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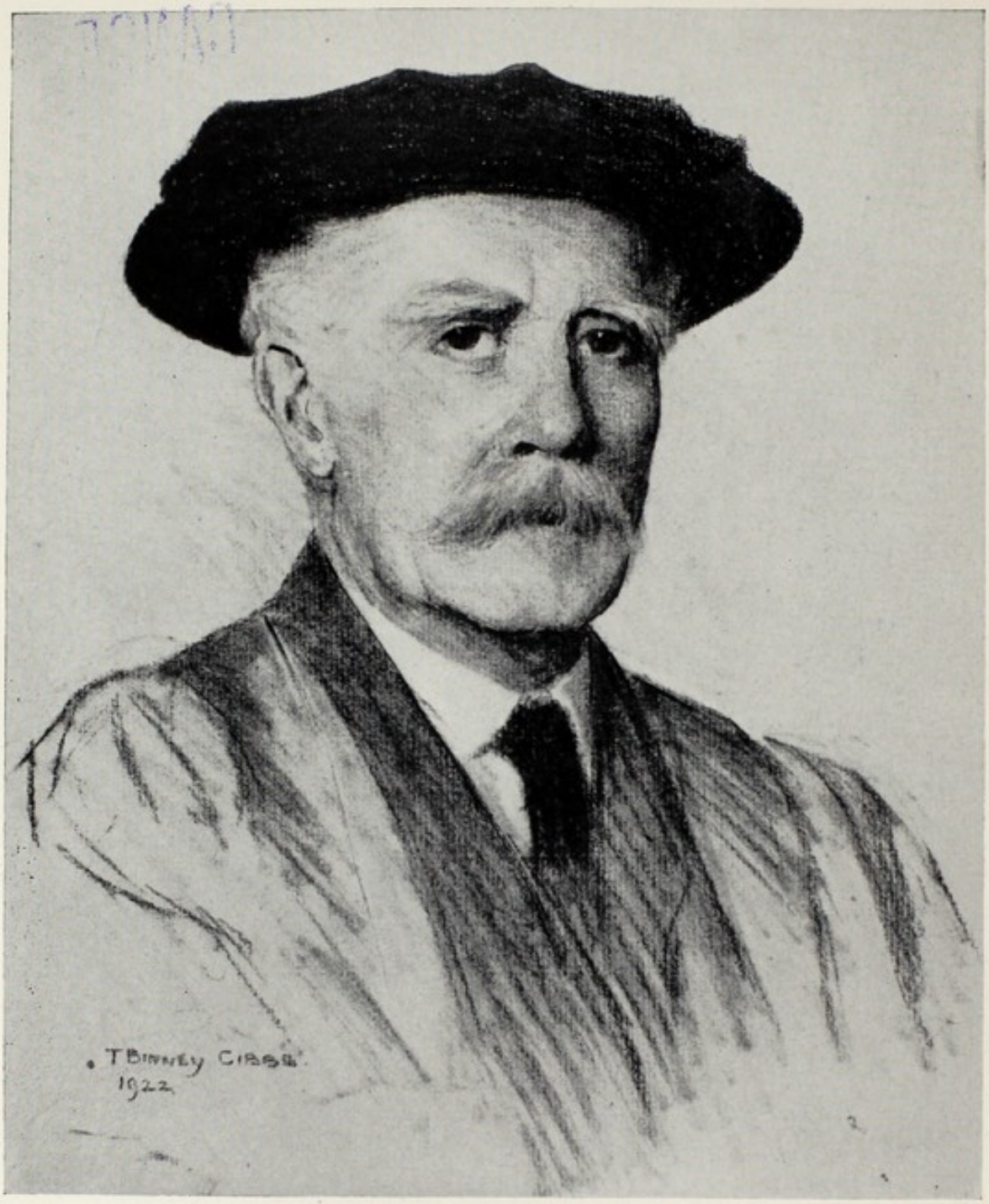

SIR ARCHIBALD E. GARROD

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(From a previously unpublished crayon drawing made in 1922.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.)

HERITABLE DISORDERS of CONNECTIVE TISSUE

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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

A second edition of this book has been made worth while by the steady increase of interest in genetic disorders of connective tissue, as well as in all diseases of connective tissue and in the entire field of medical genetics. Furthermore, clinical experience and investigations in the hereditary disorders of connective tissue have been considerably extended. The first edition was a limited publication based on a series of articles which appeared in the *Journal of Chronic Diseases*. In this second edition over eighty illustrations have been added to round out the clinical and pathologic descriptions, the text has been expanded by about one hundred thirty pages, and the literature since the preparation of the first edition has been surveyed.

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 case of the individual patient and to size it up with reference to the family background, with which he is most likely to have first-hand familiarity. He can best evaluate what may be excessive loose-jointedness and "ganglingness," mild pectus excavatum, pigeon breast, kyphoscoliosis, 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.

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*Asboe-Hansen, G. (editor): Connective Tissue in Health and Disease, Copenhagen, 1954, Ejnar Munksgaard.

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

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. Cases of 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 and for the tendency to multiple hemorrhages in patients with pseudoxanthoma elasticum.

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 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.

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 and for the stiff joints of the Hurler syndrome.

The *endocrinologist* is frequently consulted by the parents of the 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 generalized disorders of connective tissue and are 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 far from original (witness the following quotation from Harvey as well as the dedication), notion of mine: that clinical investigation of pathologic states is as legitimate a method for studying biology as any other; specifically, that 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 which is trying to fit together the vari-shaped 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.†

The Johns Hopkins Hospital VICTOR A. McKUSICK

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*Erbpathologie der Stütgewebe beim Menschen, in Handbuch der Erbbiologie, vol. 3, 1940.

†From letter written by William Harvey in 1657, six weeks before his death. Quoted by Sir Archibald Garrod in The Lessons of Rare Maladies. Lancet **1**:1055. 1928.

ACKNOWLEDGMENTS

The original investigations referred to in this book were supported in part by a grant from the Daland Fund of the American Philosophical Society held at Philadelphia for Promoting Useful Knowledge and in part by grants-in-aid from the National Institutes of Health, Public Health Service.

The late Dr. Joseph Earle Moore encouraged these studies, by wise suggestions improved their published form, and in general made this book possible.

To 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 manuscript.

It would be impossible to enumerate 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, 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. 52.

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.

The interest and experience of James B. Sidbury, Jr., in the Hurler syndrome were of great assistance during that phase of the study. Dr. Harry Butler and other members of the staff of the Rosewood State Training School, Ownings Mills, Maryland, cooperated with me in the study of the patients at that institution.

Conversations with Dr. Karl Meyer of Columbia University have been stimulating and informative.

Dr. Ernst Oppenheimer, in preparing the German translation of the first edition, made several worth-while suggestions which have been incorporated in this second edition.

Mrs. Hermina Grimm Bird was of great bibliographic assistance.

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 infrequent 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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Heritable Disorders *of* Connective Tissue

*We must analyze, and seek to interpret partnerships in disease.**
—Jonathan Hutchinson

1. THE CLINICAL BEHAVIOR OF HEREDITARY SYNDROMES†

BECAUSE of the light they shed on normal mechanisms, many of the inherited ailments of man have importance far out of proportion to their numerical significance. Such is the case, at least potentially, with the hereditary disorders of connective tissue. This consideration, together with the increasing recognition of internal medical ramifications of these diseases, prompted this survey.

To be discussed are generalized hereditary disorders of connective tissue. Many local hereditary malformations and anomalies can be construed as heritable disorders of connective tissue. These will not be discussed, but rather attention will be concentrated on those heritable diseases which seem to represent abnormality of a single element or biochemical mechanism of connective tissue wherever it is found throughout the body. These include the Marfan syndrome, the Ehlers-Danlos syndrome, osteogenesis imperfecta, the Hurler syndrome, and pseudoxanthoma elasticum. On the basis of the information available, the nature of certain conditions—Paget's disease of bone, the Brailsford-Morquio syndrome, the Werner syndrome, osteodermatopoikilosis, achondroplasia (chondrodystrophia fetalis), fibrositis (myositis) ossificans progressiva, Léri's pleonostosis, and others—as possible generalized heritable disorders of connective tissue can only be speculated.

Heritable disorders of connective tissue will be discussed in the following order:

1. The Clinical Behavior of Hereditary Syndromes
2. The Biology of Normal Connective Tissue
3. The Marfan Syndrome
4. The Ehlers-Danlos Syndrome
5. Osteogenesis Imperfecta
6. Pseudoxanthoma Elasticum
7. The Hurler Syndrome
8. Concluding Comments

In Table 1 is presented the connective tissue areas in which clinically evident abnormalities occur in five of these syndromes. The italicized items indicate the

---

*From Hutchinson, Jonathan: Arch. Surg. **4**:361, 1893.

†It is claimed[4] that the correct pronunciation of this word is "syndrŏmē," not "syndroam."

Table 1. Heritable Disorders of Connective Tissue in Man. A Synopsis of Symptoms

Disorders	*Skin*	*Joints*	*Eye*	*Bone*	*Cardiovascular System*	*Fascia*	*Inheritance*	*Fundamental Defect*
Ehlers-Danlos syndrome	*Fragility; hyperelasticity*	*Hyperextensible*	Ectopia lentis; microhemorrhages of retina		Dissecting aneurysm?	Eventration of diaphragm, hernia	Autosomal dominant (low penetrance)	In formation of collagen wicker-work?
Pseudoxanthoma elasticum	*Dystrophy* in wear-and-tear areas		Bruch's membrane, crazing of: *angioid streaks*		Peripheral arteries, medial sclerosis of; *hemorrhages*		Autosomal recessive; occasionally? dominant	Dystrophy of collagen?
Osteogenesis imperfecta	Thin; abnormal scar formation	Hyperextensible	Sclera, thinning of: *blue sclerotics*	*Brittle bones;* otosclerosis (*deafness*)		Hernia	Autosomal dominant	Maturation of collagen?
Marfan's syndrome		Hyperextensible	Suspensory ligament of lens: *ectopia lentis*	Excessive length of long bones: *dolichostenomelia* (long, thin extremities)	Aortic media: *aneurysm*	Hernia	Autosomal dominant	Defect of elastic tissue?
Hurler's syndrome	Roughening; nodular thickening	*Limitation of mobility*	*Clouding of cornea*	Dwarfism; *dysostosis multiplex*	Intimal deposits in coronary arteries; valvular lesions	Hernia	1. Autosomal recessive 2. Sex-linked recessive	Qualitative and/or quantitative abnormality in formation of mucopolysaccharide or structural polysaccharide?

Italicized items indicate predominant manifestations in the case of each syndrome.

predominant manifestations in the case of each. Overlap of manifestations is particularly noteworthy.

Certain features of the behavior of the hereditary syndromes discussed here are common to entities involving other tissues which share, *inter se,* enzymatic mechanisms. The hereditary syndromes of connective tissue serve particularly well in demonstrating these features.

As stated above, the several disorders which will be discussed later are *generalized* abnormalities of connective tissue, although predominant presenting manifestations are likely to bring individual cases to the attention of specialists such as dermatologists, ophthalmologists, and orthopedists. Many students of hereditary disease syndromes were in the past preoccupied with germ layers. They were content if all components of a syndrome could be related to a single germ layer and were much perplexed when certain manifestations deviated from the single germ layer hypothesis. When it is appreciated that the abnormality involves one element of connective tissue wherever it is found, no perplexity is occasioned by the occurrence, for example, of ocular involvement in Marfan's syndrome, the other manifestations of which are clearly mesodermal in origin.

Some of the abnormalities resulting from these connective tissue disorders are not congenital malformations in the usual sense but have the nature of *abiotrophies,* the term suggested by Gowers[1] for neurologic disorders in which a tissue is capable of function for only a limited time because of an innate constitutional weakness. For instance, in pseudoxanthoma elasticum the chararcteristic skin changes are rarely discernible before the latter part of the second decade. Furthermore, wear and tear determine predominant localization of the skin lesions in the areas of flexion, of exposure to weather, of irritation by garments, and so on.

The complex clinical syndromes resulting from these disorders of connective tissue are in each instance the result of a *single* mutant *gene,* the action of which has wide repercussions because of its control of some basic biochemical process. The alternative possibility is that of gene linkage, i.e., that the major individual manifestations of a given syndrome are determined by separate genes located in close proximity on the same chromosome. The arguments for a single gene basis of these complex syndromes are as follows:

1. It is unlikely, although possible, that several genes would undergo mutation simultaneously to reproduce these syndromes again and again with such exactitude.

2. "Crossing-over" tends to separate linked characteristics so that in the course of a few generations there is no longer any particular association in a given individual. It is true that for closely neighboring genes the rate of "crossing-over" is so low that the relatively few human generations available to study may, in any one kinship, be inadequate to demonstrate separation of the components of a given syndrome. However, in the population at large, the situation is as stated by Snyder[2]:

> The occurrence of genetic linkage between the genes for two traits does not change the association for these traits in the population from what it would be if they were not linked. Stated conversely, a correlation between two traits in a free-breeding population does not indicate genetic linkage between the genes for these traits.*

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*From Snyder, L. H.: Principles of Gene Distribution in Human Populations, Yale J. Biol. & Med. **19**:817, 1947.

Monogenic production is provided strong support when one component of a given syndrome is present in a grandparent and a child but is absent in the parent. The failure to appear in the parent could be accounted for by crossing-over, but if such had occurred, reappearance in the next generation would be inexplicable.

3. The most telling argument for a single gene mechanism lies in the possiblity of relating all manifestations of these multifaceted syndromes to a single fundamental defect. For example, in osteogenesis inperfecta, the manifestations in the skin, sclera, and bone can be related to a single defect, which may concern the maturation of collagen.[3] If it is possible to construct a convincing "pedigree of causes," relating all clinical manifestations of the syndrome to the basic defect in a descendant fashion, additional strong evidence for the single gene basis of the syndrome has been provided. Gruneberg[4] has constructed such a "pedigree of causes" for certain complex single gene syndromes of the mouse.

4. In the mouse, vinegar fly, and other species there occur syndromes that have as diverse components as any which occur in man and which by more rigorous genetic tests than are possible in man appear to result from a single gene.[5]

"Pleiotropic" is the term customarily applied to these single genes which are responsible for complex syndromes. The implication is that one gene has several actions. It is likely that in fact the gene has but one action and that the apparent multiplicity of its effects is merely the result of the involvement in several processes of the single biochemical step which is controlled by the gene in question. In the strict sense, then, it may be that no gene is truly pleiotropic.

One occasionally hears statements such as, "That is one of these congenital-familial affairs with which anything can occur." It should not be necessary to emphasize the direct corollary of the single gene proposition: the clinical picture in each of these syndromes is as clear-cut and specific (with, of course, the clinical variability discussed below) as the clinical picture produced by a pathogenic microorganism. In many respects, hereditary disease differs from infectious disease only in that the etiologic agent is a mutant gene operating from within rather than a bacterium invading from without. The virologists have rather long been aware of the basic analogies between their field and that of the geneticist.[6] It is true that in the present state of our ignorance, it is impossible, in the case of some syndromes, to relate all components to a unitary biochemical anomaly. For example, in the syndrome of polyposis of the small intestine and melanin spots of the buccal mucosa, lips, and digits,[7] there is no obvious common denominator. Even in such a situation, however, the other arguments listed above make a single gene mechanism likely.

Yet another theoretically possible mechanism for a multifaceted syndrome is a chromosomal accident, such as translocation, inversion, or deletion. The simultaneous disturbance of a group of genes would account for the syndromal association of diverse manifestations. Chromosomal aberrations have been demonstrated as the basis of three multifaceted syndromes—mongoloid idiocy,[18] the Turner syndrome,[27] and the Klinefelter syndrome.[28] But these are all abnormalities of chromosome number. In each there is either an extra chromosome present or one chromosome missing, presumably because of the accident of nondisjunction in parental gametogenesis. Human karyology will probably soon advance to the point that more subtle abnormalities can be recognized.

Wide *variability* in the clinical severity of the manifestations of these syndromes is the rule. This variability is demonstrated particularly dramatically by the syndrome of osteogenesis imperfecta (see later). By the geneticist the clinician's "degree of severity" is referred to as "expressivity." Penetrance, on the other hand, is an all-or-none affair. There will be fundamentally affected individuals in whom the manifestations are so mild that they do not deviate sufficiently from certain ones of the normal group to permit recognition as abnormal. These cases, the cases of incomplete penetrance, of *forme fruste,* correspond to the subclinical cases of infectious diseases. The familiar bell-shaped Gaussian curve probably accurately describes the distribution of cases as to severity (expressivity) (Fig. 1). The three vertical lines of the diagram indicate threshold of penetrance. These lines cross the distribution curve on the side constituted by cases of lesser grades of severity.

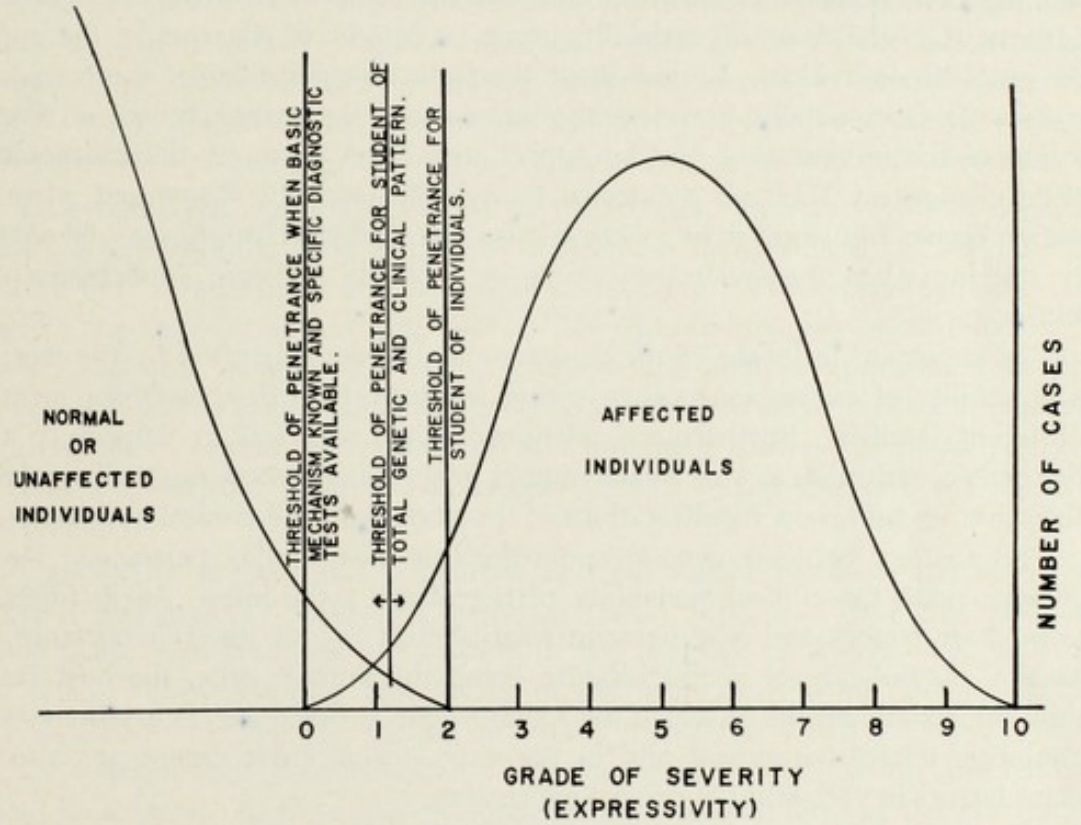

Fig. 1. The interrelationship of penetrance and expressivity in hereditary syndromes. (See text.) (Inspired by Dr. H. Bentley Glass.)

At this end also the curve is overlapped by the normal distribution curve. The majority of recognizable cases are of intermediate severity; there are some very severe cases and some very mild ones. Those affected individuals in the zone of overlap have mild manifestations which, because of their occurrence as "normal variations" in a small proportion of the normal population, cannot be recognized as abnormal when the individual is studied. For the student of the individual, then, the threshold of penetrance is at the point of overlap of the two curves. A certain number of additional cases can be recognized by the student of the total genetic and clinical picture, by one who investigates the entire family in detail. (There are risks, of course, that some unaffected individuals will be incorrectly classified as affected.) It seems probable that when the basic defect in each of these syndromes is known and when a specific method for demonstrating the defect becomes available.

all cases of each syndrome will be identifiable. At this point the threshold of penetrance will be moved back to the limit; and penetrance, an artificial concept at the best, will no longer have significance for these syndromes.

In the case of the multifaceted syndromes of the type discussed in this book, each component may have partially independent behavior so far as penetrance and expressivity are concerned. For example, in the case of the Marfan syndrome, any one of the three major components (ocular, aortic, skeletal) may be present with little or no involvement in the other two areas.

Wide variability in clinical expression is one basis for the phenomenon of "skipped generations" in these syndromes.

The variability in severity of manifestations is both interfamilial and intrafamilial. Interfamilial variability is greater, as a rule, than intrafamilial variability. Assuming that the basic biochemical defect is the same in all instances of a given syndrome, then the basis of variability must be sought in the rest of the genetic make-up of the individual. By and large the factors responsible for this variability are obscure. Occasionally, however, the influence of the genetic milieu on the expression of the mutant gene can be appreciated. For example, the characteristic skeletal changes of Marfan's syndrome tend to be partially submerged when the mutation occurs in pyknic stock; contrariwise, the skeletal changes may be particularly striking when the syndrome occurs in normally asthenic (dolichomorphic) stock.

The important influence of the genetic milieu is demonstrated by the fact that less variability of expression occurs within a family than does between members of different families. Furthermore, identical twins, identical in respect to their entire gene constitution as well as the mutant gene, usually show onset of symptoms at the same age and show manifestations of the same type and clinical severity.

The analogy between genetic and infectious disease has pertinence also in connection with the clinical variability of hereditary syndromes. As in infectious disease, host factors and host-parasite relationships are of great importance, the "parasite" in the case of genetic disease being the mutant gene, the host factors mainly the genetic milieu in which the mutant gene is operating. Variations in the intrauterine microenvironment and in the extrauterine environment are also important factors in variability of clinical expression.

Another possible genetic basis of variability in the severity and general behavior of a hereditary disorder is multiple allelism. There may be several variants of one "pathologic" gene, i.e., several alleles for one locus, each with somewhat different quantitative or qualitative effects. In the case of a dominant trait variability in the heterozygotes can theoretically result from multiple allelism of the "normal" partner of the mutant gene.

The five disorders with which I am mainly concerned in this book illustrate all the more common modes of inheritance. The Marfan syndrome, the Ehlers-Danlos syndrome, and osteogenesis imperfecta behave as autosomal dominants, as a rule. Pseudoxanthoma elasticum and the Hurler syndrome are most frequently autosomal recessives. A less frequent variety of the Hurler syndrome is inherited as a sex-linked (x-linked) recessive trait.

It is a generalization with genetic disorders that wider variability occurs with "dominant" disorders than with "recessive" ones. The suggestion has been made[8]

that natural selection tends to choose those genotypes in combination with which the deleterious mutant gene has less devastating effects. The result may be that in time the injurious effects become suppressed in the heterozygote and expressed only in the homozygote. When a hereditary disease has progressed to this stage in its biologic evolution, the disease trait will then display the genetic behavior termed "recessive." It should not be necessary to point out that whether a disease is transmitted as a dominant or a recessive has no predictible bearing on the incidence of the disease trait in the population. See Figs. 18*C*, 28*A*, 35, and 38*A* for examples.

Two features are frequently displayed by recessive disease traits: (1) a relatively high incidence of consanguinity in the group of parents of affected individuals; and (2) the occurrence of multiple cases in one sibship without involvement of other near relatives (a feature which often led recessive traits to be referred to as "familial").* In the case of recessive traits, mild manifestations should always be sought in heterozygous individuals, such as the parents of an affected person. That subtle changes are rather frequently found in heterozygous "carriers"[10] is an indication that dominance and recessivity are only relative distinctions (see below). See Fig. 43*A* for a pedigree of an autosomal recessive trait.

In general, the sex-linked variety of the Hurler syndrome follows, of course, Nasse's law enunciated early in the last century for hemophilia: that it occurs only in males but is transmitted only by females, and so on. The typical pedigree in the case of a sex-linked trait (see Fig. 86*H*, p. 254) has the pattern which Bateson[15] referred to as the "knight's move," a simile which will be appreciated by chess players. (Pedigree charts for rare genetic traits tend to show a *vertical* pattern of the involvement of relatives in the case of a dominant trait, a *horizontal* pattern in the case of a recessive trait, and an *oblique* pattern in the case of a sex-linked recessive trait.)

Can one be certain that a disorder is a sex-linked recessive and not a sex-limited (male-limited) autosomal dominant trait? The main way this distinction can be made with certainty is by study of the progeny of affected males. In the case of sex-linked recessive traits none of the male progeny of affected males is affected (assuming that the mating is with a noncarrier female). Ideally, in the case of a sex-limited dominant trait, half the male progeny of an affected male should be affected. In the apparently sex-linked recessive form of the Hurler syndrome, reproduction does not occur; therefore, the crucial test is not available.

Theoretically, one can anticipate affection of half the offspring of an individual who is affected with a dominant trait (which is likely to be in heterozygous form) and who is married to an unaffected individual, as is also usual with relatively uncommon disorders under discussion here. Theoretically, in sibships with one individual affected by a disorder inherited as a recessive, there should be three unaffected sibs for each affected one. Actually, in the case of recessive disorders if one collects all sibships with at least one affected individual, one will arrive at

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*Another mechanism for the occurrence of multiple affected sibs from two unaffected parents is "germinal mosaicism" for a dominant trait. At some stage in embryonic development mutation occurs in part or even all of the germinal cells of one parent; that is, mutation occurs in a germinal anlage cell. The abnormality cannot express itself until the next generation. Thereafter it behaves like any other dominant. Reed and Falls[20] suggested that this may have happened in one family with aniridia, hereditary absence of the iris, and MacKenzie and Penrose[21] published a pedigree of ectrodactyly which is consistent with germinal mosaicism.

a figure for affected versus unaffected sibs which deviates appreciably in the direction of an excess of affected individuals. The reason for the lack of agreement obviously lies in ascertainment. All offspring of parents who, husband and wife, are both heterozygous for the recessive trait are not counted because the only way we have for recognizing such married couples is the occurrence of an affected child. Because of the relatively small size of human families, many of the couples will not have enough children to make it likely that a child will be affected according to the 1 in 4 probability; hence the surplus of affected individuals. Methods[11] have been devised for "correcting" the expected ratios of affected to unaffected sibs for sibships of various sizes. When this correction is made, statistically significant agreement of "observed" with "expected" should result if the disorder is truly recessive.

If a parent is affected by a recessive trait, all children, even if apparently normal, must be at least "carriers" of this trait in heterozygous form. If both parents are affected by a recessively inherited trait, all children are affected.

The terms "genotype" and "phenotype" are used, respectively, to refer to the genetic constitution of the individual and to his physical, or somatic, make-up. Corresponding to the word "gene," which is, of course, in much more general usage to indicate the heritable factor controlling a character in question, the Germans use the word "phene" to indicate the particular characteristic controlled by the gene. Experience with other syndromes such as retinitis pigmentosa and Friedreich's ataxia[9] indicates that although the fundamental defect appears to be identical in the several instances (i.e., the "phenotype" is identical) the mode of inheritance may be "dominant" in one pedigree, "recessive" in another. This and the theoretically unstable, evolutionary state of dominance make it necessary to scrutinize each pedigree individually. It is axiomatic that "the phenotype is not necessarily an indication of the genotype." The axiom is well demonstrated in the case of the Hurler syndrome, which may display either recessive autosomal or sex-linked recessive mode of inheritance.

The demonstration of different modes of inheritance is one method for distinguishing different entities in a category that otherwise seems homogeneous. Recognition of the separate entities probably has true significance since it is likely that the different entities have their basis in slightly different biochemical aberrations. The defect may involve a different enzyme in the chain or network of biochemical steps leading to the same phenotype.

Again using the Hurler syndrome as an example, it is found that there are very slight phenotypic differences between the two genetic varieties of the syndrome *(v. seq.)*. It is interesting, and highly significant, that in Knud Faber's *Nosography*[12] the Copenhagen professor of medicine assigned to Gregor Mendel a significant role in the definition of individual disease entities.

Another way in which seemingly identical entities can be distinguished is by linkage relationships. In hereditary elliptocytosis the trait displays genetic linkage with the Rh locus in some families but not in others.[22] In those instances in which linkage is not demonstrated the two loci appear to be on separate chromosomes or to be so far apart on the same chromosome that linkage is not detectable. A different enzymatic defect is therefore possible.

Recessivity and dominance are somewhat artificial concepts.[25,26] For many "recessive" diseases it is now possible by subtle tests to identify the heterozygous car-

riers. A true dominant, furthermore, should have the same expression whether the gene is present in either heterozygous or homozygous state. For very few rare dominant disease traits has the gene in homozygous state been observed. For this reason some have suggested the designations "conditional dominant"[23] and "provisional dominant."[24] The arbitrary nature of dominance and recessivity is indicated by sickle cell trait. The heterozygotes have red blood cells which sickle, that is, acquire bizarre shapes, when exposed to reduced oxygen tension, and roughly half the hemoglobin is of a peculiar physical and chemical type. The homozygotes also display sickling but, in addition, have a serious disease with chronic hemolytic anemia and manifestations due to clogging of small blood vessels by the misshapen red blood cells. If one were to analyze the intrafamilial distribution of the hemolytic anemia without knowledge of the sickling phenomenon, he would conclude it is a recessive. But if one examines the distribution of the sickling phenomenon, he concludes it is a dominant. Because of these considerations, sickling is sometimes referred to as an autosomal intermediate trait.

There is not space to review theories of dominance and recessivity.[16,17,25] One of the most attractive theories of dominance and recessivity is provided by studies of alkaptonuria.[19] Here the basic enzyme defect occurs at a step after a number of others. The effectiveness of the entire chain of reactions is limited at an earlier stage, i.e., a "bottleneck" exists at an earlier step and the enzyme defective in alkaptonuria is normally more than adequate to its task. Therefore, to be expressed the gene for defective enzyme must be present in homozygous state—the characteristic of a recessive gene.

"Phenocopies"—clinical syndromes, of either genetic* or acquired origin, which at least superficially resemble the particular hereditary syndrome under investigation—may confuse clinical and genetic studies. For example, the fetal infection accompanying maternal rubella may so influence development that loose-jointedness, arachnodactyly, and ocular and cardiovascular anomalies—a picture superficially resembling Marfan's disease—result. Careful study of the precise type of eye or vascular involvement is necessary to exclude Marfan's syndrome in such instances. In many individual instances, the five syndromes which are the main topic of this book phenocopy each other, as is evident from Table 1 and as will be amplified later.

Before the genetic behavior of a disorder can be investigated, it must, of course, be established that there is a significant genetic factor in its etiologic background. Beyond the scope of this review is a discussion of methods, such as twin studies, which have been used for dissecting out the separate contributions of *heredity* and *environment* to a given phenotype. However, it is important not to lose sight of the fact that the dichotomy between the two types of etiology is not a "black-and-white" proposition and both inevitably play a role in every situation. It can, for example, be argued that there are hereditary factors in all diseases; in some disorders the hereditary factor dominates, whereas in others it plays a role quite subordinate to that of the environmental one(s). The operation of environmental factors on these disorders of connective tissue which are fundamentally gene-determined is illustrated by the following observations, to select

*As originally defined by R. B. Goldschmidt, a phenocopy is a state produced by an environmental influence and simulating a genetically determined state.

three: In pseudoxanthoma elasticum the skin undergoes dystrophic change first in the areas of greatest wear and tear. In the Marfan syndrome the principal changes in the aorta occur in that portion exposed to maximal hemodynamic stress. In Paget's disease of bone, which seems to have a significant hereditary factor in its etiology *(v. seq.)*, lesions occur predominantly in those bones or parts of bones that bear the most weight or are exposed to other stresses. Another category of connective tissue disease in which both heredity and environment play etiologic roles, with the environmental factors dominating, however, is represented by several varieties of arthritis. For example, there is an impressive hereditary factor in Marie-Strümpell ankylosing spondylitis,[13] yet most would agree that environmental factors are important in its etiology.

All cases of these syndromes either inherit the abnormality or fall victim thereto as a result of *mutation* of a gene regulating the normal biochemical counterpart of the basic defect. (Although the aberration of a normal gene or, as in the case of certain of the "inborn errors of metabolism," the loss of the active component of the gene is probably what occurs in mutation, it is now clear that in many instances mutation is a matter of position change; no alteration in the gene has occurred except one involving its position on the chromosome relative to its fellow genes.) All cases of these diseases, of course, have arisen by mutation in the more or less remote past. In the case of autosomal recessive traits two mutations, i.e., one in the ancestry of each parent, must have occurred at some time in the past, or the single mutation was responsible because of consanguinity in the ancestry of the affected person.

When one encounters a "sporadic" case, i.e., an isolated instance of a disorder which is generally considered to be heritable, the following explanations must be considered:

1. The case in question may be the result of a new mutation of a dominant trait. The case resulting from the original mutation is likely to be unusually severe. In the case, for example, of a dominant trait, it is likely that the mildly affected mutants are in the minority, but by natural selection these are favored. The severely affected mutant does not survive to procreate. This principle is demonstrated by osteogenesis imperfecta *(v. seq.)*.
2. The affected individual may have a recessive gene in homozygous form.
3. The trait in question may be inherited as a sex-linked recessive, and because of fortuitous circumstances the pedigree may not be such as to make this mode of inheritance evident.
4. At least theoretically possible is dependence of the phene on two or more complementary but independently inherited dominant genes. Neither gene alone can produce abnormality. The patient who is the "sporadic" case would, in this situation, derive one dominant gene from each parent.
5. As demonstrated in Fig. 1, it is possible that the trait in question is inherited as a dominant but all affected members of the family except the "sporadic" case have the disorder in such subtle form that it defies detection.
6. The "sporadic" case may be an individual with a dominant trait in homozygous form, the disorder in the heterozygous form (e.g., in the parents) being so mild as to escape recognition. It may seem that, since a trait which is very mild in the heterozygous state is by definition recessive, this category is no different from the second listed above. This consideration does point up the fact that domi-

nance and recessivity are rather arbitrarily defined; the heterozygous kinfolk of persons affected by a trait generally considered to be recessive may have subtle manifestations.[10]

7. Somatic mutation may account for some cases. For example, in retinoblastoma, this phenomenon is thought to account for at least some of the cases in which a hereditary factor is not demonstrable. In sporadic cases of unilateral Sturge-Weber's disease (cerebrotrigeminal angiomatosis) somatic mutation is at least a possibility. Since the mutation occurs after the germinal anlagen are formed, the mutant gene cannot be transmitted It might seem unlikely that somatic mutation could account for generalized disorders of connective tissue because the mutation must occur early and probably before the differentiation of germinal anlagen has commenced. However, in severe sporadic cases reproduction usually does not occur.

8. Severely affected sporadic cases might result from some type of chromosomal aberration.

9. The sporadic case may be a nongenetic phenocopy.

In addition to these possibilities, it may, of course, be that the case is only apparently "sporadic," the patient having been the product of illegitimate conception and the unseen parent having in fact been affected.

The term "heritable" was selected for the title of this book (rather than "inherited" or "hereditary") to express the fact that in a given individual the disease, although capable of being transmitted to the offspring, may not have been inherited but rather have arisen by mutation. Since even in the latter instance the abnormality occurs first in the germinal product of one or the other parent, it becomes a philosophical question whether the affected individual should be said to have inherited the trait or to have become affected at his earliest conception.

The factors responsible for the original mutation in these disorders are unknown.

Anticipation[9] has previously been considered a bona fide phenomenon in hereditary diseases that are inherited as "dominants": it seemed that with successive generations the disease in question developed at a progressively younger age, until finally the gene might become extinct in that line through failure of the affected individuals to reproduce. It is now generally held that, when it is observed, anticipation is either an artifact of ascertainment, (e.g., awareness of the existence of the disease in the family permits its recognition at an earlier age) or is merely happenstance. Fig. 35 in the section on the Marfan syndrome presents the pedigree of one of the few instances I have encountered where anticipation might be operating in these syndromes. In this case anticipation was probably accidental.

The technique for charting of pedigrees that will be followed in this book involves the use of circles for females, squares for males, solidly "blacked-in" symbols to indicate affected persons, and arrows to indicate the propositus (-a). The term *propositus,* or proband, refers to the affected individual who first brings the kindred to the attention of the medical geneticist.

It is desirable to avoid eponyms wherever possible, and it is preferable to employ designations which indicate as precisely as possible the fundamental nature of the disease entity under consideration. In the present state of our knowledge, however, there are good reasons to use eponyms for many syndromes: (1)

Eponyms do not prejudice the search for the fundamental abnormality in each case. They do not conceal our ignorance of the basic defect. For the Hurler syndrome the name "lipochondrodystrophy" was used because of the erroneous notion that the basic defect is one of cellular fat metabolism. (2) By not using one feature of each complex syndrome as the designation, the eponym does not convey the impression that the presence of said feature is a *sine qua non* for the diagnosis or that said feature occurs exclusively as a component of the particular syndrome. "Arachnodactyly" is a poor term for the Marfan disease because the fingers of many of the victims are no more spidery than those of many normal persons. Cutis hyperelastica and cutis laxa are poor terms for the Ehlers-Danlos syndrome since skin abnormalities may be relatively unimpressive in persons with striking joint hypermobility. The pity is not that eponyms are employed in these diseases but rather that there are no phonetically satisfactory or widely accepted eponyms to use in connection with disorders such as osteogenesis imperfecta and pseudoxanthoma elasticum, in which the defect is much broader in its localization than merely bone or skin, respectively.

Many individual manifestations occur in more than one of these syndromes resulting from defective connective tissue. For example, loose-jointedness with flatfeet, pseudoclubfoot, habitual dislocation of joints, etc. may be a striking feature of the Marfan disease, the Ehlers-Danlos syndrome, and osteogenesis imperfecta. Hypotonicity and underdevelopment of skeletal musculature occur in the Marfan syndrome, osteogenesis imperfecta, and the Ehlers-Danlos syndrome. Impressively blue sclerae sometimes occur with Marfan's disease and, on the other hand, arachnodactyly may occur with osteogenesis imperfecta. Dissection of the aorta and ectopia lentis occur primarily in the Marfan syndrome but also occasionally in the Ehlers-Danlos syndrome. Because of this overlap as to individual components it is desirable, in the absence of a specifically descriptive title, to refer to these diseases by eponyms or by some relatively noncommittal name rather than by a single manifestation which may be neither specific for the syndrome nor an invariable feature.

In summary, it may be pointed out that, as is dramatically illustrated by these hereditary disorders of connective tissue, one gene may have many effects. But contrariwise, many different genes may individually or in combination produce a particular abnormal trait. The resulting complexities of clinicogenetic analysis are apparent.

REFERENCES

1. Gowers, W. R.: Abiotrophy, Lancet **1**:1003, 1902.
2. Snyder, L. H.: Principles of Gene Distribution in Human Populations, Yale J. Biol. & Med. **19**:817, 1947.
3. Follis, R. H., Jr.: Osteogenesis Imperfecta, a Connective Tissue Diathesis, J. Pediat. **41**:713, 1952.
4. Gruneberg, H.: Animal Genetics and Medicine, New York, 1947, Paul B. Hoeber, Inc.
5. Caspari, E.: Pleiotropic Gene Action, Evolution **6**:1, 1952.
6. Burnet, Sir Macfarlane: The Riddle of Influenza Virus, Endeavour **14**:5, 1955.
7. Jeghers, H., McKusick, V. A., and Katz, D. H.: Generalized Intestinal Polyposis and Melanin Spots of the Oral Mucosa, Lips and Digits, New England J. Med. **241**:993, 1031, 1949.
8. Fisher, R. A.: The Genetical Theory of Natural Selection, Oxford, 1930, Clarendon Press.
9. Neel, J. V., and Schull, W. J.: Human Heredity, Chicago, 1954, University of Chicago Press, pp. 66 and 75.
10. Neel, J. V.: Clinical Detection of Genetic Carriers of Inherited Disease, Medicine **26**:115, 1947.
11. Stern, C.: Principles of Human Genetics, San Francisco, 1950, W. H. Freeman Co.

12. Faber, K. H.: Nosography, ed. 2, New York, 1930, Paul B. Hoeber, Inc.
13. Hersh, A. H., Stecher, R. M., Solomon, W. M., Wolpaw, R., and Hauser, H.: Heredity in Ankylosing Spondylitis, Am. J. Human Genet. **2**:391, 1950.
14. Vertue, H. St. H.: Medical Mispronunciation, Guy's Hosp. Gaz. **68**:237, 1954.
15. Bateson, W.: An Address on Mendelian Heredity and Its Application to Man, Brain **29**:157, 1906.
16. Wright, S.: Physiological and Evolutionary Theories of Dominance, Am. Naturalist **68**:24, 1934.
17. Fisher, R. A.: The Evolution of Dominance, Biol. Rev. **6**:345, 1931.
18. Jacobs, P., Baikie, A. G., Brown, W. M. C., and Strong, J. A.: The Somatic Chromosomes in Mongolism, Lancet **1**:710, 1959.
19. Seegmiller, J. E.: In Clinical Conference on Alcaptonuria, Ann. Int. Med. **47**:1210, 1957.
20. Reed, T. E., and Falls, H. F.: A Pedigree of Aniridia With a Discussion of Germinal Mosaicism in Man, Am. J. Human Genet. **7**:28, 1955.
21. MacKenzie, H. J., and Penrose, L. S.: Two Pedigrees of Ectrodactyly, Ann. Eugenics **16**:88, 1951.
22. Morton, N. E.: The Detection and Estimation of Linkage Between the Genes for Elliptocytosis and the Rh Blood Type, Am. J. Human Genet. **8**:80, 1956.
23. Levit, S. G.: The Problem of Dominance in Man, J. Genetics **33**:411, 1936.
24. Snyder, L. H., and David, P. R.: Penetrance and Expression; *In* Sorsby's Clinical Genetics, St. Louis, 1953, The C. V. Mosby Co., pp. 9-26.
25. Allison, A. C., and Blumberg, B. S.: Dominance and Recessivity in Medical Genetics, Am. J. Med. **25**:933, 1958.
26. Childs, B., and Sidbury, J. B., Jr.: A Survey of Genetics as It Applies to Medicine, Pediatrics **20**:177, 1957.
27. Ford, C. E., Jones, K. W., Polani, P. E., de Almeida, J. C. C., and Briggs, J. H.: A Sex-Chromosome Anomaly in a Case of Gonadal Dysgenesis (Turner's Syndrome), Lancet **1**:711, 1959.
28. Jacobs, P. A., and Strong, J. A.: A Case of Human Intersexuality Having a Possible XXY Sex-Determining Mechanism, Lancet **1**:302, 1959.

*If by some magic solution one could dissolve all the connective tissue of the body, all that would remain would be a mass of slimy epithelium, quivering muscle and frustrated nerve cells.**
—Arcadi

2. THE BIOLOGY OF NORMAL CONNECTIVE TISSUE

CONNECTIVE tissues, the supporting structures of the body, include cartilage, ligaments, tendons, fascia, joint capsules, the subepidermal portions (corium) of the skin, important elements of the heart valves and aorta and smaller blood vessels, and finally bone. In general, connective tissue consists of cellular and fibrous constituents embedded in the so-called ground substance. Reference is made to textbooks of histology (e.g., Fig. 45 of reference 21) for graphic presentation of the structural interrelationships of these elements.

In connection with his theory that organs are composed of a limited number of tissues, Bichat (1771-1802) distinguished fibrous tissue as one variety. About 1830 Johannes Müller (1801-1858) assigned the generally used designation "Bindegewebe." Schwann discovered the connective tissue cells.

THE CELLULAR ELEMENTS

Virtually all the other endogenous elements of connective tissue are elaborated by the fibroblast, the main cellular constituent of connective tissue, or by its congeners, such as the osteoblast and the chondroblast. Sometimes the term "fibrocyte" is used and in the older literature, "lamellar" or "fixed tissue cell." Other cellular elements include the mast cell and wandering cells such as macrophages. (The mast cell,[59] which has long been implicated in the formation of heparin, has been thought to be concerned also in the formation of hyaluronic acid.[23]) Some information has accumulated about the enzymatic processes involved in the formation of acid mucopolysaccharides.[20] In general, however, details of the biochemical processes by which the fibroblast manufactures the other elements of connective tissue are obscure.

The pedigree of the cells called fibroblasts in tissue culture is an uncertain matter, even though few other cells have been subjected to such extensive study by this technique. The spindle-shaped cells derived from various tissues and organs and referred to as fibroblasts have different functional properties in spite of identical morphology.[43,44]

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*Arcadi, J. A.: Bull. Johns Hopkins Hosp. **90**:334, 1952.

Modulation and differentiation are important features of the biology of the fibroblast. Differentiation[45] indicates a maturation of the cell with specialization of function and usually increased structural complexity; with this specialization the potentiality to develop along certain lines is lost—a chondroblast cannot, for example, develop into a fat cell even though both are descendants of a common mesenchymal cell. Modulation is the term used to indicate changes in cells of such a type that the fundamental nature of the cell, as a fat cell, let us say, is not lost although the functional capacity has been quantitatively altered and the structural features which permit identification of the precise species of the cell may be lost. Differentiation and modulation in the group of connective tissue cells are particularly complex matters.

THE FIBROUS CONSTITUENTS

The fibrous constituents of connective tissue comprise two main groups: collagenous and elastic. The reticulin fiber would be classified by some as a separate category (see below), but most consider it a member of the collagen group although its precise relationship to the classical collagen fiber is moot.

Collagen must be defined in terms of its properties. It is a fibrous protein occurring in wide, straight, unbranching white bundles which possess high tensile strength and low elasticity.*

Collagen fibers at times have a tensile strength as high as 100 kg./cm.^{2}, as high as some metals.[66] Collagen has characteristic 640 Å periodicity by small angle x-ray diffraction and by electron microscopy. It contains two unique amino acids, hydroxyproline and hydroxylysine.[65] The former is in relatively large amounts and is used in quantitative determination of collagen.[12,13] It contains large amounts of glycine. Aromatic and sulfur amino acids are present only in low concentration.

The biologic importance of collagen in the individual organism and in the phylogentic series is tremendous. Collagen represents approximately 30 per cent of the total protein of the human body. In the vertebrate animal it is what cellulose is to plants. As the matrix of bone[33,39b] it was referred to as "ossein" in the older literature. Even the vitreous humor of the eye contains fibers with the properties of collagen, the so-called "vitrosin" of Gross.[26] That it is not limited to vertebrates is indicated (as merely one example) by the fact that collagen is the skeleton of the invertebrate sponge familiar in household and other usage.

The economic importance of collagen dates back to prehistory when the manufacture of leather[8] and glue was first undertaken. Isinglass, made from the swim bladder of fish such as the sturgeon, was also collagenous in nature. It was in leather manufacture that one property of collagen, thermal shrinkage (at 60° to 65° C.) was discovered and used in judging adequacy of tannage. (Some of the best studies of collagen have been directly or indirectly supported by the leather industries. For example, Highberger[62] has been in the employ of the United Shoe Machinery Corporation of Beverly, Massachusetts, and Gustavson[61] works at the Swedish Leather Research Institute in Stockholm. Grassmann[60] works at the Max Planck Institute for Protein and Leather Investigation [Max Planck-Institut

*See page 137 for a discussion of the several definitions of elasticity. As used here, the term refers principally to extensibility.

Table 2. Characteristics of Collagen
(A Partial Tabulation)

Category Based on Method of Study	*Characteristic Features*
Histologic properties[11a]	Tinctorial characteristics: Acid fuchsin—bright red staining Periodic acid and Schiff's reagent—faint red staining Silver methods—not well stained Dilute acids and alkalis—swelling
Electron microscopic features	640 Å periodicity
Chemical features	14% hydroxyproline by weight; hydroxylysine also unique amino acid; low content of tyrosine, methionine, and histidine; absence of cystine and tryptophane; 1% hexosamine (associated carbohydrate)
Shrinkage characteristics	Temperature: 60°-65°C. (shrinkage to about one-third original length) Certain electrolyte solutions
Behavior toward enzymes	Attacked by pepsin Attacked by "collagenases" of *Clostridium histolyticum* and *Cl. welchii*[11b] Resistant to trypsin, chymotrypsin, papain, hyaluronidase
Isotrope tracer studies of metabolic turnover rate	Relative metabolic inertia[3]
X-ray crystallography	Characteristic pattern(s)[1]
Immunology	Very low antigenicity of unaltered collagen,[14] viz., use for suture material

für Eiweiss- und Lederforschung] in Regensburg). Gustavson[61] has demonstrated that thermal shrinkage is the result of breaking of crosslinks in the collagen molecule which occur mainly through hydrogen bonding between hydroxyl groups of hydroxyproline and the keto-imide groups of adjacent helices. Gustavson[79q] has further suggested the intriguing possibility that *in vivo* "tanning" may be the basis of some changes seen with aging and in pathologic states.

The importance of collagen in pathology will be evident to a medical audience since the concept of "collagen vascular diseases" has seemingly gained such wide acceptance. Further medical implications appear to be represented by certain of the hereditary disorders of connective tissue under discussion here.

These implications—biologic, economic, and medical—have been responsible for very extensive investigations of the nature of collagen[1,2,7,9,11] by scientists of diverse interests and perspectives. The result has been, in the past at least, a situation like the elephant that was examined by the six blind men. Recently several excellent symposia have effected a synthesis of the diverse bits of information.

Neither the ultrastructure of collagen nor the mode of its formation,[11m,40] is established in full detail or beyond debate. A concept which perhaps is most consistent with the information available is as follows: The building blocks of collagen, the tropocollagen unit in the terminology of Gross, Highberger, and Schmitt,[41] is elaborated by the cell, possibly intracellularly, and is extruded into the extracellular environment where ionic and other conditions favor its orderly

linear aggregation into the collagen fibril. The tropocollagen unit is thought to have a length (and periodicity) of about 2,200 Å, and the 640 Å periodicity of the finished product is conceived by Schmitt and collaborators as the result of a staggering of the building blocks in their lining up side to side. The discovery that it is possible to solubilize collagen and then reconstitute it from solution was responsible for much of this concept. Physicochemical studies indicate that the tropocollagen unit is a thin, rigid rod with a molecular weight of 300,000 to 310,000 by osmolarity and by light scattering, and with dimensions of about 14 Å by 2,000 Å.[25] Although the larger collagen aggregates are very little extensible and in no way approach elastic fibers in this respect, electron optical observations of collagen fibrils[4] indicate that considerable extensibility of these smaller units is possible. Abnormality in the fibrillar organization may be important in the genesis of the abnormal extensibility of tendons, joint capsules, and ligaments in certain of the heredity disorders of connective tissue.

The work of Jackson and Smith[72,73] has done much to help establish a view that has had some support hitherto: a collagen precursor is excreted by the fibroblast (or a congener) and transformed into the collagen fiber extracellularly. These workers used osteoblasts and grew them in a fibrin-free medium, thus disproving one theory of collagenesis. Appreciable amounts of protein-bound hydroxyproline appeared before typical collagen fibrils were demonstrable. Subsequently many fibrils appeared without a significant rise in hydroxyproline. During the period of collagen fibrogenesis the osteoblasts displayed cytoplasmic granules which stained intensely with PAS. The osteoblast was found to be capable of converting L-proline to hydroxyproline.[73]

The carbohydrate content of collagen is low. What is present may be derived from ground substances playing the role of interfibrillary cement. In pure collagen, hydroxyproline is present as about 14 Gm. per 100 Gm. protein (8.6 Gm. per 100 Gm. amino nitrogen) and glycine in roughly twice as great a proportion. The polar side groups of collagen appear to be located at the areas of the bands displayed by x-ray diffraction and by electron microscopy. These are the reactive areas where stains and tanning agents operate.

The relative metabolic inertia of nonsoluble collagen is a very striking feature.[3] The turnover rate is slightly higher in bone than in tendon, and in younger animals, but is much lower than in proteins of cells and plasma. Soluble or extractable collagen,[6a] which according to the trinitarian breakdown of connective tissue elements followed here must be considered part of the ground substance, has a considerably higher rate of turnover.[5] No collagenase comparable to that produced by Clostridia has been demonstrated in man, with the exception of the extraction by Schmitt and Sizer[27] of material with the properties of collagenase from the cells around embedded collagenous sutures. Keech[76,77] has demonstrated interesting variability in the sensitivity of collagen from different human individuals to the action of collagenase. A few exhibited a high degree of resistance to digestion; others showed more digestion than the average. It would be very interesting to know whether or not sensitivity to collagenase is genetically determined and whether there are any correlations with disease. Is there any characteristic variation in collagenase sensitivity in the heritable disorders of connective tissue?

Reticulin fibers have most of the same properties as collagen fibers, most important the 640 Å periodicity. The main difference is their small diameters,

stainability by silver, and a relatively high concentration of associated polysaccharide. Reticulin fibers predominate in the embryo and in the adult animal are relatively abundant in parenchymatous organs, in lymph nodes and spleen, around muscle bundles and fat globules, and in association with amorphous material in epithelial basement membranes. The differences from collagen fibers may be a matter of fiber size or diameter of the individual fibrils in a bundle. Given a collagen bundle and a reticulin bundle of the same over-all diameter, the reticulin bundle may stain with silver because it has a great many more component fibrils of small diameter and correspondingly greater total fibril surface area. Staining with silver is a surface phenomenon as demonstrated by Gross. Whether reticulin is precollagen or immature collagen (not to be confused with procollagen or soluble collagen) is perhaps not too important a consideration. The concept of Gross and others that it is not a progenitor of collagen is based on the fact that it is present in the adult organism seemingly without ever being transformed into collagen and that electron microscopic evidence for aggregation of reticulin fibers (of small diameter) into collagen fibers is lacking. Reticulin fibers are present in the adult organism, in the corium, for example, and are possibly present in as great absolute amounts as at any earlier stage in ontogeny. In the adult, however, the reticulin fibers are "swamped" by the preponderance of collagen fibers. Several observations[78] suggest that reticulin of granulation tissue is different from that of basement membranes.

Elastic fibers[38] are large branching refractile structures, light yellow or brown, depending on their age; with a high degree of extensibility; extreme insolubility; indestructibility in relation to heat, drastic pH changes, and enzymes; a low content of polar amino acids; and, finally, certain distinctive tinctorial characteristics. The nature of their staining by orcein and related dyes is not at all well understood; the staining bears no relationship to pH, and there is no other evidence that salt linkages are involved.[29]

Whereas collagen is present in areas where a pliant but relatively nonextensible building material is necessary (ligaments, tendons, fascia, joint capsules), elastic fibers serve important functions in areas such as the media of the aorta (where they are responsible for the compression chamber, reservoir, or *Windkessel* hemodynamic function of that structure), in the elastic cartilage of the ear, and in ligaments with large elastic components such as those of the foot and the ligamenta flava of the spine. In the skin, elastic fibers are found mainly in the outermost layer of the corium. The leather industry has been a source of information on elastic fibers as well as on collagen. The outer part of the corium represents the grain layer of leather, so-called because it swells less with tanning and produces grain, which may or may not be desirable in the particular instance. Empirically, "bating"—treatment of the hides with pancreas—was practiced in order to remove the grain layer. Balo and Banga[15] subsequently found that the basis of the "bating" process is the presence of elastase in pancreas (see below).

Chemically, elastic fibers have approximately the same concentration of nonpolar groups, such as glycine, as does collagen. However, there are virtually no polar amino acids such as hydroxyproline, glutamine, and arginine. The relative absence of reactive amino acid side chains is probably responsible, at least in part, for the unique properties of elastin.

Much less is known about the ultrastructure of the elastic fiber than of the collagen fiber. X-ray diffraction studies suggest that in the relaxed state the molecules of elastin are disorganized as in the case of unstretched rubber. Also as in rubber, positive areas of refringence appear with stretching. Gross has found that the double helical structures earlier described by him[35] in electron photomicrographs of material derived from aorta were in fact not elastic fiber elements but trypsinogen[32] in the enzyme preparation used in removing nonelastic elements. One view[16] of the chemical constitution is that a pro-elastin core is embedded in a matrix of combined pro-elastin and elastomucin. There is produced in the pancreatic islet tissue, an elastase[15,28] for which there is an inhibitor produced elsewhere in pancreas. Elastic fibers are moderately susceptible to digestion by trypsin, resistant to digestion by pepsin; this is the converse of the situation with collagen.

Studies with radioisotope tracer methods[10] indicate what is probably an even lower level of metabolic activity than in collagen. With aging there is a chemical alteration in elastin,[9IIb] including a change in the amino acid profile and an increased affinity for calcium and basophilic dyes.

Formation of elastic fibers in tissue culture is observed with more difficulty than in the case of collagen fibers.[46,47,48] Some workers[49] conclude that in several ways collagen participates in elastofibrogenesis and that there is an intimate interrelationship between the two. There appears to be evolving a general principle that the extracellular components of connective tissue are not the "free agents" they have generally been considered in the past. Increasingly, evidence accumulates for an intimate interrelationship between collagenous and elastic fibers. For example, Keech and Reed[75] demonstrate that by a variety of means, chemical, enzymatic, and physical, so-called "moth-eaten fibers" (MEF) can be produced from either type of fiber. The MEF are conceived of as an intermediate form.

THE GROUND SUBSTANCE

The term ground substance is a mistranslation of that used by the early German histologists, *Grundsubstanz,* meaning "fundamental substance." Although the ground substance has long been known (in 1861 there was enough information to justify a review of the subject by Köllicker), the most intensive investigations followed the discovery of the "spreading factor" by Duran-Reynals and Suner in 1929[50] and the studies of mucopolysaccharides of the ground substance and of hyaluronidase in the laboratory of Karl Meyer at Columbia University beginning in the early 1930's.[51]

The ground substance is the extracellular, extrafibrillar, amorphous matrix of connective tissue. It has components derived from the fibroblast, such as acid mucoprotein, acid mucopolysaccharide, and dispersed (soluble or pro-) collagen, and components not elaborated locally, such as water, ions, small organic molecules such as glucose, cell metabolites, plasma proteins, and others. It is important not to equate ground substance to acid mucoproteins and acid mucopolysaccharides, as has become a frequent practice, since on a quantitative basis, and possibly on a functional basis, some of the other constituents such as plasma proteins, soluble collagen, and neutral mucoproteins are as important. Another assumption which may be fallacious is that changes in serum mucoprotein (which is neutral) reflect changes in acid mucopolysaccharide of the ground substance; chemically the two are quite distinct.

*Table 3. Acid Mucopolysaccharides of Connective Tissue**

I. Nonsulfated mucopolysaccharides
1. Hyaluronic acid
2. Chondroitin
II. Sulfated mucopolysaccharides
1. Chondroitin sulfate A
2. Chondroitin sulfate B
3. Chondroitin sulfate C
4. Heparitin sulfate
5. Keratosulfate

*From Meyer, K., Hoffman, P., and Linker, A.: The Acid Mucopolysaccharides of Connective Tissue; *In* Tunbridge, R. E., et al. (eds.): Connective Tissue, A Symposium, Springfield, Ill., 1957, Charles C Thomas, Publisher.

There are several presumably distinct acid mucopolysaccharides in connective tissue (Table 3). All are polymers of high molecular weight and contain hexosamine and hexuronic acid moieties.[64] Hyaluronic acid, which has been identified in synovial fluid, vitreous humor, and umbilical cord, is composed, among other moieties, of glucosamine and glucuronic acid. It is digested by hyaluronidase. Chondroitin, which has been isolated only from cornea, differs from hyaluronic acid by the replacement of glucosamine by galactosamine; its properties are similar, however. Meyer distinguishes three chondroitin sulfates (A, B, and C) on the basis of solubility, optical rotation, and enzymatic properties. All contain galactosamine, not glucosamine. ChSA has been demonstrated in cartilage, bone, cornea, aorta, and ligamentum nuchae. ChSB, in which the hexuronic acid moiety is iduronic acid, not glucuronic acid, has been isolated from skin, tendon, heart valves, ligamentum nuchae, and aorta. ChSC has been found in cartilage, umbilical cord, tendons, and nucleus pulposus. Keratosulfate, the only sulfate mucopolysaccharide free of uronic acid, has been isolated from cornea, where it represents about 50 per cent of total mucopolysaccharide. Heparitin sulfate, which as its name indicates has chemical, physical, and other properties resembling those of heparin, has normally been found only in aorta.

Metabolically mucopolysaccharides are rapidly turned over. The availability of S^{35} and description of its use in the study of acid mucopolysaccharides by Djiewiatkowski[52] in 1949 has permitted some insight into problems of the metabolism of these materials. Studies of mucopolysaccharide formation in microorganisms and in cell cultures have likewise been helpful. Production of components of the ground substance in tissue culture has been observed.[53,54]

Metachromatic staining of connective tissues, as by toluidine blue, is a function largely of mucopolysaccharides.[36,37] (Metachromasia is a term introduced by Ehrlich in 1877 to indicate the property of a tissue to stain one color when exposed to a dye of a different color.)

In the mammalian organism hyaluronidase has been identified with certainty only in testis.

The importance of the ground substance is evident when one considers that it must be traversed by all materials entering and leaving the cells.[6b] The concept[7,34,42] that mucopolysaccharides function like a reactive gel of the ion-exchange resin group is an intriguing but as yet unproved concept. It is at least theoretically possible that changes in the concentration or state of polymerization might modify

greatly the capacity of connective tissues to bind inorganic ions and water. Hyaluronic acid, highly hygroscopic in the purified state, may be concerned in water-binding by tissues. It may also serve as a lubricant and shock absorber. Chondroitin sulfate, because of its highly charged anionic groups, may function[11f] as a cation exchange resin.

Jackson[24] has presented data which he interprets as indicating an important role of mucopolysaccharide in the organization and certain properties of collagenous structures such as tendon. Trypsin will digest gelatin but not native collagen. The characteristic shrinkage temperature of native collagen is altered by treatment directed at the matrix.

The evidence[55,56,57] on the role, if any, of mucopolysaccharide in collagen fibrogenesis is held by some[78] to be conflicting and inconclusive. However, some connection is thought to exist.[79a]

FURTHER CONSIDERATIONS

The indications of an intimate interrelationship between the several elements of connective tissue, e.g., between collagen and elastin, between mucopolysaccharide and collagen, etc., are numerous. The details of these interrelationships are not yet fully known.

In addition to these general features of connective tissue, which undoubtedly assist in the understanding of the heritable disorders to be discussed, there are some specific questions about the biology of connective tissue which come to mind with study of these diseases. For example, to mention only a few, in the Marfan syndrome: What does the suspensory ligament of the ocular lens have in common with the media of the aorta? What controls longitudinal growth of bone? In pseudoxanthoma elasticum: What is the nature of Bruch's membrane of the eye and what does it have in common with the corium? What is the basic nature of orceinophilic staining; specifically, if it is dystrophic collagen which stains in this disease, what change has occurred to result in this tinctorial simulation of elastin? In the Ehlers-Danlos syndrome: What is responsible for the tensile strength of the skin and for its elasticity? What is the organization of collagen bundles in ligaments, tendons, and joint capsules and what is the relationship between this organization and the stretchability of these structures? What determines the elastic properties of the collagen and elastin molecules, and of fibers of these proteins? In osteogenesis imperfecta: What is the normal organization of apatite on collagen which accounts for the important structural properties of bone, and in this disease, what change in collagen has occurred to disrupt the normal collagen-apatite relationship? In disorders such as osteogenesis imperfecta and pseudoxanthoma elasticum is there any abnormality of amino acid sequences[79z] comparable to the abnormalities demonstrated by Ingram[80] in the aberrant hemoglobins? In connection with the full discussion of each of the entities, what is known in answer to these questions and others will be presented. Unfortunately, much remains to be learned in all these areas.

REFERENCES

1. Baer, R. S.: The Structure of Collagen Fibrils; *In* Advances in Protein Chemistry, New York, 1952, Academic Press, vol. 7, p. 69.
2. Borasky, R.: Guide to the Literature on Collagen. Agricultural Research Adm., Philadel-

phia, 1950, U. S. Department of Agriculture (Eastern Regional Research Laboratory).

3. Neuberger, A., Perrone, J. C., and Slack, H. G. B.: Relative Metabolic Inertia of Tendon Collagen in Rat, Biochem. J. **49**:199, 1951.
4. Schmitt, F. O., Hall, C. E., and Jakus, M. A.: Electron Microscope Investigations of the Structure of Collagen, J. Cell. & Comp. Physiol. **20**:11, 1942.
5. Harkness, R. D., Marko, A. M., Muir, H. M., and Neuberger, A.: The Metabolism of Collagen and Other Proteins in the Skin of Rabbits, Biochem. J. **56**:558, 1954.
6. Rothman, S.: Physiology and Biochemistry of the Skin, Chicago, 1954, University of Chicago Press. (a) Felsher, Z.: Collagen, Reticulin and Elastin, Chap. 17, p. 391, (b) Wells, G. C.: Connective Tissue Ground Substance, chap. 18, p. 418.
7. Joseph, N. R., Engel, M. B., and Catchpole, H. R.: Interaction of Ions and Connective Tissue, Biochem. et Biophys. Acta **8**:575, 1952.
8. McLaughlin, G. D., and Theis, E. R.: The Chemistry of the Leather Industry, New York, 1945, Reinhold Publishing Corp.
9. Ragan, C. (ed.): Josiah Macy, Jr. Foundation Conferences on Connective Tissues.
   I. (1950) (a) Angevine, D. M.: Structure and Function of Normal Connective Tissue, p. 13. (b) Bennett, G. A.: Pathology of Connective Tissue; Fibrinoid Degeneration, p. 44. (c) Meyer, K.: Chemistry of Connective Tissue; Polysaccharides, p. 88. (d) Perlmann, G. E.: Enzymatically Modified Ovalbumins, p. 101. (e) Ragan, C.: Effect of ACTH and Cortisone on Connective Tissues, p. 137.
   II. (1951) (a) Gersh, I.: Some Functional Considerations of Ground Substance of Connective Tissues, p. 11. (b) Lansing, A. I.: Chemical Morphology of Elastic Fibers, p. 45. (c) Travell, J.: Pain Mechanisms in Connective Tissues, p. 86. (d) Porter, K. R.: Repair Processes in Connective Tissues, p. 126. (e) Morrione, T. G.: Regression of Scar Tissue, p. 159.
   III. (1952) (a) Lillie, R. D.: Connective Tissue Staining, p. 11 (b) Wyckoff, R. W. G.: The Fine Structure of Connective Tissues, p. 38. (c) Robb-Smith, A. H. T.: The Nature of Reticulin, p. 92. (d) Fischel, E. E.: Hypersensitivity and the Hyperadrenal State, p. 117.
   IV. (1953) (a) Ashley, C. A., Schick, A. F., Arasimavicius, A., and Hass, G. M.: Isolation and Characterization of Mammalian Striated Myofibrils, p. 47 (b) Fell, H. B.: The Effect of Vitamin A on Organ Cultures of Skeletal and Other Tissues, p. 142. (c) Meyer, K.: Outline of Problems to Be Solved in the Study of Connective Tissues, p. 185.
   V. (1954) (a) Zweifach, B. W.: The Exchange of Materials Between Blood Vessels and Lymph. (b) Gaudino, M.: Interstitial Water and Connective Tissues. (c) Asboe-Hansen, G.: Hormonal Effects on Connective Tissue.
10. Slack, H. G. B.: Metabolism of Elastin in the Adult Rat, Nature **174**:512, 1955.
11. Randall, J. T. (ed.): Nature and Structure of Collagen (Symposium), New York, 1953, Academic Press.
   (a) Jacobson, W.: Histological Survey of the Normal Connective Tissue and Its Derivatives, p. 6. (b) Robb-Smith, A. H. T.: Significance of Collagenase, p. 14. (c) Cruickshank, B., and Hill, A. G. S.: Histochemical Identification of a Connective Tissue Antigen, p. 27. (d) Kramer, H., and Little, K.: Nature of Reticulin, p. 33. (e) Slack, H. G. B.: Metabolism of Collagen in the Rat, p. 51. (f) Hoppey, F., McCrae, T. P., and Naylor, A.: X-ray Crystallographic Investigation of the Changes With Age in the Structure of the Human Intervertebral Disk, p. 65 (g) Armstrong, D. M. G.: Donnan Membrane Equilibrium in Collagen-Water Systems, p. 91. (h) Robinson, C.: The Hot and Cold Forms of Gelatin, p. 96. (i) Jackson, S. F., Kelly, F. C., North, A. C. T., Randall, J. T., Seeds, W. E., Watson, M., and Wilkinson, G. R:. The Byssus Threads of Mytilus edulis and Pinna nobilis, p. 106. (j) Brown, G. L.: Kelly, F. C., and Watson, M.: Quantitative Paper Chromatography of Amino Acids in Collagen, p. 117. (k) Stack, M. V.: Properties of Dentine Collagen, p. 124. (l) Martin, A. V. W.: Fine Structure of Cartilage Matrix, p. 129. (m) Jackson, S. F.: Fibrogenesis in vivo and in vitro, p. 140. (n) M'Ewen, M. B., and Pratt, M. I.: Scattering of Light by Collagen Solutions, p. 158. (o) Brown, G. L., and Kelly, F. C.: Electrophoresis of Collagen Solutions, p. 169. (p) Jackson, D. S.: Chondroitin Sulphate as a Factor in the Stability of Tendon, p. 177. (q) Jackson, S. F., and Randall, J. T.: The Reconstitution of Collagen Fibrils From Solution, p. 181. (r) Consden, R.: Observations on the Composition of Human Subcutaneous Tissue, p. 196. (s) Bowes, J. H. Elliott, R. G., and Moss, J. A.: Some Differences in the Composition of Collagen and Extracted Collagens and Their Relation to Fibre Formation and Dispersion, p. 199. (t) Harkness, R. D., Marks, A. M., Muir, H. M., and Neuberger, A.: Precursors of Skin Collagen, p. 208. (u) Randall, J. T., Brown, G. L., Jackson, S. F., Kelly, F. C. North, A. C. T., Seeds, W. E., and Wilkinson, G. R.: Some Physical and Chemical Properties of Extracted Skin Collagen, p. 213. (v) Randall, J. T.: Physical and Chemical Problems of Fibre Formation and Structure, p. 232. (w) Cowan, P. M., North, A. C. T., and Randall, J. T.: High-Angle X-ray Diffraction of Collagen Fibres, p. 241. (x) Seeds, W. E.: Infra-red Absorption and Collagen Structure, p. 250.

12. Lowry, O. H., Gilligan, D. R., and Katersky, E. M.: The Determination of Collagen and Elastin in Tissues With Results Obtained in Various Normal Tissues From Different Species, J. Biol. Chem. **139**:795, 1941.
13. Neuman, R. E., and Logan, M. A.: The Determination of Collagen and Elastin in Tissues, J. Biol. Chem. **186**:549, 1950.
14. Waksman, B. H., and Mason, H. L.: The Antigenicity of Collagen, J. Immunol. **63**:427, 1949.
15. Balo, J., and Banga, I.: The Elastolytic Activity of Pancreatic Extracts, Biochem, J. **46**:384, 1950.
16. Hall, D. A., Reed, R., and Tunbridge, R. E.: Structure of Elastic Tissue, Nature **170**:264, 1952.
17. Perl, E., and Catchpole, H. R.: Changes Induced in the Connective Tissues of the Pubic Symphysis of the Guinea Pig With Estrogen and Relaxin, Arch. Path. **50**:233, 1950.
18. Meyer, K., and Rapport, M. M.: The Mucopolysaccharides of the Ground Substance of Connective Tissue, Science **113**:596, 1951.
19. Gross, J.: Connective Tissue Fine Structure and Some Methods for Its Analysis, J. Gerontol. **5**:343, 1950.
20. Dorfman, A.: Metabolism of the Mucopolysaccharides of Connective Tissue, Pharmacol. Rev. **7**:1, 1955.
21. Maximow, A. A., and Bloom, W.: A Textbook of Histology, Philadelphia, 1942, W. B. Saunders Co.
22. Meyer, K., and Rapport, M. M.: Hyaluronidases, Advances Enzymol. **13**:199, 1952.
23. Asboe-Hansen, G.: The Origin of Synovial Mucin. Ehrlich's Mast Cell—a Secretory Element of Connective Tissue, Ann. Rheumat. Dis. **9**:149, 1950.
24. Jackson, D. S.: The Nature of Collagen-Chondroitin Sulfate Linkages in Tendon, Biochem. J. **56**:699, 1954.
25. Boetker, H., and Doty, P.: On the Nature of the Structural Element of Collagen, J. Am. Chem. Soc. **77**:248, 1955.
26. Gross, J., Matoltsy, A. G., and Cohen, C.: Vitrosin: A Member of the Collagen Class, J. Biophys. & Biochem. Cytol. **1**:215, 1955.
27. Schmitt, F. O., and Sizer, I. W.: Personal communication.
28. Banga, I., and Balo, J.: Elastin and Elastase, Nature **171**:44, 1953.
29. Weiss, J.: The Nature of the Reaction Between Orcein and Elastin, J. Histochem. & Cytochem. **2**:21, 1954.
30. Bowen, T. J.: Physical Studies on a Soluble Protein Obtained by the Degeneration of Elastin With Urea, Biochem. J. **55**:766, 1953.
31. Bowes, J. H., and Kenten, R. H.: Summary of Published Results (1900-1946) on Amino Acid Composition of Gelatin and Collagen, Leather Manuf. Res. A., pp. 1-22, 1947.
32. Gross, J.: Fiber Formation in Trypsinogen Solutions: An Electron Optical Study, J. Proc. Exper. Biol. & Med. **78**:241, 1951.
33. Blackett, N. M.: On the Organization of Collagen Fibrils in Bone, Biochim. et Biophys. Acta **16**:161, 1955.
34. Day, T. D.: The Mode of Reaction of Interstitial Connective Tissue With Water, J. Physiol. **109**:380, 1949.
35. Gross, J.: The Structure of Elastic Tissue as Studied With the Electron Microscope, J. Exper. Med. **89**:699, 1949.
36. Braden, A. W. H.: The Reactions of Isolated Mucopolysaccharides to Several Histochemical Tests, Stain Technol. **30**:19, 1955.
37. Gomori, G.: The Histochemistry of Mucopolysaccharides, Brit. J. Exper. Path. **35**:377, 1954.
38. Hass, G. M.: Elastic Tissue, Arch. Path. **27**:334, 543, 1939.
39. (a) Reifenstein, E. C., Jr. (ed.): Metabolic Inter-relations, With Special Reference to Calcium. Transactions of the Fifth Conference, Josiah Macy, Jr., Foundation, New York, 1953. (b) Robinson, R. A., and Watson, M. L.: Electron Micrography of Bone, p. 72.
40. Gross, J., Highberger, J. H., and Schmitt, F. O.: Some Factors Involved in the Fibrogenesis of Collagen in Vitro, Proc. Soc. Exper. Biol. & Med. **80**:462, 1952.
41. Gross, J., Highberger, J. H., and Schmitt, F. O.: Collagen Structures Considered as States of Aggregation of a Kinetic Unit. The Tropocollagen Particle, Proc. Nat. Acad. Sc. **40**:679, 1954.
42. Gray, J.: The Properties of Inter-Cellular Matrix and Its Relations to Electrolytes, Brit. J. Biol. **3**:167, 1926.
43. Parker, R. C.: The Races That Constitute the Group of Common Fibroblasts, J. Exper. Med. **58**:401, 1933.
44. Gerarde, H. W., and Jones, M.: The Effect of Cortisone on Collagen Synthesis in Vitro, J. Biol. Chem. **201**:553, 1953.
45. Fawcett, D. W.: Cell Differentiation and Modulation; *In* An Introduction to Cell and Tissue Culture by the Staff of the Tissue Culture Course, Cooperstown, N. Y., 1949-1953, Minneapolis, 1955, Burgess.

46. Bloom, W.: Studies on Fibers in Tissue Culture. II. The Development of Elastic Fibers in Cultures of Embryonic Heart and Aorta, Arch. exper. Zellforsch. **9**:6, 1929.
47. Odiette, D.: La fibre élastique dans les cultures de tissues in vitro (deuxième mémoire), J. physiol. et path. gén. **33**:475, 1935.
48. Odiette, D.: La fibre élastique dans les cultures de tissues in vitro. Étude histo-physio-pathologique, J. physiol. et path. gén. **32**:715, 1934.
49. Hall, D. A., Keech, M. K., Reed, R., Saxl, H., Tunbridge, R. E., and Wood, M. J.: Collagen and Elastin in Connective Tissue, J. Gerontol. **10**:388, 1955.
50. Duran-Reynals, F., and Suner Pi, J.: Exaltation de l'activité du staphylocoque par les extraits testiculaires, Compt. rend. Soc. biol. **99**:1908, 1929.
51. Meyer, K., and Palmer, J. W.: The Polysaccharide of the Vitreous Humor, J. Biol. Chem. **107**:629, 1934.
52. Djiewiatkowski, D. D.: Rate of Excretion of Radioactive Sulfur and Its Concentration in Some Tissues of the Rat After Intraperitoneal Administration of Labeled Sodium Sulfate, J. Biol. Chem. **178**:197, 1949.
53. Vaubel, E.: The Form and Function of Synovial Cells in Tissue Cultures, J. Exper. Med. **58**:85, 1933.
54. Bollet, A. J., Boas, N. F., and Bunin, J. J.: Synthesis of Hexosamine by Connective Tissue (in Vitro), Science **120**:348, 1954.
55. Mancini, R. E., and de Lustig, E. S.: Acción de la hialurinadasa sobre los fibroblastos in vitro, Rev. Soc. argent. biol. **26**:7, 1950.
56. Schmitt, F. O., Gross, J., and Highberger, J. H.: A New Particle Type in Certain Connective Tissue Extracts, Proc. Nat. Acad. Sc. **39**:459, 1953.
57. Kramer, H.: The Nature and Formation of Normal and Abnormal Connective Tissue, D. Phil. Thesis, University of Oxford, 1952. Cited by Robb-Smith.[58b]
58. Asboe-Hansen, G. (ed.): Connective Tissue in Health and Disease, Copenhagen, 1954, Ejnar Munksgaard Forlag.
(a) Asboe-Hansen, G.: Introduction, p. 9. (b) Robb-Smith, A. H. T.: Normal Morphology and Morphogenesis of Connective Tissue, p. 15. (c) McManus, J. F. A.: Histochemistry of Connective Tissue, p. 31. (d) Meyer, K.: Chemistry of Ground Substance, p. 54. (e) Kulonen, E.: Chemistry of Collagen, p. 70. (f) Dorfman, A.: Metabolism of Mucopolysaccharides, p. 81. (g) Boström, H.: Sulphate Exchange of Sulpho-mucopolysaccharides, p. 97. (h) Duran-Reynals, F.: The Spreading Reaction, p. 103. (i) Mathews, M. B., and Dorfman, A.: Inhibition of Hyaluronidase, p. 112. (j) Iversen, K.: Hormonal Influence on Connective Tissue, p. 130. (k) Banfield, W. G.: Aging of Connective Tissue, p. 159. (l) Howes, E. L.: Connective Tissues in Wound Healing, p. 159. (m) Altshuler, C. H., and Angevine, D. M.: The Pathology of Connective Tissue, p. 178. (n) Teihum, G.: Cortisone, Ascorbic Acid and Changes in the Reticulo-endothelial System, p. 196. (o) Sprunt, D. H.: Connective Tissue and Infection, p. 208. (p) Cavallero, C.: Influence of Hormones on Infection, p. 214. (q) Simpson, W. L.: Connective Tissues and Cancer, p. 225. (r) Rinehart, J. F.: Histogenesis and Pathogenesis of Arteriosclerosis, p. 239. (s) Klemperer, P.: Collagen Diseases, p. 251. (t) Ragan, C.: Arthritis, p. 263. (u) Asboe-Hansen, G.: Systemic Connective Tissue Disorders Pertaining to Dermatology, p. 274. (v) Godtfredsen, E.: Mesenchymal Aspects in Ophthalmology, p. 296. (w) Zachariae, L.: Fibroses Due to Injury, p. 308.
59. Riley, J. F.: Pharmacology and Functions of the Mast Cells, Pharmacol. Rev. **7**:183, 1955.
60. Grassmann, W.: Unsere heutige Kenntnis des Kollagens, Das Leder **6**:241, 1955.
61. Gustavson, K. H.: The Chemistry and Reactivity of Collagen, New York, 1956, Academic Press, Inc.
62. Schmitt, F. O., Gross, J., and Highberger, J. H.: Tropocollagen and the Properties of Fibrosis Collagen, Exper. Cell Res. Supp. **3**:326, 1955.
63. Dorfman, A., and Mathews, M. B.: The Physiology of Connective Tissue, Ann. Rev. Physiol. **18**:69, 1956.
64. Kent, P. W., and Whitehouse, M. M.: Biochemistry of Amino Sugars, New York, 1955, Academic Press, Inc.
65. Hamilton, P. B., and Anderson, R. A.: Hydroxyproline in Proteins, J. Am. Chem. Soc. **77**:2892, 1955.
66. Castor, C. W.: Approaches to the Study of Connective Tissue, Bull. Rheumat. Dis. **9**:177, 1959.
67. Lillie, R. D.: Histopathologic Technique and Practical Histochemistry, New York, 1954, The Blakiston Co., chap. 16, p. 333.
68. Baker, B. L., and Abrams, G. D.: The Physiology of Connective Tissue, Ann. Rev. Physiol. **17**:61, 1955.
69. Campani, M.: Function of Mast-Cells, Lancet **1**:802, 1951.
70. Morrione, T. G.: The Formation of Collagen Fibers by the Action of Heparin on Soluble Collagen, J. Exper. Med. **96**:107, 1952.
71. Riley, J. F.: The Riddle of the Mast Cells, Lancet **1**:841, 1954.
72. Jackson, S. F., and Smith, R. H.: Studies on the Biosynthesis of Collagen. I. The Growth of Fowl Osteoblasts and the Formation of Collagen in Tissue Culture, J. Biophys. & Biochem. Cytol. **3**:897, 1957.

