Lymphology 22 (1989) 103-110

SUMMARY OF SYMPOSIUM ON ELEPHANTIASIS AND THE MANAGEMENT OF THE SWOLLEN LIMB

September 6, 1988, Oxford, U.K.

A symposium on elephantiasis and the management of the swollen limb was held as part of a combined meeting of the International Society of Dermatology with the International Society of Dermatopathology in Oxford, U.K.

An afternoon session was devoted to the swollen limb and in particular lymphedema. Issues such as etiology, pathophysiology, epidemiology, investigation, and treatment were addressed. Comparison between lymphedema in the Developing and Developed countries was emphasized. Dr. Peter Mortimer, Consultant Dermatologist at St. George's Hospital and the Royal Marsden Hospitals and Chairman of the British Lymphology Interest Group organized the symposium and acted as moderator for the afternoon proceedings. Also taking part were Professor Marlys Witte, past President of the International Society of Lymphology and the 1988 Oxford Litchfield lecturer, Professor S. Jamal, Professor of Plastic Surgery in Madras, India (sponsored by Zyma U.K. Ltd.), and Dr. Peter Knox, Biochemist and ex-Vice Dean, St. George's Hospital Medical School and currently Senior Research Manager, Glaxo Group Research, U.K.

"WHAT CAUSES A SWOLLEN LIMB"-- Physiological considerations

Dr. Knox got the proceedings underway by addressing the issue of normal fluid homeostasis and in particular its control. He described the closely regulated movement of fluid from the blood vessel through the interstitium to the lymphatic and noted that lymph was similar to interstitial fluid in terms of its composition. Both were of low cellularity. Under normal circumstances only a small proportion of plasma proteins traverse the blood capillary membrane and enter the interstitium from where they exit via the lymphatics. In inflammation the leakage of protein from the blood compartment into the interstitium increases considerably. Normally, the predominant protein to leak into the interstitium is albumin. This is because all other proteins are much larger and have more difficulty in crossing the capillary membrane which tends to act as a sieve. During inflammation, however, larger proteins such as immunoglobulins are able to leak more readily into the interstitial space. This arrangement therefore maintains the bulk of immunoglobulin in the blood vascular compartment only releasing it into tissues during inflammation. Lymph collected by direct cannulation of a collecting lymphatic on the dorsum of the foot can be analyzed. Under normal circumstances with the subject walking on a treadmill as little as 0.5 to 1.5mls of lymph are produced per hour. Lymph analysis when taken in relation to interstitial fluid is best performed soon after cannulation because 6 hours later the lymph to plasma protein ratio rises sharply as does the cellular content of the lymph.

Edema signifies an expansion of the interstitial fluid volume. This circumstance arises either from increased interstitial fluid formation or from reduced interstitial drainage. The lymphatics are

important regulators of interstitial fluid drainage and failure of this system results in "lymphedema." Edema can alternatively develop when interstitial fluid formation exceeds the capacity of lymphatics to drain the fluid filtered as occurs, for example, in inflammation where the pathophysiology is potentially reversible and recovery virtually complete. "True" or lymphostatic lymphedema tends to be a more insidious and progressive process. The nature of lymphedema is such that the gradual tissue build-up of protein and fluid is counterproductive stimulating an inflammatory infiltrate and subsequent fibrosis with worsening of remaining lymphatic function.

"THE SIZE OF THE PROBLEM"-- Epidemiology/diagnosis

In developing countries (Professor Jamal)

