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PATHOGENESIS AND STAGING OF SCLERODERMA[1]

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Abstract. Scleroderma is reviewed as a complex disease of vascular, connective-tissue, and inflammatory reactions. If the scleroderma syndromes related to occupational, immunologic, inflammatory, metabolic, and genetic factors are recognized, then true progressive systemic scleroderma (PSS) appears to be a disease of vascular fibrosis with secondary inflammatory phases. The primary pathology appears to be a fibromucinous change of the vascular endothelium. The vessels also demonstrate altered reactivity to cold and to serotonin. Biopsy of the skin of the inflammatory or mesenchymal scleroderma may reveal (by positive direct immunofluorescence) deposition of globulins at the basement membrane zone. Evaluation of scleroderma is discussed and a system of clinical staging of PSS is proposed which relates the organ involvement to the prognosis.

Key words: Scleroderma; Pathogenesis

Scleroderma may be defined as a disease complex of vascular changes, fibrosis, and inflammation that to varying degrees involves skin and visceral organs. Older classifications depended on clinical observation and clearly separated cases of vascular fibrosis (acrosclerosis) from cases of inflammatory fibrosis, often without vascular change (diffuse scleroderma). This simple clinical separation continues to have some value because it can readily give a more benign prognosis of acrosclerosis. However, it does not adequately account for the cases of mesenchymal scleroderma ("mixed" connective tissue disease) or other syndromes that have been recognized. It is important to recognize that vascular-fibrosis forms of scleroderma may also occur in patients whose primary disease is lupus erythematosus or dermatomyositis. Similarly, patients with vascular-fibrosis forms occasionally have secondary inflammatory phases that may or may not change the long-term prognosis. By a division based on the presence or absence of vascular changes, the elements of scleroderma are used to establish the major syndromes. The primary event in scleroderma may include changes of vessels or fibroblasts, or an inflammatory response, or any combination of the three.

Scleroderma
Vasculopathy↔Sclerosis↔Inflammation

Vascular-Fibrosis Form of Scleroderma

Vascular fibrosis is the most common form of scleroderma and is best described as true scleroderma. The term acrosclerosis indicates cutaneous and visceral sclerosis associated with vascular changes. Raynaud's phenomenon, which occurs in 80–90% of patients with scleroderma, is the major indicator of this vascular sclerosis (76). The female predominance in the disease is particularly high. The presence of chronic Raynaud's phenomenon and chronic sclerodactylia with calcinosis, telangiectasia, and various visceral lesions comprises the Thibierge-Weissenbach or "CRST" syndrome. Vascular fibrous lesions account for the visceral changes in the gastrointestinal tract, lungs, kidney, muscle, and skin. Norton & Nardo (54) noted the severe loss of tissue substance associated with vascular fibrosis in visceral lesions; atrophy, as well as fibrosis, occurs in gastrointestinal and musculoskeletal tissue and other viscera (17). The degree and localization of vascular fibrosis make possible the recognition of certain unique acroscleroderma syndromes (Table I).

The primary vascular lesion is noninflammatory fibromucinous endothelial proliferation in the small vessels of the skin and viscera. In most organs the large vessels are normal; only in small arterioles (100 μm to 2 mm) is this pathology demonstrable

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Table I. *Syndromes of vascular scleroderma*

Acrosclerosis
Raynaud's with sclerodactylia
Intestinal scleroderma
Pulmonary interstitial fibrosis
Renal scleroderma
Cardiomyopathy

(Fig. 1). In the kidney the interlobular arteries are involved (62). The vascular change occurs without inflammation, although secondary inflammation has been described in visceral lesions (12). Secondary hyaline change of the vessel wall may be found, particularly in the kidney, and adventitial sclerosis also may be observed. Biopsies of the dermis rarely demonstrate the vascular lesion, although some thickness of the dermal vessel wall has been described (55). On electron microscopic examination the basement membrane of small vessels in skeletal muscle has been reported to be markedly thickened (54); no similar study of other organs has appeared in the literature. However, an increase in capillary mitosis in sclerodermatous skin has been reported recently (22).

The vascular lesions of small skin vessels of the extremities can be demonstrated by direct vision (8) and angiography (16, 69). Measurements of skin temperature, heat loss, blood flow, and clearance of radioactive isotopes have shown severely depressed circulation in sclerodermatous skin (14, 18, 42, 46, 70). Whenever functional blood flow studies have been done, tissue affected by scleroderma has been found to have diminished circulation. Reduced plasma renal flow has been noted in visceral sclerosis (43); and malignant hypertension and death from renal failure are common with end-stage scleroderma. Reduced lung perfusion and pulmonary hypertension are often early signs of scleroderma (64, 74). Peritoneal clearance may be lessened in scleroderma (9).