73. Smith, R. H., and Jackson, S. F.: Studies on the Biosynthesis of Collagen. II. The Conversion of ^{14}C-L-proline to ^{14}C-hydroxy-proline by Fowl Osteoblasts in Tissue Culture, J. Biophys. & Biochem. Cytol. **3**:913, 1957.
74. Schmitt, F. O.: Cell Constitution; *In* Willier, Weiss and Hamburger (eds.): Analysis of Development, Philadelphia, 1955, W. B. Saunders Co., p. 46.
75. Keech, M. K., and Reed. R.: Enzymatic Elucidation of the Relationship Between Collagen and Elastin; an Electron Microscopic Study, Ann. Rheumat. Dis. **17**:23, 1958.
76. Keech, M. K.: Transformation of Collagen to "Elastin" in Dermal Collagens With Varying Sensitivity Towards Collagenase, Ann. Rheumat. Dis. **17**:23, 1958.
77. Keech, M. K.: The Effect of Collagenase on Human Skin Collagen. Comparison of Different Age-Groups and of Cases With and Without "Collagen Disease," Yale J. Biol. & Med. **26**:295, 1954.
78. Jackson, D. S.: Some Biochemical Aspects of Fibrogenesis and Wound Healing, New England J. Med. **259**:826, 1958.
79. Tunbridge, R. E., et al. (eds.): Connective Tissue, a Symposium, Springfield, Ill., 1957, Charles C Thomas, Publisher.
(a) Astbury, W. T.: Introduction, p. 1. (b) Asboe-Hansen, G.: On the Structure and Function of the Mast Cells, p. 12. (c) Sylvén, B.: On the Topographical Cytochemistry of Tissue Mast Cells, p. 27. (d) Neuberger, A.: Observations on the Presence and Metabolism of Plasma Proteins in Skin and Tendon, p. 35. (e) Gross, J.: Studies on the Fibrogenesis of Collagen. Some Properties of Neutral Extracts of Connective Tissue, p. 45. (f) Jackson, D. S.: The Formation and Breakdown of Connective Tissue, p. 62. (g) Jackson, S. F.: Structural Problems Associated With the Formation of Collagen Fibrils *in vivo*, p. 77. (h) Meyer, K., Hoffman, P., and Linker, A.: The Acid Mucopolysaccharides of Connective Tissue, p. 86. (i) Snellman, O.: Evaluation of Extraction Methods for Acid Tissue Polysaccharides, p. 97. (j) Delaunay, A., and Bazin, S.: Combinaisons in vitro collagène-mucopolysaccharides et modifications apportés à ces combinaisons par des sels et des polyosides bactériens, p. 105. (k) Gillman, T., Hathorn, M., and Penn, J.: Micro-Anatomy and Reactions to Injury of Vascular Elastic Membranes and Associated Polysaccharides, p. 120. (l) Snellman, O., Ottoson, R., and Sylvén, B.: On the Nature of the Metachromatic Ground Substance Polysaccharides of Healing Wounds, p. 136. (m) Schwarz, W.: Morphology and Differentiation of the Connective Tissue Fibers, p. 144. (n) Grassmann, W., Hofmann, U., Kühn, K., Hörmann, H., Endres, H., and Wolf, K.: Electron Microscope and Chemical Studies of the Carbohydrate Groups of Collagen, p. 157. (o) van den Hooff, A.: A Few Remarks on Connective Tissues Rich in Mucoid, p. 172. (p) Robb-Smith, A. H. T.: What Is Reticulin? p. 177. (q) Gustavson, K. H.: Some New Aspects of the Stability and Reactivity of Collagens, p. 185. (r) Verzár, F.: The Ageing of Collagen, p. 208. (s) Partridge, S. M., Davis, H. F., and Adair, G. S.: The Composition of Mammalian Elastin, p. 222. (t) Hall, D. A.: Chemical and Enzymatic Studies on Elastin, p. 238. (u) Banga, I., and Baló, J.: The Structure and Chemical Composition of Connective Tissue, p. 254. (v) Bowes, J. H., Elliott, R. G., and Moss, J. A.: The Composition of Some Protein Fractions Isolated From Bovine Skin, p. 264. (w) Orekhovitch, V. N., and Shpikiter, V. O.: Procollagens as Biological Precursors of Collagen and the Physio-Chemical Nature of These Proteins, p. 281. (x) Muir, H. M.: The Structure of a Chondroitin Sulphate Complex From Cartilage, p. 294. (y) Reed, R.: The Architecture of the Collagen Fibril, p. 299. (z) Grassmann, W., Hannig, K., Endres, H., and Riedel, A.: Amino-Acid Sequences of Collagen, p. 308. (aa) Bear, R. S., and Morgan, R. S.: The Composition of Bands and Interbands of Collagen Fibrils, p. 321.
80. Ingram, V. M.: Gene Mutations in Human Haemoglobin; the Chemical Difference Between Normal and Sickle Cell Haemoglobin, Nature **180**:326, 1957.
81. Slack, H. G. B.: Some Notes on the Composition and Metabolism of Connective Tissue, Am. J. Med. **26**:113, 1959.

*In an era when slenderness and ectomorphy are being equated with long life, it may be wise to point out an exception.**

3. THE MARFAN SYNDROME

HISTORICAL SURVEY

In 1896[101] the gross skeletal manifestations of the syndrome which bears his name were described by Marfan,† who called the condition *dolichostenomelia* (long, thin extremities) (see Fig. 2*B*). The condition was renamed arachnodactyly by Achard in 1902.[3] (Marfan had used the similie "pattes d'araignée," spider legs.) Salle[136] in 1912 reported necropsy observations in the case of a 2½-month-old infant who died with cardiac symptoms and showed generalized dilatation of the heart and patent foramen ovale. Boerger[24] first clearly related ectopia lentis to the other manifestations. As is usually the case, vague references to cases of what was certainly this syndrome can be found in medical reports antedating the definitive descriptions. For instance, Williams,[183] an ophthalmologist in Cincinnati, in 1876 described ectopia lentis in a brother and sister who were exceptionally tall and had been loose-jointed from birth.

Weve of Utrecht,[177] publishing in 1931, first clearly demonstrated the heritable nature of the syndrome and its transmission as a dominant trait. Furthermore he conceived of this syndrome as a disorder of mesenchymal tissues and accordingly designated it *dystrophia mesodermalis congenita, typus Marfanis.*

The major cardiovascular complications, namely, aortic dilatation and dissecting aneurysm, were first clearly described in 1943 by Baer and his associates[11] and by Etter and Glover,[42] respectively. Again, although earlier reports of the aortic complications can be discovered (e.g., reference 29 and Fig. 3), these later authors first drew attention to them and opened the way for clearer recognition of the internal medical implications of this syndrome in adults.

It is difficult to imagine a better description of the Marfan syndrome than that given by Bronson and Sutherland[29] in 1918 in the case of a 6-year-old child with aneurysm of the ascending aorta which ruptured into the pericardium.

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*From Editorial: New England J. Med. **256**:39, 1957.

†Antoine Bernard-Jean Marfan (1858-1942), Parisian professor of pediatrics, did much to establish pediatrics as a specialty in France and elsewhere. He was the author of several widely read textbooks and monographs on pediatric topics and editor of *Le Nourrisson* for a great many years. In addition to the syndrome under discussion here, his name is often attached to Marfan's law (that immunity to pumonary phthisis is conferred by the healing of a local tuberculous lesion) and Marfan's subxiphoid method for aspirating fluid from the pericardial sac.[257] (For other biographic details, see references 6, 7, 8, 74; for portrait, see Fig. 2*A*).

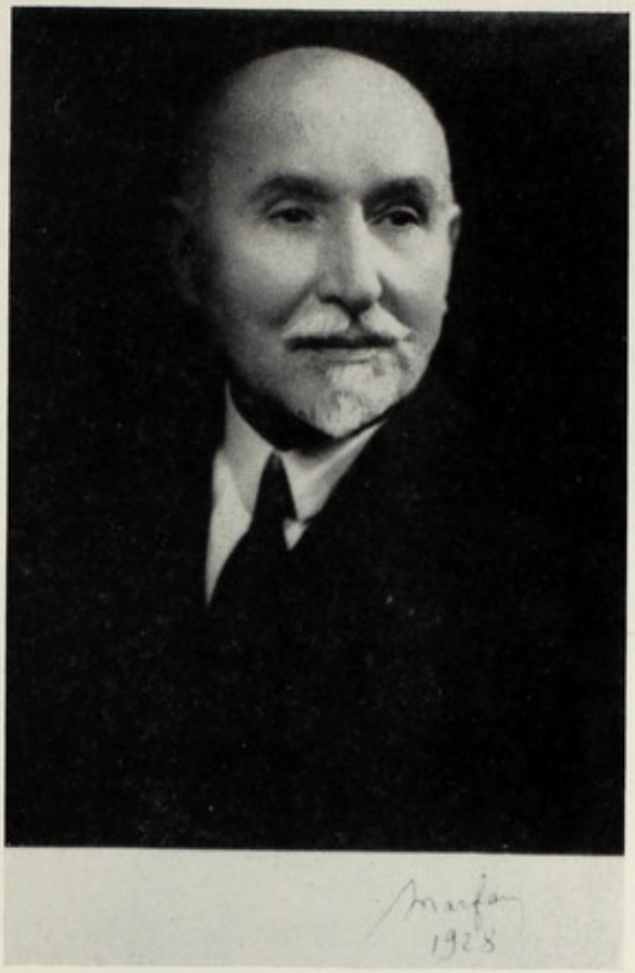


Fig. 2*A*. Marfan. (Courtesy Académie de médecine, Paris.)

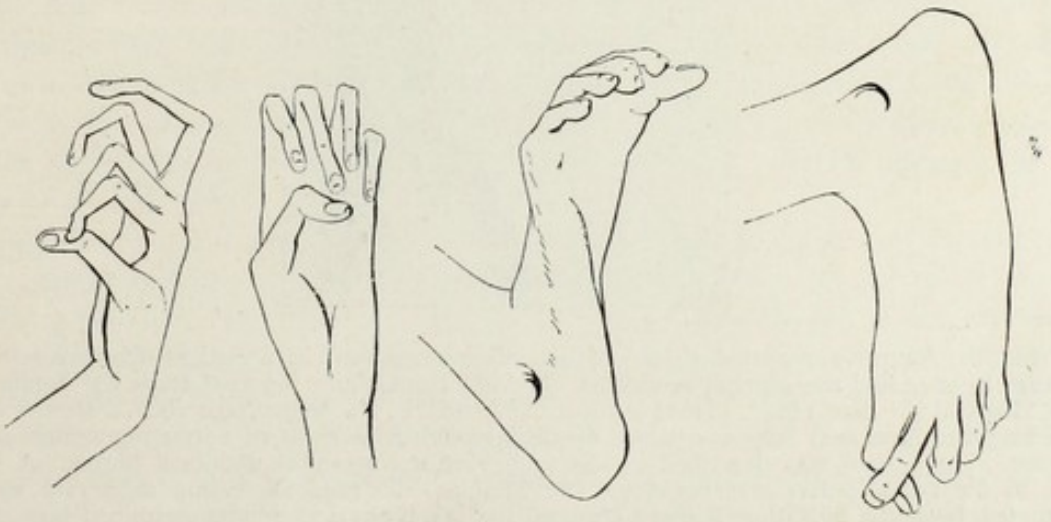


Fig. 2*B*. Arachnodactyly in Marfan's case. (From Marfan, A. B.: Bull. et mém. Soc. med. hôp. Paris **13**:220, 1896.)

"The unusual shape of his head and ears and the looseness of his joints attracted attention early in infancy." Inguinal hernia was repaired surgically at the age of 2 years, and a left diaphragmatic hernia was discovered by x-ray examination. He was always undernourished but was sensitive and mentally advanced for his age, with a quaint way of expressing himself and "a sense of humor of his own." The forehead was high and full, the palate highly arched. The ears were large without the normal folds of the pinnae. The joints were lax, the limbs flail-like, and the elbows showed definite subluxation. There were lordosis and pigeon breast with an increased prominence of the right side of the chest which showed better expansion. A pulsating mass was discernible to the right of the sternum. Although no diastolic murmur was mentioned, the left ventricle was hypertrophied at autopsy. There was also partial coarctation proximal to the left subclavian artery. The authors presented a detailed review of reports previous to that

Fig. 3. An early reported case[251] of dissecting aneurysm in a patient who in retrospect appears to have had the Marfan syndrome. In 1909 MacCallum reported from the Johns Hopkins Hospital the case (Med. 15454; autopsy 2087) of "L. R., Negro, age 30 . . . slender built." The man had been seen one year before death, at which time signs of aortic regurgitation were present. The patient was described in life as having a congenital umbilical hernia. A difference in the radial pulses was noted by Dr. Thomas McCrae. Dissecting aneurysm was not suspected, however, by Osler, Rufus Cole, and the other physicians who examined him. There was paralysis of the left recurrent laryngeal nerve. The mother and several brothers had died, as well as the patient's only child, who died at the age of 2 years. No definitely corroboratory features of the family history were recorded, however, and no note of ocular abnormality was made. The ascending aorta, as shown here, resembles that seen in Fig. 16*G*. Furthermore the pronounced dilatation in the region of the sinuses of Valsalva suggests the Marfan syndrome. (From MacCallum, W. G.: Bull. Johns Hopkins Hosp. **20**:9, 1909.)

time; many of these cases also are reasonably clear instances of the Marfan syndrome.

"Marfan's syndrome," or better, "the Marfan syndrome," is, in my opinion, the preferred designation until such time as the basic defect is known and an accurate name based thereon can be devised. (F. Parkes Weber[173] was of the same view.) Arachnodactyly is, on the one hand, not striking in some patients, and, on the other hand, occurs with other developmental disorders, both acquired and genetic.

Probably at least 400 cases of the Marfan syndrome have been reported in the literature. By intensive searches of multiple sources, I was able in the last six years to collect 74 kinships in which at least one bona fide affected person has occurred. Thirty-three of these definitely affected families are represented in Figs. 3 to 38. The total number of definitely affected persons in these pedigrees approaches 200. In this study, the Wilmer Ophthalmological Institute of the Johns Hopkins Hospital was the largest single source of propositi. However, other sources included pediatricians, orthopedists, endocrinologists, and cardiologists. The Medical Examiner's Office was another fruitful source; tracing the relatives of young individuals dying of dissecting aneurysm of the aorta revealed several affected kinships. Under continuing study are the following aspects: survivorship, relative incidence of the several manifestations of the syndrome, intrafamilial and interfamilial variability, and other aspects, including incidence of sporadic versus familial cases, racial incidence, sex differences, etc.

CLINICAL MANIFESTATIONS

Fig. 44 (p. 119) presents a "pedigree of causes" in which the several manifestations of the Marfan syndrome are related to the hypothesized, but, as yet, undefined fundamental defect of connective tissue. See also Fig. 46.

The Skeletal Aspects (see Figs. 4*A* to 4*J* for the various body types encountered). Dolichomorphism characterizes the skeletal abnormality of the syndrome. The victim often suggests the subject of an El Greco painting.* The extremities are long, and characteristically the lower segment (pubis-to-sole) measurement is in excess of the upper segment (pubis-to-vertex) measurement and the arm span in excess of the height. In general, the more distal bones of the extremities tend to demonstrate this excess length most strikingly. Arachnodactyly is the result (Figs. 9*A* to 9*C*).

Skeletal proportions are more important than actual height. It is true that these patients are often very tall. One patient was 6 feet tall at the age of 12 years.[30] Another patient[180] was 7 feet tall. The tallest patient encountered in our investigations was 6 feet 7 inches. As indices of arachnodactyly it has been proposed[180] that the hand-height ratio should be greater than 11 per cent and the foot-height ratio greater than 15 per cent. Furthermore, it is stated that the finger, especially the middle finger, should be one and one-half times greater than the length of the metacarpal. Excessive length of the inferior patellar ligament has been proposed as a useful diagnostic index. There is so much overlap with the normal that all

*Astigmatism is thought to have been the basis for El Greco's distorted representations, as in "St. Martin and the Beggar" (National Gallery, Washington, D. C.). Actually the legs are not disproportionately long in El Greco figures.

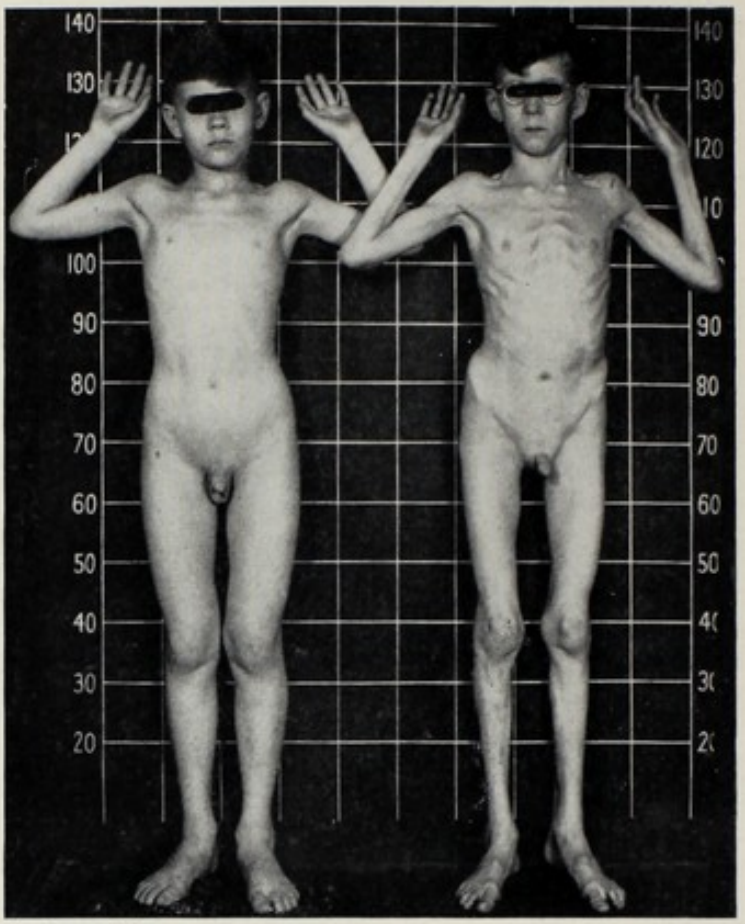


Fig. 4*A*. Brothers, one with Marfan's syndrome. The one on the left is normal, 10 years of age. M. D. (A59949), on the right, is only 8 years old. He shows ectopia lentis, contracture of the fifth fingers (see Fig. 10*A*), heterochromia iridis (right iris, blue; left, light green), Horner's syndrome on left, lack of subcutaneous fat, high palate, scoliosis and thoracic deformity, and abnormal electroencephalogram. This is probably a sporadic case (original mutation). Contracture of the fifth fingers (clinodactyly or camptodactyly) occurred in other patients of this series (e.g., J. A. M., A65283). Photograph, May, 1953. Heterochromia iridis occasionally is found as an isolated hereditary abnormality, transmitted probably as a dominant.[210] It is sometimes due to birth injury to the cervical sympathetics.

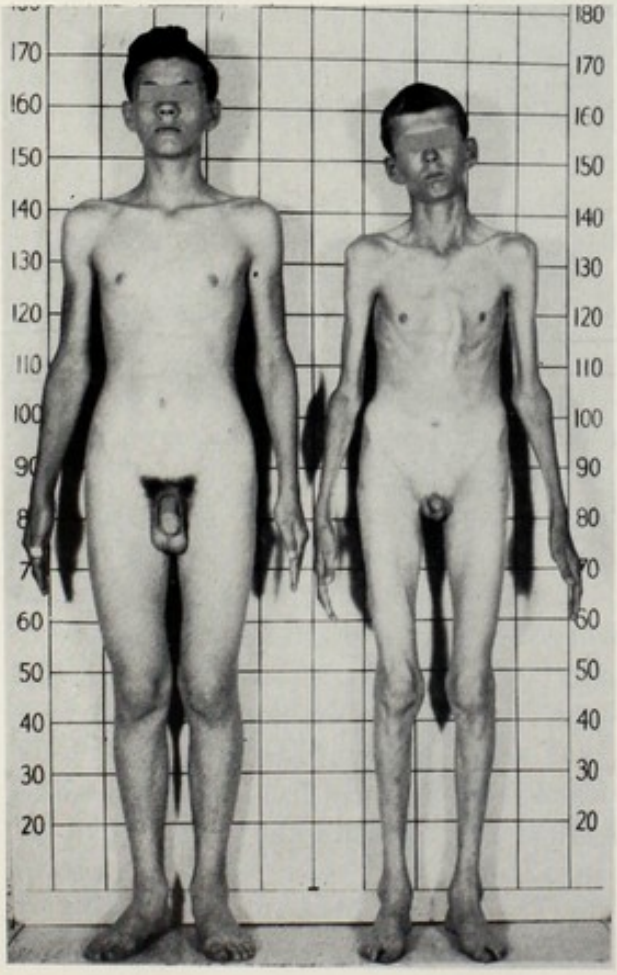


Fig. 4*B*. Same brothers as shown in Fig. 4*A*. Photograph, June, 1958. The older unaffected brother has now outstripped the affected brother in height.

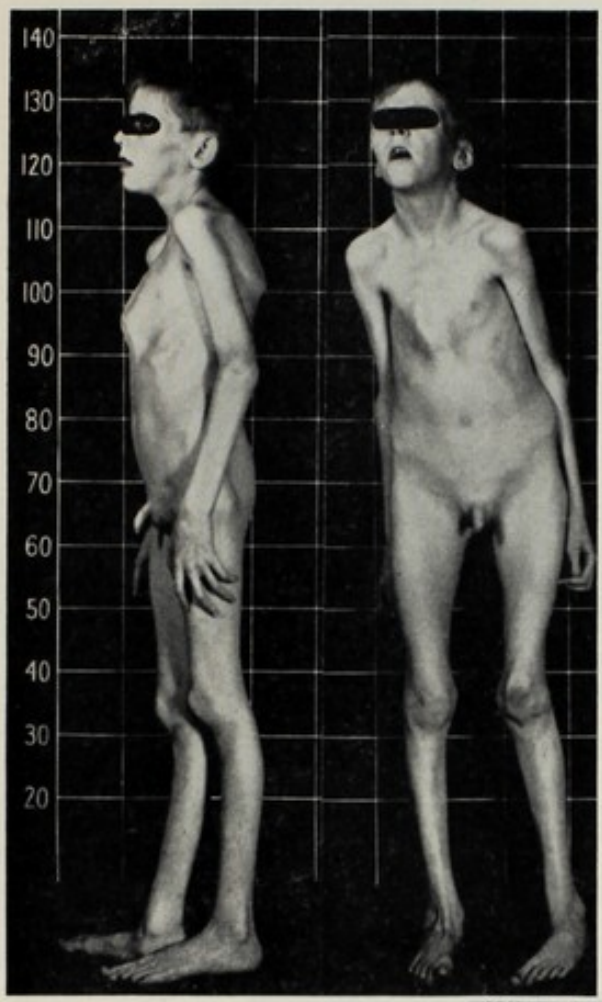


Fig. 4*C*. C. A. B. (B9912; 692938), 7 years old. Pronounced pectus carinatum. Normal mentality. Nystagmus. Bilateral ectopia lentis. "Rocker-bottom" feet. Sparce subcutaneous fat. Photograph, August, 1954.

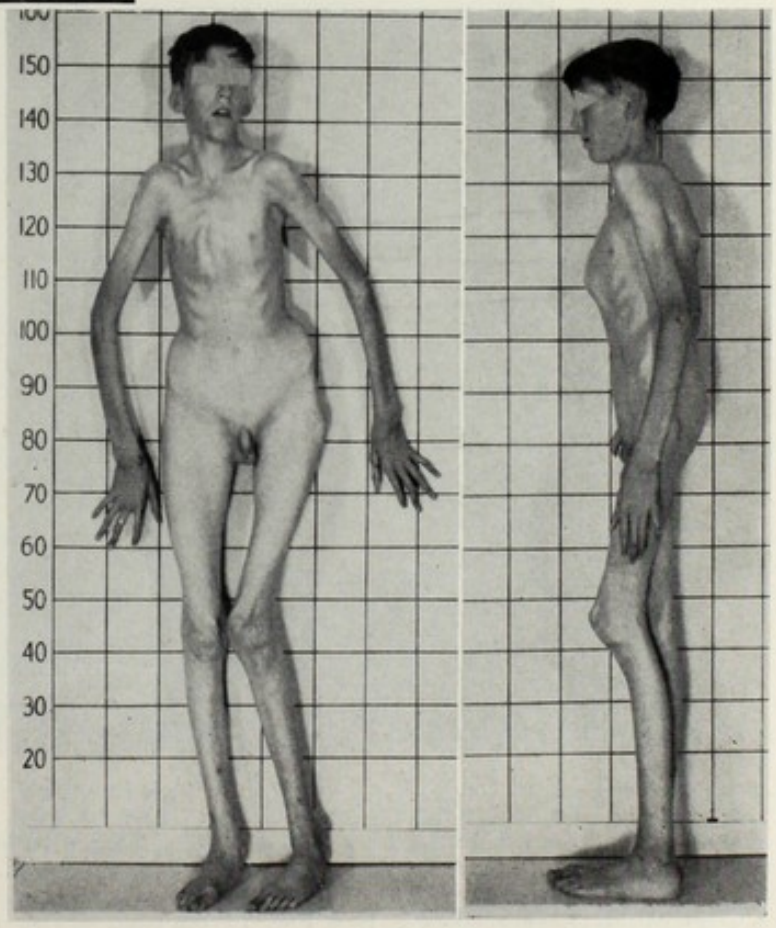


Fig. 4*D*. Same patient as shown in Fig. 4*C*. Photograph, August, 1958.

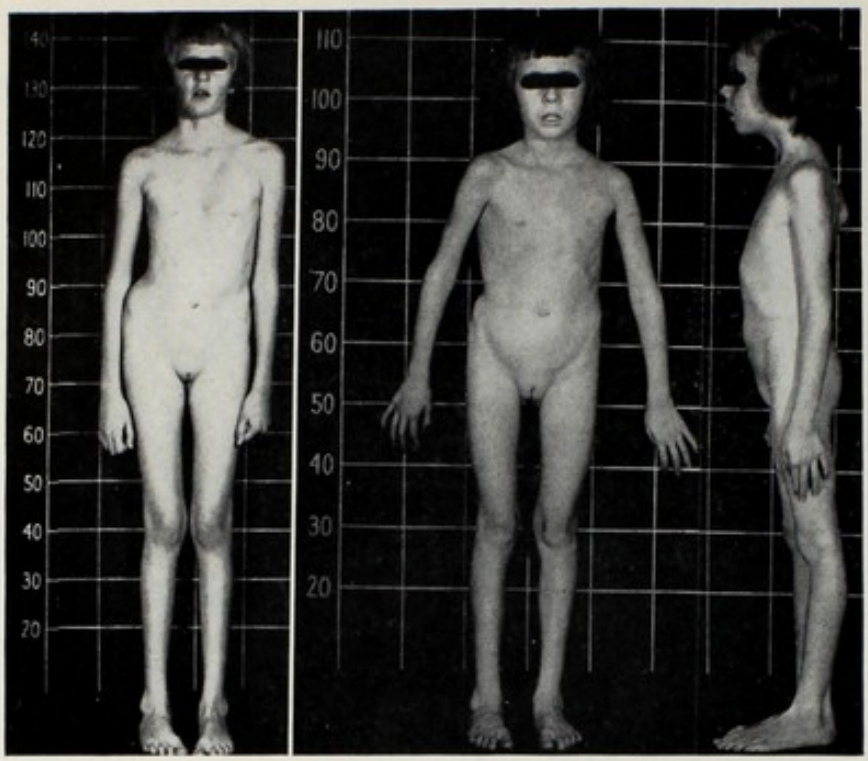


Fig. 4*E*.

Fig. 4*F*.

Fig. 4*E*. M. McG. (A92675), 7 years of age. Bilateral ectopia lentis. Severe pectus excavatum. Highly intelligent. Frequent respiratory infections. Loud systolic murmur of unclear origin. The mother has the full-blown syndrome and is sightless in one eye from spontaneous retinal detachment. This child died at the age of 10 years. The clinical picture was that of mitral regurgitation with progressive cardiac enlargement. Atrial fibrillation had its onset eight months before death. The mitral valve showed three cusps and abnormally short chordae tendineae. The left antrium was huge, with thickened endocardium. Both ventricles were grossly dilated.

Fig. 4*F*. D. W. (B8430), 4 years 2 months of age, is thought to have minimal dilatation of the ascending aorta and mitral regurgitation. Also has kyphoscoliosis and ectopia lentis. Parents appear unaffected but paternal great grandfather was 6 feet 7 inches tall.

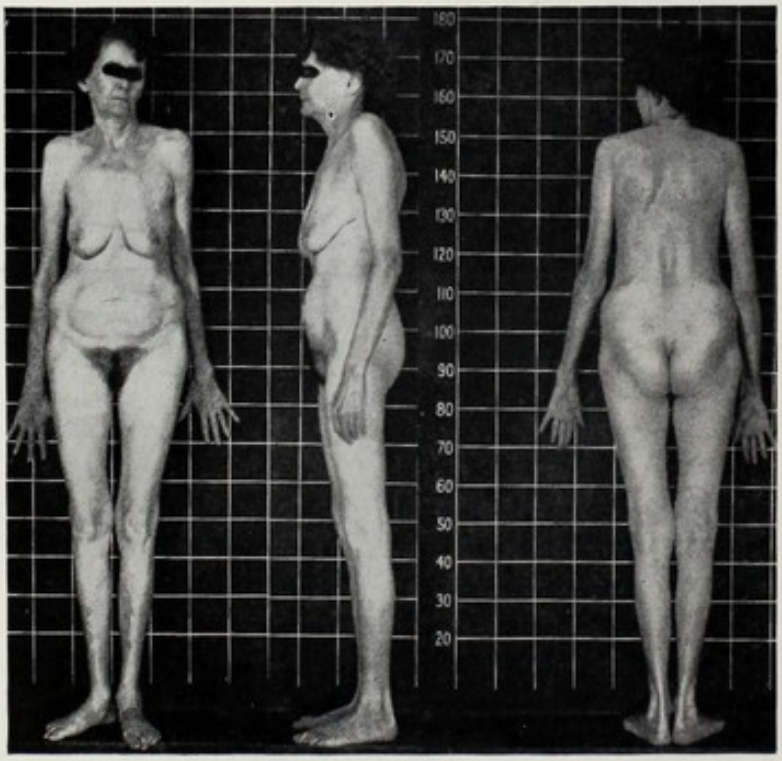


Fig. 4*G*. M. P. (362804), 53 years old, one of the oldest patients with the Marfan syndrome I have had the opportunity to examine. (I have recently seen a 59-year-old man with the Marfan syndrome manifested by ectopia lentis, dolichostenomelia, and aortic aneurysm. One man with probable Marfan's syndrome was killed accidentally at the age of 82 years. He was still well preserved at that time. He was 75 inches tall and fathered at least two full-blown cases of Marfan's syndrome [see Fig. 23 on page 81 for the x-ray film of one] and four probably affected individuals out of sibship numbering twelve in all.) Extensive pedigree of Marfan's syndrome. Systolic crunch (extracardiac sound) present for many years.

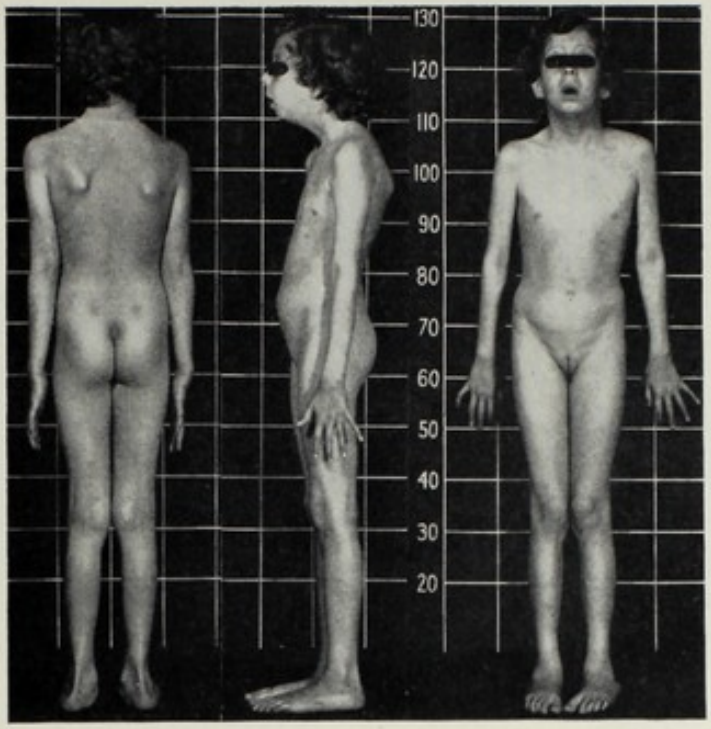


Fig. 4*H*. D. L. F. (516670), 7 years of age. The ptosis was thought to be part of the general muscular hypotonia which was so severe that amyotonia congenita was suspected when the patient was seen at the age of 4 years. Umbilical and bilateral inguinal hernias have been repaired surgically. The feet are very long, flat, and narrow. Kyphoscoliosis is evident. No ectopia lentis or ocular abnormality other than ptosis demonstrated. Intelligent. The ptosis has been corrected surgically since these photographs were taken. The patient may represent a new mutation. Possibly the bilateral ptosis is an independent mutation.

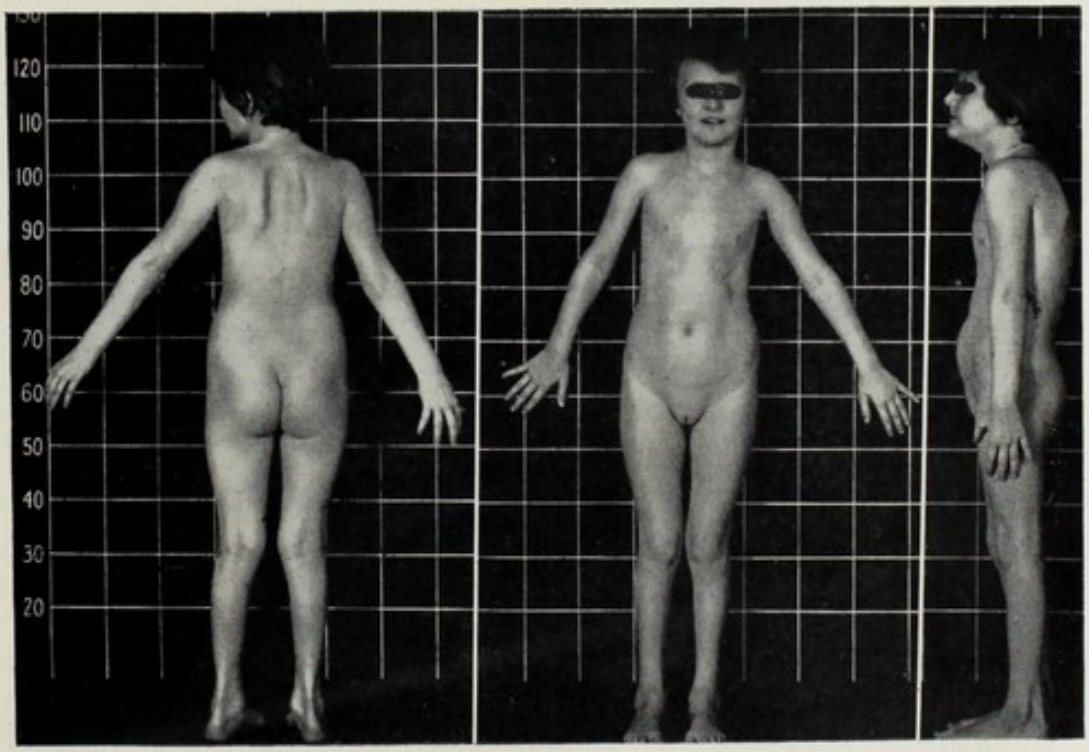


Fig. 4*I*. J. A. L. (661948), 5 years 8 months of age. Ectopia lentis. Probably *de novo* mutation. Shown very well is the eversion of the feet with low position of the internal malleolus ("rocker bottoms"). Child bright, but highly nervous. Photograph, January, 1954.

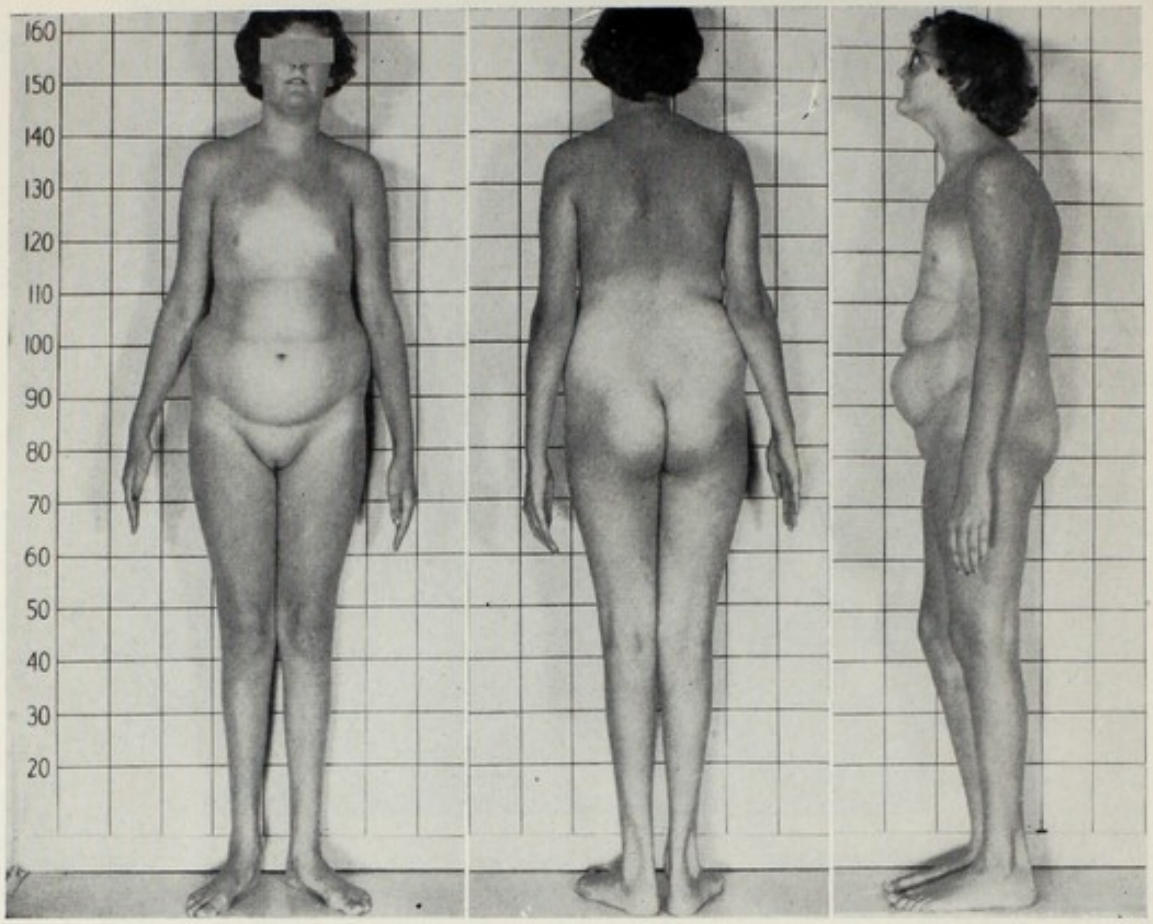


Fig. 4*J*. Same patient as shown in Fig. 4*I*, at age 10 years. Photograph, August, 1958. Sparcity of subcutaneous fat is not demonstrated by all cases of the Marfan syndrome.

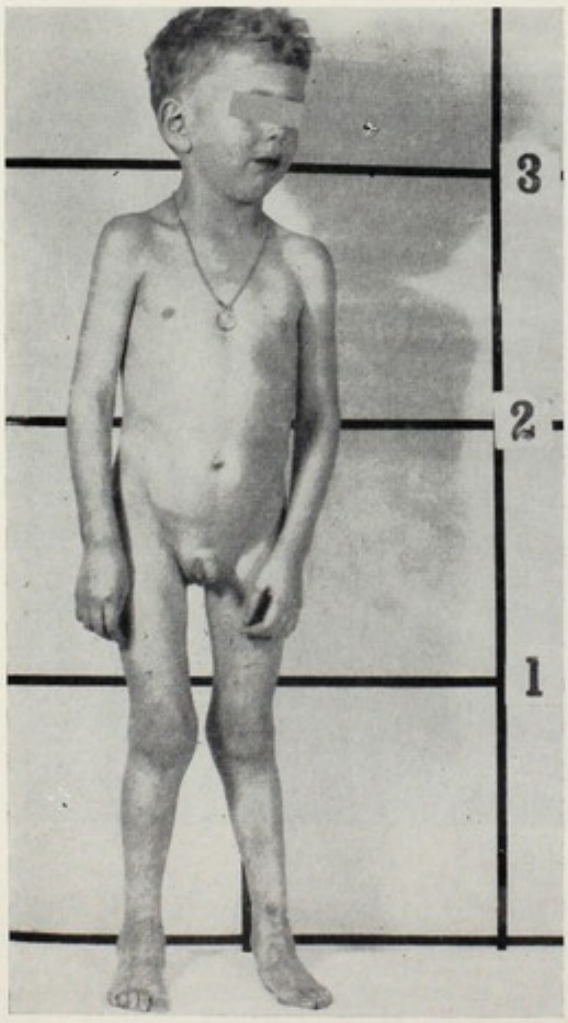


Fig. 5. Photograph of M. D., affected male shown in Figs. 4*A* and 4*B*, taken in February, 1948 (3½ years of age). Dolichostenomelia is often less impressive at this age.

measurements cannot be relied on as the sole diagnostic criterion in individual cases. More significance can be attached to them if they are particularly abnormal or if they represent marked deviations from the measurements in certain other members of the family.

Possibly the index of most usefulness, or at least one which is as reliable as any, is the ratio of upper segment (US) to lower segment (LS). The lower segment is measured from the top of the pubis symphysis to the floor. The upper segment is derived by subtracting this value from the height. As is indicated by the familiar illustration provided by Stratz in 1902 (Fig. 6), the legs grow relatively faster than the trunk during postnatal life. Resultingly, the mid-portion of the body moves progressively downward. The US-LS ratio is roughly 0.93 in the white adult, having been higher in the prepubital period. The individual born with the

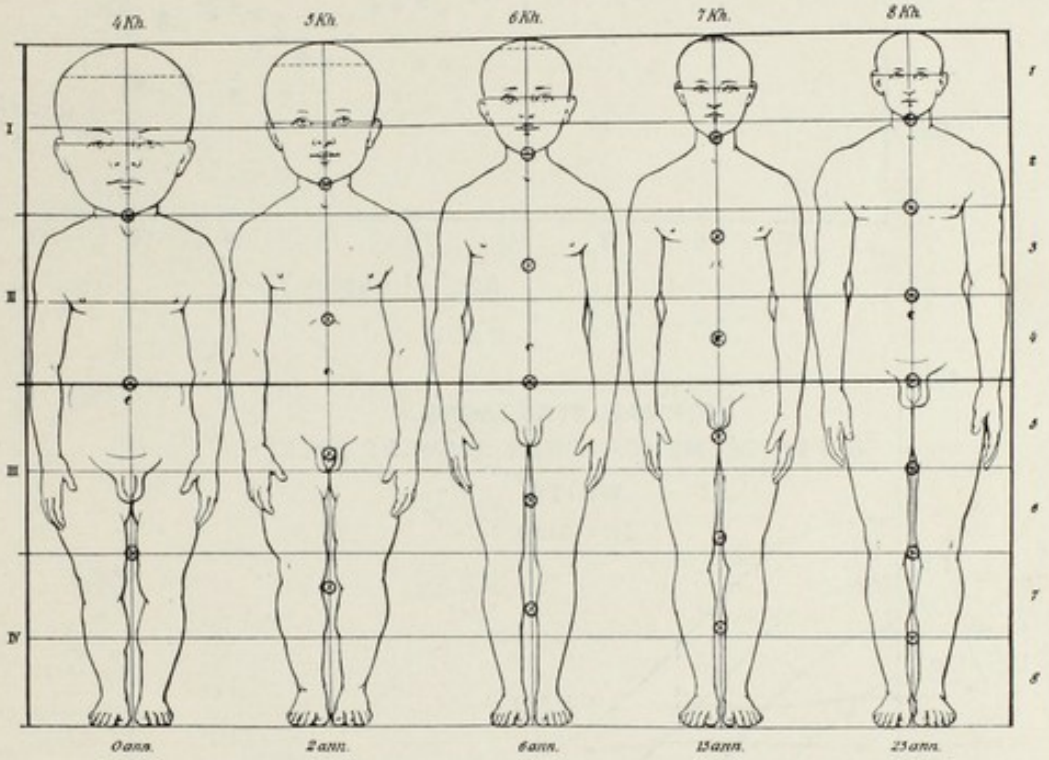


Fig. 6. Ordinarily the adult skeletal proportions are not attained until after puberty. There is evidence that the body proportions (as indicated by upper segment-lower segment ratio) is different now that at the turn of the century when this diagram was made, and that the pattern differs in whites and Negroes. This diagram will require redrawing on the basis of the data presented in Fig. 7. (From Stratz, C. H.: Der Körper des Kindes, Stuttgart, 1902, Ferdinand Enke.)

"Marfan gene" tends already to have an abnormally low segment ratio. Furthermore, he passes more rapidly through the sequence shown in Stratz' drawing, overshoots the mark, and ends up with a segment ratio in the vicinity of 0.85.

Because there are no recent data on whites and no published data whatever on Negroes, measurements of segments were made on 2,100 Baltimore school children of both races and sexes. The data are presented in Fig. 7. They should prove useful in the evaluation and follow-up of cases of the Marfan syndrome, as well as in the study of the hemoglobinopathies, endocrinopathies, and other disorders which influence body proportions. It is planned to increase the data at both ends of the age span shown in Fig. 7 and to extend them to about age 30 years.

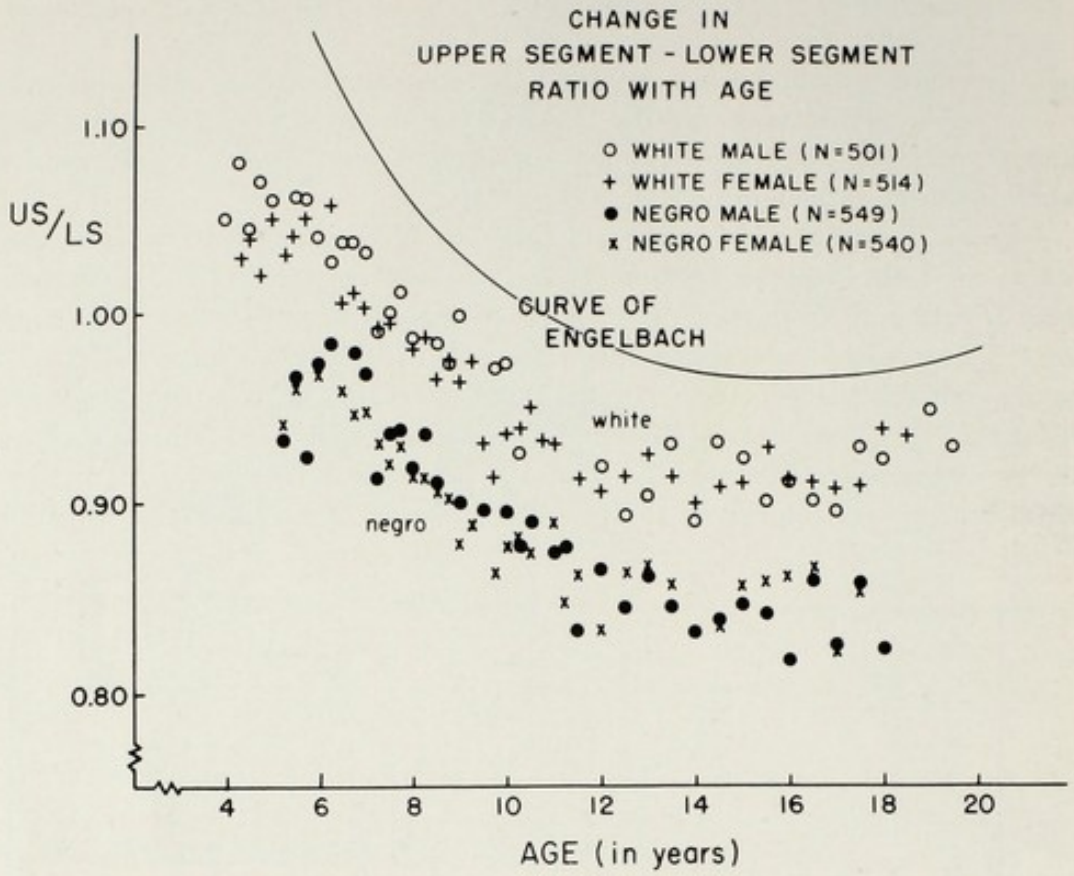


Fig. 7A.

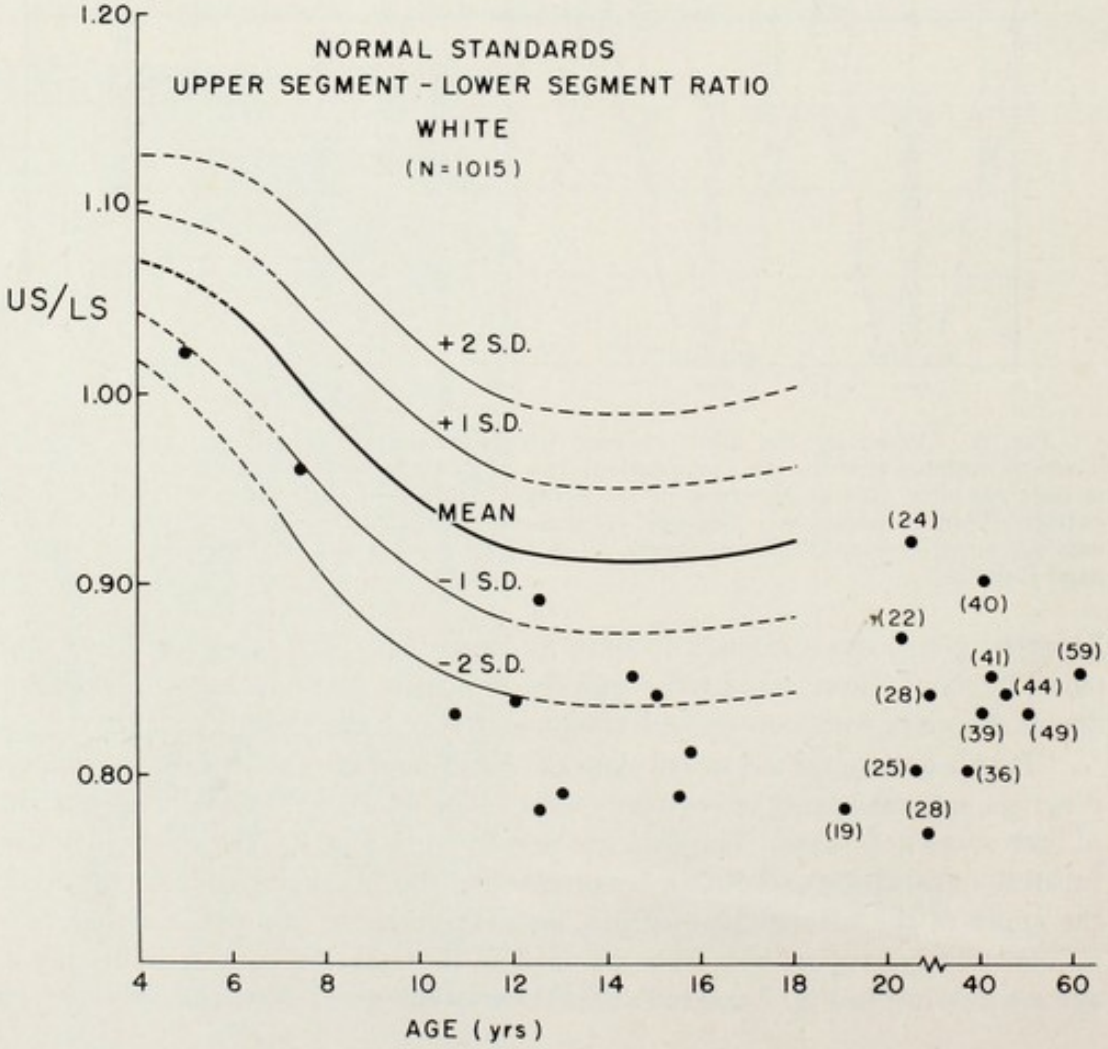


Fig. 7B.

Figs. 7A and 7B. For legend see opposite page.

The photographs in the nude on the measured grid cannot be relied on for more than a rough estimate of body proportions. Errors in estimating the site of the pubic symphysis and parallax made for poor reproducibility and poor checks with direct measurements.

The dip in the US-LS ratio at the stage of puberty, with subsequent slight rise, is noteworthy. If puberty is delayed the dip may be even more striking. The possibility of the Marfan syndrome was raised in the patient (E. K., 766137) shown in

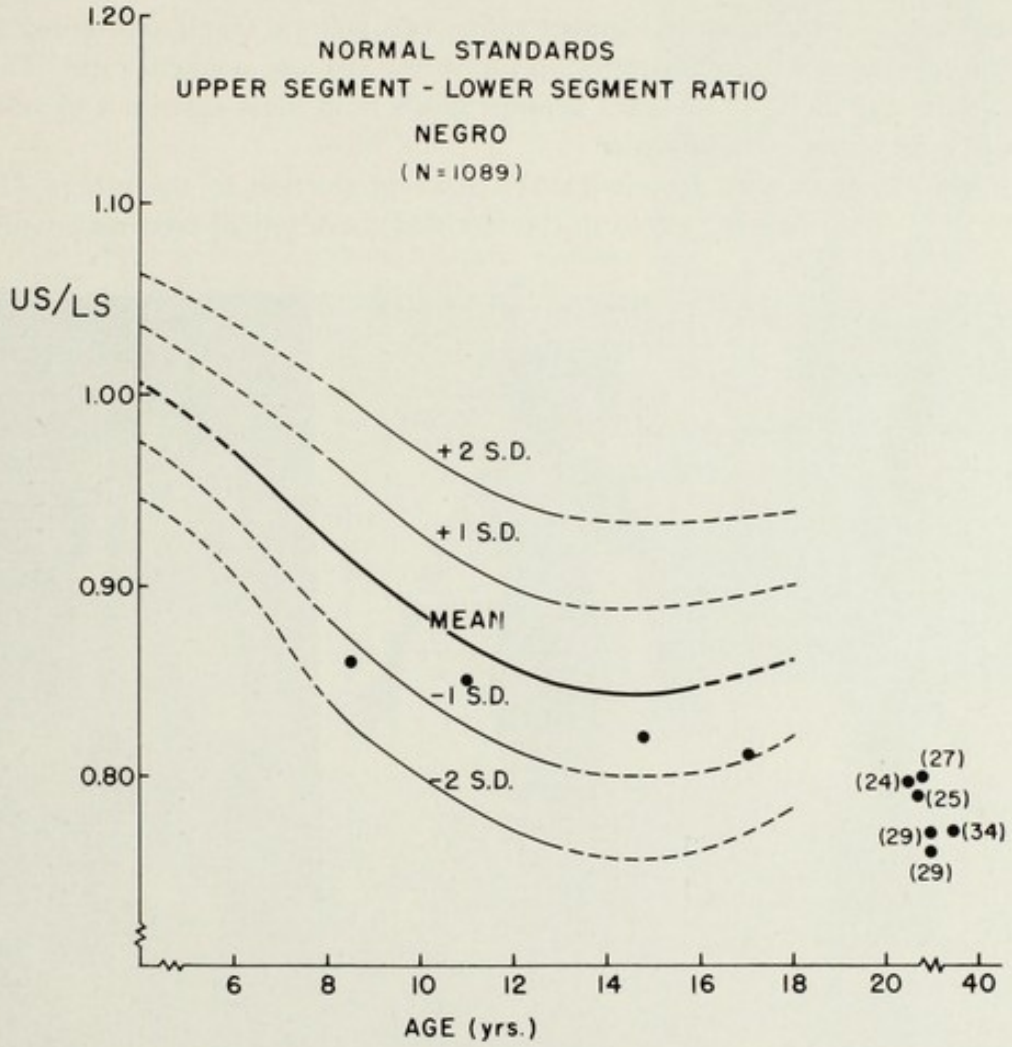


Fig. 7C.

Figs. 7*A*-7*C*. The upper segment-lower segment ratio (US/LS) as a gauge of the skeletal changes in the Marfan syndrome. Because of the lack of recent data on US/LS in either whites or Negroes, measurements were made in 1959 on over 2,100 Baltimore school children. In brief, the findings were as follows: (1) Engelbach's data,[40] compiled from measurements made by various observers in whites only, between about 1860 and 1928, are not presently applicable for either race (Fig. 7*A*). (2) At all ages there is a significantly lower US/LS in Negroes than in whites (Fig. 7*A*). (3) Negroes have a slightly shorter upper segment and slightly longer lower segment than do whites. As a result the US/LS is strikingly different. (4) Within both racial groups no significant sex difference in the mean US/LS or the standard deviations of the means could be demonstrated, at least in the measurements up to the age of about 15 years. This is the rationale for considering the sexes together in Figs. 7*B* and 7*C*. It will almost certainly be necessary to consider the sexes separately in presenting data now being collected on persons 15 to 30 years of age.

As shown in Figs. 7*B* and 7*C*, the US/LS of most patients with the Marfan syndrome fell in the abnormally low range. Measurements on thirty-four patients are shown. The number in the parentheses is the age in years.

(From data of McKusick, V. A., Ferguson-Smith, M. A., Leeming, J. T., and Merryman, C. F., to be published.)

Fig. 41*B*. The presence of gynecomastia strengthens the impression of anomalous pubertal transition.

Sickle cell anemia is a recognized cause of growth disturbance which can result in body proportions resembling those of the Marfan syndrome. The patient (D. M., 659463) shown in Fig. 41*A* is an example. The osseous hyperemia which accompanies hyperactivity of the bone marrow in the long bones may be the mechanism.

In cases of the Marfan syndrome the occurrence of kyphoscoliosis with shortening of the trunk also reduces the segment ratio; two factors, trunk shortening and extremity lengthening, are collaborating in producing the low segment ratio. However, before the age of 10 or 12 years kyphoscoliosis is in most cases not of sufficient severity to be of major significance.

At times the great toes are elongated out of proportion to the others (Fig. 9*B*).[47,163,189,264] This may be related to the fact that the terminal center of ossifica-

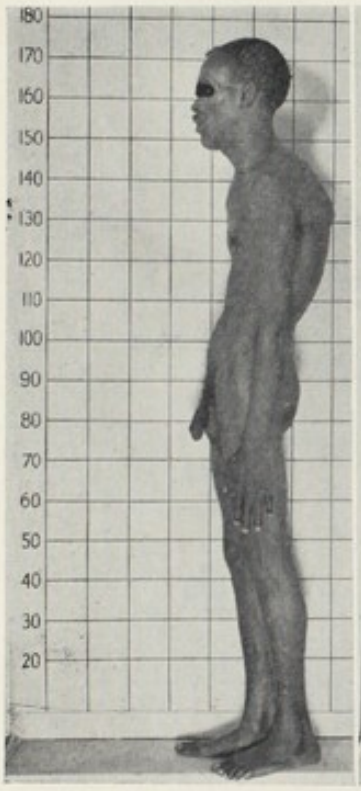


Fig. 8*A*.

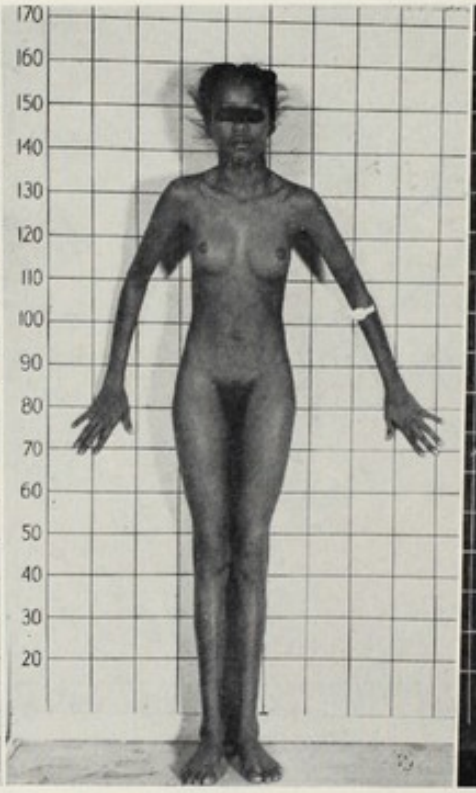


Fig. 8*B*.

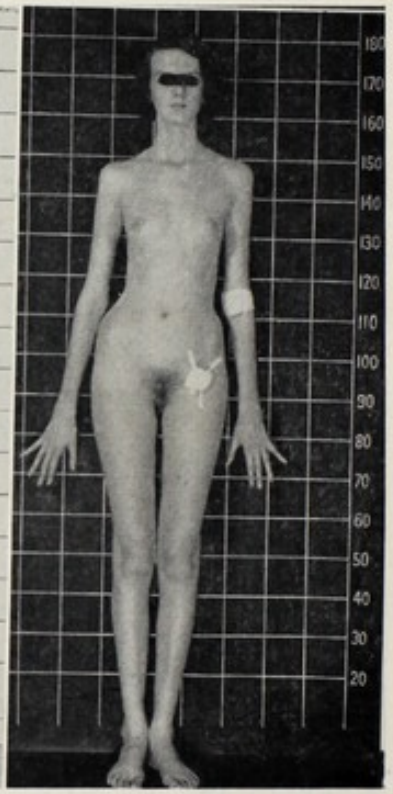


Fig. 8*C*.

Figs. 8*A*-8*C*. Confusing and uncertain cases.

Fig. 8*A*. L. M. (611512), 45-year-old Negro man, sustained an injury to his chest one year before this photograph. Shortly after the accident he began to have paroxysmal nocturnal dyspnea and was found to have profound aortic regurgitation. The left ventricle and first portion of the ascending aorta are enlarged. Spinal deformity has become progressively more impressive in this patient. There is no ectopia lentis. For geographic reasons, the family investigation is not entirely satisfactory, but no suspicions of the Marfan syndrome are present on this score either. (The patient died two years after this photograph was taken. Unfortunately, autopsy was not performed.)

Fig. 8*B*. W. F. (651498), 12 years old. Two years previously acute encephalitis occurred, followed by mental deterioration with positive neurologic signs. No ectopia lentis. The mother, who is normal, has the same skeletal proportions.

Fig. 8*C*. R. G. W. (697871), only 13 years old. Myopic astigmatism but no ectopia lentis. Loud precordial systolic murmur of unidentified cause. Cardiac catheterization unrevealing. The extreme dolichostenomelia and the pelvic asymmetry make Marfan's disease very likely. The diagnosis cannot be established in the absence of positive family history or ectopia lentis.

Figs. 9*A*-9*C*. H. W. (464314), 17 years old. Died suddenly at home eighteen months later. The patient was moderately crippled by the skeletal abnormality. Pain in the joints, especially those of the knees, seemed to be related to the loose-jointedness. A long follow-up in an orthopedic clinic. Ectopia lentis. Referred because of spontaneous retinal detachment.

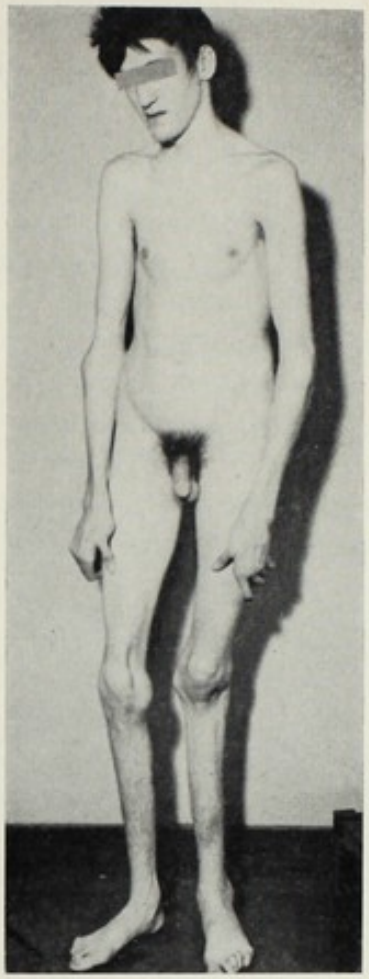


Fig. 9*A*.

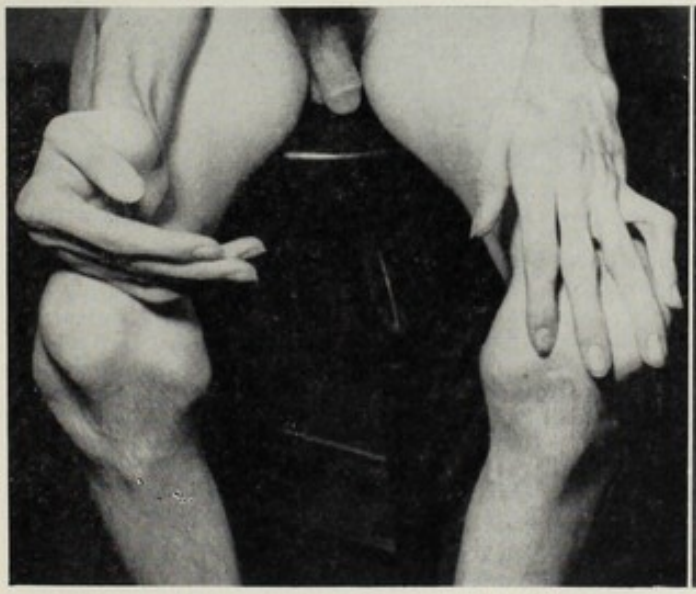


Fig. 9*B*.

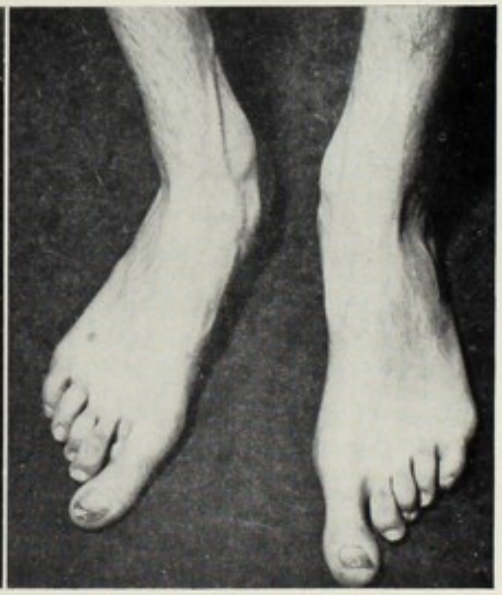


Fig. 9*C*.

Fig. 9*A*. General view.

Fig. 9*B*. Striking arachnodactyly with partial contractures of fingers. Children delight in doing contortions with their fingers but should not be permitted to do this since serious damage may result.

Fig. 9*C*. Extraordinary length of the great toes is well demonstrated. Even more pronounced excess of length of great toe shown by case illustrated by Whitfield and his associates.[180]

tion normally appears somewhat earlier in the metatarsus of the great toe than of the others. (The long bones of the hands and feet usually grow from one terminus only or predominantly. The first metatarsal has a proximal epiphyseal junction, whereas the epiphysis is distal in the other metatarsals—another point of difference in development of the first and other toes.) The ribs participate in the excessive longitudinal growth with formation of pectus excavatum (Fig. 4*E*), "pigeon breast" (Figs. 4*C* and 4*D*), or less symmetrical varieties (Fig. 11*A*) of thoracic cage deformity. The bones of the skull and face are likewise affected, with resulting dolichocephaly, highly arched palate, long, narrow face, and prognathism. There may be "spurring" of the heels as a result of excessive length of the os calcis.

Redundancy and "weakness" of joint capsules, ligaments, tendons, and fascia is repsonsible for a large group of manifestations which include pes planus, genu recurvatum, hyperextensibility of joints, habitual dislocation of hips,[63] patella,[110] clavicles, mandible, and other joints, ganglia,* hernias, synovial diverticula,* and

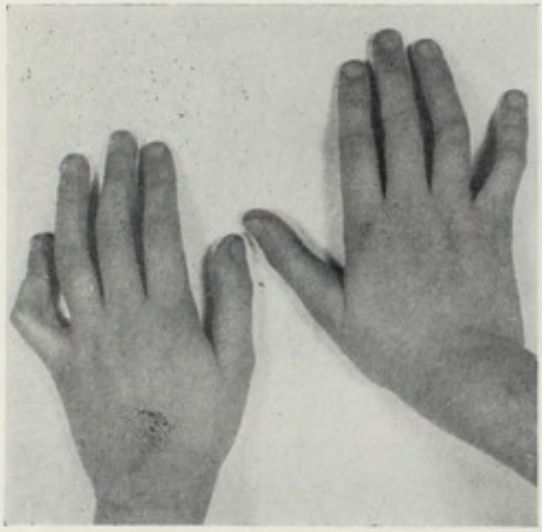


Fig. 10*A*.

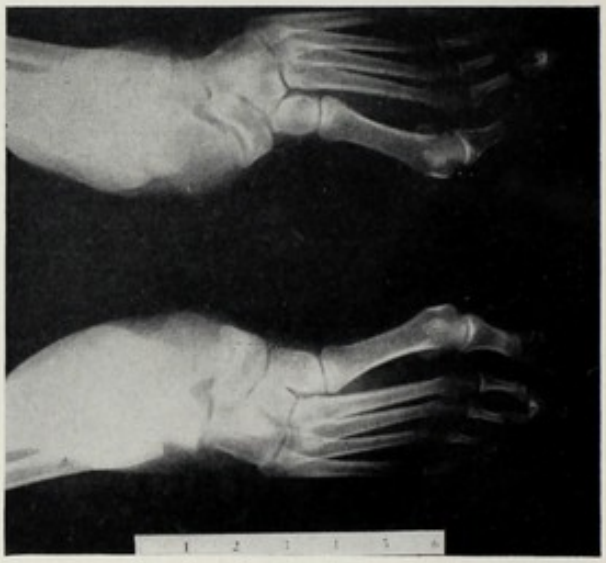


Fig. 10*B*.

Fig. 10*A*. Flexion deformity (clinodactyly) of fifth fingers, particularly on left. Taken at age of 38 months in M. D. (A59949), who is shown at a later age in Fig. 4*A*. Other patients in this series have shown this feature.

Fig. 10*B*. X-ray films of feet in case with so-called "rocker bottoms," i.e., pronounced flat feet. Patient J. M. (544088) ; see also Fig. 21.

kyphoscoliosis. The "flat feet" are often so advanced that the internal malleolus almost literally rests on the floor (Fig. 10*B*). Much less commonly a pes cavus deformity is present.[301] Kyphoscolosis can be very severe (Fig. 11*B*). In rare instances, hemivertebra is responsible in part for spinal deformity.[90] At times, the spinal deformity has been thought to be due to Scheuermann's epiphysitis.[99] Scoliosis is likely to increase rapidly during the years of maximal vertebral growth from 11 to 15 years of age. Early recognition of scoliosis is assisted by examining the patient in a bending forward position. This maneuver renders asymmetry more obvious because of angulation of the ribs on one side.[273] While the deformity is still slight much can be accomplished by means of exercises and other measures.

*In one case,[14] a peculiar pelvic cyst communicating with the lining of the sacral canal occasioned difficulties in delivery.

Nelson[264] emphasizes the presence of a large spinal canal, the enlargement being in depth or width or both.

Sinclair[278] found complaints of musculoskeletal nature of sufficient severity "to warrant medical attendance" in twenty of forty cases of the Marfan syndrome. Of the twenty, seven had low back pain. Two of these were at first considered to have ankylosing spondylitis. In five cases there was joint effusions; of these, three had been diagnosed as tubercular, one as rheumatic fever, and one as rheumatoid arthritis. Hip joint pain was severe in two. Metatarsalgia was prominent in three patients.

Even femoral hernias occur rather commonly in men with Marfan's syndrome, and diaphragmatic hernia has been present in some of our patients and in some of those reported.[242] Hydrocele is occasionally present.

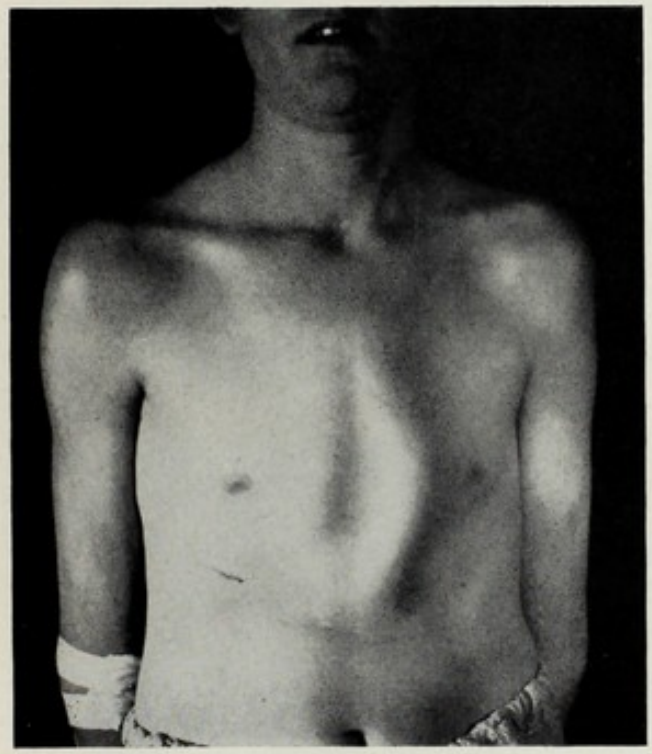


Fig. 11*A*.

Fig. 11*B*.

Fig. 11*A*. Asymmetrical pigeon-breast type of chest deformity in 14-year-old boy (J. S., 543026) with full Marfan's syndrome. This particular type of anterior chest deformity seems to be of frequent occurrence in Marfan's syndrome. At the age of 18 years, the patient was 73 inches tall. Incomplete right bundle branch block is present. The patient's father was 6 feet 7 inches tall, and at the age of 28 years died suddenly on a bus. He had been observed for two years for aortic regurgitation which had been considered rheumatic in origin.

Fig. 11*B*. Marked spinal deformity in 14-year-old F. D., one of first cases of aortic aneurysm with arachnodactyly reported by Baer and his co-workers.[11] (See reference 11 for photographs of the external appearance of this patient; also p. 356 of reference 181.)

Muscular underdevelopment and hypotonia is a frequent[46,160] but by no means invariable feature. This feature has been so striking as to suggest a primary disorder of muscle in some instances. (The converse error of diagnosis—primary muscular dystrophy called Marfan's syndrome—has occurred in isolated instances—Figs. 39*A* and 39*B*.) It is probable that the muscular manifestations are secondary to the abnormality of bones and joints and to abnormality of the perimyal connective tissue and are not due to primary involvement of the muscle cell itself. This view

is supported by the finding of a normal creatinine coefficient, an index of total muscle mass.[165]

Pronounced sparsity of subcutaneous fat is a striking feature of most cases (Figs. 4*A* and 4*C*) and is not easily reconciled with a fundamental defect of connective tissue. In children, it may be that the rapid growth accounts for the failure to store fat. One patient, who was thin as a child, has become exceedingly obese

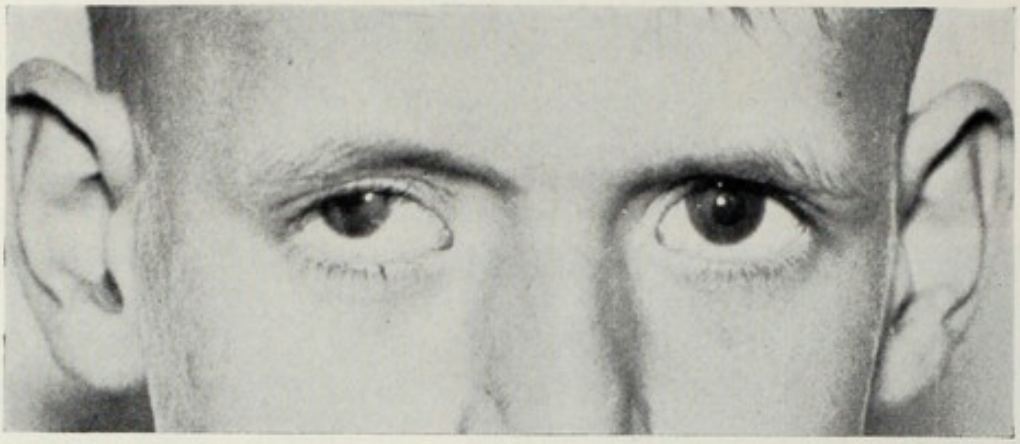


Fig. 12*A*. Dislocated lens in R. C. (241676), then 6 years of age. Chronic "malnutrition," bilateral inguinal hernias, slow physical development, and diastasis recti. At the age of 22 years he was 73 inches tall, weighed 150 pounds, and wore a size 12-AAA shoe. He was inducted into the Army and served six months before his eye condition was ascertained. The slight divergent strabismus is evident. Also one can make out the forward bulging of the nasal portion of the right iris with failure of more complete dilatation of the pupil in that segment because of anterior synechiae.

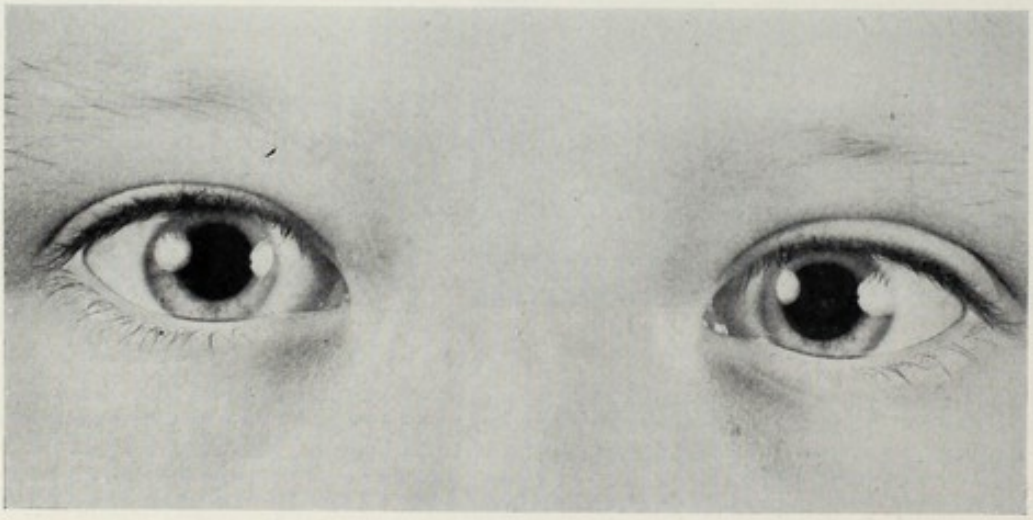


Fig. 12*B*. Bilateral dislocation of the lenses in J. A. L., same patient shown in Figs. 4*I* and 4*J*. Both lenses are displaced toward the nose. The margin of the lens crosses the pupil from about 12 o'clock to 6 o'clock.

in recent years (she is now 25 years old), due in large part to inactivity associated with the blindness produced by bilateral retinal detachment (Figs. 13*A* and 13*B*). As demonstrated in Fig. 4*J*, etc., others of these patients may have abundant subcutaneous fat.

Van Buchem[295] concluded that bone age is in advance of chronologic age and that the epiphyses tend to close earlier than normal. In our group of patients no marked deviation was observed, although no systematic controlled observations

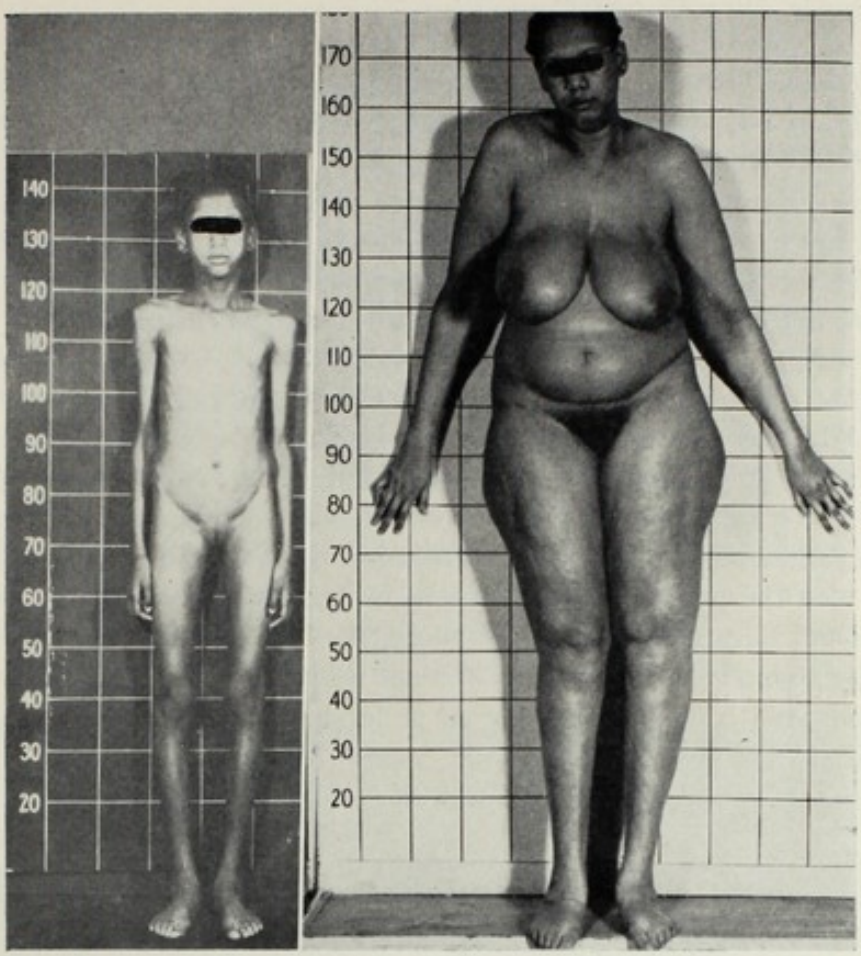


Fig. 13*A*.

