SPECIAL ARTICLE

The Concept of Connective-Tissue Disease

By Paul Klempner, M.D.

If the title of this symposium* had come to the attention of the staff of the Massachusetts General Hospital in 1811, the physicians would have been bewildered because the term, "connective tissue" would have been unfamiliar to them. If, however, its meaning had been explained in contemporary medical expressions, they would have accepted the proposition of diseases of the "cellular tissue" without reservation. An all-pervasive component of the human body had been known for more than a century under the name of tela or membrana cellulosa, and its significance for the economy of the human body in health and disease had been generally recognized. Albrecht von Haller had devoted a full chapter to it in his Elementa Physiologiae in 1767 and Theophile Bordeu, of Montpellier, had written a book on the maladies of the cellular tissues in the same year. A variety of morbid states was ascribed to it, and it was believed to be the principal seat of the important though rather vague disease entity of inflammation as it was diagnosed at that time by the general clinical criteria of fever and pain. But, more specifically, Bichat in his general Anatomy expressed the belief that it was implicated in rheumatism, and in 1836 Bouillaud explicitly maintained that the coincidental affections of the joints and of the heart in rheumatic fever are the expressions of a morbid state of the cellular tissues. But when Johannes Mueller in 1838 defined it clearly and proposed the term connective tissue, it lost its assumed important role in physiology and pathology and was in the words of Henle, "assigned the lowest rank among the so-called organized tissues."

Again, it came to the fore when Virchow discovered that this essentially fibrillar tissue was populated in adult life with cells and when he assigned to them the role of multipotent germinal elements, which under pathologic conditions could give rise to a variety of morbid new formations. The cells of the inflammatory territory, of the tubercle, and above all of all neoplasms including carcinoma derived, according to him, from proliferation of connective-tissue cells. This extravagant claim collapsed when Thiersch and Waldeyer proved the origin of carcinoma from epithelial cells and when Cohnheim demonstrated that polymorphonuclear leukocytes are derived from emigration through the vascular walls.

The significance of the connective tissue for the comprehension of diseases was rejected. The medical opinion of subsequent times was expressed by Buttersack in 1910, when he maintained that it was a neglected stepchild of clinical medicine. But it was not excluded from the considerations of the more esoteric morphologic sciences. Its composition of cells, fibers, and a homogeneous matrix, referred to as "Grundsubstanz," was recognized early, and the origin and interrelationship of the intercellular components continued to arouse the interest of histologists, embryologists, and comparative anatomists during the nineteenth century.

*This essay was presented as the introduction to a symposium held at the 150th Anniversary Convocation of the Massachusetts General Hospital. The title of the symposium was "Connective Tissue and Certain of Its Diseases." It was moderated by Dr. Walter Bauer and participated in by Drs. Jerome Gross, "The Fibrous Elements;" Harry Bostrom, "The Mucopolysaccharides;" Maclyn McCarty, "Etiologic Factors in Connective Tissue Disease;" and Henry G. Kunkel, "Immunological Factors."
and twentieth centuries. The technics available for investigation were in the main those of morphology; they were inadequate for a satisfactory solution of the fundamental problems of fibrillogenesis, of the chemical nature and origin of the homogeneous matrix, and of the genetic interrelationship between the cells and the intercellular components. How progress of biophysics and of biochemistry have advanced our knowledge of the connective tissue in health and disease will be expertly discussed by the next two speakers on the program.

The necessity of pathogenetic inquiry into morbid states began to dawn upon scientific medicine in the middle of the last century when the sterility of a static, mere clinic-anatomic correlation had become evident. With the discovery of microorganisms, etiology became the focus of investigation and classification of diseases. The original enthusiasm for exclusive etiologic research abated, however, and it became obvious that the factor of the reaction of the host organism had also to be entered into the equation. It was in the third decade of this century that allergy prominently came to the fore in the considerations of the pathology of human diseases in general, and, in particular, of that group with which we are concerned today. It is relevant for our discussion that the hypersensitivity hypothesis was conceived by Klinge because he had observed similar histopathologic alterations in the connective tissue both in human diseases as well as in the sensitized animal body.

