PROGRESS IN

Arthritis

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Edited By

**John H. Talbott, M.D.**

*And*

**L. Maxwell Lockie, M.D.**

Dedicated To The Memory Of

Stockton Kimball, M.D.

1902 - 1958

Dean of the University of Buffalo School of Medicine

1946 - 1958

A Brilliant Student

An Esteemed Physician

and

A Loyal Colleague

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# Preface

THIS VOLUME is designed to present discussions by recognized authorities on selected subjects in the broad field of arthritis, rheumatism and connective tissue disorders. "Progress," in the sense implied, signifies a thorough, current evaluation of the individual subject material by the writer of the special chapter. We feel that the timeliness of such a book is underscored by the fact that within the span of our professional experience, the study and treatment of arthritis has been elevated from that of a poorly understood clinical subject to its present high state, in which it is the object of tremendous curiosity.

Innumerable forces and factors have contributed to this metamorphosis. The indefatigable zeal of Drs. Philip Hench, Russel Cecil, Walter Bauer, Ralph Boots and a few others has stimulated the pursuit of a more adequate understanding of various phases of this symptom complex. Without such leaders current progress would be far less impressive. The tremendous impact following the use of adrenocorticosteroids and ACTH has greatly accelerated and lent impetus to research in this extremely important area of medicine.

Another vital force responsible for progress in this field is the availability of funds for research and education. In 1957, the National Institute of Arthritis and Metabolic Diseases alone had a budget of more than 20 million dollars, a major portion of which was allocated for education and research in the field of arthritis and connective tissue disorders. The Arthritis and Rheumatism Foundation as well as other foundations, together with pharmaceutical manufacturing companies and interested private individuals, each has contributed toward the support of the investigators and clinicians who are now able to exploit to a maximum the isotopes, histochemistry, electromicroscopy, immuno-chemistry and enzymes, to mention a few of the related scientific tools currently available. "Progress in Arthritis" is not an all-inclusive volume as is the Rheumatism Reviews, published from time to time in the Annals of Internal Medicine and sponsored by the American Rheumatism Association. Instead, subjects have been chosen that have seemed to us to be worthy of appraisal, and various authors were assigned who were capable of preparing the respective manuscripts. We do not hold necessarily to each and every one of the opinions expressed; in some instances, one or both of us may be rather strongly opposed to some of the printed opinions. This symposium, therefore, is a presentation of individual views, not the summation of the beliefs of the undersigned.

J. H. TALBOTT, M.D.
L. M. LOCKIE, M.D.

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# Fibrin-like Substances in Collagen-Vascular Diseases

by David S. Howell

ONE OF THE UNSOLVED MYSTERIES in the pathology of collagen-vascular diseases is the origin of fibrin-like substances in several characteristic lesions. During the last decade, medical investigators have detected noteworthy differences in the composition of these materials and have developed new techniques for their study. Despite the publication of lucid reports,[35, 36, 57] misconceptions persist among those not familiar with the subject, viz., that fibrin-like substances are the trademark of collagen-vascular diseases, that their appearance is uniform and that they result primarily from hypersensitivity reactions. The purpose of this study is to clarify these impressions and to discuss important clinical aspects of related research.

## HISTORY

As employed here, fibrinoid or fibrin-like substances* (henceforth termed FLS) refer to microscopic granular or fibrillar matter that is eosinophilic, acellular and refractile, revealing some of the tinctoral characteristics of fibrin found with few exceptions in areas of tissue injury. The use of this term precludes any attempt to distinguish between the FLS within blood vessel walls and that within extravascular connective tissue, or between the FLS intimately associated with collagenous fibers and that lying freely in tissue spaces. In addition to the so-called collagen-vascular diseases (rheumatic fever, rheumatoid arthritis, systemic lupus erythematosus, polyarteritis nodosa, scleroderma and, possibly, dermatomyositis), FLS have been described in association with peptic ulcers, Buerger's disease, acute appendicitis, arteriosclerosis, kidney lesions of diabetes mellitus, exudative pneumonitis, tuberculosis, granuloma annulare, subacute bacterial endocarditis, the trophoblastic layer of placental tissues and a variety of experimental tissue responses.[1, 3, 39, 48, 62] Inclusion of these assorted entities is based on a broad definition of FLS without any implications of chemical identification.