Professor Jamal commented that the swollen limb is common in developing countries, yet no reliable statistical data exist as to its incidence or etiology. A swollen limb in conjunction with malnutrition, hypoproteinemia, and anemia is prevalent in all developing countries and poses no difficulties in diagnosis. Whereas edema due to filariasis is the commonest cause in endemic countries, the diagnosis is often not properly made or managed in its early stages. The only available data on the prevalence of lymphedema worldwide as cited from Dr. J.R. Casley-Smith is 90 million patients compared to 20 million from operations and radiotherapy for treatment of breast cancer, 2 million primary lymphedema, and 300 million edemas from chronic venous insufficiency. These figures add up to 430 million or 3 in every 20 people in the world having had a swollen limb. While this total appears inflated, there may be many individuals with subtle or subclinical swelling. Professor Jamal described the lifecycle of the filarial parasite noting that the adult male and female worms live in the lymphatics of man for at least 5 to 10 years. Larvae of the worms penetrate the human body through a puncture wound made by the proboscis of the female mosquito acting as a vector. The larvae enter the lymphatics and migrate to lymph nodes. Diagnosis of filariasis depends acutely on fever with lymphadenitis, lymphangitis, cellulitis, and dilatation of peripheral lymphatics. Infestation of the male genitalia presents as funiculitis, epididymitis, orchitis, and hydrocele. Some chronic manifestations of filariasis include hydrocele, elephantiasis of the leg, arm, breast, genitalia, and chyluria. Diagnosis during an acute infection depends on finding microfilaremia. Long-term, the lack of antifilarial antibodies in a patient residing in a non-filarial endemic area excludes the possibility of filariasis.

In developed countries (Professor M. Witte)

Chronic lymphedema due to filariasis arises from a lack of good public health care in the developing world. In the Western world, paradoxically, the majority of patients with lymphedema arises from ready access to modern health care, viz. surgery and radiotherapy for the treatment of cancer. Professor Witte maintained there was simply no data on the prevalence of lymphedema in the Western world. Figures from Dr. Casley-Smith may be exaggerated but, on the other hand, if one defines a swollen limb as a swelling of any part of that limb at any time then it is axiomatic that everyone is affected. Thus, before we can determine prevalence we need to define the problem denoting what constitutes lymphedema and what simply constitutes a swollen limb. In a sense, any edema signifies some inadequacy of lymphatic drainage and therefore is commonplace. On the other hand, if one reserves the definition of lymphedema as that of a primary abnormality of the lymphatic system then lymphedema is comparatively rare. Professor Witte reiterated that most limb swelling is due to increased lymph or interstitial fluid formation whereby the capacity of the lymphatics to drain surplus interstitial fluid is exceeded and is not strictly lymphedema. True lymphedema arises from a failure of the lymphatic sys-

tem to drain normal amounts of tissue fluid because of obstruction or obliteration of lymphatic pathways. Typically the edema fluid is high in protein content. Presumably the high protein concentration incites tissue inflammation and the subsequent fibrosis and fat deposition characteristic of chronic lymphedema. Having defined lymphedema, its incidence is obscure because series are often biased according to the interest of the investigating physician or surgeon. Lymphedema may be a diagnosis of exclusion. First consideration in a swollen limb is usually venous insufficiency and only after negative noninvasive (e.g., duplex scanning) or invasive (e.g., phlebography) imaging is lymphedema considered. Because at times of only limited physical disability created by swollen limbs, lymphedema treatment is often nihilistic. Patients treated for cancer are typically reassured that at least the cancer has been satisfactorily arrested and those with filarial lymphedema manage to ambulate despite at times a grotesquely deformed leg. Too little consideration is given to the compromised quality of life created by persistent swelling. Finally, there may be diffuse lymphatic obstruction within a limb, but as yet without overt edema. This circumstance is generally neglected or unrecognized.

Dr. Mortimer noted that the prevalence of lymphedema in the U.K. is not known. If one considered any chronic swelling to signify a compromised lymphatic system then the condition was extremely common particularly in the elderly or infirmed. Figures relating to the prevalence of chronic swelling due to an obstructive lymphatic system such as following breast cancer treatment were available. Approximately one-third of patients undergoing axillary dissection and radiotherapy for breast cancer develop arm swelling. As more than 20,000 new patients with breast cancer are diagnosed annually in the U.K., this figure would point to an excess of 6,000 new patients who ultimately develop lymphedema. Because, however, all 20,000 patients undergo treatment, they all have some degree of iatrogenic obstruction to the arm lymphatic system and yet only 1/3 develop overt arm edema.

