

Cutting edge developments in lymphedema treatment and research British expert Dr. Peter Mortimer speaks out

Once doctors feel that the hot science might lead to better investigation, better treatments and better understanding - then they might become more interested



I got into the area of lymphatic research and treatment when I was training as a senior medical resident at Oxford University. My boss (Professor Terence Ryan) sat me down and said, "You should do some research. Why don't you try lymphatics, because I guarantee that in a couple of years you'll be a world expert." At the time I was extremely flattered. I interpreted this as a compliment on my abilities but what he was really getting at was that if I was working on lymphatics I would probably be the only person working on lymphatics and so it wouldn't be difficult to become a world expert! That's how I got into it.

I started doing research on skin biopsies, looking at lymphatics and trying to identify them. Inevitably I would see patients with lymphedema. I looked at the literature and thought "this is terrible; no one really knows what to do". This was in the early 1980's.

I had heard of the Foeldi Clinic in Germany which treated people with lymphedema so I paid my own way and visited the clinic. Michael Foeldi was wonderful to me. He had no reason to be because I wasn't a very important person - I was only there because I had an interest. I remember him taking me to the clinic and showing me around. Then he took me around to his home, sat me down in the garden and said, "All right - fire some questions at me." I did and from that moment on I was hooked.

After I came back from the Foeldi Clinic I said we have got to do this - the results look good to me. So I set up a clinic first in Oxford; then when I moved back to London I set up a similar clinic at the Royal Marsden Hospital because that's where the bulk of the patients were at that stage.

I trained as we do in the UK: in internal medicine first and then sub-specialize in a particular area of medicine; for me that area was dermatology. This differs from North America where dermatologists are not necessarily internists. I am now consultant dermatologist at St. George's Hospital and also at The Royal Marsden Hospital in London, which is Europe's biggest cancer center. We see a lot of lymphedema there.

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Since proving my research pedigree I've become Professor of Dermatological Medicine, the medicine being added because of my extended practice outside of dermatology. In fact, I really don't do general dermatology anymore because my practice is pretty well entirely made up of lymphedema and lymphatic diseases.

In the twenty years that I have been working in lymphedema I've seen greater awareness of this condition although we've still got a long way to go. I've seen the therapists take up the baton of the patients to train and provide treatments that do work in lymphedema. So the position of being told, there is nothing that can be done, is no longer there. And that certainly was the view when I started in lymphedema.

It was difficult seeing the non cancer patients in a cancer center and so in about 1997 I started a comprehensive lymphedema clinic at St. George's. At that clinic 90% of lymphedema patients are non-cancer.

In Britain our experience is that non cancer lymphedemas out-number cancer-related lymphedemas 3 to 1

In North America it is believed that the largest numbers of people with lymphedema are breast cancer survivors and that people who are born with or acquire lymphedema make up a very small proportion of the population. In Britain our experience is that non cancer lymphedemas out-number cancer-related lymphedemas 3 to 1. I think it's because it's a hidden population of patients that just never get past their family practitioner. They're not ill so they are given diuretics and sent on their way. Their quality of life may be compromised. They may not be getting cellulitis - they just get swelling so they

manage it. As time goes on without treatment they develop more serious problems. They adapt and get on with it ...

I accept that the more severe lymphedemas that develop from birth are uncommon but we underestimate how many lymphedemas there are out there in the community and are not recognized as such. These people show up in venous insufficiency or wound care clinics and often have skin problems.

I was part of a team of researchers in Britain who published a study in the October 2003 issue of the Quarterly Journal of Medicine: "Lymphoedema: an underestimated health problem" where we looked at the population of South West London of over 600,000 people. What we found is that in people over 65 years of age, 1 in 200 had chronic lymphedema. 29% of the people we looked at had had an acute infection (cellulitis) in the affected area, with 27% of those being admitted for intravenous antibiotics. Individuals stayed in the hospital for treatment on average 12 days, which cost the National Health Service £2,300.00 pounds (over \$5,000.00 in Canadian dollars). Lymphedema caused time off work in close to 80% of these individuals affecting the employment status in 9%. Quality of life was below normal, with 50% experiencing pain or discomfort from their edema.

Chronic edema is a common problem with at least 100,000 patients suffering in the UK alone, a problem poorly recognized by health professionals.

We concluded that lymphoedema arising for reasons other than cancer treatment is much more prevalent than generally perceived, yet resources for treatment are mainly cancer-based, leading to inequalities of care. Chronic edema is a common problem in the community with at least 100,000 patients suffering in the UK alone, a problem poorly recognized by health professionals.

Lymphedema is generally thought of as swelling related to a fault in lymph drainage and fluid filtration into the tissue. But any edema indicates some degree of lymph drainage failure.

Lymphedema is often due to venous disease where extra fluid pours into the tissue which the lymphatics can't cope with. Swelling occurs with venous disease because the lymphatics are failing. You might call that a mixed vein and lymphatic condition but when it comes down to the wire, the treatment is the same. In fact conventional treatments work very well with mixed lymphatic and venous edema.