In 1880 Neumann first used the word fibrinoid, finding the materials in the surface of inflamed membranes.[49] Since that time, such descriptive phrases as fibrinoid degeneration, fibrinoid swelling, fibrinoid necrosis and fibrinoid change have arisen to describe associated pathologic processes, e.g., those

*Phrase used in reference no. 41.

which occur in the evolution of rheumatoid subcutaneous nodules. It was not until 1933 that Klinge suggested common features in the pathogenesis of rheumatic fever, rheumatoid arthritis, polyarteritis nodosa and dermatomyositis based on the presence of similar pathologic changes—the most conspicuous being fibrinoid degeneration.[38] In 1938, Masugi and Yä-Shu added scleroderma,[44] and in 1942 Klemperer, Pollack and Baehr included systemic lupus erythematosus.[37] The designation diffuse collagen disease was devised to refer to the similar morbid alterations of connective tissue in this group. In the same patient, these diseases either seemed to undergo transition from one to the other or else were demonstrated to coexist. Rich in 1946 summarized his observations supporting the possibility of their similar pathogenesis.[52] He studied the disseminated vascular and connective tissue lesions in man resulting from hypersensitivity to sulfonamides, iodides and foreign proteins, and compared them with pathologic changes in anaphylactically sensitized animals. Striking differences in the FLS of systemic lupus erythematosus were reported by Klemperer,[35] and in 1950 he cautioned against the assumption that all these diseases had a common pathogenesis.[34] Many of the studies since that time have been directed toward evaluation of hypersensitivity mechanisms and identification of substances in the fibrinoid lesions.

## CLINICAL ASPECTS OF FLS

Although attempts have been made to subclassify FLS on the basis of histologic and histochemical differences, their interpretation often is troublesome because of uncontrollable factors which influence staining reactions. Fibrin, available in highly purified form, has been studied extensively in this regard. Methods of fixation,[64] alterations of ionic strength in the buffer used, pH, length of staining, dye concentration,[55] urea-solubility of the fibrin and presence or absence of critical amounts of albumin or glutathione[17] have been shown to affect profoundly the uptake of dyes by fibrin. Despite the limitations of available methods, considerable information has been accrued through morphologic studies.

*Rheumatic Fever.* The principal locations of FLS are in the subcutaneous nodules (fig. 1), heart valve lesions, Aschoff bodies, areas adjacent to fibrinous pericarditis, synovial membranes (fig. 2) and rheumatic pneumonitis. FLS first appear in rheumatic fever nodules as an increased volume of material between the fibrillar structures, often in a region of focal vasculitis. Fibroblasts and other cells migrating into the vicinity assemble in a palisade manner and connective tissue fibers regenerate. FLS may develop either intimately associated with collagenous fibers or separate from them, and gradually become swollen, refractile, eosinophilic and granular. In a later stage only amorphous granular debris remains in the central zone which has become necrotic.[3] This process may continue in some lesions to liquefaction and