PATHOPHYSIOLOGY

Filariasis (Professor M. Witte)

Professor Witte reminded us that the lymphatic system is an integrated circuit composed of lymph, lymphatic vessels, lymph nodes, and central organs such as the spleen, where fluid, protein, and cells continually circulate. One approach to understanding pathophysiology is through available techniques of investigation. First, lymphatics can be visualized by direct lymphography. Peripheral lymphatics are visualized by relying on the principle of macromolecular drainage. Vital dyes which adhere to protein are taken up by the lymphatics after intradermal injection and render then readily visible and thereby accessible for cannulation. Radiocontrast is instilled and lymphangiograms obtained. Cannulation also allows lymph to be sampled. By studying an obstructed lymphatic system, the normal role and function can be better understood. Both animals with experimental obstruction and patients with secondary lymphedema can be studied. Segments of lymphatics can be removed and tested *in vitro* and the ability of lymphatic vessels to contract can be quantified. With recent advances in cell culture techniques, lymphatic endothelium can now be grown in monolayer. Growth potential and permeability properties can then be investigated.

Congenital lymphedema may be of two types--(1) due to aplasia or hypoplasia of peripheral lymphatics, and (2) due to enlarged, dilated peripheral lymphatics; the clinical presentation may, nonetheless, be similar. Subclinical edema may antedate swelling by many months to years. Professor Olszewski showed in his experimental model that one does not require superimposed infection to produce chronic trophic changes of lymphedema. Professor Witte also described her experience with isotope lymphography (lymphangioscintigraphy) using technetium labeled human serum albumin injected intradermally as

tracer. The comparison between radiolabeled albumin and technetium labeled colloid demonstrated a better image of the albumin within lymph channels, whereas the colloid better localized regional nodes. Experiments using infected ferrets as an experimental counterpart for filariasis proved revealing. L3 microfilarial larvae were initially injected into the feet, scrotum, or inguinal areas of the ferret. Three months later, typical acute tropical eosinophilia with pulmonary manifestations developed. Later some of the ferrets developed chronic lymphedema. Whole body lymphangioscintigraphy demonstrated obstructed lymph channels. Many ferrets without overt edema when sacrificed were also found to have obstructed lymphatics with live adult worms within dilated lymphatics between the popliteal and femoral nodes. The mechanism whereby the worms produced lymphedema remains perplexing. Videotapes revealed ongoing trauma to the lymphatic wall and in particular the valves by active, undulating adult worms. Professor Witte surmised that this phenomenon is at least one major contributor to lymphatic damage. Other possibilities include the host immunologic response to the adult worm or worm products. It was noteworthy that within 10 days of microfilarial inoculation, hindlimb lymphatics were already dilated. This dilatation occured long before evidence for lymphatic obstruction and long before an inflammatory reaction occurred.

Dr. Mortimer asked if lymphedema could be prevented by treating filariasis at the stage of "obstructed lymphatics" before swelling ensues. Professor Witte commented that the problem lies with the drugs that although effective against microfilarae are ineffective against the adult worms. Theoretically, therefore, treatment would have to be given within a matter of days following infection unless a more effective drug against the adult worms is forthcoming.

Dr. Ryan asked if simple dilatation of the lymphatic was sufficient for "failure" or did there have to be a paralytic mechanism to promote insufficient contractility and thereby impair lymph propulsion. Professor Witte replied that one experiment where lymph from an infected animal had been infused into the lymphatic system of a normal animal promoted dilatation of the recipient lymphatic vessels suggesting a humoral factor underlies the initial dilatation and impaired lymph propulsion.

Lymph sampling (Dr. Knox)

Dr. Knox described observations made in patients with nonfilarial lymphedema, animal models with lymphedema, and finally patients with lymph swelling due to filariasis.

