

**ELEPHANTIASIS, ELASTIN, AND CHRONIC WOUND HEALING:
19TH CENTURY AND CONTEMPORARY VIEWPOINTS RELEVANT
TO HYPOTHESES CONCERNING LYMPHEDEMA, LEPROSY,
ERYSIPELAS, AND PSORIASIS – REVIEW AND REFLECTIONS**

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ABSTRACT

Both wound healing and lymphedema have fibrosis of the skin in common. They also share destruction of elastin by elastases from neutrophils as a significant feature. These are not new observations, and the writings of Unna and Kaposi are recalled. The contemporary observations on elastin by Gerli and his team are discussed in the light of these much earlier opinions.

Keywords: elephantiasis, wound healing, elastin, elastases, fibroblast, leprosy, erysipelas, psoriasis

Macdonald (1) has proposed that the discipline of wound healing should embrace lymphedema, and a World Health Organization (WHO) white paper on both should serve as a background to WHO taking them more seriously. Much needed for their management is general knowledge about care of the skin.

During the last few decades, management of wound healing and management of lymphedema have come to the fore as disciplines that are both staged into early and late phases of skin responses to injury affecting the vascular systems of the skin with varying degrees of transudation, exudation, and bleeding, followed by inflammation with its four cardinal signs. Swelling accompanies

both wound healing and lymphedema, and a later third stage of organization includes fibrosis and precedes re-modeling. It is this organization phase that embraces a major feature of repair which is overgrowth of tissues. The skin is the most affected organ, and it is skin care that is most often demanded for wound healing and lymphedema. Destruction of elastin is a significant feature of lymphedema and has been noted in wound healing (2).

It was in a review of the lymphatic system in a skin physiology textbook (3) that I first gave the necessary emphasis on elastin as a feature of the healthy lymphatic that essentially contributes to its function (*Fig. 1*). Unna was quoted and in several Dermatology texts since that time (4-9), his views have received reemphasis. Like adipose tissue, which I have also reviewed (10), I see elastin as a neglected component of global significance because of the part played in infectious diseases such as leprosy Buruli ulcer and lymphatic filariasis. Gerli and his colleagues (11,12) have further developed and refined this concept although earlier observations are not featured in their publications. The concept is that healthy lymphatics of the skin are provided with a network of elastin fibers that does three things: 1) Provides snap back and enhanced response to external movements. 2) Links the lymphatic to the epidermis (13).

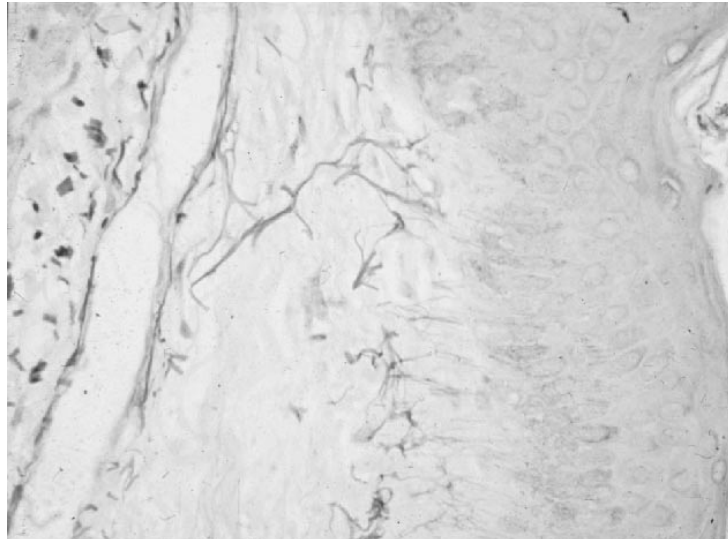


Fig 1: Orcein stain shows elastin fibers surrounding a lymphatic in the upper dermis and linking it by a tangential fiber to the overlying epidermis. Blood vessels in the normal upper dermis do not show a similar appearance and relationship to elastin.

3) Acts as a preferential pathway or guideline from the epidermis to the lymphatic for Langerhans cells and macromolecules entering or manufactured by the body's first line immune- surveillance system (14).