Fig. 13*B*.

Fig. 13*C*.

Figs. 13*A* and 13*B*. L. T. (221183), at the age of 8 years (Fig 13*A*), at the age of 23 years (Fig. 13*B*). At 8 years the patient is virtually the same height as M. D. (in Fig. 4*A*), also 8 years old. The patient became almost completely blind from bilateral retinal detachments. With the inactivity associated therewith, she became very obese, as demonstrated in Fig. 13*B*. White atrophic striae appeared on the shoulders, upper arms, hips, and thighs, as has been described previously in obese patients with Marfan's syndrome.[178] The patient probably had rheumatic fever with carditis as a child, but no residua are detectable. She has demonstrated, in addition to ectopia lentis, accessory rudimentary sixth digit bilaterally, highly arched palate, pupils which react poorly to mydriatics.

Fig. 13*C*. Prison photograph of the proposita's father (B. R.). The character of the spectacles suggests hyperopia, an unusual although occasional finding in the Marfan syndrome. He had several admissions to the Norfolk, Virginia, General Hospital (A46772) for hernia repair, for acute dissection of the aorta (age 38), for varicose veins, and for pain in the low back. The final hospital admission was to the St. Luke's Hospital, Newburgh, New York, because of severe pain up and down his back. Profound aortic regurgitation and a pulsating abdominal mass were discovered. Serologic tests for syphilis were negative. The patient died suddenly (age 39). Autopsy revealed old dissection of the aorta with recent rupture into the pericardial cavity and tamponade. Both the father and the father's father of this man seem to have had the Marfan syndrome, making a total of four generations affected.

were undertaken. Certainly the excess length of the legs is not due to delayed closure of the epiphyses. The excess length is often demonstrable at birth (Fig. 14*I*) and throughout childhood and adolescence.

The Eye. Ectopia lentis, almost always bilateral, is the hallmark of ocular involvement in this syndrome (Fig. 12*A*). The suspensory ligaments, when visualized with the slit lamp, are redundant, attenuated, and often broken. The lower ligaments are more likely to be defective, with displacement of the lens upward as the usual finding. The lens is often abnormally small[49,87,88] and spherical. Iridodonesis, tremor of the iris, is often a tip-off to the presence of dislocation of the lens. Occasionally the edge of the dislocated lens is visible through the undilated pupil, or, of course, there may be complete dislocation of the lens into the anterior chamber. To exclude minor subluxation it is necessary to dilate the pupil fully and perform a slit-lamp examination. Bowers[204] describes an interesting family in which members would seek the presence of dislocation by gently shaking the infant or small child while observing the eye in bright sunlight. The appearance of the dislocated lens was aptly compared to the bubble in a spirit level.

Heterochromia iridis was present in at least two patients in this series (see Figs. 4*A* and 23).

Myopia is usually present in rather high degree. The excessive length of

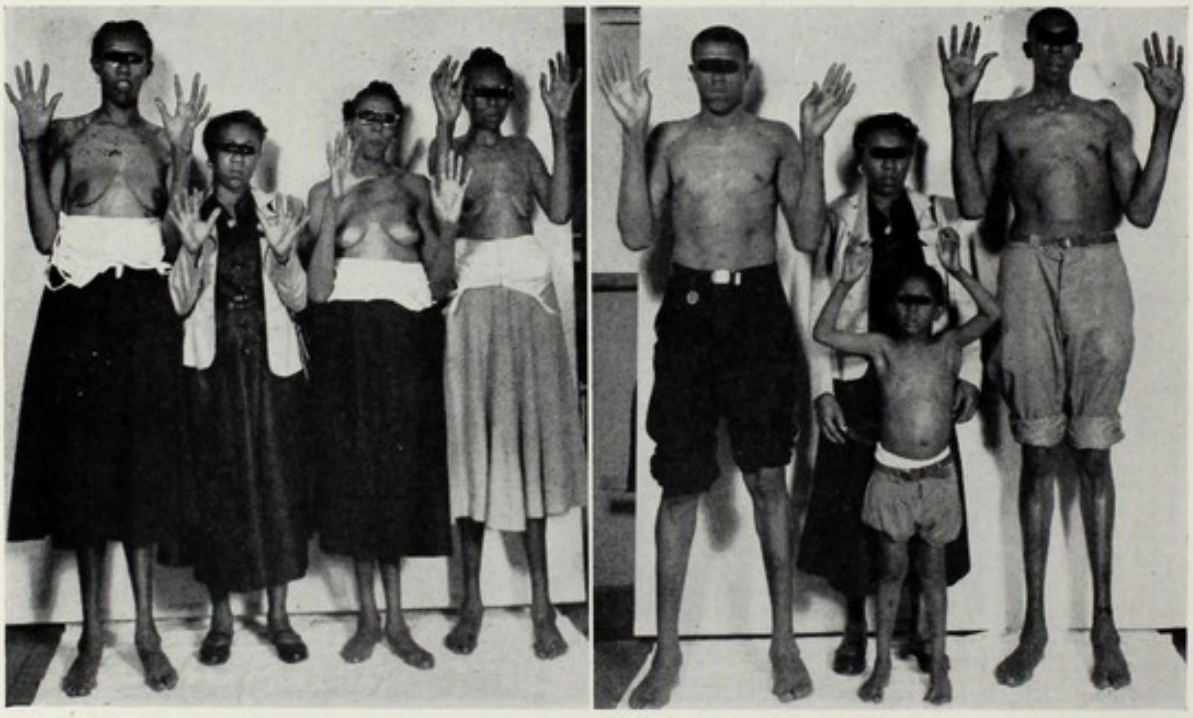


Fig. 14*A*. Fig. 14*B*.

Figs. 14*A* and 14*B*. A normal individual (III-12) and her five siblings affected by the Marfan syndrome (III-15, III-14, III-13, III-11, and III-8). In Fig. 14*B* is a 4-year-old affected member (IV-13) of the next generation, son of III-8. (The numbers refer to those in a pedigree published in Fig. 28*A*.) Individual III-11 subsequently died of bacterial endocarditis engrafted on a mitral valve probably affected by connective tissue changes of the Marfan syndrome.[92] There was chromatropic degeneration of the ascending aorta and pulmonary artery, as well as advanced congenital cystic disease of the lungs. Individual III-14 is 78 inches tall. (History numbers: 176836, 176837, 176838, 103632, 637693, 637694, 392843.) The father of the sibship (W. R. 101043) died suddenly at home at the age of 43 years, presumably of aortic rupture. He was well known as a case of Marfan's syndrome and had been under treatment for a cardiac ailment with aortic regurgitation for about two years. (Individual III-15 of the pedigree, the adult male on the far left in Fig. 14*B*, died in 1956 with aortic regurgitation.)

the eyeball, resulting in myopia, appears to indicate involvement of the sclera, fundamentally a ligamentous structure, in the basic connective tissue defect. The scleral defect is occasionally expressed in the cornea as keratoconus[191] or as megalocornea[151] (G. H., B50120).

The sclera may be impressively blue in the Marfan syndrome.[23] Clouding of the cornea occurs occasionally; this is probably not a primary element of the connective tissue disease but rather a result of the secondary iritis and glaucoma.

Spontaneous retinal detachment occurs with what is probably an unusually high incidence and is a frequent complication of lens extraction. Retinal detachment is probably related in part to the long myopic eyeball and therefore indirectly to the connective tissue defect; that there is a more direct relationship is strongly suspected[72] because of the high incidence in Marfan's syndrome even without more than a moderate degree of myopia. The pupil is often difficult to dilate in Marfan's syndrome and the dilator muscle appears to be hypoplastic.[137]

Ectopia lentis per se would probably represent relatively little impairment of vision. Severe myopia (20 diopters in Boerger's[24] case), retinal detachment, and

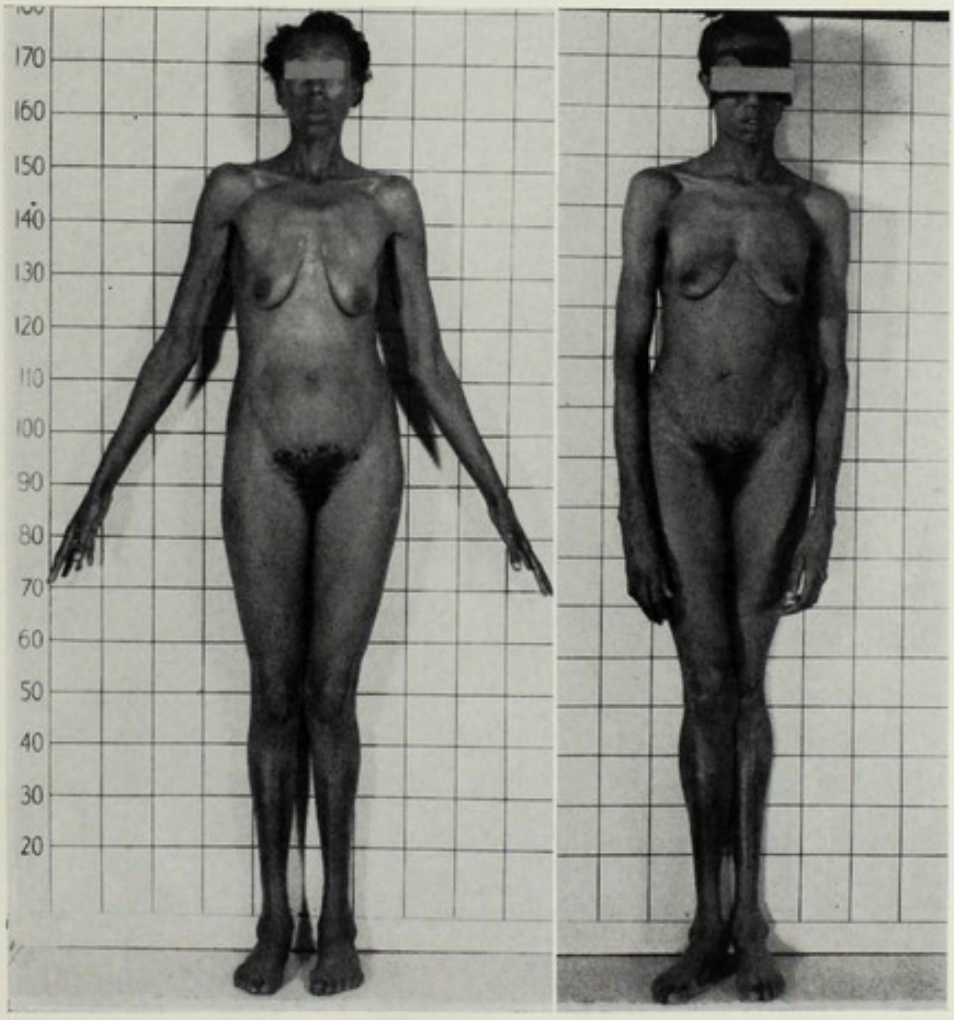


Fig. 14*C*. Fig. 14*D*.

Fig. 14*C*. P. R. (103632), individual III-8 in Fig. 28*A*, 33 years of age. Bilateral ectopia lentis and dolichostenomelia. The patient died at the age of 34 years. Autopsy revealed pulmonary embolus. The base of the aorta was thin-walled. An anomalous flap of the mitral valve caused mitral regurgitation.

Fig. 14*D*. H. R. (176837), individual III-13 in Fig. 28*A*, 29 years of age. Bilateral ectopia lentis and dolichostenomelia.

the iritis and/or glaucoma which may result from the ectopia lentis are often responsible for severe limitation of visual acuity or even total blindness. The lens may become secondarily cataractous.

I was previously suspicious that estimations that only 50 to 70 per cent of cases of clean-cut Marfan's syndrome have ectopia lentis were incorrectly low as a result of inadequate examination of the eyes and that virtually 100 per cent of cases would display at least minor redundancy of the suspensory ligament if subjected to maximal mydriasis and slit-lamp examination. It may be true that the first estimate above is indeed too low. However, we have now observed patients with advanced Marfan's disease with characteristic habitus, involvement of other members of the family, and dissection of the aorta with autopsy demonstration of pathognomonic changes in the media, who did not have ocular abnormality on most careful examination. For example, in the two brothers shown in Figs. 21*A* and 21*B* there were characteristic changes discovered in the skeleton and aorta but no ectopia lentis. However, three of the five children of one of the men do show ectopia lentis, as well as skeletal changes.

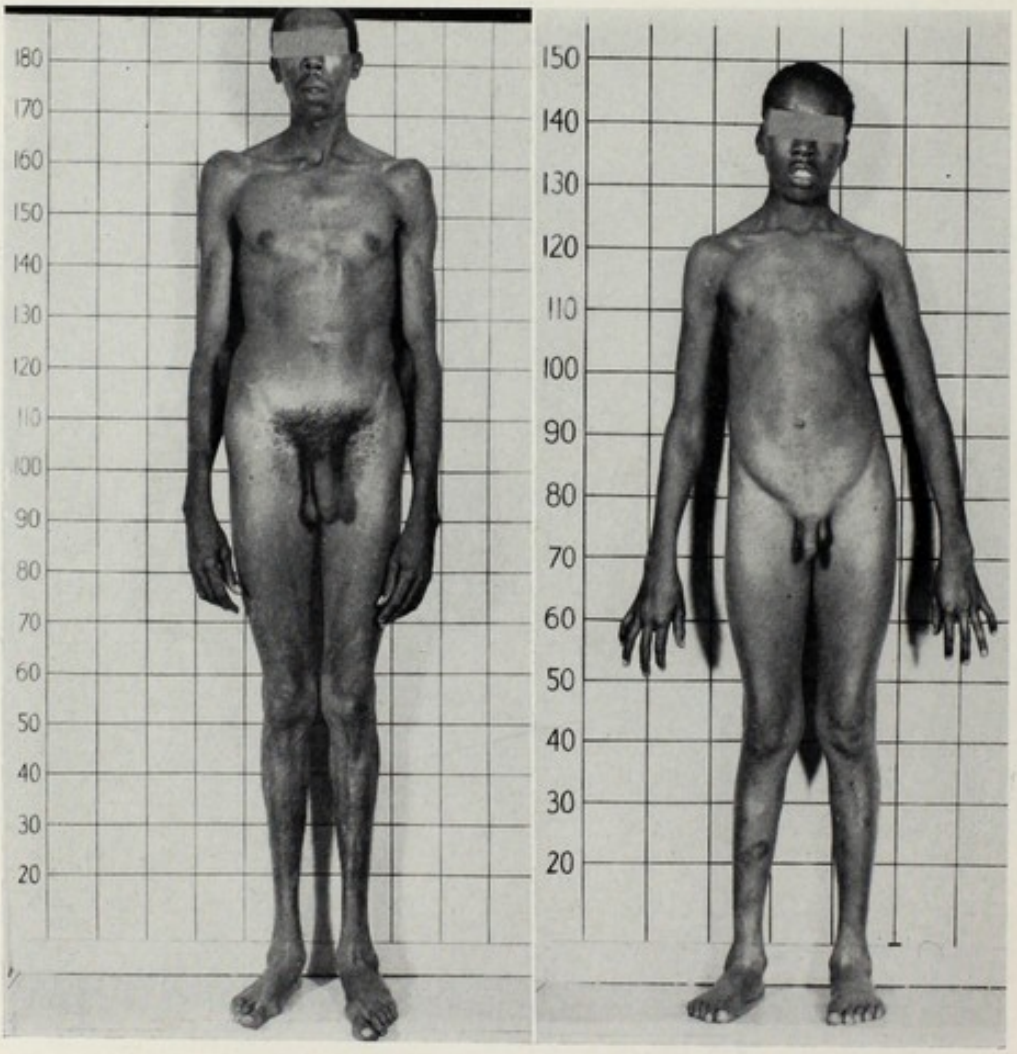


Fig. 14*E*. Fig. 14*F*.

Fig. 14*E*. L. R. (176838), individual III-14 in Fig. 28*A*, 24 years of age. Bilateral ectopia lentis and dolichostenomelia.

Fig. 14*F*. J. R. (637698), individual IV-8 in Fig. 28*A*, 11 years of age. Bilateral ectopia lentis and dolichostenomelia.

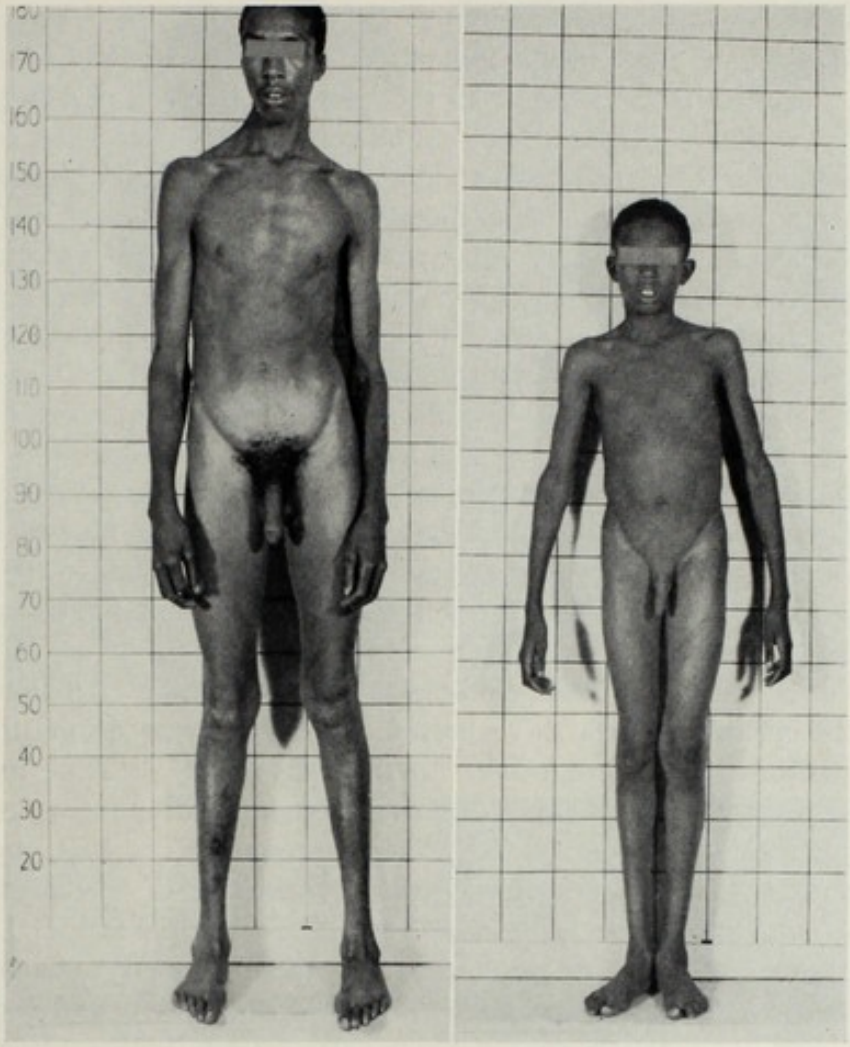


Fig. 14*G*.

Fig. 14*H*.

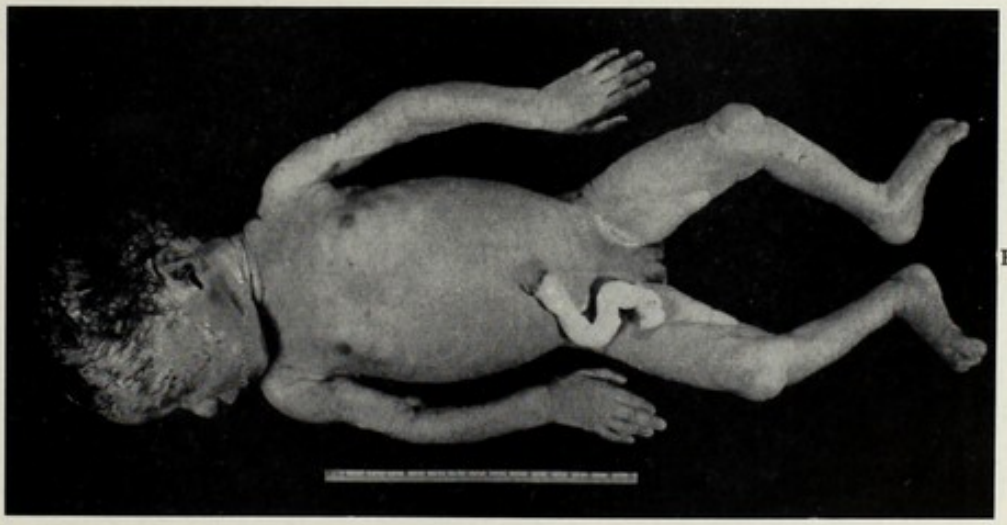


Fig. 14*I*.

Fig. 14*G*. Same patient as shown in Fig. 14*F*, 15½ years of age.

Fig. 14*H*. P. R. (637693), individual IV-13 in Fig. 28*A*, 9½ years of age. Bilateral ectopia lentis and dolichostenomelia.

Fig. 14*I*. The stillborn infant (autopsy 29095) of patient shown in Fig. 28*B*. The infant is believed to be affected. For her age (8½ months) the foot was probably long (7.25 cm. as compared with 6.5). The crown-heel measurement was 46 cm. (usual, 43.5) and the crown-anus dimension 30.5 cm. (usual, 28 cm.). See reference 247 for normal standards used in these studies. The infant showed no other abnormality on gross and histologic study, except an abnormality of pulmonary lobation of the type described in cases of the Marfan syndrome. Specifically the aorta was grossly and histologically normal!

The Cardiovascular System.[61,92,254,277] Since most of the early autopsies in cases of this syndrome were in infants and children (who might have not yet developed the characteristic changes in the great vessels) and since interatrial septal defect was found (probably largely by coincidence) in several of the cases, this malformation and "congenital heart disease" in general came to be considered the usual form of cardiovascular involvement. As more adult cases were recognized, it became apparent (1) that an inborn weakness (with subsequent degeneration) of the media of the aorta and main pulmonary artery is of much more statistical importance and more functional importance in the individual patient, and (2) that this abnormality is an abiotrophy, not a congenital malformation. The abnormality of the media may result in diffuse dilatation of the ascending aorta or pulmonary artery, in dissecting aneurysm, or in a combination of dilatation and dissection. Striking involvement of the pulmonary artery occurs[11,92,166] much less commonly than the corresponding involvement of the aorta. However, a clinical picture like that of so-called[77] "congenital idiopathic dilatation of the pulmonary artery" may occur,[213] as well as dissecting aneurysm of the pulmonary artery.[5,182] (See Figs. 29 and 36.)

In the aorta, dilatation usually begins in the aortic ring* and intrapericardial portion of the ascending aorta as suspected clinically and as demonstrated in patients dying before further progression of their disease.[91,175] This, together with stretching of the aortic cusps, may produce profound aortic regurgitation before clear roentgenologic signs of aortic dilatation are present (Figs. 16*D*, and 21 to 25). If syphilis, rheumatism, and bacterial endocarditis can be excluded, traumatic rupture of an aortic cusp is often suspected.[15,92] (See Figs. 15*A* to 15*D*.)

Furthermore, a deceptive prominence of the pulmonary conus and main pulmonary artery may be produced by the dilated aortic base and compound the confusion.[11,92,112] (Dilatation of the pulmonary artery itself contributes to the prominence). In a recent case (J. M., J.H.H. 544088) the aneurysm at the base of the aorta apparently caused partial obstruction of outflow from the right ventricle with the development of progressive right axis deviation by electrocardiogram. In these cases, the second heart sound in the pulmonary area may be unusually loud due to close proximity of the pulmonary artery to the anterior chest wall.

Aortic dilatation is usually progressive. The patient may be free of symptoms for five or more years after the development of aortic regurgitation, but once angina pectoris or symptoms of left ventricular failure have developed, he seldom lives more than two years. On the whole, the prognosis is quite similar to that of syphilitic aortitis.[174] In fact, the similarities of the two diseases are in many respects striking. It seems to matter little whether the defect of the media is produced by the spirochete from without or the mutant gene from within.

As in syphilitic aortitis with aortic regurgitation, revision in the prognostic evaluation of aortic regurgitation in the Marfan syndrome is necessary on the basis of recent experience. From our own series it is now clear that the asymptomatic period may extend for appreciably more than five years. Furthermore, patients have survived five years or longer after the onset of major symptoms.

(Text continued on page 69.)

*The term "aortic ring" is recognized to be inexact and difficult to define in precise anatomic terms. As used here it refers to the very base of the aorta, particularly the sinuses of Valsalva and the lines of attachment of the aortic cusps.

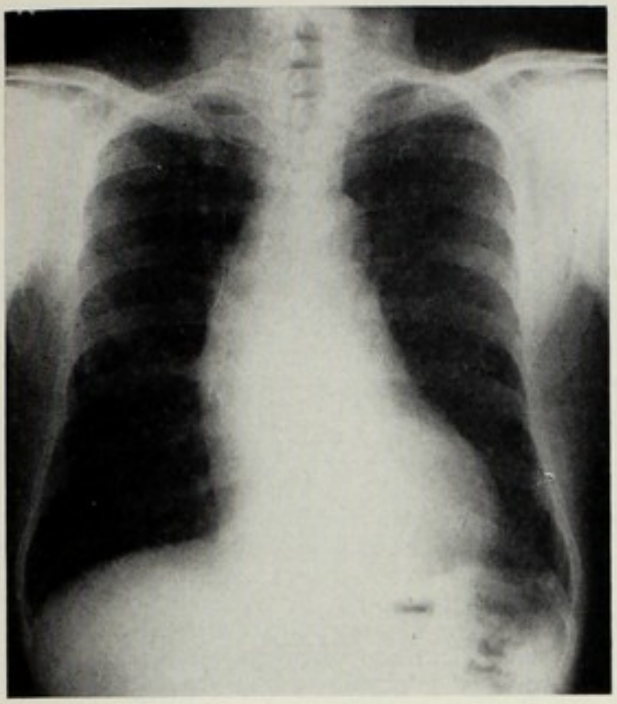


Fig. 15*A*.

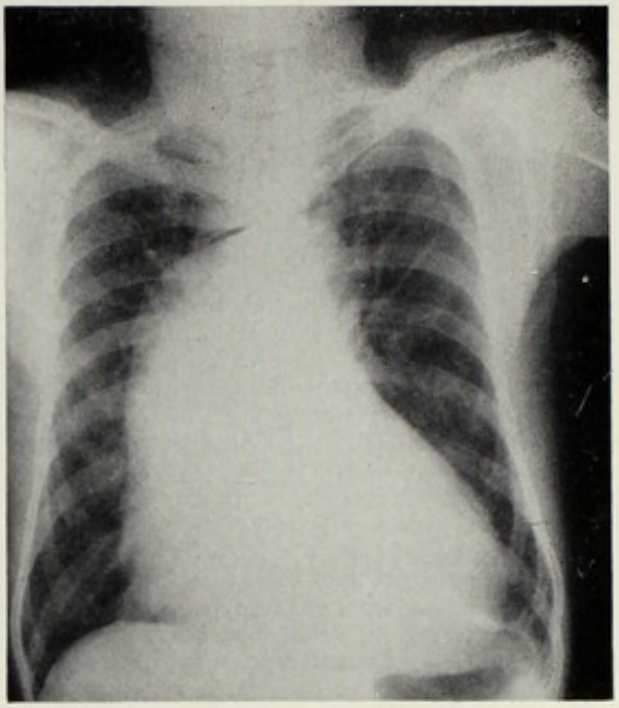


Fig. 15*B*.

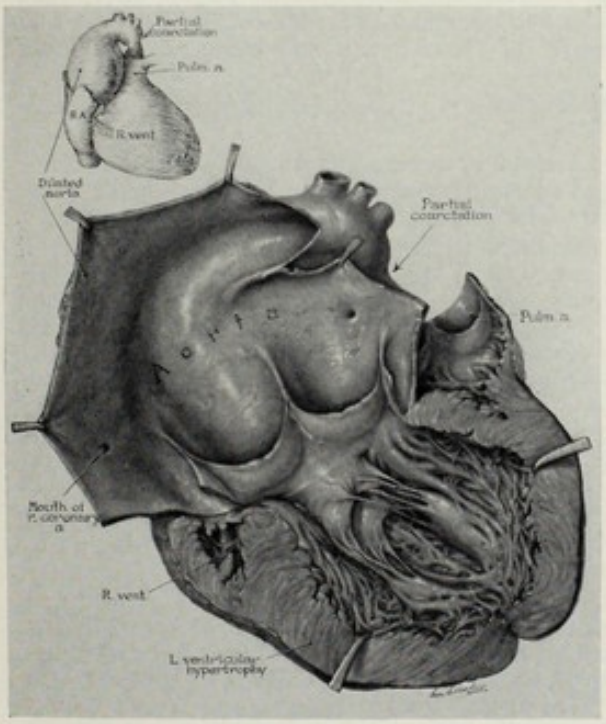


Fig. 15*C*.

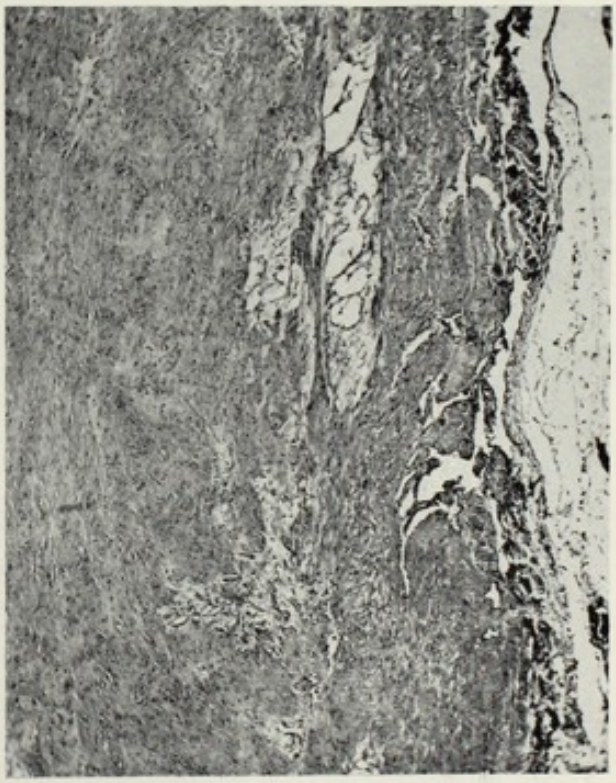


Fig. 15*D*.

Figs. 15*A*-15*D*. *A*, Dilatation of the ascending aorta is present but is not impressive. Patient L. K. (film taken eighteen months before death). *B*, Film four months before death, same patient. *C*, Sketch of the heart and great vessels as visualized at autopsy in patient L. K. Mild coarctation was present. Dilatation limited to the ascending aorta and tremendous sacculation of the aortic cusps are conspicuous features. Note the relatively high position of the coronary ostia. *D*, Histologic section from the ascending aorta in same case.

(Continued on next page.)

(Legend continued.)

L. K. (J.H.H. 571745), a white man born in 1913, was first admitted to this hospital in May, 1951. On April 16, 1951, while riveting at an aircraft plant he noted the rather sudden onset of severe steady pain in his right chest radiating down the right arm. This disappeared in a few hours, and he was essentially asymptomatic thereafter but was aware of profuse sweating, particularly of the hands and feet.

Examination revealed that the blood pressure was 195/40/0. He was a slightly built man of average height. There was alternating external strabismus and the pupils were rather small but normally reactive. No other ocular abnormality was detected at that time. There were pronounced cardiac and peripheral signs of aortic regurgitation.

There was no history of rheumatic fever or syphilis and no laboratory or clinical evidence of syphilis or bacterial endocarditis. There was a story that in his work as a riveter the instrument which he held in front of his chest had, on several occasions, slipped, striking his chest forcefully. The possibility of traumatic rupture of an aortic cusp was considered most likely. In fact this was considered so likely by his physicians that with their assistance the patient succeeded in making a $4,000 settlement with his employer! The history of his having been previously turned down for insurance was not elicited.

The patient was virtually asymptomatic until September, 1951, when he began to have attacks heralded by very profuse sweating and consisting of pain under the lower sternum, severe palpitation, and coughing. Rapid eating and excitement would precipitate the attacks. They occurred most often about midnight.

The patient's second admission was in May, 1952. At that time Dr. F. W. Dick first noted that the patient had iridodonesis bilaterally and that the edge of ectopic lenses could be seen with the ophthalmoscope. From the age of 10 years the patient had worn glasses for myopia, and bifocals from the age of 19 years. Examination revealed profuse sweating, even in a cool room. The lid slits were wide and there was lid lag; these were interpreted as probably being related to the effort to accommodate. (The excessive sweating was probably that frequently seen with left ventricular failure.) The head was round and the neck rather short. There was kyphosis without scoliosis. Muscular development was on the whole rather poor. The shoulders were rounded and scapulae moderately winged. His height was 5 feet 7 inches, fingertip-to-fingertip span 5 feet 11 inches. Pubic symphysis to heel dimension was 34 inches (over half his total height). There was syndactylism of the second and third toes bilaterally. At this time there was a diastolic thrill at the right border of the sternum and mediastinal dullness was increased to the right.

It was now very apparent that the patient had Marfan's syndrome. Superannuated dissecting aneurysm of the aorta was considered likely.

The remainder of the patient's life was characterized by severe attacks of sweating, anginal pain, and orthopnea. At no time were there signs of right-sided failure. Comparison of early and late films are presented in Figs. 15*A* and 15*B*. The patient died Jan. 23, 1953.

At autopsy (No. 24360) his height was determined to be 5 feet 6 inches. (There is a discrepancy among the various reported measurements.) The kyphosis was again described. The significant findings were limited to the heart which weighed 980 grams (Fig. 15*C*). The increased weight was almost entirely the result of very marked left ventricular hypertrophy. The ascending aorta was the site of pronounced fusiform dilatation. The aortic valve ring was dilated to about four times the normal circumference. The sinuses of Valsalva were greatly dilated, and the aortic valve cusps themselves were relatively enormous baggy structures. The aortic dilatation stopped at the mouth of the innominate artery. Beyond the mouth of the left subclavian the aorta narrowed sharply in a typical, although only partial (about 40 per cent), stenosis of the isthmus.

Microscopic sections of the aorta (Fig. 15*D*) revealed replacement of most of the media by scar tissue. There were some areas of cystic medial degeneration. Elastic tissue stains revealed marked disruption, fragmentation, and sparcity of elastic fibers.

After the death of the patient, an investigation revealed, in the records of an insurance company, information that the patient was turned down for insurance in 1944 because of aortic regurgitation. Therefore an aortic diastolic murmur had been present for at least nine years before death and for several years before symptoms of significance. It should also be noted that he had had varicose veins which required surgical treatment.

Comments. The aorta was not conspicuously dilated at the time the patient was first seen, in spite of the presence of striking aortic regurgitation. A possibly useful point may be a finding at fluoroscopy at the time of the first admission: "The lower right border of the heart in the region of the right atrium showed a marked increase in amplitude of pulsation. The pulmonary artery segment on the left side of the heart also pulsated vigorously, although the vascular markings of the lung were if anything decreased." In some of these cases the outflow tract of the right ventricle and base of the pulmonary artery are evidently displaced forward and to the left (by the dilatation of the base of the aorta), simulating enlargement of these structures.[112] On the other side the intrapericardial portion of the aorta may be responsible for displacement and active pulsations in the right atrium.

(Continued on next page.)

(Legend continued.)

A feature of equal diagnostic significance and of considerable genetic interest is the relative submersion of the full-blown skeletal manifestations when the Marfan mutation occurred in this pyknic stock. When first seen the patient did not impress anyone as being beyond the normal range as to habitus. Discovery of ectopic lenses resulted in the observer being more impressed with the habitus. Comparison with his brothers and sisters would likewise have impressed the physician with the patient's abnormality. Other members of the family were about 5 feet 3 inches tall and were very heavily muscled, with short powerful extremities and stubby fingers. The moral to the diagnostician is obvious. Although extensive studies of the families were not undertaken, several cases in the literature probably illustrate this same phenomenon.[156]

This case bears many resemblances to Case 3 of Tung and Liebow.[160] The type of aortic involvement which they illustrate is almost identical to that in Fig. 15*C*. Their patient, who died of aortic insufficiency at the age of 42 years, had had two herniorrhaphies and had varicose veins. Although the authors state that "no suggestion of arachnodactyly nor of any other external sign of Marfan's syndrome [was] recorded by any of several senior physicians who were concerned with the care of this man," it must be noted that he died in 1932, which was before a single case of the Marfan syndrome had been reported in the internal medical literature of this country and over ten years before the association of aortic dilatation and arachnodactyly was first clearly described.[11]

(From McKusick, V. A.: Circulation **11**:321, 1955.)

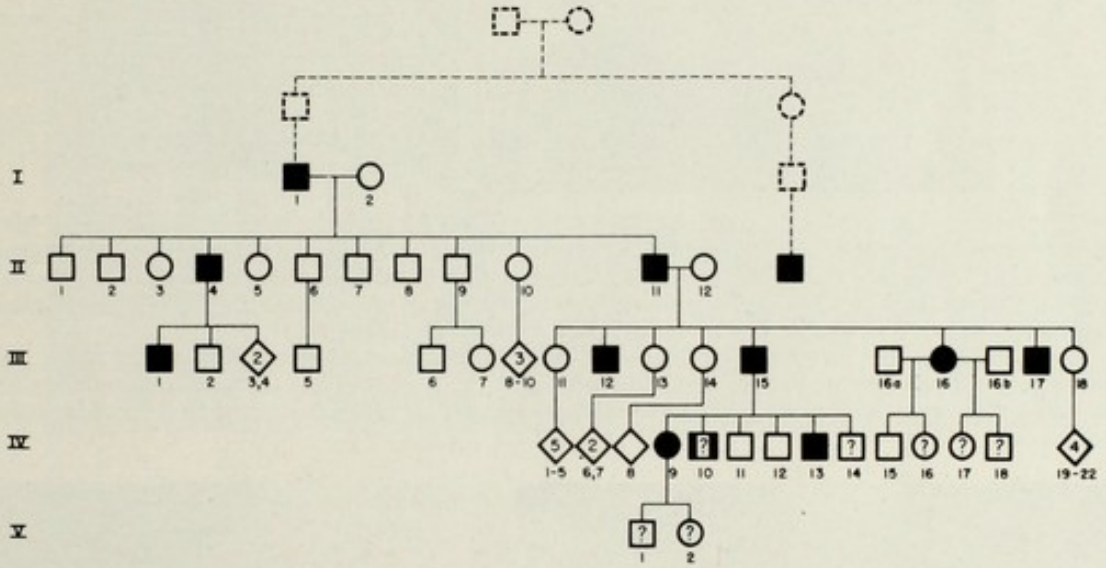


Fig. 16*A*. Pedigree of the F. kinship.

II. *1*, Charles; died of acute indigestion at age 47 years. *4*, Grant; about 6 feet 4 inches tall, died at age 35 years; two of his children died at 8 and 12 months, respectively. *8*, Henry; examined; unaffected.

III. *1*, James Aloysius; typical Marfan syndrome; 6 feet 4½ inches tall, size 13 shoe; ectopia lentis with secondary cataract formation; complete loss of vision from bilateral detachment of retina; early aortic diastolic murmur. *11*, Josephine; examined; unaffected. *12*, Clarence (352936); at age 32 years found to have complete detachment of right retina; left lens dislocated and cataractous; partial detachment of left retina; died at age 34 years, 18 days after onset of congestive heart failure attributed to syphilitic heart disease because of finding of aortic regurgitation. *13*, Blanche; examined; unaffected. *15*, Theodore (see Fig. 16*B*); typical Marfan syndrome, with cardiovascular death in 1952. *16*, Leona (see Figs. 16*C* to 16*E*); typical Marfan syndrome, with autopsy confirmation of dissecting aneurysm of the aorta. *17*, James Leon (424834); ectopia lentis with severe secondary iridocyclitis and glaucoma; detachment of right retina; 75 inches tall, weight 172 pounds, kyphoscoliosis, varicocele; lax sternocleidomastoid joints, mobile patellae, flat feet, cardiomegaly with globular shape by x-ray examination; no murmurs. This individual and Theodore and Clarence "always looked just like twins." Positive serologic test for syphilis.

IV. *9*, Mary Isabelle (844914), born 1939; definitely affected, with bilateral dislocation of lenses. *10*, James Leroy (844924), born 1940; possible slight lens dislocation. *11*, James Arthur (844925), born 1944; normal. *12*, John Edward (844922), born 1945; normal. *13*, David Theodore (844921), born 1950; definite Marfan syndrome; 38 inches tall at 30 months of age; long, peculiarly shaped head; dislocated lenses. *14*, Joseph Melvin (844923), born 1952; normal.

V. *1*, James Allen (844915), born 1945; uncertain status. *2*, Mary Anne, born 1947; uncertain status.

Fig. 16*B*.

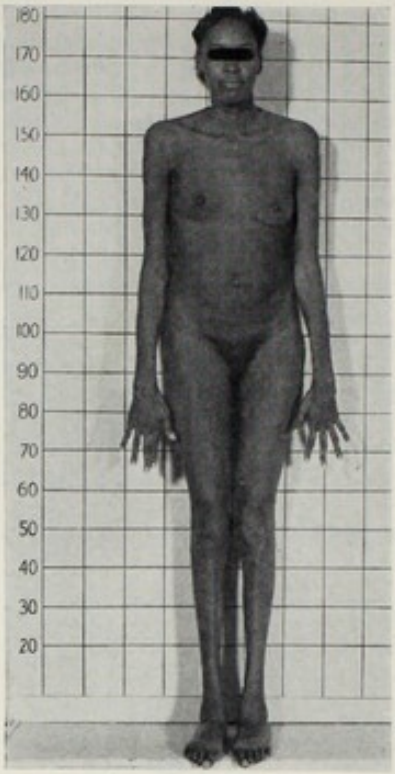
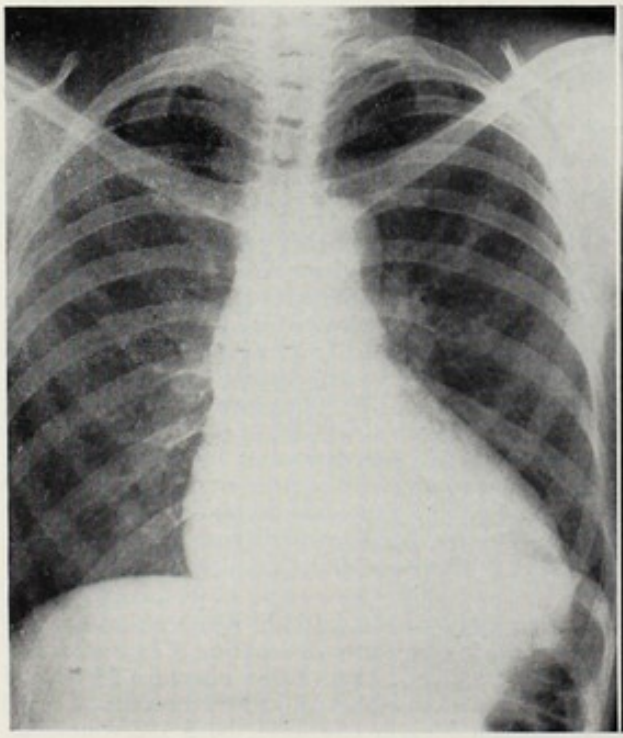


Fig. 16*C*.

Fig. 16*B*. Carnival snapshot of III-15 (T. F.). Arachnodactyly is evident. In his left hand he holds his spectacles. He died suddenly at the age of 33 years, two weeks after consulting a physician for exertional dyspnea. Aortic regurgitation had been discovered. An optometrist reports that he had "a decided miosis and the ophthalmoscopy showed the media to be cloudy." He was myopic. Worked as farm laborer until a few days before death.

Fig. 16*C*. L. F. Y. (690823), 33 years old. Patient died of effects of severe aortic regurgitation. Autopsy revealed characteristic changes in the media of the aorta and pulmonary artery with old dissecting aneurysm of the ascending aorta. The dissection may have occurred during pregnancy.

Fig. 16*D*.



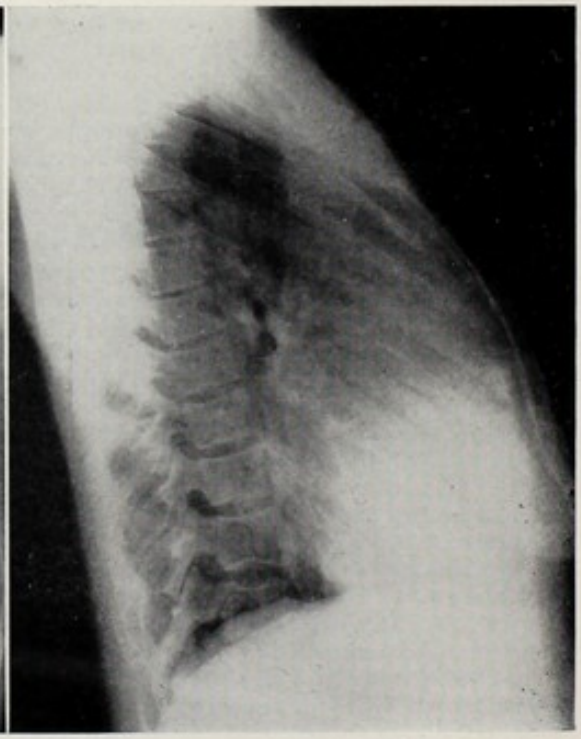


Fig. 16*E*.

Figs. 16*D* and 16*E*. Posteroanterior and lateral views of chest in L. F. Y. It is remarkable that enlargement of the aorta is not more evident. In lateral view there is opacification behind the sternum.

Chest pain, which may have features usually associated with angina pectoris but more often is imperfectly relieved by nitroglycerin is a rather frequent finding in the Marfan syndrome. In some the pain may be due to relative coronary insufficiency and of the same nature as the pain that occurs with aortic regurgitation, on a rheumatic basis, for example. In other cases, aneurysmal dilatation of the aorta, even before it is radiologically evident, may be the basis. Furthermore, chest pain may be striking before aortic regurgitation of hemodynamic significance develops. In one patient (A. S.) the pain was present for ten years before death occurred suddenly at the age of 35 years. In two other patients (R. C., 155970; A. D., 341643) chest pain was present for five and eight years, respectively, before death. Coronary ostial anomalies of apparently congenital type

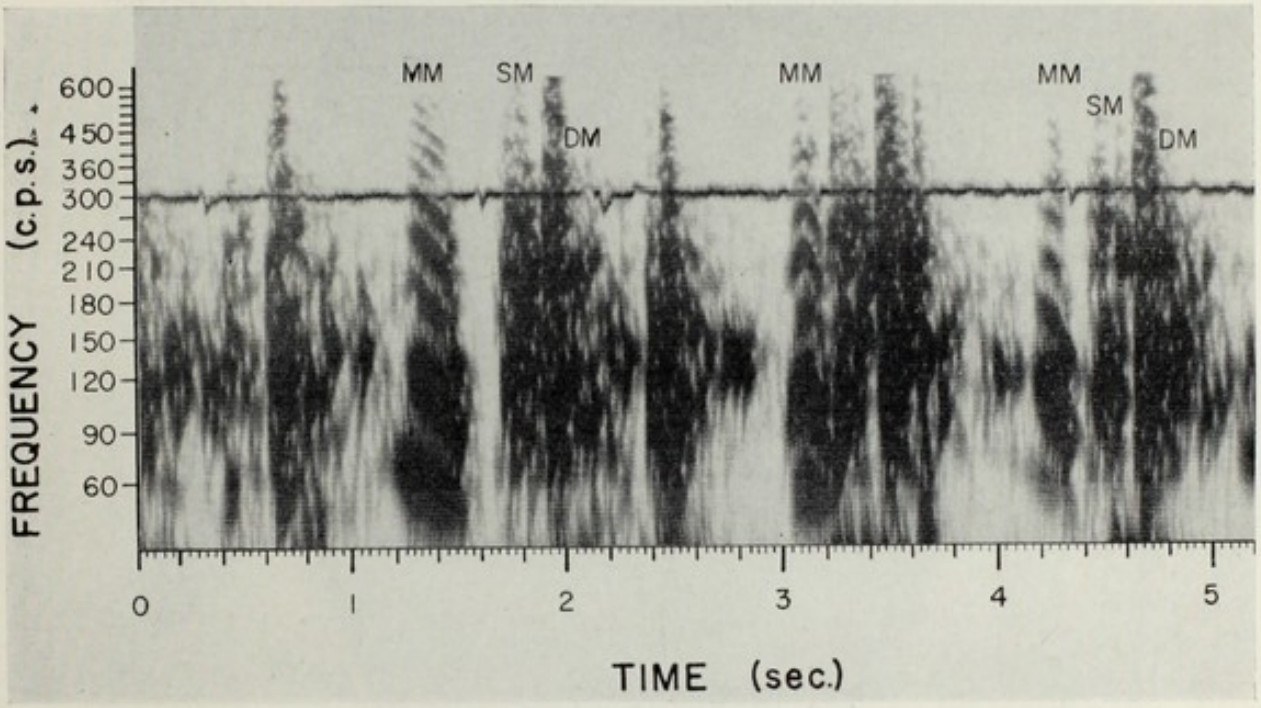


Fig. 16*F*. A spectral phonocardiogram of the sounds as recorded at the base of the heart in L. F. Y. Bigeminy is present as indicated by the electrocardiogram. There is a systolic murmur *(SM)* and a decrescendo diastolic murmur *(DM)*. Near the end of the long diastolic periods which followed the extrasystoles there is a murmur *(MM)* which is strikingly musical as indicated by the conspicuous harmonics. When the bigeminy was absent and the rate higher with short diastole, the murmur did not occur. (From McKusick, V. A., Murray, G. E., Peeler, R. G., and Webb, G. N.: Bull. Johns Hopkins Hosp. **97**:136, 1955.)

occur in some cases. Granting the importance of other factors in the angina pectoris of the Marfan syndrome, one cannot help but wonder if one factor may not be the pronounced dragging of the large blood-laden aortic cusps on the coronary ostia in diastole and the dilated aorta during systole.

The onset of aortic dilatation may be as early as the fifth year or as late as the sixth decade. The oldest reported patient with aortic insufficiency without evident aortic dilatation was 56 years of age.[76] In one reported case,[162] dilatation of the ascending aorta with aortic regurgitation and marked left ventricular hypertrophy resulted in the death of a 10-month-old infant; in another case,[146] death occurred at 55 years. In my series the youngest patient with outspoken aortic regurgitation was 2 years old (see Fig 26*A*). The oldest patient with aortic regurgitation is

59 years old (H. B., 621760). He shows no radiologic evidence of dilatation of the ascending aorta.

The dilatation is almost always confined to the ascending aorta proximal to the innominate artery. However, in Case 3 of Thomas and co-workers[159] the descending aorta was also involved. Furthermore, at least two instances of fusiform aneurysm of the abdominal aorta have been described recently.[82]

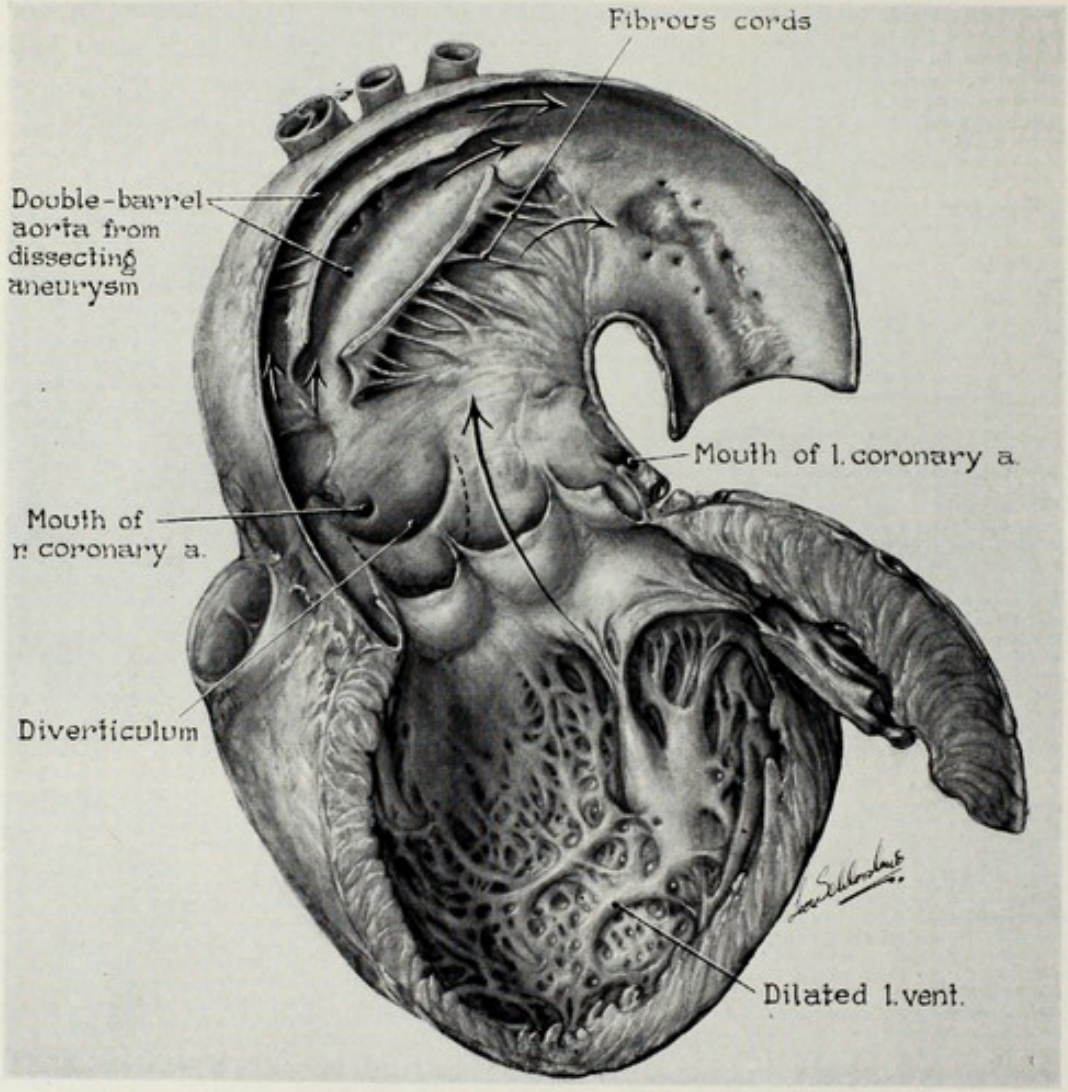


Fig. 16*G*. The autopsy specimen in patient L. F. Y. A chronic dissection of the ascending aorta is present. The patient died of heart failure. The drawing demonstrates three structures which might vibrate periodically with production of a musical murmur as seen in Fig. 16*F*: (1) the fibrous cords which traverse the false channel; (2) the lip of the inner tube of the double-barrel aorta; (3) the lip of the "diverticulum" above the sinuses of Valsalva. Why any one of these three structures should be incited in late diastole with production of the musical murmur shown in Fig 16*F* is not clear. (From McKusick, V. A., Murray, G. E., Peeler, R. G., and Webb, G. M.: Bull. Johns Hopkins Hosp. **97**:136, 1955.)

One of our patients (H. B., 621760), 59 years of age, has what appears by ordinary radiography to be a well-circumscribed orange-sized aneurysm of the descending thoracic aorta. Aortograms show both the thoracic and abdominal aorta to be diffusely dilated, with buckling in the lower thoracic area as well as in the abdomen, creating a false impression of saccular aneurysm at these sites.

Fig. 27 describes another of our cases in which cylindrical aneurysm was limited to the abdominal aorta. The ascending aorta was clinically unaffected. Van Buchem[295] described rupture of the abdominal aorta with cystic medial necrosis in a 20-year-old man who, because of striking skeletal changes, probably had the true Marfan syndrome, although the rest of the family was unaffected and no subluxation of the lenses was discovered. Langeron and his colleagues[82] described two cases of abdominal aneurysm in the Marfan syndrome. Hardin,[234a] in a case of full-blown Marfan syndrome in a 21-year-old man, described a fusiform abdominal aneurysm extending from the level of the renal arteries to the bifurcation

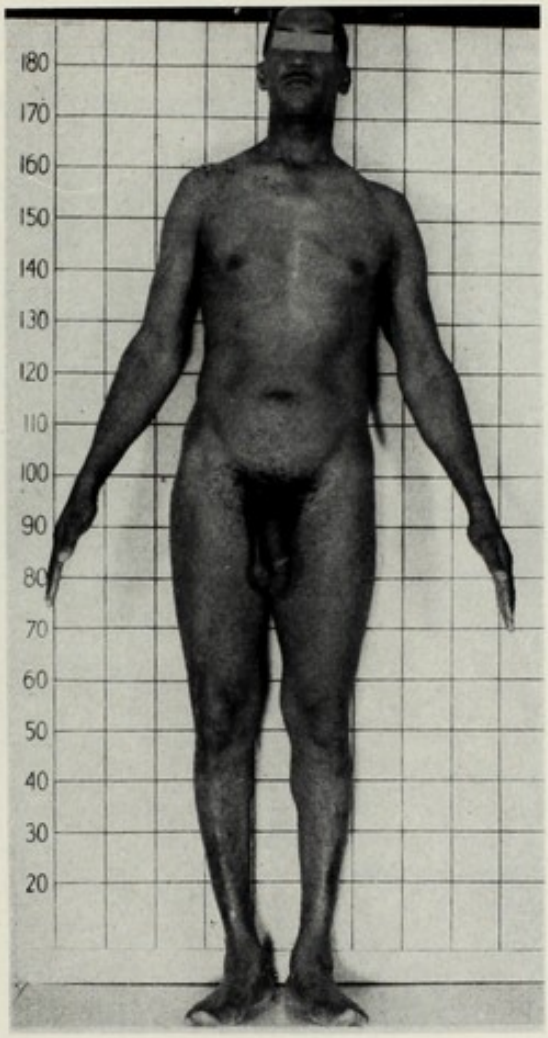


Fig. 16*H*. J. A. F. (816419), individual III-1 in Fig. 16*A*, 33 years of age. Bilateral ectopia lentis, dolichostenomelia, and mild aortic regurgitation.

of the aorta. It had ruptured into the inferior vena cava. At autopsy, although the abdominal aorta showed the histologic changes characteristic of the Marfan syndrome, "the thoracic aorta, pulmonary artery, and remaining arteries showed intact elastic fibers." Davis and his colleagues[218a] performed a total replacement of the abdominal aorta in a patient subsequently proved to have the Marfan syndrome, and I am told that Dubost of Paris has performed a similar operation in a case of the Marfan syndrome. Dissection exclusively in the aorta beyond a mild coarctation at the usual site has been described.[168] In one reported case,[194] dissect-

ing aneurysm was limited to the portion of the aorta between the mouth of the left subclavian artery and the level of the diaphragm; there seemed not to be other abnormality of the aorta.

Several cases (e.g., reference 106) have had cystic medial necrosis, dissection, and internal tears in the abdominal as well as the ascending aorta. Thrombosis of the abdominal aorta with production of the Leriche syndrome is described[219] but was probably not more than a coincidental complication in that case.

By examining a large number of patients with ectopia lentis and by studying the relatives of established cases of Marfan's syndrome, we discovered six patients who appeared to be in the early stages of aortic dilatation with aortic regurgitation.[92] In none was there then evident dilatation of the ascending aorta (Figs. 21*B*, 24*A*,

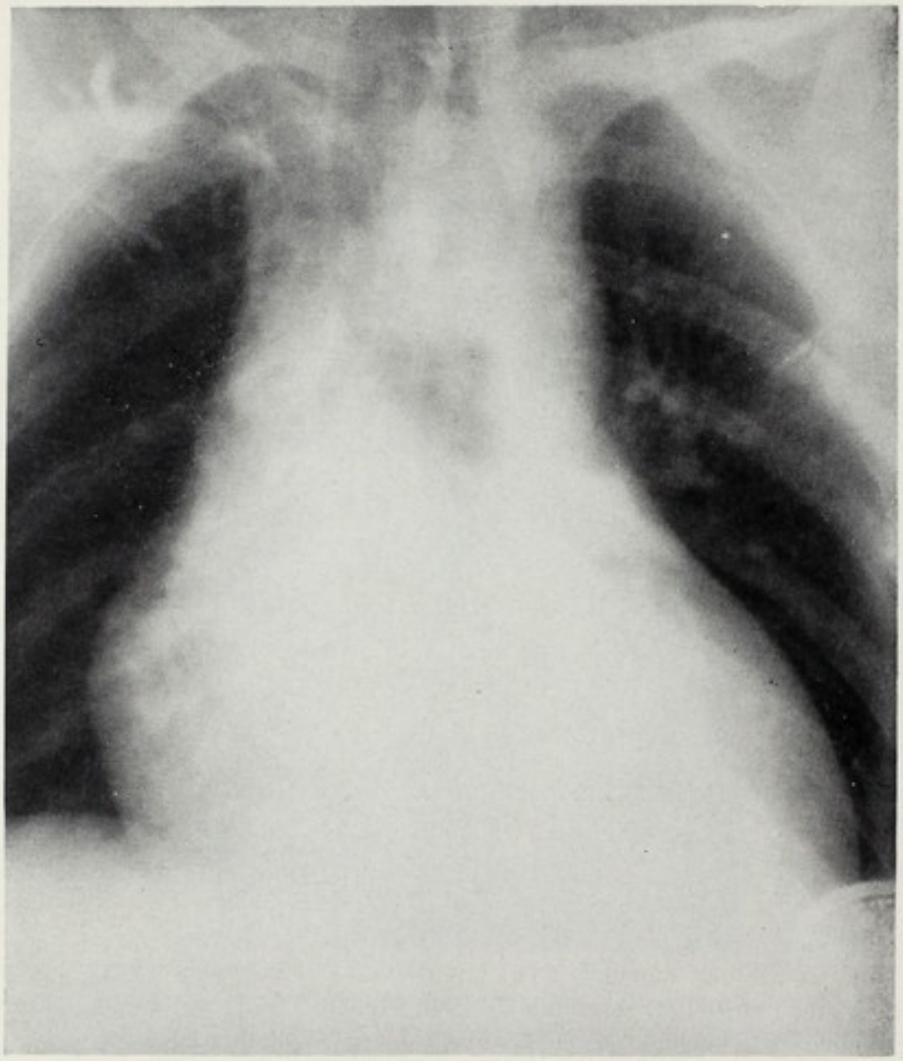


Fig. 17*A*.

Figs. 17*A* and 17*B*. S. C. (575946), a veterinarian, had ectopia lentis and skeletal proportions of the Marfan syndrome. He died at the age of 37 years during an attempt at surgical repair of the ascending aorta. With the episode of dissection in October, 1955, a musical systolic murmur developed over the ascending aorta. This sign, a valuable diagnostic clue in such cases, probably owes its origin to vibration in intimal lip or fibrous bands in the ascending aorta. Angiocardiogram (*A* and *B*) showed striking dilatation of the base of the aorta within the shadow of the heart, surpisingly little enlargement of the later portion of the ascending aorta, failure of opacification of the innominate artery, the lumen of which was tamponaded by a medial dissection, and, finally, pseudocoarctation of the type so typical of the Marfan syndrome. (From McKusick, V. A.: Ann. Int. Med. **49**:556, 1958.)

24*B* and 25*B*). One of the six (Fig. 25*B*) died of aortic aneurysm about three years after first detection of aortic regurgitation. The others remain without particular cardiac symptoms, after an interval of six years in three of them.

Recent years have witnessed a crescendo of interest in the subject of aneurysm of the sinuses of Valsalva.[196,227] Steinberg and Geller[285] have demonstrated such aneurysms, by means of angiocardiography, in patients with the Marfan syndrome, and we have had similar experiences (see Figs. 17*A* to 17*C*). Actually the "aortic sinus aneurysms" which occur in the Marfan syndrome behave clinically in quite a different manner than do those to which this term is perhaps more legitimately applied. Rupture into the right side of the circulation has not been observed in the Marfan syndrome to my knowledge; the aneurysm is not, with occasional exception, limited to one aortic sinus. The possibility of the Marfan syndrome should not be abandoned, however, in cases of rupture of an aortic sinus into the right side of the

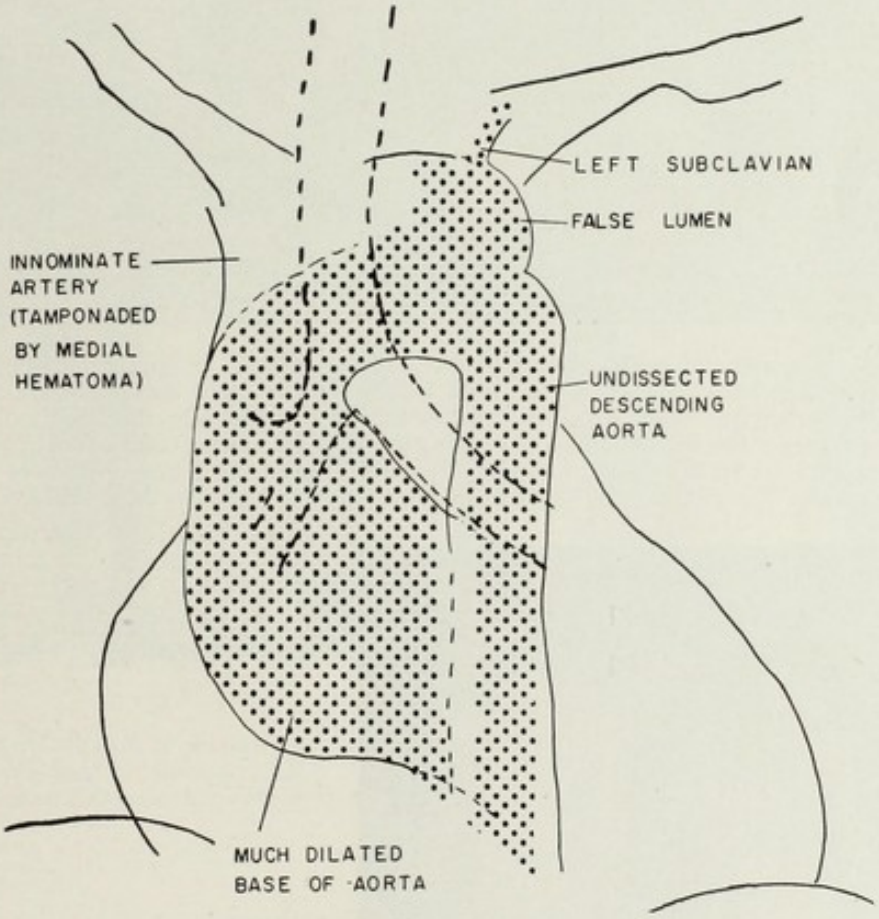


Fig. 17*B*.

Fig. 17*B*. For legend see opposite page.

heart. In one reported case,[267] a 36-year-old male, the following statement suggesting the Marfan syndrome was made: "Until his attack he was perfectly fit and served in the army during the Second World War in a low category on account of defective eyesight and flat feet."

Dissecting aneurysm may occur as the first aortic complication or may be superimposed on diffuse dilatation of the ascending aorta.[98] There is evidence that dissection may occur in the first decade of life; possibly the oldest reported case of dissecting aneurysm in Marfan's syndrome was that of a 52-year-old woman.[48]

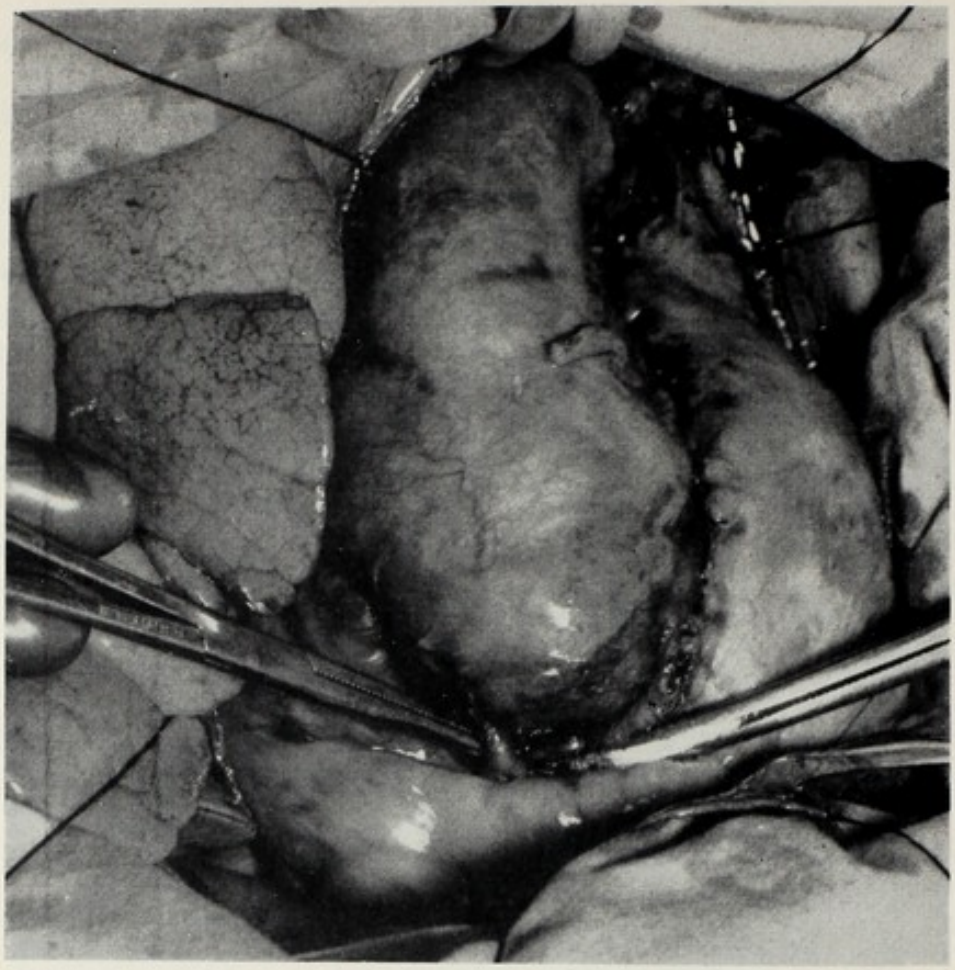


Fig. 17*C*. The gourdlike appearance of the ascending aorta as exposed through a surgical incision in the right interior thorax. A clamp lies under the right coronary artery. Unusually high displacement of this vessel made operation difficult, as did also the high extension of the aortic commissures. The patient died during surgery. The mother of this patient died of the cardiac complications of the Marfan syndrome at the age of 40 years. An older sister of the patient has the Marfan syndrome. (From McKusick, V. A.: Ann. Int. Med. **49**:556, 1958.)

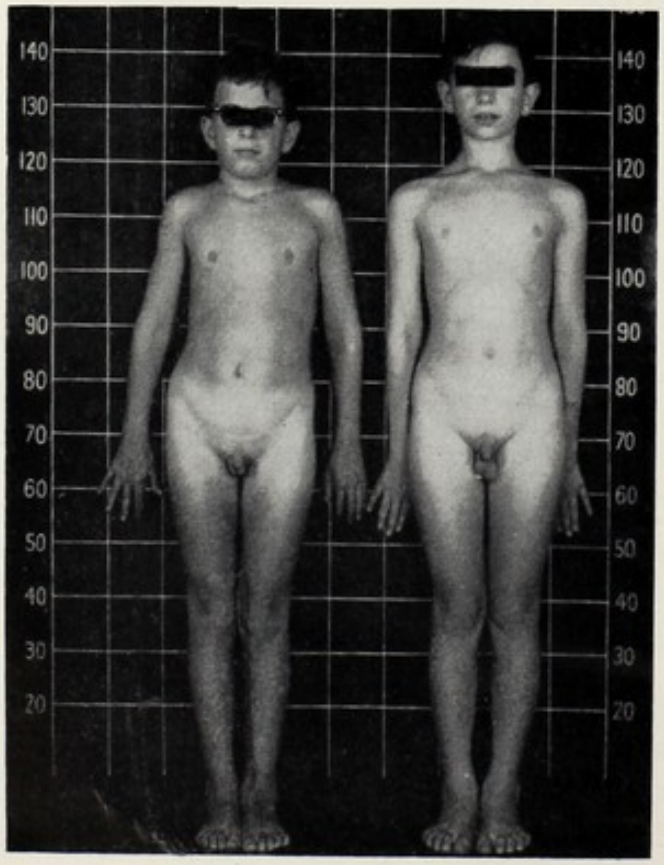


Fig. 17*D*. The proband's sons, one affected (left), one unaffected, are seen here. R. C. (783343), the affected boy, 8¾ years old, has grossly visible dislocation of the lenses, myopia, and mild thoracic kyphosis. The normal brother is 12 years old; another brother, 4 years of age, is also normal. (From McKusick, V. A.: Ann. Int. Med. **49**:556, 1958.)

The patient may survive for a number of years after first dissection of the aorta and even after a "leak" into the pericardium. Because of the aortic regurgitation, which results either from the dissection itself[64,127] or from the associated dilatation of the aortic ring, confusion with rheumatic[83] or syphilitic[60] heart disease is frequent. In a recently autopsied case at this hospital, leaking of the original dissecting aneurysm into the pericardial sac led to the misdiagnosis of tuberculous pericarditis. The patient survived five years after the first pericardial episode. Dissection apparently occurs with increased frequency during pregnancy.[107,141,143] In chronic dissecting aneurysm of the aorta, there may be little enlargement of the aorta evident on x-ray (see Figs. 16*D*, 16*E*, and 21*C* to 21*E*). In our

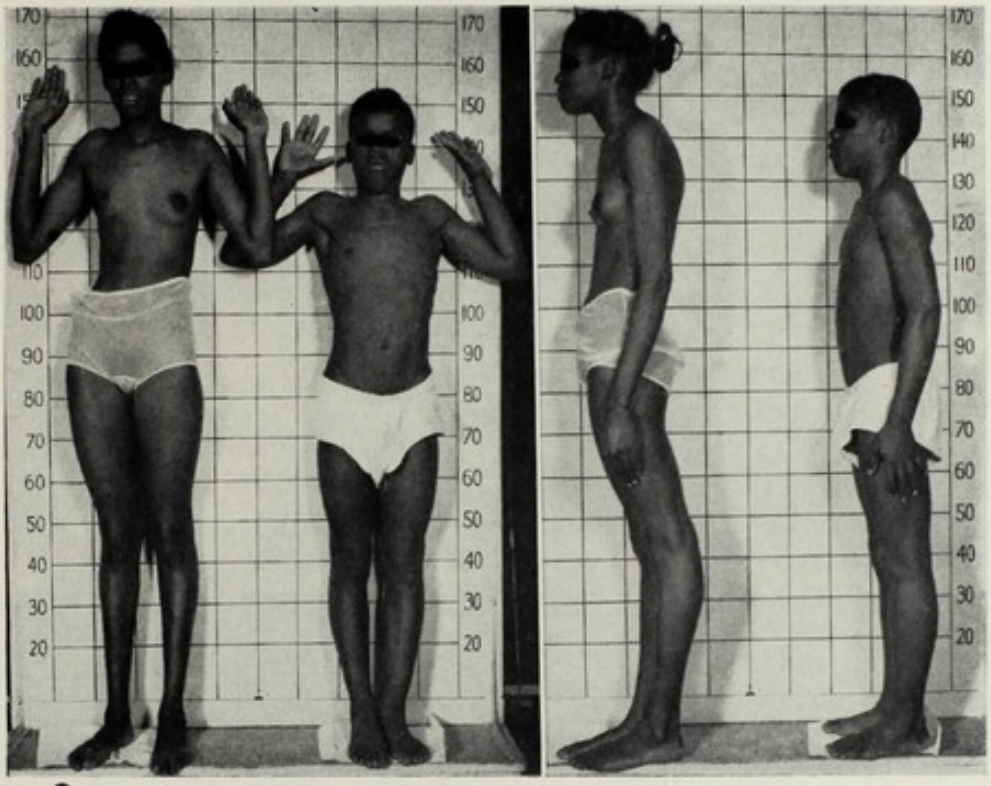


Fig. 18*A*. Fig. 18*B*.

Figs. 18*A* and 18*B*. Fourteen-year-old S. S. (366788), II-6 of the pedigree (Fig. 18*C*), and her normal 12-year-old brother, II-7. Note the kyphoscoliosis, genu recurvatum, excessively long legs, and strabismus. Ectopia lentis is present.

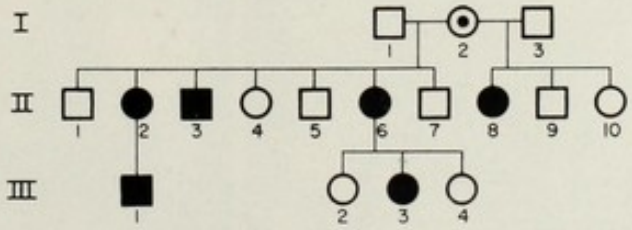


Fig. 18*C*. This pedigree illustrates how submerged the manifestations of Marfan's syndrome can be. Individual I-2 had had at least three affected offspring by one husband and one affected offspring by a second husband. Both husbands are unequivocally normal from the skeletal, ocular, and vascular points of view. The mother is 5 feet 8 inches tall, moderately long of limb, poorly muscled, and severely myopic (−6D), but has no ectopia lentis by careful ophthalmoscopic examination. (For the last I am indebted to Dr. J. E. Mishler of Atlantic City, N. J.) These manifestations are consistent with forme fruste of the Marfan syndrome but would not be recognizable as such without the knowledge of this pedigree. (Status of pedigree in 1959, six years after photographs in Figs. 18*A* and 18*B* were taken.)

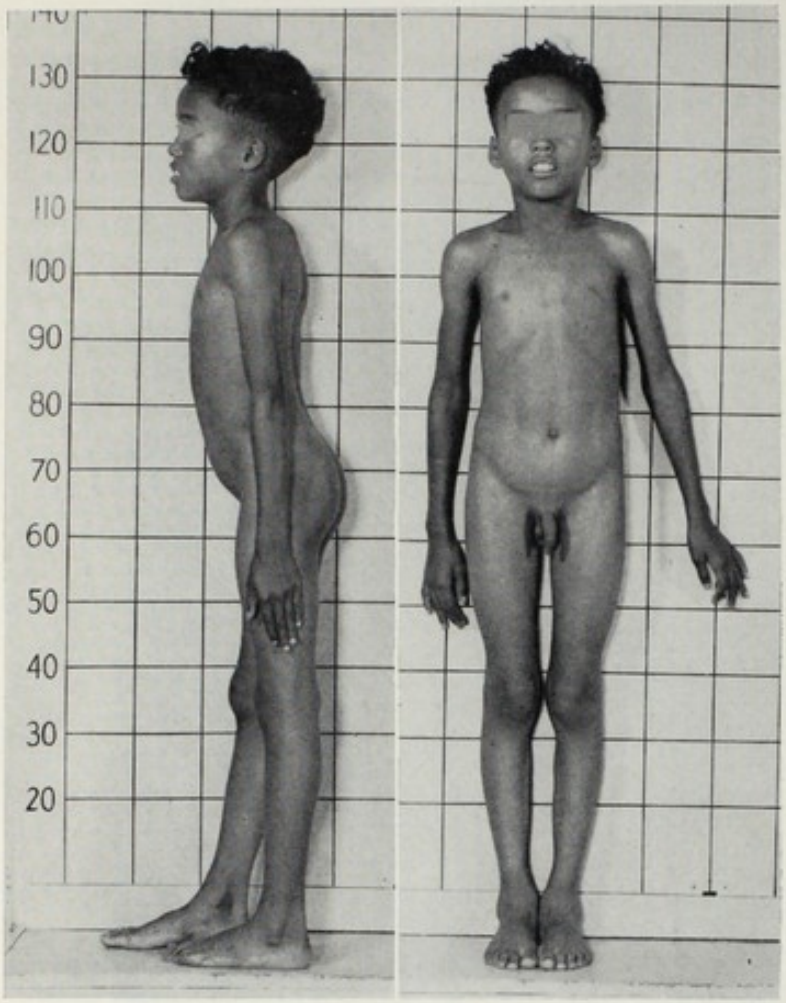


Fig. 18*D*. Two views of S. S. (719604), individual III-1 of the pedigree in Fig. 18*C*. Born March 1, 1948. Photograph, Aug. 6, 1956. When first examined at home in 1953, the patient was judged to be normal. It is now clear that slight bilateral lens dislocation is present. A faint aortic diastolic murmur was heard in 1958. The chest is asymmetrically deformed to a minor degree. Arachnodactyly and loose-jointedness are not impressive.