Impaired circulation due to vessel fibrosis does not explain the whole complex vascular response of scleroderma. Lewis (44) believed that an abnormal vessel response to cold temperatures was the primary event. The unusual response of scleroderma skin vessels to cold has been studied with preparations of isolated vascular smooth muscle (85). A rapid depression of the response to catecholamines with cold temperature (Fig. 2) and a lowered threshold of response to catecholamine were found. These, as well as an elevated catecholamine dose–response curve at 27°C, indicate that Lewis (44) was correct in his assumption of a special cold-sensitive response of vascular smooth muscle. This physical alteration of a pharmacologic response must relate in part to the vessel pathophysiology of scleroderma.

Vascular smooth muscle receptors respond to a number of pharmaceutical agents. An increase in the number, variety, or responsiveness of receptors would determine the responsiveness of the vessel. Studies of the catecholamine (epinephrine, norepinephrine, and isoproterenol) response of scleroderma skin vessel strips do not show any abnormalities of the threshold or dose–response curve (84). Catecholamine metabolism in patients with scleroderma is normal (59, 65). Responses of isolated vessel strips to bradykinin and prosta-

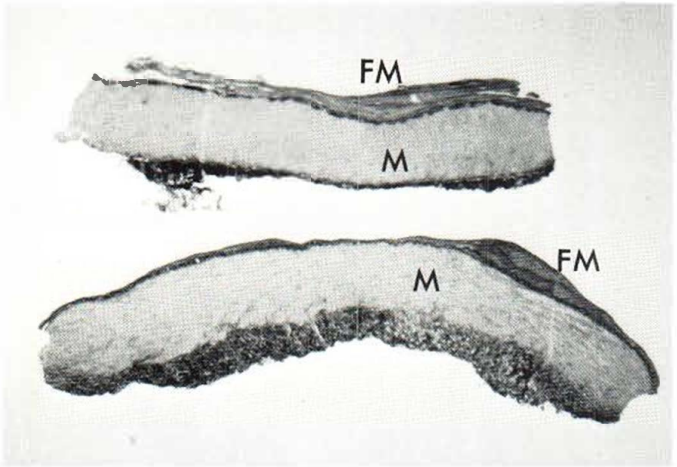

Fig. 1. Longitudinal sections of 800-μm subcutaneous vessel from wrist of patient with scleroderma. Media (*M*) and adventitia (*A*) are normal. Note lamellated fibromucinous (*FM*) plaque representing endothelial lesion of scleroderma. (Elastic-van Gieson; ×4.5).

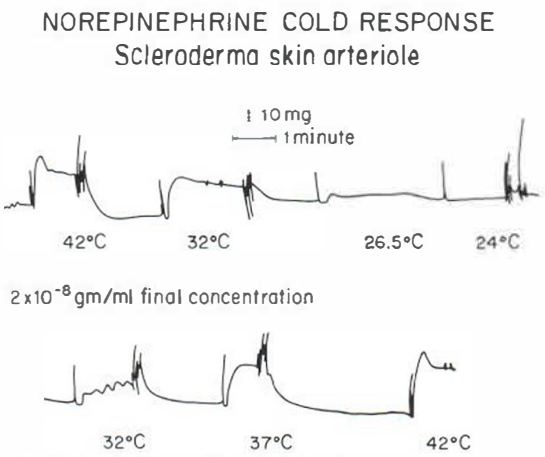

Fig. 2. Variation, with reduction in temperature, of response of skin vessel strips to catecholamine. Normal vessels respond until temperatures of 5 to 10°C are attained.

glandin E_2 have been normal (84). Prostaglandins potentiate the effects of catecholamines on the vasculature, and studies of this in sclerodermatous vessels are needed. Angiotension has been reported to be particularly active in scleroderma (63) but this also requires further study.

Hypersensitivity of isolated strips of vascular smooth muscle from sclerodermatous skin of four of five patients with Raynaud's scleroderma (i.e., systemic vascular fibrosis, acroscleroderma) and visceral disease shows that receptor response may be related to the pathophysiology of scleroderma (84). All five patients demonstrated the fibromucinous endothelial change of the vessel studies, which indicates that microscopic pathology and serotonin hypersensitivity are not interdependent. The metabolism and excretion of serotonin in scleroderma patients are normal (75). However, in vitro studies by Halpern et al. (25) demonstrate that intra-arterial serotonin in normal persons causes the same vascular spasm and delayed relaxation as is induced by cold in patients with Raynaud's phenomenon (49). Scherbel & Harrison (66) produced prolonged vasospasm by intracutaneous injection of serotonin into the dorsum of the hand.

