Lymphology 35 (2002) 129

LETTER TO THE EDITOR

NEW POSSIBILITIES IN THE PATHOGENESIS OF SECONDARY LYMPHEDEMA

In his letter [Lymphology 35 (2002), 41-42], Professor Olszewski rightly stresses the high incidence of arm lymphedema after mastectomy. However, the "rough" surgical technique and later infections to which he refers cannot be the whole story.

The conundrum which faces all lymphologists is the time scale of the process. All too often a good initial result comes to grief months or years later, with lymphedema emerging even in the absence of overt episodes of dermatolymphangitis. The clinician may then be faced with the gradual but remorseless atrophy of regional lymphatic structure and function, which no treatment can reverse. In any discussion of the subject ideas about fibrosis, chronic infection, venous insufficiency, hemadynamic changes, failure of the lymphatic pulse, autonomic deficit, etc. are usually advanced but none of them amounts to an adequate explanation of this insidious decay. It is time to look elsewhere and recent research in other fields may be pointing the way.

Studies of the amyloid-like proteins found in Alzheimer's disease have revealed that the immediate precursors of the characteristic fibrils are highly cytotoxic to mammalian cells (1,2). Note that the mature fibrils are non-toxic, only the evanescent "protofibrils" are damaging. The molecular basis is complicated but an explanatory review is available (3). The propensity to form such toxic protofibrils seems to be inherent in most soluble proteins and can occur spontaneously *in vivo*. The implications of these findings for the pathogenesis of lymphedema are striking. Even sub-clinical lymphedema would provide enough relatively stagnant plasma proteins to initiate the generation of toxic protofibrils. Initially, these would be removed by specialized macrophages but the number of such cells in peripheral tissue fluid is low (4). Sooner or later they would be overwhelmed and the toxic aggregates would be free to enter the still functioning lymphatics. In this way, the toxic onslaught would be focused on the lymphatic vessels which would gradually wither and die, thus completing the vicious circle of more lymphedema, more toxic aggregates and more lymphatic damage.

Of course, this is only an hypothesis; yet it provides a necessary but sufficient explanation of secondary lymphedema, and it is susceptible to experimental test by those who have the appropriate facilities.

REFERENCES

1. Bucciantini, M, N Gianonni, F Chiti, et al: Inherent toxicity of aggregates implies a common mechanism for protein misfolding disease. Nature 416 (2002), 507-511.
2. Walsh, DM, I Klyubin, JV Fadeera, et al: Naturally secreted oligomers of amyloid and protein potently inhibit hippocampal long term potentiation *in vivo*. Nature 416 (2002), 533-539.
3. Ellis, RJ, TJT Pinheiro: Danger–misfolding of proteins. Nature 416 (2002), 483-484.
4. Barfoot, R, S Denham, LA Byure, et al: Some properties of dendritic macrophages from peripheral lymph. Immunology 294 (1989), 233-239.

J.G. Hall, MB, PhD, FRCPath
Emeritus Professor of Immunology
University of London
Late Institute of Cancer Research
C/o 14 Banstead Road South
Sutton
Surrey SM2 5LF, United Kingdom