Heritable disorders of connective tissue

THIRD EDITION • VICTOR A. McKUSICK

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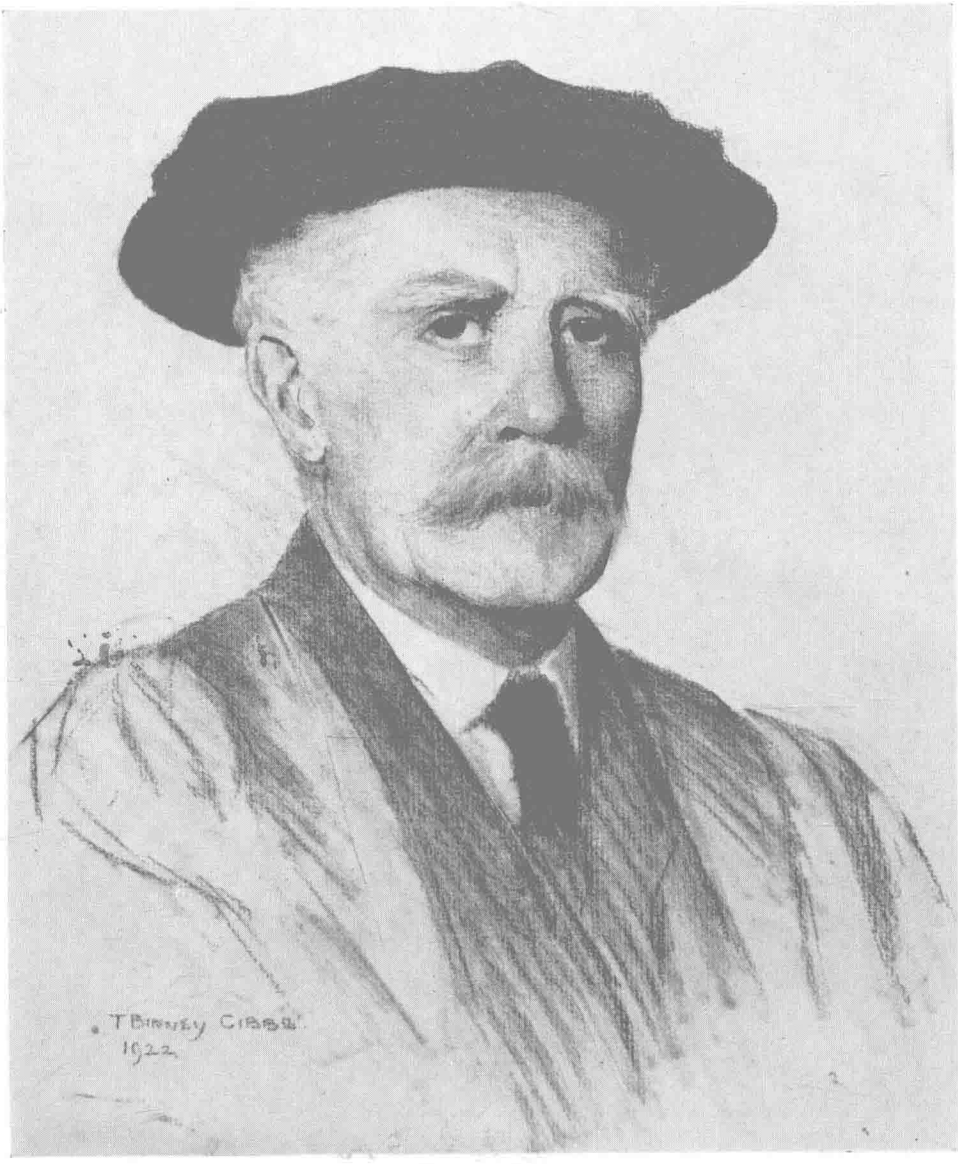

SIR ARCHIBALD E. GARROD

Author of Inborn Errors of Metabolism (1909, 1923) and Successor to Osler as Regius Professor of Medicine at Oxford

(From a previously unpublished crayon drawing made in 1922. Reproduced here through the kindness of Sir Archibald's daughter, Miss Dorothy A. E. Garrod.)