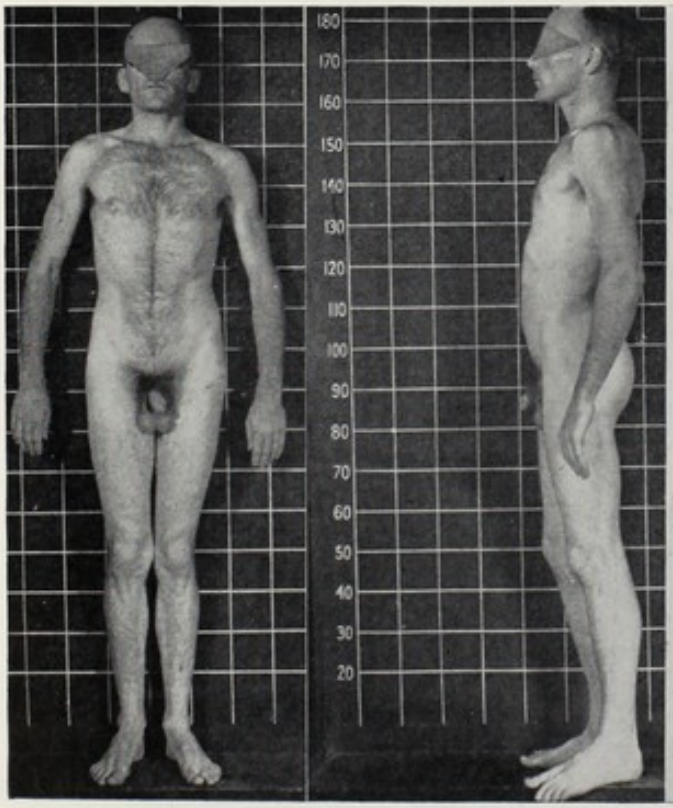


Fig. 19.

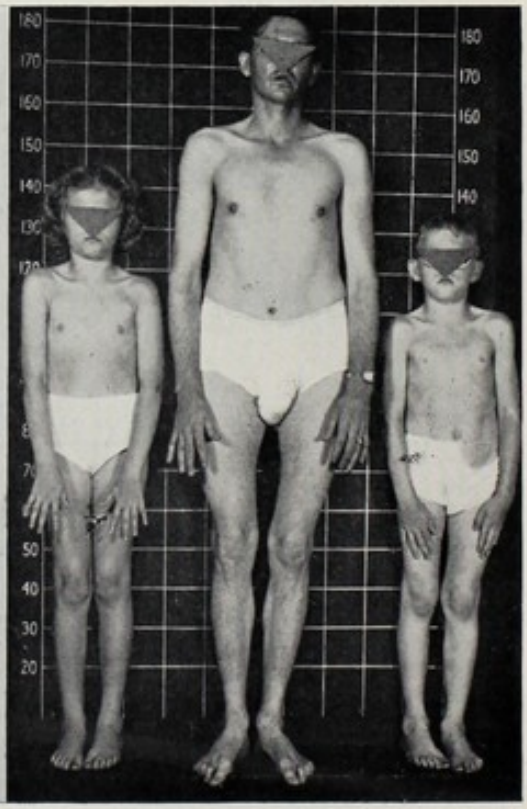


Fig. 20.

Figs. 19 and 20. For legends see opposite page.

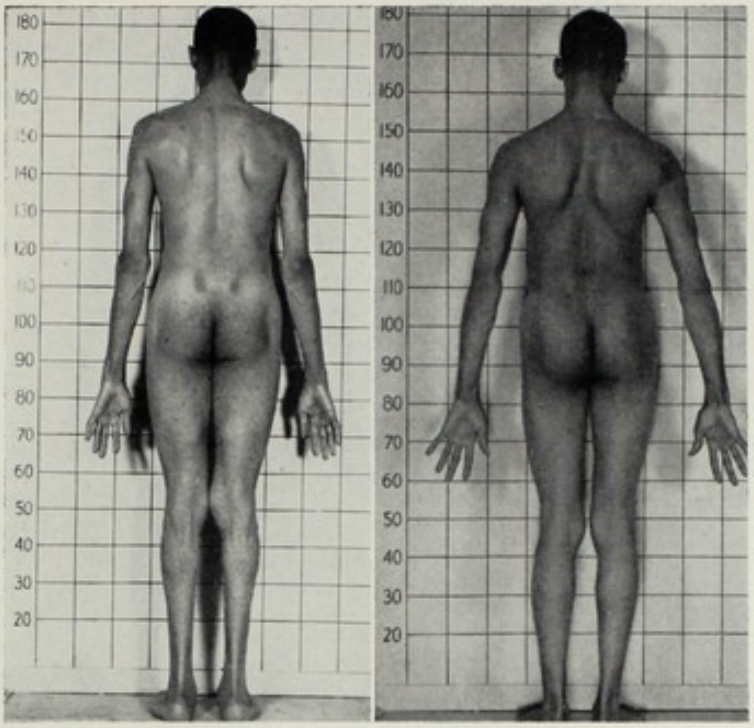


Fig. 21*A*. Fig. 21*B*.

Figs. 21*A* and 21*B*. Brothers with the Marfan syndrome without ocular manifestations.

Fig. 21*A*. J. M. (544088) had genu valgum, severe pes planus, and dolichostenomelia but no ectopia lentis. In 1950 an episode of chest pain accompanied by pericardial friction rub was interpreted as pericarditis and treated for presumed tuberculous etiology. Signs of aortic regurgitation developed thereafter. In 1953, there occurred at least one other episode of chest pain with pericardial friction rub. The effects of aortic regurgitation became progressively more severe and were the cause of death in April, 1955, at the age of 30 years. Autopsy revealed superannuated dissecting aneurysm of the ascending aorta and dilatation of the aorta above the aortic ring. The aorta had apparently "leaked" into the pericardial sac almost five years before death. (Known to us is a second case [S. T., 691351] in which the patient was still living following leakage about 18 months before. The diagnosis of Erdheim's disease was established at operation for aneurysm of the ascending aorta. Sando and Helm[275] reported survival of a patient for four and one-half years after acute dissection accompanied by a pericardial friction rub.)

Fig. 21*B*. W. M. (702409), 27 years of age, was discovered to have aortic regurgitation when examined in connection with his brother's illness. He had dolichostenomelia and spinal curvature. Although the left ventricle is large, no dilatation of the aorta is demonstrable. He is asymptomatic.

(See next page for Figs. 21C to 21F.)

Fig. 19. C. H. (687485), 28 years old. Ectopia lentis. Lenses correcting for aphakia worn from age of 5 years. Brother, father, two paternal aunts, and two cousins are living and have the Marfan syndrome. Paternal grandmother and great grandmother likewise had it. Father blind in both eyes and aunt blind in one eye from secondary glaucoma. Patient in Army for 45 months. Note deformity of knees. This and many of the other members of this group of photographs make it clear that on superficial inspection the habitus may not seem impressively or abnormally dolichostenomelic.

Fig. 20. Father, E. C., and two children, Anna (593933), 9 years of age, and Robert (441759), 7 years of age, all with ectopia lentis and skeletal proportions, albeit not striking, consistent with the Marfan syndrome. The father's brother had had a "leaky heart" for several years and died suddenly at the age of 35 years.

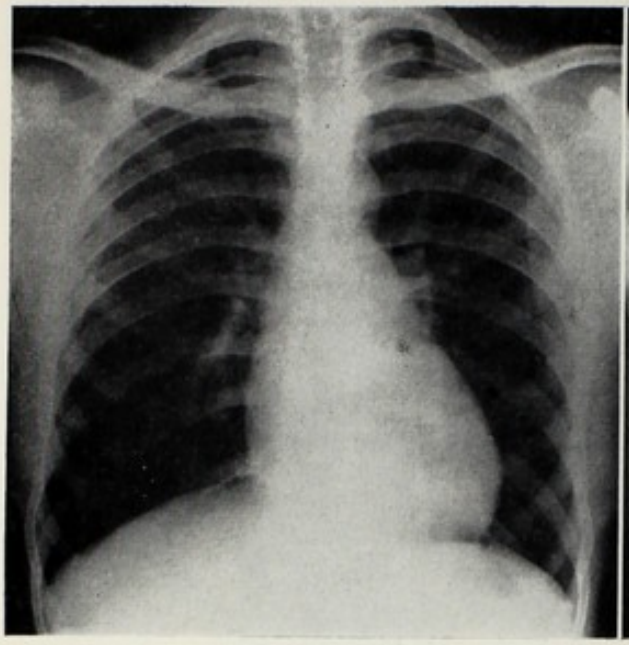


Fig. 21*C*.

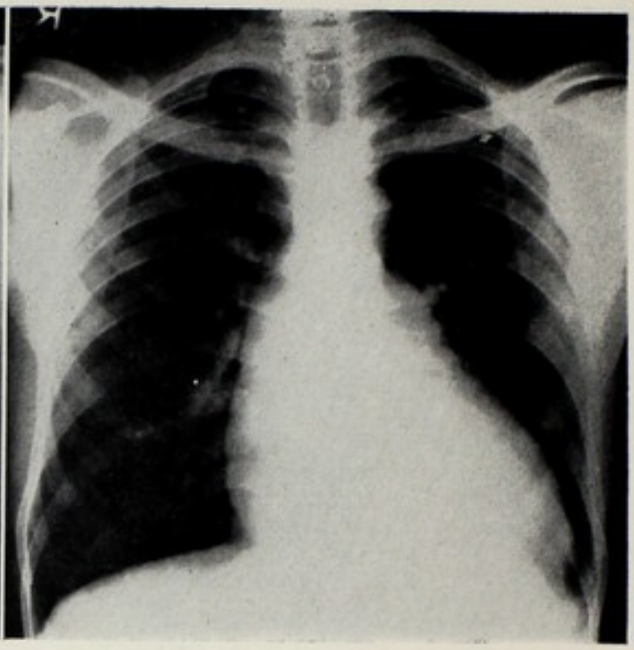


Fig. 21*D*.

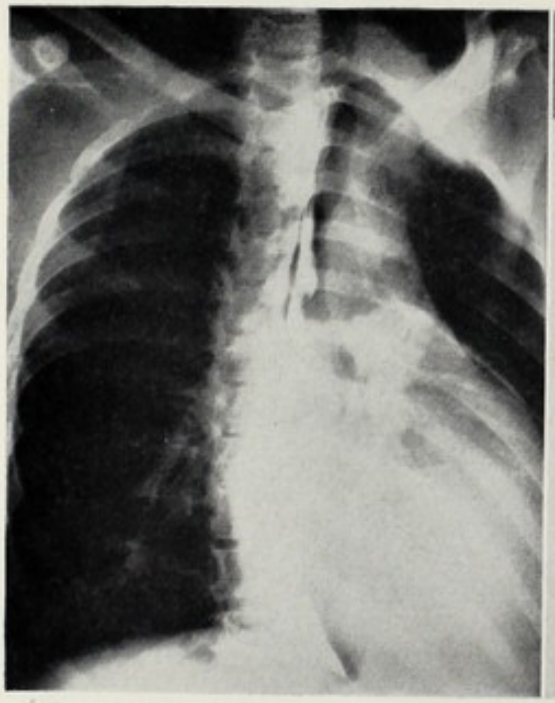


Fig. 21*E*.

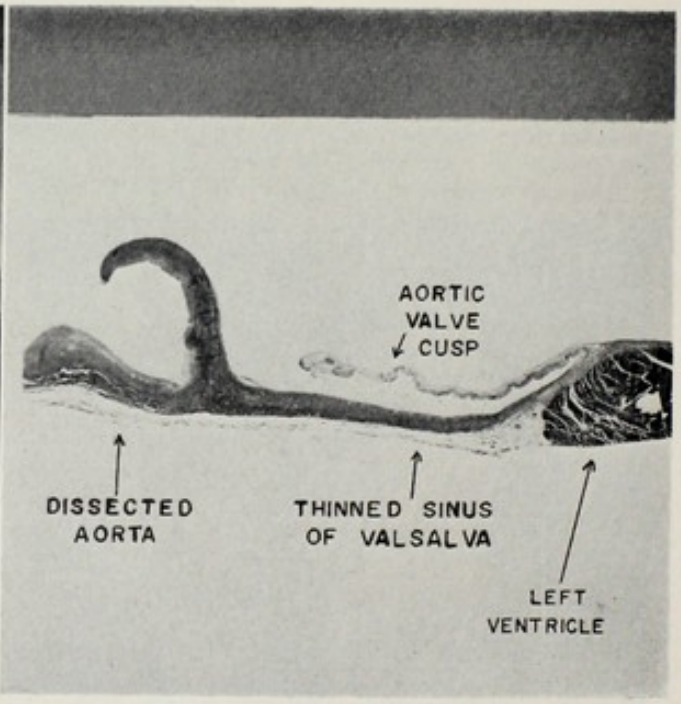


Fig. 21*F*.

Fig. 21*C*-21*E*. Series of x-ray films of J. M.

Fig. 21*C*. Taken in 1950 about one month after the initial episode of leakage into the pericardial sac.

Figs. 21*D* and 21*E*. The appearance in the last year of life. Enlargement of the aorta is not impressive in *D*, but the main pulmonary artery is prominent. In the right anterior oblique *(E)* the barium-filled esophagus is displaced by a structure which necropsy demonstrated to be an aneurysm of the sinus of Valsalva. In the left anterior oblique (not shown here), again the aorta does not appear particularly dilated.

Fig. 21*F*. Microscopic section (×4) of aortic valve area in J. M. (see Fig. 21*A*). The old dissection, the thinning of the sinus of Valsalva, and the minor fibrous thickening of the aortic valve are demonstrated.

experience, when full family investigations are made, Marfan's syndrome is found to be a leading "cause" of dissecting aneurysm in persons under the age of 40 years. Gore[57] reported that three of twenty-two patients had arachnodactyly. This, however, was not a detailed clinicogenetic study. At least 17 per cent of the reported cases of dissecting aneurysm under the age of 40 years were recognized instances of the Marfan syndrome.[236] The true proportion is probably higher. For example, Spenser[281] described dissecting aneurysm during pregnancy in a "tall, thin" woman

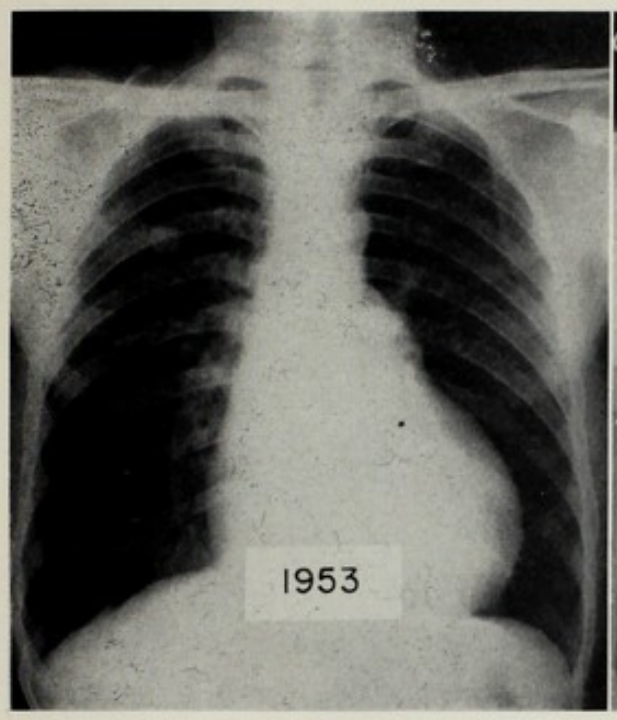


Fig. 22*A*.

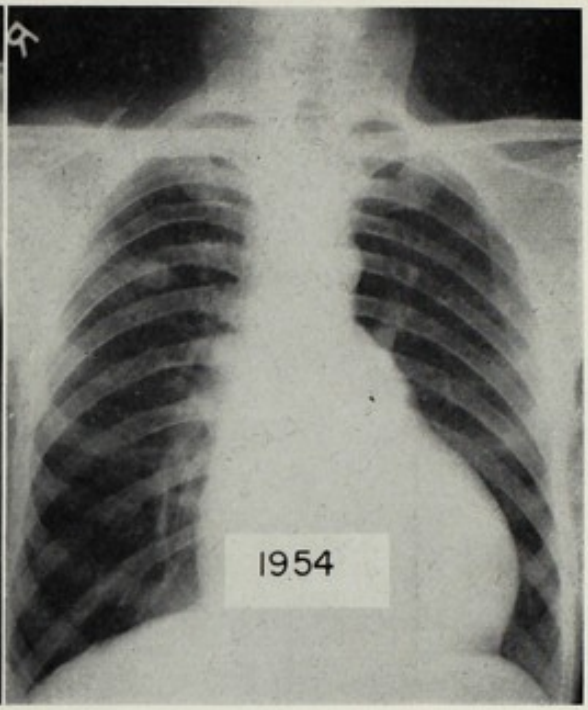


Fig. 22*B*.

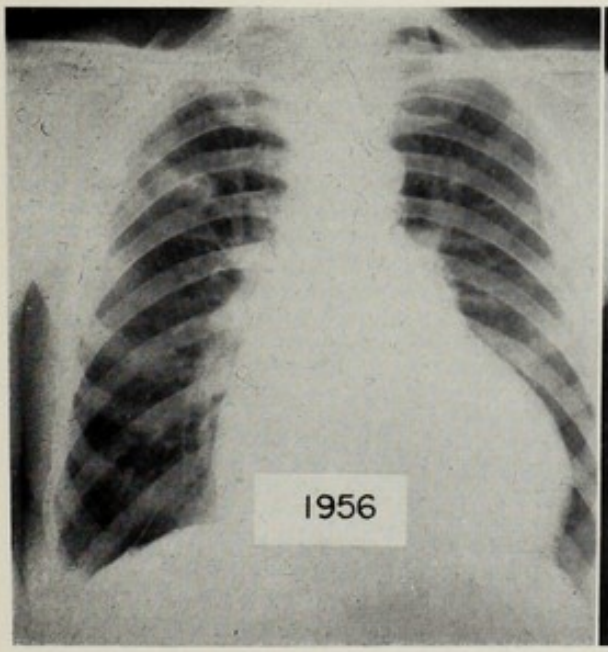


Fig. 22*C*.

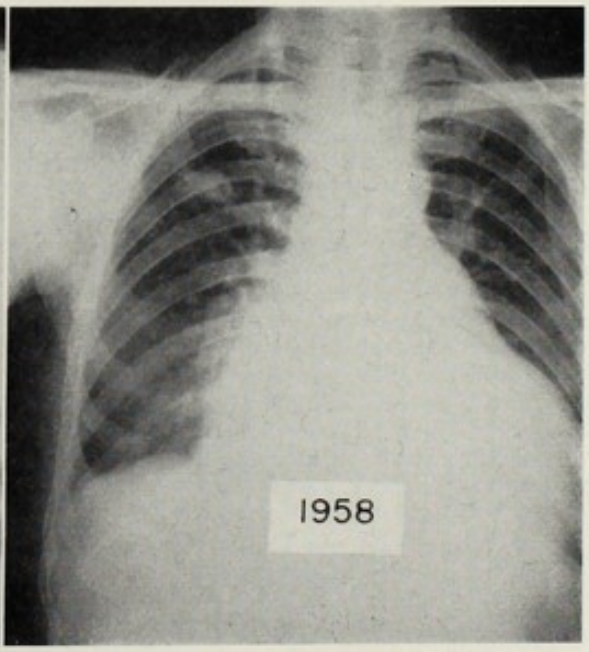


Fig. 22*D*.

Figs. 22*A*-22*D*. For legend see next page.

of 32 years. Griffith and his colleagues[232] reported on a dissecting aneurysm in a 34-year-old woman and her 14-year-old daughter, both of whom were said to have been "delicate physically."

The occurrence of aortic regurgitation with dissecting aneurysm is well recognized in the English-speaking medical world since the publication by Resnik and Keefer[127] in 1925. Hamman and Apperly's[64] explanation that the aortic regurgitation results from deformation of the aortic ring by the intramural hematoma is the generally accepted one. Obviously another mechanism for the association is pre-existing dilatation of the aortic ring on the basis of the same defect of connective tissue which led to the dissecting aneurysm.

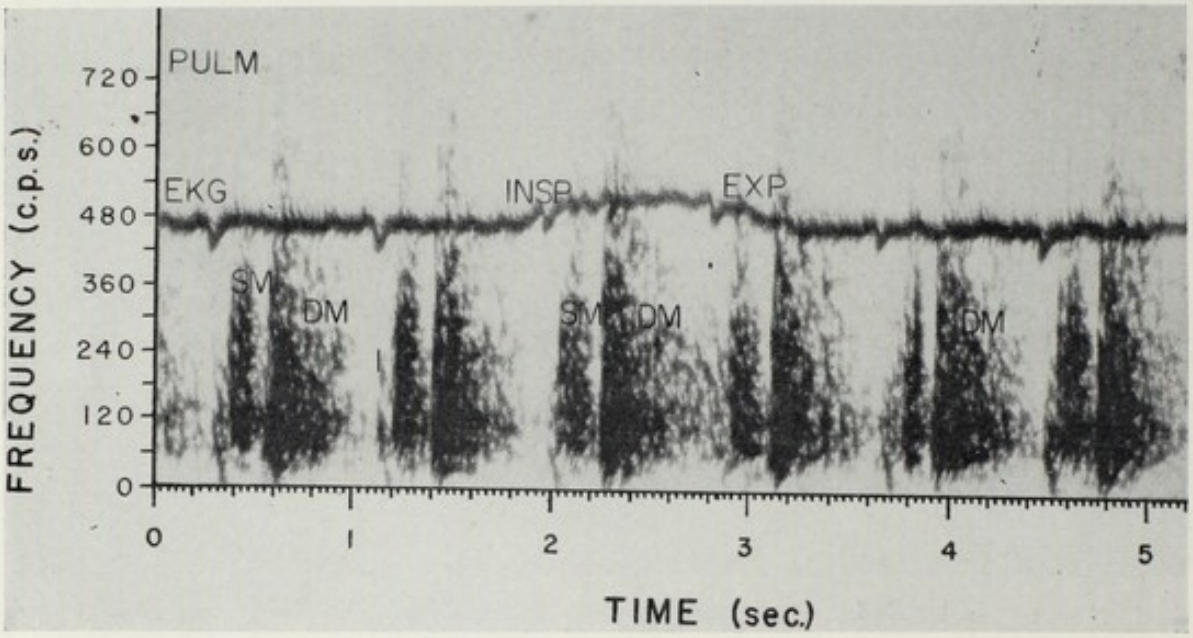


Fig. 22*E*.

Figs. 22*A*-22*E*. Eight-year survival after onset of cardiac symptoms in the Marfan syndrome. A. D. (341643), Negro male born in 1907, was well until 1950, when there was onset of chest pain and dyspnea. Late in 1951 chest pain and attacks of paroxysmal nocturnal dyspnea became especially frequent. The chest pain had the pattern typical of angina pectoris. At first it was relieved by nitroglycerin; later this drug seemed to have little effect. Throughout the eight years of observation the murmur and other signs of aortic regurgitation were present. Also, at the apex what was interpreted as an Austin Flint murmur was described. During the last three years of life a bizarre "crackling" systolic murmur was described at the apex. It was also described as "crunching" and compared to "footsteps in gravel." It disappeared on deep inspiration. Numerous serologic tests for syphilis and two treponemal immobilization tests were negative. Progressive widening of the QRS complexes, to a maximum of 0.13 second, occurred in the period of observation. Atrial fibrillation developed in the last two weeks of life. The patient died in 1958.

The man was described as "tall," "thin," "asthenic," and "long-armed." His height was twice measured as 70½ inches. Vision acuity was essentially normal. Although no slit-lamp examination was performed, numerous standard ophthalmoscopic examinations showed no abnormality. There was no hernia or spinal deformity. The patient had had no children; his family was not available for study.

A, X-ray, 1953. *B*, X-ray, 1954. *C*, X-ray, 1956. *D*, X-ray three days before death in 1958. Dilatation of the aorta is conspicuous in its absence. The pulmonary artery segment is prominent throughout. *E*, Spectral phonocardiogram in pulmonary area, January, 1957. The findings are typical of severe aortic regurgitation, with no features pathognomonic for the Marfan syndrome.

Autopsy revealed findings similar to those shown in Fig. 15*C* except that the marked dilatation was limited more to the area of the sinuses of Valsalva. The histologic changes included loss of elastic fibers, spaces occupied by metachromatically staining material, whorls of disorganized smooth muscle fibers, and much dilated vasae vasorum.

In patients with the Marfan syndrome the sudden development of a murmur, especially a musical buzzing murmur over the ascending aorta, may be a valuable clue to the presence of dissection. The murmur, which may be either systolic or, less commonly, diastolic (see Fig. 16*F*), appears to be produced by vibrations excited in some of the anomalous structures—lips, fibrous cords, narrowed branches of the aortic arch—created by the dissection (see Fig. 16*G*). The early diastolic murmur created at the aortic valve may be musical in quality[242] and, as in the

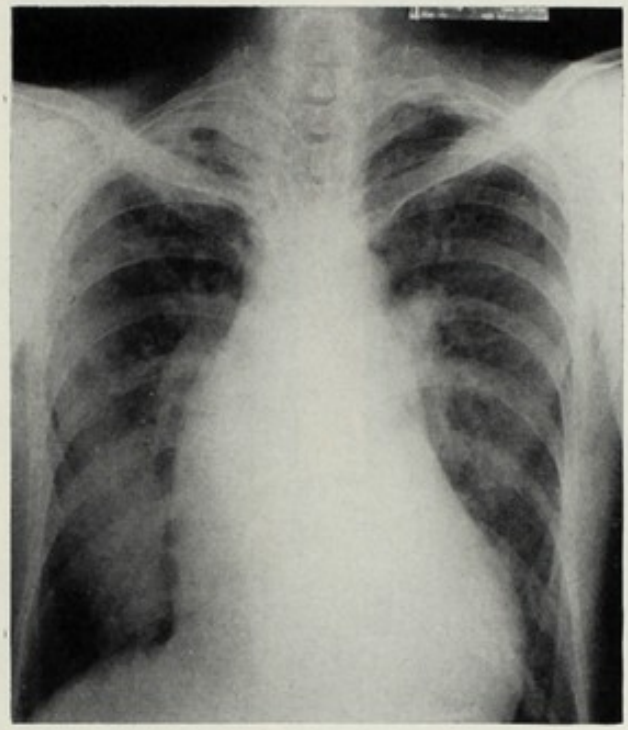


Fig. 23. The x-ray film of this 49-year-old man (B. L. 195805) shows prominence of the pulmonary artery and inconspicuous dilatation of the ascending aorta. These features, together with the murmur of aortic regurgitation and the associated Austin Flint murmur, lead to the diagnosis of rheumatic heart disease with combined aortic and mitral lesions. This was the case in spite of the fact that the patient was 75½ inchest tall, had spinal and thoracic deformities (a suggestion of which is indicated by the figure), and had had ectopic lenses removed 10 and 13 years previously. The patient had pneumonia twice in youth and had an operation for varicose veins at the age of 25 years. Scholastic performance was outstanding, with graduation from college at the age of 18 years. A bout of iritis prompted removal of the right lens in 1937. In 1940 the left lens was removed because of dislocation into the anterior chamber. Detachment of the retina on the left was discovered at that time. There was heterochromia iritis with normal brown pigmentation on the right and greenish coloration on the left. The patient was accepted for service in the Army and, while there (1947), had his first bout of severe chest pain with extension to the arms, neck, and epigastrium. A second episode of probable aortic dissection occurred later in 1947 and a third in 1948. The episode in 1948 was characterized by severe low back pain radiating into the lower abdomen and genitalia. The diagnosis of rheumatic heart disease was based on the prominence of the pulmonary artery segment (due actually to displacement by the dilated aorta), a diastolic murmur at the apex (which was probably either radiation of the murmur of aortic regurgitation or an Austin Flint murmur or both), and displacement of the esophagus by what was interpreted as left atrium (possibly indeed left atrium enlarged from chronic left ventricular failure or possibly the aortic aneurysm, see Fig. 21*E*). The patient died at home in 1950.

The father, 6 feet 3 inches tall, was killed by a bus at the age of 82 years. He probably had the Marfan syndrome in mild form; he sired several affected children and his wife appears to have been unaffected. Of eleven siblings of the proband, two, always puny, died at 8 and 10 years of unknown causes; two had the same habitus as the proband; a fifth has definite Marfan syndrome. This man, now 49 years old, is 70½ inches tall, weighs 178 pounds, and wears an 11½-C shoe. He was discharged from the Army when he lost the sight in one eye. Detachment of the retina was discovered at the age of 40 years. He has severe myopia and flatfeet, is stoop-shouldered, is said to have a heart murmur, and has had left inguinal herniorrhaphy. (From McKusick, V. A.: Circulation **11**:321, 1955.)

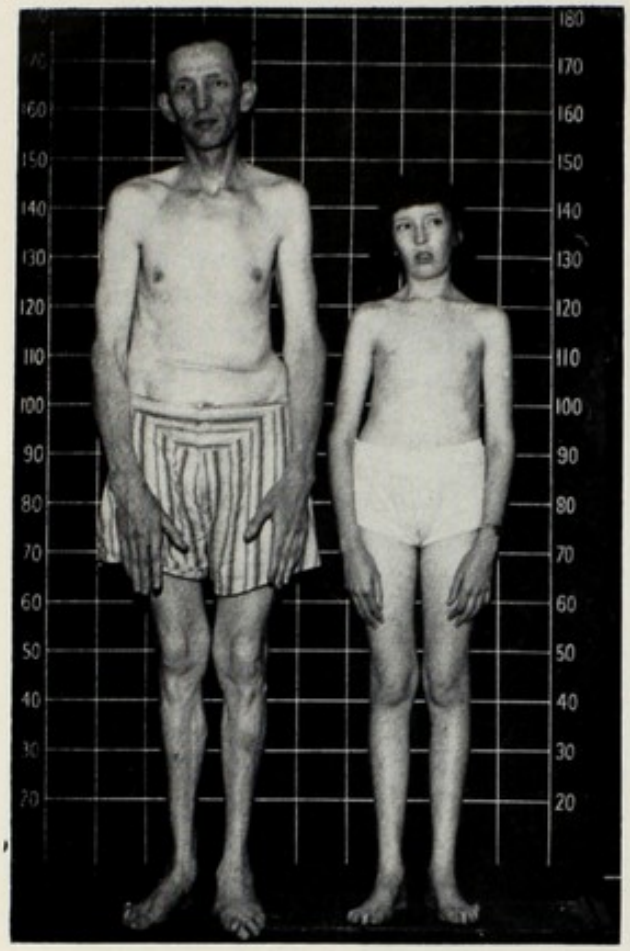


Fig. 24*A*.

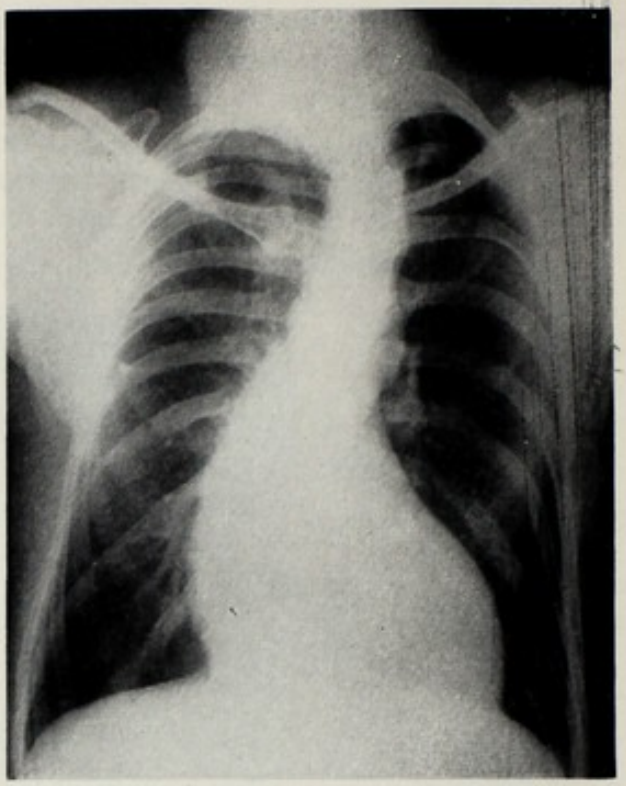


Fig. 24*B*.

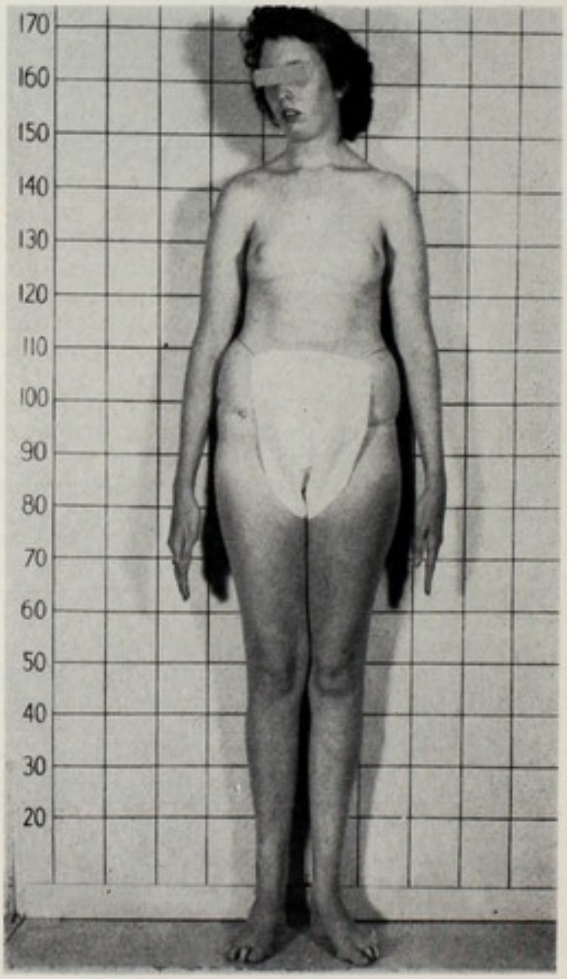


Fig. 24*C*.

Fig. 24*A*. Both the man (E. F., 194515) and his daughter (M. V. F., 565451) have bilateral subluxation of the lenses, spinal curvature, and dolichostenomelia (long, thin extremities). The man has had femoral and inguinal hernias repaired. The girl is only 9 years old. In 1950 the man had no cardiac murmurs. In 1953 he was found to have well-marked aortic regurgitation. Photograph, June, 1953. At this time the patient also had a crescendo holosystolic murmur of partially musical quality at the apex (see Fig. 317 in reference 253). (From McKusick, V. A.: Circulation **11**:321, 1955.)

Fig. 24*B*. The chest x-ray film of the man in Fig. 24*A* reveals no apparent dilatation of the ascending aorta. (The scoliosis obscures the picture.) Fluoroscopy likewise failed to establish dilatation of the aorta. (From McKusick, V. A.: Circulation **11**:321, 1955.)

Fig. 24*C*. Photograph of daughter shown in Fig. 24*A*, August, 1958.

case of many musical murmurs, may be very loud. Bean[195] had such a case in his series of precordial noises audible at a distance from the chest. Baer and his associates[11] stated that one of their patients had a loud "systolic murmur" audible two inches from the chest.

In general, the clinical picture of dissecting aneurysm in the Marfan syndrome is little different from that in persons without this syndrome, except that in the Marfan syndrome aortic regurgitation is more likely to be present (as a result of pre-existing dilatation in the first part of the aorta), the average age is about twenty years younger than that for other dissecting aneurysms, and hypertension is usually absent. As in any dissecting aneurysm, the patient may demonstrate inequality of the radial pulses.[268]

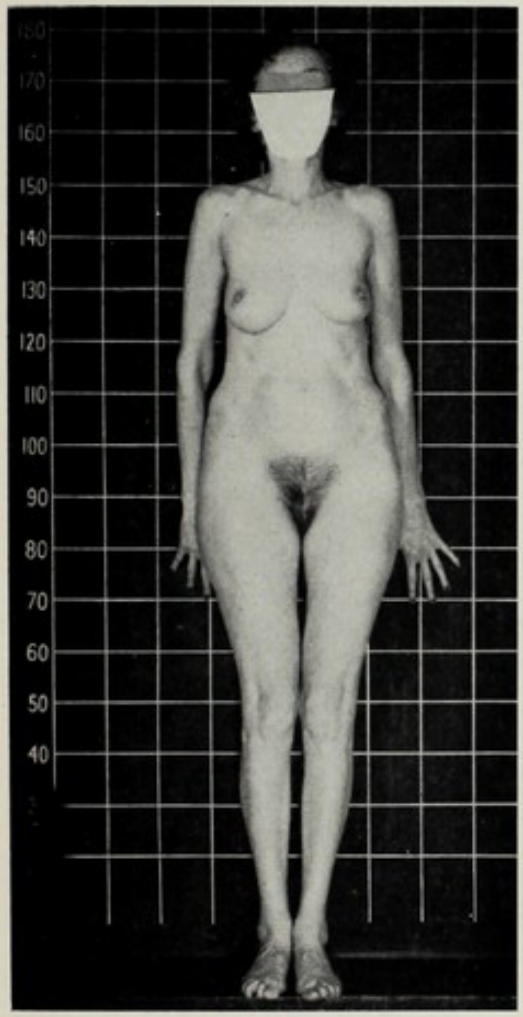


Fig. 25*A*.

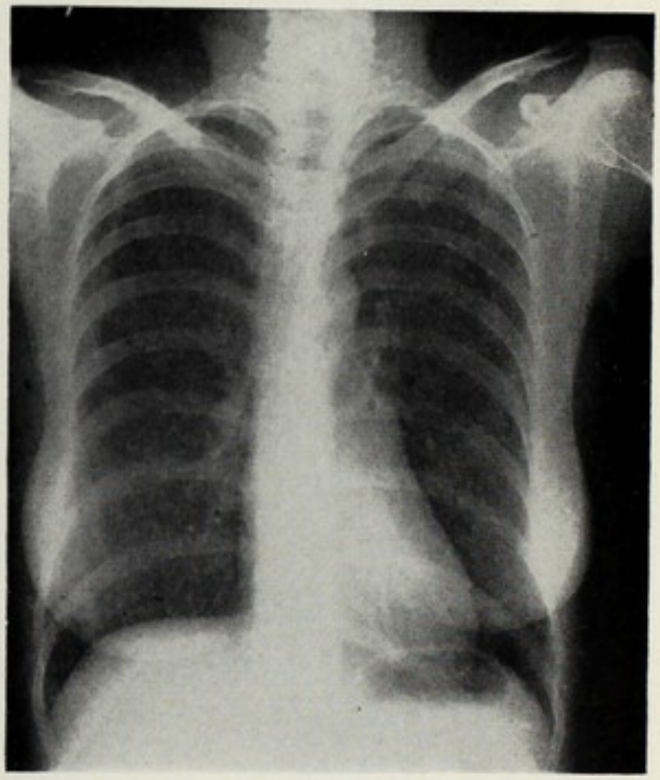


Fig. 25*B*.

Fig. 25*A*. M. B. (697662), 46 years old. Ectopia lentis, moderate dolichostenomelia, and spinal curvature.

Fig. 25*B*. Although at the time of these studies (February, 1955) the patient was asymptomatic and the cardiovascular silhouette normal, an aortic diastolic murmur was present. The patient died in December, 1957. Diagnosis: aortic aneurysm. (Systolic clicks were recorded at the apex in 1955. The multiple clicks were described by the stethoscopist as a systolic crunch. Because of the mild chest deformity and the general loose-jointedness, the clicks are thought to have been produced by movement of joints of the thoracic cage. See Fig. 146 in reference 253.)

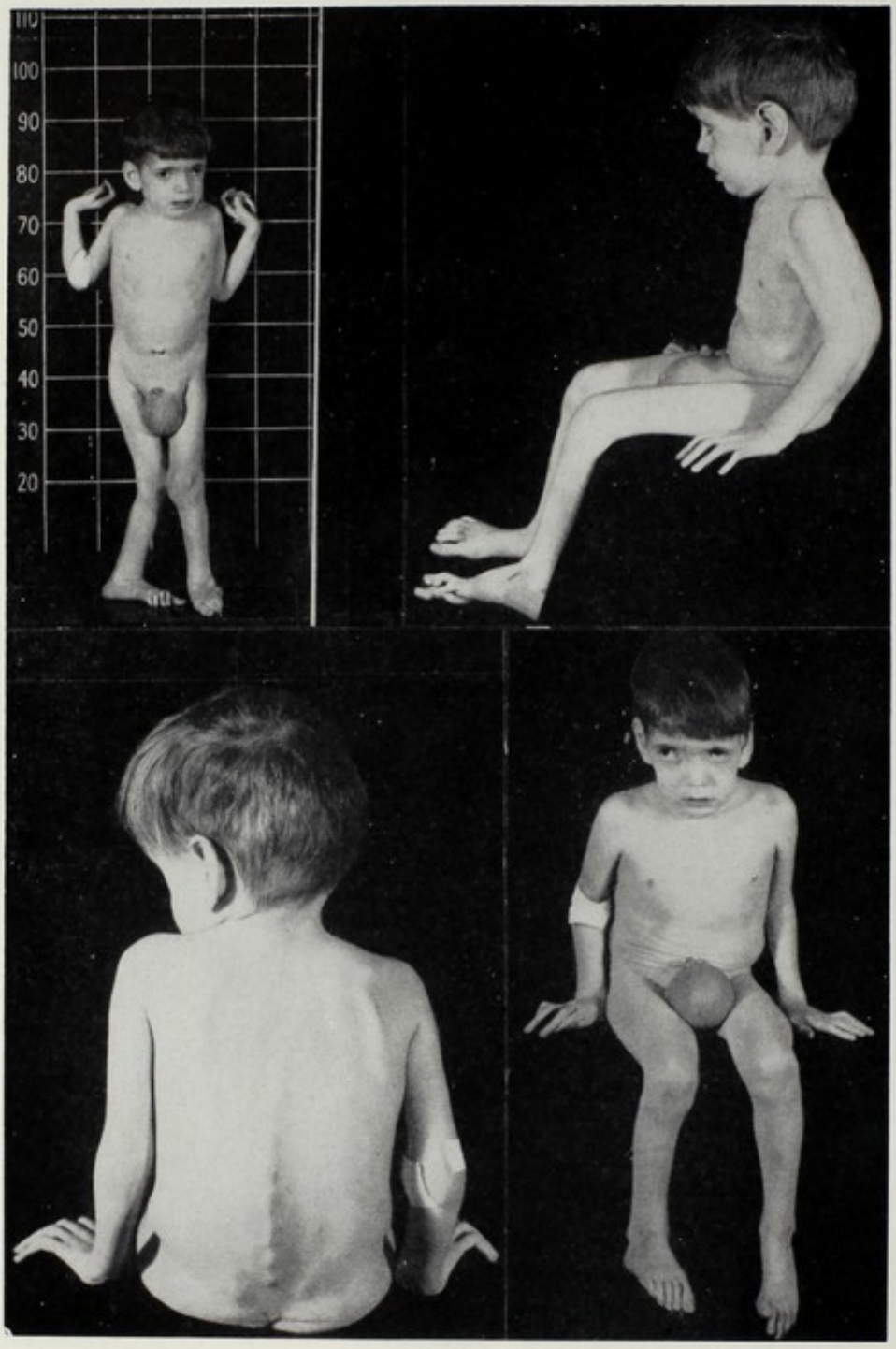


Fig. 26*A*

Fig. 26*A*. J. M. G. (795394), 26 months of age, has full-blown aortic regurgitation. The family history is negative. Dislocation of both lenses with striking iridodonesis, characteristically misshapen head and ears, kyphoscoliosis with "cat-back" in sitting, arachnodactyly, and a large left inguinal hernia are present. (From McKusick, V. A.: Ann. Int. Med. **49**:556, 1958.)

Figs. 26*B*-26*D*. Two older children (Fig. 26*B*) and both parents (Figs. 26*C* and 26*D*) show no stigmata of the Marfan syndrome. The patient is probably the product of a new mutation. He died at the age of 3½ years. Autopsy revealed characteristic changes in the ascending aorta.

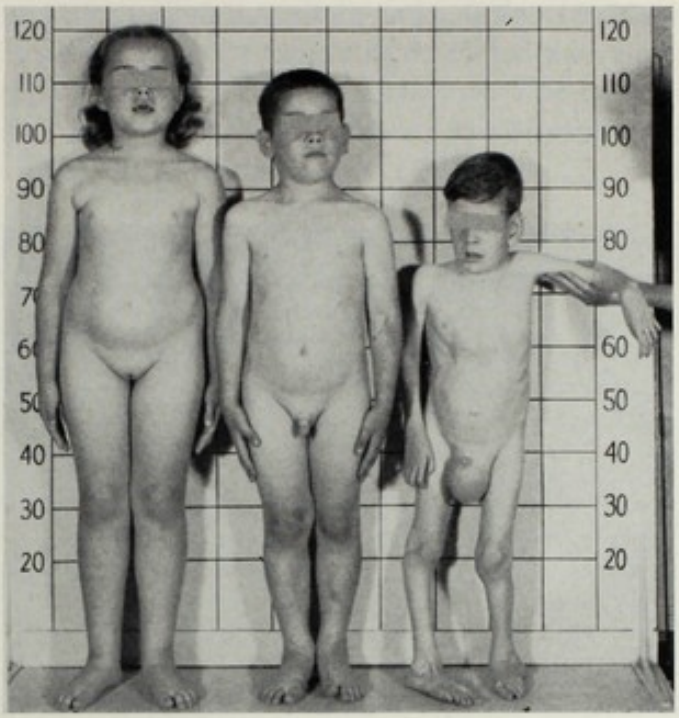


Fig. 26*B*.

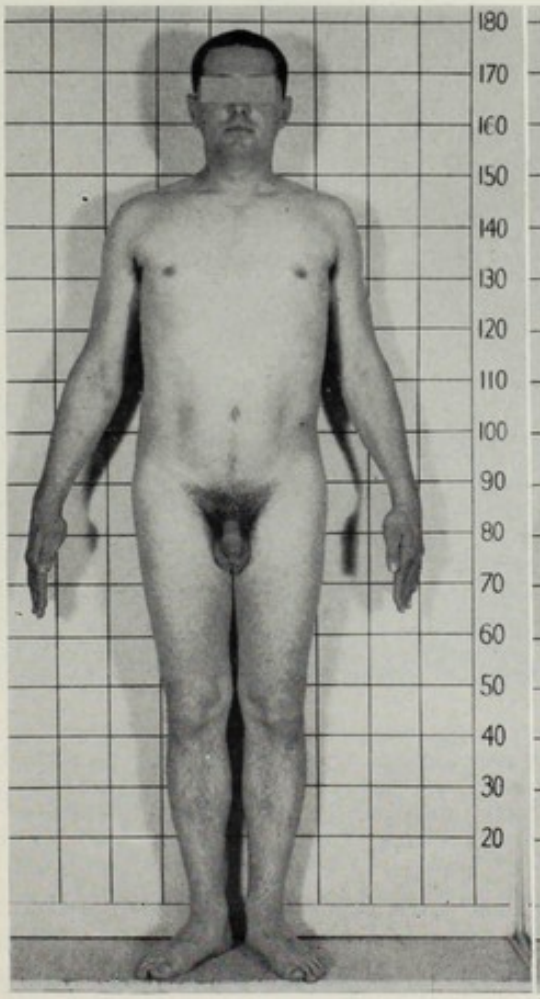


Fig. 26*C*.

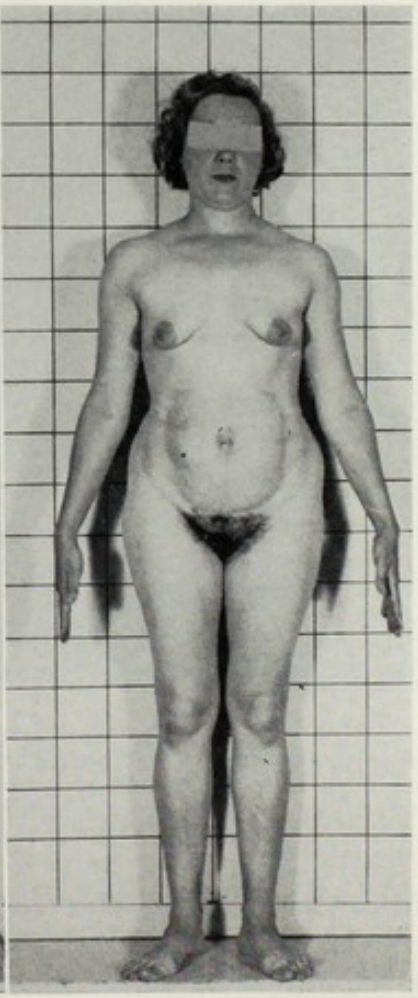


Fig. 26*D*.

Figs. 26*B*-26*D*. For legend see opposite page.

I have not observed calcification of the ascending aorta in the Marfan syndrome. This fact may be helpful in differentiating the aortic involvement of the Marfan syndrome from that of syphilis in which calcification is frequent.[252]

Involvement of the aortic cusps has already been described. The aortic valve is sometimes bicuspid (e.g., Fig. 29); whether this is the case in the Marfan syn-

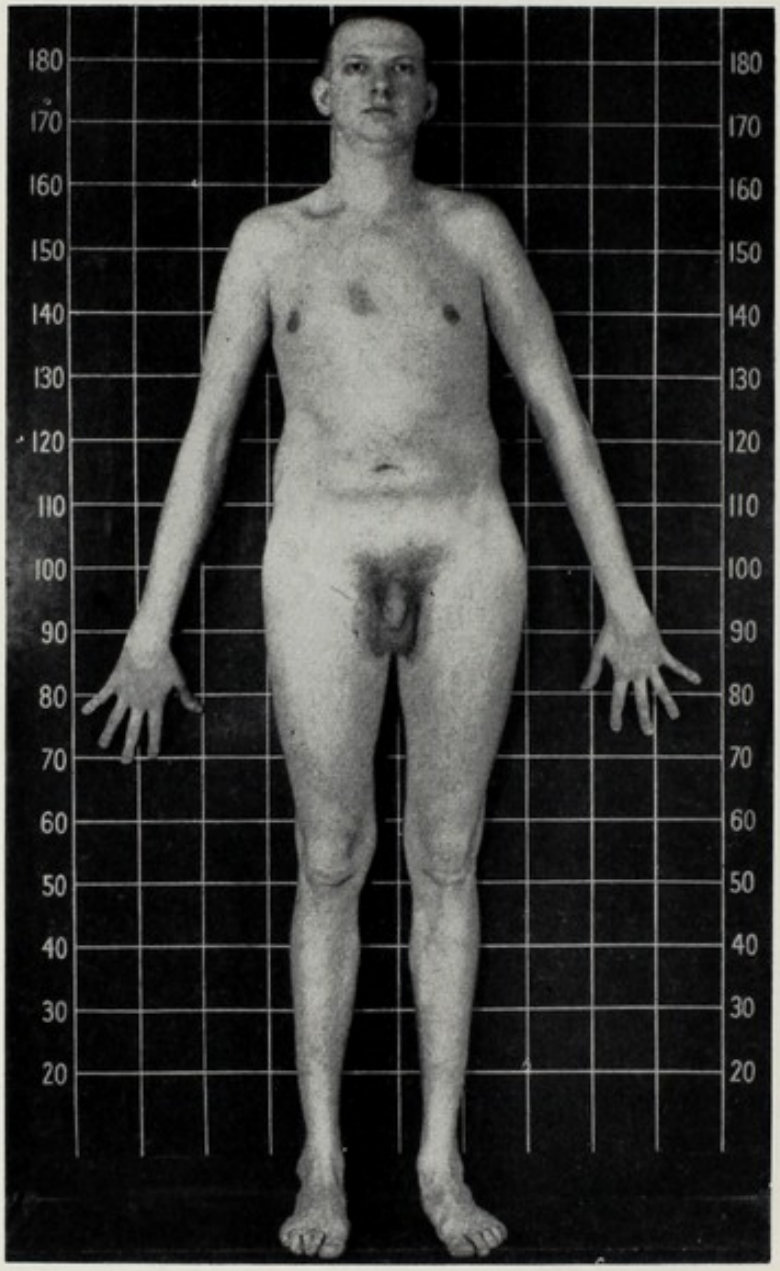


Fig. 27*A*. E. K. (760410), 26 years of age, was admitted for consideration of surgical correction of an abdominal aneurysm. The skeleton was considered to be typical of the Marfan syndrome. Both lenses were displaced upward and outward. The patient was partially deaf, but this was of the conductive type, was largely limited to the left ear, and was readily accounted for on the basis of old otitis media. (From McKusick, V. A.: Ann. Int. Med. **49**:556, 1958.)

drome more often than one would expect with this relatively frequent abnormality is not certain. The mitral cusps and chordae tendineae may be redundant, with resulting mitral regurgitation. Subacute bacterial endocarditis may become engrafted on the valvular abnormality.[92,108,170] (See Figs. 27*A* and 27*B* for a case of bacterial endocarditis with the Marfan syndrome.) Murmurs of obscure origin

are frequently encountered. Some may be on the basis of redundant chordae tendineae with incompetence of atrioventricular valves. These murmurs may be partially musical. In one patient (S. C., 575946) with a musical mitral systolic murmur, autopsy revealed a tear at the insertion of the posterior mitral cusp, amounting to a partial avulsion of the cusp.

A striking early systolic click heard not only at the aortic area but also at the apex is a frequent sign of dilatation of the ascending aorta in the Marfan syndrome. It is thought to represent a snapping of the aortic wall early in systolic

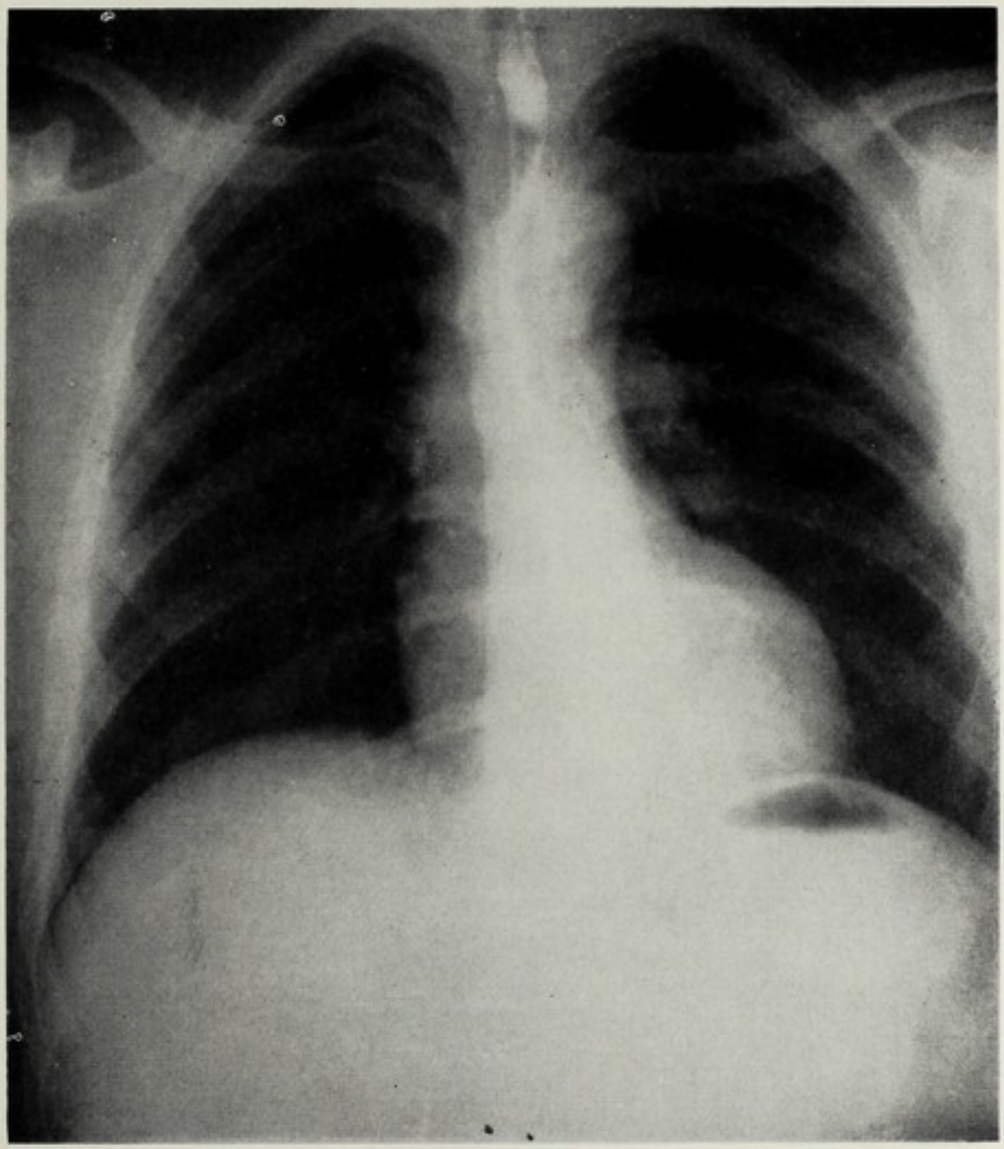


Fig. 27*B*. There was no aorta regurgitation. The thoracic aorta seems normal radiologically down to a point just above the diaphragm, where it became abruptly larger. (From McKusick, V. A.: Ann. Int. Med. **49**:556, 1958.)

ejection.[253] Extracardiac clicks and other extraneous sounds are frequent because of the thoracic deformity, the loose-jointedness of the bony thorax, and the cardiac enlargement.

It is now clear that involvement of the mitral and possibly the tricuspid valve with regurgitation may be the predominant cardiovascular lesion in the Marfan syndrome and may lead to early death. Figs. 4*E* and 29 illustrate such

cases. Redundancy of the chordae tendineae may be responsible, at least in part, for the valvular dysfunction. Tricuspid, or even quinquecuspid, mitral valves have been present in some cases. See Fig. 14*C* for reference to mitral anomaly.

I had previously thought that occasionally the pathophysiologic effects of interatrial septa defect can dominate the clinical picture. However, the only patient in my experience who might corroborate this impression (Fig. 29) proved on autopsy to have an intact atrial septum. Because of the gracile habitus which patients with atrial septal defect frequently display, the Marfan syndrome is fre-

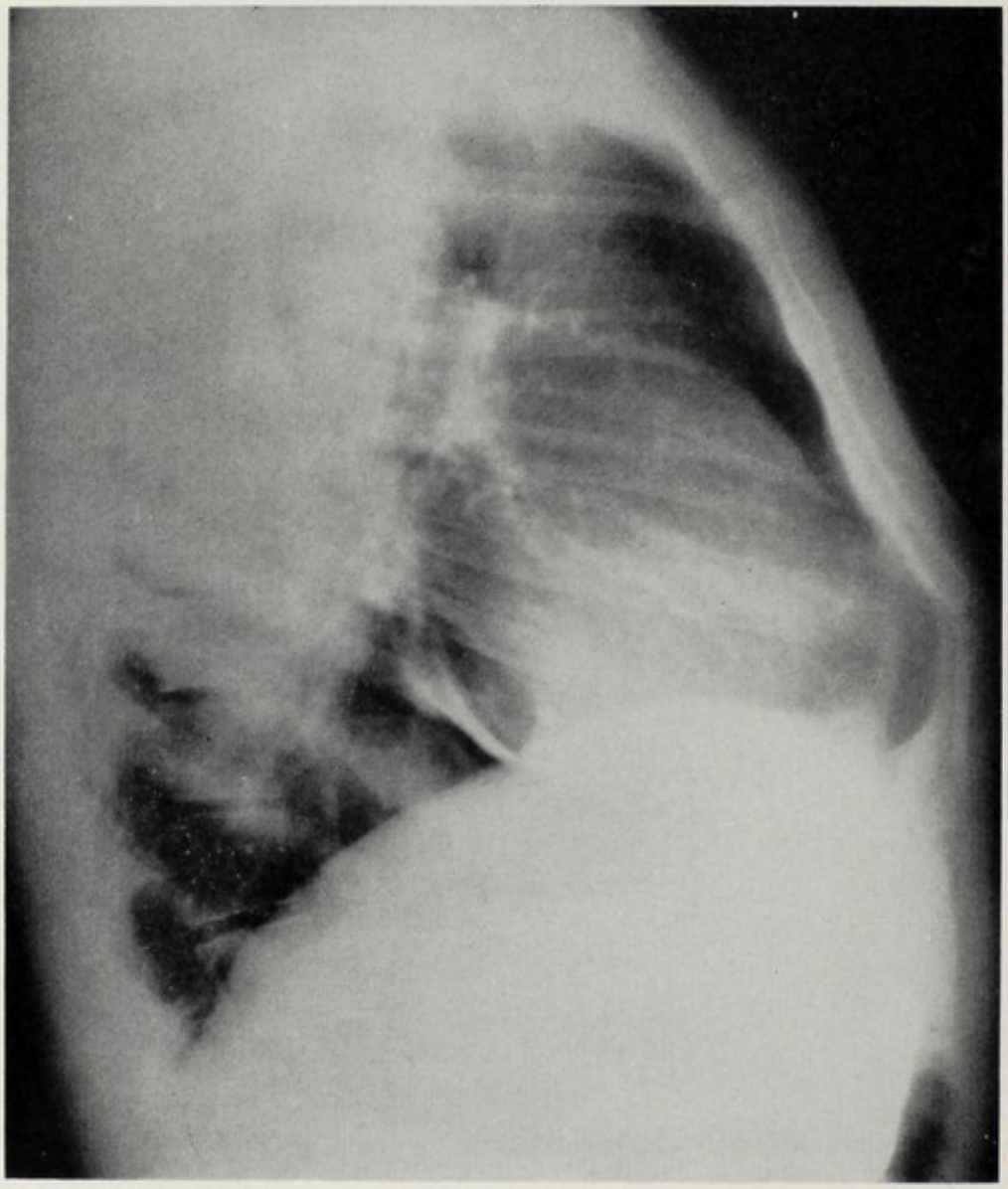


Fig. 27*C*. The deformity of the sternum is evident. (From McKusick, V. A.: Ann. Int. Med. **49**:556, 1958.)

quently suspected. Such patients indeed have arachnodactyly; however, most do not have ectopia lentis or the characteristic family history to allow one to conclude that the true Marfan syndrome is present.

In 1955 I wrote as follows: "Notwithstanding careless statements of previous reviews, no autopsy-confirmed or even clincally convincing case of interventricular septal defect has been reported." Since that time, however, at least one case of

autopsy-proved ventricular septal defect with the Marfan syndrome* has been reported[292] and I have had an opportunity to study such a case, a 15-year-old girl with typical Marfan syndrome including ectopia lentis and clinically typical VSD confirmed by cardiac catheterization (Fig. 30).†

In Cockayne's case[33] the diagnosis was only suspected clinically. There is a report[86] of possible tetralogy of Fallot with Marfan's syndrome. Two cases of

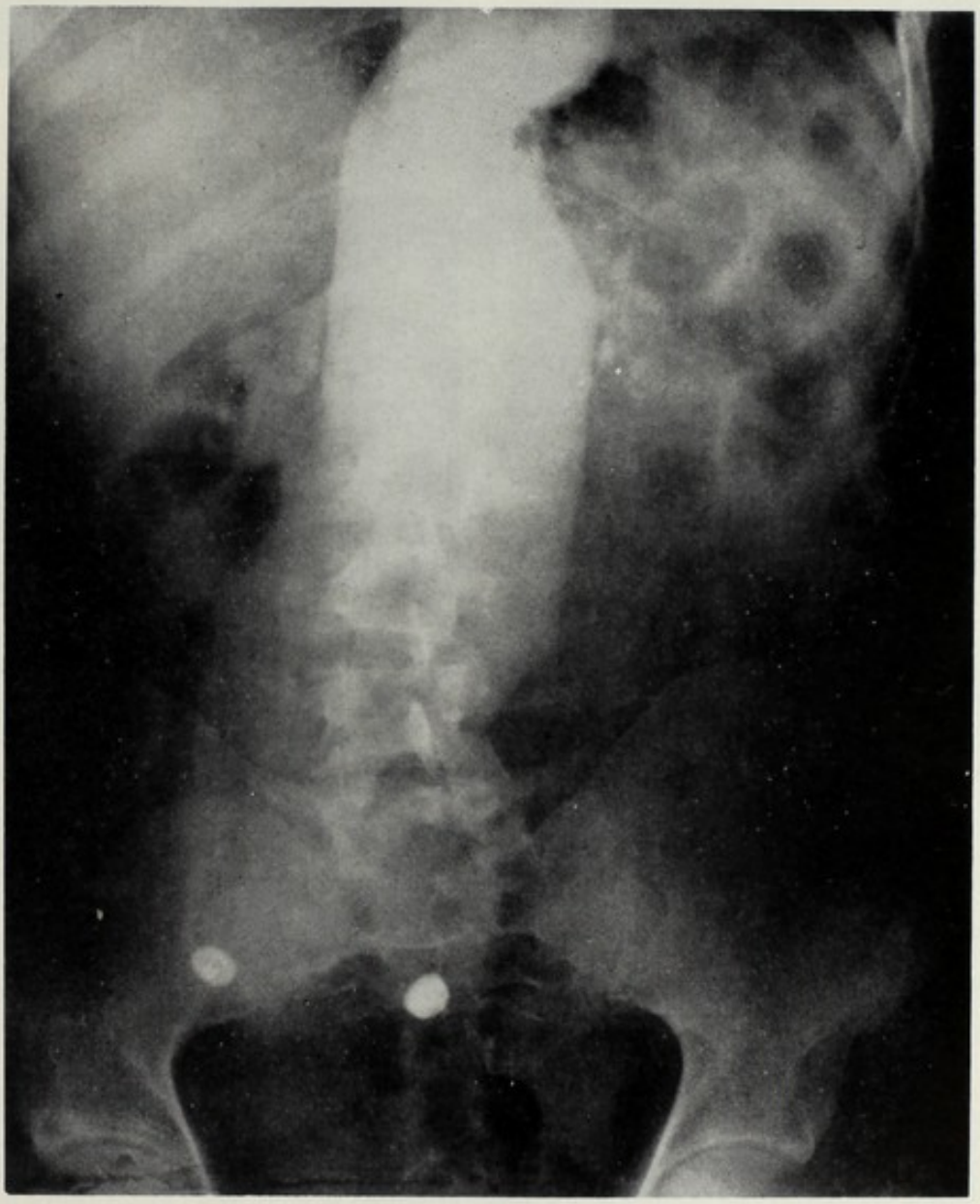


Fig. 27*D*. The enlargement of the aorta was shown by aortography to be cylindric and to extend the full length of the abdomen. The aneurysm was easily felt and seen on abdominal examination. (From McKusick, V. A.: Ann. Int. Med. **49**:556, 1958.)

*In this case[292] the diagnosis of the Marfan syndrome is in some question, since there was no ectopia lentis and no positive family history. The patient had both patent ductus arteriosus and ventricular septal defect. The habitus suggesting that of the true Marfan syndrome may have been merely that rather often seen with these lesions.

†I am indebted to Dr. Donald Nelson and Dr. Peter Luchsinger of the District of Columbia General Hospital, Washington, D. C., for calling this patient to my attention and providing catheterization data.

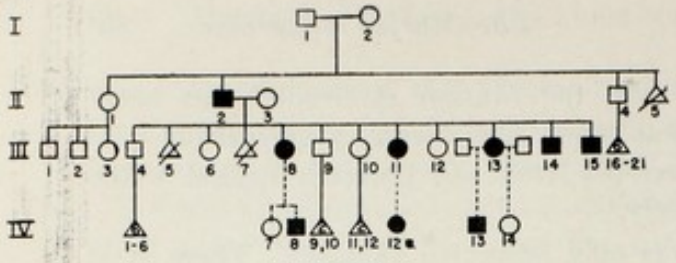


Fig. 28A.

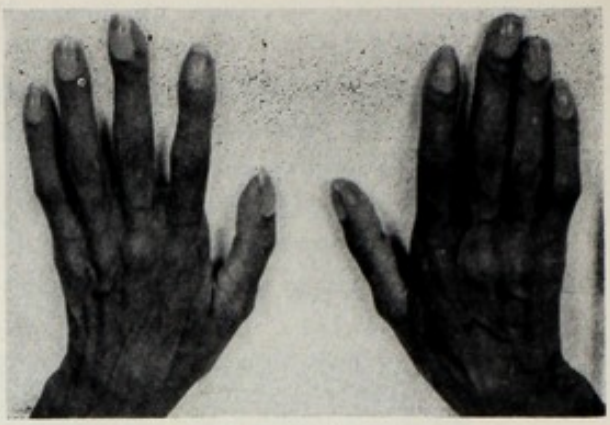


Fig. 28C.

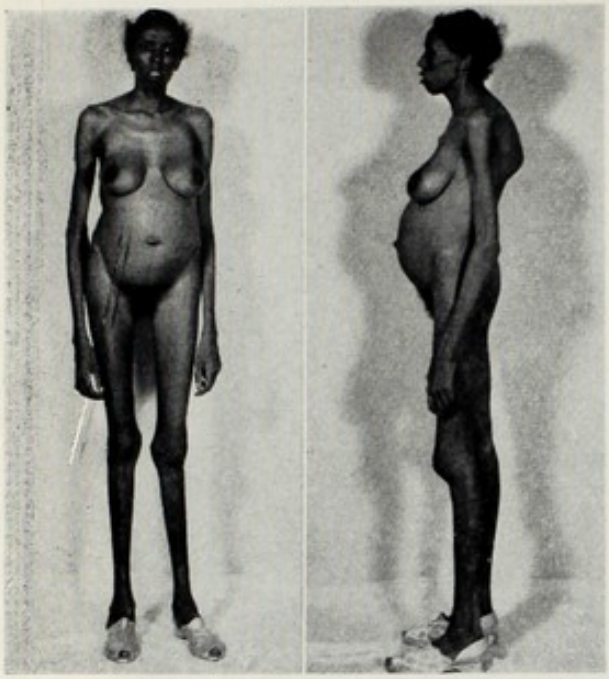


Fig. 28B.

Fig. 28D.

Figs. 28A-28D. *A*, Pedigree of the family of patient M. E. R. (III-11). Individual II-2 may have been the original mutant. However, illegitimacy is so much more frequent than mutation that one can never be certain. *B*, Patient M. E. R. *C*, The combination of arachnodactyly and clubbing of the fingers relates to Marfan's disease and subacute bacterial endocarditis from which the patient M. E. R. suffered. *D*, The mitral valve showing bacterial vegetation.

M. E. R. (J.H.H. 176836), a Negro woman born in 1929, is a member of a family which has been known to Johns Hopkins Hospital for about twenty-five years and in which at least 9 cases of Marfan's syndrome (including this patient) have occurred. (The patient is individual III-11 in the pedigree presented in Fig. 28A.) The father of the patient, a well-documented instance of this syndrome, died of dissecting aneurysm of the aorta at the age of 43 years. Of four siblings of the patient with this disease, three have signs consistent with interatrial septal defect.

The patient demonstrated bilateral ectopia lentis, severe myopia, pronounced dolichostenomelia, very poor muscular development, severe kyphoscoliosis, pes planus, and, by x-ray films, pulmonary emphysema with bleb formation. She recalled nothing suggestive of acute rheumatic fever. Most of her life she had been subject to exertional dyspnea.

The patient became pregnant early in November, 1953. After about four months there was increase in her lifelong exertional dyspnea and the appearance of ankle edema and orthopnea, which required two pillows. In early April, 1954, there was onset of evening fever, night sweats, and aching joints, especially knees and ankles. Tender red spots appeared on the palms and soles.

Physical examination revealed as new findings petechiae, embolic nodes of the palms, splinter hemorrhages of the nail beds, and clubbed fingers. A loud harsh systolic murmur was audible over the entire precordium and the second pulmonic sound was accentuated.

Six blood cultures demonstrated a *Streptococcus viridans* which was late in growing out and atypical in morphology due probably to streptomycin and penicillin which had been administered before admission to the Osler Medical Clinic. The patient's white blood cell count was 10,000 to 12,000 and hematocrit 26 per cent. Treatment with penicillin in large doses was instituted with seemingly successful results.

On the patient's twentieth day in the hospital premature labor began as a result of septic infarction of the placenta, and an infant weighing 1,700 grams was born. The infant, which demonstrated pronounced dolichostenomelia, lived only a very few minutes. Autopsy in the case of the infant revealed no cardiovascular lesion, and the cause of death in not completely clear. There was an abnormality of pulmonary lobation such as is frequently seen in the Marfan syndrome.

(Continued on opposite page.)

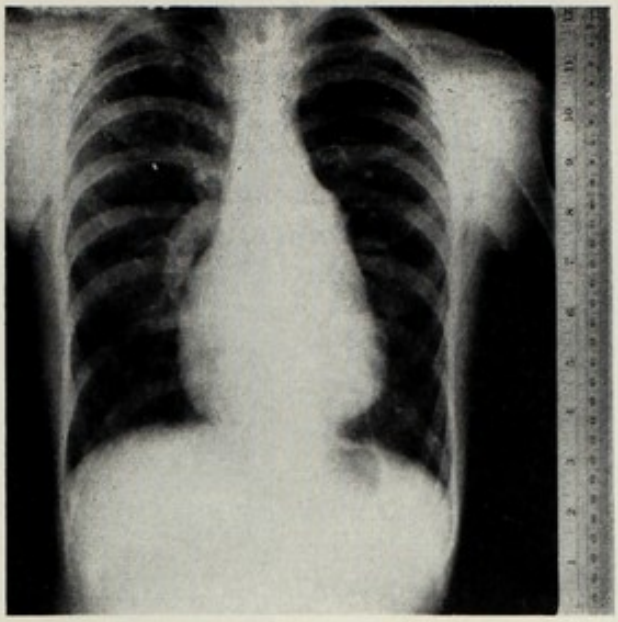


Fig. 29. X-ray film in case of Marfan syndrome in which atrial septal defect was incorrectly thought to be present.

M. E. C. (J.H.H. A98174), born in 1940, was first referred to Dr. Helen B. Taussig in November, 1952, for investigation of a congenital heart defect with paroxysmal tachycardia. The father was 76 inches tall and asthenic and had a spinal curvature and ectopia lentis but no evidence of cardiovascular abnormality. A single sibling, male, was unaffected.

In this case a heart murmur had been described before the age of 2 years. Except that she never gained weight well and could not keep up with the other children at play, the patient was relatively well until April, 1952, when she had a first attack of paroxysmal tachycardia lasting several hours. Two more attacks occurred, one in May and a second in September, 1952.

The patient was a tall, slender white girl of better than average intellect. She was 64 inches tall and weighed 79 pounds. She wore glasses for ectopia lentium, which had been discovered at the age of 5 years. The palate was high. The chest was long, with convex scoliosis of the thoracic spine toward the right. The heart was not enlarged. However, a loud systolic murmur accompanied by a thrill was heard in the second and third intercostal spaces to the left of the sternum. The patient stood with rather marked pronation of the feet at the heels and moderate abduction. There was minimal genu valgum.

On fluoroscopy the right atrium was seen to be enlarged and the main pulmonary artery was prominent and active. There was moderate hilar dance. The left atrium and the ventricles appeared to be normal in size. During the recording of the electrocardiogram short paroxysms of atrial tachycardia occurred. There was a higher degree of right axis deviation than would have been anticipated as normal for this age. Leads II and III showed changes in the ST-T complex interpreted as "right ventricular strain pattern." The QRS complexes were notched in most leads. X-ray films revealed no structural abnormality of the vertebrae.

It was my previous impression that this patient had atrial septal defect. It was commented that surgical repair is probably worth while in such a patient, provided there is no evidence of involvement of other parts of the cardiovascular system or too severe skeletal involvement.

Subsequent events and the findings of autopsy proved the diagnosis of ASD to be incorrect Late in 1955 a spinal operation for correction of deformity was performed. Thereafter, an infection with chronically draining sinuses necessitated readmission to the hospital. Following a débridement operation the patient died during a sudden bout of arrhythmia. The findings in the heart included bicuspid aortic valve and multicuspid mitral valve. The left coronary artery had two accessory ostia at the sinus of Valsalva. The mitral valve had five cusps and the line of closure was thickened and nodular. Histologically this area showed "basophilic degeneration." The interatrial septum was perfectly intact. There was pulmonary emphysema. (I am indebted to Dr. John Franklin of Norfolk, Virginia, for information on this patient.)

(From McKusick, V. A.: Circulation **11**:321, 1955.)

(Legend continued from opposite page.)

The patient died of uncontrollable heart failure about two weeks after delivery. Fig. 28*D* shows the mitral valve with its vegetations in this case. No evidence of rheumatism was discovered. The media of the aorta and the pulmonary artery showed extensive chromotropic degeneration.

Chest x-ray in this patient (not illustrated) showed increased bronchovascular markings and evidences of bleb formation. At autopsy all lobes of the lungs, especially the upper ones, were cystic. Some of the cysts were as much as several centimeters in diameter. They were lined by columnar epithelium and contained strands of smooth muscle in the walls.

(From McKusick, V. A.: Circulation **11**:321, 1955.)

tetralogy of Fallot with stigmata suggestive of the Marfan syndrome (see Fig. 31 for one of these) have come to my attention,[92] but the absence of involvement of other members of the family and the failure of ectopia lentis to be found in the patients make the diagnosis of the Marfan syndrome uncertain. I am inclined to think that these are not cases of the Marfan syndrome. In yet another case (Fig. 32), dolichostenomelia (without, however, an abnormal segment ratio), congenital clouding of the cornea, and large interventricular septal defect are associated. Four siblings, two older and two younger, are unaffected as are all other members of the family, in so far as can be determined. Furthermore, no abnormality of the lens is detectable. This case seems most likely the result of infection or other abnormality of the intrauterine environment.

Van Buchem[295] concluded that mild pulmonary stenosis was present in one of his patients. However, the systolic gradient across the valve was only 35 mm. Hg. It is possible that there was only relative pulmonary stenosis from dilatation of the pulmonary artery (which was present).

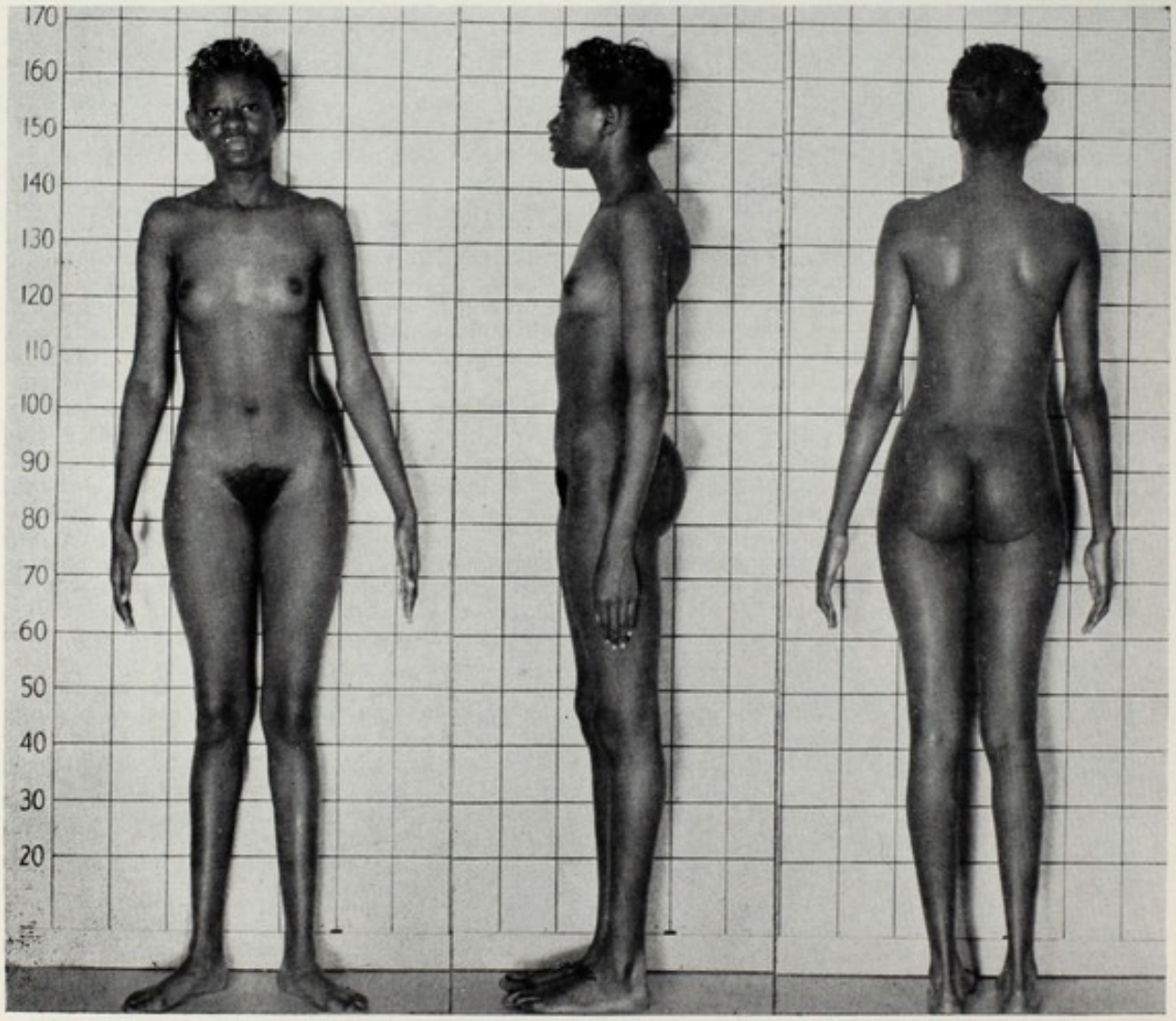


Fig. 30. G. H. (815634), 15 years of age, has bilateral subluxation of the lenses, spinal curvature, and the habitus typical of the Marfan syndrome. Clinical signs of ventricular septal defect are corroborated by the data of cardiac catheterization (courtesy Dr. Donald Nelson and Dr. Peter Luchsinger, District of Columbia General Hospital, Washington). In my personal experience this is the only case of ventricular septal defect in a patient with Marfan syndrome. (From McKusick, V. A.: Bull. New York Acad. Med. **35**:143, 1959.)

