CLINICAL ROENTGENOLOGY OF COLLAGEN DISEASES

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Edited by

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This book is dedicated to

my wife,

eight children

and

teachers, colleagues, associates,
students and friends who have
helped to make my life
meaningful

PREFACE

My special interest in collagen diseases began in the spring of 1957 when my erstwhile chief Dr. Leo George Rigler, at the University of Minnesota, called me into his office one day. He stated that he had been invited to speak in a symposium on pulmonary diseases and that his topic was to be "collagen diseases of the lung." He asked me to gather some material from our files.

After Dr. Rigler presented the material we had collected, Dr. Harold Peterson, who replaced Dr. Rigler as Professor of Radiology at the University of Minnesota in 1957, asked me to present the material in augmented form as a refresher course at the American Roentgen Ray Society meeting in 1958. The course was presented five consecutive years at the annual meeting of the society.

Following this, Dr. Lewis Etter, as Editor of American Lectures in Roentgen Diagnosis for Charles C Thomas, Publisher, asked me to present the material in the form of a monograph. Following much delay occasioned by a big work load with small staff the objective has finally been accomplished.

I am indebted to many people who have helped in the production of this monograph. Dr. A. N. K. Menon, now Dean of the Stanley Medical College, Madras, India, helped collect clinical data when he was a graduate student in radiology at the University of Minnesota. Externes and residents at Charity Hospital have also supplied clinical data on patients at that institution. Miss Norma Johnson and Mrs. Alantin Runyan provided useful assistance in typing the manuscript and Mr. Malcolm Barberot supplied the photographs.

I am also indebted to Dr. Lewis Etter in his role as Editor, and to Mr. Payne Thomas of Charles C Thomas, Publisher for thoughtful encouragement. Figures 1-2, 9-12, 31-32, 36-37, 43-46, 47-49 are reproduced from previous publication in the *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine*, for which I must thank Charles C Thomas, Publisher.

Finally, I am happy to acknowledge encouragement from teachers, colleagues, residents and medical students who have stimulated me throughout my medical career, and to my family for the forbearance shown during the many nights and weekends I had to expend in preparing this material.

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Chapter I

INTRODUCTION

THE GENERIC term "diffuse collagen disease" was proposed by Klemperer, Pollack and Baehr (52) for a group of diseases of obscure origin characterized by a systemic alteration of the extracellular components of connective tissue. Collagen is an intercellular substance. Connective tissue contains fibroblasts, elastic fibers, reticulum, and intercellular ground substance. In the normal state, the collagen and ground substance are inconspicuous by the usual staining technics.

In the diffuse collagen diseases, there are significant alterations in the cellular structure and the ground substance. This change is called "fibrinoid degeneration," a term applied successively by Neumann in 1880 (23), Gerlach in 1923 (12), and Klinge in 1933 (19).

Evidence of proliferation, degeneration, and inflammation may be demonstrated microscopically. A proliferative reaction is associated with an increase in the number of fibroblasts and an increase in intercellular substance. In other instances, degenerative changes predominate. Inflammatory change is indicated by leucocytic infiltration. Hematoxylin and eosin stain produces a strong eosinophilic reaction when collagen becomes granular and the ground substance visible. Silver stain brings out strands of fibrin. Gross (15) discusses the basic importance of collagen and describes experiments and observations relative to its chemical structure and formation. He states that "collagen is perhaps the most abundant protein in the animal kingdom. It is the major fibrous constituent of skin, tendon, ligament, cartilage and bone. Its properties are diverse and remarkable. In tendon, it has a tensile strength equal to that of a light steel wire; in the cornea it is as transparent as water. It accounts for the toughness of leather, the tenacity of glue and the viscousness of gelatin." It

accounts for a third of the protein in the human body. Its nature has been clarified by dissolving it and allowing its molecules to reassemble into fibers which are studied by means of the electron microscope.

In a review of the general nature, pathological chemistry, and pathological morphology of various collagen diseases Ehrich (7) maintains that the common denominator of the various disorders lies in their pathogenesis. More precisely, it lies in the production of abnormal gamma globulins apparently by plasma cells, causing injury to the general mesenchyme. However, Good (225) reported instances of collagen disease in agammaglobulinemia.

