

UNPROVEN CONCEPTS NEEDING CORRELATION AND FURTHER STUDY IN LYMPHOEDEMA

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Lymphoedema is a chronic medical condition and a range of questions remain regarding its aetiology, pathophysiology, and management. In this article, the author discusses a range of unproven concepts in lymphoedema and draws attention to some possible mechanisms. The author also produces some hypotheses on which to base some experiments.

Key words

Elastin destruction
Fibrosis
Hypoxia
Podoconiosis
Yoga

A range of research in lymphoedema remains to be undertaken. Here, the author examines seven topics that require further study, from yoga to elastin destruction.

1. Fibrosis in lymphoedema and scarring have much in common

There is much concern about removing fluid and macromolecules in lymphoedema management. But it is not always remembered that much more of the excess girth in 'big legs' is contributed by collagen (Casley-Smith et al, 1980), and it is surprising how this can be reversed, sometimes even in a short time.

In a previous publication (Ryan, 2009) it was pointed out that some 19th century authors (see Hebra and

Kaposi, 1874; Unna, 1896) believed that fibrosis exceeded oedema, which in elephantiasis is 'slight' by comparison, and should be blamed on inflammation as a consequence of bacterial activity or on venous insufficiency. Today, these authors would recognise the generally held opinion that the phases of wound healing following inflammation include fibrosis, which leads to remodelling and scarring triggered by infection and venous conditions, and these contribute to lymphoedema – and vice versa lymphoedema is present at some time in many wounds (Macdonald and Ryan, 2010). Of course, it is not just collagen that is increased but often also hyperkeratosis and increased adipose tissue must be explained.

Lipoedema is difficult to reverse and the reason why adipose tissue is linked to lymphatic failure is discussed by reference to both old and new literature on the genesis of adipose tissue (Ryan, 2006; Klein et al, 2007). It was no surprise to find obesity and lymphatic failure genetically linked (Karkkainen et al, 2001; Harvey et al, 2005).

Factors disrupting the upper dermis and encouraging fibrosis that will be discussed are chronic upper dermal expansion, neutrophils, hypoxia, cooling, and colloidal silica in an alkaline environment.

I have suggested before that the answer to lymphoedema lies in the transduction of biochemical signals by mechanical forces (Ryan, 1989), preferably at an optimal temperature of 37°C. The epidermal–dermal relationship is disrupted in lymphoedema by chronic expansion of the upper dermis, with the added destruction of a normally protective elastin system (Ryan, 2010). This has immediate and inevitable consequences, whereas destruction of collecting ducts and lymph nodes by cancer, surgery, or filariasis results in lymphoedema only after some time and in a minority of those injured.

2. Lipodermatosclerosis and venous failure

In the phlebology literature there are valid explanations of fibrosis leading to lipodermatosclerosis passing through a stage of high venous pressure, leakage, fibrin deposition and impaired fibrinolysis, and catalysing of TGFβ (Pappas et al, 2007).

Anyone standing immobile for long enough will experience neutrophil sequestration (Moyses et al, 1987) and impaired fibrinolysis in the lower legs (Browse et al, 1977), two phenomena resulting in fibrosis much studied in the 1970s. It has only recently been realised that, in spite of lipodermatosclerosis being a process deep in the skin, the

major tissue expansion occurs in the upper dermis (Gniadecka, 1995). One effect of this is loss of skin pliability, another is waterlogging of the epidermis, which stimulates its repair mode and cytokine production (Hu et al, 1998; Ryan, 2004).

Several studies have shown a gradating increase in skin stiffness down the leg to the toes (Di Palma et al, 1942; Di Palma and Foster, 1942; Midrha and Odham, 1985; Gniadecka et al, 1994; Malm et al, 1995; Olsen et al, 1995). It was Di Palma and Foster (1942), using indentation of the skin with a weight, that first showed that age, sex, seasonal, and cooling influenced indentation. The authors thought the redness observed after indentation of the skin was hyperaemia. To some extent it probably was (see Ryan, 1973), but the weight was also dispersing upper dermal tissue fluid.

In lymphoedema it should not be forgotten that there is additional venous congestion and angiogenesis. This increased blood volume is quickly decreased by elevation, stretch, and compression (Bader et al, 1986). Such a decrease should have an impact on tissue tension and the mechanical stretch of the tissues (by tissue fluid) will be reduced. As such, everyone immobile for long enough will show an early Stemmers sign; hardening of the skin of square shaped toes so that the skin cannot be picked up due to fibrosis. It is a response within the normal range of lymphatic overload occurring to a mild degree in about one fifth of adults. Lymphosyntigraphy, which is sensitive to even mild impairment of lymphatic function, picks up impaired drainage of the lymphatics in the lower leg in many normal looking people who regularly stand or sit for prolonged periods.