Serotonin has been related to scleroderma before; in one study (23) four patients with carcinoid syndrome had pulmonary and myocardial fibrosis and increased sclerosis of the extremities. In another (50), the tumor most frequently observed with scleroderma was carcinoma of the lung (usually bronchial adenocarcinoma of the alveolar type), in which blood serotonin may be increased (10, 29). Boucek and associates (5, 6) demonstrated that some tissue cultures of fibroblasts respond to serotonin stimulation by increasing growth. The relation of the vessel changes to fibrosis might conceivably involve tissue response to the same mediator, serotonin, but the fibrosis also may be related to decreased circulation, or an immunologic or toxic response to the primary vessel pathology.

The fibroblast could also be the origin of a primary lesion for scleroderma. LeRoy (40) described slow growth of fibroblasts in scleroderma, a finding confirmed by Titus & Winkelmann (71). Kovacs & Fleischmajer (38) were able to increase the growth of sclerodermatous fibroblasts toward normal values by the addition of 10% fetal calf serum. LeRoy (41) found sclerodermatous fibroblasts to be morphologically normal by light and electron microscopy. He emphasized that they synthesize more hydroxyproline-rich, salt-soluble collagen than do control fibroblasts (41). Increased salt-soluble collagen has been extracted by many authors from skin biopsies of patients with scleroderma. This has been used as a sign of disease activity (79, 88), particularly when coupled with evidence of reducible aldiimmine bonds (28). The dermis in scleroderma is not hypercellular, does not contain abnormal collagen or protein, and has no major increase in polysaccharides (81). Measurements of increased polysaccharides in skin and urine correlate generally with severely ill patients and not with a specific type of disease or prognosis (26, 39).

The chromosomes of the scleroderma leukocyte and fibroblast have been reported to be abnormal. Ring forms, marker chromosomes, and increased breakage were observed by Emerit et al. (19) and Pan et al. (57), but Breathmach et al. (7) could not reproduce these results. Emerit et al. (19) later reported a serum factor that caused chromosomal abnormalities. Most recently, Tolchin et al. (72) noted a significant increase in chromosome abnormalities occurring in the leukocytes of patients with rheumatoid arthritis and systemic scleroderma treated with cytoxan.

Scleroderma could be considered as the aggressive counterpart of the slow, indolent fibroses of plantar and palmar fascia, Dupuytren's contracture, and carpal tunnel fibrosis. Recently, sclerosing syndromes involving the mesentery and retroperitoneal tissue and biliary cirrhosis have been

Table II. *Sclerodermoid syndromes*

Metabolic	Immunologic	Environmental	Neoplastic	Genetic
Porphyria	Lupus erythematosus	Vibration	Carcinoid	Werner's syndrome
Amyloid	Dermatomyositis	Silicosis	Other malignancy	Phenylketonuria
Biliary cirrhosis	Sjögren's syndrome	Polyvinylchloride		
	Scleromyxedema			

described. Methysergide and practolol can cause this abdominal fibrosis. The association of biliary cirrhosis with scleroderma was first reported by Murray-Lyon et al. (53) and Reynolds et al. (60). Patients with primary biliary cirrhosis and scleroderma who also have polymyositis (78) or Sjögren's syndrome (51) have been reported. This indicates that an inflammatory, immunologic, or "mixed" connective tissue explanation also may be considered. Two cases with thyroid nodules containing Hurthle cells have been reported in association with this primary biliary cirrhosis–scleroderma syndrome (45, 78). The question of primary sclerosis or primary vascular change cannot be answered, but the fibrous endothelial proliferation has been observed in the small vessels of the liver in patients with primary biliary cirrhosis and scleroderma.