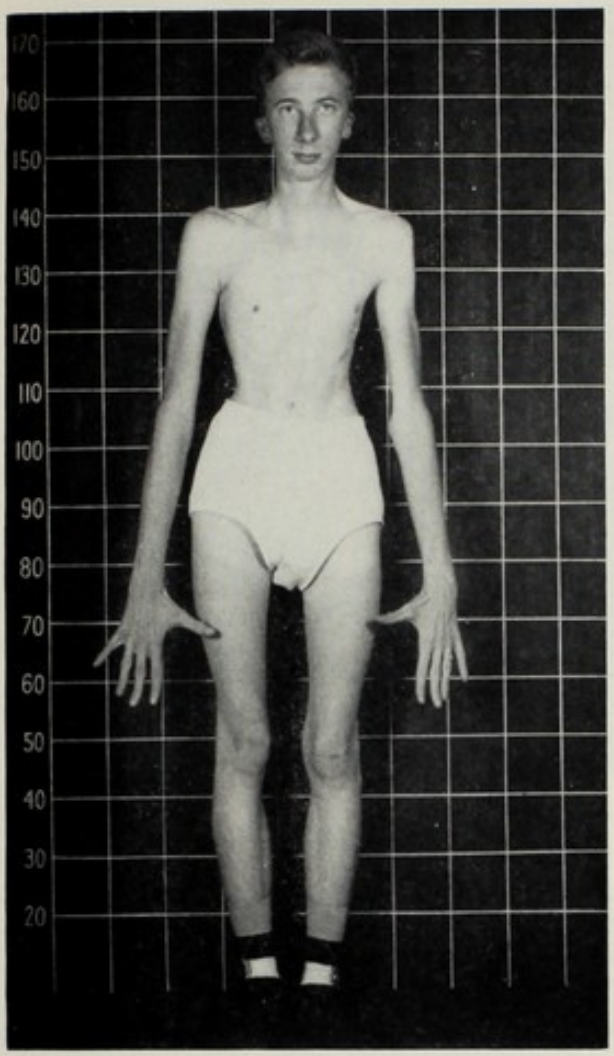


Fig. 31*A*.

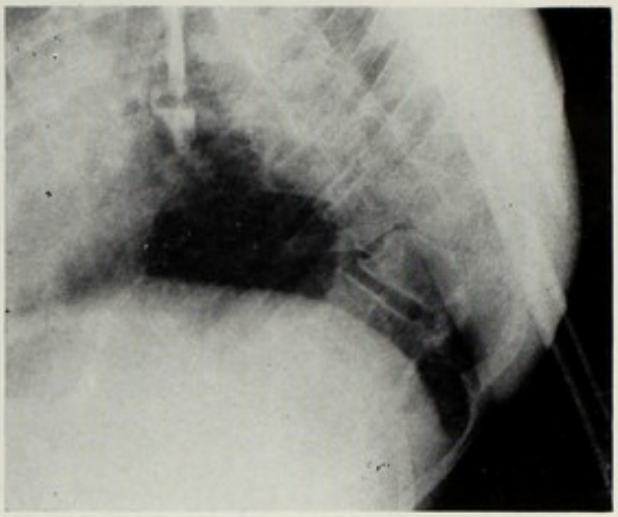


Fig. 31*B*.

Figs. 31*A* and 31*B*. A case (J.H.H. 525256) of tetralogy of Fallot with stigmata suggesting Marfan's syndrome. The absence of ectopia lentium and of other affected persons in the family makes the diagnosis of the Marfan syndrome dubious. There are malformed pinnae, long fingers (Fig. 31*A*) and hemivertebra (Fig. 31*B*), but these are nonspecific manifestations of the Marfan syndrome. Note also the facial asymmetry. (In yet another patient with tetralogy of Fallot [J.H.H. 482041] cleft palate, pes planus, talipes equinovarus, and long fingers are present, but in general the diagnosis of the Marfan syndrome is uncertain because of lack, as in the above patient, of ectopia lentis and positive family history.) (From McKusick, V. A.: Circulation **11**:321, 1955.)

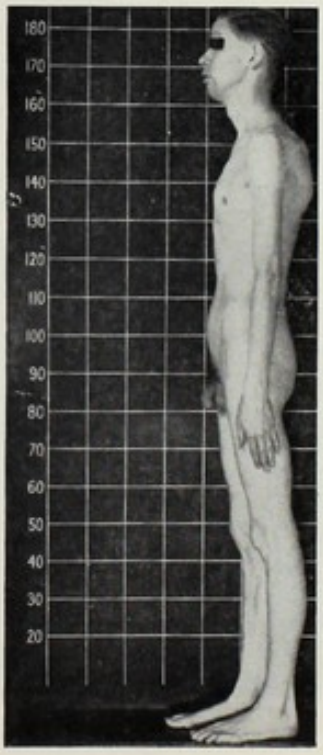


Fig. 32. The patient, R. R. (704121), 30 years of age, has clouding of the cornea, dolichostenomelia, and probable large interventricular defect. It is likely that this is due not to Marfan's syndrome but rather to intrauterine insult of unidentified variety. The upper segment-lower segment ratio does *not* suggest the Marfan syndrome.

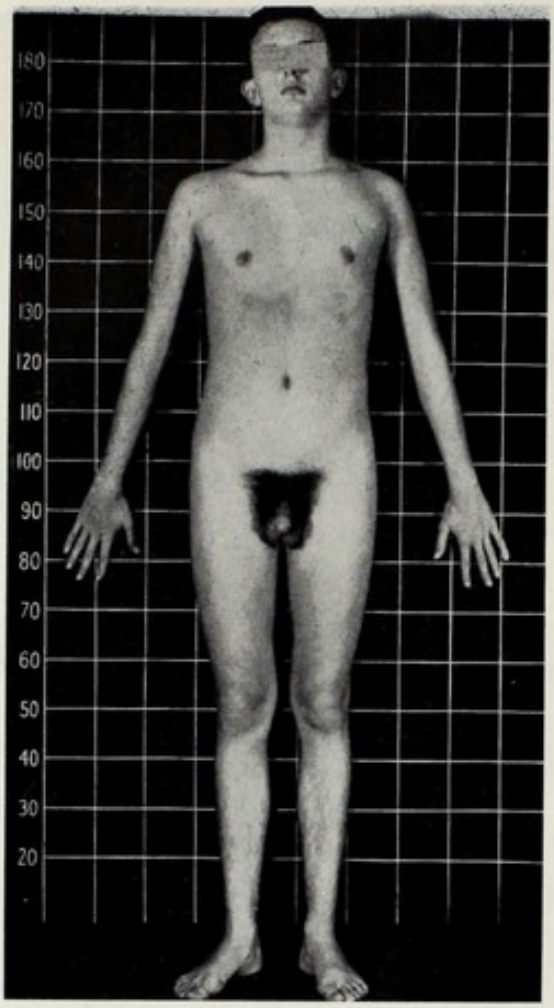


Fig. 33*A*.

Figs. 33*A*-33*E*. D. D. (758872), 16½ years old, has skeletal proportions compatible with the diagnosis of the Marfan syndrome (*A*), slight bilateral ectopia lentis, very small posteroanterior dimension of the thorax, and asymmetrical deformity of the anterior chest (*B*). Only mild pectus excavatum is present; however, its effects are greatly exaggerated by the small posteroanterior dimension, i.e., pronounced flat-chestedness. As in all cases of pectus excavatum, the thoracic spine is seen unusually clearly and little cardiac shadow is seen on the right of the midline (*C*). Both the spine and the sternum appear to impinge on the thoracic cavity (*D*). Multiple clicks in systole were present in this (*E*) as in other cases of the Marfan syndrome.

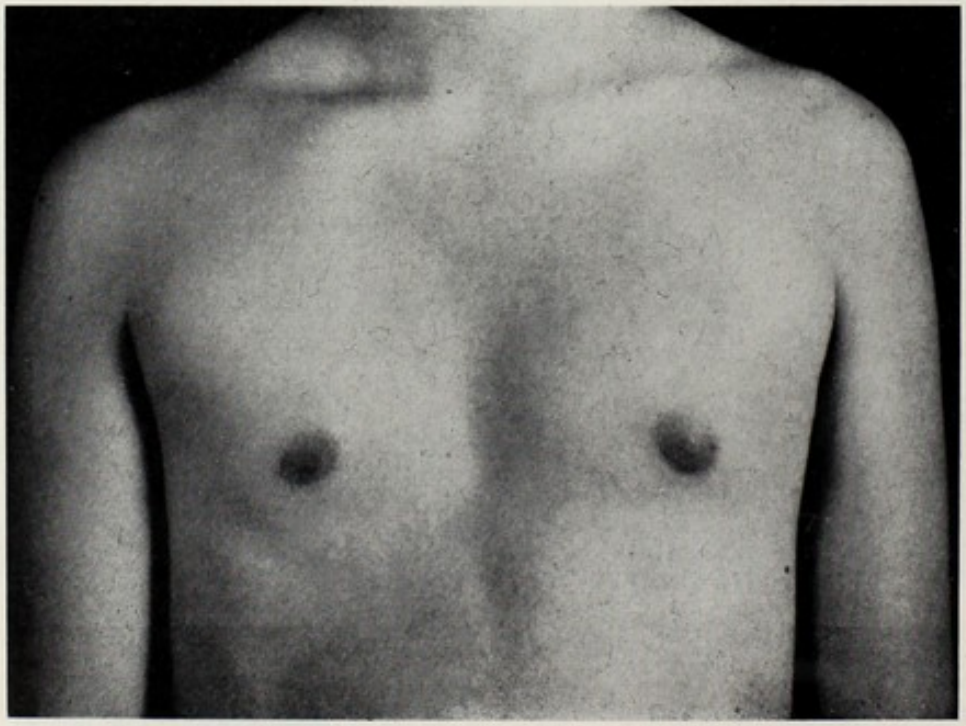


Fig. 33*B*.

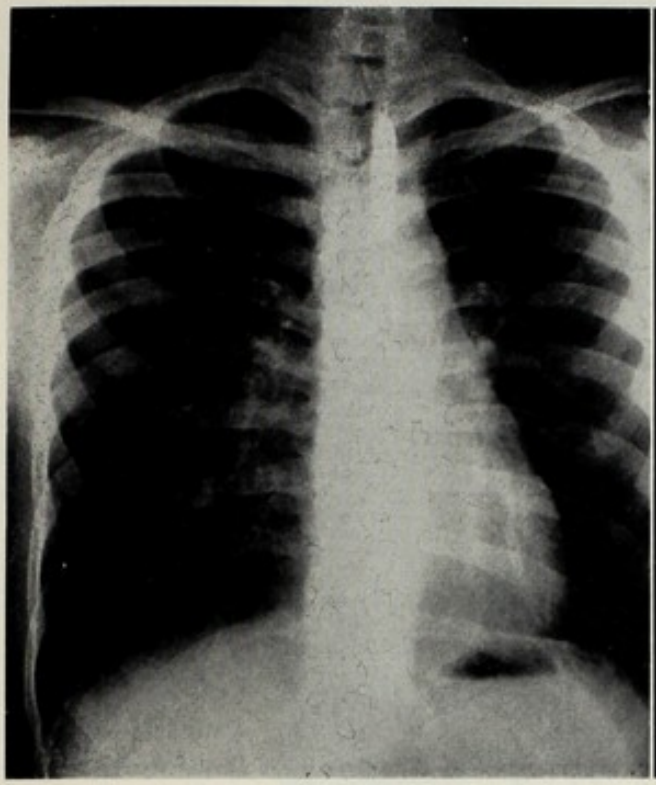


Fig. 33C.

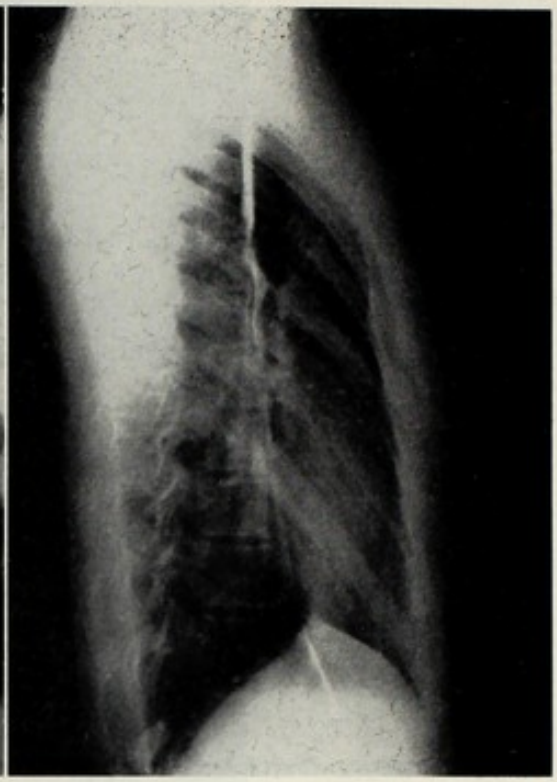


Fig. 33D.

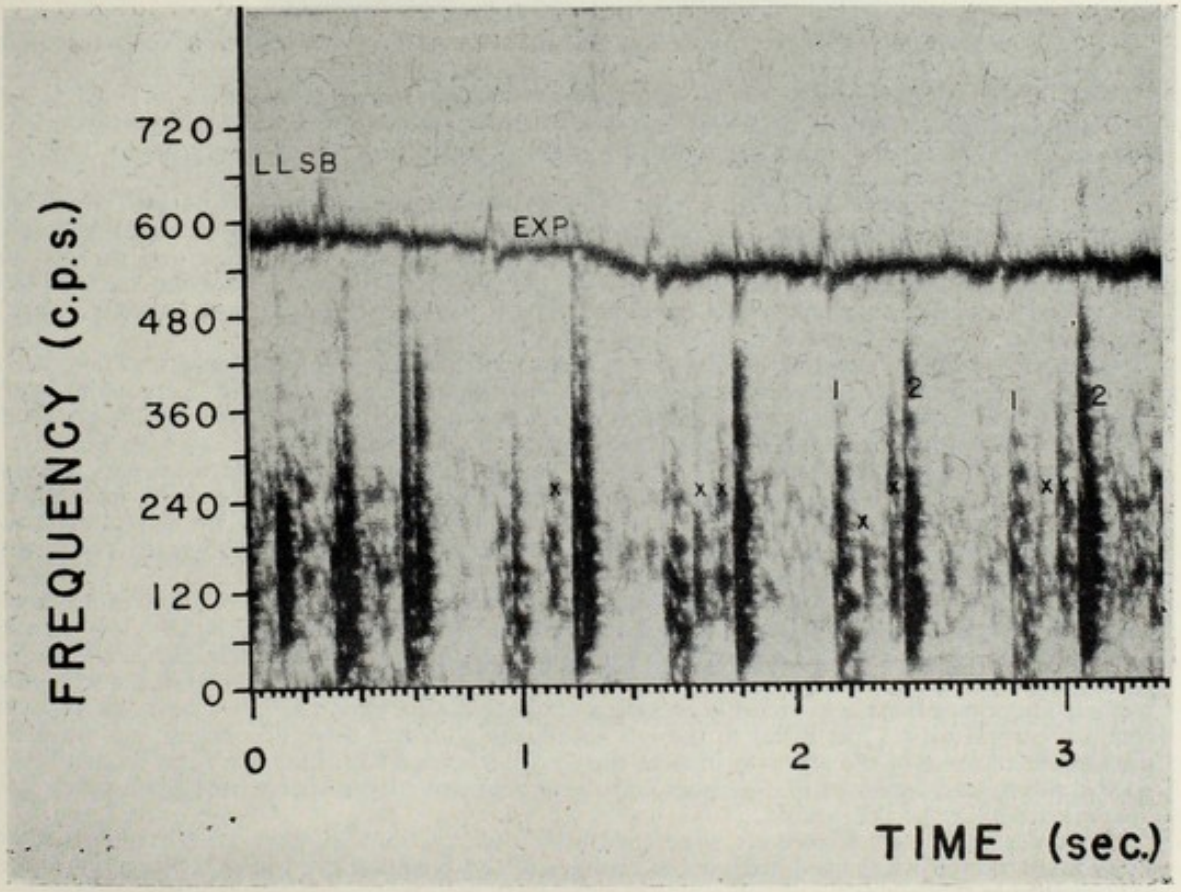


Fig. 33E.

Figs. 33C-33E. For legend see opposite page.

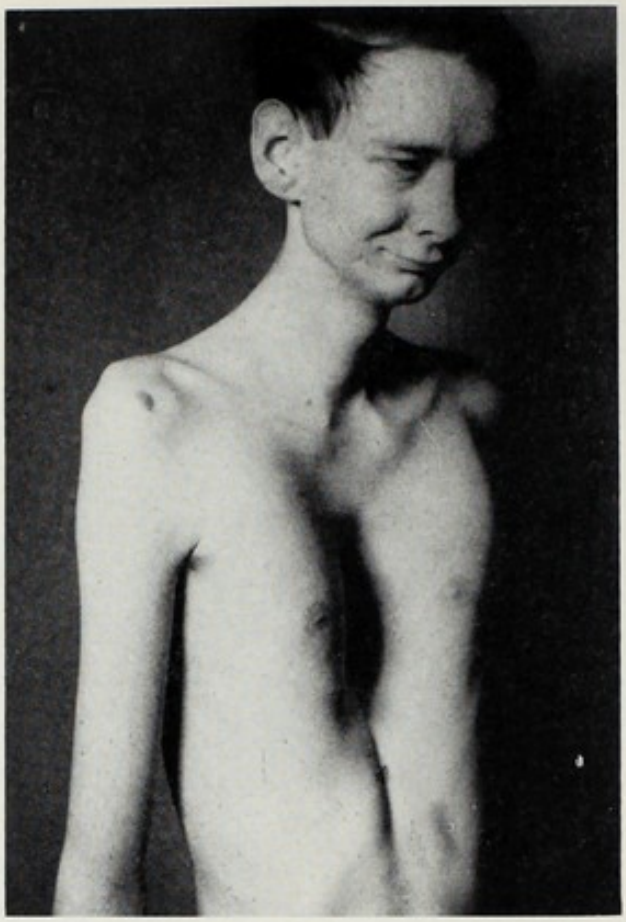


Fig. 34. Severe pectus excavatum in the Marfan syndrome. K. B., a 24-year-old white man, was admitted to the Medical College of Virginia Hospital after a year of increasing dyspnea. Twenty-four days before admission he had suddenly become markedly dyspneic and had severe palpitation and substernal pain. About two weeks before admission he had a second episode of pain and palpitation. Following the first attack his dyspnea progressed more rapidly than before and he also became orthopneic.

Physical examination revealed a slender, underdeveloped, undernourished man who was dyspneic even at rest. There was pronounced pectus excavatum. The heart was markedly displaced to the left with the point of maximum impulse in the midaxillary line and the seventh and eighth intercostal spaces. The left anterior chest wall heaved with each heart beat. There was a loud continuous machinery-like murmur over the base of the heart, with a systolic thrill. Blood pressure was 90/40 in the right arm and 110/32 in the left.

On Nov. 5, 1949, surgical repair of the pectus excavatum was performed.[21] The patient withstood the operation well and remained in a satisfactory condition until forty-eight hours later, when he suddenly went into circulatory collapse and died in less than two hours after developing pronounced distention of the cervical veins.

At autopsy the body measured 72 inches in length. The arms and legs were very slender and long with poor muscular development. The left leg was shorter than the right and showed partial clubfoot. Bilaterally the first and second toes were unusually long but the fourth toes were shorter than normal. There were flexion deformities of the fingers, deformed teeth with malocclusion, bifid uvula, and lumbar kyphosis.

The heart weighed 550 grams. The increase in weight and size was the result of left ventricular hypertrophy and dilatation. The pericardial sac contained 880 ml. of blood. The ascending aorta and first portion of the arch were markedly dilated, and, in addition, there was a dissecting aneurysm of the wall extending from an intimal tear about 3 cm. above the aortic ring to the point where there was slight coarctation of the aorta between the left subclavian and left common carotid ostia. Just distal to the left subclavian a second dissection began and extended throughout the rest of the aorta to involve the first portion of both iliac arteries. A small rent on the anterolateral surface of the ascending aorta represented the spot where perforation into the pericardial sac had occurred.

Histologically both dissections were endothelialized and showed some atheroma formation. In addition, the media showed pronounced changes of the type described in other cases of aortic abnormality in this series.

Siegenthaler[277] reports an equally severe instance of pectus excavatum in the Marfan syndrome.

(From McKusick, V. A.: Circulation **11**:321, 1955.)

Much has been written about cardiac disability in pectus excavatum.[45,48,105,157] Furthermore, since originally proposed by Flesch[50] in 1873, excessive longitudinal growth of the ribs has been thought to be the mechanism in many cases. As stated above, this appears to be the pathogenesis of the pectus excavatum in the Marfan syndrome. The hereditary nature of pectus excavatum has been appreciated.[114,135,147,153] Many times the patients with pectus excavatum are described as being unusually tall and thin, with spinal curvatures. Despite all these considerations, it has not been properly appreciated that the pectus excavatum may be but one manifestation of a generalized disorder of connective tissue in which primary involvement of the cardiovascular system may occur. In Fig. 34 we have presented the case of a 24-year-old man with severe pectus excavatum, who died of rupture of the aorta shortly after surgical repair of the chest deformity.[21] Autopsy revealed aortic changes typical of the Marfan syndrome. An aortic diastolic murmur had been present before operation. In the surgical literature, there are two cases which may have been instances of the Marfan syndrome. One patient[83] was 6 years old and was described as having "systolic and diastolic murmurs and cardiac incompetence." The other,[125] 23 years old and 74 inches tall, had congestive heart failure and atrial fibrillation and was specifically described by his physician as thin, gangling, loose-jointed, and round-shouldered. In another instance, a case reported by Sweet,[158] the patient has been discovered to have typical Marfan's syndrome.[179]

Wachtel and his associates[297] suggest that cardiac disability in pectus excavatum can result from four factors: (1) Due to twisting and distortion of the great veins, venous return may be impeded. (2) Restriction of diastolic expansion may further limit delivery of more blood on demand. (3) Impingement on the atria leads to supraventricular arrhythmias. (4) Respiratory reserve is decreased from impairment of the intercostal component of respiration. The heart may appear to be larger than it in fact is because of (1) displacement of the heart into the left hemithorax with mild clockwise rotation and (2) pancaking of the heart with increase in the transverse dimension. Electrocardiographic variations, e.g., rSr′ or rSR′ pattern in V_1, are secondary to the influence of the chest deformity on cardiac position and rotation.

Prolongation of the P-R interval of the electrocardiogram occurs commonly in the Marfan syndrome[11,30,103] but is usually absent except in the presence of aortic regurgitation. It is interesting to speculate that aneurysmal dilatation of the aortic ring may compromise atrioventricular conduction by pressure on the conducting tissue. Bundle branch block also occurs.[30,103,156] One patient (J. S., 543026), 18 years of age, with unequivocal ocular and skeletal signs of the Marfan syndrome has right bundle branch block as the only cardiovascular abnormality demonstrable by extensive studies, including cardiac catheterization. A brother of this patient, who probably suffers from a *forme fruste,* demonstrates inverted P waves bespeaking an ectopic pacemaker. The father, who was 78 inches tall, had aortic regurgitation and died suddenly at the age of 28 years; he had either ectopic pacemaker or prolongation of the P-R interval with superimposition of P waves on T waves.

There is one report[86] of dilatation of the left external carotid artery. No histologic study was made. Dilatation of the ascending aorta was also present in that patient. We have observed pronounced dilatation of the left common carotid in a

13-year-old boy (B. F., 724330), with characteristic skeletal changes of the Marfan syndrome and with ectopia lentis but no clinical evidence of change in the aorta. Except for these two rather similar observations, no abnormalities of peripheral arteries have been described. Dissection may, of course, extend out branches of the aorta for an appreciable distance, but the media has usually appeared normal histologically.[85] In one case (S. C., 575946), the splenic artery was friable at autopsy and was found to be the site of cystic medial necrosis. Varicose veins probably occur more frequently and in more severe form in the Marfan syndrome than ordinarily would be expected.[301]

The coarctation has rarely been of great functional significance. There is no reason, however, why it might not be in occasional instances. Seemingly the coarctation has not been resected in any case of the Marfan syndrome. Dissecting aneurysm occurs with increased frequency in coarctation,[67] and although the hypertension is doubtlessly a contributing factor, the possibility of a connective tissue abnormality being responsible for both the coarctation and the dissection must be considered. One patient in my series (L. Y., J.H.H. 392843) has hypertension and a small left radial pulse but no significant discrepancy in arm and leg pressures.

The changes at the aortic isthmus in the Marfan syndrome (see Fig. 15*C*) have many of the features of what the angiocardiographers, who are largely responsible for discovering the disorder, call "pseudocoarctation." Even the "figure-of-three" sign may be present on conventional radiography of the chest. One would be suspicious of the presence of the Marfan syndrome in a patient such as that described by Steinberg[283] in whom pseudocoarctation was associated with dilated sinuses of Valsalva.

The combination of aortic regurgitation with coarctation may confuse the diagnosis of coarctation. The pulses in the legs may seem normal unless the absence of the collapsing quality is noted.

Whitfield and his associates[180] described a case of simple hypoplasia of the aorta with the Marfan syndrome. They suggested that the increased resistance resulting from the reduced aortic diameter might have been responsible, at least in part, for the cardiac hypertrophy observed in their case. Since hypoplasia of the aorta as a primary entity is a nebulous entity at the best, this interpretation is suspect.

Hypertension, presumably without coarctation, was present at the age of 12 years in one reported case.[233] In another patient,[311] hypertension had been present from at least the age of 24 years and the Smithwick operation was performed at the age of 27 years. Hypertension has been present at least from the age of 26 years in two of our cases (L. Y., 392843; C. S., 596716). Presumably the presence of hypertension places the patient in double jeopardy from rupture of the aorta.

In one reported case,[142] bacterial endaortitis was thought to be present.

Other cardiovascular abnormalities have been described, but in most the diagnosis of the Marfan syndrome is insecure. For example, Burry[208] described a 37-year-old mentally defective woman with negative family history and no ectopia lentis who did, however, have a moderate degree of myopia and had presumably characteristic skeletal proportion. Supravalvular aortic stenosis was present. Bingle[202] described a 32-year-old woman with patent ductus arteriosus,

cystic medial necrosis of the aorta, dilatation of the aortic ring, and dissection of the ascending aorta with rupture into the pericardial sac. Grossly, there was an area of calcification and scarring in the wall of the left atrium and, histologically, fragmentation and sparsity of elastic fibers. Family history was not provided. Although the patient was 68½ inches tall, body proportions were not described. There were "no changes in eyes."

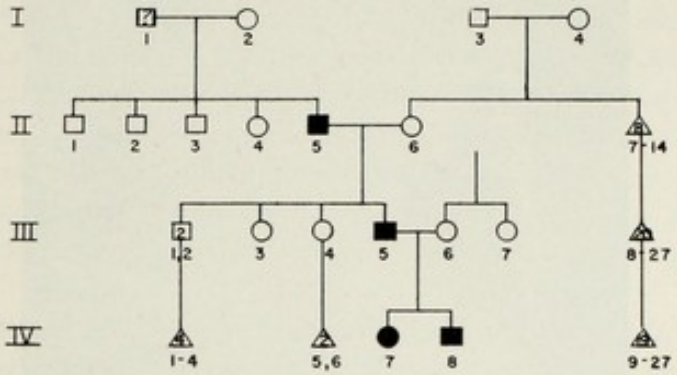


Fig. 35. By way of summary of the aortic complications of the Marfan syndrome, I present the story and pedigree of a family which was unusually heavily affected. Individual I-1 died suddenly in 1897 at the age of 47 years, presumably of apoplexy. This may have been dissecting aneurysm. The son of this man (II-5) died at the age of 27 years after a very brief illness of undiagnosed nature. He was 6 feet tall, was always very thin, and had been sent to Texas at one point for suspected tuberculosis. He became ill at noon one day and was dead at 5 A.M. the following day. He was said to have had no pain but developed hematuria in the last afternoon of the day he became ill.

Most of the remainder of the story of this family is told in the words of individual III-6, an intelligent observer and cooperative informant. Her husband (III-5) died in 1945 at the age of 32 years. "His heart condition was diagnosed as endocarditis by a heart specialist. He was apparently in good health up to two months prior to his death. He was 6 feet 2½ inches tall and in the last two years of his life he weighed more than ever before—175 pounds—and appeared to be in excellent health, except for his failing eyesight. He was working exceptionally hard due to the war time manpower shortage. He was appointed to a job which necessitated a great deal of coast-to-coast flying at high altitudes. It was on one of these trips that he was taken ill. He returned home, was put to bed and given medicine, to which he responded beautifully. He insisted on going on another trip and lived one month after his return. He was hospitalized, but his case was pronounced hopeless. He had a hernia operation two years before his death. A routine checkup before the anesthesia showed no heart condition then."

The daughter of this man (IV-7) "was born May 17, 1937. She was always frail. She and her brother had whooping cough when they were 6 and 5 years old. Her heart started enlarging at that time. She was extremely nearsighted and wore glasses from the age of 3 years. She had a bad spinal curvature that we first noticed when she was 10 years of age. The family doctor did not advise a brace or cast as she was so frail and her heart was getting increasingly worse. During her last illness, which lasted six weeks, the doctor said that her heart was just as it would have been in a person in his forties who had had rheumatic fever in his youth, that her heart was just worn out. She died at the age of 12½ years and was 5 feet 2 inches tall in spite of a very bad curvature. She had a brilliant mind and was at the top of classes in spite of her many handicaps. Both of the children were thin to the point of looking emaciated."

The brother of this girl (IV-8) "was born Nov. 27, 1938. He and Catharine looked like twins and were as nearly like their father as was possible. He was well as a baby and up to the time that he had whooping cough at the age of 5 years. After that long siege of coughing the doctor discovered that he had a heart murmur. His heart enlarged so that his chest protruded. He complained of chest pain occasionally. He died suddenly in August, 1946. His sister said after he died that he had complained of severe chest pains a couple of days before but he didn't tell anyone else. He developed hernia when he was about 2 years old, but it never seemed to bother him. He had a bad case of influenza the winter before he died and had a bad cough that lingered all winter and we felt hastened his death."

At age 7 years, this last patient was 53 inches tall and weighed 51 pounds. He showed arachnodactyly, hypotonia, hammertoes, thin and translucent skin, ectopia lentium, cardiomegaly, dilatation of the aorta, aortic systolic and diastolic murmurs, left axis deviation (by electrocardiogram), deformity (not described in detail) of the hip joints and skull (by x-ray examination). The lenses in this case were displaced downward and outward.

(From McKusick, V. A.: Circulation **11**:321, 1955.)

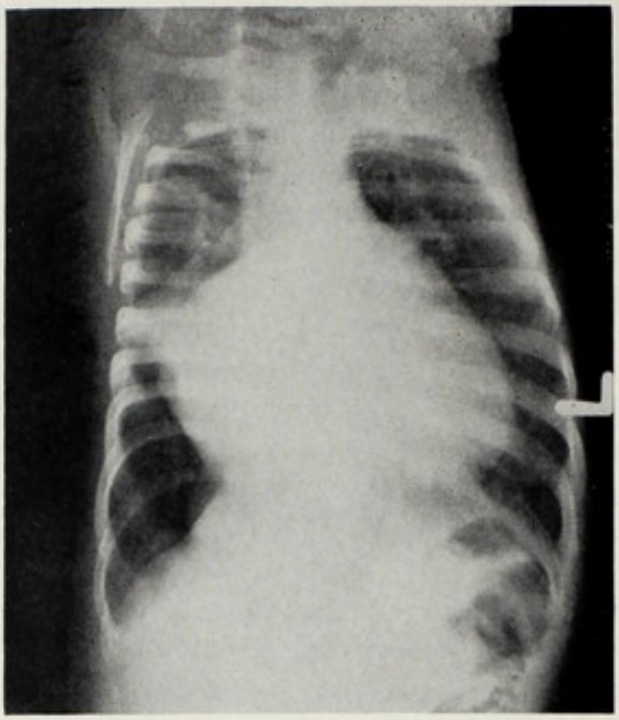


Fig. 36. X-ray film of the chest in infant B. J. P. A pulmonary anomaly is evident, as well as pronounced cardiomegaly.

B. J. P. (H.L.H. A93754) was born Nov. 9, 1951. She weighed 6 pounds 11 ounces and was thought to be healthy. The mother had had no pregnancies in the nineteen years between this one and that which occurred in 1933. The mother first learned of the child's heart murmur when the child was 4 months old. The child was never able to sit up or roll over by herself. When first seen at the age of 6 months, the following findings were recorded: The left side of the face was smaller than the right. Respirations were rapid (about 50 per minute). There was a pigeon-breast deformity of the thorax. The pulse was regular at a rate of 150 per minute. Femoral pulses were full. The heart was enlarged beyond the left midclavicular line. A systolic thrill was palpable over the entire precordium but was maximm in the left midprecordium. A harsh systolic murmur had the same location. The liver edge was 1.5 cm. below the right costal margin. There was no clubbing or cyanosis.

Fluoroscopy revealed great cardiac enlargement to both left and right with globular shape. The right ventricle was definitely enlarged in the oblique views. The right lower lung field had a distinctly abnormal appearance. It lacked the usual lung markings and was unusually radiolucent. There was a question of atelectatic lung (? right middle lobe) at the right heart border. By electrocardiogram the P waves were broad and notched. The P-R interval was 0.16 second, which is long considering the patient's age and heart rate of 150 per minute. Very large R waves in the leads from the left of the precordium suggested left ventricular hypertrophy. The hematocrit was 29.5 per cent, with hypochromic, microcytic cell indices.

Late in May, 1952, the patient developed physical and x-ray signs of consolidation in the right upper lobe and became febrile. These signs were altered little by the administration of several different antibacterial agents. The heart was extremely overactive and shook the whole bed. Occasionally the murmur assumed a to-and-fro quality, especially at the lower left sternal border. The liver enlarged in size. Subsequently signs of consolidation of the entire right lung appeared. On July 31, 1952, it was noted that both lenses were displaced mediad and that dilatation of the pupil with phenylephrine was only partially successful. Ophthalmologic consultants observed that the patient was extremely myopic with small lenses. In the last weeks of life there was an episode of hematuria related, perhaps to sulfadiazine therapy. Death occurred on July 10, 1952, when the patient was only 8 months old.

Autopsy (No. 23761) revealed that the right lung was partially atelectatic. The left lung was normal. The pulmonary artery was larger in circumference than the aorta. The foramen ovale was imperfectly closed. All chambers of the heart showed hypertrophy of their walls and dilatation. The hypertrophy of the right atrium was particularly marked. Microscopically there were no lesions of the myocardium. However, the wall of the pulmonary artery and, to a lesser extent, that of the aorta showed typical changes of Marfan's syndrome. The media contained vacuoles filled with the metachromatically staining material, and there was derangement and relative sparsity of elastic fibers. The wall of the pulmonary artery was thicker than that of the aorta. At the time of the gross examinations the bronchial tree was injected with radiopaque material and radiograms were made. To the surprise of the prosector no abnormality was identified.

(Continued on opposite page.)

Other Manifestations. Special attention is directed to certain manifestations which were indicated by dashed lines in the "pedigree of causes" presented in Fig. 44: e.g., in the cardiovascular system—coarctation* of the aorta,[49,92,168,295] patent ductus arteriosus,†[5] anomaly of valvular cuspation, interatrial defect,[9] and possibly pulmonary stenosis[295]; in the skeletal system—spina bifida occulta,‡ hemivertebra, and cleft palate[130,301]; in the eye—microphakia, hypoplasia, or aplasia of the dilator-pupillae muscle, coloboma lentis, and coloboma iridis.[242] These are not among the more common manifestations, yet they occur sufficiently often in the Marfan syndrome to be considered more than coincidental associations. Their occurrence is difficult to reconcile with a unitary theory of a connective tissue defect unless one assumes that the presence of said defect during embryogenesis provides an abnormal environment in which these anomalies, congenital malformations in the usual sense, occur with increased incidence. In accordance with this last and not improbable proposition, these particular manifestations can be considered *secondary* ones.

Whether deafness is a specific manifestation of the Marfan's syndrome and, if so, what its mechanism is,[87] cannot be stated at present. It is said to occur in 6 per cent of cases.[123] Everberg[223a] concluded that deafness is an integral feature and that it is of nerve (perceptive) type.

Pulmonary malformations are described in autopsy reports and various pulmonary complications in clinical reports.[63,78,92,111,118,124,136,161] (Fig. 36.) Repeated spontaneous pneumothorax has been described.[4,75,78,233] Spontaneous pneumothorax sometimes occurs as a familial disorder in the absence of evident Marfan syndrome[205] and also occurs in association with the Ehlers-Danlos syndrome (p. 150). Brock[206] favored the presence of hereditary lung cysts as the anatomic substrate.

Occasionally congenital cystic disease of the lung occurs, probably as an integral part of the Marfan syndrome. In patient M. R. (J.H.H. 176836; see Figs. 37*A* and 37*B*), very extensive disease of this type was discovered at autopsy. The stillborn child of this patient showed abnormal lobation of the lungs but no congenital cystic disease. Without an exhaustive review of the literature, it was possible to find three cases of cystic disease of the lung in which stigmata suggestive of the Marfan syndrome were described.

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*Mild coarctation is common (Figs. 15*A* to 15*D*). Occasionally severer, functionally significant coarctation is found.[295]

†Patent ductus arteriosus must be very rare in the Marfan syndrome.[194] Apert[9] is frequently quoted as having described such a case; his patient in fact had "trou de Botal" (patent foramen ovale), not "ductus de Botal."

‡Encephalocele in the forehead area occurred in one patient (J. D., 184805). Internal hydrocephalus is also reported.[113,124]

(Legend continued from opposite page.)

Comments. Obviously the most informative feature of this case is the advanced change in the pulmonary artery, which undoubtedly resulted in pulmonary regurgitation and was a leading factor in the infant's death at the age of only 8 months. Ectopia lentium, myopia, microphakia, arachnodactyly, retardation of ability to sit or roll over complete the picture of Marfan's syndrome.

This kinship illustrates one of the difficulties of genetic research in man. The illegitimacy of this infant and the presence of a legitimate wife of the father of the propositi made the utmost tact and resourcefulness necessary for collecting even these few data. The father of the infant is about 74 inches tall, has long hands and feet, and wears spectacles. Examination was not possible and no further pedigree information was obtained.

(From McKusick, V. A.: Circulation **11**:321, 1955.)

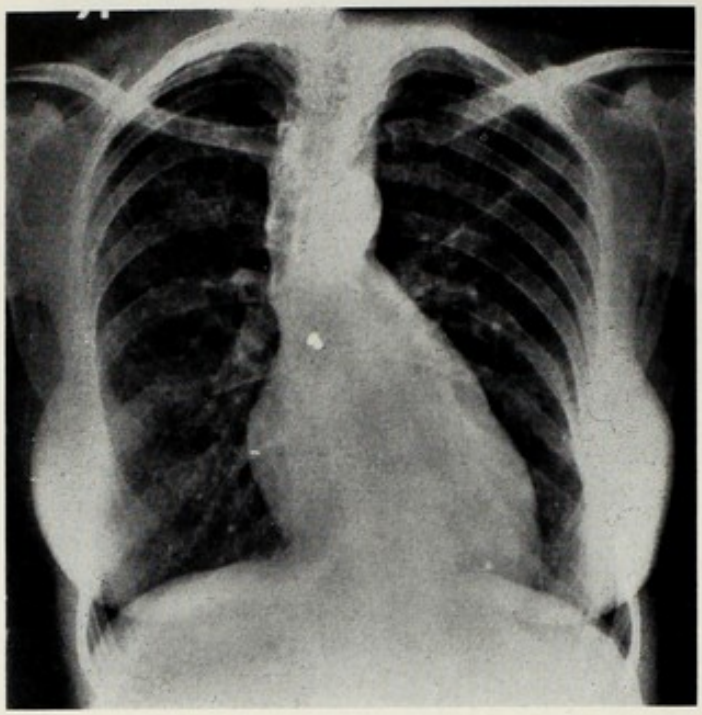


Fig. 37*A*. X-ray film of the chest in M. R. (176836) from whom other illustrative materials are demonstrated in Figs. 14 and 28. Scoliosis, cardiac enlargement, increased pulmonary markings, and questionable bleb formation in the lungs are demonstrated.

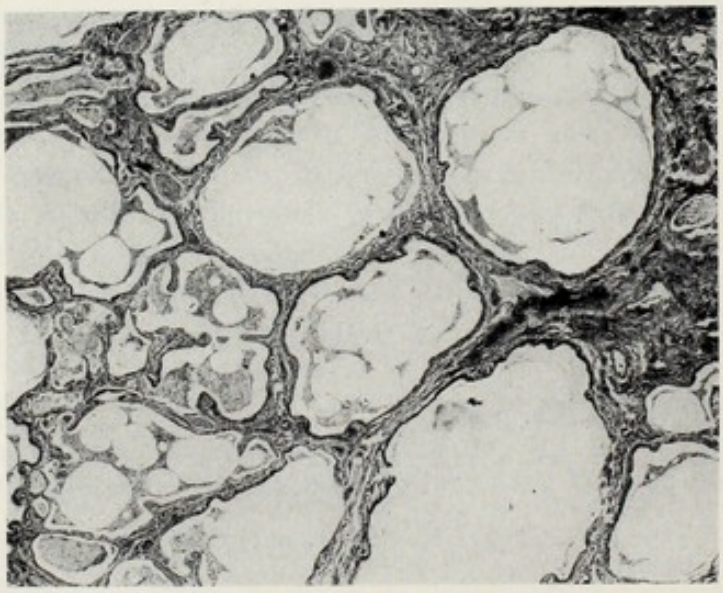


Fig. 37*B*. Same patient as shown in Fig. 37*A*. At autopsy the lungs weighed 1,350 grams. There was exudation of copious edema from the cut surfaces. Bilaterally the upper lobes were involved by large, bleblike cavities filled with large amounts of greenish fluid. To a lesser extent, the middle lobe and both lower lobes were cystic. Histologically the cysts were large and conglomerate and lined with columnar epithelium. Some of the cysts were several centimeters in diameter. In the walls of many, thin strands of smooth muscle were identified. This photomicrograph was made at a magnification of ×25; reduced ⅓. The pulmonary cysts are clearly demonstrated.

1. A 26-year-old male medical student (Case 9 in reference 111) had had three attacks of spontaneous pneumothorax. He died following an attack of severe chest pain. Dissecting aneurysm of the aorta with rupture into the pericardium was discovered. Histologically there was cystic medial necrosis. Both lungs showed diffuse cystic changes regarded as congenital.

2. A 26-year-old housewife (Case 13 in reference 111) with striking dolichostenomelia had had increasing dyspnea and, at the end of her second pregnancy, frank congestive failure. X-ray examination showed dilatation of the outflow tract of the right ventricle; ECG showed right axis deviation and the so-called P-pulmonale. Post-mortem examination disclosed diffuse cystic changes in both lungs and widely patent foramen ovale.

3. A 12-year-old child[132] was found at autopsy to have multiple simple cysts throughout both lungs, patent ductus arteriosus, aneurysm of the pulmonary artery, and anomalous coronary artery.

The case of Lillian[246] showed lung cysts, but the diagnosis of the Marfan syndrome is not completely certain.

Congenital cystic lung disease is probably a secondary component of this syndrome; i.e., the presence of the connective tissue defect during embryogenesis conditions its development but is not as directly responsible for it as for some of the other manifestations. The Marfan syndrome can join Hand-Schüller-Christian disease[148,164] and tuberous sclerosis[18,19] in the group of systemic abnormalities associated with a type of cystic disease of the lung.

The voice in patients with the Marfan syndrome sometimes is rather high pitched, with a timbre sufficiently characteristic that one author[204] thought he could recognize affected persons over the telephone.

Congenital cystic kidneys were described[203] in one case of arachnodactyly, but the evidence presented is inadequate for the reviewer to be certain that the genuine Marfan syndrome was present.

There are other manifestations that occur less frequently, often in no more than single reported cases, than those termed "secondary" above. In the case of these, it is more likely that the anomaly occurs only coincidentally with the bona fide features of Marfan's syndrome. When the case in question is a sporadic one, it may be valid to assume that the mutagenic factor might have caused more than one mutation simultaneously. Furthermore, in a given family, if the anomaly in question occurs in only one of the persons affected by Marfan's syndrome, or, better yet, if the anomaly also occurs in one or more members of the family unaffected by the Marfan syndrome, the manifestation in question should not be considered part of the Marfan syndrome.

Contrary to previous emphasis,[36,87,113,140] mental retardation is not, in my opinion, a component of this syndrome. Usually the patients are at least as bright as their siblings. Sometimes their innate intelligence is not fully realized because of the limitation of opportunities imposed by severe visual impairment and other physical handicaps. One patient in our series (F. D.), who died at the age of 14 years, wrote a book of verse, which was published, and composed short dramas for enacting by her playmates. In severe sporadic cases in infants and children, there may be mental retardation, but this has, in my opinion, a separate basis, possibly an independent mutation. Another basis for confusion is the fact that a picture including arachnodactyly and suggesting the Marfan syndrome occurs with acquired developmental abnormalities such as rubella and other maternal illness, maternal exposure to x-ray, and Rh incompatibility. These patients are likely to show mental retardation.

Haber[233a] points out that a rare but characteristic *skin lesion* may be associated with the Marfan syndrome. It is called Miescher's elastoma, or elastoma intrapapillare perforans verruciforme. The lesions occur particularly on the neck and grossly appear as small nodules or papules. Histologically these are cysts occupied by whorls of material which have the tinctorial characteristics of elastic fibers and which seem to have erupted into the epidermis from the upper corium. In 1952 Storck[289a] of Zurich described a patient with typical Marfan syndrome and skin lesions he classified as Kyrle's hyperkeratosis follicularis et perifollicularis in cutem penetrans. However, Miescher reported to Haber[233a] that the skin lesions were histologically more characteristic of Miescher's elastoma. In 1958 Anning[190a] of Leeds, England, described a young man in whom the diagnosis of Miescher's elastoma was made at the age of 18 years and who died at the age of 20 years of dissecting aneurysm of the aorta. (From the report of Meara[259a] one can conclude that Miescher's elastoma may occur also with the Ehler-Danlos syndrome.)

I have not seen unusual skin lesions in cases of the Marfan syndrome but have only recently, following the report of Haber, searched specifically for them. Miescher's elastoma may prove to be another external signpost to the presence of internal disease.

Prognosis: One man almost certainly affected with the Marfan syndrome (see Fig. 23) was killed accidentally at the age of 82 years. The oldest patient we have studied is 59 years old (H. B., 621760). He has severe aortic regurgitation. Bowers[204] describes two patients with the Marfan syndrome still living at 61 and 66 years of age. Among sixteen dead affected members of a large family, Bowers[204] found the average age at death to be 43 years in the males and 46 years in the females. One individual survived to 73 years; another died at 9 years.

INCIDENCE AND INHERITANCE

The sexes are equally affected[91,123] The aortic complications do seem to occur more frequently in men.[92] Manual labor may be responsible for this. There is no racial or subracial concentration of cases. The syndrome has been reported in Negroes,[53,92] Chinese,[31,66] Japanese,[168] Hindu,[20] and Jews.[91] It has, furthermore, been reported in natives of virtually every European country. Its incidence in the American Negro is probably essentially the same as in the white population. It has occurred in American Indians.[56]

The Marfan syndrome is an uncommon, but by no means rare, disorder. Its incidence is certainly far greater than the general conception of the medical public. The connective tissue defect of the Marfan syndrome is a leading cause of dissecting aneurysm of the aorta in the younger decades. There is reason to believe that there is an appreciable number of very mild cases *(forme fruste)* in whom the connective tissue defect has little or no effect on health or longevity.

Preposterously high estimates of the number of sporadic cases (those derived presumably from *de novo* mutation), as opposed to inherited cases, have been made. My own experience would indicate that no more than 15 per cent of all cases are new ones. Higher estimates, up to 70 per cent by some writers, are the result of incomplete family studies. How often this mutation occurs in a total population is hard to determine. Attempts at estimation of gene frequency or of

mutation rate are beset by difficulties, such as diagnostic doubts in mild cases, the impossibility of ascertaining mild cases unless severe cases are present in the family, variability in the age of onset of the aortic manifestations, and the mimicry of phenocopies. These difficulties attend the study of other incomplete dominant traits such as dystrophia myotonica. On the basis of as complete ascertainment as possible and using Haldane's method[249] which assumes that mutation replaces those genes lost because of reduced effective fertility of affected persons, Lynas[287] estimated the mutation rate to be 5 per million genes per generation in the population of Northern Ireland:

$$\mu = \tfrac{1}{2}(1-f)x = \tfrac{1}{2}(1-\tfrac{1}{2})\,\frac{36}{1{,}370{,}921}$$

x = proportion of persons with the Marfan syndrome in the population.
f = the effective fertility of affected persons, when unity is the average fertility.

When the mutation rate was estimated from the incidence of sporadic cases a similar estimate was obtained.[238] A minimal figure for prevalence of the Marfan syndrome was 1.459 per 100,000 of the population and for gene frequency, one-half this value, 0.729 per 100,000 genes.

The pattern of inheritance is that of a simple Mendelian autosomal dominant (Figs. 16, 24, 28, 35, and 38). Parental consanguinity has not been an im-

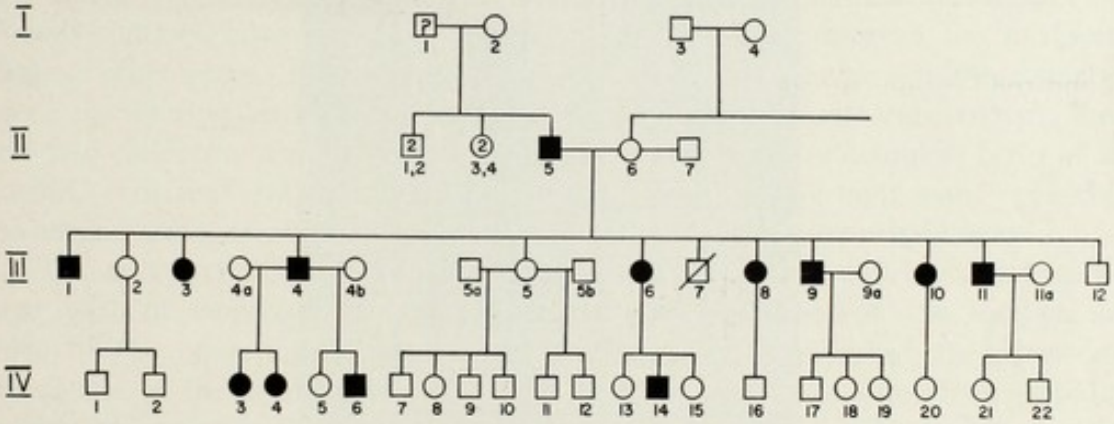


Fig. 38*A*. The Marfan syndrome in three and probably four and more generations. *I-1,* Died at 39 years of age after brief illness. *II-1,* John Peter S., died at age 50 years of dissecting aneurysm of aorta; had bad eyes. *III-1,* John A. S., born Sept. 29, 1913; has ectopia lentis and severe myopia; strabismus. *III-2,* Elizabeth S. M., born 1915; unaffected; requires hearing aid. III-3, Hilda S. S., born 1918; ectopia lentis, severe myopia, chest deformity, and dolichostenomelia. *III-4,* Joseph William S., born 1921; ectopia lentis, left myopia, and dolichostenomelia (see Fig. 38*B*). *III-5,* Frances S. Z. O., born May 9, 1922; small left posterior pole cataract; one of her six children deaf; probably unaffected. *III-6,* Naomi S. M., born Jan. 27, 1924; ectopia lentis, severe myopia, and "tongue-tied," with indistinct speech. *III-7,* died at one year of "summer complaint." *III-8,* Mildred S. D., born July 10, 1928; ectopia lentis and severe myopia. *III-9,* Frank Martin S., born April 9, 1931; ectopia lentis, severe myopia, dolichostenomelia, severe pneumonia twice as child, slight sternal depression and left chest deformity, and hernia. *III-10,* Nancy Patricia S. M., born 1932; ectopia lentis and myopia. *III-11,* Walter Raymond S., born Feb. 5, 1934; ectopia lentis, myopia dolichostenomelia, history of severe pneumonia, and chest deformity. *III-12,* Jerome S., born 1935; unaffected apparently, but had operation for severe strabismus in 1949. *IV-3,* Katherine S.; affected. *IV-4,* Mary Dorothy Diane S., born Dec. 19, 1943; bilateral immature cataract and ectopia lentis; affected. *IV-6,* Probably affected. *IV-14,* Harry Douglas M., Jr., born 1945; trouble talking like mother; chicken breast and myopia. *IV-15,* Sophronia M., born 1947; apparently unaffected; trouble talking distinctly. (In a family of 12 children—see generation III—the chance of 8 or more children being affected is almost one in four.) (From McKusick, V. A.: Ann. Int. Med. **49**:556, 1958.)

pressive feature, but exceptions are described.[26] In a few instances, a recessive mode of inheritance seemed to be indicated by the presence of multiple affected members of one sibship with ostensibly normal parents. In only one of the pedigrees of this type which have come to my attention has it been practicable to do thorough investigations of parents and patients (Figs. 18*A* to 18*D*). In the one kinship in which this was possible, I was forced to conclude that the mother was probably affected by a *forme fruste*. This woman had had at least three affected children by one man and one affected child by a second. The occurrence in one male and three females excluded the possibility of a sex-linked recessive trait. There was,

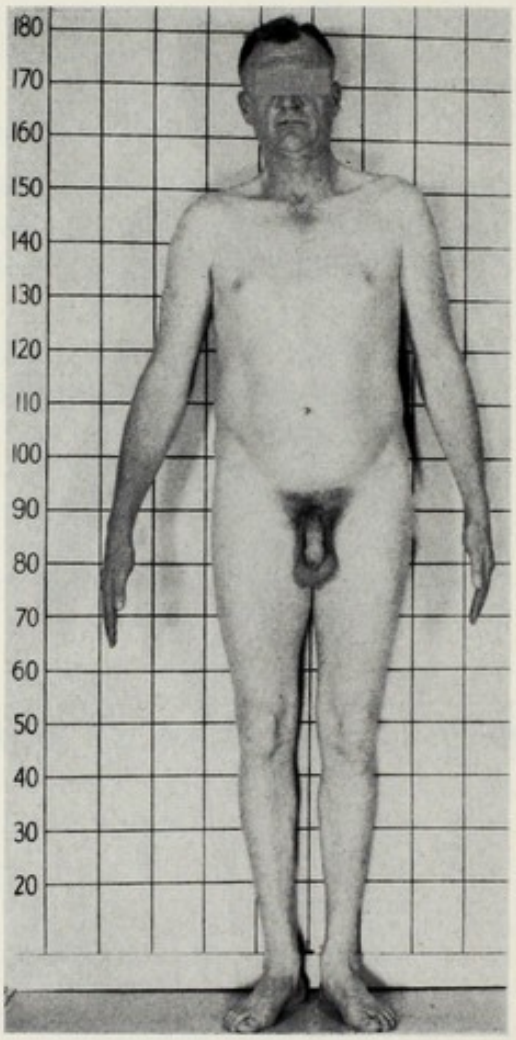


Fig. 38*B*. Individual III-4 (810977) in Fig. 38*A*, 38 years of age. The skeletal proportions are certainly not strikingly dolichostenomelic. The patient has substernal pain, suggesting angina, but no cardiac abnormality by x-ray or electrocardiogram examination. He has suffered also from back pain following a fall at work. Bilateral ectopia lentis is present.

therefore, no question but that each of the victims inherited the disease rather than getting it by *de novo* mutation and that the mother carries the gene. On examination, she was found to be 5 feet 8 inches tall, to be moderately long of limb without typical arachnodactyly, and to be myopic but free of ectopia lentis on careful ocular examination. This pedigree demonstrates how it is possible for the student of the full clinical and genetic picture to recognize cases which would be missed otherwise. (There are risks, of course, of counting cases as affected that are in fact not.)

Lynas[248] observed one pedigree (A2) of three affected children from apparently normal parents. Two of the three were, however, not definite cases. In another pedigree (A9) each of two unaffected brothers produced one affected child. Again, however, only "slight signs" were present in one of these.

To my knowledge there has never been an opportunity to observe the effect of the gene in homozygous state; that is, the union of two affected persons has not been described. Skipping of generations has never been observed in any thoroughly studied pedigree.[68]

Steinberg and his colleagues[286] have reported on 2-year-old identical twins with the Marfan syndrome and "unperforated aortic sinus aneurysm." Becker[197] described identical twins, both affected, in a family with multiple cases of the Marfan syndrome.

Bowers[204] has traced the disease through six generations of a single family with a total of about thirty-three affected persons.

Lynas and Merrett[250] could find no evidence of genetic linkage between the Marfan trait and the following traits: sex, color vision, phenylthiocarbamide tasting, and ABO, Rhesus, Lewis a and b, Luther, Kell, P, and MNS blood groups.

Partial submersion of the manifestations of this syndrome, depending apparently on the rest of the genetic milieu in which the mutant gene is operating, has been observed.[92] For instance, when the mutation occurs in unusually pyknic stock, the victim's habitus may be much less impressively unusual (Figs. 15*A* to 15*D*).* No protection against ocular or aortic abnormality seems to be afforded thereby, however. Lynas[248] seems also to have observed the modifying effects of other genes. In one pedigree a woman with the Marfan syndrome married twice. By the first husband, a "non-Marfan" but tall man with tuberculosis, there were two children: one died in infancy and one had a severe complete form of the Marfan syndrome. By the second husband, "a small square-built man," one child was normal and a second had only mild skeletal and cardiac manifestations.

The fact that in some families pronounced aortic and skeletal abnormalities occur without demonstrable abnormality of the lens seems to be further evidence of the operation of the genetic milieu on expression of the syndrome. Differences in the severity of the several components of the syndrome, including absence of some cardinal ones, is not inconsistent with the view that a single mutant gene is primarily responsible for the abnormality.

DIFFERENTIAL DIAGNOSIS

Given stigmata suggestive of the Marfan syndrome, one can be most confident of the diagnosis if ectopia lentis is present in the patient or if other members of the family are unequivocally affected (see Figs. 8*A* to 8*C*).[258]

For example, how can one be certain of the diagnosis of the Marfan syndrome in the case reported as such by Sinha and Goldberg,[279] when the patient "did not

*By assigning, to affected and unaffected individuals, a score for upper segment-lower segment ratio based on the number of standard deviations by which each individual deviates from the mean for his race, age, and sex (Fig. 7), it will probably be possible to test this clinical impression. From initial observations it appears that when the scores for patients with the Marfan syndrome are lower (that is, deviate more on the negative side of the mean), then the average score for his normal first degree relatives is in the low normal range. When the normal relatives have high normal scores, the Marfan patients do not have as markedly low US/LS values.

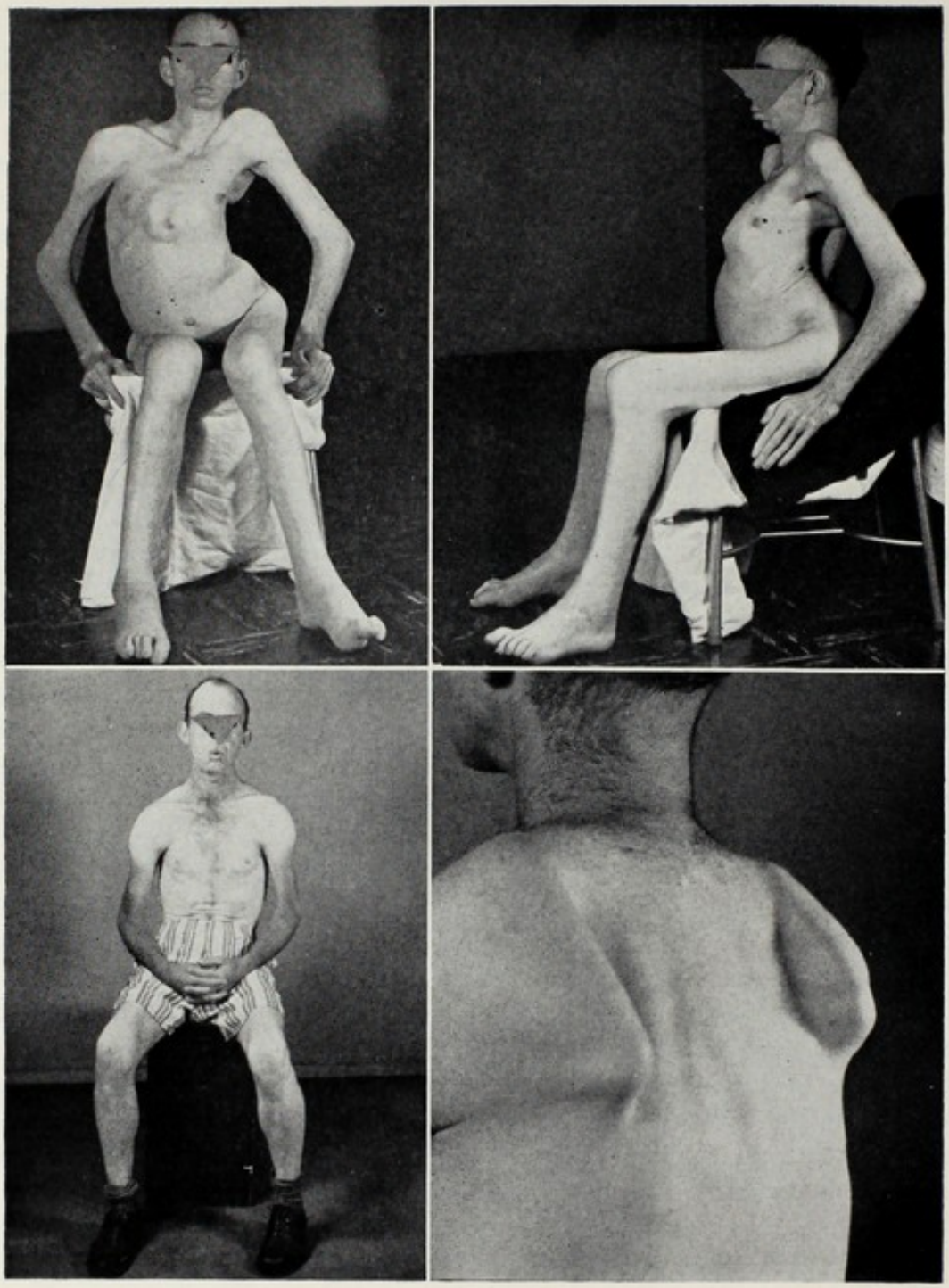


Fig. 39*A*.

Fig. 39*B*.

Fig. 39*C*.

Fig. 39*D*.

Figs. 39*A* and 39*B*. W. M. (Mary Imogene Bassett Hospital No. 54659) was thought to have Marfan's syndrome because of aortic regurgitation, severe spinal deformity, and arachnodactyly. Clinical evidence for bacterial endocarditis was present. At autopsy the heart lesions appeared to be rheumatic with superimposed valvular infection. (I am indebted to Dr. Jas. Bordley, III, for knowledge of this patient and permission to include him here.) Numerous pigmented nevi were present in this patient.

Figs. 39*C* and 39*D*. D. M., brother of W. M. The finding of muscular dystrophy in this brother makes it likely that W. M. (in Figs. 39*A* and 39*B*) likewise had muscular dystrophy. The disease trait appears to be recessive in this family. In D. M. note the wasting of the upper arms, especially the left, the asymmetry of the face in whistling, and the winging of the scapulae. There is no arachnodactyly. Spinal deformity as severe as that in W. M. is sometimes seen with muscular dystrophy.[150] The proper classification of the muscular dystrophy in these brothers is uncertain. The parents are living and well. No other cases are known in the family. The brother in Figs. 39*C* and 39*D* has four children who show no sign of disease. This is probably an autosomal recessive form of muscular dystrophy, which is thought by Becker[198] and others[287a] to occur at times. (The writer is indebted to Dr. Chas. Ellicott for studying this patient.)

Fig. 40*A*.

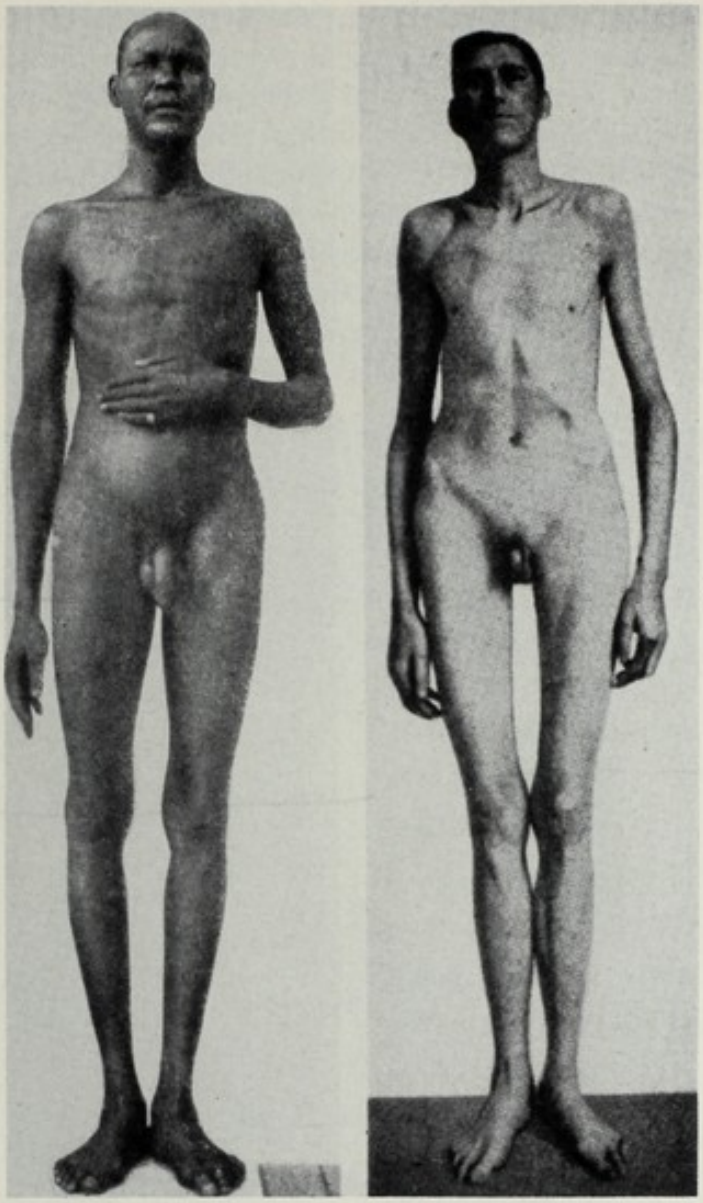


Fig. 40*B*.

Figs. 40*A* and 40*B*. Phenocopies of the Marfan syndrome. (From Bauer, J.: Innere Sekretion, Ihre Physiologie, Pathologie und Klinik, Berlin and Vienna, 1927, Julius Springer.)
Fig. 40*A*. The Denker Negro.
Fig. 40*B*. Eunuch. Bauer's[13] brief clinical description and the skeletal proportions suggest the Klinefelter syndrome.

have tall features or long fingers," there was no ectopia lentis, "the family history was noncontributory," and the histologic changes possibly typical of the aorta in the Marfan syndrome (p. 116) were not described? Rather numerous uncertain cases are being reported.[202,203,208,228a,248,271] Note that the Marfan syndrome can undoubtedly exist in sporadic, nonfamilial cases and ectopia lentis can occasionally be absent in patients known to be affected because of family data. It is merely pointed out that usually one cannot be certain of the diagnosis when neither ocular nor familial features are present.

The possibility of the Marfan syndrome is encountered in many situations such as that of aortic regurgitation, otherwise unexplained, in an individual of asthenic and possibly dolichostenomelic habitus. Measurements taken alone are indicative but not completely conclusive. Measurements must be evaluated in the light of a rough evaluation of the average habitus of the family of which the pos-

sibly affected individual is a member.* In the first decade of life, comparison of upper and lower segment measurements and of arm span with height is of greater significance because of the relatively short extremities during this period.[154] (For normal values for these measurements during this period see references 40 and 181 or, better, Fig. 7.) The lack of complete specificity of such measurements is indicated by the occurrence of excessively long extremities on an anthropologic basis in the Denker Negro[102] and on a pathologic basis in the eunuch,[13,229,262] in the Klinefelter syndrome (Fig. 40), and in patients with sickle cell anemia. In Wilkins' textbook[181] he pictures in the nude a Negro female patient who had had prepubital castration for strangulated dermoid cysts. The skeletal proportions are strikingly

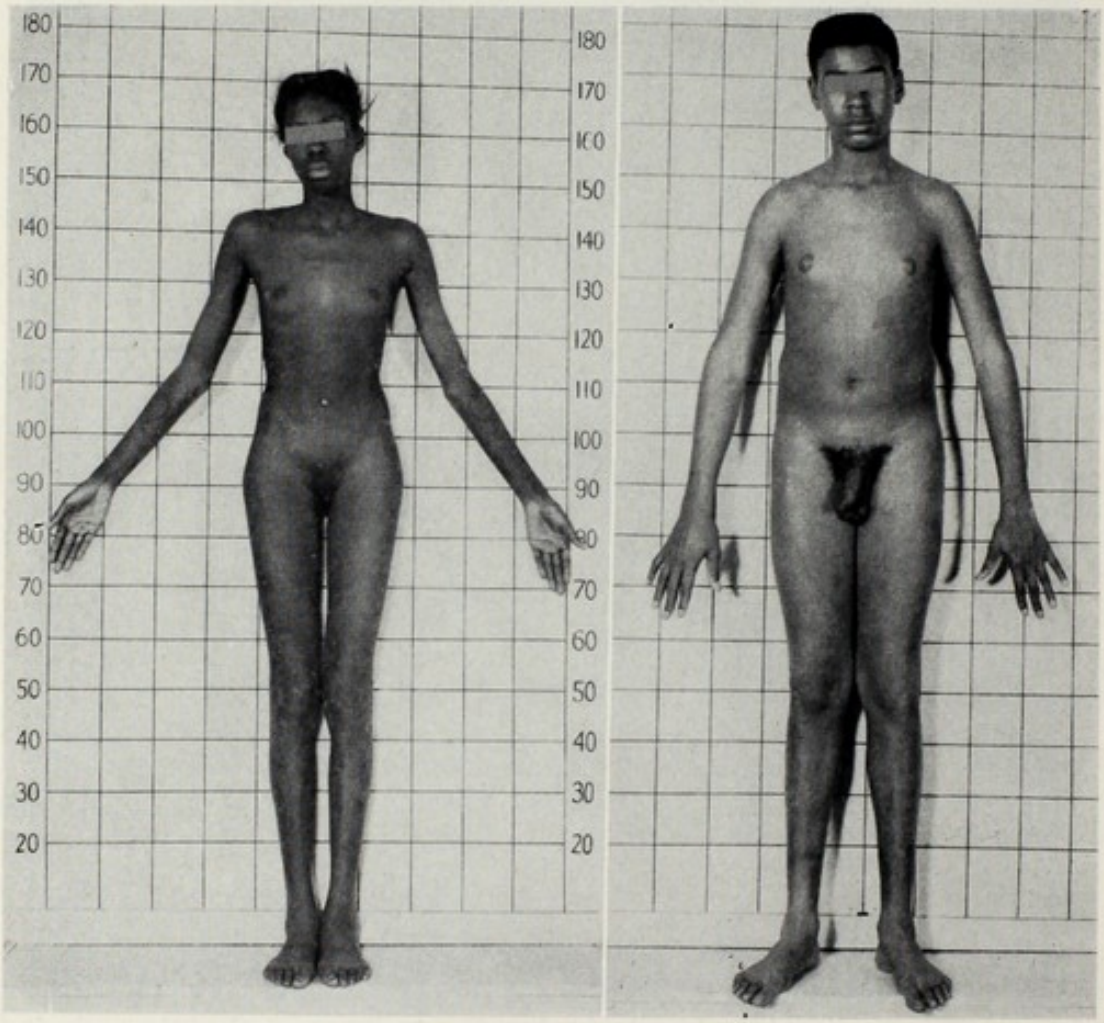


Fig. 41*A*. Fig. 41*B*.

Fig. 41*A*. Sickle cell anemia. D. M. (659463), 14½ years old, has no ectopia lentis or family history suggesting the Marfan syndrome but does have well-documented sickle cell anemia.

Fig. 41*B*. Adolescence. E. K. (766137) was referred because of gynecomastia. There is no ectopia lentis or family history suggesting the Marfan syndrome.

suggestive of the Marfan syndrome. The rule of thumb for identification of arachnodactyly—longest digit at least 50 per cent longer than the longest metacarpal—has proved to have both positive and negative error. In the Negro in particular, the Marfan syndrome is often suggested by skeletal proportions (Fig. 7). A famous con-

*See footnote, p. 107.

temporary Negro basketball star is said to be 75½ inches tall, with an arm span of 84-86 inches. Sheldon[144] refers to this habitus as Nilotic dysplasia, since, according to him, inhabitants of the upper Nile area and their descendants display it most often. The Watussi tribe of Uganda is very tall.

Delayed puberty may be accompanied by Marfan-like body proportions. In one case (E. K., Fig. 41*B*) adolescent gynecomastia was also present. As noted on page 88, the gracile habitus of many patients with atrial septal defect often leads to a mistaken diagnosis of the Marfan syndrome (Fig. 41*D*). The high incidence of chest deformity in patients with congenital malformations of the heart[259] may further increase the confusion with the Marfan syndrome.

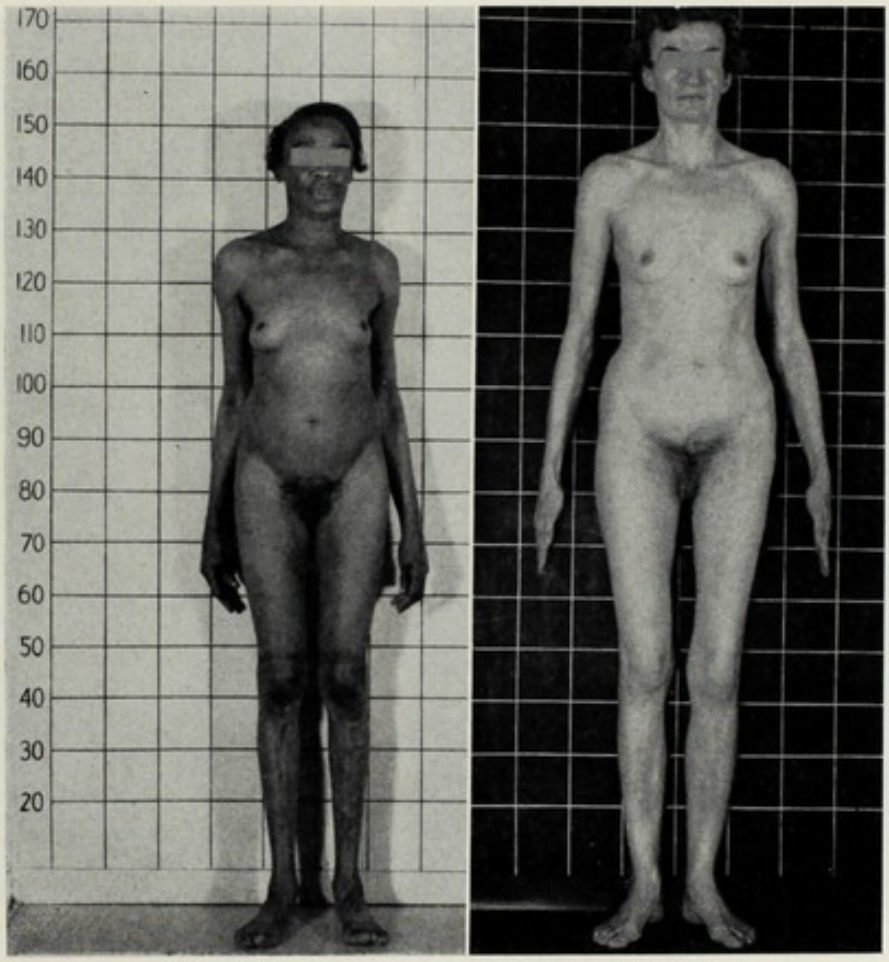


Fig. 41*C*. Fig. 41*D*.

Fig. 41*C*. Syphilitic aortitis and ectopia lentis. S. J. (802999), 58 years old, has atrophy of the irides, bilateral ectopia lentis, optic atrophy, choroiditis, and secondary glaucoma. Aortic regurgitation is accompanied by blood pressure of 170/60 mm. Hg and enlargement of the left ventricle and left atrium. The family history is not indicative of the Marfan syndrome.

Fig. 41*D*. Dolichostenomelia in atrial septal defect. M. L. (713241), 50 years of age, had a secundum type of ASD repaired surgically. There is no ectopia lentis or family history to suggest Marfan syndrome.

A picture mimicking in some respects that of the Marfan syndrome can result from Rh incompatibility and from intrauterine rubella infection. Ectopia lentis does not occur in these cases. However, deafness, ocular and cardiac defects, hypotonia, and even arachnodatyly may occur. The presence of some manifestations, such as anophthalmos, which is never encountered in the Marfan syndrome, is a point in favor of one of these other possibilities. Cases simulating Marfan's syndrome have

occurred apparently as a result of the occurrence during early pregnancy of febrile illness of unspecified type[54] and of x-ray therapy.[152] (See Fig. 32.)

Institutions for mental defectives often list an unbelievably high percentage of patients with arachnodactyly. This should not be taken to indicate Marfan's syndrome, in the majority of instances at any rate, since other evidence indicates that mental retardation is not an integral component of this syndrome and since it is clear that arachnodactyly is a nonspecific manifestation with many possible causes. The patient described by Benda,[17] for example, does not appear to have had the true Marfan syndrome. I would question the correctness of the diagnosis of the Marfan syndrome in the proband of family A5 of Lynas[248]: The proband, a female,

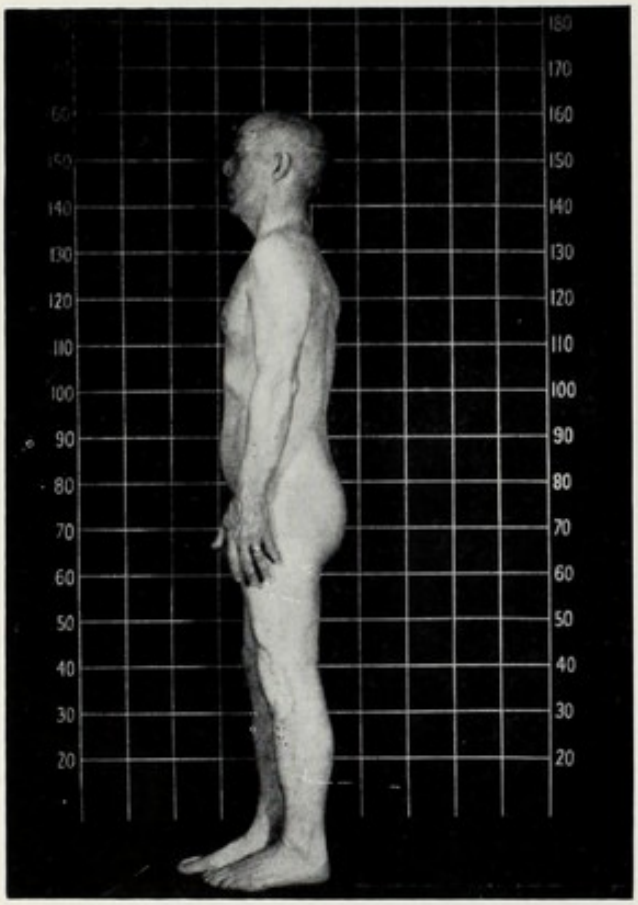


Fig. 42*A*.