3. Destruction of elastin by oedema and neutrophils

One hypothesis is that elastin supports the lymphatics in the upper dermis, helping them to be responsive to movement (Mortimer et al, 1983; 1984a; 1984b; 1985; Ryan and DeBerker, 1995; Solito et al, 1997). It is also possible that the strictly tangential orientation

to the epidermis, and the presence of a hydrophobic coating with vitronectin and plasminogen activator inhibitor, as well as other agents, exist to make cell movement easier (Werth et al, 1988; Hintner et al, 1991) and to give the elastin fibres the property of a 'guidewire'.

This term was first given to them by Hauck (1985) when observing the passage of lipid along elastin fibres in the mesentery. I have argued that it would be impossible for Langerhans cells to be so rapidly transported from the epidermis – taking essential immune information to lymph nodes – without such guidewires (Ryan, 2000).

Mallon et al (1997) showed that in lymphoedema there is a deficit in immunity affecting the induction of contact sensitivity. Interestingly, in psoriasis – in which an impairment of initial lymphatic function has long been postulated (Mortimer et al, 1984c) – there is also a impairment in Langerhans cell migration (Cumberbatch et al, 2006).

In studies of elastin in persons affected by leprosy, carbon inoculated into the skin prior to biopsy was shown to flow along elastin fibres outside the granuloma; the elastin was destroyed within the granuloma and no carbon could be detected therein (Ryan et al, 2002). Sonnex and Ryan (1987) demonstrated increased induction of contact dermatitis by prior application of methyl nicotinate to the skin, which Kaiser (1991) showed increased transport and clearance of technesium colloid by the lymphatics. Ruocco et al (2009) have long written about this defective immunosurveillance concept in descriptions of immune failure in the limbs of patients with lymphoedema.

Although elastin, by resisting tissue expansion in the upper dermis, helps to maintain tissue hydrostatic forces and aids the dispersal of water. Unna (1896) showed it fragments if too much water is inoculated. People with genetic disorders impacting elastin do not get lymphoedema any more frequently than the rest of the population, so

one has to suppose that the orderly replacement of elastin by collagen provides an endogenous sleeve with sufficient stiffness to prevent swelling. This is the case in the less distensible elastotic skin of aging solar damage. In excised skin, the lymphatic and elastin system contract and, as Lubach et al (1990) showed, the physiological functional status of excised skin can only be recovered by restoring 'long stretch' elastic recoil by placing the skin under tension in all directions. Excised elastotic, solar damaged, skin does not contract and skin with its 'short stretch' tight collagen weave, acting as an endogenous sleeve, neither develops lymphoedema nor so easily contact dermatitis.

Where there is no lymphatic system (such as in bone, adipose and brain tissues, the eye) fluids and macromolecules are dispersed perfectly satisfactory. The skin has to be different to these other organs because it is an outer sleeve protecting against a external threatening environment and has an immunosurveillance function.

The superficial network of initial lymphatics in the upper dermis, if possessed of a well-orientated collagen support from birth, is capable of functioning well enough to ensure preferential rapid transport into the low resistance pathways of the collecting ducts, even without the fine tuning of upper dermal elastin. After birth, traumatic events result in scarring, in which collagen orientation is less orderly.

Elastin is destroyed by neutrophil elastase (Parrish et al, 1974). It is of interest that neutrophils are largely replaced by eosinophils in the new born inflammatory process as the skin meets a threatening environment for the first time (Ryan, 2003). Eosinophils do not release elastases. The 'day one' skin phenomenon of erythema neonatorum is an eosinophilic response to the skin meeting the outside world for the first time. It is an age at which the skin is growing fast, and such rapid skin growth with the destruction of elastin at that time would be disastrous.

Neutrophils replace eosinophils a few days after birth, when scarring becomes an end point of wound healing. It is relevant that neutrophils accumulate in the legs, especially when immobile, and contribute to the sclerotic pathology of venous insufficiency (Coleridge Smith, 2002).

While the increase in collagen explains brawny or non-pitting oedema, what exactly does the loss of elastin contribute to, at one and the same time? It is clearly an important loss, as is the disturbance of fibrillin which goes with it (Gerli and Alessandrini, 1995; Solito et al, 2007)

By what stimulus and mechanism does collagen get made by the fibroblast? There are tissues, such as bone, that build their calcium on a network of collagen that is clearly a response to mechanical stress. Collagen deposition in response to wounding is clearly less so in embryos, who do not scar, and much more so in those with a tendency to excessive scarring (Ferguson and O’Kane, 2004). Diseases such as scleroderma confer a fibrosis problem and an autoimmune process may be responsible.

In this whole field, whether one is discussing normal bone, skin pliability, diseases such as scleroderma, or wound healing and scarring processes, the number of publications on collagen manufacture by the fibroblast is gigantic. Therefore, it is surprising that no-one asks the question: “why is collagen formed in lymphoedema?”