Our hypothesis is that destruction of elastin contributes to lymphatic dysfunction, and it occurs most commonly due to activation of elastases mostly derived from neutrophils. But this is not a new idea, and was well described in the 19th century.

If one focuses for a moment on elastases, then importance must be assigned to the neutrophil and macrophages, which are rich in elastases and, worth noting, that the eosinophil is not. As I illustrated in a study of leprosy (15), lymphatics lose their elastin adjacent to a granuloma. Parish (16) emphasized that localization of infection was determined by inflammatory cells, and it is possible that the cutting of the connection of elastin to the lymphatic is part of the process of localization. But, it is also a factor in the changing resilience of the tissue after wounding.

I have also suggested (14) that the Langerhans cell's brisk movement from the

epidermis to the lymphatic is too rapid to happen without mechanical guidance and that its failure to move readily in psoriasis could be due to the release of elastases from the neutrophils that are a feature of that condition (17).

The historical texts that first described but also confused the terminology of leprosy, lymphedema, erysipelas/cellulitis, and psoriasis are nevertheless informative about this topic and I have been consistent in quoting from such historical texts regarding each of these disorders over the past forty or so years.

19th Century Observations

If one reads dermatology textbooks of the 19th century and turns to the chapters on edema or elephantiasis, growth of tissues is well described.

Contemporary writers on the history of massage for lymphedema usually begin by referring to Winiwarter (18) *Die Elephantiasis* and to Vodder (19), who laid much emphasis on the techniques employed for shifting of lymph. However, the term elephantiasis as

earlier writers emphasized is applied to a condition in which an excess of lymph is often less noteworthy than the hypertrophy of the many tissue components. Furthermore, prior to the mid-19th century, the term elephantiasis was used to describe several disorders including leprosy. Two references are particularly helpful when searching for the early descriptions of elephantiasis.

Hebra and Kaposi (20) describe in great detail the early Greek, Roman, Arabic, and later European writings on swelling of limbs and genitalia and include the conditions which most contemporary practitioners would recognize as lymphedema. But they state *“we use the term Elephantiasis Arabum to indicate a hypertrophy of the fibrous tissue of the cutis and of the sub-cutaneous connective tissue.”* This is an emphasis on overgrowth and *“we convince ourselves, at the same time, that the oedema is, at any rate, slight in proportion to the thickening of the leg, and in the sense of resistance is much more considerable than in ordinary dropsy, anasarca, and resembles that of sclerema.”* Later focus on lymph has refined approaches to its removal but somewhat ignored the issue of how one manages hypertrophy. In this text by Kaposi the dilated lymphatics, the recurrent inflammatory episodes, and the effect of elevation and bandaging are well described.

The second main historical review is by Erasmus Wilson (21), which better than most describes the disease leprosy *Elephantiasis Graecorum* (noted by the Greeks) and conveys how confusing was this early misuse of the term. Equally confusing at this time in the mid-19th century was the use of the term lepra for psoriasis.

Unna's book (22) is of great interest because of its insight into both lymphedema and tissue hypertrophy in response to edema. He describes very well the different responses of the tissues affected by edemas of differing etiology. His descriptions of the damage done to elastic tissue and the hypertrophy of collagen have not been surpassed. For anyone interested in the likely effect of massage on a

tissue depending on structure, this is essential reading. This 19th century text is thoughtful and discursive especially about the collaboration between the lymphatic and venous system in a wide ranging description of skin diseases. The following are some illustrative quotes.

P23 – *“Every oedema of the lymph spaces separates the elastic fibres.”* On this page he also makes the point that when edema is due to external injury of epithelium, abundant mitoses swarming in the basal prickle layer is *“an unfailing symptom”* and which today we would recognize as a repair response for which skin care is well justified.

P26 – Following whealing with stinging nettles: *“The rapid forcible dilation of these pre-existing lymph channels is evidenced in the irregular course of the overstretched, frequently torn elastic fibres, here and there crowded together into bundles.”* This theme of the destruction of the elastic tissue is returned to frequently (viz p39).

