Fibrosis is the central defect in systemic sclerosis. It is, of course, manifest in the skin, lungs, and gastrointestinal tract where fibrosis contributes directly to organ malfunction. Fibrosis is also fundamental to the vascular lesion in scleroderma, where intimal fibrosis causes structural vascular disease that plays a key role in digital ischemia, in renal disease and in pulmonary hypertension. At the same time, vascular disease appears to have a second independent pathogenesis with functional vascular abnormalities preceding structural changes. In addition, changes in nailfold capillaries and cutaneous and visceral telangiectasia appear to result from endothelial damage that might lead to vascular fibrosis. Indeed, vascular disease per se, via hypoxia and/or endothelial cytokines might play a provocative role in initiating fibrosis. Finally, evidence has accumulated that the immune system is activated in scleroderma and plays a key role in at least some organ systems, such as fibrosing alveolitis of the lungs and cutaneous disease. Carwile suggested that the immune system might have something to do with regulating fibroblast behavior. During my fellowship with Carwile several years later, that idea became a foundation for many years of work. Subsequent studies in our laboratory showing that the immune system might play a role in fibroblast “imprinting” via clonal selection and/or activation were an outgrowth of those initial interactions we had (4-6). It is quite possible, of course, that vascular events might lead to fibroblast changes in a similar manner, possibly also acting by enhancing sensitivity to TGFβ (7, 8).

What’s wrong with the scleroderma fibroblast?

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Clin Exp Rheumatol 2004; 22 (Suppl. 33):
S64-S65.

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RHEUMATOLOGY 2004.

Key words: Fibroblast, scleroderma,
pathogenesis.
Carwile was a true student of the disease: he had an ability to pose the appropriate questions and hypotheses. He formed a foundation for experimental studies in scleroderma that will have a lasting effect on fundamental and clinical investigations in scleroderma.

References