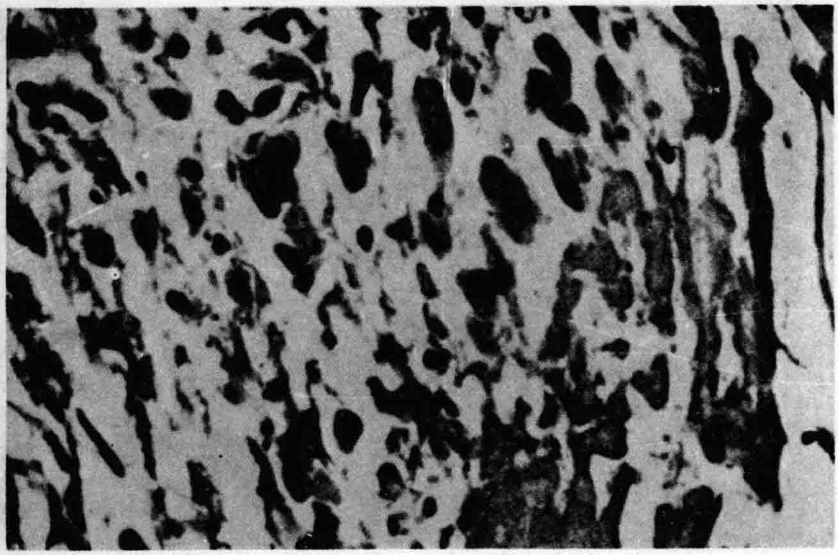

FIG. 1. Swollen irregular fibrinoid material between cells in a subcutaneous nodule of rheumatic fever. (Courtesy of Arthritis and Rheumatism Foundation.)

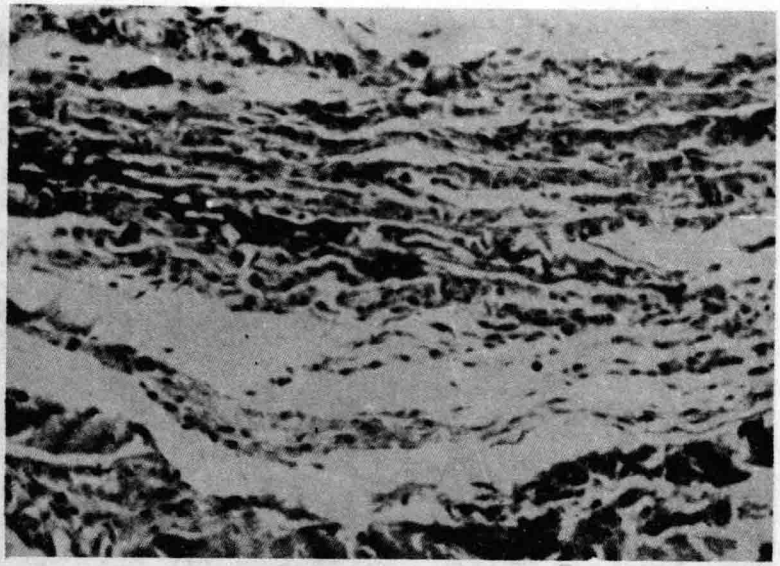

FIG. 2. "Fibrinoid change" in synovial membrane of acute rheumatic fever. There is intimate association of fibrin-like substances with swollen and acidophilic collagenous fibers. Interspersed between fibroblasts is an infiltration of mononuclear cells. (Courtesy of Arthritis and Rheumatism Foundation.)

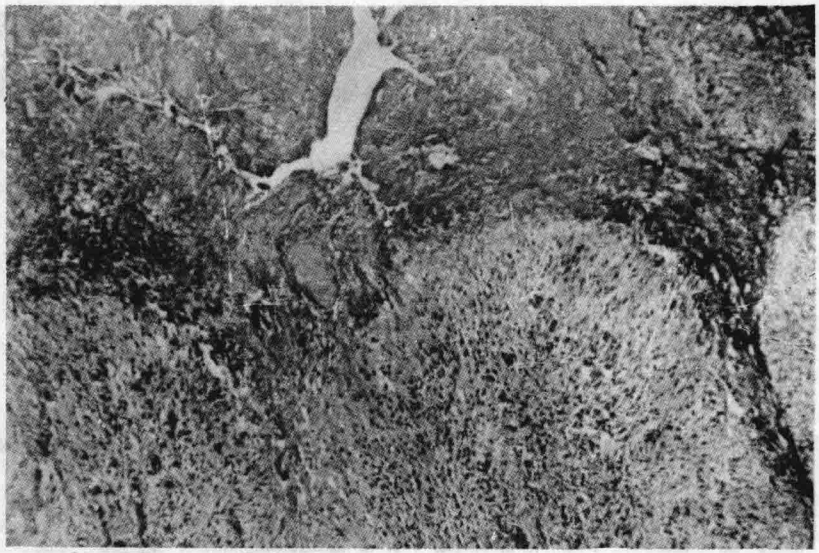

FIG 3. Synovial membrane of rheumatoid arthritis. Palisaded cells and extrusion of masses of fibrinoid substances from beneath the synovial surface forming "rice bodies." (Courtesy of Dr. L. Sokoloff.)

