

COMMENTARY

**MISSTEPS WHEN MICE WITH LYMPHATICALLY
INSUFFICIENT TAILS LEAP FROM MOLECULAR BIOLOGY
TO HUMAN CLINICAL LYMPHOLOGY**

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ABSTRACT

A cautionary note is provided about making translational leaps from molecular biology and murine lymphedema models to clinical lymphology.

Keywords: lymphedema, animal models, inflammation, translational medicine, molecular lymphology

Tabibiazar et al recently published a notable paper entitled “Inflammatory manifestations of experimental lymphatic insufficiency” (1). The authors studied an experimental model of acute post-surgical lymphedema in tails of mice. They performed in vivo imaging of impaired immune traffic. They found marked acute inflammatory changes (sheets of neutrophils) in the dermis and the subdermis. Accordingly, and perhaps not surprisingly, the molecular pattern in the RNA extracted from the whole tissue was dominated by the upregulation of genes related to acute inflammation. Also upregulated were those concerned with immune response, complement activation, wound healing, fibrosis, and oxidative stress response.

The Editorial Commentary accompanying the paper, designated as “Perspectives,” is “envisaged for experts to discuss the clinical practice or public health

implications of a published article.” It was, nonetheless, written from the perspective of molecular biologists (2) and contains several serious mistakes:

1. According to the authors, “the increased interstitial pressure (in human lymphedema) may collapse the veins, further aggravating the condition and in severe cases even necessitating amputation.” In the course of over a quarter of a century, more than 50,000 patients suffering from lymphedema have been treated in the Földiklinik. Not in a single case have the veins been found to be collapsed by an increased interstitial pressure! Disturbances in venous circulation are only present in phlebo-lymphedema (subfascial CVO), in cases of primary lymphedemas accompanied by valveless veins, and in lymphedemas complicated by severe varicosity, leading to suprafascial CVI.

There is only one indication in industrialized countries for amputation: angiosarcoma, or, even more rarely, another malignant tumor. In the surgery-oriented book *Diseases of the Lymphatics* (3), the word “amputation” is mentioned only once: in the section “Lymph/Chyle reflux into the lower limbs.” The authors state: “Do not perform an amputation!” Among our 50,000 patients, amputation was never indicated.

2. According to the authors “for lymphedema... current medical practice still relies on ancient procedures, such as manual lymph drainage...” Today every clinical lymphologist is well aware of the time honored fact that Combined Decongestive Treatment (CDT) is comprised of: cure and care of the skin; manual lymph drainage (MLD); remedial exercises; and compression. The cornerstone of this tetrad is compression! Although compression has been employed for the treatment of lymphedema – as for phlebopathies! – for millennia, no expert ever questions its effectiveness. Besides CDT, in suitable cases, lymphedema, as well as its secondary deformities, may also be treated by surgery, including microsurgery.

3. Schneider and his co-authors state, that “research progress in the field (of the treatment of lymphedema) has been hampered by the lack of suitable experimental animal models.” They seem to be unaware of the pertinent literature. Starting with Drinker et al (4) and Homans et al (5), who produced in 1934 chronic lymphedema in dogs, later several other authors have described suitable models of secondary lymphedema. In the book *Lymphedema*, published in 1977, there is a chapter entitled “The experimental basis for the surgical treatment of lymphedema” (6). By using the models devised by Clodius, conservative methods of treatment (CDT, drugs, genes) could be studied as well. These models are more suitable for this purpose than the mouse-tail model since even Schneider et al themselves point out, that “a mouse tail lacks lymph nodes which may play a critical role in fostering the immune response and inflammation in human lymphedema.” The model of Clodius includes lymph nodes, as do other models cited by Schneider. There have been several earlier reports on mouse tail lymphedema models (vide infra) not cited in Tabibiazar et al.

4. Aside from highlighting the paper of Tabibiazar et al, the authors of the

Commentary should have called attention to observations made long ago by Winiwarter (7), Professor of Surgery in Lüttich, that lymphedema is a form of inflammation. In his book, published in 1892, entitled *The Surgical Diseases of the Skin and the Interstitium* (the German translated into English), lymphedema constitutes one of the chapters! Curiously, the inflammation described by many others since then in both human lymphedema and the aforementioned earlier animal models does not involve “sheets of polymorphnuclear neutrophils” as in Tabibiazar et al but other populations of white blood cells – monocytes, lymphocytes, mast cells, etc. These acute inflammatory cells in Tabibiazar et al, are more characteristic of acute bacterial infection (which often complicates chronic lymphedema and may also precipitate lymphedema). The granulation tissue associated with deep wound healing, or localized tissue necrosis seem to be unique to Tabibiazar’s preparation and perhaps not provoked by the type of “sham operation” used as a control.

5. Related to the originality of the mouse tail model. In 2003, Boardman and Swartz (8) also described a mouse-tail model – they called it a “collagen dermal equivalent” model – in order to study fluid channel formation, cellular infiltration, protein expression and lymphangiogenesis. Even earlier, Slavin and colleagues (9) extensively described a mouse tail lymphedema model describing lymphatic imaging and improvement with pedicle grafting.

6. There has also been evidence presented previously of upregulation of genes related to inflammation in humans suffering from lymphedema and its reversal by CDT (10).

CONCLUSION

Due to the vast specialization in modern medicine, the limits of our knowledge have to be recognized. To avoid the criticism: “Si

tacuisse, philosophus mansisses” [“If you would have remained silent, you still would be a philosopher”](11), clinical lymphologists should exercise caution not to comment on the suitability of an immunohistochemical marker employed by molecular biologists to distinguish between lymphatics and veins. On the other hand, molecular biologists, even those holding medical degrees but without specialized clinical experience and historical perspective, should be as cautious when leaping from molecular observations in a acute mouse tail model to comments about the treatment of patients suffering from lymphedema.

REFERENCES

1. Tabibiazar, R, L Cheung, J Han, et al: Inflammatory manifestation of experimental lymphatic insufficiency. *PLoS Med* 3 (2006), e254. DOI: 10.1271/journal.pmed.0030254.
2. Schneider, M, A. Ny, C Ruiz de Almodovar, et al: A new mouse model to study acquired lymphedema. *PLoS Med* 3 (2006), e254. DOI: 10.1371/journal.pmed.0030264.
3. Browse, N, K. Burnand, P. Mortimer: *Diseases of the Lymphatics*. Arnold, London, 2003.
4. Drinker, CK, MJ Field, J Homans: The experimental production of edema and elephantiasis as a result of lymphatic obstruction. *Am. J. Physiol.* 108 (1934), 509–516.
5. Homans, J, CK Drinker, M Field: al: Elephantiasis and the clinical implications of its experimental reproduction in animals. *Ann. Surg* 100 (1934), 812-832.
6. Clodius, L (Ed): *Lymphedema*. Thieme, Stuttgart, 1977.
7. Winiwarter, A: *Die Chirurgischen Krankheiten der Haut and des Zellgewebes*. Enke, 1892.
8. Boardman, KC, MA Schwartz: Interstitial flow as guide for lymphangiogenesis. *Circ. Res.* 92 (2003), 801-808.
9. Slavin, S, AD Van den Abbeele, A Losken, et al: Return of lymphatic function after flap transfer for acute lymphedema. *Ann. Surg.* 229 (1999), 421-427.
10. Foldi, E. et al: Effect of complex decongestive physiotherapy on gene expression for the inflammatory response in peripheral lymphedema. *Lymphology* 33 (2000), 19-23.
11. Boethius, AMS (Born 480, died 524). *De Consolatione Philosophiae*.

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