Transepidermal water loss

Until recently, an unrecognized key to lymphedema

The barrier function and its role in lymphatic overload

By Terence Ryan

Anyone caring for the disabled will be aware of the increasing prevalence of survival into old age and the frequency of both obesity and diabetes. It is natural and common sense to blame lymphatic failure as the prime cause of lymphedema, but Hebra and Kaposis in the second half of the 19th century thought that venous overload might be a contributor[13]. By the 1900s, inflammation was recognised as a contributor and Castellani (1965) continued for 50 years to emphasise this. In the last decade more attention has been given to adipose tissue; it has been long known that lymphedema encourages fat cells in the thickened dermis[5] and that removing fat by liposuction is therapeutic[3]. Mice bred to develop lymphedema are obese[1].

FIGURE 1

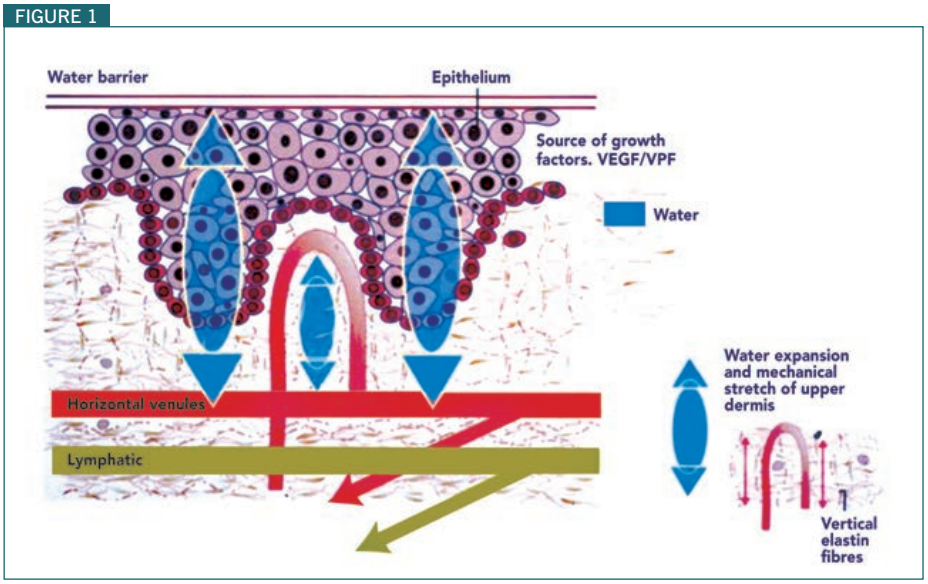

Diagram illustrating dominance of the epidermis over blood capillary bed and lymphatics.

In recent years it is has been realised that the mediators of inflammation found in the dermis are manufactured and released from the epidermis when it is in repair mode and are not the products only of dermal macrophages and white cells[15].

For more than 100 years, entry points for bacteria have been a discussion point for the management of lymphedema. For a much shorter period, almost every discussion about the skin and its diseases has focused on its function as a barrier and the malfunction of deep crevasses and cracks. The value of restoring the barrier when it is failing has been emphasized. In the management of elephantiasis due to filariasis it was realised that treating entry points such as between the toes or avoiding pin pricks and other inoculations was advisable. What must now be emphasized is that the slightest injury to the epithelium affecting its barrier function makes it change its behaviour to a repair mode. In health and at rest the epidermis is an organ almost without mitotic figures, mostly anaerobic and undemanding of oxygen and it is not manufacturing cytokines and growth factors. After injury its basal cells begin to divide and multiply, its upper layers then also demand oxygen and the epidermis releases numerous stimulants to its blood vessels in the upper dermis. This results in neutrophils arriving on the scene. They demand 50 times more oxygen and secrete destructive agents such as elastases.

The practice of prescribing long term antibiotics to treat bacteria entering through the epidermis introduced a topic for discussion such that treating entry points in this way did not always work. Studies in Brazil[7, 8] and India[16, 18] however pointed out that regular washing and the use of emollients compared to daily penicillin, proved that prescribing such antibiotics was not so often necessary when and if the skin was cared for.