FIG. 4. Rheumatoid subcutaneous nodule demonstrating central region of fibrinoid necrosis surrounded by palisaded cells and a rim of young connective tissue fibers. (Courtesy of Arthritis and Rheumatism Foundation.)

in others to cicatrization. Fibroblasts can migrate on the bridgework thus formed by FLS and young collagenous fibers can be supported by it. Whereas in subcutaneous nodules the new fibrillar material takes the typical blue stain of fibrin with phosphotungstic acid hematoxylin, this color rarely develops in the FLS of Aschoff bodies.

*Rheumatoid Arthritis.* Subcutaneous nodules of rheumatoid arthritis resemble those of rheumatic fever. In addition to appearing beside the fibrinous exudates on the synovial membrane, FLS may generate well below the synovial surface (fig. 3). Here, particularly early in disease, fibroblasts form palisades, as in peripheral nodules (figs. 4 and 5).[9, 41] Sokoloff has evidence that some masses of FLS may be extruded on the synovial surface as "rice bodies" (fig. 3).[56] FLS are seen in cartilage beneath an eroding pannus, in pleura, pericardium, myocardium, heart valves and the connective tissue supporting skeletal muscle, and vasuclar walls.

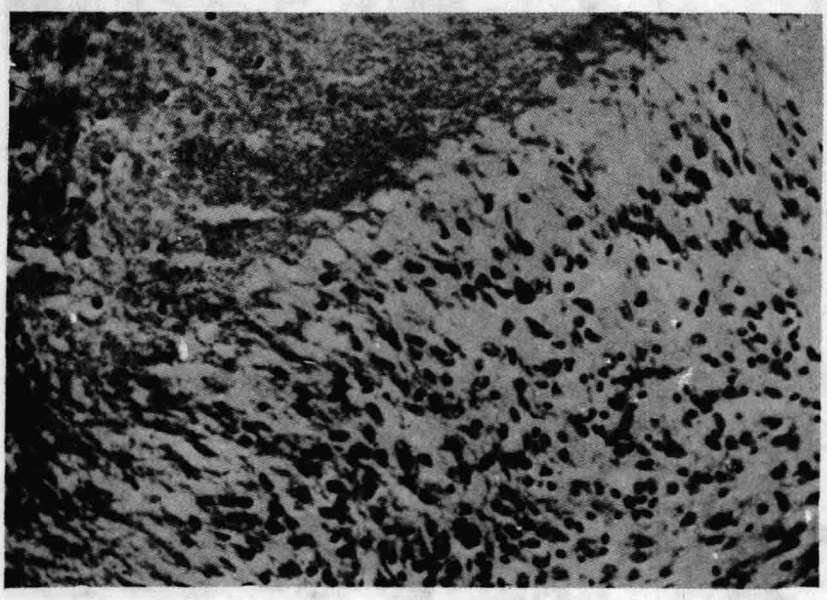

FIG. 5. Portion of fig. 4 slide. Collagenous fibers disappear in fibrinoid necrotic zone where pycnotic nuclei are visible. (Courtesy of Arthritis and Rheumatism Foundation.)

*Systemic Lupus Erythematosus.* Fibrinoid material deposits between the basement membrane and Bowman's capsule in the kidney. The glomerular tufts often contain intensely eosinophilic and thickened glomerular capillary walls—wire-loop lesions (fig. 6). Hyaline thrombi occur in parts of many or

in a few glomeruli (fig. 7). The characteristic halo surrounding these plugs is uncommonly manifested by other collagen-vascular diseases.[8] Eosinophilic change and baso-eosinophilic smudges or intensely basophilic (hematoxylin) bodies are scattered throughout the heart wall and are observed in the verrucous lesions of Libman-Sachs endocarditis. Basophilic deposits may be in the synovial membrane (fig. 8) and in skin also. These materials stain positively with Feulgen's reagent and show ultraviolet light absorption in the range of desoxyribonucleic acid.[34, 36] Small amorphous clumps identified in blood smears have the same staining properties and comprise the central inclusion bodies of L.E. cells. Further studies on the histochemical nature of these clumps suggest that in their formation from nuclear matter, histone has been removed, and the depolymerization of desoxyribonucleic acid is questioned.[21]