The immunopathologic concept, which so decisively influenced research on that group of etiologically obscure maladies that collectively are called diseases of the connective tissue or collagen diseases, is based upon the recognition of structural changes of this component of the human body. The selection of the term can thus be well defended and, I believe, even more the heuristic idea expressed by it. Our attention was drawn to the hypersensitivity concept when our microscopic observations had disclosed connective-tissue changes in systemic lupus erythematosus that seemed identical with those singled out by Klinge for his etiologic interpretation. We must always acknowledge that he was the first to recognize the significance of fibrinoid connective-tissue damage for explanation of the pathogenesis of human disease. We opposed only his far-reaching conclusion that hypersensitivity is exclusively responsible for the morphologic alteration. Moreover, we believed that the nature of the lesion was not adequately defined by tinctorial methods available at that time. We questioned the postulated identity of the fibrinoid substance in such heterogeneous conditions as malignant nephrosclerosis, subacute bacterial endocarditis, and certain nephritides with that in rheumatic fever and rheumatoid arthritis, polyarteritis, and dermatomyositis, to which subsequently generalized scleroderma and systemic lupus erythematosus were to be added. We cautioned therefore that the validity of his pathogenetic synthesis was not sufficiently supported. We considered that it was not yet justified to identify the pertinent disease entities etiologically and asked for continued patient analysis of the striking microscopic changes. Realizing that our knowledge of the connective tissue was still incomplete, we recommended more penetrating investigations that might reveal factors other than hypersensitivity that influence its morphologic appearance. Since we believed that the term, "allergic disease," was premature, we thought it should be replaced by a nonprejudicial designation. Because of the seat of the characteristic histopathologic lesions we proposed the term "collagen diseases." Today, I am perfectly satisfied to have it replaced by the less controversial term, "connective-tissue diseases." I do not want to bore you with the arguments as to why we originally selected the first name. My only remark may be that the older term focuses attention upon the intercellular components of this tissue, which are obviously more implicated than the cells in the basic morbid process.

It is always interesting to look back upon the evolution of knowledge in medicine, and there might even be merit in surveying in what intricate way much knowledge has been
gathered. It was fortunate that at the time we were alerted to the significance of the connective tissue in disease the interest of biochemists and biophysicists began to be centered upon its intercellular components, the fibers and the homogeneous matrix. I shall not enter into a discussion of their important disclosures but may be permitted to make only a general remark regarding their correlation with the problems with which the physician is urgently concerned. I realize that contact between the exact sciences and the complex questions of medicine can be made only slowly. I admire the caution with which the basic scientist approaches the mysteries of morbid states. I hope that investigations of connective-tissue diseases with reference to the molecular biology of the collagen fibers will bring results as significant as those that were achieved in the study of experimental pathologic conditions like scurvy and lathyrisn. Equal attention must be paid to the conspicuous alterations of the homogeneous ground substance in the group we are concerned with, such as increased metachromasia and fibrinoid. The former expresses possibly a deviated activity of the fibroblasts, the latter evidently reflects the interchange between the blood plasma and the connective tissue; this has been repeatedly demonstrated by the fluorescent antibody method of Coons and Kaplan.

What I want to stress is the necessity of full coordination of the observations of the medical investigator with the explorations of basic science. How rewarding such an intimate liaison can be, for the advance of our comprehension of the connective-tissue diseases becomes evident if one surveys the recent spectacular revelations in the area of autoimmunization, to use this term for brevity’s sake, studies with which Dr. Kunkel has been so prominently identified. When Louis Gross in 1932 observed the hematoxylin bodies in lupus under the microscope, their significance was not realized. But they were identical with the L.E. cells discovered by Hargraves 16 years later, by the way, also microscopically.

I should like to close my introduction with a few remarks regarding the advances in our comprehension of the nature of the maladies collected under the term “connective tissue” or “collagen diseases.” Objections have frequently been made against the term and concept, which was allegedly based on morphologic grounds only. Some reviewers have maintained that the unclear concept represents a step back to the empty nosology of centuries past, or that with the application of mystified concepts one does not acquire an actual knowledge of the real nature of things. I can reply to these censures only with the question: Has the term or concept arrested the progress of knowledge of any of the relevant diseases? It is a misconception to assert that the concept was ever intended to be more than a heuristic idea submitted to stimulate investigations that might promote a better understanding of a group of puzzling diseases. Those of us who have spoken of collagen or connective-tissue diseases certainly did not want to limit such explorations to the narrow confines of morphologic research and have stated so repeatedly. But morphologic observations did broaden the perspective of investigations in different areas of biology. It has to be admitted that the alterations of structure do not explain the protean clinical picture of the diseases in question. It is conceivable that morphologic explorations might no more contribute to the deeper understanding of the nature of the puzzling maladies that affect the connective tissues. Research of the future is oriented toward disentangling the complex problem of etiology. It was a wise provision of our moderator to divide the topic of this symposium into a discussion of the seat and of the cause of certain diseases of the connective tissue. But what we aim at is integration of these two aspects, the vision that has always guided the inquiry of the connective-tissue-disease group of the Massachusetts General Hospital.*

*This paper is published without references to the literature. Those who wish to consult with relevant articles of the past are referred to a longer presentation of the same subject which appeared in the American Review of Respiratory Disease, 83: 331, 1961.
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