Inflammatory-Fibrosis Form of Scleroderma

The inflammatory-fibrosis syndromes of scleroderma are recognized as unusual, overlap, or "mixed" states. The presence of the unique features of myositis, arthritis, vasculitis, thyroiditis, or tumor frequently confuses the physician. These unique syndromes with secondary features of vascular-fibrosis scleroderma linked through Raynaud's phenomenon may occur coincidentally with aggressive cutaneous and visceral vascular-fibrosis acroscleroderma. They may also occur as episodes in the long course of vascular-fibrosis acroscleroderma. I have observed patients with primary lupus erythematosus with fever, arthritis, pleural effusions, nephritis, and Raynaud's phenomenon develop sclerosis of the face, arms, hands, and body which resolves with steroid and antimalarial therapy, leaving minimal residual sclerosis but arthritis and serologic reactions that required continued steroid therapy. Similarly, patients with primary inflammatory myositis (established by examination, electromyogram, serum enzymes, and muscle biopsy) may develop sclerosis abruptly at the onset of the disease or progressively as the Raynaud's phenomenon becomes prominent or the edema of skin and muscle develops. Episodes of inflammatory myositis have occurred during the course of scleroderma treated successfully with steroids for over 2 years only to return to the chronic acroscleroderma problem with minimal residuals. The evolution of a sclerodermatous skin problem to vasculitis or periarteritis nodosa is not common, but is occasionally observed (73). Circulating immune complexes should be found in such cases and tissue biopsy will demonstrate immunoglobulins and components of complement by immunofluorescence. Livedoid vasculitis is observed every year in patients with scleroderma, in whom it is one cause of chronic ulceration of the ankles (86). Its recent disclosure as an immune-complex disease of the skin (67) provides the closest link yet of scleroderma to such disease.

Alarcón-Segovia et al. (1) recently indicated that most patients with scleroderma have Sjögren's syndrome. They used a series of tests to confirm this, including labial biopsy. Although they did not study circulating antibody to ductal tissue, they did note a fibrous-inflammatory reaction of the salivary and labial glands. This parotid salivary gland reaction is similar to that of the scleroderma synovia observed by Clark et al. (13) and Rodnan (61). Fibrosis and varying degrees of lymphocytic synovitis are related to the positivity of the rheumatoid factor test and to articular symptoms. There are two groups of patients, those with fibrosis and those with inflammation. Only rare cases of rheumatoid arthritis with scleroderma have been observed. In the past, only a few cases of Sjögren's syndrome and scleroderma have been reported and I believe the findings of Alarcón-Segovia et al. (1) show these same two groups, fibrosis and inflammation. Specific study of tissue for functional, immunologic and inflammatory changes will help to indicate if all patients with scleroderma are suffering from xerostomia.

Table III. *Carcinoma and scleroderma*

Primary site of tumor	No. of reported cases
Lung	37
Gastrointestinal tract	20
Lymph nodes (lymphoma)	13
Breast	12
Skin	9
Uterus	4
Ovary	4
Esophagus	2
Prostate	2
Thymus	1
Total	104

The description by Sharp et al. (68) of a unique form of scleroderma (based on the presence of an antibody to an extractable nuclear antigen as well as myositis, features of lupus erythematosus, splenomegaly, and response to steroids) has met with mixed reception. For such patients, Winkelmann (81) had used the term "mesenchymal" scleroderma, the equivalent of "diffuse" scleroderma as described by O'Leary & Waisman (56) and Tuffanelli & Winkelmann (77). All of the states I have described as inflammatory-fibrous scleroderma would fit partially into this category; all show some response to corticosteroids. To recognize the types of inflammation associated with sclerodermatous states and to know that anti-inflammatory therapy will be helpful in these cases are major responsibilities of the physician.

A major consideration for scleroderma as an immunologic disease is the frequent occurrence of antinuclear antibody (ANA). The correlation of the speckled pattern of immunofluorescent ANA with scleroderma emphasizes this (11). The description of the greater specificity of the nucleolar pattern for scleroderma has lost some of its importance because of its low incidence. Jordon et al. (36) pointed out the frequent occurrence of the ANA in scleroderma (13 of 27 cases), but noted that it was not correlated with the severity of the disease or its course. Jabłońska & Chorzelski (30) confirmed this in part, demonstrating that only 29 of 47 patients with acrosclerosis were ANA-positive. Their study of 23 cases of diffuse scleroderma included 18 with positive ANA tests. The positive results did not correlate with globulin level, sedimentation rate, or the presence of visceral changes. Complement-fixing ANA occurred equally in both types of cases and no relation to kidney involvement could be demonstrated. Jabłońska & Chorzelski state, "There is no evidence of a pathogenic significance for ANF [ANA] in scleroderma".