You get patients who perhaps have had a bit of heart failure or chest problem and they got edema of

their legs as a result but if you examine their legs after five years they've got all the hallmarks of lymphedema there. That's because the lymphatics have failed in the face of this onslaught of the fluid caused by the more systemic problems, i.e. heart failure - but it's still lymphedema.

The types of edema that we see associated with treatment of cancer, Crohn's disease and some arthritic conditions, are in fact related to an underlying genetic weakness in lymph drainage which already exist...

It is my belief that many of the types of edema that we see associated with treatment of cancer and other conditions such as Crohn's disease and some arthritic conditions, are in fact related to an underlying genetic weakness in lymph drainage which already exist. If you take Crohn's disease, for example, the pathology of Crohn's disease is effectively lymphedema of the gut. Gastroentologists don't call it that, but that is what it is.

In rheumatoid arthritis, individuals can get lymphedema of one or both upper limbs as well prior to the development of the disease. It's a rare complication that we have studied using lymphoscintigraphy and we have showed categorically that it is lymphedema (Kiely P. et al., J. Rheumatol. 1995; 22: 214-217). I'm not saying the rheumatoid arthritis is caused by lymphatic problem but I'm saying that a small number of patients get lymphedema because of rheumatoid arthritis. So there are many different areas in medicine where lymphedema raises its head. Unless you think lymphatically, a physician just won't comprehend or even go there and think of lymphedema.

I've published in many areas on lymphedema - my current interest is lymphedema related to other conditions such as breast cancer and genetic disease. I have two areas of funded research which I am overseeing right now: genetic research and laboratory research of breast cancer related lymphedema - an area which I have been working on for 13 years.

We've shown that the cancer surgery does not cause lymphatic obstruction which is what was thought to have happened

The more work we do to unravel the mechanisms giving rise to breast cancer related lymphedema, the more complicated it gets. I haven't got an answer, but the reason it's such a difficult condition to understand is that the mechanisms at work are not just obstruction of lymph drainage in the axilla. We've shown categorically that the cancer surgery does not cause lymphatic obstruction which is what was thought to have happened. Our current view is that problems may actually start in the muscle compartment deep down in the forearm or the upper limb following cancer treatment.

Lymphedema may occur first in the muscle compartment and then other lymphatics have to work extra hard to drain the lymph for long periods of time. The limb may succeed in doing that but eventually the lymphatics fail in different parts of the limb and that may well explain why swelling can occur more than 15 to 20 years after cancer treatment. It may also explain why some people get swelling in different areas of the arm such as the hand, and others don't. But the bottom line is, it's complicated.

There are different types of lymphedema as well which respond differently to different types of treatments. If we get away from the breast cancer model for a moment and look at lower limb lymphedema - the focus of our other area of research through genetic research - we find that there are two known genes for lymphedema.

There are two known genes for lymphedema: when you know what's gone wrong you stand a good chance of being able to correct it



The first is the gene that causes Milroy disease which is congenital familial lymphedema. The other condition is lymphedema distichiasis syndrome (LDS) which shows itself through a double row of eyelashes with swelling developing after puberty. Our research has demonstrated that the mechanisms are completely different in Milroy's disease than it is for LDS. In Milroy disease the lymphatics in the skin are actually absent or very small. The gene which controls the lymphatic development doesn't make the smallest peripheral lymphatic vessels grow properly in the lower limbs.

In LDS we have a completely different form of lymphedema where the fault lies with the collecting lymphatics in the legs and groin which are too large. This coupled with faulty valves results in the lymph goes up the leg and then falling back down again. The vessels don't pump effectively or when they do pump, the valves which would normally stop lymph falling back down your leg, fail.

Through our study of LDS we have begun to realize that there is actually a closer relationship between how veins and lymphatics develop than we originally thought. If one system is abnormal it is likely that the other one may be affected as well. The reason they are linked is because we now know that lymphatics develop originally from veins. Although they form different systems, there maybe a bit of

interchangeability in terms of the potential of these lymphatic cells to be one or the other. If something goes wrong during fetal development, veins and lymphatics may both be affected.

We are collecting family histories related to our genetic research. At this moment we have over 70 families with the commonest form of inherited lymphedema called Meige's disease. We hope shortly to be able to search for genes in the biggest of those families; that's how you find which genes or disease-causing mutations can create different types of lymphedema. Once you understand that, then you can understand the cascade of what goes wrong. And when you know what's gone wrong you stand a good chance of being able to correct it.

Over the last seven years we've started to understand more about the genes and proteins which program the lymphatics. That has enabled us to develop markers for lymphatics which means we can identify lymphatics. Because of that, lymphatics are now being recognized in tumors. Work in humans and in animals are showing the relationship between growth of lymphatics (called lymphangiogenesis) and the spread of cancer may be very important so this is a very hot topic at the moment in cancer science. By blocking some of the molecules in a lymphatic that currently attract a cancer cell it may be possible in the future to prevent the spread of the cancer. The forefront of cancer science is really trying to get a handle on that at the moment.