Cannulation of pedal lymphatics in patients with unilateral lower limb swelling unrelated to filariasis was performed. The normal and swollen limbs were compared. Both lymph and plasma were collected and results expressed as lymph to plasma ratio. No qualitative difference in lymph proteins was found between lymph from a lymphedematous limb and its normal contralateral counterpart. There was, however, an overall increase in the concentration of all protein moieties normally found in lymph. Total protein concentration was on the average doubled with lymphedema. The lack of qualitative changes indicates that blood capillary permeability was unaffected and that the capillary membrane was "sieving" normally. These observations favor that the quantitative changes in protein concentration in lymphedema are not determined by abnormalities in the blood capillaries. Albumin was the dominant protein in both the normal and lymphedematous limb.

Experimental lymphedema is difficult to reproduce. Ligation of lymphatics results in transient edema. Repeated weekly ligation of lymphatics for up to 14 weeks resulted in more prolonged edema but resolution still occurred. Infusion of latex intralymphatically proved more successful in reproducing lymphedema. However, after 6 or 7 weeks the swelling subsided. Repeat lymphangiography demonstrated that there was recanalization of lymphatics despite extensive destruction of draining lymph nodes.

Analysis of lymph sampled from the experimental animals with lymphedema showed similar changes to patients: i.e., doubling of total protein concentration and no qualitative change in protein composition.

Studies performed in filarial patients revealed similar lymph/plasma ratios as in experimental lymphedema. Cannulation of lymphatics in filarial limbs produced enormous quantities of lymph as compared to only 1ml in 4 hours for a normal limb over a 4-hour period. The lymph quality and quantity gradually decreased in volume and the protein concentration approached that found in the normal leg. It was concluded that the twice normal protein concentration in the lymphedematous limb was due to lack of forward lymph flow *in situ*.

Dr. Knox proposed physiological lymphedema occurs when controlling Starling forces are deranged as happens with prolonged limb dependency and immobility (e.g., long aircraft flights). Damage to lymphatics through trauma or infection are reversible by recanalization and regeneralization of lymphatics. Opening of collateral drainage pathways also serve to prevent lymphedema. Swelling need not necessarily follow some lymphatic impairment even if permanent. But repeated cycles of lymphatic injury eventually results in disrupted lymph dynamics. Thereafter an excess of fat and fluid is deposited and fibrosis ensues and a stage of irreversible lymphedema is reached. It is possible in filariasis, after inducing lymphedema, that the adult worm no longer plays a critical role and the condition becomes self-destructive.

Dr. Mortimer noted there were parallels between filarial lymphedema and lymphedema following cancer therapy. Lymphedema is a late-stage process. There is a critical need to examine lymphatic obstruction at an early stage before overt swelling but when lymphatics are already dilated.

The role of silica in aggravating filarial lymphedema was raised. The generally held view was that silicates can induce lymphatic blockage and were probably important factors in lymphedema in East African mountain areas. Professor Jamal, on the other hand, maintained that silica was absent in the soil in many areas endemic for filariasis and therefore was not a major feature of filarial lymphedema.

Professor Witte commented that the role of lymph nodes in lymphedema development needs to be clarified. Lymph nodes are commonly fibrotic and therefore "obstructive" but it is not known whether this response is a cause or an effect of lymphedema.

In filariasis different species of worm have different affinities for regions of the lymphatic system wherever the host entry site. This tropism for specific areas (e.g., *B. malayi* swelling predominates in the lower leg whereas *W. bancrofti* often targets the external genitalia) is a complete mystery.

It probably requires recurrent infections and repeated inoculations of filarial parasites for elephantiasis to evolve from chronic lymphedema. Dr. Mortimer reiterated that repeated injury to regional lymphatics is necessary before lymphedema ensues. This circumstance is demonstrated by the patient with venous ulceration of the leg where supposed chronic entry of bacteria with subsequent cellulitis and lymphangitis eventually results in the characteristic features of lymphedema in the lower leg and foot.

Dr. Burge asked what was responsible for the proliferative skin changes of elephantiasis. Dr. Knox replied that while analyzing peripheral lymph for growth factors he had found fibroblasts in culture proliferating at a far greater rate when grown in media enriched with lymph in contrast to plasma.