Dedicated
to the memory of

SIR ARCHIBALD E. GARROD (1857-1936)

and

to all who believe, as he did, that the clinical investigation of hereditary disorders can shed light on normal developmental and biochemical mechanisms

Preface

It has been ten years since some of this material was first published as a series of articles in the *Journal of Chronic Diseases*. The continued interest in the heritable disorders of connective tissue and their continued importance to clinical medicine and the biology of connective tissue are notable. In the interval, understanding of these diseases from both the clinical and the biologic points of view has increased appreciably. The collagen molecule has become more familiar in its physicochemical details, although it has far to go to match that paragon of protein molecules—hemoglobin. Characterization of the nature and metabolism of mucopolysaccharides has also advanced.

In connection with the Marfan syndrome, surgical treatment of the aortic complications is entirely a development of the last decade. An exciting discovery is that an inborn error of metabolism (homocystinuria) is responsible for a clinical picture which, because of ectopia lentis and vascular disease, simulates the Marfan syndrome. The vascular complications of the Ehlers-Danlos syndrome have become better appreciated. The existence of a recessive form of osteogenesis imperfecta now seems more likely. Evidence for involvement primarily of the elastic fiber in pseudoxanthoma elasticum has forced revision of the view held ten years ago. Furthermore, the recessive inheritance and histopathologic features, as well as the experience with homocystinuria, suggest that an inborn error of metabolism should be sought. The example of homocystinuria also suggests that alkaptonuria deserves classification as a heritable disorder of connective tissue.

Nosology has advanced farthest in this field in the mucopolysaccharidoses. Whereas in 1955 the nature of gargoylism as a mucopolysaccharidosis was recognized on histochemical grounds and two genetic forms, the autosomal recessive and the X-linked, were distinguished, characterization of the mucopolysaccharidiuria and identification of at least four other distinct varieties are developments of the last decade.

It is especially the generalist—the *general practitioner* and the *internist* and *pediatrician* without particular subspecialization—to whom the problems related to the several syndromes discussed here are of importance and to whom this book is addressed. He is in the best position to size up the total situation in the individual patient and with reference to the family background, with which he is most likely to have firsthand familarity. He can best evaluate what may be excessive loose-jointedness and "ganglingness" or mild pectus excavatum, pigeon

breast, kyphoscoliosis, and flat feet. In the light of the general manifestations and the family background he can best appraise the significance of internal medical manifestations, which may be integral parts of a generalized syndrome.

Asboe-Hansen* has made the following cogent comment:

> Connective tissue connects the numerous branches of medical science. Without connective tissue, medicine would come to pieces, even non-viable pieces, just like the cells of the human body.

The ubiquity of connective tissue is responsible for its unifying influence on medicine, referred to in the statement quoted above. Furthermore, its ubiquity is responsible for the fact that concern with the problems of generalized and hereditary disorders of connective tissue extends also to many divisions of medical science and practice.

The *ophthalmologist* sees grave changes in the eyes in pseudoxanthoma elasticum, in the Marfan syndrome, and in homocystinuria and sees less serious, yet significant, alterations in osteogenesis imperfecta, the Ehlers-Danlos syndrome, and the mucopolysaccharidoses.

The *otologist* sees the patients with the Hurler syndrome, those with osteogenesis imperfecta, and rarely those with the Marfan syndrome.

The *orthopedist* is concerned with the cases of osteogenesis imperfecta, the Ehlers-Danlos syndrome, the Hurler syndrome, and sometimes the Marfan syndrome. Patients with fibrodysplasia ossificans progressiva are frequently seen by him.

The *general surgeon* repairs the hernias of the patient with the Marfan syndrome, the Ehlers-Danlos syndrome, osteogenesis imperfecta, or the Hurler syndrome.

The *hematologist* is consulted for the bruisability in the Ehlers-Danlos syndrome, for the tendency to multiple hemorrhages in patients with pseudoxanthoma elasticum, and for the multiple venous and arterial thromboses in homocystinuria.

The *gastroenterologist* is likely to encounter a case of pseudoxanthoma elasticum if he treats a sizable group of patients with gastrointestinal hemorrhage.