In another approach, Parker (58) studied ribonucleoprotein (RNP) antibodies by diffusion and precipitin techniques and correlated them with ANA. He found ANA nucleolar fluorescence in 15 of 18 "true" scleroderma patients; and none of these patients had a positive precipitin reaction with soluble RNP. RNP antibodies were observed in 9 of 10 patients with "mixed" or mesenchymal connective tissue disease but in only 2 of 18 patients with scleroderma.

The recognition of the antibody to extractable nuclear antigen (ENA) and its positive correlation to mesenchymal or "mixed" scleroderma have been hampered by the nature of the ENA test.

Winkelmann et al. (83) found by biopsy of skin involved by scleroderma that IgM-band immunofluorescence was present in all patients with mesenchymal scleroderma ("mixed" connective tissue disease) but absent in all with acroscleroderma. Jabłońska et al. (31) had previously reported positive skin biopsy immunofluorescence in 5 to 10 patients with scleroderma but did not relate it to the type of disease. Prospective studies are under way to test the hypothesis that direct immunofluorescence of scleroderma skin is the most specific way to recognize the inflammatory fibrosis form of scleroderma.

The thymus has been reported to be atrophic and also hyperplastic in scleroderma. Lymphocyte transformation studies in scleroderma have been reported as normal. Auto-transformation of lymphocytes occurs in autologous serum containing ANA, but not in ANA-negative sera (32). It will occur with normal lymphocytes. This may explain the results of the studies of chromosome abnormalities in scleroderma performed by Emerit et al. (19). DNA stimulation of scleroderma lymphocytes will occur in either autologous or normal serum. Such studies have been interpreted as indicating immune-complex transformation rather than delayed hypersensitivity. In addition, delayed hypersensitivity skin tests are normal in patients with scleroderma (87) and intradermal DNA skin tests are negative (20). Lymphocyte cytotoxicity was demonstrated by Currie et al. (15) when scleroderma lymphocytes were mixed with fibroblast, epithelial, and muscle cell cultures.

Table IV. *Staging of acrosclerodermа*

Stage I	Skin, esophageal, calcinosis, musculoskeletal
Stage II	Pulmonary, intestinal
Stage III	Cardiac, renal

Serum did not produce the same effect, but the authors do not state whether or not the lymphocytes were washed. Lymphocytes of most patients, and particularly those with myopathy, were stimulated by muscle antigen. The occurrence of scleroderma with Hashimoto's thyroiditis, Sjögren's syndrome, and myositis—immune diseases of lymphocytic infiltration—suggests that delayed hypersensitivity may be involved in scleroderma in some cases, particularly the mesenchymal or inflammatory type.

Prognosis

The 5- and 10-year survival data from the study of Tuffanelli & Winkelmann (76) correlate closely with the data of Bennett et al. (2) based on life table methods. In both studies 5-year survival was about 70% and 10-year survival, about 50%. Medsger & Masi (48), dealing with a population of male veterans, noted a 44% 5-year and a 35% 7-year survival. Thus, men with scleroderma have a more severe disease and shorter survival. No racial differences have been observed, but age has a definite effect on prognosis; the studies by Bennett et al. (2) and Medsger & Masi (48) clearly show that prognosis is worse for patients over 50 (a 5-year survival, 50%, and 10-year survival, 30%). Equally interesting is the fact that 5-year survival of patients aged 40 years or less is 95%. However, the reader must recognize that these data are derived from unclassified cases of scleroderma.

Organ system involvement. Current and past studies indicate that cardiac and renal involvement have a uniformly poor prognosis. Cannon et al. (12) noted that 60% of their 210 patients with scleroderma who died during a 20-year period had signs of renal disease, yet only 10% of those without signs of renal disease died during this period. Medsger & Masi's (48) 17 patients with renal scleroderma all died within 10 months. Renal scleroderma is fatal, and only renal transplantation has been of help so far.

Myocardial disease, as indicated by cardiac enlargement and signs of congestive heart failure, is a serious sign. James (34) and Bennett et al. (2) found that a wide range of electrocardiographic changes had no effect on prognosis. Smoking and alcohol intake adversely affected prognosis in Medsger & Masi's cases (48).

Bennett et al. (2) state that scleroderma of the trunk carries a poor prognosis. Tuffanelli & Winkelmann's study (76) termed this "generalized" scleroderma and indicated that the more areas involved, the worse the prognosis. Of greater importance is the rapidity of development of sclerosis, whether cutaneous or visceral; rapid extension of the process is associated with a limited prognosis.

Farmer et al. (21) indicated that pulmonary sclerosis was not of prognostic importance, but Bennett et al. (2) found pulmonary changes at initial diagnosis helpful in deciding the severity of disease and noted radiologic evidence to be particularly helpful.

