Scleroderma is characterized by the relentless development of microvascular obliteration and interstitial fibrosis with a widely variable clinical expression. The etiology and pathogenesis of this disorder are not known. A brief discussion of pathogenesis can be divided into extracellular matrix, fibroblast activation by cytokine and/or growth factors, and autoimmune features.

EXTRACELLULAR MATRIX

The hallmark of SSc is taut skin. Edematous initially, the skin becomes eventually hidebound. Excessive quantities of types I and III collagens, fibronectin, and several different proteoglycans can be demonstrated in the skin and also can be observed in tissue culture to be increased in concentration by measuring both message (mRNA) and protein product levels of these connective tissue components. The earliest increases in synthesis are in fibronectin, type III collagen, and proteoglycan synthesis (glycosaminoglycan synthesis, the carbohydrate moiety of proteoglycans). Later increases in type I collagen can be demonstrated. The connective tissue deposited in scleroderma skin and in visceral organs is qualitatively similar in all respects to the connective tissue deposited in wound healing, or other examples of human fibrotic disease, such as cirrhosis of the liver, pulmonary fibrosis, and atherosclerosis. It has
been demonstrated that N-terminal collagen propeptides, released in the processing of procollagen to collagen, can inhibit further collagen biosynthesis. Whether this feedback inhibition mechanism participates in the failure to regulate collagen biosynthesis noted in scleroderma remains to be demonstrated. In large measure, the regulatory mechanisms relevant to fibronectin and proteoglycan are completely unknown, both in health and in scleroderma. Evidence for collagen stimulatory and collagen inhibitory factors has been obtained by the fractionation of peripheral blood mononuclear cell supernatants (1).

Fibroblast activation can be demonstrated, in addition to the expression of increased matrix synthesis discussed above, by the presence of as yet subtle and only partially characterized abnormalities of growth regulation. Lesional cells from involved skin of scleroderma patients are resistant to the induction of quiescent synchronization of the cell cycle by serum deprivation, suggesting an unregulated, endogenous capacity for cell proliferation as a potential pathogenetic feature of the disease. In addition, an insensitivity to the anchorage-dependent, mesenchymal cell growth factor, platelet derived growth factor (PDGF) suggested that PDGF, which can be expressed by platelet aggregation and alpha granule release or by de novo synthesis by activated macrophages or stimulated endothelial cells, may participate in the growth regulatory abnormality of scleroderma fibroblasts. As more of the intricate biology of growth factor-cell receptor interactions are revealed by receptor methodology and proto-oncogene expression and regulation, it seems likely that other factors, such as transforming growth factor-β (TGF-β) or some of the B-cell growth and/or differentiation factors, may provide multiple signals for the phenotypic expressions of fibroblast activation.

Whether the immune response provides signals for fibroblast activation
remains to be precisely defined. Interleukin 1, a monocyte product, is slightly proliferative for fibroblasts and in addition IL1 interacts with tumor necrosis factor (TNF), alpha and beta, in such a way that waves of fibroblast activation can be contemplated in vivo during monocyte activation (antigen-specific or antigen-nonspecific). Interleukin 2 and its product, the lymphokine-activated killer cell, can, via a potent injury capacity to endothelial cells and subsequent platelet release, activate fibroblasts in the interstitium. Interleukins 3 & 4 are also capable of fibroblast activation via their capacity to expand and differentiate cells of the mast cell-basophil lineage. Mast cells have a number of molecules at their command which activate fibroblasts, including histamine, serotonin and selective proteinases. Other products of T-cell activation, including TNF and lymphotoxins and other partially characterized factors have been shown to activate fibroblasts; the precise mechanism of the activation and the precise molecular domain of the signal for activation remain to be precisely defined. Cytokines could be important in their own right, as well as in a capacity to enhance the fibroblast responses to competence and progression growth factors. It will be an exciting chapter in the understanding of scleroderma to see the cytokine-growth factor interactive mechanisms unfold over the next few years. Modulatory effects of autocrine mechanisms via eicosonoid and leukotrines molecular signals may also be important here. Data regarding the remarkable effects of TGF-β on endothelial cell growth and receptor expression will be presented (2).

Autoimmunity in scleroderma has become increasing interesting, despite the realization that the biological significance of the very selective manifestations of autoimmunity in this disease remains unclear. More than 95% of patients with scleroderma are reactive with one or another nuclear or cytoplasmic antigen. The major well-characterized contenders are
centromere-kinetocyte epitopes, topoisomerase I epitopes, RNA polymerase I epitopes and other nucleolar antigens. It would be intriguing to attempt to link the origin of these autoantibodies to the state of fibroblast activation but these areas of investigation have progressed along independent lines to this point. Autoimmunity to type IV collagen and to the attachment protein laminin have been observed in scleroderma as well, but again the biological significance of the autoimmune phenomena remains to be elucidated.

Much new information is available in the study of scleroderma. It is hoped that this conference will provide insights into the common and interactive pathways which might promote a new and comprehensive hypothesis of pathogenesis on which to design experiments for future investigators.

REFERENCES