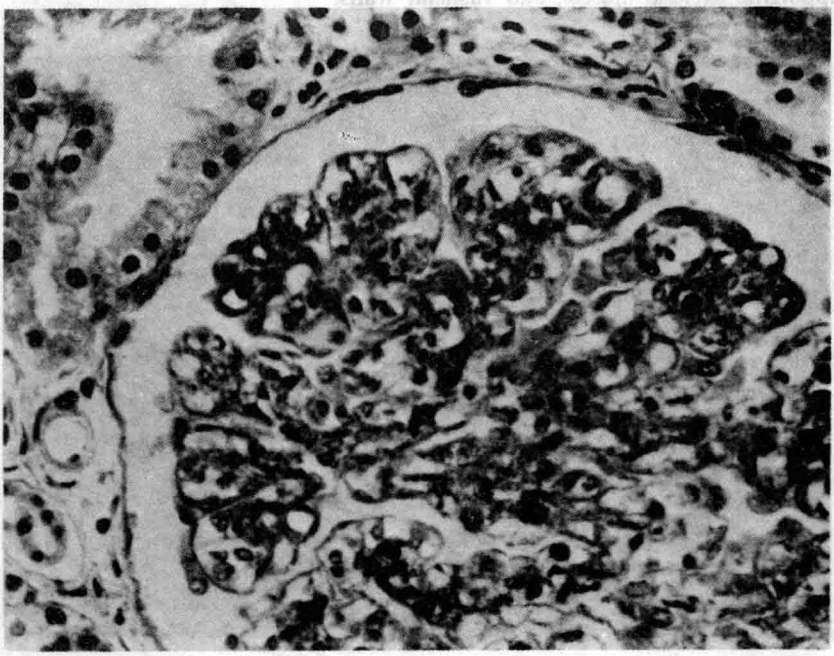

FIG. 6. Another example of fibrinoid substances in the kidneys of systemic lupus erythematosus. Thickened baso-eosinophilic walls of the glomerular capillaries comprise so-called wire-loop lesions. Hyaline thrombi and wire-loop lesions often occur independently. (Courtesy of Bunim, J. J. et al.: Circulation *14*: 125, 1956.)

*Scleroderma.* The most frequent site of involvement is the glomerular capillaries of the kidneys. In the capillary walls, the thickened eosinophilic regions differ in texture from that of wire-loop vessels of lupus kidneys.

Often there is difficulty demonstrating FLS in the lesions of patients with widespread progressive systemic sclerosis. The appearance of the lesions in scleroderma kidneys resembles closely that of necrotizing arteriolitis of malignant hypertension. Inasmuch as the small arteries of the kidneys in scleroderma reveal fibrinoid changes and sclerosis, it is likely that similar arterial changes occur in the afflicted extremities, partially explaining the development of Raynaud's phenomenon.[57]