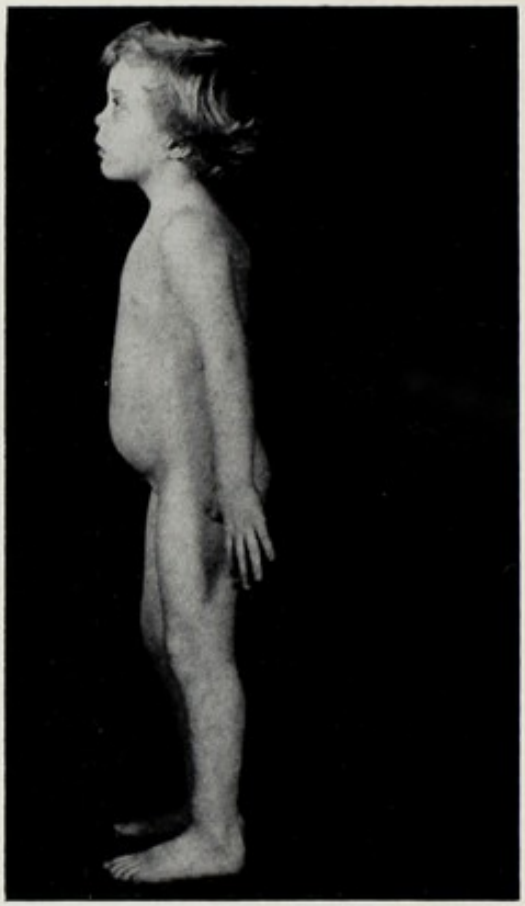
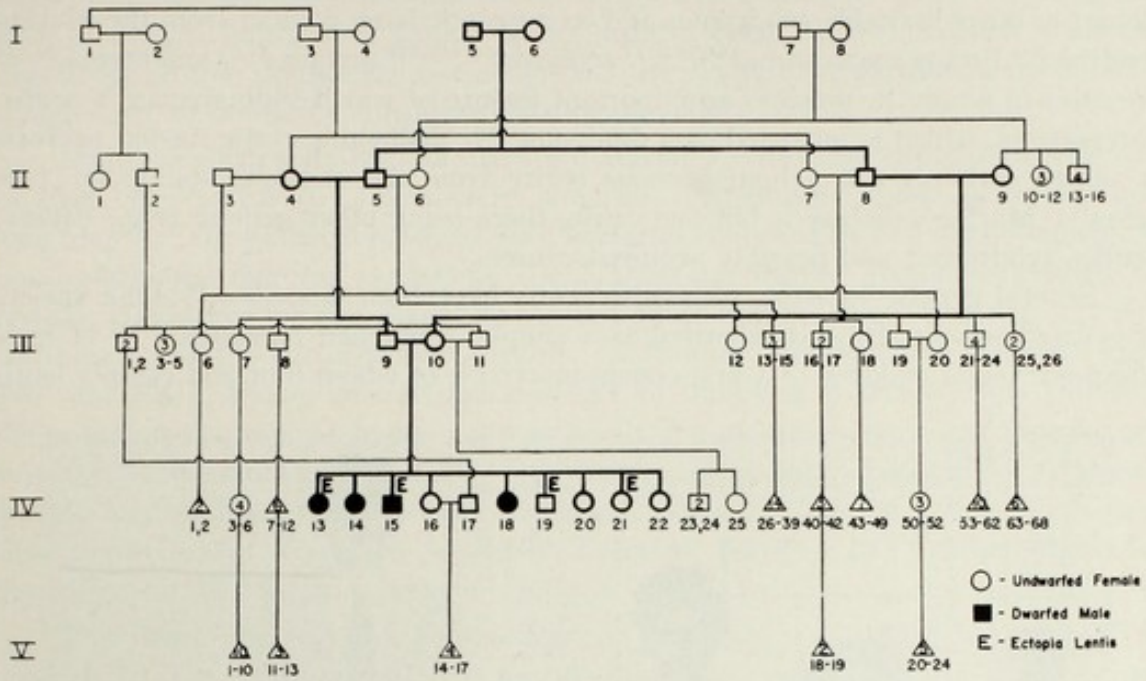


Fig. 42*B*.

Figs. 42*A* and 42*B*. Shown here are father and daughter, both with the Weill-Marchesani syndrome (ectopia lentis and brachymorphism). The skeletal manifestations are the antithesis of those of Marfan's syndrome. The daughter has a cleft palate and is mentally defective. No definite cardiovascular abnormality has been identified in cases of this syndrome. Compare these father-daughter pictures with that in Fig. 24*A*. (From McKusick, V. A.: Circulation **11**:321, 1955.)

was the only one of five children affected. She was a mental defective and "inclined just to sit and drool." The hands and fingers were very long and slender and showed marked clubbing due to bronchiectasis. The feet were abnormally small, however. Very severe kyphoscoliosis was present. The palate was broad and domed, not high and arched, and there were no eye and cardiac signs. "However, the clinicians are satisfied that she should be included as a case of arachnodactyly." Although by definition archnodactyly was present, it is very doubtful that this is a case of the true Marfan disease.



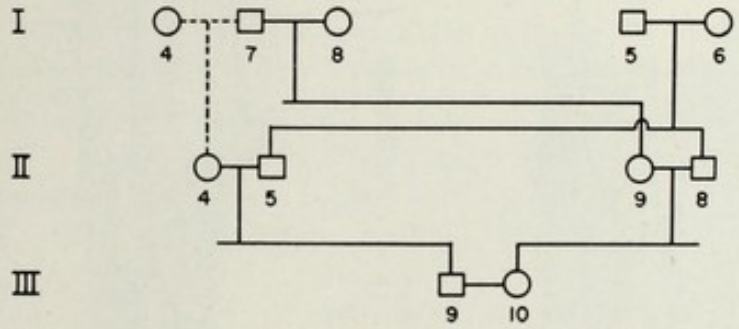


Fig. 43*A*.

Figs. 43*A*-43*C*. These are illustrations of a sibship,[93] children of a consanguineous marriage, in which four of eight members had ectopia lentis and four had primordial, or ateliotic, dwarfism. In two individuals there was coincidence of the two pathologic traits. The pedigree is consistent with the view that the two traits were independently inherited as autosomal recessives. In the past, observations on the inheritance of primordial dwarfism have been consonant with this theory of inheritance and it has been thought that ectopia lentis, as an isolated trait, is at times inherited as an autosomal recessive. This material is included to illustrate, along with the example of the Weill-Marchesani syndrome (Fig. 42), that the ectopia lentis of the Marfan syndrome is not the only genetic variety of this ocular anomaly. "The phenotype is not necessarily an indication of the genotype."

A, The pedigree. The parents of the affected sibship were either first cousins or intermediate double first cousins.

B, Left to right, individuals IV-15, IV-13, and IV-18 of the pedigree. The first two also have estopia lentis with complicating glaucoma. Not photographed is individual IV-14, who next to IV-15 is the shortest member of the family. The ages of these individuals are 31, 35, and 24 years, respectively, and their heights 39, 40, and 43¾ inches.

C, The individuals, of approximately the same age, are 72 and 39 inches tall, respectively.

Other than the proportionate dwarfism, the only abnormality revealed by radiographic study of the entire skeleton in individuals IV-15, IV-13, and IV-18 was delayed fusion of the epiphyses at the iliac crests in IV-15, who is 31 years old.

(From McKusick, V. A.: Am. J. Human Genet. **7**:187, 1955.)

Several of the individual components of the Marfan syndrome occur alone or as part of other heritable syndromes and on a genetic basis distinct from the Marfan syndrome. Pectus excavatum,[114,135,147] scoliosis,[55,133,318] myopia,[37,71] and hernia,[44,176] are cases in point. Scoliosis is an important feature of von Recklinghausen's neurofibromatosis, which is inherited as a dominant.[216] Erdheim's cystic medial necrosis is almost certainly not a homogeneous entity from the etiologic standpoint (see below). Marfan's disease is but one cause, there being other genetic (e.g., Ehlers-Danlos syndrome) and possibly acquired causes.

Several genetic varieties of ectopia lentis have been described.[16] One variety of isolated ectopia lentis is inherited as a simple Mendelian recessive.[51,167] I have observed[93] eight children of a first cousin marriage, of whom four had ectopia lentis

Fig. 43*B*.

Fig. 43*C*.

Figs. 43*B* and 43*C*. For legend see preceding page.

and four had ateliotic dwarfism (a condition usually inherited as a recessive). Coincidence of the two anomalies occurred in two of the individuals. Another variety of ectopia lentis is part of the Weill-Marchesani syndrome.[92,100,175,256,261] The habitus of the victim of the Weill-Marchesani syndrome is diametrically opposite to that of the Marfan syndrome. The victim is brachymorphic, short of stature, with round head, pug nose, depressed nasal bridge, and short, pudgy hands and fingers. This syndrome is inherited as a dominant with low penetrance or as a recessive with partial expression in the heterozygote.[241] Ectopia lentis sometimes occurs with aniridia,[211] which is usually inherited as a dominant.

In approximately 70 per cent of instances of congenital ectopia lentis, the anomaly occurs as a component of the Marfan syndrome. The skeletal manifesta-

tions of the Marfan syndrome may be so unconvincing in many cases that the presence of ectopia lentis in a patient with cardiovascular signs consistent with the Marfan syndrome should lead one to suspect the diagnosis even though the skeletal changes per se cannot be considered pathognomonic.

Muscular dystrophy was confused for Marfan's syndrome in the patient shown in Figs. 39*A* and 39*B*. There were unusually pronounced spinal deformity and long fingers. The patient presented with bacterial endocarditis and aortic regurgitation—additional features suggesting the Marfan syndrome. Autopsy revealed no histologic evidence for this diagnosis but did show changes consistent with a rheumatic basis for the bacterial endocarditis. A brother, subsequently studied (Figs. 39*C* and 39*D*), shows unequivocal evidence of muscular dystrophy. In children, the pronounced muscular hypotonia may result in a picture suggesting Oppenheim's amyotonia congenita or Werding-Hoffmann's muscular atrophy.[230a] Arachnodactyly has been described[240] with amyoplasia congenita. In brief, then, it is possible for errors of diagnosis, in either direction, between the primary muscular disorders and the Marfan syndrome.

The relationship, if any, of the Marfan syndrome to "status dysraphicus" is obscure.[117] The latter condition is too ill-defined to make an analysis of relationship possible. We (see Fig. 10*A*) and others have observed bent fifth fingers, so-called camptodactyly or clinodactyly,[70] and heterochromia iridis,[36] both manifestations which are said to be characteristic of status dysraphicus. Apparently identical clinodactyly is sometimes inherited as an isolated anomaly.[70]

We have observed two patients (L. E., 677290; S. J., 802999) with ectopia lentis and syphilis. Is it possible that syphilis can cause or predispose to ectopia lentis? The association of syphilitic aortitis with ectopia lentis might occasion diagnostic confusion. Aside from the diagnostic implications the theoretic ones are great, since, as previously indicated, the clinical behavior of the aortic involvement in syphilis has certain parallels to that in the Marfan syndrome. (The rarity of dissecting aneurysm in syphilitic aortitis is a conspicuous difference, however.)

It has been emphasized above that profound aortic regurgitation may be present in patients with the Marfan syndrome for many years before dilatation of the ascending aorta become evident by x-ray examination. Some cases with severe aortic regurgitation (see Figs. 16*A* to 16*G* and 22*A* to 22*E*) never show dilatation of the aorta. The differential diagnosis of the aortic lesion can, therefore, be confusing. Syphilis, rheumatism, or bacterial endocarditis is often suspected first. When these appear unlikely from collateral evidence and when, as is so often possible in all sorts of disorders, a history of trauma is elicited, traumatic rupture of a normal aortic cusp is postulated (see Figs. 15*A* to 15*D* and reference 15). Furthermore, a deceptive prominence of the pulmonic conus and main pulmonary artery may result from displacement of these structures by the dilated intrapericardial portion of the ascending aorta. Or the pulmonary artery may be dilated because of intrinsic involvement of its media. As in any severe, prolonged aortic regurgitation with chronic left ventricular failure, the left atrium is likely to become dilated. The prominence of the pulmonary artery and left atrium, the prolongation of the P-R interval (p. 97), and the Austin Flint murmur of aortic regurgitation conspire to lead to the incorrect diagnosis of rheumatic heart disease with combined aortic and mitral lesions.

PATHOLOGY

Roark[274] estimates that at least seventy-one autopsies are reported in the literature. Autopsy was performed in eighteen of the seventy-four propositi in our series; necropsy information is available in at least ten other affected members of these families. The gross changes in the aorta, as demonstrated in Fig. 15*C* and Fig. 16*G*, are the most dramatic. There are numerous reports of dissecting aneurysm in cases of the Marfan syndrome.[30,42,61,85,86,159,161,190,209,235,258,269,270,282,300]

With the exception of the changes in the media of the great vessels and in the heart valves, no specific histologic abnormalities have been detected in this syndrome. In the media of the aorta, the most advanced changes are seen in cases of diffuse dilatation of the ascending aorta in which the process has gone on over several years' time and the patient succumbed to the effects of aortic regurgitation. In such cases, there are frequently early changes in the pulmonary artery. The early changes in the aorta are best demonstrated in those patients dying of dissecting aneurysm.

The advanced changes consist of fragmentation and sparsity of elastic fibers, irregular whorls of seemingly hypertrophied and perhaps hyperplastic smooth muscle, increase in collagenous tissue, pronounced increase in the vascularity of the media with wide dilatation of the vasa vasorum in both the adventitia and the media and cystic spaces occupied by metachromatically staining material. The net result is an aorta which is thicker (but weaker) than normal.

The early changes are those described by Erdheim[41] as cystic medial necrosis.[161] There are mild to moderate degeneration of elastic fiber elements and more or less striking cystic areas filled with metachromatically staining material.

The predominant involvement of the ascending aorta is not inconsistent with a generalized defect of some element of connective tissue, since it is the ascending portion of the aorta which bears the main brunt of hemodynamic stress. Reynolds[129] concluded that, with physiologic pulse pressures, it is only the ascending aorta which shows dilatation (i.e., increase in diameter) with each ventricular ejection. Other observers, while disagreeing with Reynolds' claim that virtually no expansile pulsation occurs beyond the arch, corroborate the finding that much greater expansion occurs in the ascending aorta (15 to 20 per cent increase over diastolic diameter in the ascending aorta, 5 per cent in the distal aorta). Engineers, textile scientists, and others concerned with testing the "strength of materials" are familiar with the fact that cyclical application of a stressing force results in structural disintegration much sooner than does steady application of the same force.

Another factor in the predominant localization in the ascending aorta may be implicit in Laplace's law (wall tension = pressure $\times$ radius). Since both pressure and radius find their largest values in the ascending aorta, the tension on the wall of that portion is greater than anywhere else in the vascular tree. In the case of aneurysm there is, by the same token, a vicious cycle or self-perpetuating action—the greater the radius, the greater the wall tension, the greater the radius, and so on.

Changes similar to the early ones in the aorta are not uncommon in the main pulmonary artery. Occasionally the changes there are as advanced as are ever seen in the aorta.[166]

The predominant localization of the pathologic changes of Marfan's syndrome, of other varieties of Erdheim's cystic medial necrosis (see later), and of syphilis,

in the ascending aorta, probably has its basis in the physical and hemodynamic considerations outlined above. The pulmonary artery has the same defect of its media but rarely gives trouble of clinical significance, probably because both blood pressure and pulse pressure are lower in the pulmonary artery than in the aorta. (In syphilis, other theories for preferential thoracic localization of the spirochete have been invoked, such as difference in the distribution of the vasa vasorum and a slightly cooler environment of the thoracic aorta. Proponents of the latter theory point to the difficulties in inducing syphilis in rabbits during hot weather and the preferential localization of spirochetes in parts of rabbit skin that have been shaved.)

Minor changes in the heart valves in the form of marginal thickening or fibromyxomatous excrescenses have been described grossly in many of the autopsied cases,[136,146,162,175] including Salle's[136] case, the first autopsied. Histologically, one case[166] was found to show "numerous lacunas in the collagenous substance of the mitral valve that were filled with a homogeneous basophilic material." This lesion resembles closely that which occurs in the media of the aorta. Fig. 21*F* represents the changes in the aortic valve in one of our cases. The pronounced sacculation and stretching of the aortic cusps is probably per se evidence of weakness of the connective tissue stroma of the valve. In the process of the stretching, breaks with fenestration of the cusp may occur.[168]

In one case (S. C., 575946) the splenic artery was grossly friable and showed advanced cystic medial necrosis on histologic examination. The splenic, iliac, innominate, both subclavian, both common carotid, both renal, and mesenteric arteries showed characteristic cystic medial necrosis in one well-studied case.[274] The intracranial arteries, inferior vena cava and common iliac veins were normal. Austin and Schaefer[191] described a case in which both common carotids were extensively involved by cystic necrosis with subsequent dissection.

The pathologic studies of the eyes have not been very helpful from the fundamental standpoint. Hypoplasia of the dilator muscle of the iris provides explanation for the miosis and poor response to mydriatics.[79,137,353]

Joint capsules, ligaments, tendons, and periosteum have shown no abnormality, but studies in these areas are distressingly few. Roark[274] could find no definite abnormality in the anterior spinous ligament or intervertebral discs.

THE BASIC DEFECT

In what element of connective tissue is the defect of the Marfan syndrome located? The histologic appearance of the aorta suggests that the primary defect may be in the elastic fiber. The pathogenic chain of events may be this[58]: The elastic fibers, constitutionally inadequate, undergo degeneration, particularly at the site of maximum hemodynamic stress, the ascending aorta. The smooth muscle elements, which normally have origin and insertion on the elastic lamellae, collapse together into disorganized whorls and undergo hyperplasia and hypertrophy. Reparative processes leave the media scarred. Secondary to the frantic hypertrophy of smooth muscle fibers and the scarring process, dilatation of the vasa vasorum occurs. (In 1933 Wolff[184] suggested that Erdheim's cystic medial necrosis might be a generalized weakness of elastic fibers. He demonstrated abnormalities in larger peripheral arteries and in the main pulmonary artery.)

What the suspensory ligament of the lens has in common with the media of the aorta is obscure. If known, the basic defect of this syndrome might be understood. Most information suggests that the suspensory ligament is collagenous in nature.[260] However, it cannot be like most collagen (see Table 1, p. 18) because it is digested by chymotrypsin, as demonstrated by the surgical technique developed by Dr. Joaquin Barraquer of Spain and introduced into the United States by Dr. Derrick T. Vail. There is more collagen in the aorta than elastic tissue.[260] The preliminary observations of Sjoerdsma and his colleagues[280] indicate an increased urinary excretion of hydroxyproline in the Marfan syndrome. Because of the unique hydroxyproline content of collagen, confirmation of these observations will tend to point the finger at collagen metabolism as the location of the basic defect.

It is possible to reconcile with a generalized connective tissue defect many of the other manifestations: the lax joint capsules, the weak ligaments, especially those with large elastic fiber representation such as the ligamenta flava of the spine, the malformed elastic cartilages of the pinnae, and the deformity of the foot where elastic fibers are abundant in the ligaments.[155] But how is one to explain the most striking feature of this syndrome, dolichostenomelia, and the other dolichomorphic features? One gets the impression that the factor that is missing during morphogenesis and growth of bone in victims of this syndrome is a binding force which placed a rein on longitudinal growth. Whether it is elastic fiber as such or some element with the properties of the elastic fiber matters not at the moment. Is some such element missing from the ground material of the cartilaginous precursors of bone? Or is the location of the defect in the periosteum? Longitudinal growth of the large bones of the extremities occurs at the epiphyseal-diaphyseal junctions. The periosteum, attached as it is to the epiphyseal cartilage, may exercise control over longitudinal growth.[299] Experiments of Ollier in 1867[109] and of others[81] since him, although not without flaw, suggest such to be the case: If a cuff of periosteum is removed from the circumference of a growing long bone, that bone will grow longer than its untampered counterpart. An inborn weakness of the periosteum might have a similar effect. The bony abnormality does not appear to be one of simple overgrowth, since the excess is limited to longitudinal growth. The bones are abnormally small in cross section. Osteogenesis may be proceeding at a normal rate in the periosteum, which slides along the diaphysis, adding bone to the circumference; the diaphysis may not attain normal transverse dimensions because the periosteal bone is spread over a greater total area.*

The failure to find abnormality of elastic tissue in the trachea, skin, spinal ligaments, and intervertebral disc[274] is disturbing to the theory implicating elastic tissue.

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*Lacroix[81] writes (p. 59) as follows: "A fibro-elastic membrane, the periosteum grows, while yielding to a traction imposed upon it, by stretching over its entire extent. Where only one zone of growth exists, as in the case of the long bones of the hand and foot, the periosteal sheath is attracted in only one direction; it is pulled in two opposite directions on the two sides of a 'neutral' zone in bones with two zones of growth. Since the diaphysis elongates only at the level of the growth cartilage, the periosteum during development slides along the bone surface at a rate and in a direction specific to each level." Later (p. 67), he writes: "Since the periosteum slides along the diaphysis which it encloses, the youngest trabeculae, those in formation at the moment of examination are not deposited at exactly the same level as those which the same zone of periosteum elaborated in the preceding days." The obliquity of the canals of the nutrient arteries has its origin in this phenomenon.

The report[192] that the affected members of one family showed abnormally low levels of serum mucoproteins was received with great interest. If confirmed, not only would the observation have diagnostic usefulness but also it might assist in pin-pointing the basic defect. Note that as stated on page 35 the elastic fiber is, in one view, composed in part of "elastomucin." Unfortunately, Dr. James T. Leeming and I have been unable to demonstrate any abnormality of serum mucoprotein in forty-six Marfan patients as compared with controls matched for age, sex, and race.

The precise element of connective tissue which is defective in Marfan's syndrome awaits identification. Nonetheless, it is possible to describe the behavior of the defect in considerable detail. (See "pedigree of causes" in Fig. 44.)

The production in rats of a somewhat analogous, but *acquired,* syndrome has been of great interest for obvious reasons. Kyphoscoliosis, hernia, and aneurysm of the aorta (dissecting, diffuse, or saccular) can be produced in rats (Fig. 45) fed a toxic agent contained in the seed of *Lathyrus odoratus.*[28,120,122] The toxic

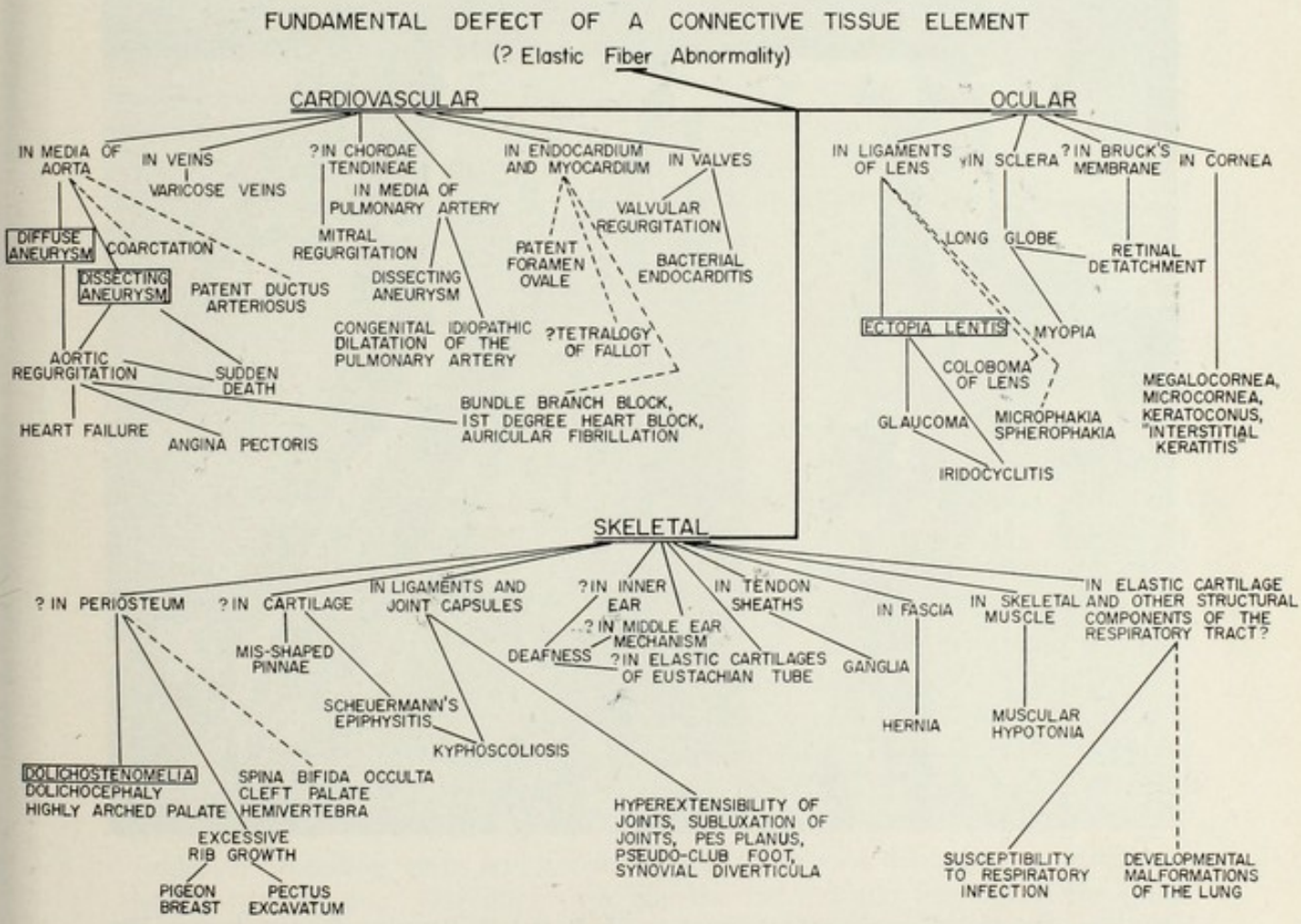
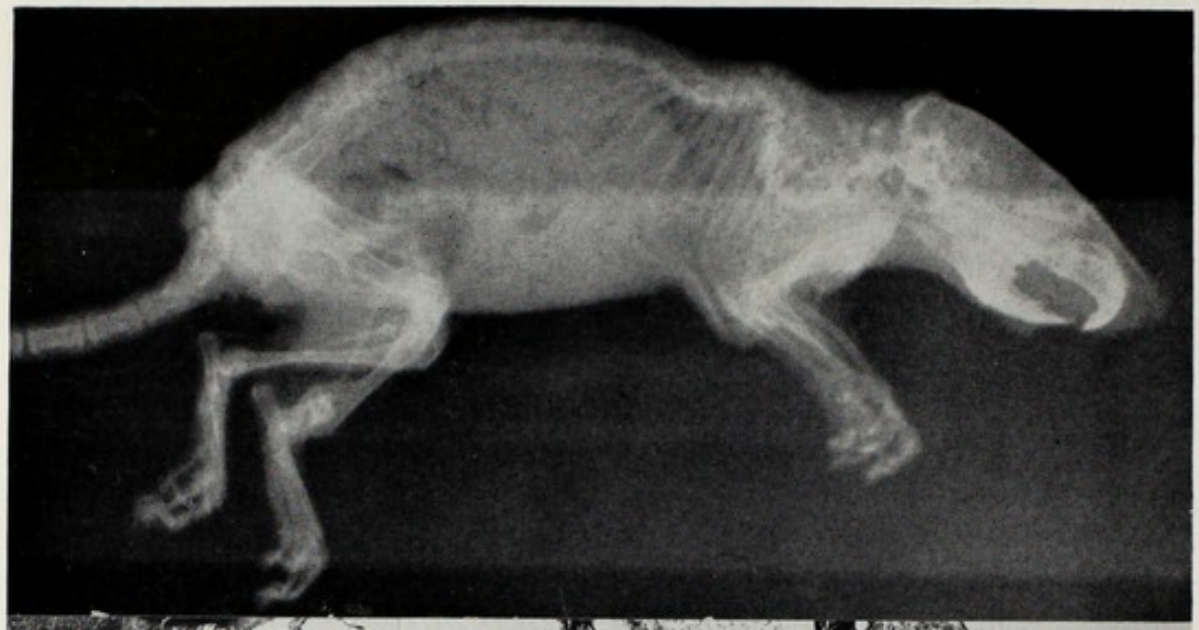


Fig. 44. Marfan's syndrome, a pedigree of causes. The chart reviews the components of this syndrome. Special attention is directed to those manifestations indicated by interrupted lines: in the skeletal system, spina bifida occulta and hemivertebra; in the heart, interatrial septal defect and coarctation of the aorta; in the eye, coloboma of the lens and microphakia. In the present state of our knowledge these congenital anomalies of the more conventional type are difficult to explain on the basis of a unitary defect of connective tissue unless one assumes that the presence of this defect during embryogenesis produces an abnormal setting in which these particular anomalies occur with increased incidence. If this is true, these less frequent manifestations indicated by the interrupted lines may be considered secondary ones. (From McKusick, V. A.: Circulation **11**:321, 1955.)

Fig. 45*A*.



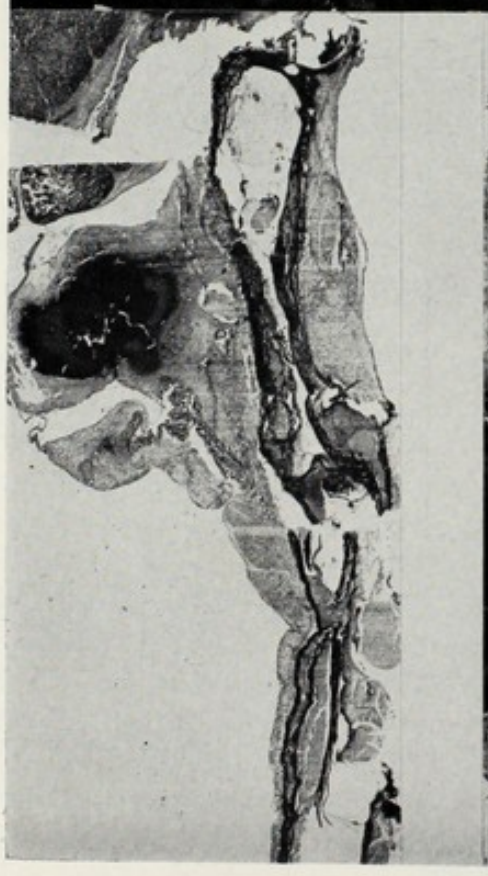


Fig. 45*B*.

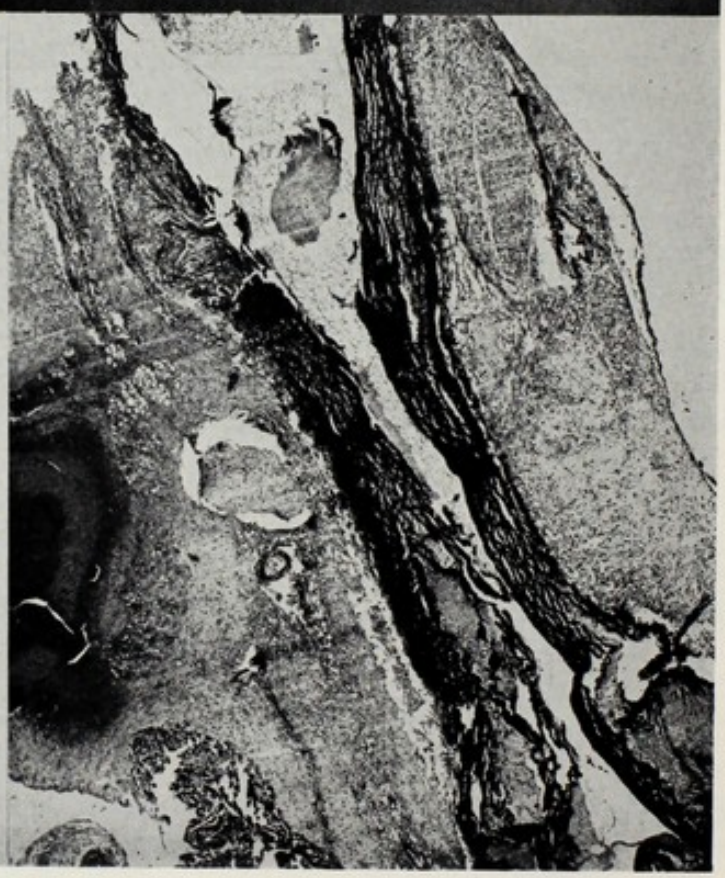


Fig. 45*C*.

Figs. 45*A*-45*C*. Experiments conducted by Dr. James R. Brayshaw,[28] as student at The Johns Hopkins University School of Medicine.

Fig. 45*A*. Deformity and pathologic fracture of spine and other bones in rat fed seeds of *Lathyrus odoratus*.

Fig. 45*B*. Dissecting aneurysm of the aorta with rupture in rat fed seeds of *Lathyrus odoratus*. Shown is the dissection of the media and the large mediastinal hematoma. Elastic tissue stain. The elastic lamellae are black. (×10; reduced 1/5.)

Fig. 45*C*. Same at higher magnification. On the left below, the wall of the aorta is grossly scarred through almost its entire thickness. (×30; reduced 1/5.)

material has been crystallized[38] and identified[138] as β (γL-glutamyl) amino-propionitrile ($HOOC-\underset{\underset{NH_2}{|}}{CH}-CH_2-CH_2-\overset{\overset{O}{||}}{C}-NH-CH_2-CH_2-C\equiv N$).

B-aminopropionitrile will also cause skeletal changes and dissecting aneurysm of the aorta.[172] Gelatin and casein appear to afford partial protection against the effects of these toxins.[34] Whether the primary difficulty is in the elastic fibers or in the intermediate material is not clear.[10,32] Possibly significant with reference to the predominant male sex incidence of dissecting aneurysm in man is the finding[297] that aortic rupture occurs much more frequently in male rats fed sweet pea seeds than in female rats. Furthermore, the simultaneous administration of androgen considerably enhanced the incidence and severity of aortic medionecrosis[298] in sweet pea-fed rats. The demonstration of increased mucopolysaccharide[32] is of interest in light of the metachromatically staining material seen in human cases of Erdheim's cystic necrosis, including that caused by Marfan's syndrome (see below). Although the basic defect in this acquired syndrome is probably not the same as that in Marfan's syndrome, studies of this sort should be helpful in elucidating some of the many mysteries that surround dissecting aneurysm in particular[79] and disorders of connective tissue in general. Clinically, Bean and Ponseti[196] have been impressed with a relatively high incidence of kyphoscoliosis in the group of cases of dissecting aneurysm of the aorta.

OTHER CONSIDERATIONS

There is, of course, no definitive treatment for this disorder. It should be noted that healing after surgical operations is normal. Herniorrhaphy, orthopedic procedures, and correction of pectus excavatum can be performed with success. (One patient went through a lienorenal shunt procedure for unrelated hepatic cirrhosis.[166]) Correction of pectus excavatum should probably be postponed until after puberty since an imperfect result may follow if there is still opportunity for excessive longitudinal growth of the ribs. The current philosophy in regard to ectopia lentis seems to favor performing lens extraction only if iritis or glaucoma develops. Hufnagel's plastic valve operation[73] was performed in a case of aortic regurgitation on this basis; because of the nature of this disease and of the operation currently practiced, its practicability here is very questionable. Evidence is presented elsewhere[95] that the Hufnagel operation produces widening of the pulse pressure (due both to increase in the systolic level and decrease in the diastolic level) proximal to the valve. This might well increase the strain on the already weakened ascending aorta and accelerate the process of dilatation or predispose further to dissection. One might fear that the valve would tear out of the aorta. This has indeed been observed.[239] In this instance the tear occurred at the junction of the aorta with the prosthesis, some months after operation. The gross appearance suggested the wear with cracking which occurs in stethoscope tubing at the junction with the metallic parts of the stethoscope. Support for the view that "wear-and-tear" is a factor in the pathogenesis of the changes observed in the aorta in the Marfan syndrome may be provided by this observation. Thrombosis with occlusion

of the valve has been described in two cases of the Marfan syndrome,[209,220] but this is probably a complication not unique to this hereditary disorder.

In two recent cases (S. L., 293069; S. T., 691351) of idiopathic cystic medial necrosis of the aorta with diffuse dilatation of the ascending aorta and profound regurgitation, Dr. Henry T. Bahnson plicated the dilated aorta and surrounded the ascending aorta as far proximally as possible with a splinting sleeve of synthetic fabric. A happy, although surprising, result of the procedure has been a pronounced decrease in the aortic regurgitation as evidenced by diminution in the diastolic murmur and manifestations of left ventricular strain and by rise in diastolic pressure to almost normal levels. These cases are historic from another standpoint; it is the first time the diagnosis of Erdheim's cystic medial necrosis has been established histologically *in vitam*.

The Bahnson operation was attempted in one case of the Marfan syndrome (S. C., 575946), with progressive dilatation of the aorta beginning at the ring and subsequently complicated by dissection of the media. Although it was possible to dissect down to a point proximal to the coronary arteries, the relatively high position of their ostia and of the commissures of the enormously sacculated cusps make it difficult to accomplish much that was worth while without interfering with these vital structures. Fay and his colleagues[226] performed the Bahnson procedure with apparent technical success in a case of the Marfan syndrome, but the patient died unaccountably twelve hours later.

Bahnson[193] has the impression that the ascending aorta is different in the case of idoipathic cystic medial necrosis than in the Marfan syndrome. Specifically, the sinuses of Valsalva seem to be involved less strikingly in the former condition. The difference is obviously an important one from the therapeutic point of view.

In a recent case of idiopathic cystic medial necrosis (B. L., 806222), total replacement of the ascending aorta by an autograft was performed by Bahnson, and in a second similar case (B. B., 822151) a synthetic fabric graft was used with success. The difficulties with application of this procedure to the Marfan cases would be the same as with the plication procedure. Baker and his colleagues[194] have reported the successful use of an aortic homograft in a case of the Marfan syndrome, but in this case the involvement of the aorta was limited to the descending thoracic portion. Total replacement of the abdominal aorta has been performed in cases of the Marfan syndrome by Davis and his colleagues in Cleveland and by Dubost in Paris (see p. 71).

A point of medicolegal importance is the relationship of trauma to the development of various manifestations of the Marfan syndrome. The development of hernia, detachment of the retina,[94,140,204] dissecting aneurysm,[25,116,165,209,220] and total dislocation of the lenses may be intimately related to trauma as a precipitating factor. In Choyce's case[214] dislocation of the lenses into the anterior chamber occurred when the patient leaned forward to pick something up from the floor. Wilson[301] suggested that the strain of sexual intercourse may contribute to deterioration of the aorta. In one of his patients, death occurred five days after marriage; in another, symptoms of left ventricular failure began after intercourse. On the other hand, a murmur of aortic regurgitation is known to have been present for sixteen years in an unmarried affected sister. "In the Marfan syndrome a sedentary spinster may outlive an athletic husband."[301]

In connection with the relation of the Marfan syndrome to other diseases or

special physiologic states, rheumatic fever, syphilis, hypertension, and pregnancy might be mentioned. The suggestion of Futcher and Southworth[53] that rheumatic fever may occur with increased incidence in these patients has not been confirmed by further observations. Syphilis and hypertension, if combined with the Marfan disease, might have particularly dire effects on the aorta.

There is now convincing evidence of a strikingly increased incidence of dissecting aneurysm of the aorta in pregnancy.[107,141,143,236,255] Conceivably, this is related to the hormone "relaxin" and to the general relaxation of ligaments and other joint structures during pregnancy.[1,2,69,115,119,126,187] Against this hypothesis is the fact that my colleagues and I[94] have been unable to induce aortic dissection in animals treated with large doses of "relaxin," with or without challenge with vasopressor agents. Rupture of the splenic artery, another rather frequently reported[276,291] accident of pregnancy, may be on a similar basis. The reduction of tensile strength of the skin during pregnancy (reference 99, p. 175) is further evidence of a generalized change in connective tissue.

We have observed three patients in whom pathologic changes occurred in the aorta in association with pregnancy. There is no evidence of the Marfan syndrome in any of these. (In addition, dissection may have occurred during pregnancy in the patient illustrated in Fig. 16*C*.)

1. A. P. (621953), Negro female, at the age of 36 years had a difficult labor with her sixth child. During a period of hard straining in labor she suddenly "felt something snap" inside her body at the level of the lower back, and an excruciating pain spread over most of the trunk. The baby was delivered by Cesarean section. A laparotomy five months later showed abdominal aneurysm, for which no treatment was attempted. She was aware of a pulsating mass in the abdomen. Palpitation, dyspnea, and profuse sweats developed. She was examined at the Johns Hopkins Hospital six years later. There was a pulsating abdominal mass, auscultatory signs of aortic regurgitation, and marked cardiomegaly. Serologic test for syphilis was negative. The patient died elsewhere; no autopsy was performed.

2. C. T., a 41-year-old mother of seven, was found six weeks before her death to have a blood pressure of 180/100 mm. Hg. She was 6 months or more pregnant. She refused hospitalization at that time. On the morning of the day of death the patient had the onset of substernal pain and profuse perspiration. The blood pressure was 225/120 mm. Hg. On the way to the University hospital the patient was suddenly seized with severe chest pain, collapsed in the car, and became very "blue." She was dead on arrival at the hospital. A post-mortem Cesarean section delivered a full-term live male child which weighed 5,089 grams. Autopsy of the mother revealed dissecting aneurysm of the aorta with rupture. (The case reported by Spenser[281] is rather similar in that post-mortem Cesarean delivery was done in a woman dead of dissecting aneurysm.)

3. D. W. (706005), a 33-year-old woman, sustained rupture of a coronary sinus into the right side of the heart, in the early puerperium.

Lindeboom and Bouwer,[85] Husebye and colleagues,[237] Novell and associates,[266] and Baker and colleagues[194] reported on dissecting aneurysm in pregnant or recently pregnant women with the Marfan syndrome, and Spenser's case[281] may be another example. Avoidance of pregnancy seems indicated, especially by more severely affected women.

Relation to Erdheim's Cystic Medial Necrosis.[134] Erdheim's disease is probably not a single entity from the etiologic standpoint. There are probably a number of possible "causes"—some genetic (like the Marfan syndrome), some acquired in nature. With the control of syphilis and rheumatic fever, cystic medial necrosis will assume increasing importance as a cause of aortic regurgitation. It must be

kept in mind particularly when there is no history of syphilis, rheumatism, and bacterial endocarditis and must *not* be excluded from consideration on the grounds that there is no radiologic evidence of aortic dilatation. Unfortunately, the diagnosis of idiopathic Erdheim's disease (Erdheim's disease without the Marfan syndrome) will for the time being need to be a diagnosis of exclusion.

Some pathologists such as Dr. A. R. Rich and Dr. Ella Oppenheimer[272] feel that the aorta in the Marfan syndrome has histologic features, specifically large whorled bundles of disorganized smooth muscle and greatly dilated vasa vasorum, which are not seen in ordinary Erdheim's disease. The changes which are considered specific for the Marfan syndrome are most likely to occur in the first part of the aorta, the part which first undergoes dilatation. Further on in the aorta the changes are indistinguishable from those of idiopathic medial necrosis. It is uncertain whether this histologic picture indicates a fundamental difference. It seems to me possible that merely the prolonged evolution or some other feature of the Marfan syndrome permits or dictates the occurrence of this particular change.

The experience with Marfan's syndrome should prove very useful in the cases of idiopathic Erdheim's disease. In both, dissecting aneurysm or fusiform dilatation* or a combination can occur. In both, the ascending aorta is most severely affected. In both, the process seems to pursue an unrelenting progression to death from rupture of the aorta or from the effects of aortic regurgitation.

There is now convincing evidence[145] that the metabolic turnover rate in the elastic skeleton of the aorta is so low† as to raise serious suspicions of complete metabolic inertia. The elastic structures of the aorta can be looked on as intended to outlive the rest of the organism. In certain unfortunate individuals, however, the elastica "gives out" prematurely. The result is Erdheim's cystic medial necrosis. Genetic inferiority is probably most frequently the basis. It has been described in brothers,[171,230] in father and son,[228] and in mother and daughter,[232] but the clinical information provided is too scant to permit exclusion of the Marfan syndrome. Erdheim's medial necrosis may be the cause of death in the first months of life or not until the ninth decade. Rupture of the aorta, possibly on a comparable basis, is said to occur in horses and occurs in epidemic fashion in turkeys,[97] where dietary factors may be responsible.

The treponemal immobilization test for syphilis has created a clinical problem in connection with patients with dilatation of the ascending aorta and aortic regurgitation, who often in the past would have been considered to be syphilitic in spite of negative serologic tests for syphilis of the conventional type. In coming years, cystic medial necrosis of the aorta, previously the exclusive property of the pathologists, will be discussed much more frequently in the clinical literature.

SUMMARY

The cardinal manifestations of the Marfan syndrome are skeletal, ocular, and aortic. Dolichostenomelia (long, thin extremities) and redundant ligaments and

*Erdheim's disease is very familiar as a cause of dissecting aneurysm. That it can also cause diffuse or fusiform dilatation of the aorta is indicated by the surgically proved cases referred to above and by reports in the literature.[35,67,131,185,186,187,303] In some of these, insufficient clinical information is provided to permit exclusion of the Marfan syndrome.

†Labella[244] suggests there may be a component of elastic fiber that is metabolically fairly active.

joint capsules characterize the skeletal changes. Ectopia lentis is the hallmark of the disorder in the eye. In the aorta, predominantly the ascending aorta, diffuse dilatation and/or dissection occur.

The only histopathologic changes described to date are those in the aorta, where degeneration of the elastic lamellae appears to be primary in the pathogenetic chain. It is tentatively proposed that the basic defect may be related to the elastic fiber.

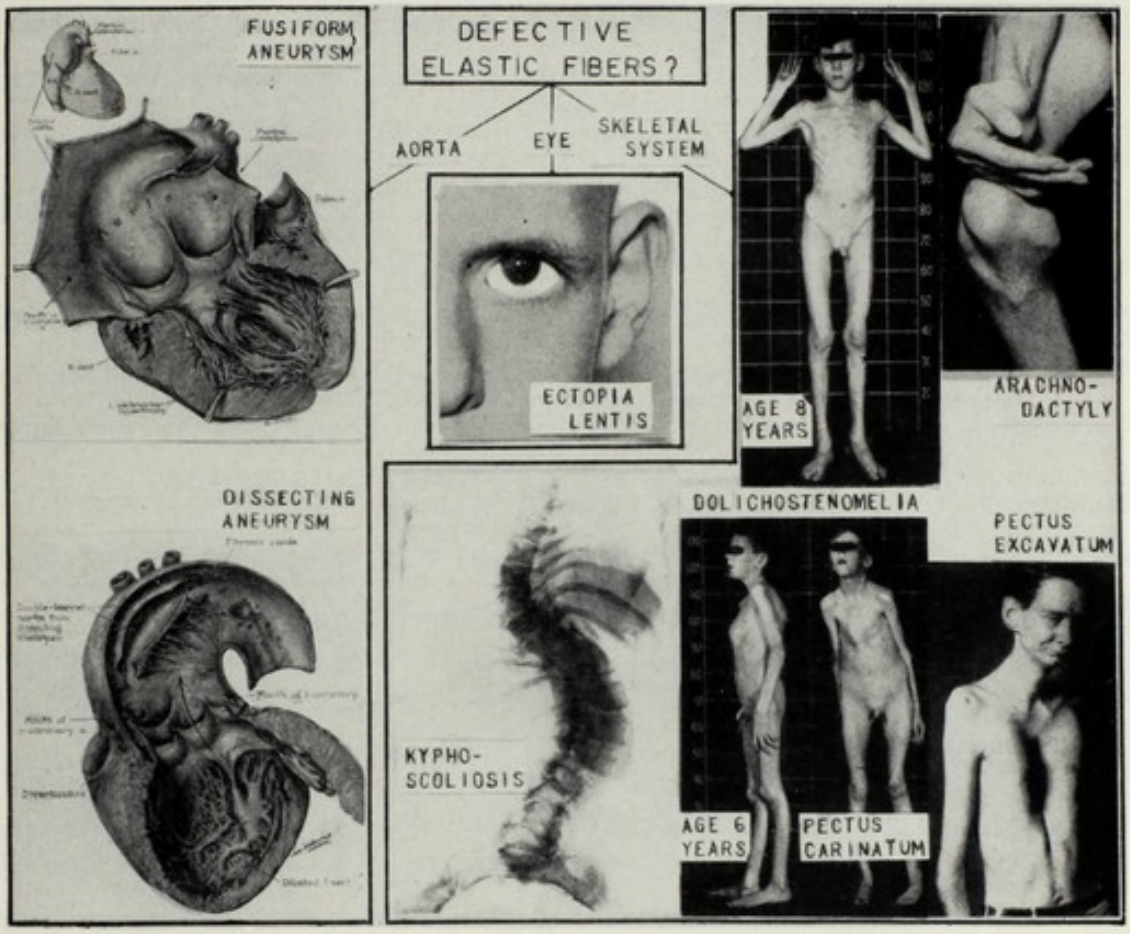


Fig. 46. A pictorial "pedigree of causes" relating the manifold manifestations of the Marfan syndrome to a postulated defect of the elastic fiber. (From McKusick, V. A.: Ann. Int. Med. **49**:556, 1958.)

The pedigrees are consistent with inheritance of this trait as a simple Mendelian dominant with a relatively high grade of penetrance.

Although certainly true cases of the Marfan syndrome occur without ectopia lentis and without other less equivocally affected members in the family, the lack of both of these features leaves the diagnosis in question in many instances.

REFERENCES

1. Abramson, D., Hurwitt, E., and Lesnick, G.: Relaxin in Human Serum as Test of Pregnancy, Surg. Gynec. & Obst. **65**:335, 1937.
2. Abramson, D., Roberts, S. M., and Wilson, D. P.: Relaxation of Pelvic Joints in Pregnancy, Surg. Gynec. & Obst. **58**:595, 1934.
3. Archard, C.: Arachnodactyly, Bull. et mém. Soc. méd. hôp. Paris **19**:834, 1902.
4. Adams, R. A., and Porter, W. B.: Marfan's Syndrome. Report of a Case, South. M. J. **42**:844, 1949.

5. Anderson, M., and Pratt-Thomas, H. R.: Marfan's Snydrome, Am. Heart J. **46**:911, 1953.
6. Anon.: Marfan's Biography, Am. J. Dermat. & Syph. **2**:143, 1942.
7. Anon.: Marfan's Biography, Presse méd. **50**:301, 1942.
8. Anon.: Marfan's Biography, Union méd. Canada **73**:1706, 1944.
9. Apert, E.: Les formes frustes du syndrome dolichosténomélique de Marfan, Nourrisson **26**:1, 1938.
10. Bachhuber, T. E., and Lalich, J. J.: Effect of Sweat Pea Meal on the Rat Aorta, Arch. Path. **59**:247, 1955.
11. Baer, R. W., Taussig, H. B., and Oppenheimer, E. H.: Congenital Aneurysmal Dilatation of the Aorta Associated With Arachnodactyly, Bull. Johns Hopkins Hosp. **72**:309, 1942.
12. Barron, A. A.: Arachnodactyly (Marfan's Snydrome), North Carolina M. J. **3**:353, 1942.
13. Bauer, J.: Innere Sekretion, Ihre Physiologie, Pathologie und Klinik, Berlin and Vienna, 1927, Julius Springer, p. 361.
14. Bean, W. B., and Fleming, J. G.: Arachnodactyly; Report of a Case Complicating Pregnancy at Term, Ohio M. J. **36**:155, 1940.
15. Bean, W. B., and Mohaupt, F. X.: Rupture of the Aortic Valve, J.A.M.A. **150**:92, 1952.
16. Bell, J.: Anomalies and Diseases of the Eye, The Treasury of Human Inheritance, Cambridge, 1932, Cambridge University Press, vol. II, part V, p. 477.
17. Benda, C. E.: Developmental Disorders of Mentation and Cerebral Palsies, New York, 1952, Grune & Stratton, Inc., p. 159.
18. Berg, G., and Vejlens, G.: Cystic Disease of the Lung in Tuberous Sclerosis, Acta paediat. **36**:16, 1939.
19. Berg, G., and Zachrisson, C. G.: Cystic-Lungs of Rare Origin—Tuberous Sclerosis, Acta radiol. **22**:425, 1941.
20. Bhat, P. K.: Bilateral Ectopia Lentis With Arachnodactyly. Marfan's Syndrome With Report of Case and Review of Literature, Antiseptic **43**:651, 1946.
21. Bigger, I. A.: The Treatment of Pectus Excavatum or Funnel Chest, Am. Surgeon **18**: 1071, 1952.
22. Binion, J. T.: Marfan's Syndrome, Am. Pract. & Digest Treat. **5**:135, 1954.
23. Black, H. H., and Landay, L. H.: Marfan's Syndrome; Report of Five Cases in One Family, A.M.A. Am. J. Dis. Child. **89**:414, 1955.
24. Boerger, F.: Ueber zwei Fälle von Arachnodaktylie, Ztschr. Kinderh. **12**:161, 1914; Monat. Kinderh. **13**:335, 1914.
25. Bornstein, F. P.: Dissecting Aneurysm of the Thoracic Aorta Due to Trauma, Texas J. Med. **50**:720, 1954.
26. Bortree, L. W.: Discussion of Strayhorn and Wells.[156]
27. Bramwell, C., and King, J. T.: The Principles and Practice of Cardiology, London, 1942, Oxford University Press, p. 29.
28. Brayshaw, J. R., and McKusick, V. A.: Unpublished observations.
29. Bronson, E., and Sutherland, G. A.: Ruptured Aortic Aneurysms in Childhood, Brit. J. Child. Dis. **15**:241, 1918.
30. Case Records of the Massachusetts General Hospital, New England J. Med. **243**:346, 1950.
31. Chang, C. E.: Marfan's Syndrome. Review of Literature and Report of One Case, Chinese M. J. **68**:433, 1951.
32. Churchill, D. W., Gelfant, S., Lalach, J. J., and Angevine, D. M.: Alterations in the Polysaccharides and Elastic Fibers in the Aortas of Rats Fed Toxic Lathyrus Factor, Lab. Invest. **4**:1, 1955.
33. Cockayne, E. A.: Arachnodactyly With Congenital Heart Disease (Patent Interventricular Septum), Proc. Roy. Soc. Med. **29**:120, 1935.
34. Dasler, W.: Partial Protection Against Odoratism by Diets High in Gelatin and Casein, Proc. Soc. Exper. Biol. & Med. **85**:485, 1954.
35. Davies, D. H.: Idiopathic Cystic Medial Necrosis of Aorta, Brit. Heart J. **3**:166, 1941.
36. Dax, E. C.: Arachnodactyly, J. Ment. Sc. **87**:434, 1941.
37. Duke-Elder, W. S.: Textbook of Ophthalmology, St. Louis, 1949, The C. V. Mosby Co., vol. IV, p. 4265.
38. Dupuy, H. P., and Lee, J. G.: The Isolation of a Material Capable of Producing Experimental Lathyrism, J. Am. Pharm. A. (Scient. Ed.) **43**:61, 1954.
39. Ellis, F. W. B.: Four Cases of Fragilitas Ossium and Blue Sclerotics, Proc. Roy. Soc. Med. **24** (part 2) :1054, 1931.
40. Engelbach, E.: Endocrine Medicine, Springfield, Ill., 1932, Charles C Thomas, Publisher.
41. Erdheim, J.: Medionecrosis aortae idiopathica cystica, Virchows Arch. path. Anat. **276**: 187, 1930.
42. Etter, L. E., and Glover, L. P.: Arachnodactyly Complicated by Dislocated Lens and Death From Dissecting Aueurysm of the Aorta, J.A.M.A. **123**:88, 1943.
43. Euzière, J., Pagès, P., Lafon, R., Mirouze, J., and Salvaing, J.: Myopathie scapulo-humérale d'Erb et dolichosténomélie; cas., Arch. franç. pédiat. **6**:651, 1951.
44. Evans, P. A.: A Hereditary Tendency to Hernia, Lancet **2**:293, 1942.
45. Evans, W.: The Heart in Sternal Depression, Brit. Heart J. **8**:162, 1946.

46. Fahey, J. J.: Muscular and Skeletal Changes in Arachnodactyly, Arch. Surg. **39**:741, 1939.
47. Fairbank, T.: Atlas of General Affections of the Skeleton, Baltimore, 1951, Williams & Wilkins Co., p. 175.
48. Faivre, G., Frenkiel, Pernot, C., and Hueber: Le coeur des dépressions sternales congénitales, Arch. mal coeur. **47**:322, 1954.
49. Fischl, A. A., and Ruthberg, J.: Clinical Implications of Marfan's Syndrome, J.A.M.A. **146**:704, 1951.
50. Flesch, M.: Ueber eine seltene Misschildung des Thorax, Virchows Arch. path. Anat. **57**:289, 1873.
51. Franceschetti, A.: Ectopia lentis et pupillae congenita als rezessives Erbleiden und ihre Manifestierung durch Konsanguinität, Klin. Monatsbl. Augenh. **78**:351, 1927.
52. Frei, C.: Ueber das Aneurysma dissecans aortae, Inaug. Dissert., Zurich, 1921, J. J. Meier.
53. Futcher, P. H., and Southworth, H.: Arachnodactyly and Its Medical Complications, Arch. Int. Med. **61**:693, 1938.
54. Ganther, R.: Ein Beitrag zur Arachnodaktylie, Ztschr. Kinderh. **43**:724, 1927.
55. Garland, H. G.: Hereditary Scoliosis, Brit. M. J. **1**:328, 1924.
56. Gilston, R. J.: Marfan's Syndrome, M. Ann. District of Columbia **24**:127, 1955.
57. Gore, I.: Dissecting Aneurysm of the Aorta in Persons Under Forty Years of Age, Arch. Path. **55**:1, 1953.
58. Gore, I.: The Pathogenesis of Dissecting Aneurysm of the Aorta, Arch. Path. **53**:142, 1952.
59. Gore, I., and Seiwert, S. J.: Dissecting Aneurysm of the Aorta: Pathological Aspects, an Analysis of Eighty-Five Fatal Cases, Arch. Path. **53**:121, 1952.
60. Gouley, B. A., and Anderson, E.: Chronic Dissecting Aneurysm of Aorta Simulating Syphilitic Cardiovascular Disease; Notes on Associated Aortic Murmurs, Ann. Int. Med. **124**:978, 1940.
61. Goyette, E. M., and Palmer, P. W.: Cardiovascular Lesions in Arachnodactyly, Circulation **7**:373, 1953.
62. Gray, H.: Arachnodactyly, Arch. Int. Med. **75**:215, 1945.
63. Green, H., and Emerson, P. W.: Arachnodactylia, Arch. Pediat. **60**:229, 1943.
64. Hamman, L., and Apperly, F. S.: Spontaneous Rupture of the Aorta With Aortic Insufficiency, Internat. Clin., Series 43, **4**:251, 1933.
65. Hamwi, G. J.: Marfan's Syndrome (Arachnodactyly), Am. J. Med. **11**:261, 1951.
66. Haridas, G.: Arachnodactylia in a Chinese Infant, Arch. Dis. Child. **16**:257, 1941.
67. Harrison, F. F.: Coarctation of the Aorta of the Adult Type, Associated With Cystic Degeneration of the Media of the First Portion of the Arch, Arch. Path. **27**:742, 1939.
68. Harrison, J., and Klainer, M. J.: Arachnodactyly; Its Occurrence in Several Members of One Family, New England J. Med. **220**:621, 1939.
69. Hartman, C. G., and Straus, W. L.: Relation of Pelvic Ligaments in Pregnant Monkeys, Am. J. Obst. & Gynec. **37**:498, 1939.
70. Hersh, A. H., DeMarinis, F., and Stecher, R. M.: On the Incidence and Development of Clinodactyly, Am. J. Human Genet. **5**:257, 1953.
71. Hofmann, W. P., and Carey, E. T.: Congenital Myopic Astigmatism in Identical Twins, Am. J. Ophth. **25**:1495, 1942.
72. Hudson, J. R.: Marfan's Syndrome With Retinal Detachment, Brit. J. Ophth. **35**:244, 1951.
73. Hufnagel, C. A., Harvey, W. P., Rahil, P. J., and McDermott, T. F.: Surgical Correction of Aortic Insufficiency, Surgery **35**:673, 1954.
74. I.A.A.: Bernard Jean Antoine Marfan, M.D., Am. J. Dis. Child. **64**:354, 1942.
75. Jequier, M.: Observations sur le syndrome de Marfan, Helvet. med. acta **10**:233, 1943.
76. Kahrs, T.: Three Cases of Arachnodactylia, Acta med. scandinav. **121**:240, 1945.
77. Kaplan, B. M., Schlichter, J. G., Graham, G., and Miller, G.: Idiopathic Congenital Dilatation of the Pulmonary Artery, J. Lab. & Clin. Med. **41**:697, 1953.
78. Katz, H. L.: Thoracic Manifestations in Marfan's Syndrome, Quart. Bull. Sea View Hosp. **13**:95, 1952.
79. Kountz, W. B., and Hempelmann, L. H.: Chromatrophic Degeneration and Rupture of the Aorta Following Thyroidectomy in Cases of Hypertension, Am. Heart J. **20**:599, 1940.
80. Kvorak-Theobald, G.: Histologic Study of an Eye From a Child With Arachnodactyly, Arch. Ophth. **24**:1046, 1940.
81. Lacroix, P.: The Organization of Bone, Translated by Stewart Gilder, Philadelphia, 1951, The Blakiston Co.
82. Langeron, T., Girard, P., Liefooghe, J., and Masson, C.: Maladie de Marfan et anéurysme abdominal, Bull. Soc. méd. hôp. Paris **70**:374, 1954.
83. Lester, C. W.: The Surgical Treatment of Funnel Chest, Ann. Surg. **123**:1003, 1946.
84. Levine, E., Stein, M., Gordon, G., and Mitchell, N.: Chronic Dissecting Aneurysm of the Aorta Resembling Chronic Rheumatic Heart Disease, New England J. Med. **244**:902, 1951.
85. Lindeboom, G. A., and Bouwer, W. F.: Dissecting Aneurysm (and Renal Cortical Necrosis) Associated With Arachnodactyly, Cardiologia **15**:12, 1949.

86. Lindeboom, G. A., and Westerveld-Brandon, E. R.: Dilatation of the Aorta in Arachnodactyly, Cardiologia **17**:217, 1950.
87. Lloyd, R. I.: Arachnodactyly, Arch. Ophth. **13**:744, 1935.
88. Lloyd, R. I.: A Second Group of Cases of Arachnodactyly, Arch. Ophth. **17**:69, 1937.
89. Lloyd, R. I.: Clinical Course of the Ocular Complications of Marfan's Syndrome, Arch. Ophth. **40**:558, 1948.
90. Lowe, R .C.: Polycythemia Vera (Erythremia). Arachnodactyly With Congenital Defect of Vertebral Column, and Familial Muscular Dystrophy in Negroes; Case Reports, Tri-State M. J. **13**:2679, 1941.
91. Lutman, F. C., and Neel, J. V.: Inheritance of Arachnodactyly, Ectopia Lentis and Other Congenital Anomalies (Marfan's Syndrome) in the E. Family, Arch. Ophth. **41**:276, 1949.
92. McKusick, V. A.: The Cardiovascular Aspects of Marfan's Syndrome, Circulation **11**:321, 1955.
93. McKusick, V. A.: Primordial Dwarfism and Ectopia Lentis, Am. J. Human Genet. **7**:187, 1955.
94. McKusick, V. A.: Unpublished observations.
95. McKusick, V. A., Hahn, D. P., Brayshaw, J. R., and Humphries, J. O'N.: Some Hemodynamic Effects of the Hufnagel Operation for Aortic Regurgitation. Studies in Models and a Patient, Bull. Johns Hopkins Hosp. **95**:322, 1954.
96. McKusick, V. A., Murray, G. E., Peeler, R. G., and Webb, G. N.: Musical Murmurs, Bull. Johns Hopkins Hosp. **97**:136, 1955.
97. McSherry, B. J., Ferguson, A. E., and Ballantyne, J.: Dissecting Aneurysm in Turkeys, J. Am. Vet. M. A. **124**:279, 1954.
98. Maier, C., Rubli, J. M., Schaub, F., and Hedinger, C.: Cardiale Störungen beim Marfanschen Syndrom, Cardiologia **24**:106, 1954.
99. Mamou, H., and Hérault, P.: Maladie de Marfan et maladie de Scheuermann, Semaine hôp. Paris **27**:3071, 1951.
100. Marchesani, O.: Jubilee Volume for Prof. Vogt, part II, Basle, 1939, Benno Schwabe & Co., p. 32.
101. Marfan, A. B.: Un cas de déformation congénitale des quatre membres plus prononcée aux extrémités charactérisée par l'allongement des os avec un certain degré d' amincissement, Bull. et mém. Soc. méd. hôp. Paris **13**:220, 1896.
102. Martin, R.: Lehrbuch der Anthropologie, Jena, 1928, Gustav Fischer.
103. Marvel, R. J., and Genovese, P. D.: Cardiovascular Disease in Marfan's Syndrome, Am. Heart J. **42**:814, 1951.
104. Master, A. M., and Stone, J.: The Heart in Funnel-Shaped and Flat Chests, Am. J. M. Sc. **217**:392, 1949.
105. Méry, H., and Babonneix, L.: Un cas de déformation congénitale des autre membres: hyperchondroplasia, Bull. et mém. Soc. méd. hôp. Paris. **19**:671, 1902.
106. Moses, M. F.: Aortic Aneurysm Associated With Arachnodactyly, Brit. M. J. **2**:81, 1951.
107. Nodes, J. D. S., and Henes, F.: Total Rupture of an Aneurysm of the Splenic Artery Immediately After Labor, Tr. Obst. Soc. London **42**:305, 1900.
108. Olcott, C. T.: Arachnodactyly (Marfan's Syndrome) With Severe Anemia, Am. J. Dis. Child. **60**:660, 1940.
109. Ollier, L. X. E. L.: Traité expérimental et clinique de la régénération des os et production artificielle du tissu osseux, Paris, 1867, Masson & Cie.
110. Ormond, A. W.: The Etiology of Arachnodactyly, Guy's Hosp. Rep. **80**:68, 1930.
111. Oswold, N., and Parkinson, T.: Honeycomb Lungs, Quart. J. Med. **18**:1, 1949.
112. Parker, A. S., Jr., and Hare, H. F.: Arachnodactyly, Radiology **45**:220, 1945.
113. Pasachoff, H. D., Madonick, M. J., and Drayer, C.: Arachnodactyly in Four Siblings With Pneumoencephalographic Observations of Two, Am. J. Dis. Child. **67**:201, 1944.
114. Peiper, A.: Ueber die Erblichkeit der Trichterbrust, Klin. Wchnschr. **1**:1647, 1922.
115. Perl, E., and Catchpole, H. R.: Changes Induced in the Connective Tissue of the Pubic Symphysis of the Guinea Pig With Estrogen and Relaxin, Arch. Path. **50**:233, 1950.
116. Pierce, R. E.: Traumatic Dissecting Aneurysms of the Thoracic Aorta, U. S. Armed Forces M. J. **5**:1588, 1954.
117. Pino, R. H., Cooper, E. L., and Van Wien, S.: Arachnodactyly and Status Dysraphicus; a Review, Ann. Int. Med. **10**:1130, 1937.
118. Piper, R. K., and Irvine-Jones, E.: Arachnodactyly and Its Association With Congenital Heart Disease; Report of a Case and Review of the Literature, Am. J. Dis. Child. **31**:832, 1926.
119. Pommerenke, W. T.: Experimental Ligamentous Relaxation in Guinea Pig Pelvis, Am. J. Obst. &. Gynec. **27**:708, 1934.
120. Ponseti, I. V., and Baird, W. A.: Scoliosis and Dissecting Aneurysm of the Aorta in Rats Fed With Lathyrus Odoratus Seeds, Am. J. Path. **28**:1059, 1952.
121. Ponseti, I. V., and Shepard, R. S.: Lesions of the Skeleton and of Other Mesodermal Tissues in Rats Fed Sweet-Pea *(Lathyrus odoratus)* Seeds, J. Bone & Joint Surg. **36-A**:1031, 1954.
122. Poynton, F. J., and Maurice, W. B.: Arachnodactyly With Organic Heart Disease, Tr. Clin. Soc. London **75**:21, 1923.

123. Rados, A.: Marfan's Syndrome, Arch. Ophth. **27**:477, 1942.
124. Rambar, A. C., and Denenholz, E. J.: Arachnodactyly, J. Pediat. **15**:844, 1939.
125. Ravitch, M.: Pectus Excavatum and Heart Failure, Surgery **30**:178, 1951.
126. Reis, R. A., Baer, J. L., Arens, R. A., and Stewart, E.: Traumatic Separation of Symphysis Pubis During Spontaneous Labor With Clinical and X-ray Study of Normal Symphysis Pubis During Pregnancy and Puerperium, Surg. Gynec. & Obst. **55**:336, 1932.
127. Resnik, W. H., and Keefer, C. S.: Dissecting Aneurysm With Signs of Aortic Insufficiency, J.A.M.A. **85**:422, 1925.
128. Reynolds, G.: The Heart in Arachnodactyly, Guy's Hosp. Rep. **99**:178, 1950.
129. Reynolds, S. R. M., Light, F. W., Sr., Ardran, G. M., and Prichard, M. M. L.: Qualitative Nature of Pulsatile Flow in Umbilical Blood Vessels With Observations on Flow in the Aorta, Bull. Johns Hopkins Hosp. **91**:83, 1952.
130. Ross, L. J.: Arachnodactyly: Review of Recent Literature and Report of Case With Cleft Palate, Am. J. Dis. Child. **78**:417, 1949.
131. Rottino, A.: Medical Degeneration in a Non-ruptured Aorta Appearing Syphilitic Macroscopically, Arch. Path. **27**:320, 1939.
132. Rubin, E. H.: Diseases of the Chest, Philadelphia, 1947, W. B. Saunders Co.
133. Rutherford, W. J.: Hereditary Scoliosis, Brit. M. J. **2**:87, 1934.
134. Rywlin, A.: Medionecrosis idiopathica cystica unter dem Bilde des diffusen Aortenaneurysmas. Beziehungen zur Marfanschen Syndrom, Frankfort. Ztschr. Path. **63**:187, 1952.
135. Sainsbury, H. S. K.: Congenital Funnel Chest, Lancet **2**:615, 1947.
136. Salle, V.: Ueber einen Fall von angeborener abnormen Grosse der Extremitaten mit einen an Akronemegalia erinnerden Symptomenkomplex, Jahrb. Kinderh. **75**:540, 1912.
137. Sautter, H.: Aplasie des Dilatator pupillae beim Marfanschen Symptomenkomplex, Klin. Monatsbl. Augenh. **114**:449, 1949.
138. Schilling, E. D., and Strong, F. M.: Isolation, Structure and Synthesis of a Lathyrus Factor From L. Odoratus, J. Am. Chem. Soc. **76**:2848, 1954.
139. Schilling, V.: Striae distensae als hypophysäres Symptom bei basophilem Vorderlappenadenom (Cushingschem Syndrom) und bei Arachnodaktylie (Marfanschem Symptomenkomplex) mit Hypophysentumor, Med. Welt. **10**:183, 1936.
140. Schneider, W. F.: Arachnodactyly; Unusual Complication Following Skull Injury, J. Pediat. **27**:583, 1945.
141. Schnitker, M. A., and Bayer, C. A.: Dissecting Aneurysm of the Aorta in Young Individuals, Particularly in Association With Pregnancy, With Report of Case, Ann. Int. Med. **20**:486, 1944.
142. Schorr, S., Braun, K., and Wildman, J.: Congenital Aneurysmal Dilatation of the Ascending Aorta Associated With Arachnodactylia; Angiocardiographic Study, Am. Heart. J. **42**:610, 1951.
143. Sheehan, H. L.: The Pathology of Obstetric Shock, J. Obst. &. Gynaec. Brit. Emp. **16**:218, 1939.
144. Sheldon, W. H.: Atlas of Men. A Guide for Somatotyping the Adult Male at All Ages, New York, 1954, Harper & Bros., p. 338.
145. Slack, H. G. B.: Metabolism of Elastin in the Adult Rat, Nature **174**:512, 1955.
146. Sloper, J. C., and Storey, G.: Aneurysms of the Ascending Aorta Due to Medial Degeneration Associated With Arachnodactyly (Marfan's Disease), J. Clin. Path. **6**:299, 1953.
147. Snyder, L. H., and Curtis, G. M.: An Inherited "Hollow Chest," Koilosternia, a New Character Dependent Upon a Dominant Autosomal Gene, J. Hered. **25**:445, 1934.
148. Sosman, M. C.: Xanthomatosis, J.A.M.A. **98**:110, 1932.
149. Starke, H.: Zur Pathogenese des Marfan-Syndroms, Von Gräfe's Arch. Ophth. **151**:384, 1951.
150. Stephens, F. E.: Inheritance of Diseases Primary in the Muscles, Am. J. Med. **15**:558, 1953.
151. Stephenson, W. V.: Anterior Megalophthalmos and Arachnodactyly, Am. J. Ophth. **28**:315, 1954.
152. Stettner, E.: Wachstum und Wachstumsstorungen, Monatschr. Kinderh. **80**:387, 1937.
153. Stoddard, S. E.: The Inheritance of "Hollow Chest." Cobbler's Chest Due to Heredity—Not an Occupational Deformity, J. Hered. **30**:139, 1939.
154. Stratz, C. H.: Der Körper des Kindes, Stuttgart, 1902, Ferdinand Enke.
155. Straub, H.: Die elastischen Fasern in den Bändern des menschlichen Fusses, Acta anat. **11**:268, 1950.
156. Strayhorn, D., and Wells, E. B.: Arachnodactylia With Aneurysmal Dilatation of the Aorta, Tr. Am. Clin. & Climatol. A. **59**:205, 1947.
157. Sutton, G. E. F.: Cardiac Anomalies Associated With Funnel Chest, Bristol M. Clin. J. **64**:45, 1947.
158. Sweet, R. H.: Pectus Excavatum. Report of Two Cases Successfully Operated Upon, Ann. Surg. **119**:922, 1944.
159. Thomas, J., Brothers, G. B., Anderson, R. S., and Cuff, J. R.: Marfan's Syndrome. A Report of Three Cases With Aneurysm of the Aorta, Am. J. Med. **12**:613, 1952.

160. Thursfield, H.: Arachnodactyly, St. Bartholomew's Hosp. Rep. **53**:35, 1917-1918.
161. Tobin, J. R., Jr., Bay, E. B., and Humphries, E. M.: Marfan's Syndrome in the Adult. Dissecting Aneurysm of the Aorta Associated With Arachnodactyly, Arch. Int. Med. **80**:475, 1947.
162. Traisman, H. S., and Johnson, F. R.: Arachnodactyly Associated With Aneurysm of the Aorta, Am. J. Dis. Child. **87**:156, 1954.
163. Traub, E.: Epiphyseal Necrosis in Pituitary Gigantism, Arch. Dis. Child. **14**:203, 1939.
164. Troxler, E. R., and Niemetz, D.: Generalized Xanthomatosis With Pulmonary, Skeletal and Cerebral Manifestations: Report of a Case, Ann. Int. Med. **25**:960, 1946.
165. Trüb, C. L. P.: Aortenwanderkrankung (Medianecrosis aortae idiopathica), Aortenzerreissung und Arbeitsunfall, Monatsschr. Unfallh. **54**:321, 1951.
166. Tung, H. L., and Liebow, A. A.: Marfan's Syndrome. Observations at Necropsy With Special Reference to Medio-necrosis of the Great Vessels, Lab. Invest. **1**:382, 1952.
167. Usher, C. H.: A Pedigree of Congenital Dislocation of the Lenses, Biometrika **16**:273, 1924.
168. Uyeyama, H., Kondo, B., and Kamins, M.: Arachnodactylia and Cardiovascular Disease, Am. Heart J. **34**:580, 1947.
169. Vejdonsky, V.: Marfan's Syndrome, Lék. Listy. **1**:539, 1946.
170. Viva-Salas, E., and Sanson, R. E.: Sindrome d Marfan, sin cardiopatia congenita y con endocarditis lenta conformada por la autopsia, Arch. Inst. cardiol. México **18**:217, 1948.
171. v. Meyenburg, H.: Ueber spontane Aortenrupture bei zwei Brudern, Schweiz. med. Wchnschr. **20**:976, 1939.
172. Wawzonek, S., Ponseti, I. V., Shepard, R. S., and Wiedenmann, L. G.: Epiphyseal Plate Lesions, Degenerative Arthritis and Dissecting Aneurysm of the Aorta Produced by Amino-nitriles, Science **121**:63, 1955.
173. Weber, F. P.: Familial Asthenia ("Paralytic") Type of Thorax With Congenital Ectopia of Lenses, a Condition Allied to Arachnodactyly, Lancet **2**:1472, 1933.
174. Webster, B., Rich, C., Densen, P. M., Moore, J. E., Nicol, C. S., and Padget, P.: Studies in Cardiovascular Syphilis. III. The Natural History of Syphilitic Aortic Insufficiency, Am. Heart J. **46**:117, 1953.
175. Weill, G.: Ectopie du cristallin et malformations générales, Ann. d'ocul. **169**:21, 1932.
176. West, L. S.: Two Pedigrees Showing Inherited Predisposition to Hernia, J. Hered. **27**:449, 1939.
177. Weve, H.: Ueber Arachnodaktylie (Dystrophia mesodermalis congenita, typus Marfanis), Arch. Augenh. **104**:1, 1931.
178. Weyers, H.: Zur Kenntnis der Arachnodaktylie und ihrer Beziehungen zu anderen mesodermalen Konstitutionsanomalien, Ztschr. Kinderh. **67**:308, 1949.
179. White, P. D.: Personal communication.
180. Whitfield, A. G. W., Arnott, W. M., and Stafford, J. S.: "Myocarditis" and Aortic Hypoplasia in Arachnodactylia, Lancet **1**:1387, 1951.
181. Wilkins, L.: The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence, Springfield, Ill., 1950, Charles C Thomas, Publisher.
182. Wilkinson, K. D.: Aneurysmal Dilatation of the Pulmonary Artery, Brit. Heart J. **2**:255, 1940.
183. Williams, E.: Rare Cases, With Practical Remarks, Tr. Am. Ophth. Soc. **2**:291, 1873-1879.
184. Wolff, K.: Ueber die Ursachen der sogenannten spontanen Aortenzerreissungen, Virchows Arch. Path. Anat. **289**:1, 1933.
185. Wolff, K.: Unbekannte Erkrankung der Säuglingsaorta mit Schmund des elastischen Gewebes, Virchows Arch. Path. Anat. **285**:369, 1932.
186. Yetta, M., and Laski, S. L.: Aneurysmal Dilatation of the Aorta Associated With Cystic Medial Necrosis, Am. Heart J. **33**:516, 1947.
187. Young, J.: Relaxation of Pelvic Joints in Pregnancy: Pelvic Arthropathy of Pregnancy, J. Obst. &. Gynaec. Brit. Emp. **47**:493, 1940.
188. Young, M. L.: Arachnodactyly, Arch. Dis. Child. **4**:190, 1929.
189. Albanese, A.: Sulla dolicostenomelia, Arch. ortop. **47**:539, 1931.
190. Anderson, A., Spencer, H., and Staffurth, J. S.: Dissecting Aneursym and Medial Degeneration of the Aorta in Marfan's Syndrome, St. Thomas's Rep. **7**:146, 1951.
190a. Anning, S. T.: Elastoma Intrapapillare Perforans Verruciforme (Miescher), Proc. Roy. Soc. Med. (Sect. Dermat.) **51**:932, 1958.
191. Austin, M. G., and Schaefer, R. F.: Marfan's Syndrome, With Unusual Blood Vessel Manifestations. Primary Medionecrosis Dissection of Right Innominate, Right Carotid, and Left Carotid Arteries, A.M.A. Arch. Path. **64**:205, 1957.
192. Bacchus, H.: A Quantitative Abnormality in Serum Mucoproteins in the Marfan Syndrome, Am. J. Med. **25**:744, 1958.
193. Bahnson, H. T., and Nelson, A. R.: Cystic Medial Necrosis as a Cause of Localized Aortic Aneurysms Amenable to Surgical Treatment, Ann. Surg. **144**:519, 1956.
194. Baker, C. B., Wilson, T. K., and Woods, J. M.: Marfan's Syndrome; a Successful Aortic Homograft for a Dissecting Aneurysm of the Thoracic Aorta, Canad. J. Surg. **1**:371, 1958.