INVESTIGATIONS

In developing countries (Professor Jamal)

Professor Jamal emphasized that a reliable clinical history and examination was usually adequate to correctly diagnose lymphedema. Observations and techniques useful in clinically evaluating and monitoring lymphedema include (1)

spreading out or obliteration of dermal creases, (2) dermal thickening as judged by pinching a fold of skin, (3) pitting on pressure, and (4) limb circumference at various fixed levels (important to gauge progress of the disease and response to treatment). Techniques useful for research include tonometry and limb volumetry.

Professor Jamal described his experience with more than 200 direct oil-contrast lymphangiograms in filariasis. In no instance had edema clearly worsened following use of this imaging technique.

How to investigate filarial lymphedema is a difficult question. As adult worms inhabit the lymphatics and lymph nodes long before microfilariae are detectable or immunodiagnostic tests are positive and before swelling develops, investigation needs to begin early in the disease and should in some way image either the worms or detect lymphatic dilatation. Direct contrast (conventional) lymphography is invasive and cumbersome and at the present isotope lymphography (lymphangioscintigraphy) holds promise as the best screening test, providing both functional and anatomical information. Nuclear Medicine equipment is, however, prohibitively expensive and not as widely available in developing countries as standard x-ray machines.

Developed countries (Dr. Mortimer)

The problem confronting the clinician is usually the differential diagnosis of the swollen limb. Whereas lymphatic dysfunction may be totally or partly to blame, it is not always possible to decide on clinical grounds alone what is the dominant precipitating cause. Direct contrast lymphography remains the gold standard for visualization of lymphatics and lymph nodes. However, it is invasive and difficult to perform with notable edema and provides solely anatomical rather than functional data. Isotope lymphography is essentially noninvasive for demonstrating peripheral lymphatic function. A radiolabeled colloid is usually injected interstitially. As with all macromolecules, the tracer is taken up by peripheral lymphatics and transported toward regional nodes. The nodal uptake after 2 hours under controlled conditions including a period of standardized exercise provides semiquantitative information about absorption rate. This technique is useful as a screening test for lymphatic dysfunction within a swollen limb. Some definition of lymphatic channels can be seen and specific patterns identified. For example, in Milroy's disease with aplastic peripheral lymphatics there is virtually no movement of tracer from the injection site. Experience with this technique in over 100 lower limb examinations demonstrated good reproducibility to standardized conditions and a clear division between normal limbs and those with suspected lymphatic insufficiency. In addition to classical examples of primary and secondary lymphedema, impaired lymphatic function was demonstrated in patients with recurrent cellulitis (greater than 3 attacks) and those with venous ulceration and edema. Interestingly, the healthy contralateral extremity of patients with unilateral limb edema have thus far had uptake in the normal range.

Dr. Ryan wondered if gamma camera availability in developing countries was adequate to allow the test to be widely applied. Professor Jamal thought not, and the capital cost of installing such equipment was prohibitively high. Measurement of lymphatic function using simple external radioactive detectors was considered more feasible.

The value of ultrasound in detecting dilated lymphatics was queried. The consensus of opinion was that lymphatics would need to be comparatively large before they could be successfully imaged using this technique. Nonetheless, improved resolution in time may make this imaging modality potentially useful.

TREATMENT

Medical management (Dr. Mortimer)

In the developed countries, lymphedema has often been and continues to be largely a complication of treatment (usu-

ally radical operations and irradiation of regional nodes). Unfortunately, there is as yet no comparable surgical solution to the problem of "iatrogenic" edema. Consequently the condition is managed in many different ways. Lymphedema is typically irreversible because it usually presents at a late stage. This is not to say that the limb size cannot be effectively reduced. Unfortunately, a nihilistic attitude prevails in the U.K. and the most common form of treatment is long-term diuretic drugs. Physical therapy is available in many countries and particularly in Europe. The details of treatment varies but the fundamental principles do not. They are essentially directed to controlling lymph formation and encouraging lymph drainage by collateral routes.

1) Limb positioning is important as prolonged dependency tends to exacerbate swelling as intravascular hydrostatic pressure rises. A lymphedematous extremity is no exception. Elevation at or near heart level is optimal. Further elevation is unnecessary and probably unwise. Not only is it uncomfortable for the patient but autoregulatory mechanisms come into play which tend to augment blood capillary perfusion. Marked elevation also does not further improve lymph drainage.