Kelly (18) reviews the structure of normal connective tissue, the metabolic processes involved, the pathology of collagen diseases, their chemical and serological changes, clinical features, therapy and etiology. He states that Klemperer's original concept that fibrinoid accumulation is a degenerative form of collagen is wrong and that the term "collagen disease" from a strictly morphological point of view is misleading. It would be more correct to speak simply of systemic connective tissue disease. However, the terms "collagen disease" or "collagen disorder" persist and are still commonly used in medical parlance.

Classification. The term "collagen disease" was applied by Klemperer *et al.* to acute disseminated lupus erythematosus in 1941 and to generalized scleroderma in 1942; later dermatomyositis was included. Polyarteritis obviously belonged in this group and most observers included rheumatoid arthritis and rheumatic fever (including rheumatic pneumonitis).

Wegener's granulomatosis is also considered as a collagen disorder. This is a syndrome characterized by sinusitis, necrotizing granuloma of the upper and lower portions of the respiratory tract, renal insufficiency, arthralgia and diffuse vasculitis, with circumscribed and occasionally cavitating pulmonary parenchymal lesions which may resemble metastatic tumor. This may be a renal-respiratory subtype of polyarteritis.

Talbott and Ferrandis (33) include thrombotic thrombocytopenic purpura in their classification of collagen diseases because the specific lesions (endothelial proliferation in the blood ves-

sels) possess the staining characteristics of collagen and because hypersensitivity may play a role in the etiology of this condition as well as other collagen disorders.

Bunim (6) emphasizes the systemic nature of Sjogren's syndrome and the variations in the clinical syndrome which may be presented. The diagnosis of Sjogren's syndrome is generally based on a trial of keratoconjunctivitis sicca, xerostomia (with or without enlargement of the salivary glands) and rheumatoid arthritis (Sjogren, 1933), but it may also be made when any two of these three features are present. In some cases, systemic lupus erythematosus, scleroderma, or polyarteritis may replace rheumatoid arthritis in Sjogren's complex.

Many other conditions are listed by various writers under the collagen disorders. These include polymyositis, Schonlein's purpura, serum sickness, Loeffler's pneumonia, thromboangiitis obliterans, blood group incompatibility, malignant hypertension, erythema nodosum, erythema multiforme, pemphigus and anaphylactoid purpura.

At times, unusual or rarely seen and poorly defined syndromes are described as possibly being related to the collagen disorders. If an unusual disease process involves the connective tissue or small vessels of several organ systems, and especially if this is accompanied by hypergammaglobulinemia or eosinophilia, it is likely to be thought of as another syndrome belonging in the collagen group. Engfeldt and Zetterstrom (9) report two cases of "disseminated eosinophilic collagen disease" which involved multiple internal organs, the skeletal muscle and skin and were accompanied by pronounced eosinophilia and hypergammaglobulinemia. At autopsy, the organ lesions consisted of focal tissue degeneration and necrosis with mainly eosinophilic infiltration. Nonspecific changes in the smaller blood vessels included thrombosis and endarteritic narrowing of the lumina.

Zeuler and Apt (36) presented four cases in children eighteen months to three years of age under the title "disseminated visceral lesion associated with extreme eosinophilia." These patients had hyperglobulinemia and the clinical manifestations included hepatomegaly, pulmonary infiltrations, asthmatic complaints, joint symptoms, urticaria, and convulsions.

Cunningham and Hammond* presented the case of a five-year-old white girl in a paper entitled "pulmonary hemosiderosis associated with a collagen vascular syndrome." This patient had a painful swelling of the knee diagnosed as rheumatoid arthritis, which responded to aspirin therapy. Two years later she developed cough, listlessness and pallor. She was found to have widespread small nodular opacities on the chest roentgenogram and an iron-deficiency anemia. Hemosiderin-laden macrophages were found in gastric washings, and a lung biopsy showed pronounced hemosiderosis. She also had albuminuria, hematuria and hyperglobulinemia. Two weeks later autopsy revealed pronounced pulmonary hemosiderosis, arteritis of multiple organs, pericarditis, myocarditis, subacute glomerulonephritis, and arthritis.

In this text, chief consideration will be given to the following:

1. Systemic lupus erythematosus.
2. Polyarteritis and Wegener's granulomatosis.
3. Systemic scleroderma.
4. Dermatomyositis.
5. Rheumatic pneumonitis.

Additional chapters will be devoted to the collagen diseases in children and differential diagnosis of collagen disorders.