195. Bean, W. B.: Precordial Noises Heard at a Distance From the Chest; *In* Monographs in Medicine, Baltimore, 1952, Williams & Wilkins Co. p. 22.
196. Bean, W. B., and Ponseti, I. V.: Dissecting Aneurysm Produced by Diet, Circulation **12**:185, 1955.
197. Becker (Naumberg): Linsenektopie in der I., (II.) und III. Generation, Klin. Monatsbl. Augenh. **94**:547, 1935.
198. Becker, P. E.: Dystrophia Musculorum Progressiva; Eine genetische und klinische Untersuchung der Muskeldystrophien, Stuttgart, 1953, Georg Thieme Verlag.
199. Benavides, P.: Sindrome de Marfan, Principia Cardiologica **3**:193, 1956.
200. Bergstrand, C. G.: Arachnodactylia: Pathological Anatomy in Connection With a Case, Acta paediat. **30**:345, 1943.
201. Berlin, R.: Familial Occurrence of Pneumothorax Simplex, Acta med. scandinav. **137**:268, 1950.
202. Bingle, J.: Marfan's Syndrome, Brit. M. J. **1**:629, 1957.
203. Booth, C. C., Longbridge, L. W., and Turner, M. D.: Arachnodactyly With Congenital Lesions of the Urinary Tract, Brit. M. J. **2**:80, 1957.
204. Bowers, D. (Kelowna, British Columbia): In press.
205. Boyd, D. H. A.: Familial Spontaneous Pneumothorax, Scot. M. J. **2**:220, 1957.
206. Brock, R. C.: Recurrent and Chronic Spontaneous Pneumothorax, Thorax **3**:88, 1948.
207. Burian, H. M.: Chamber Angle Studies in Developmental Glaucoma. Marfan Syndrome and High Myopia, J. Missouri M. A. **55**:1088, 1958.
208. Burry, A. F.: Supra-aortic Stenosis Associated With Marfan's Syndrome, Brit. Heart J. **20**:143, 1958.
209. Cabot Case No. 43011: Marfan's Syndrome With Old and Recent Dissecting Aneurysm, Fibrinous Pericarditis With Effusion, Hufnagel Operation Two Months Before Death, Thrombosis of Valve, New England J. Med. **256**:30, 1957.
210. Calhoun, F. P.: Causes of Heterochromia Iridis With Special Reference to Paralysis of the Cervical Sympathetics, Am. J. Ophth. **2**:255, 1919.
211. Callahan, A.: Aniridia With Ectopia Lentis and Secondary Glaucoma, Am. J. Ophth. **32**:28, 1949.
212. Cartellieri, L., and Kleinsorge, H.: Neurologische Störungen beim Marfan-Syndrom, Nervenartz **24**:376, 1953.
213. Castellanos, A., Jr., Ugarriza, R., de Cardenas, A., and Cano, L. A.: Sindrome de Marfan. Reporte de seis casos en una misma familia, Arch. del Hosp. Universitario (Havana) **9**:353, 1957.
214. Choyce, D. P.: Anterior Dislocation of the Lens in Marfan's Syndrome, Brit. J. Ophth. **41**:446, 1957.
215. Coffey, J. H., Barker, D. E., and Friedlander, J. H.: Dissecting Aneurysm With Marfan's Syndrome, Texas J. Med. **51**:79, 1955.
216. Crowe, F. W., Schull, W. J., and Neel, J. V.: A Clinical, Pathological and Genetic Study of Multiple Neurofibromatosis, Springfield, Ill., 1956, Charles C Thomas, Publisher.
217. Crump, J., Mikelberg, R. M., and Recknagel, E. M. S.: Arachnodactyly (Marfan's Syndrome), J. Am. M. Women's A. **13**:62, 1958.
218. Das Gupta, B. K., and Basu, R. K.: Bilateral Dislocation of the Lens Under Voluntary Control in Marfan Syndrome With Cardiovascular Anomaly, Brit. J. Ophth. **39**:566, 1955.
218a. Davis, J. H., Benson, J. W., and Miller, R. C.: Thoracoabdominal Aneurysm Involving Celiac, Superior Mesenteric and Renal Arteries. Report of a Case Successfully Treated by Resection and Nylon-Graft Replacement, A.M.A. Arch. Surg. **75**:871, 1957.
219. Dexter, M. W., Lawton, A. H., and Warren, L. O.: Marfan's Syndrome With Aortic Thrombosis, Arch. Int. Med. **99**:485, 1947.
220. Dimond, E. G., Larsen, W. E., Johnson, W. B., and Kittle, C. F.: Post-traumatic Aortic Insufficiency Occurring in Marfan's Syndrome, With Attempted Repair With a Plastic Valve, New England J. Med. **25**:8, 1957.
221. Editorial: Marfan's Syndrome, New England J. Med. **256**:39, 1957.
222. Ellis, R. W. B.: Arachnodactyly and Ectopia Lentis in Father and Daughter, Arch. Dis. Child. **15**:267, 1940.
223. Esteve, R.: Idiopathic Scoliosis in Identical Twins, J. Bone & Joint Surg. **40-B**:97, 1958.
223a. Everberg, G.: Marfan's Syndrome Associated With Hearing Defect. Report of a Case in One of a Pair of Twins, Acta paediat. **48**:70, 1959.
224. Fabre, J., Veyrat, R., and Jeanneret, O.: Syndrome de Marfan avec anevrysme et coarctation de l'aorte; étude anatomo-clinicque, Schweiz. med. Wchnschr. **87**:49, 1957.
225. Falls, H. F.: A Gene Producing Various Defects of the Anterior Segment of the Eye, With a Pedigree of a Family, Am. J. Ophth. **32**:41, 1949.
226. Fay, J. E., Horlick, L., Merriman, J. E., and Nanson, E. M.: A Case of Marfan's Syndrome With an Aneurysm at the Ascending Aorta, With Physiologic, Operative and Postmortem Studies, Canad. M. A. J. **78**:862, 1958.
227. Feldman, L., Friedlander, J., Dillon, R., and Wallyn, R.: Aneurysm of Right Sinus of Valsalva With Rupture Into Right Atrium and Into the Right Ventricle, Am. Heart J. **51**:314, 1956.

228. Fleming, J., and Helwig, F. C.: Medionecrosis Aortae Idiopathica Cystica With Spontaneous Rupture, J. Missouri M. A. **38**:86, 1941.
228a. Golden, R. L., and Lakin, H.: The *Forme Fruste* in Marfan's Syndrome, New England J. Med. **260**:797, 1959.
229. Gordan, G. S., and Lisser, H. (eds.): Endocrinology in Clinical Practice, Chicago, 1953, Year Book Publishers, Inc.
230. Graham, J. G., and Milne, J. A.: Dissecting Aneurysm of the Aorta: Review of 29 Cases, Glasgow M. J. **33**:320, 1952.
230a. Greenfield, J. G., Cornman, T., and Shy, G. M.: The Prognostic Value of the Muscle Biopsy in the "Floppy Infant," Brain **81**:461, 1958.
231. Griffin, J. F., and Koman, G. M.: Severe Aortic Insufficiency in Marfan's Syndrome, Ann. Int. Med. **48**:174, 1958.
232. Griffith, G. J., Hayhurst, A. P., and Whitehead, R.: Dissecting Aneurysm of Aorta in Mother and Child, Brit. Heart J. **13**:364, 1951.
233. Gupta, S. K., and Sharma, V. N.: Chronic Pneumothorax in Marfan's Syndrome, Brit. J. Tuberc. **51**:346, 1957.
233a. Haber, H.: Miescher's Elastoma (Elastoma Intrapapillare Perforans Verruciforme), Brit. J. Dermat. **71**:85, 1959.
234. Haldane, J. B. S.: The Rate of Spontaneous Mutation of a Human Gene, J. Genetics **31**:317, 1935.
234a. Hardin, C. A.: Ruptured Abdominal Aneurysm Occurring in Marfan's Syndrome. Attempted Repair With the Use of a Nylon Prosthesis, New England J. Med. **260**:821, 1959.
235. Hirst, A. E., Jr., and Bailey, H. L.: Arachnodactyly With Associated Healing Dissecting Aneurysm, California Med. **84**:355, 1956.
236. Hirst, A. E., Jr., Johns, V. J., Jr., and Kime, S. W., Jr.: Dissecting Aneurysm of the Aorta; a Review of 505 Cases, Medicine **37**:217, 1958.
236a. Humphries, J. O'N., and Pusch, A. L.: Effect of the Hormone Relaxin on the Aorta of the Guinea Pig and Rat, Clin. Res. **6**:233, 1958.
237. Husebye, K. O., Wolff, H. J., and Friedman, L. L.: Aortic Dissection in Pregnancy; A Case of Marfan's Syndrome, Am. Heart J. **55**:662, 1958.
238. Huston, W. H.: The Marfan Syndrome. A Report of an Atypical Case, Henry Ford Hosp. M. Bull. **5**:90, 1957.
239. Killip, T., III (New York City): Personal communication.
240. Kingsley-Pillers, E. M.: Arachnodactyly With Amyoplasia Congenita, Proc. Roy. Soc. Med. **39**:696, 1946.
241. Kloepfer, H. W., and Rosenthal, J. W.: Possible Genetic Carriers in the Spherophakia-Brachymorphia Syndrome. Am. J. Human Genet. **7**:398, 1955.
242. Knight, A. M., Jr.: The Marfan Syndrome, J. M. A. Georgia **46**:413, 1957.
243. Kravitz, D.: Marfan's Syndrome, Am. J. Ophth. **39**:576, 1955.
244. Labella, F. S.: Elastin, a Metabolically Active Lipoprotein, Nature **180**:1360, 1958.
245. Lavoie, R. G., and Boulanger, J.: Le syndrome de Marfan, Laval méd. **25**:453, 1958.
246. Lillian, M.: Multiple Pulmonary Artery Aneurysms; Endocarditis of Ductus Arteriosus and Congenital Pulmonary Cysts, Am. J. Med. **7**:280, 1949.
247. Low, A.: Measurements of Infants at Birth, Ann. Eugenics **15**:210, 1950.
248. Lynas, M. A.: Marfan's Syndrome in Northern Ireland; an Account of Thirteen Families, Ann. Human Genet. **22**:289, 1958.
249. Lynas, M. A.: Unpublished observations referred to in reference 287.
250. Lynas, M. A., and Merrett, J. D.: Data on Linkage in Man; Marfan's Syndrome in Northern Ireland, Ann. Human Genet. **22**:310, 1958.
251. MacCallum, W. G.: Dissecting Aneurysm, Bull. Johns Hopkins Hosp. **20**:9, 1909.
252. McCann, J. S., and Porter, D. C.: Calcification of the Aorta as an Aid to the Diagnosis of Syphilis, Brit. M. J. **1**:826, 1956.
253. McKusick, V. A.: Cardiovascular Sound in Health and Disease, Baltimore, 1958, Williams & Wilkins Co.
253a. McKusick, V. A.: The Genetic Aspects of Cardiovascular Diseases, Ann. Int. Med. **49**:556, 1958.
253b. McKusick, V. A.: Hereditary Disorders of Connective Tissue, Bull. New York Acad. Med. **35**:143, 1959.
254. MacLeod, M., and Williams, W. A.: The Cardiovascular Lesions in Marfan's Syndrome, Arch. Path. **61**:143, 1956.
255. Mandel, W., Evans, E. W., and Walford, R. L.: Dissecting Aortic Aneurysm During Pregnancy, New England J. Med. **251**:1059, 1954.
256. Marchesani, O.: Brachydaktylie und angeborene Kugellinse als Systemerkrankung, Klin. Monatsbl. Augenh. **103**:392, 1939.
257. Marfan, A. B.: Sur la ponction du péricarde et en particulier sur la ponction par voie épigastrique sous-xiphoidienne, Arch. mal. coeur **29**:153, 1936.
258. Marks, J., and Gerson, K. L.: Importance of Autopsies—an Illustrative Case, J.A.M.A. **168**:1450, 1958.
259. Maxwell, G. M.: Chest Deformity in Children With Congenital Heart Disease, Am. Heart J. **54**:368, 1957.

259a. Meara, R. A.: Ehlers-Danlos Syndrome and ?Elastoma Verruciforme Perforans (Miescher), Tr. St. Johns Hosp. Dermat. Soc. (London) **40**:72, 1958.
260. Meyer, K. (New York City): Personal communication.
261. Meyer, S. J., and Holstein, T.: Spherophakia With Glaucoma and Brachydactyly, Am. J. Ophth. **24**:247, 1941.
262. Millant, R.: Les eunques à travers les ages, Paris, 1908, Vigot Frères.
263. Neilson, G. H., and Sullivan, J. J.: Dissecting Aneurysm of the Aorta Associated With Marfan's Syndrome, M. J. Australia **1**:925, 1956.
264. Nelson, J. D.: The Marfan Syndrome, With Special Reference to Congenital Enlargement of the Spinal Canal, Brit. J. Radiol. **31**:561, 1958.
265. Norcross, J. R.: Arachnodactylia—a Report of Three Cases, J. Bone & Joint Surg. **20**:757, 1938.
266. Novell, H. A., Asher, L. A., Jr., and Lev, M.: Marfan's Syndrome Associated With Pregnancy, Am. J. Obst. & Gynec. **75**:802, 1958.
267. Oram, S., and East, T.: Rupture of Aneurysm of Aortic Sinus (of Valsalva) Into the Right Side of the Heart, Brit. Heart J. **17**:541, 1955.
268. Pappas, E. G., Mason, D., and Denton, C.: Marfan's Syndrome: a Report of Three Patients With Aneurysm of the Aorta, Am. J. Med. **23**:426, 1957.
269. Pygott, F.: Arachnodactyly (Marfan's Syndrome) With a Report of Two Cases, Brit. J. Radiol. **28**:26, 1955.
270. Reeh, M. J., and Lehman, W. L.: Marfan's Syndrome (Arachnodactyly) With Ectopia Lentis, Tr. Am. Acad. Ophth. **58**:212, 1954.
271. Reeves, J. E., and Irwin, H. R.: Marfan's Syndrome. Report of a Probable Case, California Med. **86**:183, 1957.
272. Rich, A. R., and Oppenheimer, E. (Baltimore): Personal communication.
273. Risser, J. C.: Clinical Evaluation of Scoliosis, J.A.M.A. **164**:134, 1957.
274. Roark, J. W.: Marfan's Syndrome. Report of One Case With Autopsy, Special Histological Study and Review of the Literature, Arch. Int. Med. **103**:123, 1959.
275. Sando, D. E., and Helm, S.: Acquired Coarctation in New Channel of Healed Dissecting Aneurysm, Ann. Int. Med. **37**:793, 1952.
276. Sheehan, H. L., and Falkiner, N. M.: Splenic Aneurysm and Splenic Enlargement in Pregnancy, Brit. M. J. **2**:1105, 1948.
277. Siegenthaler, W.: Die Kardio-vaskulären Veränderungen beim Marfan-Syndrom (Arachnodatylie), Cardiologia **28**:135, 1956.
278. Sinclair, R. J. G.: The Marfan Sydrome, Bull. Rheumat. Dis. **8**:153, 1958.
279. Sinha, K. P., and Goldberg, H.: Marfan's Syndrome: A Case With Complete Dissection of the Aorta, Am. Heart J. **36**:890, 1958.
279a. Skyring, A.: Personal communication.
280. Sjoerdsma, A., Davidson, J. D., Udenfriend, S., and Mitoma, C.: Increased Excretion of Hydroxyproline in Marfan's Syndrome, Lancet **2**:994, 1958.
281. Spenser, J. T.: Post-mortem Caesarian Delivery After Rupture of Dissecting Aortic Aneurysm, Lancet **2**:565, 1952.
282. Spickard, W. B.: Arachnodactyly, Description of the Clinical Characteristics With Report of Autopsied Case, Stanford M. Bull. **6**:422, 1948.
283. Steinberg, I.: Aneurysm of the Aortic Sinuses With Pseudo-Coarctation of the Aorta, Brit. Heart J. **18**:85, 1956.
284. Steinberg, I., and Finby, N.: Clinical Manifestations of the Unperforated Aortic Sinus Aneurysm, Circulation **14**:115, 1956.
285. Steinberg, I., and Geller, W.: Aneurysmal Dilatation of Aortic Sinuses in Arachnodactyly: Diagnosis During Life in Three Cases, Ann. Int. Med. **43**:120, 1955.
286. Steinberg, I., Mangiardi, J. L., and Noble, W. J.: Aneurysmal Dilatation of the Aortic Sinuses in Marfan's Syndrome; Angiocardiographic and Cardiac Catheterization Studies in Identical Twins, Circulation **16**:368, 1957.
287. Stevenson, A. C.: Comparisons of Mutation Rates at Single Loci in Man; *In* Effects of Radiation on Human Heredity, Geneva, 1957, World Health Organization, p. 125.
287a. Stevenson, A. C.: Personal communication.
288. Stewart, R. M.: A Case of Arachnodactyly, Arch. Dis. Childhood **14**:64, 1939.
289. Stolz, H. R., and Stolz, L. M.: Somatic Development of Adolescent Boys. A Study of the Growth of Boys During the Second Decade of Life, New York, 1951, The Macmillan Co.
289a. Storck, H.: Ein Fall von Arachnodaktylie (Dystrophia mesodermalis congenita), Typus Marfan, Dermatologica **104**:321, 1952.
290. Talbot, N. B., Sobel, E. H., McArthur, J. W., and Crawford, J. D.: Functional Endocrinology, Cambridge, Mass., 1952, Harvard University Press.
291. Toes, N. A.: Ruptured Splenic Artery Aneurysm During Parturition, Brit. M. J. **1**:495, 1956.
292. Tolbert, L. E., Jr., and Birchall, R. B.: Marfan's Syndrome With Interventricular Septal Defect Found at Autopsy, Ochsner Clin. Rep. **2**:48, 1956.
293. Tourniaire, A., Deyerieux, F., and Bastien, P.: Dilatation du segment initial de l'aorte: gigantisme de l'appareil valvulaire aortique, Arch. mal. coeur **44**:153, 1951.

294. Troy, J. M.: Marfan's Disease Complicated by Hemothorax, J. Indiana M. A. **48**:488, 1955.
295. Van Buchem, F. S. P.: Cardiovascular Disease in Arachnodactyly, Acta med. scandinav. **161**:197, 1958.
296. Vesely, D. G., Bray, C. B., and Bryant, V. M.: Arachnodactyly, a Case Report, J. M. A. Alabama **24**:276, 1955.
297. Wachtel, F. M., Ravitch, M. M., and Grisham, A.: The Relation of Pectus Excavatum to Heart Disease, Am. Heart J. **52**:121, 1956.
298. Wajda, I., Lehr, D., and Krukowski, M.: Sex Difference in Aortic Rupture Induced by Lathyrus Odoratus in Immature Rats, Fed. Proc. **16**:343, 1957.
299. Warwick, W. T., and Wiles P.: The Growth of Periosteum in Long Bones, Brit. J. Surg. **22**:169, 1934.
300. Whittaker, S. R. F., and Sheehan, J. D.: Dissecting Aortic Aneurysm in Marfan's Syndrome, Lancet **2**:791, 1954.
301. Wilson, R.: Marfan's Syndrome: Description of a Family, Am. J. Med. **23**:434, 1957.
302. Witkin, M.: Arachnodactyly in a Bantu Child, South African M. J. **32**:45, 1958.
303. Zanchi, M.: Medionecrosis idiopathica cystica dell'aorta ed aneurisma fusiforme puro giovanile in soggetto Basedowiano, Folio hered. et path. **7**:287, 1958.

4. THE EHLERS-DANLOS SYNDROME

HISTORICAL NOTE

None of the hereditary disorders of connective tissue, except possibly osteogenesis imperfecta, has as ancient a history as does the Ehlers-Danlos syndrome. The first definitive case* of this syndrome seems to have been described in 1682[94] by Job van Meekeren, a surgeon of Amsterdam. In Fig. 47 is presented van Meekeren's illustration of the "extraordinary dilatability of the skin" in a 23-year-old Spainard who could pull the right pectoral skin to the left ear, the skin under the chin up over the head like a beard, and the skin of the knee area out about one-half yard. On being released, the skin retracted promptly to fit snugly over the underlying structures. This phenomenon was limited to the skin of the right side of the body.

Various dermatologists, including Kopp[44] and Williams,[102] published scattered references to this condition, which was usually observed as a curiosity in "India rubber men" of side shows. Kopp's report in 1888 is particularly noteworthy, since he described the condition in father and son. Gould and Pyle[33] published the photograph made in Budapest in 1888 of an exhibitionist named Felix Wehrle, "who besides having the power to stretch his skin could readily bend his fingers backward and forward." Du Mesnil[23] in 1890, Williams[102] in 1892, working in Unna's laboratory in Hamburg, and Unna[93] himself in 1894 reported on histologic studies. In general, these authors were puzzled by the absence of more specific changes and found difficulties in the interpretation of what they did find. The contribution in 1901 by Ehlers[25] of Denmark consisted of pointing out the associated

*In *Airs, Waters and Places* Hippocrates,[51] in the fourth century B.C., described the Scythians as having markedly lax joints. "I will give you a strong proof of the humidity (laxity?) of their constitutions. You will find the greater part of the Scythians, and all the Nomades, with marks of the cautery on their shoulders, arms, wrists, breasts, hip-joints, and loins, and that for no other reason but the humidity and flabbiness of their constitution, for they can neither strain with their bows, nor launch the javelin from their shoulder owing to their humidity and atony: but when they are burnt, much of the humidity in their joints is dried up, and they become braced, better fed, and their joints get into a more suitable condition."[103] Is it possible that the cigarette paper scars of the Ehlers-Danlos syndrome were misinterpreted? Against this suggestion is the fact that burning the skin around joints became an established treatment for dislocation of joints, in the ancient world. Another statement is of much interest: ". . . they afterwards became lame and stiff at the hip-joint, such of them, at least, as are severely attacked with it." (From Adams, F.: The Genuine Works of Hippocrates, New York, 1891, William Wood & Co.)

loose-jointedness and the subcutaneous hemorrhages which are prone to occur. Danlos[15] in 1908 rounded out the clinical description with inclusion of the tumors which may develop at subcutaneous sites.

With considerable justification Jansen[127] argues that Tschernogobow[148,149] is most deserving of credit for the first detailed clinical description of this syndrome. In 1891 he presented to the Moscow Dermatologic and Venereologic Society two cases of the syndrome. He described the fragility as well as the hyperelasticity of the skin, the failure of the skin to hold sutures, the hypermobility and luxation of joints, and the molluscoid pseudotumors of the knees, elbows, and other areas. Most important, he tied all these features together as manifestations of a fundamental and generalized inadequacy of connective tissue; "Erschlaffung des Bindegewebes" were his words.

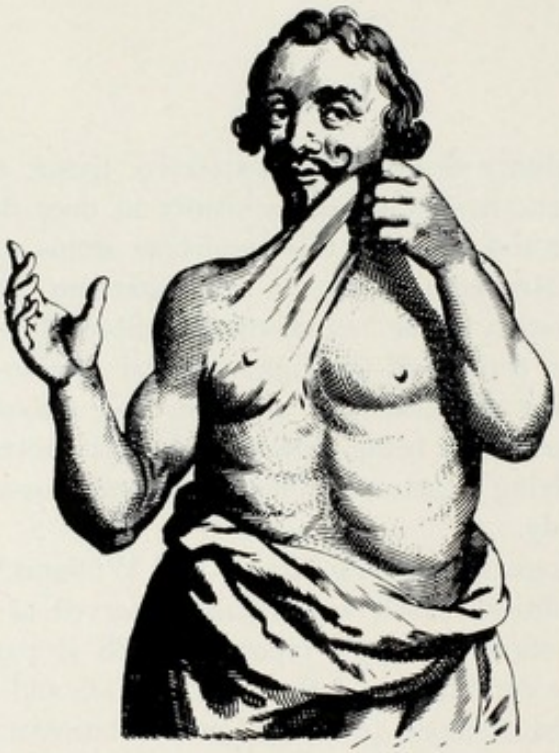


Fig. 47.—Job van Meekeren's case of "extraordinary dilatability of the skin."
"In the year 1657, in the presence of the very distinguished John van Horne and Francis Sylvius, professors of medicine in the famous academy of Leyden, as well as of William Piso and Francis vander Schagen, practitioners of Amsterdam, we saw in our hospital a certain young Spaniard, 23 years of age, by the name of George Albes, who with his left hand grasped the skin over his humerus and right breast and stretched it till it was quite close to his mouth. With each hand he first pulled the skin of his chin downward like a beard to his chest, hence he lifted it upwards to the vertex of his head so as to cover each eye with it. As soon as he removed his hand the skin contracted to reassume its proper smoothness. In the same way he pulled the skin of his right knee upwards or downwards, to the length of half an ell; then it easily returned to its natural position. It was worthwhile noting that the skin which covered the forementioned parts on the left side could not be extended since it firmly adhered to them. It has, thus far, not been possible to learn the cause [of this anomaly?]."—Translated from original Latin by Dr. Owsei Temkin.

One of Tschernogobow's patients[148] was a 17-year-old epileptic male who, in falling frequently on his face, had left there and elsewhere broad fissures running in all directions. The skin of the knees, elbows, and wrists was unusually spongy and loose, suggesting elephantiasis mollis or fibroma molluscum. Joint changes were especially pronounced on the left side, where dislocation of the elbow and

hip, dating from childhood, were present. In the second patient,[149] a 50-year-old woman, "tumors" were present not only on the elbows and knees but also on the buttocks, presumably in the vicinity of the ischial tuberosities. When one of these "tumors" was removed, it was discovered that sutures did not hold well and dehiscence of the wound occurred in a couple of days.

Many terms have been used for this syndrome or more often for its individual features. As in the case of the Marfan syndrome, the eponymic designation seems preferable, since it does not convey any connotations of the invariable occurrence of an individual manifestation or any ill-founded notion of the nature of the basic defect. "E-D" is the abbreviated label which will be used frequently in this presentation.

This survey of E-D is based on a personal study of fourteen kinships, each with at least one quite unequivocally affected person. Comparison of the findings with those reported in the literature is made.

CLINICAL MANIFESTATIONS[45,88]

The manifestations of the Ehlers-Danlos syndrome can conveniently be discussed under these headings: cutaneous, skeletal, ocular, and internal.

The Skin.[2,11,43,72,77] Characteristically, the skin in E-D is velvety in appearance and feel. It may also resemble wet chamois in feel. In the infant, it may be impressively white. It is hyperextensible, yet not lax (Fig. 48*A*).

The term *cutis laxa* is inappropriate in the typical case in young persons. Except as noted below, the skin is truly hyperelastic.*

In addition, the skin is fragile and brittle. Minor trauma may produce gaping, fish-mouth wounds. One of my patients was for a time a professional boxer, a mutilating occupation for one with this disorder. Another, 16 years old at the time of study (Figs. 48*A* to 48*G*), had had a total of 148 cutaneous stitches taken during her lifetime. Often stitches hold poorly in the skin,[38,76] and the patients and physicians resort to the use of adhesive tape. In the patient of Brown and Stock,[9] 282 stitches had been taken before count was stopped. Thomas and his associates[89] described slow healing of a skin biopsy site and dehiscence of an ocular incision for removal of an ectopic lens. Packer and Blades[63] observed

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*There is so much confusion in the biologic literature with reference to the term *elasticity* that some care must be exercised. Burton[109] writes as follows:

> Elasticity is properly defined as the property of materials which enables them to resist deformation by the development of a resisting force or "tension." All coefficients of elasticity are defined as the ratio of this resisting force (which at equilibrium is equal to the applied deforming force, or "load") to the measure of deformation produced. Thus, by the physical definition, a material of "high elasticity" resists deformation, e.g., stretching, by a large force; so that it takes a large force to produce a given deformation. A material of "low elasticity" cannot resist deformation so well, and it takes only a small force to produce the same degree of deformation. Thus glass or steel has a much higher elasticity than does rubber.
>
> Most unfortunately, popular usage of the adjective "elastic" connotes the opposite. If a material like rubber is easily stretched, it is popularly said to be "elastic" and glass is "not so elastic" as rubber. (From Burton, A. C.: Physiol. Rev. **34**:619, 1954.)

As used in this discussion of E-D, *elasticity* refers to physical properties, like those of rubber, specifically stretchability, and restoration after deformation.

Fig. 48*A*.

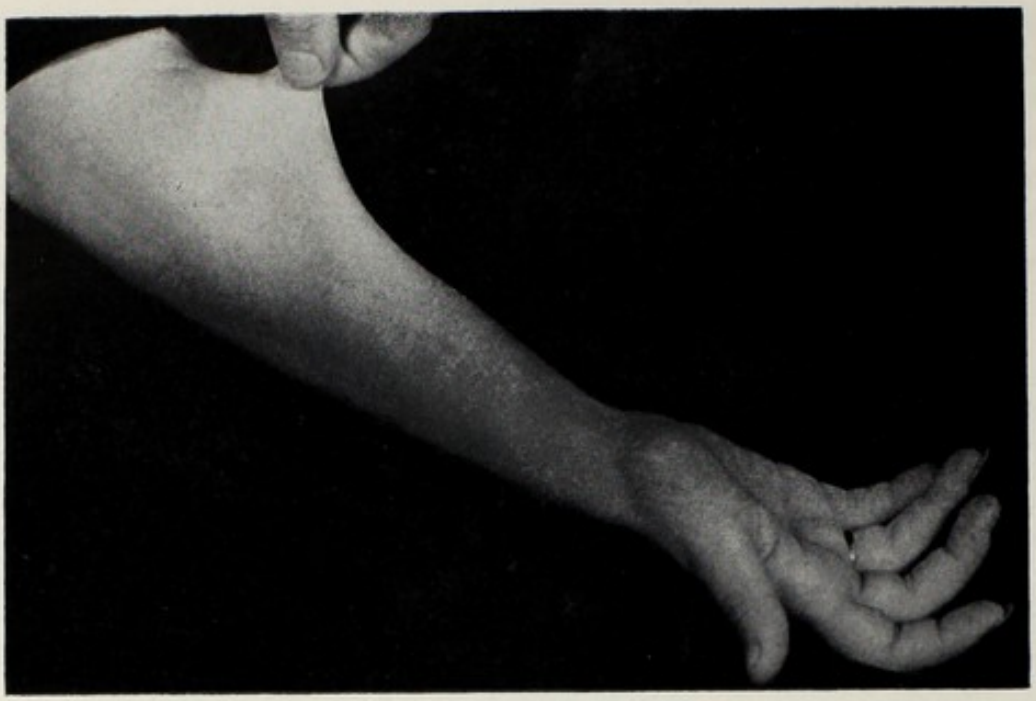


Fig. 48*B*.

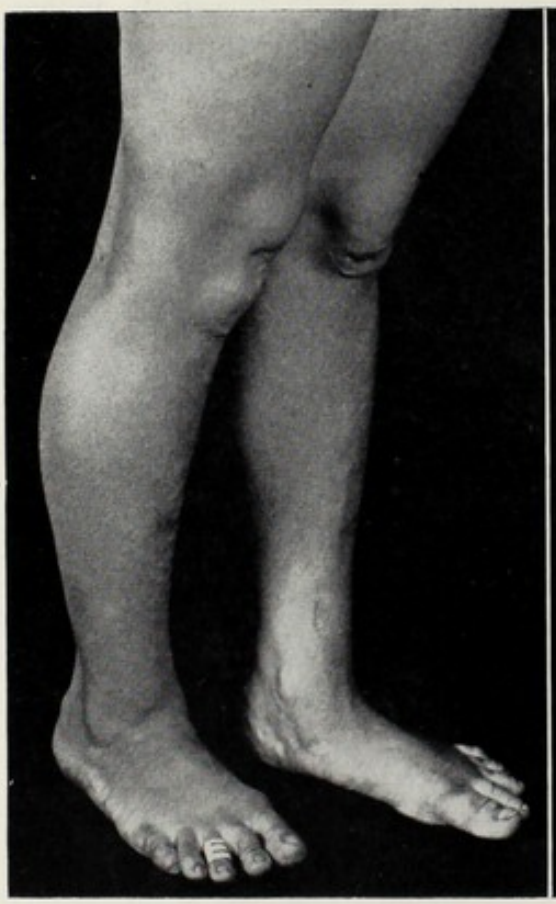
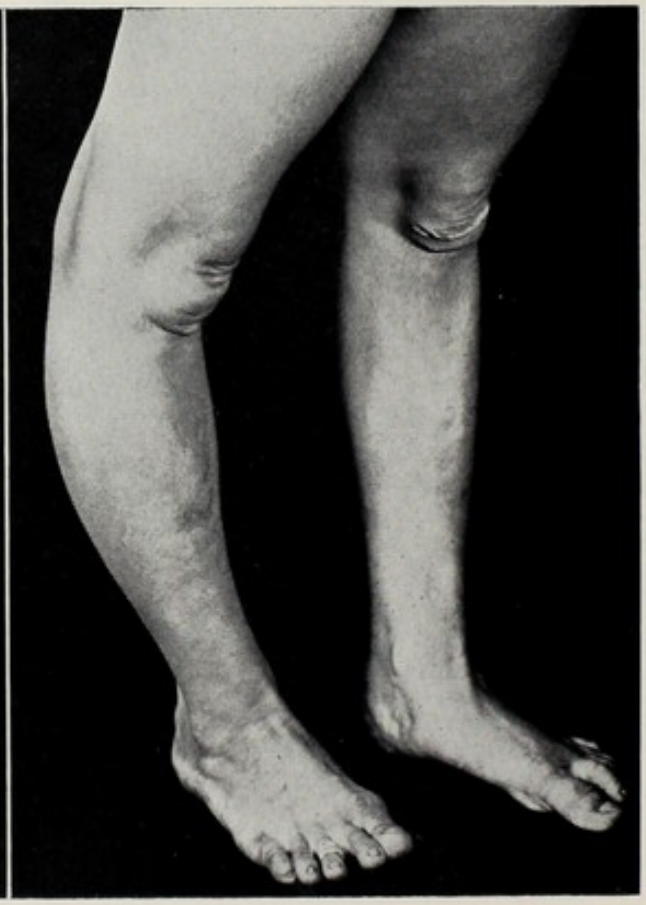


Fig. 48*C*.



Figs. 48*A*-48*G*. Changes in skin and joints of 16-year-old girl, D. V. (A41965).
Fig. 48*A*. Cutaneous hyperelasticity.
Fig. 48*B*. Normal position of knees. Note papyraceous scars over the knees and flat feet.
Fig. 48*C*. Genu recurvatum, more on the right.
Fig. 48*D*. Hyperextensibility of fifth finger.
Fig. 48*E*. Hyperextensibility of thumb. Note in the left hand the hyperextension of the index finger and the abnormal separation of the knuckles.
Fig. 48*F*. Hyperextensibility of fingers.
Fig. 48*G*. Unusual mobility of hip and knee joints.

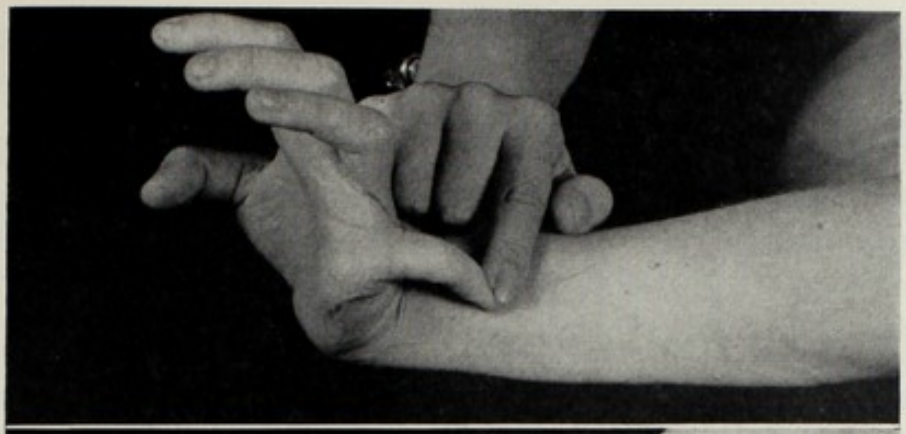


Fig. 48*D*.

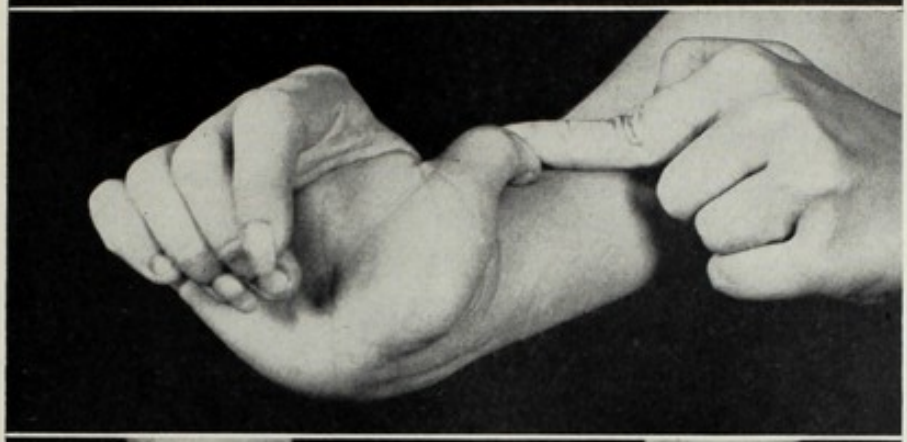


Fig. 48*E*.

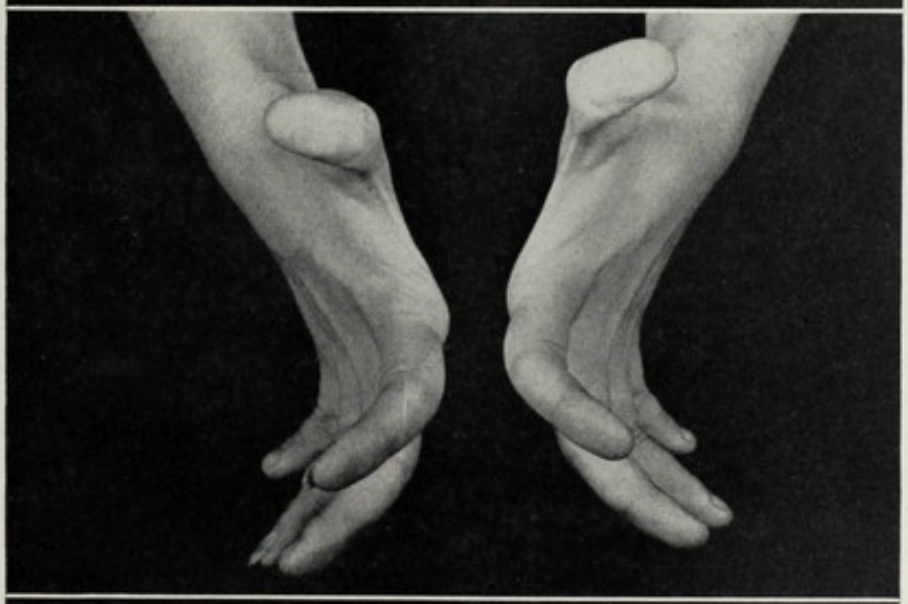


Fig. 48*F*.

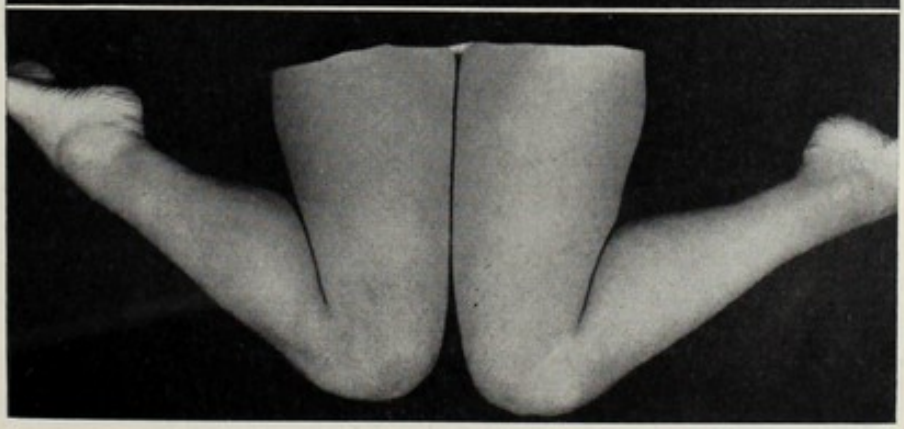


Fig. 48*G*.

Figs. 48*D*-48*G*. For legends see opposite page.

disruption of an appendectomy scar four times in thirty months. In one of my cases, a surgeon described the tissue at laparotomy as being like wet blotting paper. The tissues at autopsy are likely to be abnormally friable *(v. seq.)*.

Very little bleeding occurs from the skin wounds. On the other hand, easy bruisability is the rule and, together with other hemorrhagic phenomena, frequently leads these patients to consult hematologists. The subsequent organization and calcification of the hematomas at times result in one type of pseudotumor.

So-called molluscoid pseudotumors[64,69] develop at pressure points—heels, knees, elbows, etc. These were the basis for the misconceived term of Hallopeau and Mace de Lépinay[15,34]: juvenile pseudodiabetic xanthomatosis. Another type of tumor, small to be sure, seen in these cases is the so-called spherule which is usually pea-sized or smaller and slips about under the skin an inch or more without causing the patient any discomfort. These are small fat-containing cysts which may become calcareous.[97] They are most frequently the basis for subcutaneous calcifications which may be demonstrable radiologically,[4,35] another basis being calcified hematomas as noted above. Congenital lipomatosis has been described in association with Ehlers-Danlos syndrome by Tobias.[91] It is entirely possible, however, that the fatty tumors in his case were an integral part of the connective tissue disease. At times actual ossification occurs.[41] The subcutaneous calcifications are characteristically ovoid in shape and 2 to 8 mm. in largest dimensions. They occur principally on the legs and, to a lesser extent, on the arms. Radiologically they display a diffuse inner calcification with a more dense surrounding shell. They are not laminated like phleboliths. These characteristics, together with the facts that they are not in muscle (as are calcified parasitic cysts) and are too widely distributed to be phleboliths, should permit the radiologist to make the diagnosis of E-D.

Easily recognized changes develop in the skin overlying the knees, shins, and elbows; it becomes shiny, parchment-thin, and hyperpigmented (Figs. 48*C* and 50*B*). Resulting are the so-called "cigarette paper" or "papyraceous" scars. Telangiectases sometimes develop in the region of these atrophic scars. The skin changes may suggest those produced by exposure to x-rays.

Bleeding may occur from the gums with brushing of the teeth, from tooth sockets after dental extractions, from the pharynx after tonsillectomy, and at the site of operations on the joints.[95] Petechiae in late pregnancy and prolonged post-partum hemorrhage have been described.[78] Contraiwise, in one of my patients it is difficult to get blood for cell counts by finger puncture, and venipunctures are also difficult, seemingly because of very small and collapsed superficial veins. In another of my patients (Fig. 52), a strain of the tendons of the hamstring muscles at the knee resulted in the subcutaneous dissection of blood down to the ankle. E-D must be included in the differential diagnosis of familial hemophilia-like state. All tests of coagulation are usually normal except that the Rumpel-Leede test may be positive.[63]

Blisterlike lesions may develop, suggesting epidermolysis bullosa (see Weber's interpretation of Burrows' case[10]).

The limitation of the cutaneous changes, particularly hyperelasticity, to one side of the body, as recounted by van Meekeren[94] in 1682, is almost completely incredible but is probably possible *(v. infra)*. Limitation of integumental hyper-

elasticity to the mucous membranes, specifically those of the mouth and tongue, has been described,[21] and many cases have evidences of changes (hyperelasticity and/or fragility) at these sites.[21,50,119,147,151] It is said that affected women do not get striae gravidarum.[38]

The skin of the hands and the soles of the feet tends to be redundant (unlike most of the skin elsewhere which fits snugly) and with pressure flattens out like a loose glove or moccasin (Figs. 52*A*, 52*C*, and 52*D*). A comparable change may develop in later years at the elbows, where the skin may hang lax like a dewlap (see Fig. 52*B*). In general, late cases tend to show cutis laxa more than cutis

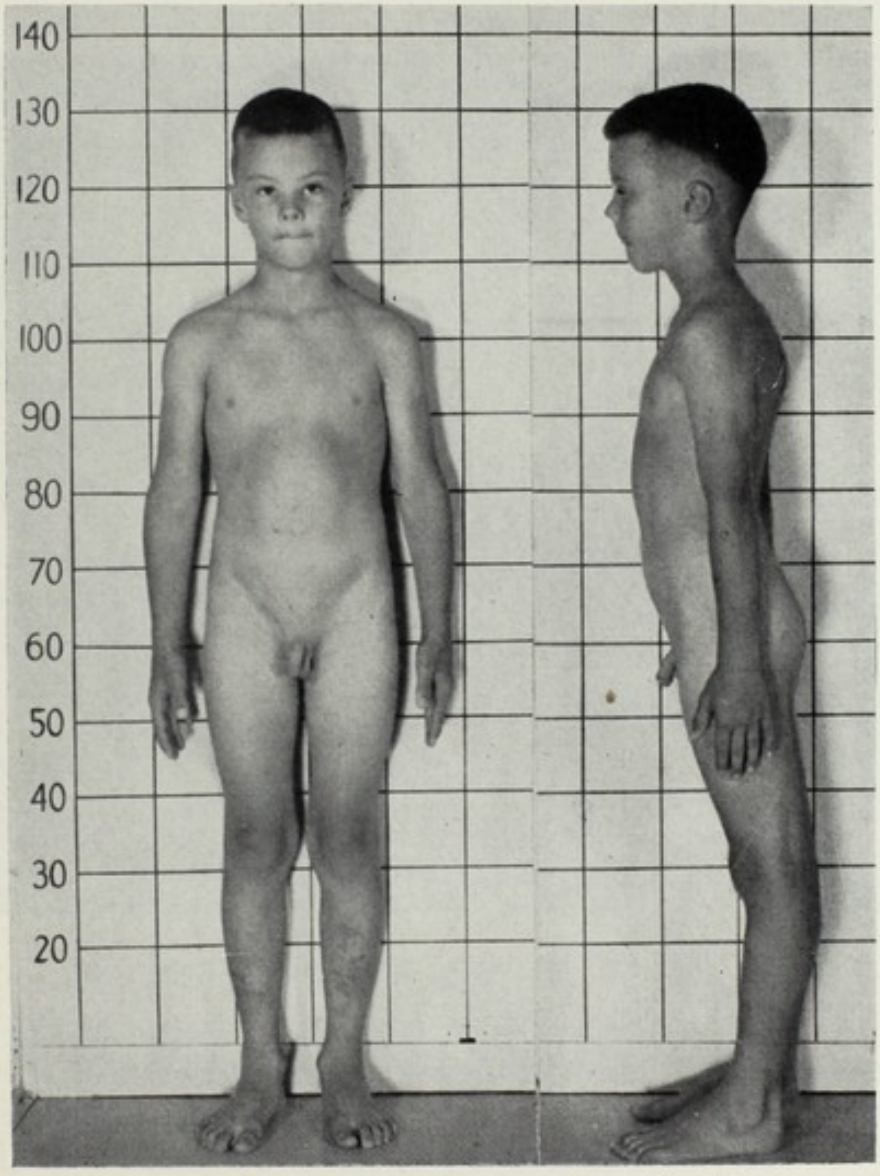


Fig. 49*A*. Fig. 49*B*.

Figs. 49*A*-49*C*. R. R. (B53739), 8¾ years of age, shows characteristic pretibial scarring, mild genu recurvatum, flat feet, and looseness of the soles. The skin generally is abnormally stretchable and the joints hypermobile. Easy brusability was the presenting complaint. An epicanthal fold (Fig. 49*C*), which is not present in unaffected members of his family, is a frequent finding in this syndrome, as is also mild retardation of growth. The characteristic scars are evident also on the forehead and right side of the face. Bilateral inguinal hernias and an umbilical hernia were repaired at the age of 2 years. No other members of the family are definitely affected. The patient has four brothers and no sisters. One brother had pectus excavatum severe enough to warrant surgical repair, and a second brother has mild pectus excavatum. (From McKusick, V. A.: Bull. New York Acad. Med. **35**:143, 1959.)

hyperelastica, whereas, as emphasized above, cutis laxa is not an accurate designation in the typical case in young persons.

"Lop ears," ears which project further than normally from the head and tend to face downward to some extent, occur commonly in E-D and also occur as an isolated heritable anomaly.[132] See Fig. 55*A*. Normally the ear makes a 30-degree angle with the head.[133]

Acrocyanosis and chilblains have been described as a seemingly integral component, by French authors in particular, [26,29,41,56,60,71,82] but by others[9,12,77] as well. There seem to be few American reports of this complaint. In general, chilblains are much less common in this country than in Europe, possibly because of our

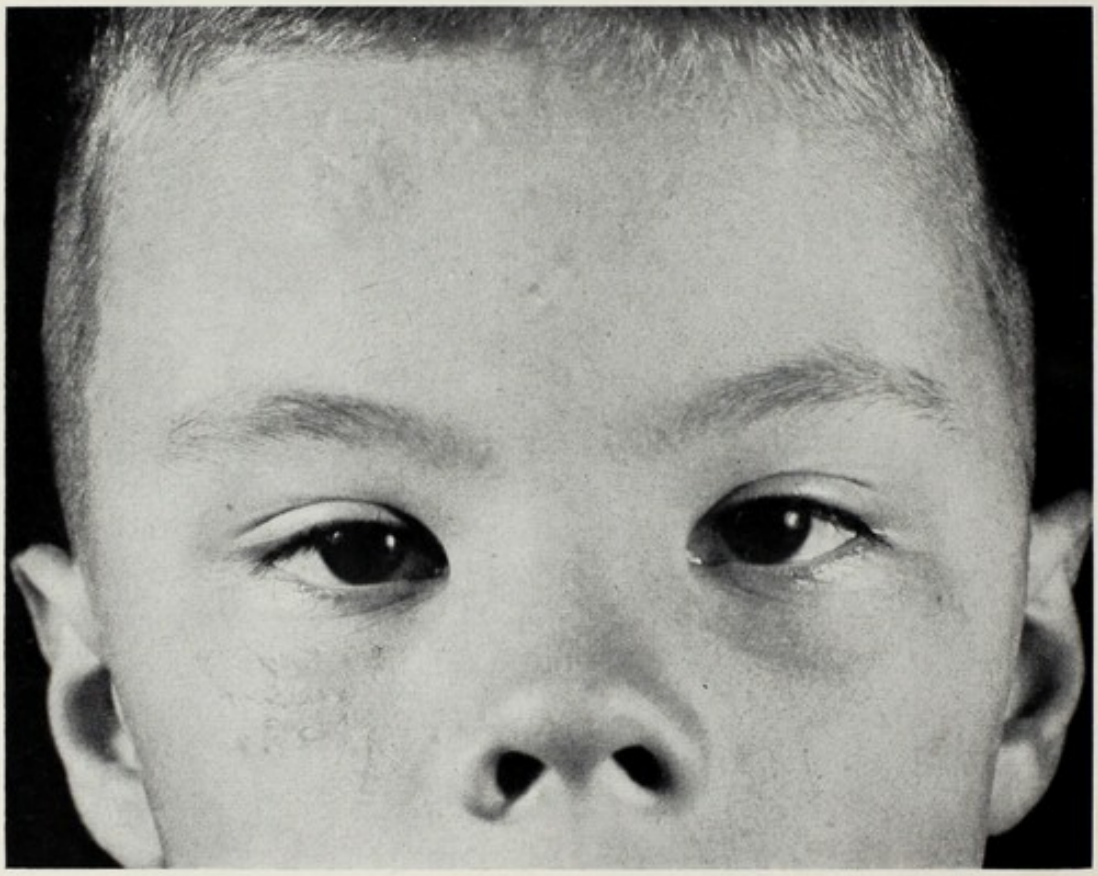


Fig. 49*C*. For legend see preceding page.

more universal use of central heating. E-D is at least one basis for acrocyanosis which "runs in a family." It may be the presenting complaint in E-D. For example, Gilbert and associates[29] described a 22-year-old man who had had cyanosis of the hands, feet, and ears from birth and displayed the other characteristic features of E-D. In the patient's family there were several other cases of "cyanosed limbs and ulcerated chilblains" in association with E-D. Burrows[10] provided an excellent photograph of the hand of one of these patients showing both joint hyperextensibility and cyanosis of the fingers. I have seen two patients (A. H., 796695; Mrs. R., P3479), both women, in whom acrocyanosis was a striking feature. They suffered severely from cold and displayed the Raynaud phenomenon.

Conceivably the abnormality with hyperelasticity, either of the supporting tissues about the arterioles or of the connective tissue in the vessel wall itself,

interferes with blood flow. My observations of difficulties in obtaining blood by finger puncture or venipuncture (see above) are significant in this connection.

The Musculoskeletal System. Hyperextensibility of the joints is characteristic (Figs. 48*D*, 48*E*, 48*F*, 50*C*, 51*A*, and 51*B*). This and the corresponding change in the skin make the victims of advanced forms of this disease the "India rubber men," "human pretzels," and contortionists of side shows. The hyperextensibility tends to become less marked as the patient becomes older. Frequently the patients have joint effusions, especially in the knees, because of traumatization as a result of the joint instability. Flat feet occur commonly (Fig. 50*B*). Clubfoot is described.[5] The loose-jointedness, in the knees in particular, may result in a gait and stance suggesting tabes dorsalis[42] (Figs. 48*C* and 52*A*). Habitual dislocation of the hip,[15,59,98] patellae,[22,59] shoulder,[65] radii,[42] clavicle,[33] and other joints is a frequent feature. As in Marfan's syndrome, the sternal ends of the clavicle may be very loose.[42] There is likely to be genu recurvatum[98] (see Fig. 48*C*). The patients are often able to pull their fingers out longitudinally for an appreciable distance and allow them to snap back into place on release. Kyphoscoliosis is likely to develop.[16,42,59,75,87,99] Spondylolisthesis has been a troublesome problem in one patient (R. W., 709823). Spina bifida occulta is described.[44] Arachnodactyly[41] and deformity of the pinnae also occur. Dental deformities are frequent,[26,42,58] and Gothic palate may be present.[40] Muscular hypotonicity and underdevelopment seem to exist in these patients. In one of my cases, a 4-year-old child, amyotonia congenita of Oppenheim was the initial diagnosis. Smith[82] describes a similar experience. Hernias occur frequently.[97] In some, repair of an umbilical hernia at a young age is necessary.

Ectopic bone formation with formation of osseous bridges between the acetabula and the femoral trochanters has been described by Katz and Steiner.[41] The pathogenesis may have involved hemorrhage from increased joint mobility.

Short stature has been a feature of some cases, e.g., Cases 3 and 4 described in detail below.

Severe leg cramps, occurring at night and at other times, such as while watching television, have been a major problem over a period of many years in one patient (Figs. 50*A* to 50*D*). Quinine and quinidine afford relief. The cramps may result indirectly from the loose-jointedness. Individuals with flat feet or disorders of the low back are prone to night cramps.

The Eye. Changes have been described in the ocular adnexa, the cornea, the sclera, the suspensory mechanism of the lens, and the fundus.

The skin about the eyes often lies in redundant folds and can be pulled out to a considerable distance like the skin elsewhere. Epicanthal folds are frequent[2,38,70,79,81,105,120,135] (see Fig. 49*C*); at least three of our patients showed them. Epicanthal folds occur, of course, in mongolism; they are also part of the facies characteristic of thalassemia; in other instances, they are inherited as a trait with no syndromal significance.) Méténier[54] has lent his name to a frequent phenomenon, namely, unusual ease in everting the upper lid. Strabismus has been encountered frequently.[1,14,81,113,127]

Blue sclerotics have been described commonly.[6,24,90] Microcornea with associated glaucoma was described in one patient[24] in whom the small size of the cornea was thought to be responsible, at least indirectly, for an impediment to ocular drain-

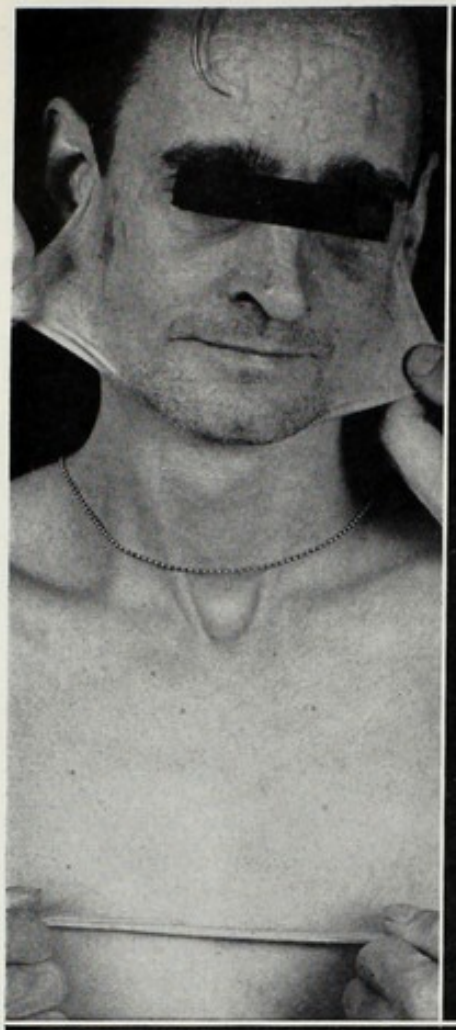


Fig. 50*A*.

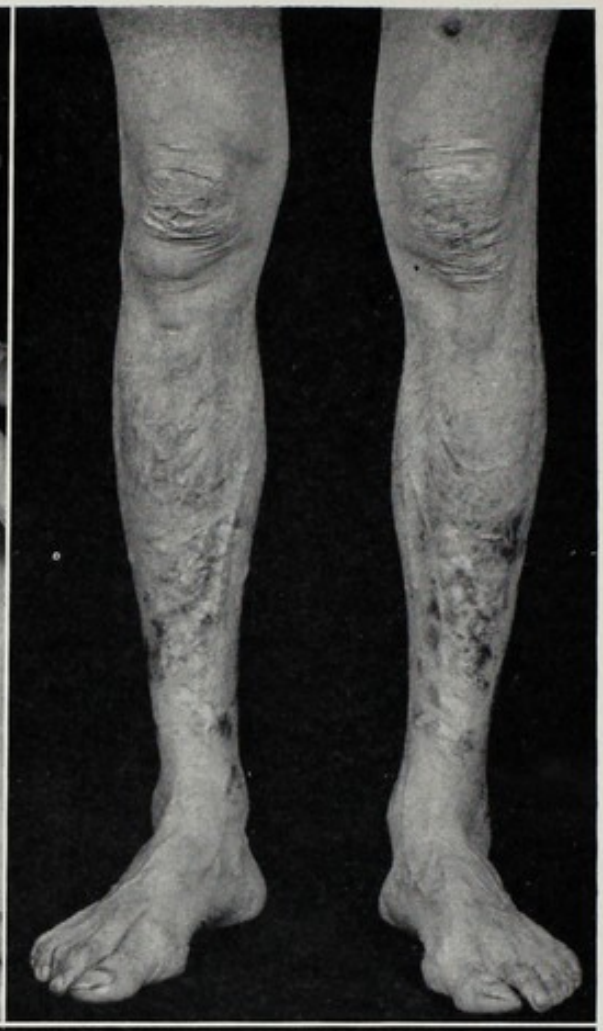


Fig. 50*B*.

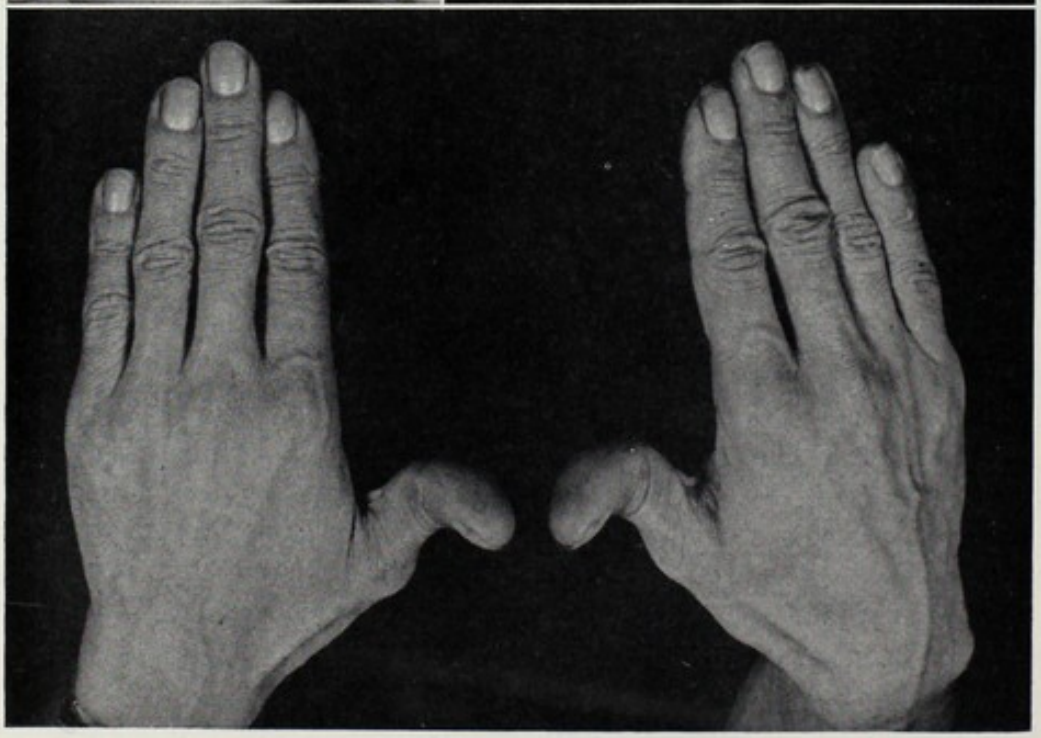


Fig. 50*C*.

Figs. 50*A*-50*C*. For legends see opposite page.

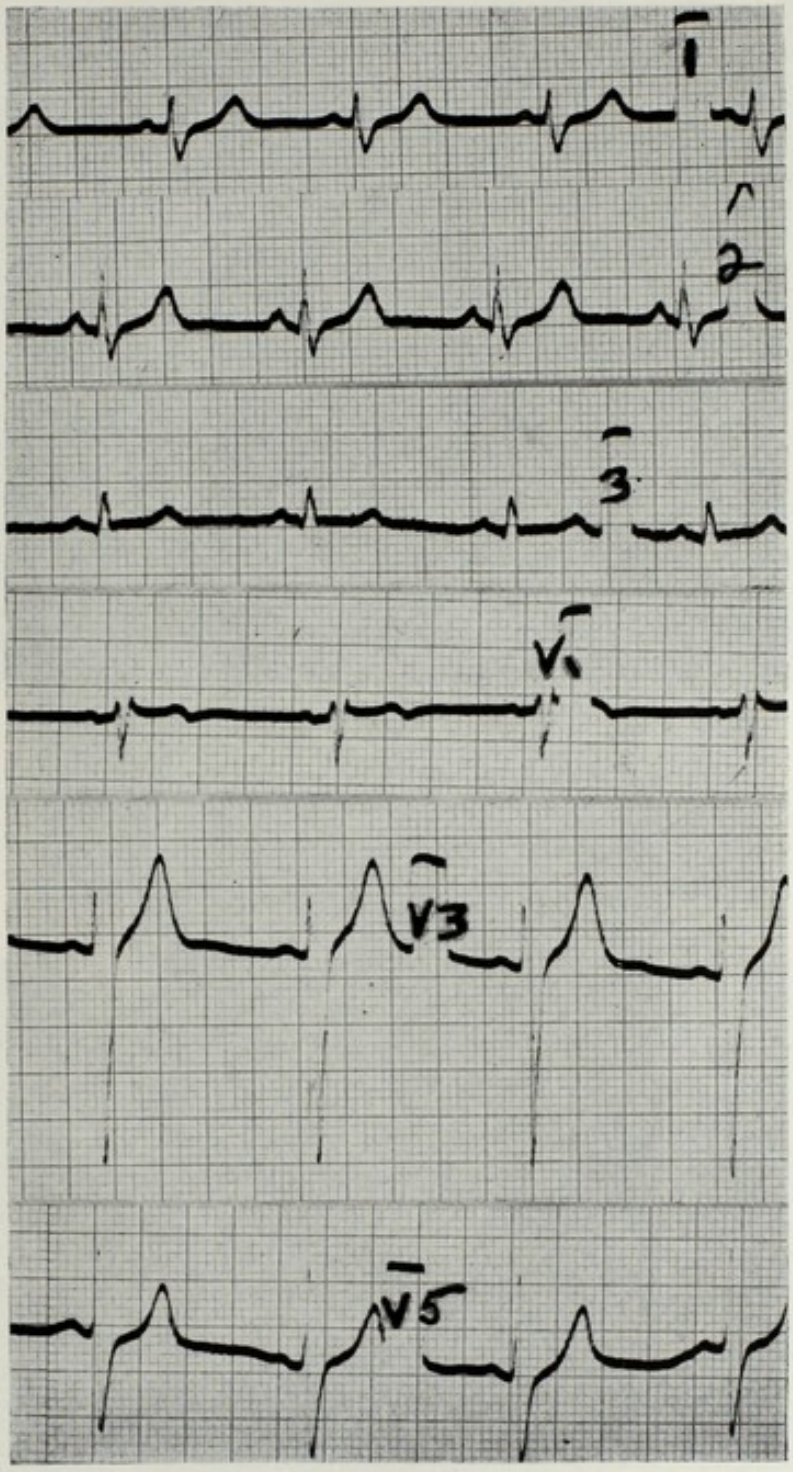


Fig. 50*D*.

Figs. 50*A*-50*D*. Patient 35 years af age (a son has the E-D syndrome).

Fig. 50*A*. Note scars of forehead and hyperextensibility of the skin. The patient was a professional boxer for a time.

Fig. 50*B*. Note the spherical tumor in the skin of the anterior aspect of the left thigh.

Fig. 50*C*. Ability to hyperextend the thumb occurs frequently as an isolated, inherited characteristic.[20,100]

Fig. 50*D*. Incomplete right bundle branch block present since at least the age of 19 years and almost certainly all of life. No other cardiovascular or internal medical disorder was demonstrable.

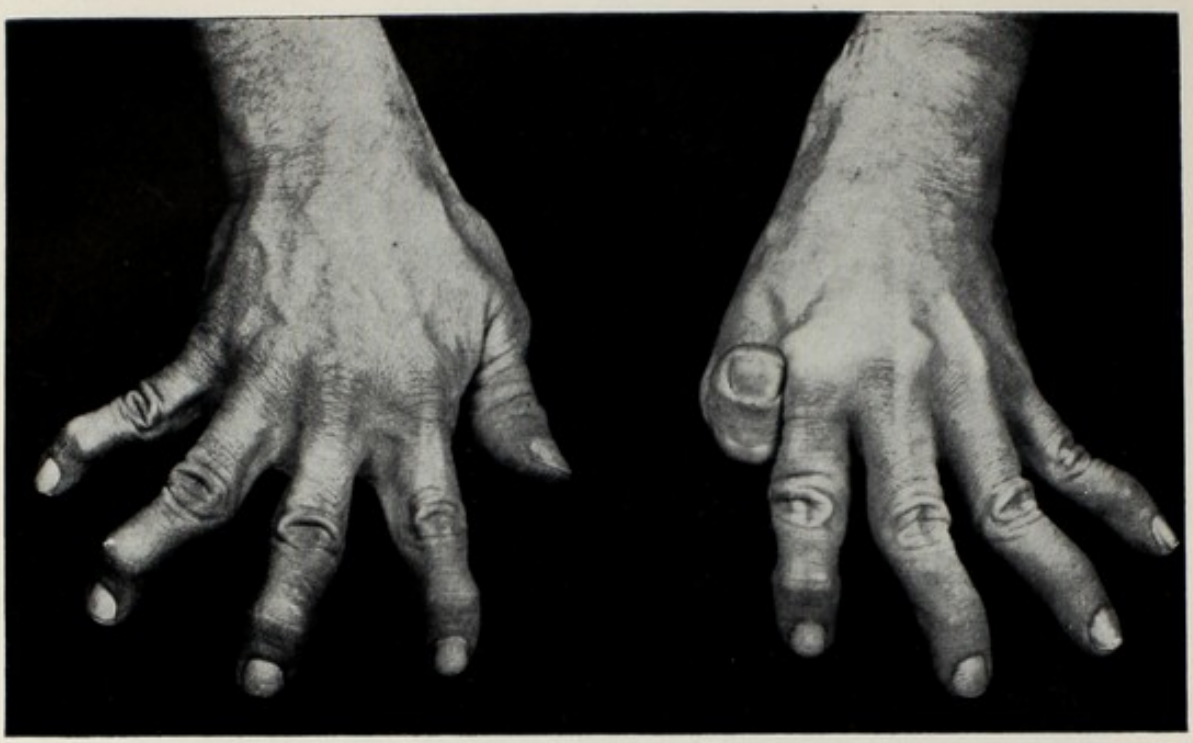


Fig. 51*A*

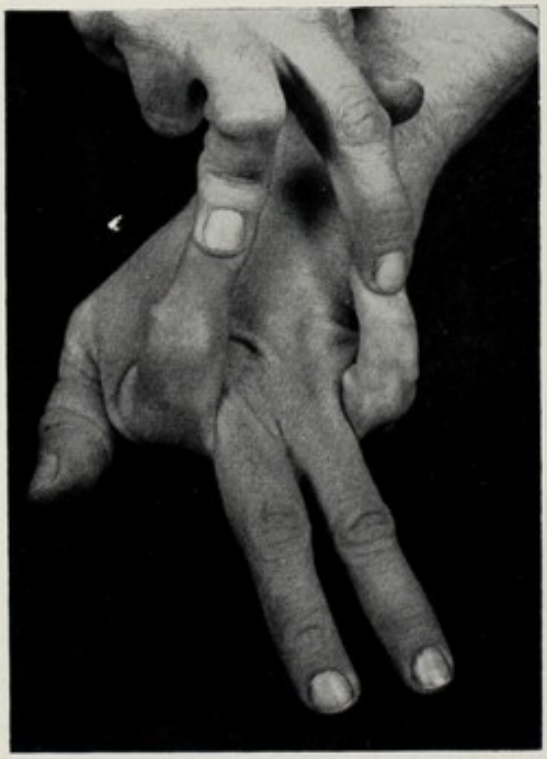


Fig. 51*B*.

Figs. 51*A* and 51*B*. C. G. (287731), 47 years old. Long history of "congenital dislocation of right hip," treated with a spica at the age of 2 years and with several operations in his twenties. Bilateral inguinal hernias repaired. Hiatal hernia is apparently responsible for epigastric and substernal pressure, which occurs especially in the recumbent position and is relieved by belching. Dehiscence followed attempts at surgical repair of the hiatal hernia. Two operations on knee for presumed trauma of automobile accident. At the age of 27 years, "relaxation of right radiocarpal joint" necessitated application of a cast. Hyperelasticity of the skin, although present, was a subsidiary feature in this patient.

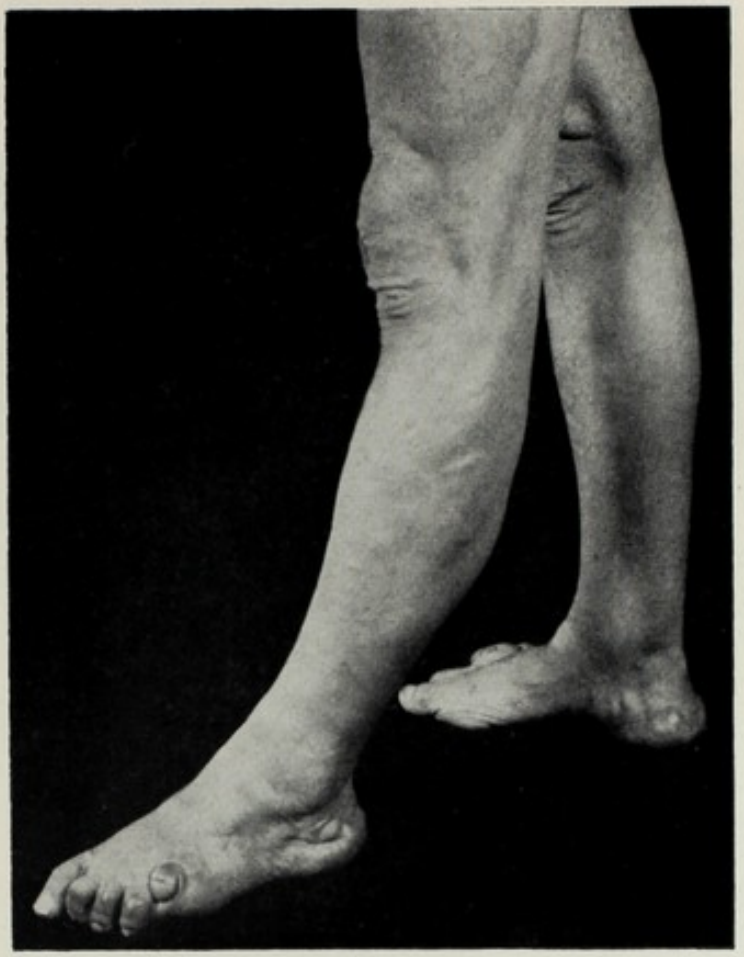


Fig. 52*A*.

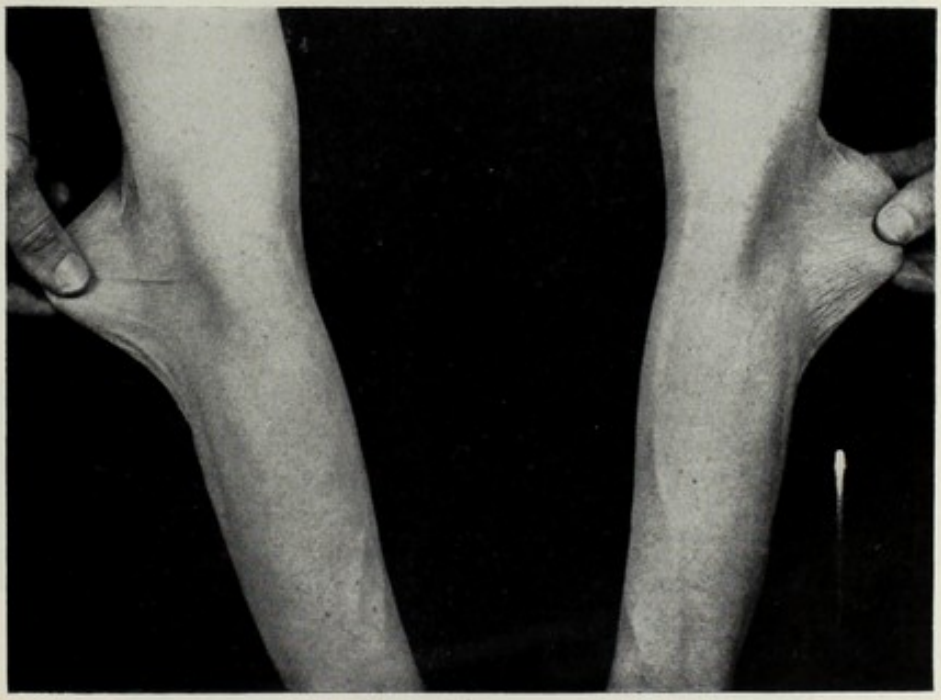


Fig. 52*B*.

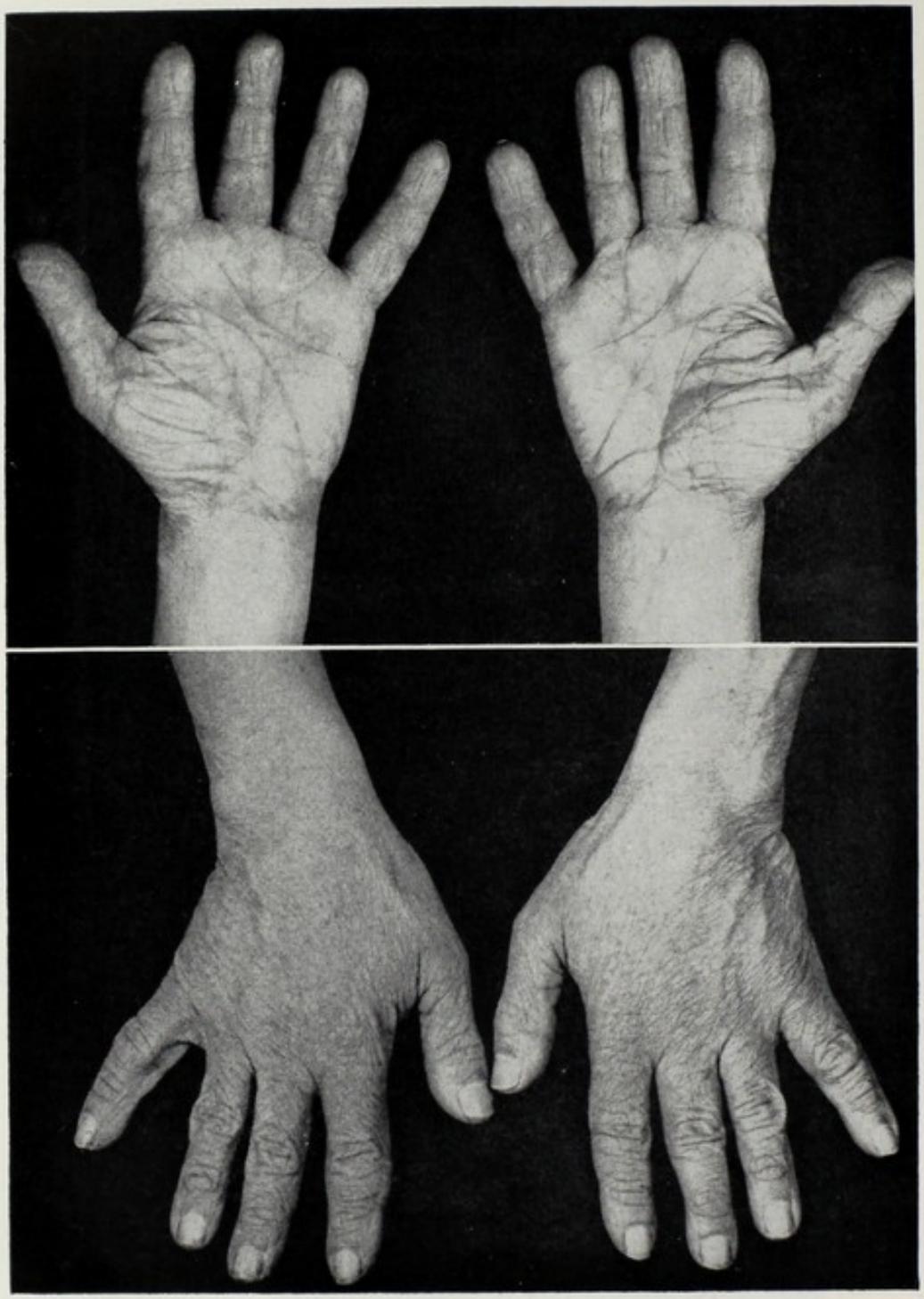
Figs. 52*A*-52*F*. K. W (667280), 48-year-old man.

Fig. 52*A*. Note deformity of feet, molluscoid tumors around heels (seen less distinctly in Fig. 48*B*). The soles appeared to be loose-fitting and like moccasins. There are cigarette paper scars over the knees.

Fig. 52*B*. Dewlaps of both elbows. A son, one of three children, may have a similar condition.

Fig. 52*C*.

Fig. 52*D*.



Figs. 52*C* and 52*D*. Lax and furrowed skin of the hands.

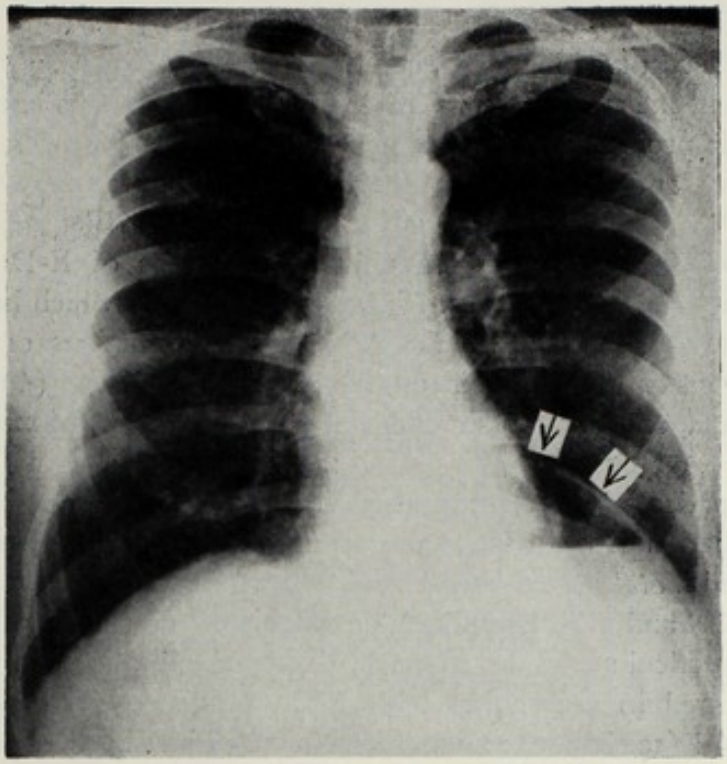


Fig. 52*E*.

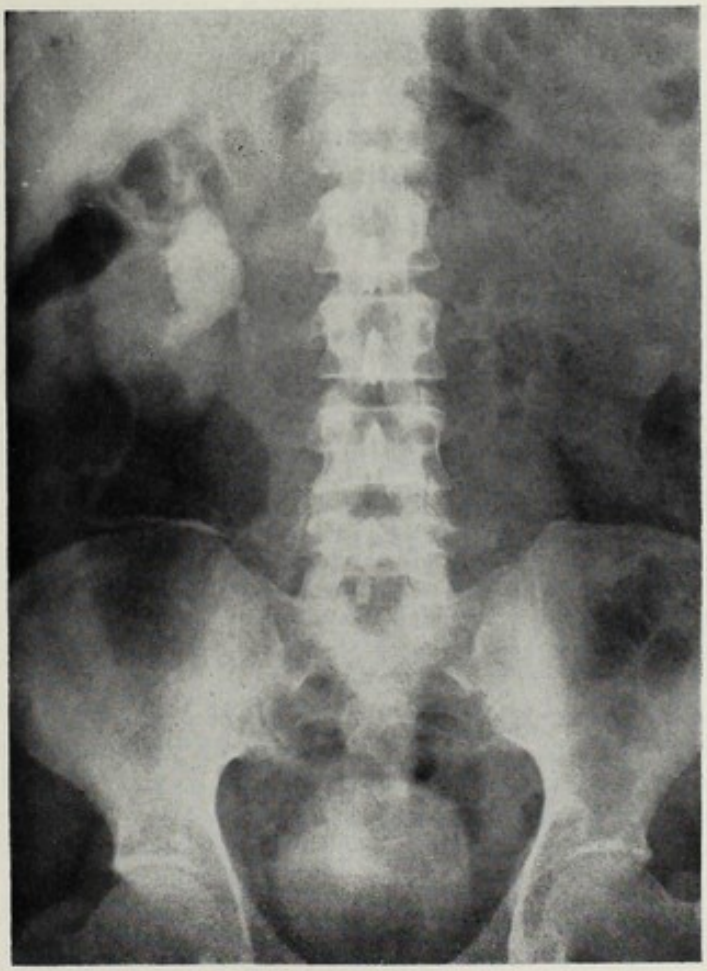


Fig. 52*F*.