One of the commonest of skin diseases, atopic eczema, has led to intensive study of barrier function and treatment when the epidermis fails. There has also been extensive

Terence. J. Ryan, DM, FRCP is Emeritus Professor of Dermatology at Oxford University in London, England and is a mentor for the Lymphoedema Programme at the Institute of Applied Dermatology in Kerala, India. He has held senior posts and founding roles in numerous international dermatology and wound healing organizations from which he has received many Lifetime Achievement Awards.

study of elderly skin which also has less effective barrier function, and dries out and cracks. Such studies have identified control of transepidermal water loss (TEWL) as a prime function of the skin[10]. It has been proven to play a role in moisturization, pliability and prevention of cracks in the surface and exfoliation. Too great water loss results in desiccation and exfoliation, such that the barrier becomes no longer effective.

The skin is designed to perform four functions: to act as a barrier, a thermoregulator, a sensory organ and because of the look-good-feel-good factor and its effect on self-esteem and body image it is also a communicator. We see people mostly before we smell or hear them. This is an especially human attribute. On the other hand, we are less aware of loss of barrier function, though it may contribute to pruritus in the elderly, except by touch when we may perceive dryness or moisturization.

FIGURE 2

Epidermal changes in lymphedema showing deep cracks in the surface which are entry points for soil irritants and bacteria.

There have been many key investigators of TEWL. Paul Matts is one of these who has also taken up elephantiasis as a major interest and has led studies of this barrier failure in lymphedema in its presentation as podoconiosis in Ethiopia. This is elephantiasis resulting from not wearing shoes and working in an irritant soil (Fig 2.). It was at first found that simply wearing shoes prevented the problem. Paul, who is a senior research scientist at Proctor and Gamble in Egham, UK, arranged for a senior nurse, Jill Brooks, to make a PhD study of trans epidermal water loss in this condition as reported by Ryan 2016.

Jill Brooks (2016) found that in podoconiosis the TEWL was severely compromised. What was gratifying was that an emollient—3% glycerine - immediately reversed this. Glycerine/glycerol has many ideal properties (Fluhr *et. al.* 2010); it holds moisture in the skin and is not expensive.

There is a new concept in the offing illustrated by a poster[9] at a meeting of the British Microcirculation Society. It addresses the family of cytokines/growth factors and receptors known as vascular endothelial growth factors VEGF; one of the inflammatory cytokines and growth factors released from the epidermis when traumatised. It postulates that while VEGFA is all about stimulus of blood vascular endothelium and was once named vascular permeability factor, the VEGFC system is all about a response to such permeability. Findings in the kidney led to a discussion about the VEGFC system which opposes VEGFAs excesses by clearance by the lymphatics and by tension dispersion by adipose tissue and could be the epidermal means of protection from permeability

> We must now realise that barrier function of the epidermis is essentially all about control of transepidermal water loss (the Matts Hypothesis) a much more subtle and refined process

overload. We could ask: is there a link here between such control and the reason VEGFC enhances both growth of lymphatics and adiposity? Some bright investigator might explore this further.

Domaszewska-Szostek *et. al.* (2016) have proposed that the cytokines in stagnant tissue fluid/lymph fluid are responsible for hyperkeratosis in human lower limb lymphedema. Of course the epidermis will be affected by the pool of cytokines and growth factors but it is important to realize that the epidermis is the conductor of affairs and a factory of the mediators when stimulated by injury. The hyperkeratosis of lymphedema contains few if any nuclei, unlike the epidermal changes of epithelial stimulus which would more resemble psoriasis, with numerous nuclei present in the upper layers due to fast turnover and in psoriasis exfoliation is more of a feature. The hyperkeratosis of lymphedema is tightly bound and little inclined to exfoliate.


Matts' hypothesis: how simple strategies can lead to better outcomes

Terrence Ryan

Conclusion

For a long time when managing lymphedema we have thought of barrier function in terms of entry points through cracks. We must now realize that barrier function of the epidermis is essentially all about control of transepidermal water loss (the Matts Hypothesis) a much more subtle and refined process which, too, can have a major role in lymphatic overload because of cytokine stimulation of excess blood vascular permeability. The management of lymphedema of course requires interventions to promote flow such as massage, breathing, and body movement. But overload must also be attended to so that the venous system benefits from elevation and ankle movements, or attention to compression in the axilla after protective fat pads are removed. Management of obesity by dietary means, exercise and sometimes liposuction may be added. The low cost intervention of caring for the epidermis by washing and applying emollients now becomes a self-help intervention of great simplicity and effectiveness. LP

A full set of references can be found online at **www.lymphedemapathways.ca**.