2) Prevention of secondary bacterial infection is critical. One attack of cellulitis and/or lymphangitis not only makes the patient systemically ill, but further aggravates limb swelling sometimes permanently. Local care of the skin, control of tinea pedis, and prompt cleansing and antisepsis following abrasions and other minor skin injuries are important therapeutic considerations.

3) External support remains the cornerstone of proper lymphedema management. This may be accomplished initially with bandages and as edema volume is reduced application of an elastic stockinette as a containment garment to maintain limb size reduction. In general, the greater the limb circumference the less elastic hosiery is effective at exerting useful external compression. Elastic hosiery should be custom fit and comfortable. Otherwise, the patient is not likely to wear the device and perhaps worse, a tourniquet effect with skin damage may ensue. Some expertise is needed to provide this form of treatment. In my experience, it is usually worth the extra effort and expense to start with lower compression hosiery, gradually building up the pressure to allow the patient to become accustomed to fitting the garment themselves, and to become acclimated to the higher external pressure. Severe lymphedema may sometimes require a double stockinette.

4) Tissue movement is a natural stimulus to lymph propulsion which increases with muscular exercise, joint motion, skin massage, or even transmitted arterial pulsation. By facilitating lymph flow even in an obstructed system, drainage is improved through collateral routes. Optimal isotonic exercises in conjunction with external support creates an effective internal massaging effect. Skin surface massage if performed correctly can provide further reduction in swelling. Attention must be given not only to the swelling in the extremity but also to the adjacent quadrant of trunk as swelling often coexists at this site. Truncal edema is improved only by skin surface massage. A reduction in truncal tissue edema and congestion allows better limb drainage through this area to the nearby normal lymph nodes, a principle promulgated by Professor Földi.

External pneumatic compression is employed widely, but little attention has been directed to what this approach achieves apart from reduction in limb size. Is macromolecular transport in the lymphedematous limb facilitated? Does truncal edema worsen? Do devices using multicompartment garments simulate massage? Nonetheless, when combined with external support, hose pneumatic compression appears to help and may be particularly useful in softening edematous limbs as trapped fluid pockets are mobilized.

Surgical management (Professor Jamal)

Medical management for the swollen

limb in the developing world is extremely difficult. The cost of hosiery is prohibitive and elastic tubing often is used as an alternative. Professor Jamal reported his experience in over 3,000 patients with filarial lymphedema. Diethylcarbamazine in doses of 300ml per day for 5 days is administered monthly to both block production of microfilaria by indwelling adult worms and also to prevent reinfection. Where simple measures such as elastic support and prevention of sepsis fail to improve edema after 2 months then operative correction is recommended.

For Grade 1 edema (i.e., spontaneously reversible on elevation)--nonoperative therapy only is used.

For Grade 2 edema (i.e., irreversible, predominantly nonpitting edema with moderate fibrosis)--a lymph nodal-venous shunt is performed. Using this technique, the draining regional lymph node and long saphenous vein are exposed. After the distal end of the saphenous vein is ligated and divided and a wedge of node excised, the proximal end of the saphenous vein is anastomosed to the cut surface of the node capsule.

For Grade 3 edema (i.e., irreversible edema with a leg circumference greater than 5cm at one or more levels compared with the contralateral leg)--a nodal-venous shunt is performed in conjunction with debulking of excess tissue while sparing the deep fascia. This procedure is carried out in one stage except in huge legs when first excess bulk on the medial side is removed followed 2 weeks later by similar debulking on the lateral portion.

For Grade 4 edema (i.e., when elephantiasis is grotesque)--the papilloma and warts are initially shaved off before proceeding to nodal-venous shunt and debulking.

Complications include local collections of lymph, lymphorrhea, hematoma, or wound infection after nodal-venous shunt, and hematoma, infection, or fat necrosis after debulking. Unfortunately, recurrence is common in treatment of Grade 4 filarial lymphedema.

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