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So, lymphatics have come of age. They are no longer in the "Cinderella" era. They are equally important not just in cancer but in the treatment of infections because one of the main functions of the lymph system is to contain and deal with infection. Again, by perhaps recognizing the proteins involved in channeling infection to a lymphatic may enable us in the future to understand how infection is dealt with and possibly refine our treatments rather than just throwing antibiotics at them.

We have been fortunate in collaborating with Kari Alitalo and his team in Finland on the genetic research. He has helped us enormously with our lymphedema distichiasis work, but he has also done a fantastic amount of work in the last 5 or 7 years in animal models. Kari has shown how you can now create lymphedema and correct it in a mouse so that it may be possible in the future to provide a growth factor to people with conditions like Milroy disease to make lymphatic vessels grow and hopefully improve that patient's condition.

On the treatment side, I am a proponent of using small doses of penicillin V prophylactically on people with lymphedema who get recurrent infections. Recurring infection or "cellulitis" is a big problem in lymphedema patients. We find over 50% of long-standing primary lymphedema patients and about 38% percent of our breast cancer patients suffer with cellulitis. Once they've had one attack the chances are that they will have another. We use antibiotics preventatively in children who get infections as well as in adults.

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Recurrent infections are a problem not only because they often make the individual very ill and very rarely can lead to death. So it is not to be taken lightly. It also makes the lymphedema worse so it's a vicious cycle. If someone has been getting more than two attacks per year our practice is to put them on prophylactic penicillin V usually for two years. But quite honestly, if I then stop it the cellulitis usually starts up again so the patient and I agree that they just stay on it.

The advantage of it over all the other antibiotics is that it's cheap, it's simple, it's the original penicillin and it seems to be safer than anything else. There is not a problem with drug resistance with this drug because most cellulitis is related to the streptococcus bacteria and penicillin always works on the streptococcus. It's been used for decades in people who have had their spleens removed, which is after all part of the lymph system, with the same principle of avoiding strep infection. And there it is accepted practice - it is not questioned.

We've just been having meetings with physicians who had a special interest in lymphedema in the UK. We were unanimous in recommending penicillin 500 milligrams daily as a proper treatment for anyone who was having two or more attacks of cellulitis per year. Taking penicillin is much safer than one attack after another of cellulitis.

We can learn a great deal from the developing world as it relates to lymphatic filariasis, that is the commonest form of lymphedema around the world but which we don't see much of in the west. Although the treatment for filariasis has reduced the burden of lymphedema in the community, the main problem is still recurrent infections in this group.

There have been interesting studies in prophylactic penicillin using the same principle, and good foot care. Obviously, people walking barefoot with lymphedema would be at increased risk of abrasions, cuts and blisters which would increase the risk of cellulitis but there needs to be more people working

on lymphedema in the developing world.

Lymphoscintigraphy can help you identify whether the patient does or does not have lymphedema - that's not always a simple question

I find the use of lymphoscintigraphy very, very useful in my practice. I do 2 to 3 lymphoscintigrams in a week in the nuclear medicine department and then once a month report the scans with the radiologists. I accept the criticism that at the moment it doesn't necessarily change the treatment but I think that it is very important to understand how the person develops lymphedema.

First of all, you want to identify whether the patient does or does not have lymphedema and that's not always a simple question. Secondly, you often want to ask the question why have they got lymphedema because although it may not make a difference in the treatment at the moment, it will when we can target different abnormalities. So to categorize the patient in my view is very important.

It also can guide you to whether there may be something like covert venous disease present. Then you can follow up with some venous studies and intervention to the veins. It can change practice, but I acknowledge that generally at this stage it probably doesn't change treatment.

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In the last 6 to 7 years there has been a huge increase in our knowledge of lymphatic science. There have been big changes, but I'm still disappointed at the lack of physician interest in lymphatics. There aren't many areas in medicine where the patient can tell the doctor more than the doctor knows, but that is certainly true for lymphedema.

Doctors can become more interested if they know that there is someone to whom they can refer their patients. In other words: the lymphedema therapist. The lymphedema therapist has a responsibility and indeed they take that responsibility seriously to educate the doctors with whom they work.

We are at a point where lymphatic science is beginning to be translated into something useful for the patients. I see lymphatic medicine becoming more fashionable. Eventually it will be recognized and not just dismissed or perhaps not even thought about in the first place. I am confident about that.

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manage the patients. Once doctors feel that the hot science might lead to better investigation, better treatments and better understanding. Then they might become more interested.

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1. Lymphoedema: Advice on Treatment. Regnard C., Badger C., Mortimer P. 2nd edition, 1993. Beaconsfield Publishers Ltd, Beaconsfield, England. ISBN 0-906584-32-9.
2. CancerBacup: Understanding Lymphoedema. ISBN 1-901276-58-9.
3. Lymphoedema Support Network. www.lymphoedema.org/lisn (for fact sheets on lymphedema and newsletters on research topics)

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