The transduction of biochemical signals by mechanical forces has long been an interest, and the number of publications on this relationship continue to grow (Ryan, 1989; 1990a; 1990b; 1995; Rossi et al, 2007; Bhadal et al, 2008).

That is the mechanical part of the story, but today it is a story expanded by a vast literature on growth factors and cytokines. TGFβ being perhaps the most important. To get this story in full, one must turn to the hypertrophic scarring literature (Ferguson and O’Kane, 2004).

4. Thomas Hunt’s hypoxia studies in wound healing

Of all the literatures, I find that of wound healing to be the most relevant when looking at hypoxia. Fibrosis is stimulated by many biochemical processes and, in wound healing, the increased metabolism of collagen and its side product was used by Thomas Hunt and his associates to measure the effectiveness of wound healing. The collagen side product hydroxylated collagen was used as a marker of hypoxia and they studied it over a 50-year research period that included investigations of the influence of retinoids versus steroids.

In his recent lecture to the European Wound Management Association honouring this work, Hunt (2010) once again emphasised the central role of hypoxia in delaying wound healing, and related it to the two enzymes: NADPH-linked oxidases and prolyl hydroxylases. The former converts molecular oxygen to both superoxide and hydrogen peroxide that chemoattracts leukocytes. Prolyl hydroxylase determines the deposition of collagen.

One effect of the NADH–NADPH equation is the production of lactate as a side product. It is also a stimulus to VEGF (Constant et al, 2000). NADPH is mechano-sensitive and thus all that is described above about mechanical transduction is relevant to the VEGF role in upper-dermal angiogenesis.

Arbault et al (1997) showed that the release of large quantities of hydrogen peroxide from a fibroblast by mechanical distortion could be inhibited by NADPH oxidase inhibitors. Grote et al (2003) showed that mechanical stretch affecting NADPH controlled the release of metalloproteinases, which influences collagenase and therefore the removal of collagen too.

Hunt (2010) also discusses perfusion and reperfusion with resultant hypoxia and oxygen free radicals as another part of the story, and activation of the sympathetic nervous system yet another story. Both hypoxia and oxidative stress have been demonstrated to occur in lymphoedema, lymphatic filariasis (Pal et al, 2006) and podoconiosis (Addisu et al, 2010).

5. Yoga and the sympathetic nervous system

One contributor to hypoxia is vasoconstriction. One cause of which is overactivity of the sympathetic nervous system. Enhancing the antisympathetic effects of the parasympathetic system is a feature of traditional Asian medicine, and with this in mind the author has no difficulty in believing that the changes induced by traditional Indian medicine illustrated in **Figure 1** are explicable.

Vaqas and Ryan (2003) suggest that some low technology, self-help manoeuvres were enough to improve lymphoedema. They require a complex of interventions provided by manual



Figure 1. An example of the reduction in lymphoedema achieved over a 56-day period using integrated therapy at the Institute of Applied Dermatology, Kerala, India.

lymph drainage (MLD) and complex decongestive therapy and by even more complex integrated therapy.

The first effect of the Indian system is a reduction of inflammatory episodes and the possibility to discontinue antibiotics. Most likely, this is due to herbal washes and restoration of skin barrier function. At the same time, the elevation and other manoeuvres affecting the venous system reduce venous leakage and tissue tension. As Hu et al (1998) demonstrated, reduction in water content in the upper dermis occurs within 2 hours of elevation.

Elsewhere the importance of emollients in reducing transepidermal water loss (TEWL) has been described, with a number of studies linking epidermal cytokine production and TEWL (Man et al 1999; Ryan, 2004). When TEWL is 'switched off', the epidermal cell ceases releasing cytokines to attract neutrophils. Relevant also is the study of increased TEWL when there is venous insufficiency (Angelova- Fischer et al, 2010). With ultrasound, such venous insufficiency can be demonstrated in a wetter epidermis when there is expansion of the upper dermis. This is reduced by elevation.

Reduction of even a little of the excess oedema in the upper dermis lowers tissue tension. Yoga exercises, breathing, good posture, and leg elevation reduces overload from venous hypertension and also clears central dilated lymphatics and thereby aids lymph flow.

Yoga also controls for the better any imbalances between the sympathetic and parasympathetic nervous systems that negatively impact lymphoedema. Breathing manipulation during yoga has been traditionally through the nose and with one nostril blocked.

Breathing with forced expiration through the right nostril ('hissing like a dragon') stretches the lung tissues and sets into play sympathetic nervous vasoconstriction. Through the left nostril, such breathing stimulates the vagus

parasympathetic nerve and decreases sympathetic nerve discharges (Bkargava et al, 1988; Telles et al, 1996; Jain et al, 2005; Jerath et al, 2006). Mental relaxation and slow breathing increases parasympathetic tone.

