or obstruction. Koga et al (10), in a series of 659 patients with probable filariasis, suggested that chyluria in 41% was apparently exacerbated by another condition and often remitted with effective therapy of those other conditions. The early studies of Witte in 1988 (11) in the ferret using lymphangioscintigraphy convincingly demonstrated lymphatic dilation and impairment of flow in the face of patent lymphatics as they subsequently documented in lymphangioscintigrams of patients along with bursts of tracer transport observed after light massage (12). It may be that studies such as those of Sinzinger and Oguogho (13) on nitric oxide and isoprostanes will provide the clues to functional obstruction.

TRADITIONAL APPROACHES TO MANAGEMENT

For some years I have drawn attention to the public health issue that a majority of people use traditional medicine. It is locally available, sustainable, and low cost. I told the workshop that we have a duty to check that it is safe. Compared to Western medical therapy, its record is good providing the prescriber is well trained or in the case of some local traditions, experienced. For example on Mafia Island, coconut oil is a habitually used emollient. There is no reason to prescribe anything else as an emollient but before actively promoting it, its safety might be checked up upon. Does it carry clostridia or heavy metals? We might research whether it has antiseptic or anti-inflammatory properties.

In India I have begun a program in Kerala with The Institute of Applied Dermatology to examine Indian Systems of Medicine. The rationale for this is that where a country has a high prevalence of LF in rural areas with ethnic communities and unfamiliar languages, it is foolhardy for Western (allopathic or biomedically) trained practitioners to impose a morbidity control program which no one can afford and many cannot understand. Our initial studies show that traditional medicine is effective, safe, and cheap, and many of its components are better understood and provided in India than elsewhere. These preliminary studies led by Dr. Narahari, a dermatologist heading an evidenced-based and ethically advanced program of clinical research into Ayurvedic management of lymphedema, cover the use of herbal preparations for the skin barrier repair and Yoga posture movement breathing and massage.

A full report of this workshop will be published as a supplement of the *American Journal of Tropical Medicine and Hygiene.*

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