Bluestone et al. (4) found involvement of the small intestine relatively common but not always associated with malabsorption. Medsger & Masi (48) noted no effect of gastrointestinal signs on survival. With nausea and vomiting, intermittent diarrhea, and signs of obstruction, the intestinal changes are more serious.

Laboratory tests. Elevated sedimentation rate has been related to a poor prognosis by Farmer et al. (21) and Medsger & Masi (48), yet this does not appear to be the case for younger patients in the latter study. It is important that patients with normal sedimentation rate may die within 2 years of the onset of scleroderma. Anemia (<10 g/dl) is uniformly recognized as a poor prognostic sign.

Hemoglobin concentrations of 12 to 13 g/dl are more common and less important. Serologic tests are important only if they indicate mesenchymal scleroderma ("mixed" connective tissue disease). Medsger & Masi (48) noted no relation of ANA, rheumatoid factor, or globulin values to survival. Laboratory tests that reflect cardiac or renal changes indicate a more limited survival.

Association Syndromes

It is now apparent that many syndromes of scleroderma exist in addition to "true" scleroderma or vascular fibrosis scleroderma (acrosclerosis). Some of these syndromes may be acquired by known means (Table II). The vibration syndrome related to Raynaud's disease has long been recognized and

recently systemic scleroderma also has been reported (3). The occurrence of scleroderma in miners has been accepted as related to the pneumoconioses, but recently it has been pointed out that all miners use vibrating tools (3). The recent description of scleroderma with polyvinyl chloride exposure indicates a direct pathologic effect producing the vascular-fibrosis syndrome (27, 47, 52, 80); this may provide an experimental model for the disease. Sclerodermas with phenylketonuria and porphyria raise the question of the effects of metabolic changes on the development of sclerosis (33). The variety of relationships of scleroderma to other states, some of which produce mediators, hormones, or metabolites, is best exemplified by the relationship between scleroderma and cancer.

Cancer and scleroderma. Tuffanelli & Winkelmann (76) found that only 2.3% of their 727 patients with scleroderma studied retrospectively had malignant tumors. Since that time, a series of isolated reports have noted the occurrence of malignancy with scleroderma. Monti (50) recently summarized the literature and reported four cases of bronchogenic carcinoma. Table III further updates this material and emphasizes the predominance of lung cancer in patients with scleroderma. The second clinical feature of importance is the marked predominance of females (ratio 5 to 1). No extrinsic factor is apparent to account for these features. Carcinoma of the lung has been demonstrated to produce serotonin (29); the blood levels are increased but return toward normal with surgery (10). In a susceptible female, this might enhance the scleroderma.

The problem of the relationship of scleroderma to carcinoma may be placed in perspective by the two case reports on carcinoma of the esophagus in scleroderma. In one case, the carcinoma occurred after 20 years of dysphagia and esophagitis and is probably secondary to ulceration (35); this is similar to carcinoma of the skin occurring in ulcers of sclerodermatous skin. In the second case, a fungating, primary esophageal tumor was discovered only 10 months after the onset of the signs of scleroderma (37). Ultimately, it will be possible to distinguish primary and secondary tumors in scleroderma.

The Staging of Scleroderma

This discussion has emphasized reasons for the complex nature of the scleroderma problem. However, the more complicated, inflammatory cases are relatively rare. If they are recognized and excluded, the remainder will be vascular-fibrosis scleroderma (acroscleroderma), with various degrees of cutaneous and visceral involvement and rapidity of progression. Guseva et al. (24) attempted to relate stage and degree of involvement to circulation. They used clearance of radioactive tracers to determine the circulation. Two hundred patients, 82% of whom had Raynaud's phenomenon, were classified as stage I, II, or III and degree I, II, or III according to the decrease in the volume of circulation in lungs, liver, and intestine. Winkelmann (82) evolved a staging procedure for vascular scleroderma which correlated well with the prognostic factors mentioned above. The outline in Table IV presents the factors that delineate good prognosis (stage I) and bad prognosis (stage III). Intermediate classification of pulmonary and intestinal scleroderma as stage II is justified by the complications that may develop from extensive or severe focal disease of these organs. Complications such as bowel obstruction and malabsorption syndrome justify caution in estimating the prognosis for patients with intestinal involvement. It is my belief that a prospective study utilizing this staging procedure will confirm that it is possible to predict the outcome in most patients with scleroderma.

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