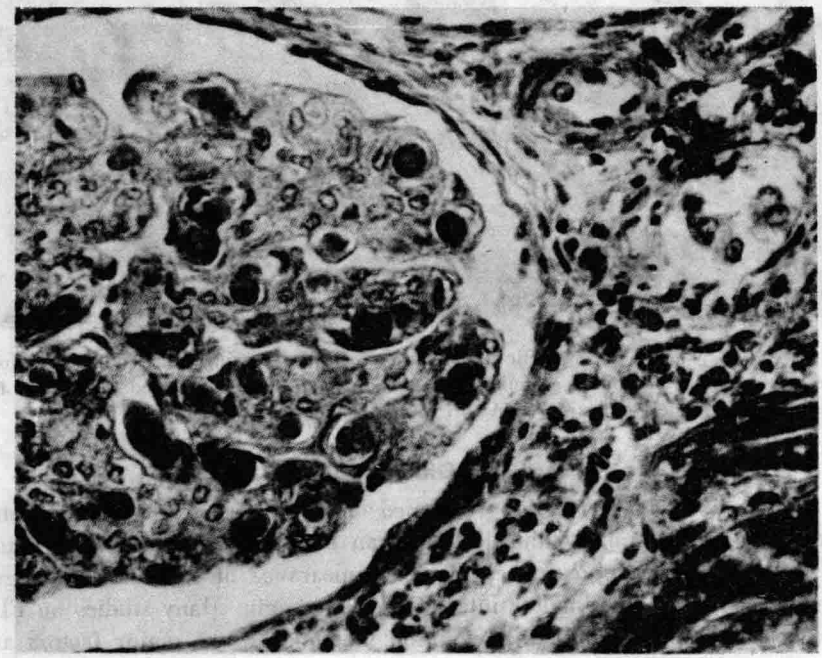

FIG. 7. Systemic lupus erythematosus kidney. Hyaline thrombi are within the lumen of glomerular capillaries. Separation of the thrombi from the walls by a space (or halo) is unusual in other collagen-vascular diseases. (Courtesy of Bunim, J. J. et al.: Circulation *14*: 125, 1956.)

*Polyarteritis Nodosa.* Cloudy swelling and necrosis of the media of middle and small-sized arteries and veins take place early, together with infiltration of polymorphonuclear leucocytes. Later these are replaced by lymphocytes, monocytes and plasma cells. Thrombosis or aneurisms may develop if the vessel wall is severely damaged. The preponderance of pathologic lesions demonstrates ample evidence of FLS in one or all of the arterial coats and surrounding connective tissue. Lesions are widely scattered and segmental. Panarteritis is illustrated in experimental lesions (fig. 13).

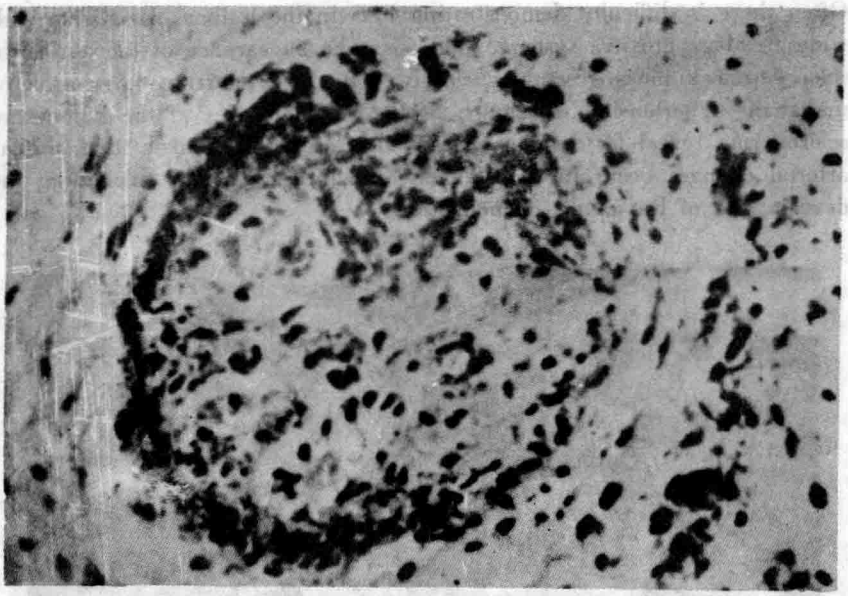

FIG. 8. Synovitis of systemic lupus erythematosus showing small inflamed blood vessels. Irregular basophilic granules (hematoxylin bodies) are scattered throughout the surrounding tissue. (Courtesy of Arthritis and Rheumatism Foundation.)

## TISSUE ORIGIN OF FLS

It is likely that in the above named diseases the majority of symptoms and signs and ultimate clinical course can be ascribed to the location and severity of tissue injury. The frequent appearance of FLS in a damaged region continues to stimulate interest in their origin. Many studies on FLS have been planned with the assumption that one or two major factors are instrumental in their production. Analysis is rendered more complex by the local deposition of nonspecific products of cellular autolysis and inflammation. Likely sources of FLS—according to present concepts—are evaluated below.