P32 – *“Physiology teaches that during rest, no lymph flows from the incised larger lymph channels of the extremities, although every superficial bloodless incision into the papillary body shows that on the surface of the cutis no inconsiderable quantities of lymph are continuously produced.”*

P32 – *“no hindrances in the way of the lymph channels from the skin to the lymph glands and from here to the subclavia, not even the complete obliteration of the thoracic duct would be sufficient to explain one single edema of the skin. We are, therefore, compelled to abandon all these theories of edema, which seek the cause of edema in lymph vessels themselves...”*

Unna makes the point (p33) that edema is most often due to leakage from the venous system. *“The lymph vessels form, physiologically, only a relief track for the lymph during the numerous alterations in calibre of the veins of the skin, brought about by every movement.”* This is a point perhaps insufficiently made in the 21st century.

Unna makes the point that in the edema

of urticaria “*Considerable pressure is necessary to dispel the edema from this part. In contrast to chronic plastic edema the acute cannot be massaged away nor does it follow the law of gravity.*” He proposes that the sharp limitations of the edema of a wheal or a rheumatic urticaria are due to the localization of venular leakage rather than any lymphatic factor, an influence that best explains the confines of even deeper swelling.

When discussing the effect of massage in chronic nephritic edema “*...the skin may be easily pitted and kneaded, it has become plastic, no elastic resistance is perceptible on pressure. The fluid which has been pressed to one side returns very slowly, a depression remains for a long time.*”

In a prolonged section devoted to elephantiasis (pp492-504), Unna describes Elephantiasis Nostras as “*an acquired, inflammatory fibromatosis of individual parts of the body, especially of the legs and genitals... regularly develops in succession to erysipelas or a series of recurrent erysipelata... every true erysipelas tends to leave the affected part more thickened. Chronic persistent erysipelas and elephantiasis nostras are closely related conditions; we know that one may pass into the other.*”

Unna clearly expresses the view that central lymphatic obstruction cannot alone explain elephantiasis but must be attributed to a complex that includes venous “*resistance to the escape of blood as well as recurrent erysipelas.*” He quotes the founder of Manual Lymphatic Drainage (MLD) viz Winiwarter (18) as finding, in a leg amputated for elephantiasis, extensive venous hypertrophy, and both authors find frequent venous thrombi in large and small veins. Unna refers to many previous authors assuming “*a primary share of the blood vessels in the production of elephantiasis swellings.*” Like other infections such as tuberculosis and syphilis, he blames fibrosis on the healing response to infection and states that “*All the elements of the skin in turn share in the hypertrophy*” except as he frequently points

out, there is almost complete atrophy of elastic tissue. All this he states is accompanied by passive dilation of the lymph vessels and lymph spaces (p498).

In a section on “Elephantiasis Filariosa, Lymph Scrotum” in which he frequently quotes Manson, Unna recognizes identical features to Elephantiasis Nostras as well as commonly a more prominent lymph stasis. He records the role of erysipelas like infections up to 50x per year and blames filaria themselves sited in the cutis for some of the hypertrophy.

Thus, these early writers emphasized overgrowth rather than edema while a century later hypertrophy of tissues was well illustrated by the studies of Casley-Smith, Clodius, and Piller (23). Indeed, like Unna they find the collection of lymph very little more than normal compared to the huge increase in collagen. What they did not emphasize is that there is one component of the tissue which is greatly reduced in lymphedema. It is elastic tissue. Credit must be given to Unna in noting that even the injection of saline will lead to the destruction of elastin.

Mechanical Tension and Collagen Production

There have been many studies showing that the fibroblast manufactures collagen as a consequence of increased mechanical tension. I developed a theory for the skin that others had used for bone and other tissues that transduction of biochemical signals by mechanical stresses is a part of the behavior of the fibroblast essential to the understanding of the skin’s response to injury (24-28). At that time, we did not know about cytokines such as TGF that might be released, but we evolved a theory of lymphatic responses that were part of the normal response of the skin to mechanical stresses. The biochemical signal was phosphorylation by cell membrane enzymes, switched from the interior of the cell to the cell surface by chemical or mechanical distortion of the membrane,

controlling factors such as cell grip and stick to surfaces (24). We suggested that this process accounted for the lymphatic endothelium's sensitivity to mechanical forces (29) and emphasized the role of activators and inhibitors of the plasminogen system in a presentation to the International Society of Lymphology Congress in Adelaide in 1985 (30). Gerli and his group (31) have recently also emphasized a similar role for mechanical stresses that influence the fibrillar components of the dermis.