Increasingly the *cardiologist* is finding the Marfan syndrome of greater importance among the "causes" of aortic regurgitation and of dissecting aneurysm of the aorta than he had previously realized. In the Hurler syndrome the cardiac involvement may bring the patient to medical attention and is frequently the cause of death at an early age. Among cases of *peripheral vascular disease,* pseudoxanthoma elasticum or homocystinuria occasionally figures as a predominant etiologic factor.

Aside from the cardiovascular manifestations, the *chest physician* will be interested in the occurrence of cystic disease of the lung in the Marfan syndrome and of rupture of the lung with pneumothorax or mediastinal emphysema in the Marfan syndrome and in the Ehlers-Danlos syndrome.

The *dermatologist* treats patients with pseudoxanthoma elasticum and the Ehlers-Danlos syndrome.

Even the *plastic surgeon* is called in to provide cosmetic relief for the unsightly changes in the skin of the neck in pseudoxanthoma elasticum.

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*Asboe-Hansen, G., editor: Connective tissue in health and disease, Copenhagen, 1954, Ejnar Munksgaards Forlag.

The *dentist* sees abnormalities, especially in osteogenesis imperfecta and the Hurler syndrome.

The *rheumatologist,* interested in connective tissues in general, is likely to see in these heritable disorders of connective tissue, derangements in purer culture and more easily analyzed form than in the acquired disorders of connective tissue such as the arthritides. Specifically, the rheumatologist may be consulted for the repeated hydrarthroses which may accompany the loose-jointedness of the Ehlers-Danlos syndrome, for the stiff joints of the mucopolysaccharidoses, and for the arthritis of alkaptonuria.

The *endocrinologist* is frequently consulted by the parents of a child with the Marfan syndrome or the Hurler syndrome and by the patient with osteogenesis imperfecta or fibrodysplasia ossificans progressiva, the incorrect supposition being that an endocrinopathy is present.

By reason of their hereditary nature, all these conditions are of interest to the *medical geneticist.*

The *pathologist,* of course, must be familiar with them, and the *radiologist* will find in every one of these syndromes diagnostic features which can be revealed by his rays.

Obviously, one objective of this book and of the clinical investigations on which it is based is a synthesis of the scattered information about several conditions which have in common the facts that they are (1) generalized disorders of connective tissue and (2) heritable, even if not inherited in the individual instance. To my knowledge, only Bauer and Bode have previously attempted such a synthesis.*

A second objective has been to see what justification could be found for a favorite, although (witness the following quotation from Harvey as well as the dedication) far from original, notion of mine: that clinical investigation of pathologic states is as legitimate a method as any other for studying biology. Specifically, the hereditary syndromes are tools for study of the normal situation—in this case for the elucidation of connective tissue. When he compares his methods as biologic tools with the electron microscope, analytical chemistry, tissue culture, and others, the clinician tends to get an inferiority complex. I will leave it to the reader to judge whether the clinical researches, which are reported here but which are in only small part my own, demonstrate that the clinician can take his place with the so-called "pure scientists" in the group now trying to fit together the varishaped pieces of the intricate jigsaw puzzle that is connective tissue.

> Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows traces of her workings apart from the beaten path; nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the usual law of Nature by careful investigation of cases of rarer forms of disease. For it has been found, in almost all things, that what they contain of useful or applicable nature is hardly perceived unless we are deprived of them, or they become deranged in some way.†

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*Bauer, K. H., and Bode, W.: Erbpathologie der Stützgewebe beim Menschen. In Handbuch der Erbbiologie, vol. 3, Berlin, 1940, Julius Springer.

†From letter written by William Harvey in 1657, six weeks before his death. Quoted by Garrod, Sir Archibald: The lessons of rare maladies, Lancet I:1055, 1928.

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To the late Dr. Richard H. Follis, Jr., I owe the largest debt of conceptual nature; his concept of osteogenesis imperfecta as a generalized unitary defect of connective tissue probably catalyzed my own thinking along these lines.

I am grateful for the patient work of Mrs. Mary von Heimburg, Mrs. Nelle Garrett, Mrs. Geneva Roberts, Miss Eugenia Morgan, and Mrs. Ruth Kimmerer in the typing and other work associated with preparation of the manuscipt.