*Collagenous Fibers.* The chemical fate of collagenous fibers in FLS has been approached by comparing fibers from pathologic and normal tissues. The principal ingredient of collagenous fibers is protein collagen. Surprising uniformity of collagen's hydroxyproline content (12 per cent in mammals) and its limitation primarily to collagen and elastin in connective tissue offer investigators a tool for study. A high hydroxyproline content in FLS might be expected if degraded collagen composes the bulk of these substances. However, when this index of collagen was applied to trypsin or alkali extracts of rheumatoid nodules, a disappointingly small amount of the amino acid

was found, and clostridial collagenase failed to digest the extracted fibrinoid material.[4 69] Furthermore, when collagen was separated from nodules and synovial membrane of patients with rheumatoid arthritis, the total hydroxyproline within the nodule could be accounted for in collagen and elastin fractions, indicating that little or none was in the extracted FLS.[31] Results support the hypothesis that either the fibrils of collagen were left intact or that decomposition resulted in rapid removal of the hydroxyproline. It would

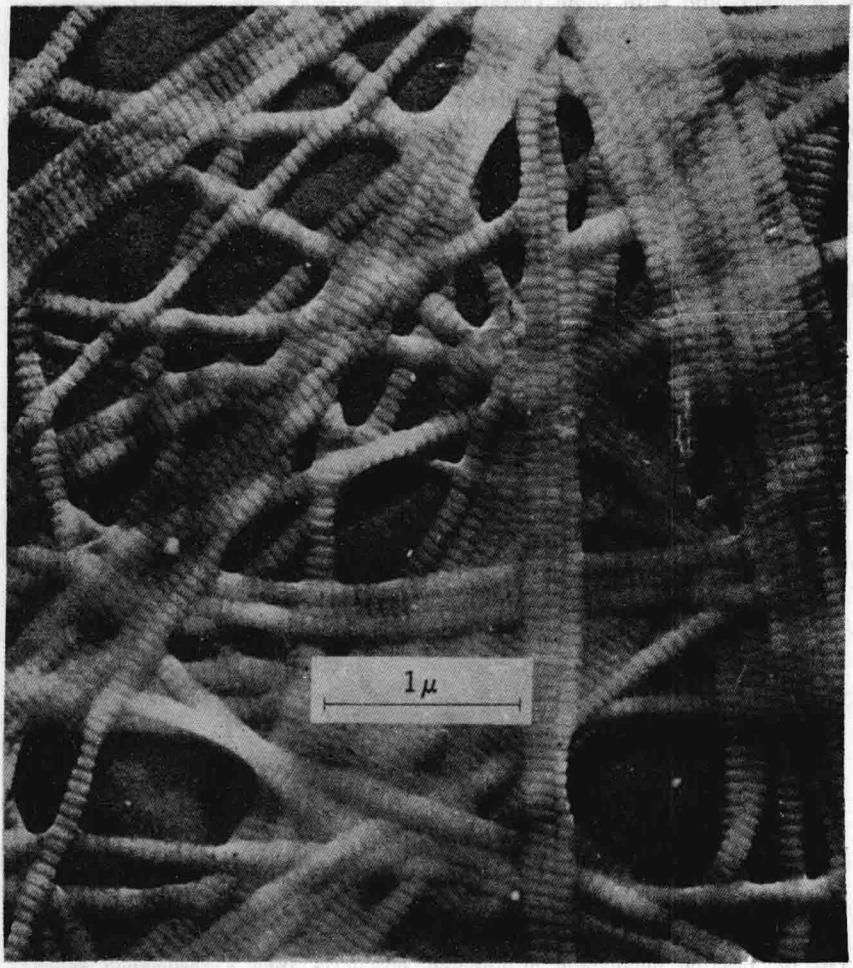


FIG. 9. Electron micrograph of bundles of normal collagen fibrils teased from human corium revealing characteristic periodicity 29000x. Fibrils obtained from subcutaneous nodules of rheumatic fever and rheumatoid arthritis have been indistinguishable from these. (Courtesy of Dr. J. Gross.)