Interrelations of Collagen Disorders

The clinical, roentgenologic, and pathologic features of the various collagen diseases may not be sharply defined in some patients. This results in transitional or overlapping forms. The clinical picture of rheumatoid arthritis may precede the development of the more widespread disease patterns of systemic lupus, polyarteritis or systemic scleroderma. Histopathologic changes of both lupus and polyarteritis have been demonstrated in the same patient at autopsy. In well-developed cases, systemic scleroderma and dermatomyositis are often difficult to distinguish clinically or pathologically (5).

Laboratory tests also testify to the overlapping nature of these disorders. The L. E. cell test is occasionally positive in col-

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Am. J. Dis. Child. 102: 255, 1961.

lagen diseases other than lupus erythematosus. The "telescoped" urinary sediment indicating both acute and chronic inflammation in the kidney is seen not only in lupus and polyarteritis but also may be demonstrated in chronic glomerulonephritis (30).

Superimposed Inflammatory and Neoplastic Disease

Pneumonitis occurs rather frequently in patients with collagen disorders, and at postmortem there may be no evidence of any histopathologic change said to be produced by the collagen disease involved. Pulmonary edema associated with cardiac or renal failure may likewise occur in the absence of characteristic pulmonary changes.

Goldberg and Baldry (13) point out that malignant disease is not infrequently associated with lupus of the skin but has rarely been observed in the visceral lesion of systemic lupus. They report a case of carcinoma of the lung in a forty-nine-year-old woman with systemic lupus who had smoked twenty to thirty cigarettes daily during all her adult life. They postulate that it is possible that systemic lupus preceded the carcinoma or that the carcinoma gave rise to the clinical picture of systemic lupus erythematosus through some mechanism of tissue sensitivity. They also point out that although dermatomyositis is rather frequently associated with visceral malignancy, only seven cases have been reported in association with scleroderma. We have seen one patient with scleroderma who also had carcinoma of the lung.

General Remarks About Roentgen Findings

Aside from the joint manifestations seen in rheumatoid arthritis and occurring in the other collagen disorders, the roentgen signs occurring in the chest are most frequent. Three observations must be kept in mind when analyzing these roentgen findings:

1. Roentgen signs in the chest may be associated with histopathologic changes characteristic of the collagen disorders (not necessarily specific changes).

2. Roentgen signs in the chest may occur in the absence of any characteristic histopathologic changes, e.g., superimposed pneumonia or pulmonary edema.

3. Patients with essentially normal chest roentgenograms may show histologic changes in the heart and lungs at post-mortem which are thought to be related to the systemic diseases involved, e.g., the vascular changes of polyarteritis may be presented with little or no roentgenographic abnormality.

It is pertinent at this point to distinguish between "characteristic" and "specific" pathologic changes. Many lesions found in the heart and lungs, as well as in other organs, are said to be associated with a disease such as SLE but are also found in other collagen diseases. These changes may be "characteristic" of SLE but not "specific," i.e., not related to SLE alone.

There are many findings that may be demonstrated on chest roentgenography in various collagen diseases. Pulmonary manifestations include pneumonitis, pulmonary edema, atelectasis, pleural effusion, large nodules (granuloma or infarct), cavitation, multiple fine nodules, interstitial fibrosis, and pneumothorax. Pulmonary calcinosis has been described in scleroderma (27) and secondary carcinoma of the lung is not infrequent in dermatomyositis.

Cardiovascular manifestations include nonspecific cardiac enlargement due to myocardial involvement or pericardial effusion, prominent hilar vessels and right heart enlargement secondary to pulmonary hypertension, and various changes associated with rheumatic heart disease. Nagele (155) has reported calcification of the annulus fibrosus in scleroderma and we have observed one child with polyarteritis who had an aneurysmal dilatation of the right coronary artery proved at autopsy.

Roentgen examination of the chest is of great value in following the clinical course of patients with known collagen diseases. The degree of involvement of the heart and lungs may be documented and the chest roentgenogram is useful in assessing remissions, exacerbations, and the results or complications of therapy. After changes are present, in most patients the chest roentgenogram will vary with the patient's clinical course.

The question arises as to whether inspection of the chest roentgenogram allows one to make a diagnosis of a collagen disorder, and whether various collagen disorders may be differentiated by the roentgenographic signs. It is true that the signs listed above