It would be impossible to name all the individuals who have assisted in accumulating the data presented. Nor can I list all the persons whose thoughts have influenced mine during the course of analyzing these disorders.

To my fellow members of the Galton-Garrod Society, founded at the Johns Hopkins University a few years ago by several of us who share an interest in human genetics, I am indebted for the pleasure and profit of many stimulating exchanges of ideas. Among others, Dr. Barton Childs, Dr. Bentley Glass, and Dr. Abraham Lilienfeld have been especially helpful to me.

The course in biophysical and biochemical cytology conducted by Professor F. O. Schmitt, Dr. Jerome Gross, and colleagues at the Massachusetts Institute of Technology, June, 1955, was of great assistance in the preparation of the brief survey of the biology of normal connective tissue.

In the study of the Marfan syndrome my studies were assisted by the contemporaneous studies of ectopia lentis by Dr. Howard A. Naquin of the Wilmer Ophthalmological Institute. Dr. Russell S. Fisher permitted me to examine the files of the Medical Examiners Office of the City of Baltimore for cases of dissecting aneurysm of the aorta in young persons. Dr. Robert A. Robinson called my attention to the experiments which are the basis for my tentative theory of the pathogenesis of dolichostenomelia and arachnodactyly in the Marfan syndrome. The editors and publishers of *American Journal of Human Genetics, Bulletin of The Johns Hopkins Hospital, Circulation, Bulletin of the New York Academy of Medicine, Medicine,* and *Annals of Internal Medicine* kindly permitted reuse of illustrative material.

Dr. William S. McLaughlin, urologist, of Hanover, New Hampshire, provided the data on the disease of the urinary tract in the patient with the Ehlers-Danlos syndrome pictured in Fig. 5-4.

In the study of osteogenesis imperfecta, Dr. George O. Eaton, chief of staff at the Children's Hospital School, permitted me to use the resources of that institution. Further kinships were identified through the cooperation of the staff of the Kernan Hospital for Crippled Children.

Dr. Stanton L. Eversole, Jr., reviewed the pathologic material in the cases of pseudoxanthoma elasticum and of the Ehlers-Danlos syndrome.

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In recent years several of my research fellows have contributed importantly in the study of several of the heritable disorders of connective tissue. Deserving particular mention are Roswell Eldridge, Richard M. Goodman, W. Bryan Hanley, R. Neil Schimke, and David Wise. Dr. A. E. Maumenee and several members of his staff in the Wilmer Ophthalmological Institute, particularly Drs. James P. Gills, Jr., Morton F. Goldberg, David Paton, and Gunter K. von Noorden, have contributed in many ways to the study of these disorders of connective tissue, almost all of which seem to have ocular manifestations. Other associates I would acknowledge—even at the risk of omitting others of the many who have contributed—are Drs. Ronald A. Bergman (Department of Anatomy), Michael A. Naughton (Department of Biophysics), Robert A. Milch (Department of Orthopedic Surgery), and Ernest W. Smith (Department of Medicine).

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The late Dr. Ernst Oppenheimer, in preparing the German translation of the first edition, made several worthwhile suggestions which were incorporated in this edition.

I am indebted to Professor Charles E. Dent, London, for directing my attention specifically to the simulation of the Marfan syndrome by homocystinuria. Dr. R. Neil Schimke was mainly responsible for a survey of cases of ectopia lentis and/or presumed Marfan syndrome in which over twenty families with homocystinuria were ascertained. We are indebted to a large number of ophthalmologists and other physicians who gave us access to patients for homocystinuria screening. Drs. A. D. Pollack and Thomas Huang studied pathologic material from patients with homocystinuria. Drs. Leonard Laster and S. Harvey Mudd, of the National Institutes of Health, did enzyme and other studies in the homocystinuric patients ascertained in the screening program.

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To the many others who directly or indirectly contributed to this book I extend my grateful appreciation. Essential to the successful pursuit of a study which is partly retrospective such as this and which concerns disorders of relatively in-

frequent occurrence are the careful recording of information by many individuals over a long period of time and its careful preservation in the archives of our hospitals and other institutions. I am deeply grateful for the contributions of many members of the staff of The Johns Hopkins Hospital over a period of many years.

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