It is likely that the loss of elastin and its replacement by collagen adds to the tension felt by the fibroblast in response to tissue fluid accumulation and generates more collagen of a type that is short stretch and encourages the build up of the endogenous stocking that partly prevents further expansion of the tissues (32). The control of this fibroblast response is, as has been learned from wound healing, a variable that provides phenotypic variations including keloid formation, and in elephantiasis, huge nodularity. It may also have much to do with the loss of elastin in the upper dermis, which would influence the exit of excess fluid and macro-molecules from the lymphatics (33), expansion of that region due to tissue fluid and its impaired response in aged skin wound healing.

Returning to Unna in 1896, one can see that anything leading to elastase production may be associated with fibrosis, and it is the presence of neutrophils in recurrent inflammatory episodes and from venous hypertension that is most significant. Unna and his colleagues looked to breakdown of the epidermal barrier to bacteria as one cause of this and venous impairment another. The call for repair of the epidermis is done by switching on its repair response (34) and the release of cytokines to recruit neutrophils to the dermis. The white cell theory of venous pathology (35) provides evidence for how venous impairment has a similar effect. Of interest, too, are studies that show immobile standing, or dependency of the legs also

causes neutrophils to arrive in the skin of the lowered leg (36).

The story begins to evolve on which a basis for current therapy of lymphedema makes more sense.

1) Epidermal barrier function when intact is not in repair mode and provides no cytokines for repair. Even minimal impairment of barrier function switches on a repair mode that pours cytokines into the dermis calling on neutrophils to arrive. Washing and emollients can switch off this response and as such it is the "First Commandment of Skin Care" (33).

2) In the newborn, there are abundant reasons why the vulnerable epidermis with its heightened entry points might not respond in this way and for a few days. It is eosinophils, lacking elastases, that are called to the scene, and the clinical response is given the name of Erythema Toxicum (37).

3) The cytokine and growth factor wave in acute wound healing (38) becomes a "tsunami" in chronic wound healing/tissue repair, and by accompanying lymphatic failure ensures that the healthy removal of such macromolecular agents and cells is delayed, and the tissues of all types are stimulated into a prolonged phase of overgrowth. This response is appropriate for wound healing but contributes to the elephantine changes of lymphedema (39), the lipodermatosclerosis of venous impairment, and the loss of epidermal integrity with entry points for bacteria and irritants.

4) It is of interest that psoriasis has often been used as a model of wound healing (40). The preferential sites for psoriasis are locations where there is excessive stretching – at the elbows and below the knees during flexion. Such stretching tears at the epidermis and sets into motion both enhanced water loss, new vessel formation (41), and a call for neutrophils (42). The extent to which lymphatics fail in this scenario has long been debated (43,44).

5) The aim of wound healing is complete restoration of the barrier function of

the epidermis, and this has proved to be a main objective of lymphedema management. Elevation and deep breathing are helpful, too (45), and one explanation is that they reduce venous overload with leakage into the tissues that contribute to lymphatic overload, fibroblast tension, and neutrophil elastases.

CONCLUSION

It can be seen that the 19th century authors were astute observers and that there is a case for controlling mechanical forces by taking the tension off the fibroblast and reducing the expansion of the tissues by reducing lymphatic overload. As Macdonald has written (1), there are common denominators that justify integrating wound healing with lymphedema. Developing a program of care merits bringing together observations and research on lymphatic function and skin diseases such as psoriasis, wounds, and lymphedema. Such information and insights may be sought in the literature of other systems of medicine. Thus, in Asia where there is recognition and treatment of different differing phenotypes (46), there may be better systems of reducing tension on the fibroblast as well as herbals that counteract some of the harm done by elastases, cytokines, and growth factors.

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