Hunt (2010) states: 'there is little doubt autonomic vasoconstriction can overcome even hyperbaric oxygen... vasodilatory stimuli might be useful for increasing delivery of adequate oxygen.' He adds that euthermia is necessary for best concentration of oxygen. The tissues of the leg of untreated lymphoedema patients, in spite of inflammatory episodes, are mostly at below 37°C. Warming the tissues vasodilates, oxygenates, and promotes collagenases, and it should be noted that Ayurvedic management of elephantiasis includes heating.

Yoga is also concerned with posture. Revisiting the debate over whether poor posture-related tilting of the pelvis causes compression of the venous system over the brim of the pelvis (Calnan et al, 1964), and whether incomplete development of the venous system in embryo also causes partial obstruction at that level (Calnan et al, 1962), raises the question of whether the posture of a straight back, stressed by yoga therapists, is helpful (Shrale and Ryan, 2011).

6. Podoconiosis

The pathogenesis of podoconiosis begins as a soft oedema ('waterbag') and finishes as severe nodular fibrosis. We are indebted to Davey et al (2007) for re-emphasising what a puzzle this form of elephantiasis is proving to be. Studies blaming silica for the condition (lack of footwear and exposure to certain soils is meant to explain the entry of silica into the skin) were undertaken by Price (1972) and Price and Henderson (1978), at one stage using a team where I directed a vascular laboratory at The Institute of Dermatology, London University.

I had discussions with Price about the possible lymphoedema link, but did not focus on lymphatics until 1976 (Ryan,

1976). Nor was I aware at that time that Price's studies lacked controls from other causes of lymphoedema.

There are fascinating studies on the genetics and biochemistry of podoconiosis (Davey et al, 2007), but they too lack controls from other causes of lymphoedema. It could be that certain genes predispose some patients to more fibrosis in lymphoedema. I have frequently seen excessive keloidal fibrosis of the legs after de-bulking surgery, and graft sites going on to developed keloids.

One feature of podoconiosis is it that rarely affects patients above the knee. The granulomatous changes seen in the lower leg would be expected to affect the collecting ducts in the thigh – as shown in early studies (Carr et al, 1980) – in which rat foot pad granulomas caused leaking thigh lymphatics. This was blamed on mast cells. Lymphoedematous tissue was used as a rich source of mast cells by Ehrlich (1949), but these have not been remarked upon in the study of podoconiosis. I now believe podoconiosis is due to destruction of the superficial initial plexus underlying the epidermis and is less a disease of the collecting lymphatics.

I have in my possession many of Heffernan's (early investigator into silicosis of the lung in miners) notebooks. In his notes, and many publications on lung silicosis (Heffernan and Green, 1928), there is not one miner described with lymphoedema.

Heffernan's reviews reveal he believed that silica of the lung was not due to an irritant properties of silica, but rather to its formation of a water absorbent colloid in an alkaline environment that upsets the physical properties of the tissues including the lymphatic endothelium. The colloid that absorbs alkaline salts, is an encouraging medium for bacteria. In the lung this is important in tuberculosis.

Heffernan found kaolin, rather than silica, in lymph nodes of the lower leg. He was strongly of the view that kaolin

and coal dust had a protective effect on the alkaline silica colloid causing the dry fibrotic nodule of the later stage.

Part of his argument relates to the fact that we are exposed to silica in many spas without ill effect; what really matters is what silica is combined with through its physical properties. This is where the concentration of other agents in the soil, and its pH, are important. It is of possible relevance that lung function is impaired in Ethiopians to the same extent in persons with podoconiosis as it is in the control population and cases of silicosis of the lung have not been reported (Morrison and Davey, 2009).

It is perhaps not so much manoeuvres to promote lymph flow that are effective in podoconiosis, but protection and treatment of the skin (Ashine et al, 2009). In Indian clinics, there is much emphasis on the use of acid soaps.

7. Two systems: superficial and deep

We are not well made to stand immobile, as has been said often about our venous system. But both veins and lymphatics have a fast-track deep system.

Both superficial and deep systems ideally work together, but can do a fair job separately. Just as different genes control superficial and deep, initial and collecting connections, so such genes may determine when the whole limb versus only the lower leg and foot is affected. The genes controlling the failure of the superficial system are different to those controlling a failure of the deep. Also of interest – since adipose tissues lies deep and have no lymphatics – is the finding that genetically obese mice have no functioning superficial lymphatic system.

Central movements emptying overfilled central and deep lymphatics will encourage emptying from the periphery. Any exercise resulting in transmission of forces to the upper dermis will have a good effect on dispersal of fluid from that site and will reduce lymphoedema by dispersal through the superficial system. Because it is not possible to prevent physiotherapy from having such an effect, I doubt whether it is proven

that reduction of lymphoedema following early mobilisation is effective only because of more central effects. **JL**

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