Fig. 52*E*. Posterior eventration of diaphragm.
Fig. 52*F*. Anomaly of ureteropelvic function, bilaterally. Nonfunctioning kidney on left.

age. Microcornea and myopia were present in Schaper's first patient.[79] Keratoconus is also described.[90]

Ectopia lentis occurred in at least one twice-reported patient.[89,90]

In one patient, the author[5] described and illustrated changes in the fundus, consisting of retinitis proliferans, pigment spots which were interpreted as residua of microhemorrhages, and detachment of the retina of secondary type (no retinal tear was detected).

Internal Ramifications. The internal manifestations of E-D have not been investigated to any significant extent. Those manifestations which have been identified include (1) diaphragmatic hernia, (2) ectasia of portions of the alimentary and respiratory tracts, (3) spontaneous rupture of the lung, (4) dissecting aneurysm of the aorta, and (5) certain congenital malformations of more conventional type.

One of my patients has eventration of the left leaf of the diaphragm (see Fig. 52*E*). Differentiation from a large posterior diaphragmatic hernia is uncertain. We have observed *hiatal hernia* in a second patient, of whom other illustrations are shown in Figs. 51*A* and 51*B*. Brombart and associates[7] described a patient in whom hiatal hernia, diverticulum of the stomach, duodenal diverticulum, and colonic diverticulosis occurred in association with E-D. *Gastrointestinal diverticula* were present in patient 4 (see below) and are demonstrated in Figs. 54*F* to 54*H*. Megaesophagus, megatrachea, and megacolon were described in another case.[56] Bladder diverticulum is described,[86] as is also ptosis viscerum[104,137] and gastric atony.[77]

In one reported patient,[63] repeated episodes of mediastinal and subcutaneous emphysema occurred, and we have observed spontaneous pneumothorax in one patient. It is to be noted that in the first case of dissecting aneurysm described below, the lungs revealed subpleural blebs, and subcutaneous emphysema was present.

Known to me are three cases of *dissecting aneurysm of the aorta,* patients in whom the diagnosis of E-D is distinctly possible. In a fourth patient, uncontrollable bleeding from a large artery was the cause of death. Interestingly, the histologic changes in the aorta in at least one of these were those of Erdheim's cystic medial necrosis and indistinguishable from those discovered in some cases of the Marfan syndrome. Abstracts of these cases follow.

Case 1. H. L. R.* A 15-year-old Negro student, with a history of always having been sickly, was thrown forcibly to the ground by a schoolmate. He complained immediately of pain in the chest extending down the right arm and soon developed signs and symptoms of circulatory collapse. He was taken to the neighboring office of a physician, where he died within ten minutes.

Autopsy revealed an adequately developed and nourished Negro male weighing 140 pounds and measuring 5 feet 6 inches in height. The skin showed many scars; some resembled burn scars. One on the right thigh was covered with thin epidermis and measured 15 by 3.8 cm. wide. An ulcer with hemorrhagic base, 25 mm. in diameter, was located on the medial aspect of the left ankle. There was considerable subcutaneous emphysema below the right rib margin.

During the dissection, the connective tissues were found to be very friable. They tore easily, and even the skeletal muscles pulled apart with incredible ease. (The autopsy was performed only a few hours after death. The tissue was not autolyzed histologically. Dr. Thoma, the

*For calling this case to my attention I am indebted to Robert K. Osborne, then a fourth-year student, Medical College of Virginia. For much information bearing on the case I am indebted to Dr. George W. Thoma, formerly Assistant Chief Medical Examiner, Commonwealth of Virginia.

prosector, had never encountered such fragility of tissues and considered it highly significant.) Fourteen hundred milliliters of blood were found in the right hemithorax. The mediastinal structures were infiltrated with blood which also had dissected along the facial planes of the neck. The lung showed multiple large emphysematous subpleural bullae and were easily torn. The heart weighed 300 grams. The gastrointestinal tract tore easily.

Histologic studies, including stains by the periodic acid-Schiff method and elastic tissue stains, were unrevealing of definite abnormality.

Further investigation of the boy's previous health and of his family revealed that he had always been sickly, did not play as actively as his contemporaries, and often complained of severe headache. He "cut" his skin easily and healed poorly. At the age of 11 years he had sprained his ankle; x-ray films of the injured part were not considered abnormal on review.

The father of the patient died at the age of 21 or 22 years of asthma. The mother died at the age of 22 years after a twenty-four-hour illness, beginning with abdominal pain, nausea, and vomiting, and characterized by progressive circulatory failure. Autopsy was not performed but the diagnosis given on the death certificate was "internal hemorrhage of unknown cause." There were no siblings of the propositus.

Case 2. J. M. M.,* a 24-year-old white man, was well until 6 A.M. on the morning of Dec. 31, 1946, when he awoke with a vague discomfort in the abdomen. In the course of two hours this developed into pain in the right flank and lower quadrant of the abdomen. By the time he was admitted to the hospital, a few hours after onset, he was in profound shock. The administration of fluids intravenously raised the blood pressure from an indeterminably low level to 90/60 mm. Hg. The white count was 25,000 and 28,000 per cubic millimeter on two determinations. The hemoglobin concentration fell from 82 to 69 per cent of normal during the afternoon. By 3 P.M. the patient was complaining of pain in the region of the right shoulder. Abdominal exploration was undertaken at 5 P.M. The abdomen contained blood-stained fluid. A large retroperitoneal hematoma involved the right kidney. There was dissection into the mesentery which was torn in several places. The surgeon compared the tissues to wet blotting paper. Bleeding and clotting times determined postoperatively were 1 and 4 minutes, respectively. The patient died at 4:15 A.M. on Jan. 1, 1947.

Subsequent investigation revealed that the patient had always bled and bruised easily. He also had sustained a number of fractures. The possibility of minor trauma during the previous evening could not be excluded.

Autopsy revealed a body measuring only 62 inches in length. Despite this, arachnodactyly was thought to be very impressive. The prosector may have been unduly impressed because of the recognized association of arachnodactyly and dissecting aneurysm. During the opening of the chest at autopsy the ribs were thought to fracture with abnormal ease. The abdomen contained 500 ml. of bloody fluid. The aorta and the renal and iliac arteries were described as hypoplastic. A dissection of the right renal artery with infarction of the kidney was discovered. Histologically the media of the aorta was thin, with numerous areas of "myxomatous degeneration" and basophilically staining material. There was some fragmentation of the elastic fibers which seemed to be normally abundant but morphologically abnormal. The renal artery showed marked fragmentation of elastic fibers.

Although the second patient was included as an instance of arachnodactyly in reports[31,32] of a series of cases of dissecting aneurysm, the short stature, the easy bruisability, and the friability of the tissues at operation and at autopsy suggest E-D. The case of MacFarlane at the Radcliffe Infirmary, Oxford (described by Mories[134]) has parallels to these two cases. A 15-year-old white boy, the elder of twins, developed a swelling in the right groin after falling from his bicycle. Trueta attempted to stop the bleeding, which was obviously the cause of the inguinal swelling, by ligature. However, all the vessels were so extremely friable that hemostasis was impossible. At autopsy, all tissues, especially muscle and fascia, were very friable and the abdominal aorta tore readily. Histologically there was said to be an in-

*I am indebted to Dr. John F. Brownsberger of Tokoma Park, Maryland, for much information on this patient.

crease in the elastica of the aorta, with degeneration and hyalinization of the collagenous elements.

Dr. S. Miles Bouton, Jr., of Lynchburg, Virginia, has informed me of yet another case:

> The boy died at the age of 14 years of dissecting aneurysm of the aorta. At the age of 7 years spontaneous rupture of the outer two coats of the sigmoid colon, with intra-abdominal bleeding, produced severe pain in the left lower abdomen and required surgical exploration. Two weeks after operation symptoms of partial obstruction of the large bowel appeared but were resolved with conservative measures. Six months later partial bowel obstruction necessitated surgical release of adhesions. Less than four weeks later, the child was sitting in school when he was seized with left upper quadrant pain radiating to the shoulder, which doubled him up. Operation revealed peritonitis secondary to perforation of the splenic flexure of the colon. About three years later, at the age of 11 years, perforation of the sigmoid colon and pelvic abscess again required operation.
>
> It was noted repeatedly that lacerations of the knees, legs, and scalp occurred unusually readily. Healing of the skin occurred normally, however. The boy tended to constipation.
>
> Later, at the age of 11 years, the boy again suffered a perforation of the colon; the transverse and descending portions of the colon were removed. Four months later the monotonous accident was repeated; the ascending colon ruptured spontaneously; the remainder of the colon was resected and the ileum was anastomosed to the rectum. In the postoperative period there was intra-abdominal hemorrhage with shock, and drainage of a subdiaphragmatic hematoma was necessary.
>
> Three years after the last surgical episode, at the age of 14 years, this apparently healthy boy, who did, however, get skin lacerations at slight provocation, went to summer camp. One night, while in bed, he suffered the onset of severe pain in the back and abdomen. He died on the way to his home.
>
> Autopsy revealed two transverse intimal tears, one in the descending portion of the arch and the other just proximal to the renal arteries. A large volume of blood occupied the left pleural cavity. The entire aorta and its branches appeared to be unusually delicate. Dissection extended from the reflection of the pericardial sac to the bifurcation of the aorta and into the right iliac artery.
>
> Histologically the bowel removed at surgery revealed disarrangement, irregular development, and, in places, marked hypoplasia of the smooth muscle elements.

There is in the literature at least one other case of abnormal friability of the intestine and uncontrollable internal hemorrhage in E-D. Jacobs,[124] in describing a case of E-D, stated that a brother, during appendectomy at the age of 37 years, was found to have very friable bowel which was covered with numerous hemorrhages. In the postoperative period wound disruption occurred and the patient died of uncontrolled gastrointestinal hemorrhage. *Spontaneous perforation of the bowel,* as discussed by Robertson and his associates,[139a] probably has multiple predisposing causes. The Ehlers-Danlos syndrome is sometimes one.

In the *heart* one reported patient had interatrial septal defect[26]; another had tetralogy of Fallot.[96] A loud systolic murmur in the pulmonary area, audible also in the left interscapular area of the back, was described in one patient.[52] One of my patients has demonstrated for many years, probably all his life, the electrocardiographic pattern of incomplete right bundle branch block without subjective or other objective cardiovascular manifestations (Fig. 50*D*).

The chordae tendineae of the atrioventricular valves are indeed tendons, and the cusps themselves and fibrous skeleton of the heart are largely collagenous. Possibly the marvel is that serious cardiac difficulties occur so relatively uncommonly in these patients. It is likely that as more experience, and especially more pathologic information, accumulate the cardiovascular involvement in E-D will fit into a

definite pattern, just as it does in the Marfan syndrome. Cases 3 and 4 described below represent cases of grave cardiac abnormality in association with E-D. In neither is the precise nature of the cardiac abnormality known.

Case 3. C. E. (B32309; 745114), a white female born in 1939, was first seen in this hospital in 1956 for opinion on her heart condition and for plastic surgery.

Apparently no other members of her family have skin, joint, or cardiac changes similar to hers. The parents and brother and sister are of average stature. Various members of the father's family were short. For example, the paternal grandfather was only five feet tall.

The patient was "very flabby" at birth. X-ray films were taken in the first days of life, probably because of dislocation of the elbows and possibly other joints (Figs. 53*A* and 53*B*). No mention of a murmur or other sign of cardiac abnormality was made to the parents until the patient was 15 months old. At that time she was still flabby and did not stand or walk. The flabbiness was no longer apparent after the age of 9 or 10 years. An endocrinopathy, probably hypopituitarism, was suspected, mainly because of the short stature. However, sexual maturation occurred normally.

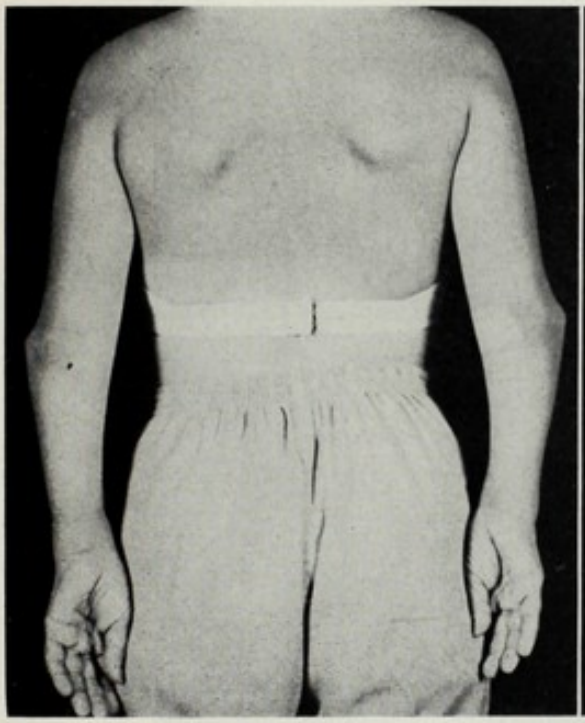


Fig. 53*A*.

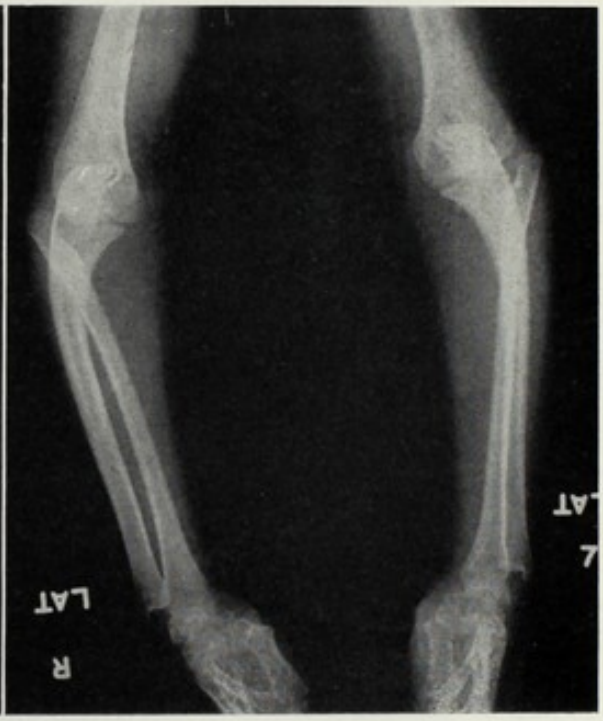


Fig. 53*B*.

Figs. 53*A*-53*G*. Case 3. *A*, Bilateral posterior dislocation of heads of ulnar bones. *B*, X-ray film of same. *C*, Hands. Note the loose, coarse-grained appearance of the skin. *D*, feet. *E*, Chest x-ray film. Note cardiomegaly. *F*, Spectral phonocardiogram showing systolic and diastolic murmurs. The same auscultatory findings were present at LLSB and apex. *G*, Electrocardiogram.

The patient lived a sheltered life. Palpitation was the only symptom definitely attributable to the heart. Both systolic and diastolic murmurs are known to have been present from the age of 10 years. At that time she weighed only 43 pounds and was 45 inches tall.

Physical examination (1956) revealed an intelligent girl only 56 inches tall. There was generalized hypermobility of the joints and elasticity of the skin. The head of each radius was dislocated posteriorly. The patient could not extend the elbow beyond a point 18 degrees from full extension. Pronation of the wrists and forearms was moderately impaired.

The nose was hooked. Malocclusion with narrowing of the anterior vertical arch of the hard palate was present. The pinnae were also mildly deformed; they were low in position and

rotated so that the lobule was located somewhat anteriorly to the external meatus and helix.

The heart was enlarged to the left anterior axillary line. The auscultatory findings were dominated by bizarre murmurs, in systole and diastole, of a scratchy quality, suggesting pericardial friction rub (Fig. 53*F*). The murmurs were maximal at the apex and left midprecordium.

Fig. 53*C*.

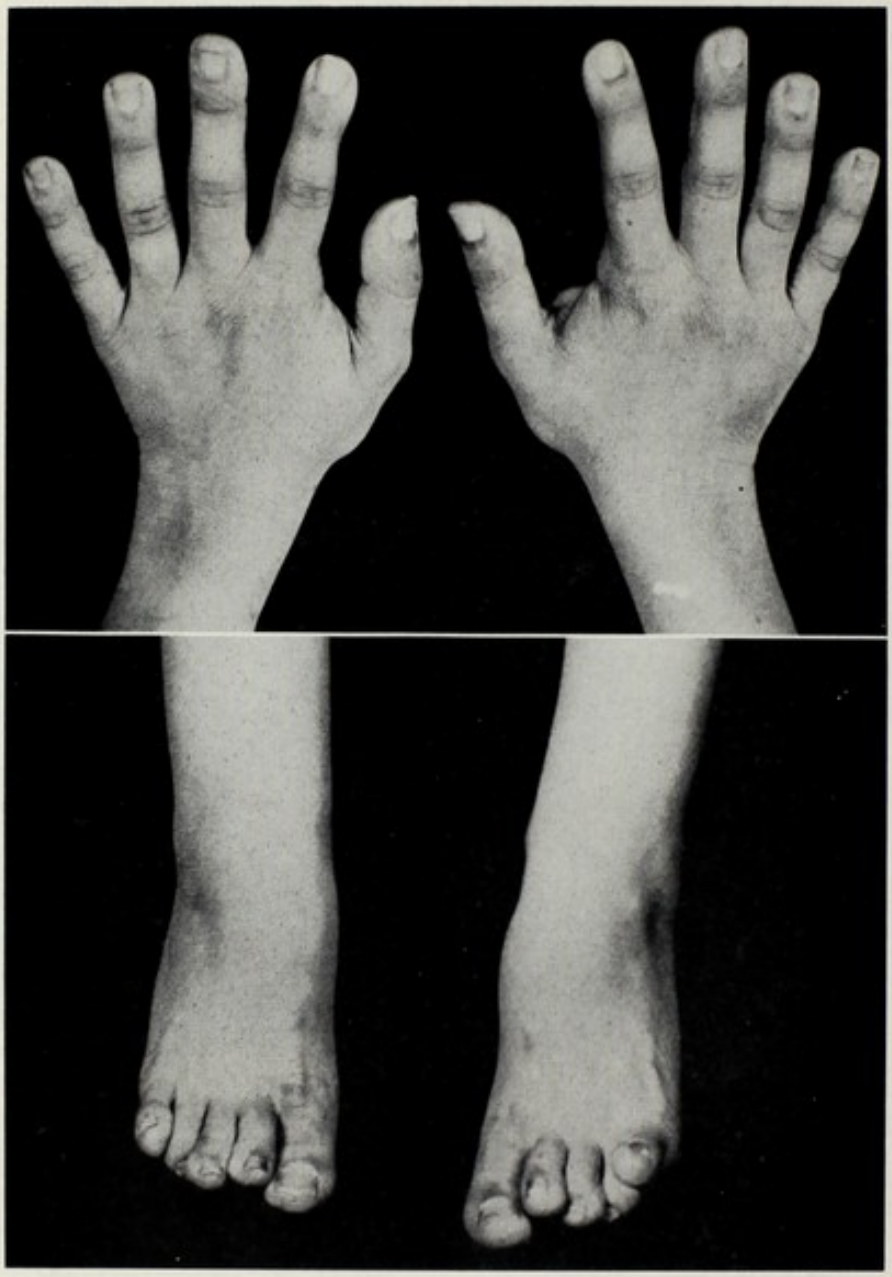


Fig. 53*D*.

Figs. 53*C* and 53*D*. For legend see preceding page.

Photographs, electrocardiograms, phonocardiograms, and x-ray films are presented in Figs. 53*A* to 53*G*. Angiocardiograms revealed dilatation of the entire right side of the heart.

Rhinoplasty and repair of both elbows by resection of the heads of the radii were performed with success. Healing following surgery was perfectly normal, and there were no late complications.

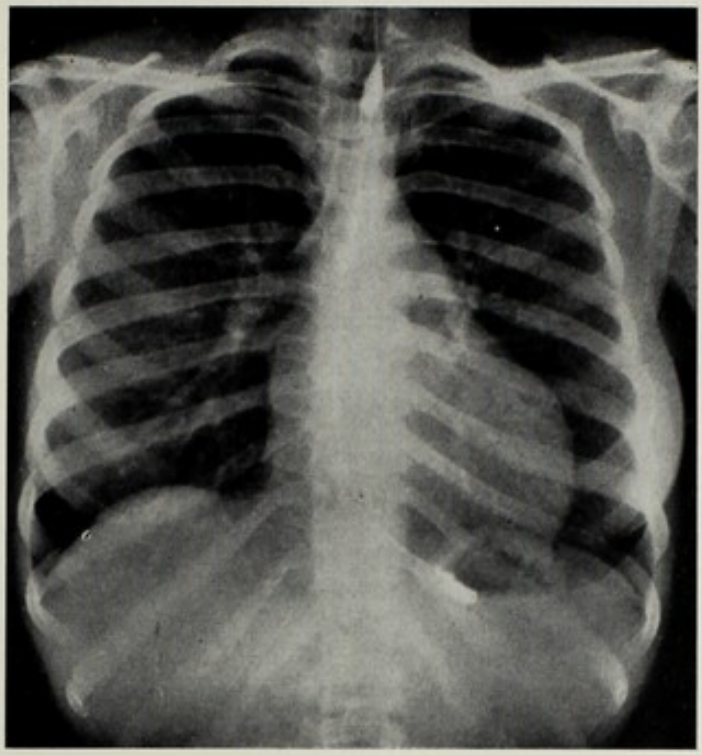


Fig. 53*E*.

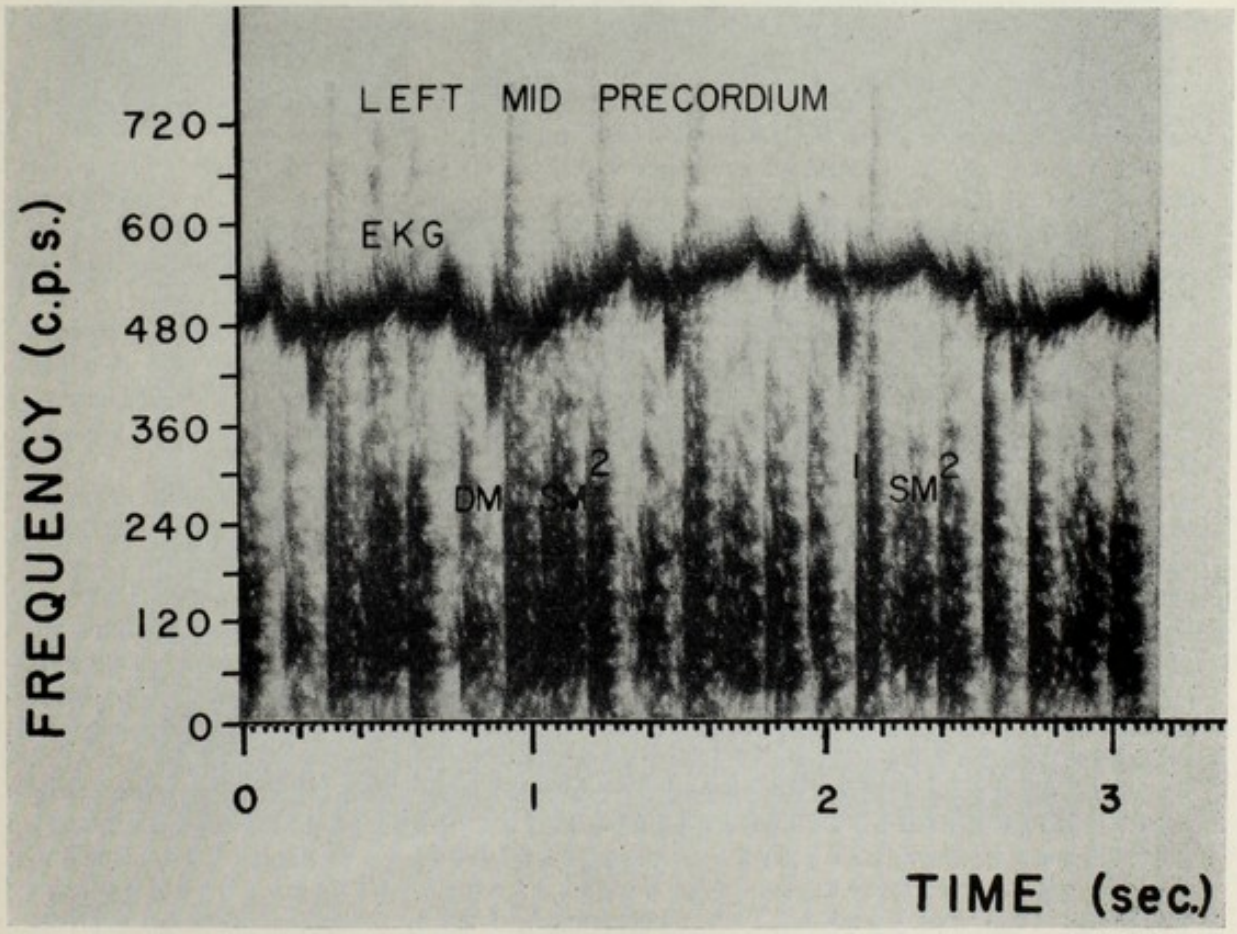


Fig. 53*F*.

Figs. 53*E* and 53*F*. For legend see page 153.

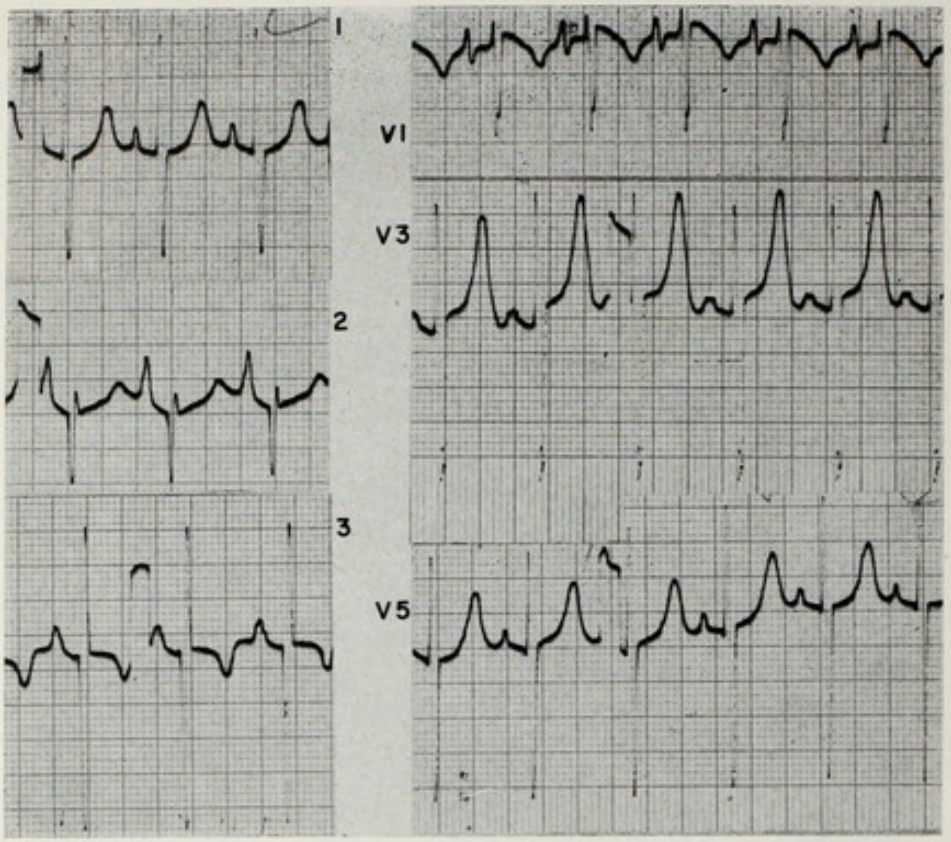


Fig. 35*G*. For legend see page 153.

Case 4. W. E. W.* (765864), a white male born in 1917, was referred to Dr. Helen B. Taussig and Richard S. Ross, for study of his heart condition.

To the patient's knowledge, no condition similar to his existed in his family. The father died of cerebral hemorrhage at 54 years. The mother, who had diabetes, died in childbirth at age 37 years. Six brothers, 20 to 44 years of age, were living and well and six sisters were likewise well. Part of the siblings were half-brothers and half-sisters. The patient had no children.

He was the shortest member of his family. He had always had unusually soft, smooth, elastic skin, with abnormal hyperextensibility of all joints. Both the joints and the skin had tended to become less elastic as he grew older. At no time was there any bleeding tendency, fragility of the skin, or unusual scarring over exposed areas. The patient had had prolapse of the rectum on several occasions.

Shortly after birth a murmur was discovered and it was described on each of many examinations as he was growing up. He was rejected for Armed Service in World War II because of the murmur. In 1948 his physician described a harsh systolic murmur loudest at the apex but audible over the entire heart, with no diastolic murmur. By x-ray examination there was left ventricular enlargement. In 1955 the first signs of congestive heart failure appeared. Left bundle branch block was discovered; how long it has been present is unknown.

Early in 1957 the patient had the onset of abdominal pain. Gastrointestinal x-ray films showed redundancy of the colon, a small diverticulum in the second portion of the duodenum, and a huge diverticulum at the ligament of Treitz.

Physical examination revealed an intelligent, moderately deaf, rather short man (Fig. 54*A*), who appeared to be about his stated age of 40 years. The head was short and round. The skin was smooth, velvety, and loose, with redundant skin of the upper lid. When stretched, the skin returned promptly to its normal position on release. All joints displayed hyperextensibility. There was pes planus, genu recurvatum, and ability to hold a pencil between the

*I am indebted to Dr. John G. Smith of Rocky Mount, North Carolina, for making the diagnosis of the Ehlers-Danlos syndrome and referring the patient to the Johns Hopkins Hospital.

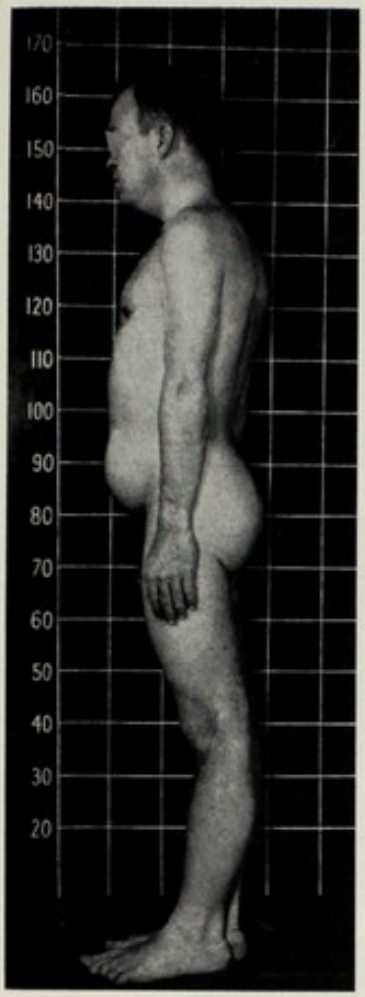


Fig. 54*A*.

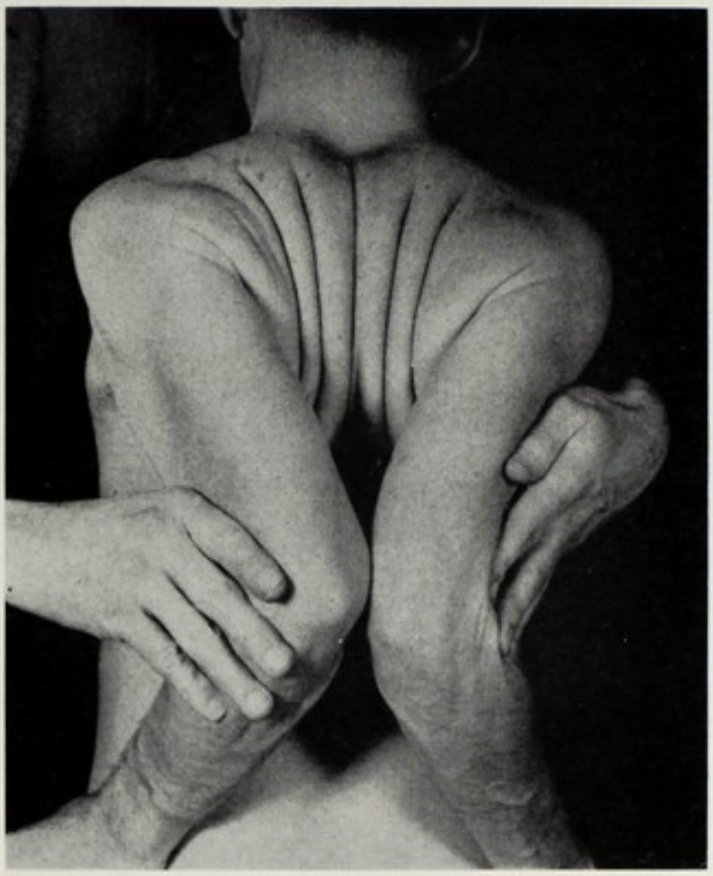


Fig. 54*B*.

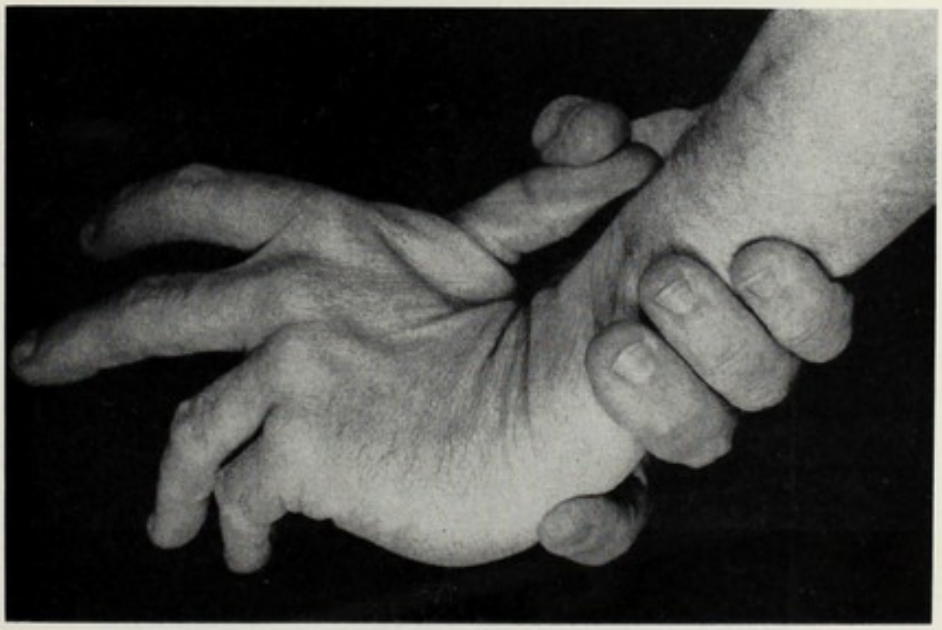


Fig. 54*C*.

Figs. 54*A*-54*K*. Case 4.
Fig. 54*A*. Lateral view. Note genu recurvatum and short stature.
Fig. 54*B*. Hyperextensibility of the shoulders.
Fig. 54*C*. Joint hypermobility. Note also the loose coarse-grained appearance of the skin resembling that in Case 1 (Fig. 52*A*).

Fig. 54*D*.

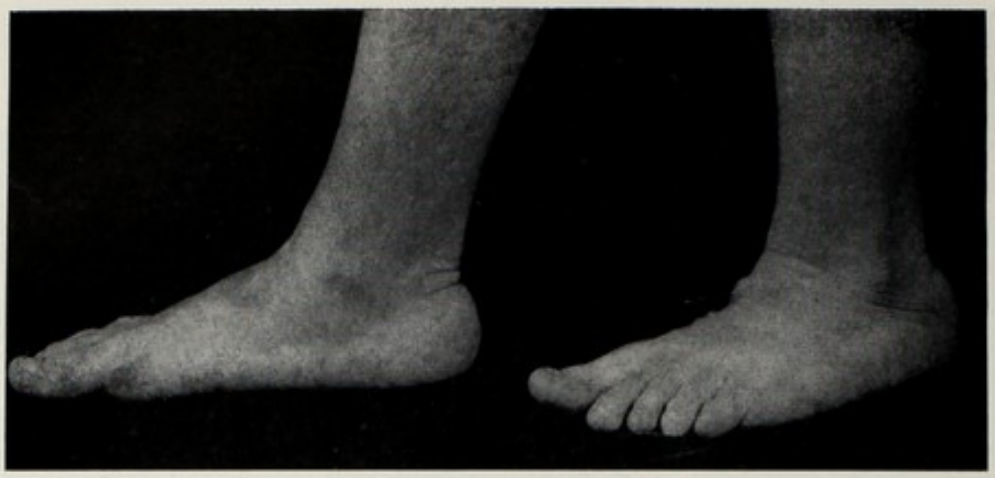


Fig. 54*E*.

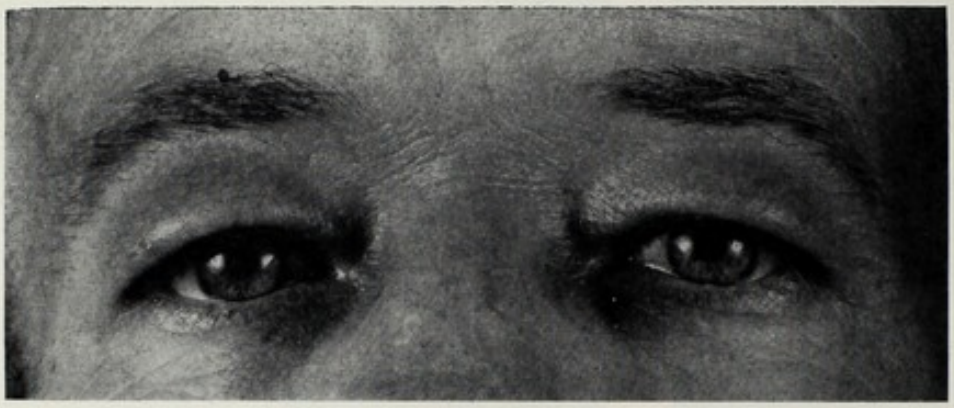


Fig. 54*F*.

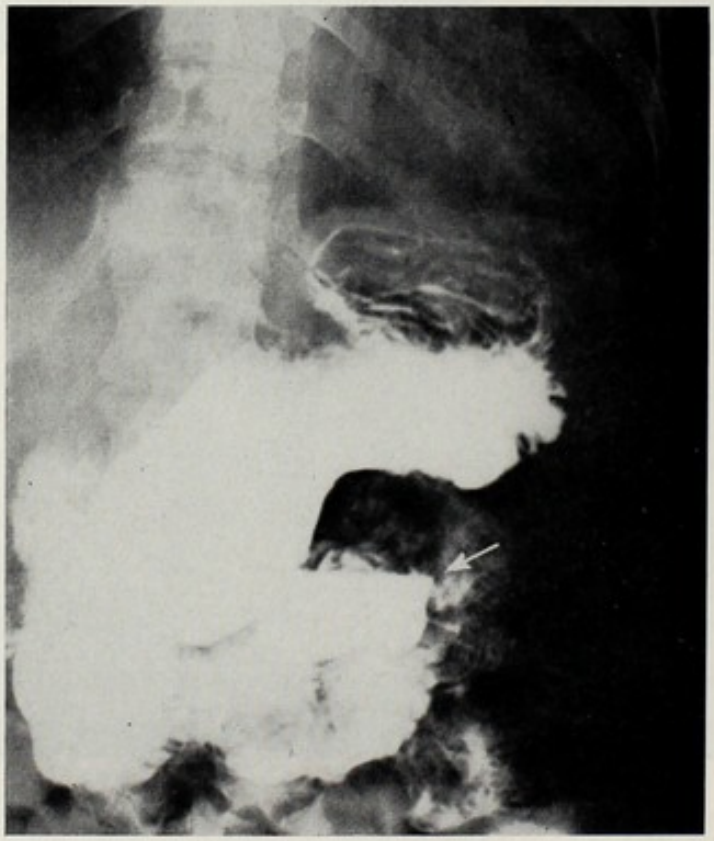


Fig. 54*D*. Flat feet; loose, redundant soles.
Fig. 54*E*. Redundant skin of lids.
Fig. 54*F*. Gastroduodenal series to show large duodenal diverticulum arising in region of ligament of Treitz and extending up behind the stomach

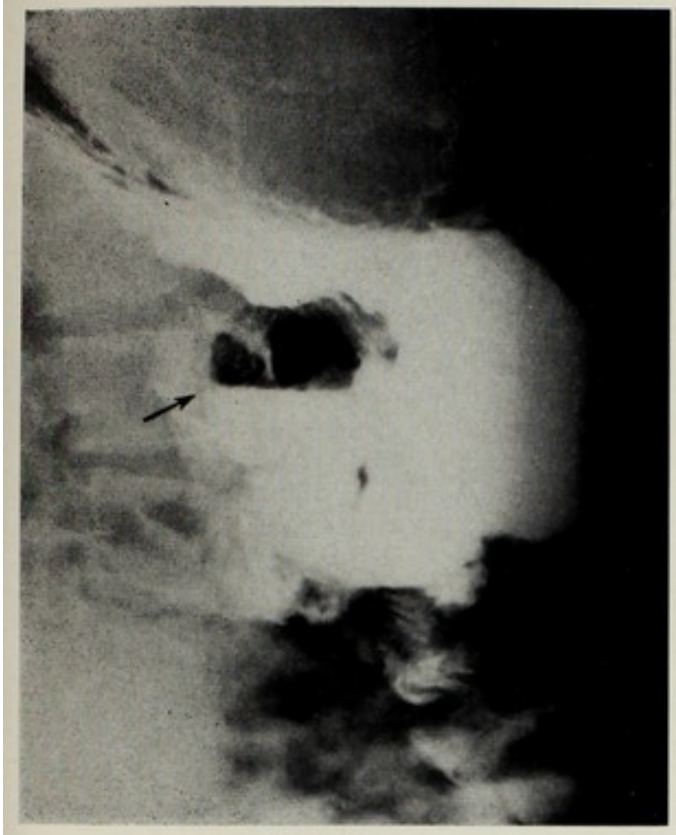


Fig. 54*G*.

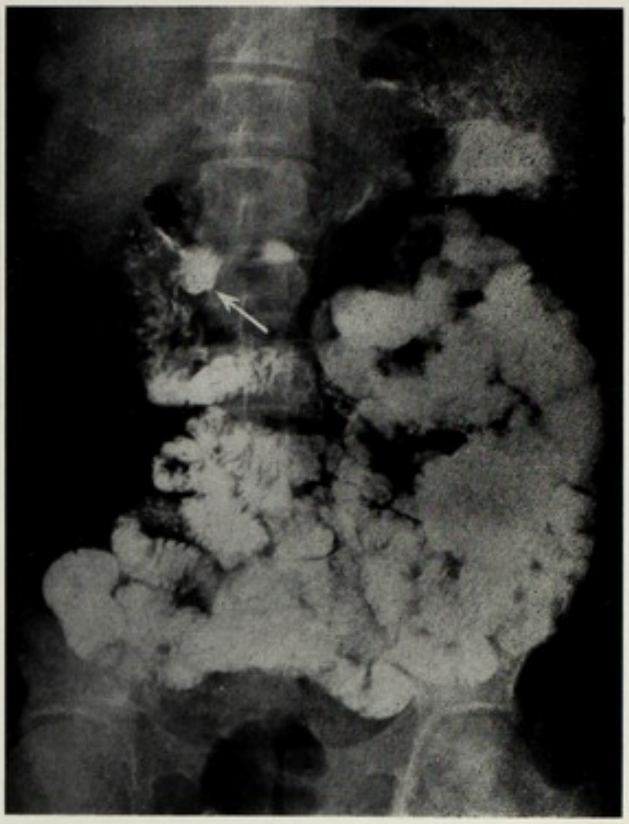


Fig. 54*H*.

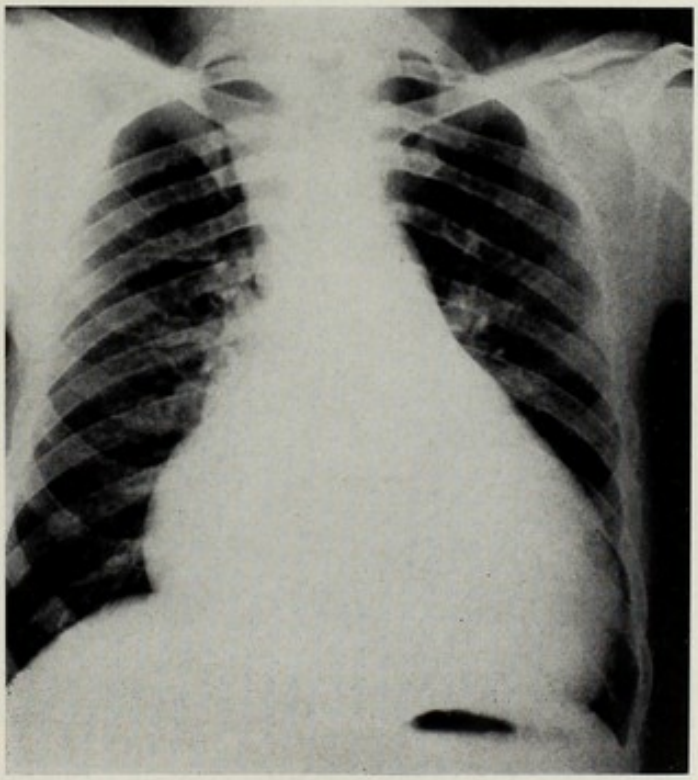


Fig. 54*I*.

Fig. 54*G*. Same as Fig. 54*F*, lateral view.
Fig. 54*H*. Gastrointestinal X-ray film showing diverticulum of second part of duodenum (arrow).
Fig. 54*I*. Chest x-ray film to show general cardiomegaly.

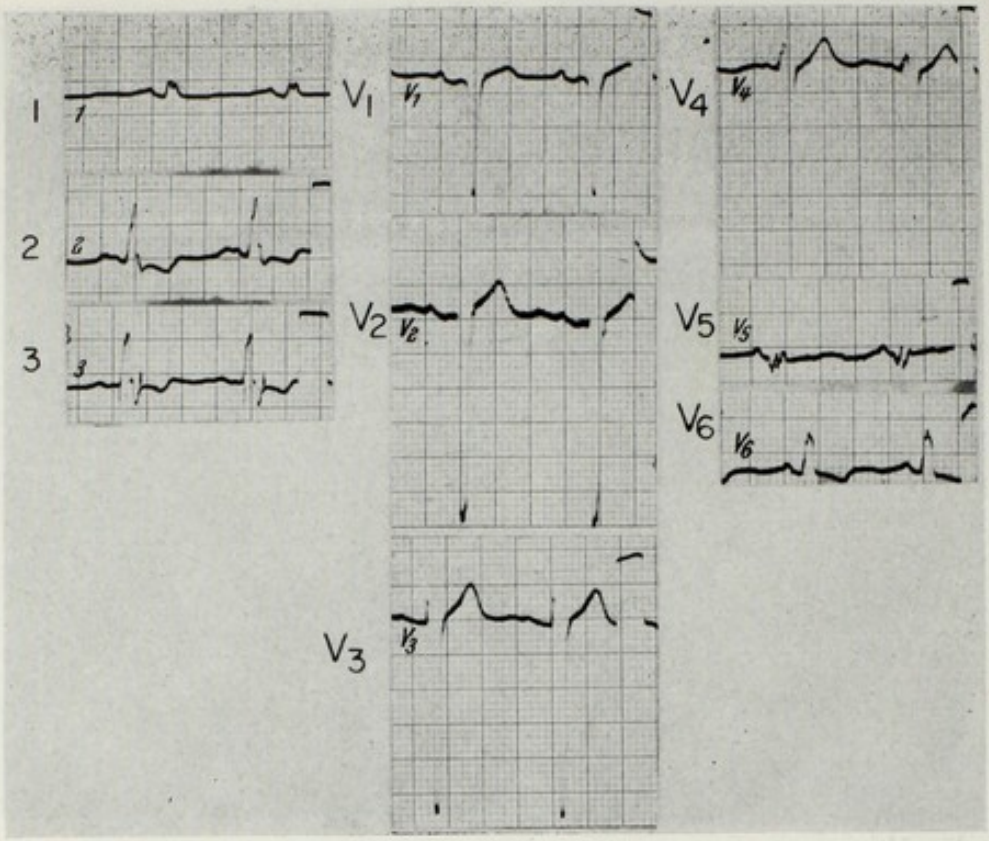


Fig. 54*J*.

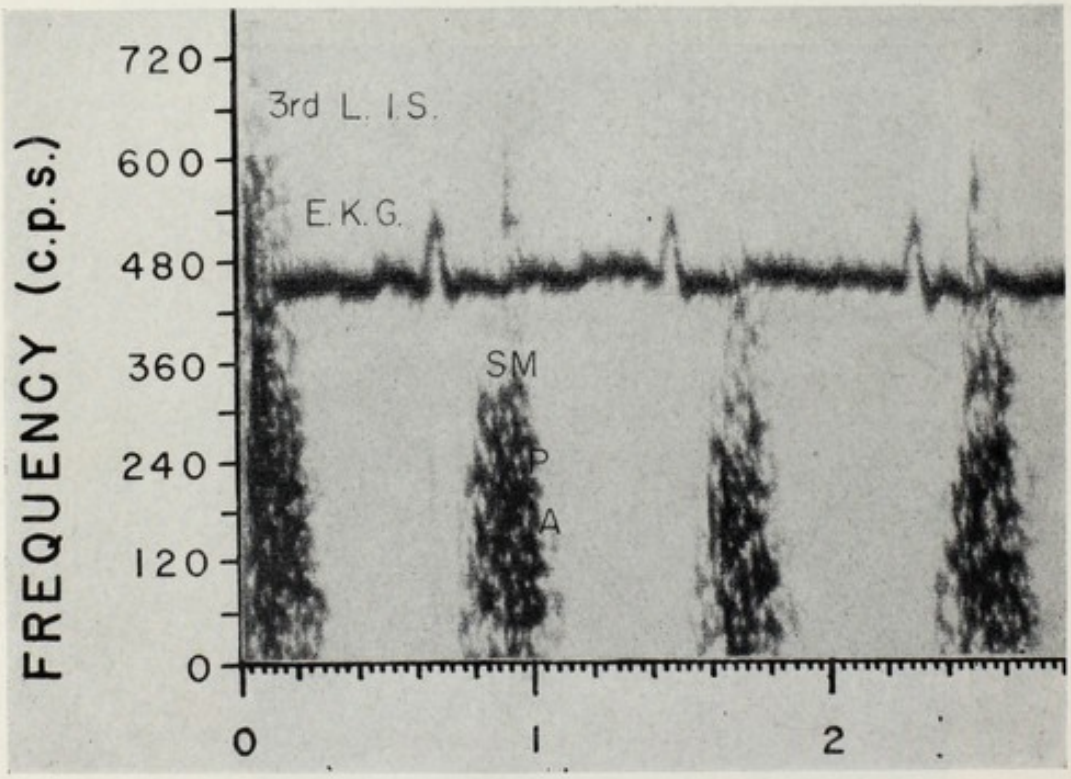


Fig. 54*K*.

Fig. 54*J*. Electrocardiogram. Left bundle branch block; broad, notched P waves.

Fig. 54*K*. Spectral phonocardiogram, aortic area. The systolic murmur is consistent with aortic stenosis. There may be paradoxical splitting of S_2. The systolic murmur may extend to the pulmonary component (which is first) but not to the aortic. Recordings at the third left interspace and in the left mid-precordial area showed a diastolic murmur of arterial type, probably indicative of aortic regurgitation.

knuckles. The hands could be folded together transversely with opposition of the thenar and hypothenar portions. Audiogram showed impairment of all tones bilaterally. (The patient was aware of impairment of hearing only in the left ear. This had begun following a purulent discharge at the age of 18 years.) The hard palate was unusually high arched.

The heart was massively enlarged (Fig. 54*I*), with a localized point of maximum impulse in the seventh interspace, just outside the anterior axillary line. At the base a grade III harsh systolic murmur was transmitted into the neck. At the apex a higher pitched systolic murmur was of approximately grade II intensity (on a base of six). A soft, decrescendo, diastolic murmur was audible down the left sternal border. The liver edge was two fingerbreadths below the costal margin. Blood pressure was 100/70 mm. Hg.

The left testis was undescended.

Serum cholesterol was 217 mg. per cent. X-ray films revealed great enlargement of the heart, involving all chambers. Right heart catheterization showed no evidence of shunt. Pressure in the right ventricle was 56/2/5 mm. Hg.

It was concluded that aortic stenosis and/or mitral regurgitation would best account for the physical findings.

Figs. 54*A* to 54*K* demonstrate the photographs, electrocardiograms, phonocardiograms, and x-ray films in this patient. Although no special search for calcified subcutaneous spherules typical of E-D was made by x-ray, one such body, oval in shape, was visible on chest x-ray examination in the skin of the left upper arm.

The patient died suddenly at home about five months after these studies. Autopsy was not performed.

Another of my patients has a bilateral congenital anomaly of the ureteropelvic junction (Fig. 52*F*). In the case of Marfan's syndrome it was pointed out that there are a number of manifestations which are congenital malformations in the conventional sense and which occur often enough to be considered bona fide components of the syndrome. It was proposed that these are secondary manifestations, that the hereditary disorder of connective tissue creates an ontogenetic setting in which certain predictable congenital anomalies occur with increased frequency. In E-D, ureteropelvic anomaly, tetralogy of Fallot, and interatrial defect may fall into this category of secondary manifestations. However, since, to my knowledge, each has been described in only one patient, it is equally reasonable to suspect that these manifestations may have occurred by coincidence.

Spina bifida occulta has been described fairly frequently.[54,127,135] Furthermore, the dental anomalies may be interpreted as falling into this category of malformations which are secondary manifestations of the basic connective tissue defect. The teeth may be irregularly formed,[49] irregularly positioned,[29,45,79] abnormally small,[48,52,69] or even absent. Crenation of the incisors has been noted.[50,52]

As a rule, mental retardation is not a feature of this syndrome. However, occasionally patients show it, probably as a coincidentally associated finding.[48,50] Severe essential hypertension occurred in one patient as a probable incidental finding.[41]

PATHOLOGY

In none of the five main disorders of connective tissue discussed in this series is the microscopic anatomy in such a disputed state as in E-D.[45]

Increase in elastic tissue of the corium has been described by many writers.[1,6,38,54,55,70,71,76,83,89,91] Some of these described morphologic abnormalities of the elastic fibers, as did Smith[82] and Pittinos,[68] who, however, did not consider

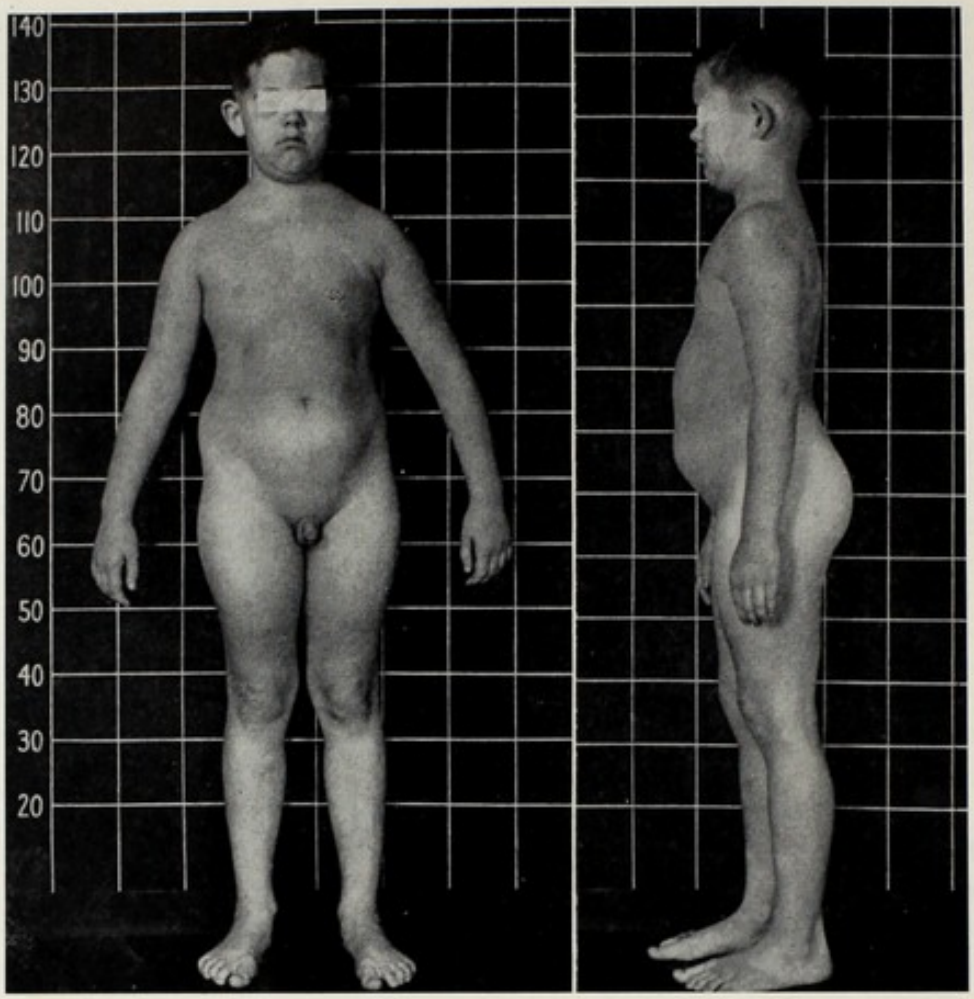


Fig. 55*A*. Fig. 55*B*.

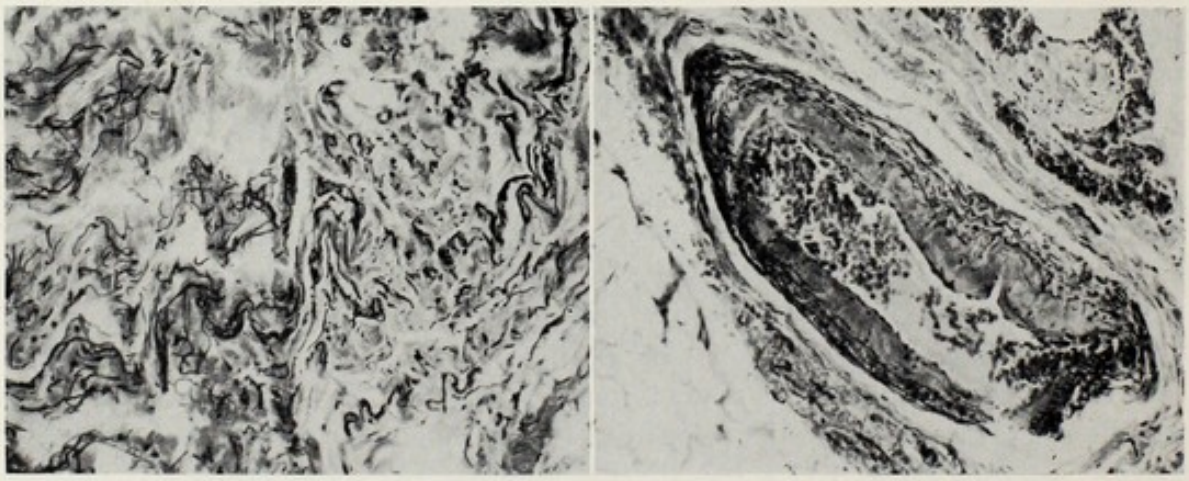


Fig. 55*C*. Fig. 55*D*.

Figs. 55*A*-55*D*. Typical E-D in 10-year-old boy (J. I., A75064). There is a normal brother 1½ years of age. The mother and father are unaffected and no similar cases are identified in the family of either parent. There is striking fragility of the skin as evidenced by many scars, e.g., of the knees, forehead, and shins. The wounds, of which dozens have occurred, are almost round, and subcutaneous areolar tissue herniates up through the break in the epidermis. The joints are strikingly hyperextensile. When not bearing weight, the pedal arches appear higher than normal, but with bearing weight the feet become strikingly flat. There is knobby redundancy of the skin of soles, especially around the heels. The fragility and hyperelasticity extends to the buccal and lingual mucosa (at one time stitches had to be taken in a cut in the

(Continued on opposite page.)

the elastic fibers to be more numerous than normal. Williams[102] and Pautrier[64] found the elastic fibers *normal*, and Brown and Stock[9] believed them to be *decreased*.

Diminution and morphologic abnormalities of collagen fibers have been described.[62,82,91] Katz and Steiner[41] report histochemical studies which they interpret as indicating increase of mucopolysaccharide of corium.

Jansen[36] points out, with excellent illustrations, that "in normal skin, a system of robust, well directed, crossing and tightly interlacing collagen fibre bundles is present. The whorled disorderly structure in hyperelastic (E-D) skin is remarkable; the collagen bundles seem to have been insufficiently united." By electron microscopy collagen and elastin were morphologically normal. This corroborates the finding of Tunbridge and his collaborators,[92] but Jansen was unable to agree that there was an absolute increase in the number of elastic fibers.

Collections of giant cells are sometimes found.[75] The subcutaneous nodules or spherules are apparently fat-containing cysts.[97] They frequently become calcified. It seems likely that they are related to minor traumata and to the general fragility of the connective tissue in which the fat deposits normally exist. Molluscoid pseudotumors which develop at pressure points are characterized by cyst formation.[127]

How much of the bleeding is due to a defect in the supporting tissues and how much due to weakness of the vessel walls themselves is not clarified by histologic studies. Abnormal, dilated, weak-appearing vessels have been described by Tobias[91] and others.[50] An abnormality (see Fig. 55*D*) of the connective tissue of the wall of small arteries was demonstrated in one of my cases, and similar changes are seen in Fig. 21 of Jansen's report.[127]

Unfortunately, studies of tissues other than skin have not been reported with the exception of an autopsy case described by Leinhart[50] and one by Nicod,[135] and, of course, the two cases of dissecting aneurysm described above. In Leinhart's patient, a 22-year-old woman who died of pulmonary tuberculosis, no internal abnormality referable to the connective tissue defect was discovered. Nicod[135] studied bone and cartilage and could detect no abnormality.

THE BASIC DEFECT

Superficial consideration of the clinical manifestations of E-D might suggest an abnormality of elastic tissue as the fundamental defect, probably a superabundance of elastic fibers in the skin and joint capsules. However, the histologic

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(Legend continued from opposite page.)

tongue) and possibly to the pharyngeal and laryngeal areas where redundancy of the mucosal lining appears to be responsible for a chronic cough, especially during the winter months. The ears are large and "floppy," with less prominent landmarks than is normally the case. There is bilaterally an epicanthal fold. The skin under the chin is loose and redundant. Bilateral cervical ribs are present; members of the father's family show this anomaly. Easy bruising has been a striking feature. The patient is less active than normal because of voluntary restriction and has become somewhat obese as a result. The regular use of bandages of the legs has helped avoid much trouble with cuts on the shins.

Biopsy of skin and skeletal muscle in the left pectoral area revealed increase in the number of elastic fibers in the corium and in the perimyal areas. Some of the arteries showed what appeared to be anomalous elastic fibers.

A, Front view. *B*, Lateral view. Note the scars of the face and knees, the knobby appearance of the soles, the flat feet, the peculiarly shaped pinnae, and the epicanthal folds. *C*, Loose collagen meshwork and unusually abundant elastic fibers (stained black) in the subcutaneous area overyling pectoral muscle (Verhoeff-van Giesen stain; ×200; reduced 3/7). *D*, Increased elastic fibers in small artery in pectoral muscle (Verhoeff-van Giesen stain; ×200; reduced 3/7).

studies by no means afford unequivocal substantiation of this theory. Brown and Stock[9] suggested, and others (notably, and most recently, Jansen[36]) maintain,[28] that the defect may reside in the collagen fibers which, because of lack of normal tensile strength, permit the skin, joint capsules, ligaments, and so forth to be stretched beyond the normal limits. The elastic fibers may function in connection with the process of restoration to normal configuration of these tissues. According to the "collagen theory," the histologic changes, both quantitative and qualitative, are interpretable as secondary effects of the abnormality of collagen. I am inclined to favor the view that the Ehlers-Danlos syndrome is another heritable disorder of collagen, biochemically, morphologically, clinically, and, of course, genetically distinct from the others which are under discussion in this book.

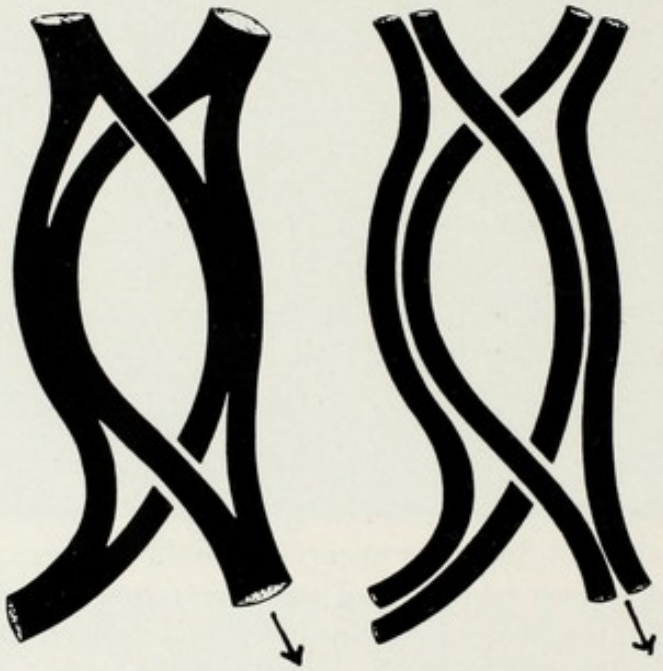


Fig. 56*A*. Fig. 56*B*.

Figs. 56*A* and 56*B*. Jansen's schematic representation of the postulated defect in collagen fasciculation in E-D. *A*, Normal; *B*, E-D syndrome. (From Jansen, L. H.: Dermatologica **110**:108, 1955.)

The comparative inextensibility of normal collagen may depend upon some specific molecular or intermolecular structure which is altered in E-D, with resulting increase in extensibility. This is assumed to be the case in the theory of Brown and Stock and has been explicitly stated by Froelich[27] and others. Jansen[36] has recently advanced a related theory, incriminating collagen but placing the defect at a higher level of organization of collagen, i.e., that E-D is a disorder of the organization of collagen fibrils into bundles and of the bundles into a strong network. He refers to the disease as one of a "defective wicker-work" of collagen. The evidence he assembles (see above, under Pathology) and the clinical aspects of the disease outlined here make Jansen's version of the "collagen theory" highly probable.

It is possible that in some patients and at some subcutaneous and articular locations production of an excessive number of elastic fibers is stimulated by the repeated and excessive stretching. In tissue culture, Maximow[53] and Bloom[3]

thought the tugging of contractile myocardial cells was a factor in the formation of elastic fibers.

The changes in the skin of the feet and hands and at the elbows of older patients fit in well with the view that the primary defect resides in the collagen fibers: the normal elastic tissue may, with the passage of time, "wear out" from excessive stress imposed upon it, and the cutis laxa (as opposed to cutis hyperelastica) of late cases become evident.

In Hungary Banga and Baló,[106] who discovered the elastolytic enzyme in pancreas, also demonstrated that normal serum contains an elastase inhibitor. In Tunbridge's department in Leeds, Hall and Saxl[121] found in two patients with E-D a concentration of elastase inhibitor in the blood which was "between 50 and 100 times as great as that in pooled normal serum." Further investigations along this line will be awaited with great interest.

INCIDENCE AND INHERITANCE

Thus far, this syndrome has been described principally in Europeans and persons of European extraction. There is one report from India[12] of the disease in a 12-year-old Hindu girl. The disorder has been seen in Japan.[137] I know of no report of the condition in Negroes and have encountered the disease in only one possible instance, the first case of dissecting aneurysm above. I have received a verbal report of another Negro with seemingly typical E-D. The Negro patient shown in Fig. 57 may have E-D.

Schaper[79] stated in 1952 that only ninety-three cases of this syndrome had been reported. Although the number is now probably well in excess of 100, it is possible that fewer of these cases have been reported than of any of the other syndromes discussed in this series. This is, in part, the result of greater difficulties of recognizing the syndrome, since cutaneous and articular hyperelasticity is a graded trait. I hazard to say, however, that in actuality this is one of the most frequent of the heritable disorders of connective tissue. My photographer, in the course of the study of other patients with E-D, recalled that his brother-in-law could do contortionist tricks with his hands. On investigation this individual was found to have had congenital dislocation of the right hip, bilateral inguinal hernias, diaphragmatic hernia, and trouble with one knee and the right wrist (Figs. 51*A* and 51*B*). Although these had all been considered unrelated, the diagnosis of the Ehlers-Danlos syndrome is quite certain and all these manifestations are clearly part of the syndrome. This patient illustrates how easy it is to overlook the generalized disorder.

The incidence of this syndrome, at least the frequency with which the diagnosis is made, relative to that of other heritable disorders of connective tissue, is indicated by the fact that available to me for study have been only fourteen kinships in which at least one bona fide instance of E-D has occurred, whereas more cases of all four other major disorders are known to me.

In at least five of the fourteen kinships I have studied, more than one affected person was identified: father-daughter; mother-son; mother-mother's cousin-daughter, father-son, mother-daughter. Since mild manifestations tend to be overlooked by laymen and since only the propositus was examined in several instances,

the above evidence can be taken only as a rough indication of the pedigree pattern that may be observed.

In 1949 Johnson and Falls[38] reviewed sixteen families reported in the literature as having more than one affected member.[33,44] In these families, a total of eighty affected individuals had been identified, of whom exactly half were male. Brown[8] found nineteen affected members in a family numbering forty-seven individuals. Johnson and Falls[38] studied the pattern of inheritance in detail and concluded that the disorder is inherited as a dominant. Two sisters with an unusually

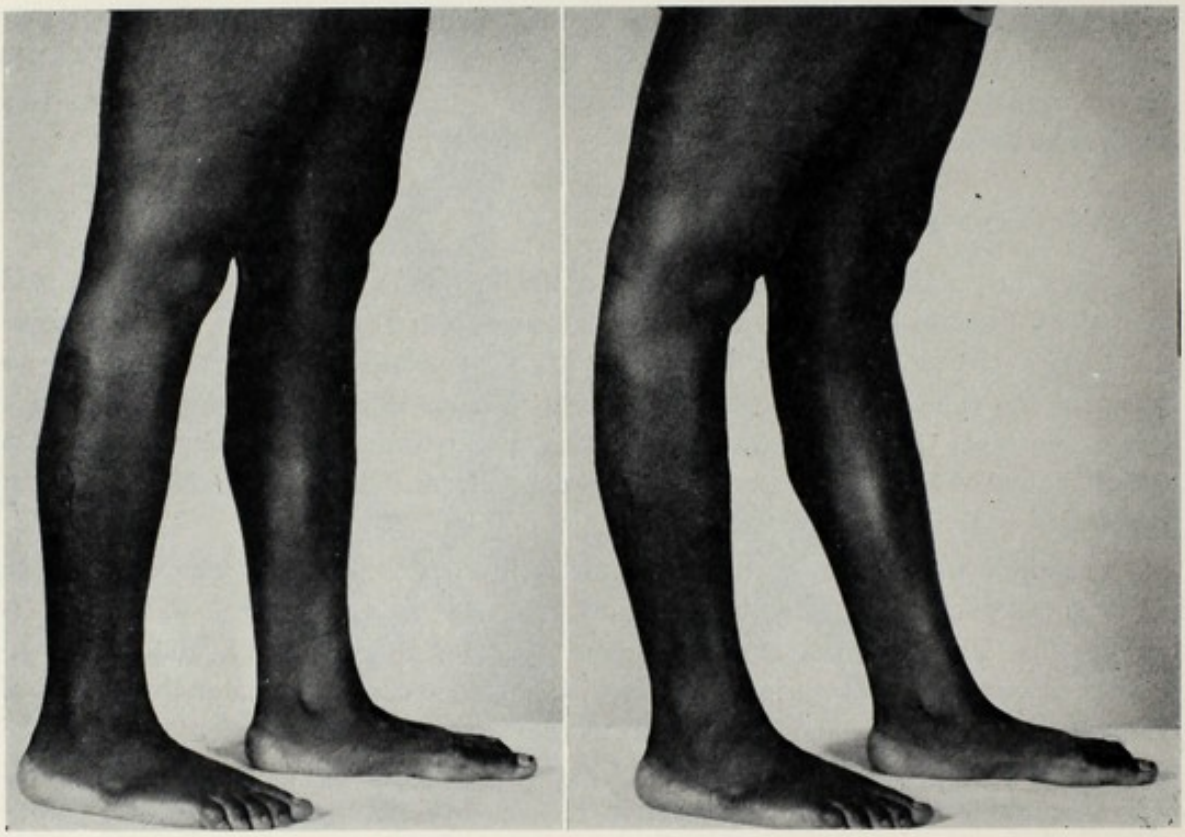


Fig. 57*A*. Fig. 57*B*.

Figs. 57*A* and 57*B*. H. L. W. (395947), an example of "simple" joint hypermobility. Seemingly no similar disorder in family. Although the knees and feet are most markedly affected, with genu recurvatum and pes planus, all joints of the body are more mobile than the average. The pes planus is of the dynamic type; the arch of the foot appears fairly normal except during weight bearing. The joint instability at the knees resulted in recurrent hydrarthroses. The patient has worn knee braces with benefit. There are no associated cutaneous or internal manifestations to suggest E-D. The patient did have strabismus (intermittent exotropia) for which resection and advancement of left medial rectus muscle was performed. This case illustrated how difficult it is to be sure of the proper diagnostic classification in a patient with manifestations which may represent an incomplete form of the E-D syndrome, especially when there is in the family no more full-blown example of the disorder.

A, Position of rest. *B*, Forced backward displacement of knees to demonstrate genu recurvatum. Note flat feet and a few scars which are suggestively papyraceous.

severe form of the disease were children of cousins, each with a mild form of the disease; this suggested to the authors that the trait might have occurred in homozygous state in these girls. Consanguinity was thought to be a factor in the cases observed by Ronchese[76] and by Weber and Aitken.[97] For an extensive review of most of the published pedigrees, see Jansen.[126,127]

Although the survey of the literature by Johnson and Falls[38] indicated a sex ratio of one, in the kindred they studied personally there were twenty-one affected males and eleven affected females. Furthermore, Jansen,[126] on the basis of a more extensive survey, concluded that the incidence of this disorder is consistently higher in males.

Coe and Silver[13] and Ormsby and Tobin[62] presented illustrations of members of three generations displaying the E-D syndrome; Stuart,[84] Mories,[134] and Husebye[123] traced it through four generations; the largest pedigree is that of Johnson and Falls,[38] with six generations affected. Here there was again clear evidence of dominant inheritance. The disease has been described in one of twins who were probably fraternal.[20]

Penetrance in this disease is probably considerably lower than in Marfan's disease, for example. This, however, is merely the result of the greater difficulty of recognizing mild and graded abnormality of the joints and skin as opposed to less equivocal manifestations, e.g., ectopia lentis, in Marfan's syndrome.

As always, the possibility of the existence of more than one genotype in this disease must be kept prominently in mind. Some minor phenotypic differences, for example, the lack of skin fragility in cases such as those shown in Figs. 53 and 54, suggest this possibility but are not sufficiently clear-cut to make one certain. Somatic mutation is a possible explanation for unilateral involvement, as in the famous case of van Meekeren. However, there are no clearly described similarly unilateral cases reported in recent times. That of Du Bois[22] is too sketchily reported to permit analysis.

MISCELLANEOUS CONSIDERATIONS

"Simple" hypermobility of joints, known also as congenital laxity of ligaments, may occur as an isolated finding,[42,73,85] with a genetic background distinct from that in E-D. For example, in Key's family[42] a sex-linked inheritance was suggested; the disorder occurred only in males. Loose-jointedness occurs also in the Marfan syndrome and with osteogenesis imperfecta, whereas reduced joint mobility is characteristic of the Hurler syndrome. In the differential diagnosis of loose-jointedness, especially in children, cerebrocortical degeneration or malformation, mongolism, cretinism, rickets, and nonspecific cachexia must be kept in mind.

Hass and Hass[122] suggest that there is a distinct entity of loose-jointedness or, as they term it, *arthrochalasis multiplex congenita,* which is a "constitutional dyscrasia of mesenchyme," has wide variability in severity, and may occur with or without skin changes. In this view E-D is apparently construed as merely those cases of arthrochalasis multiplex congenita in which skin involvement happens to be present. It seems more likely, however, that there are a number of genetic causes of loose-jointedness, and that although E-D may occur without much or any skin change, most cases do show changes in both the skin and joints.

Ellis and Bundick[115] have measured joint mobility in 500 subjects, about half male, half female, spanning eight decades of age. The gauge of mobility was extensibility of the fifth finger as shown in Fig. 58*A*. The subject placed his extended hand on a flat surface with the forearm parallel to the examining surface. The

examiner then extended the fifth finger as far as comfortably possible and measured the angle made by the proximal phalanx with the flat surface with a protractor to the closest multiple of 15 degrees. The results are charted in Figs. 58*B* and 58*C*. Most children have a high degree of mobility. Between ages 15 and 50 years a high degree of mobility is considerably more frequent in female subjects than in males.

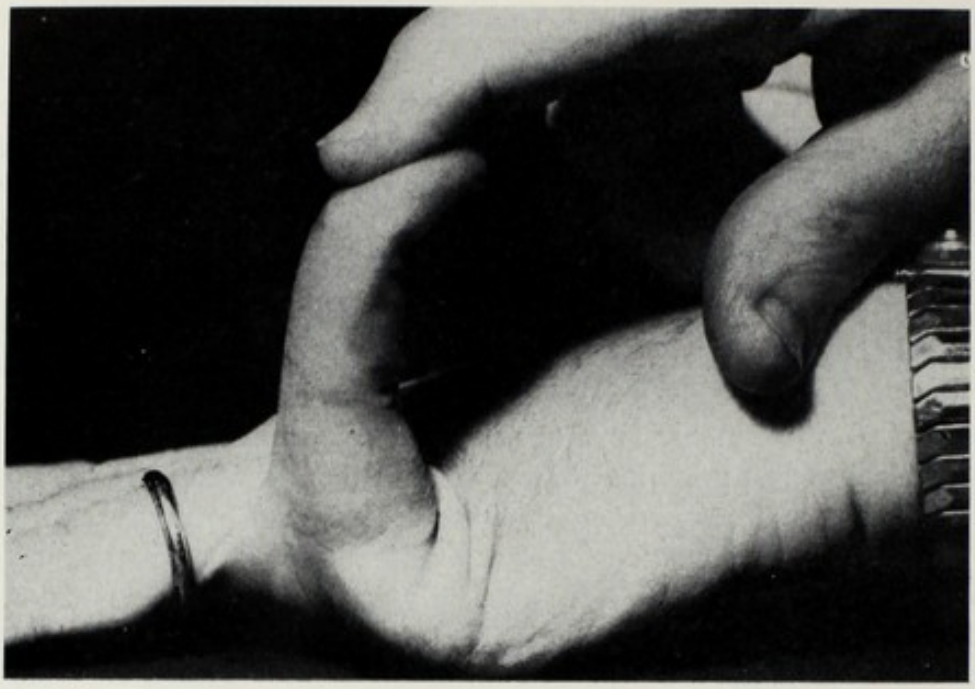


Fig. 58*A*. The Ellis-Bundick method for quantifying joint mobility.

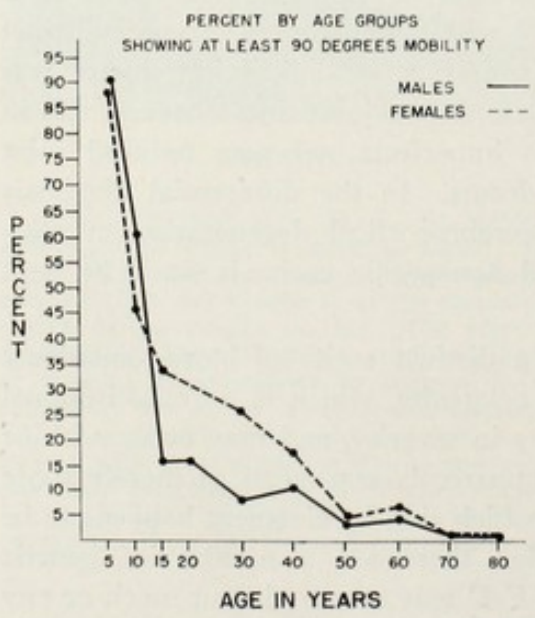


Fig. 58*B*.

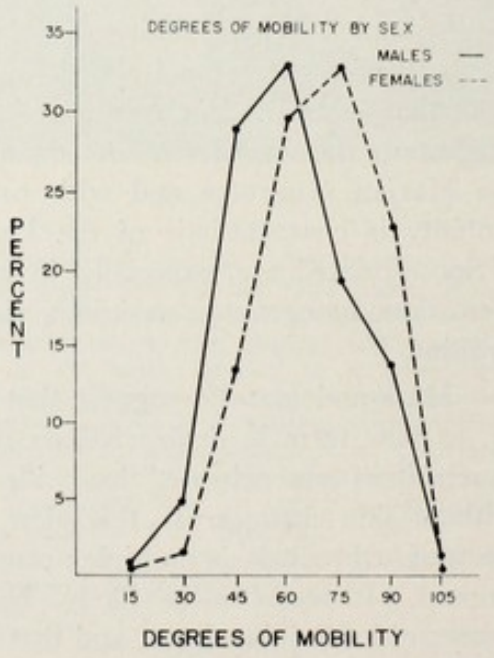


Fig. 58*C*.

Figs. 58*B* and 58*C*. Joint mobility by age and sex, as determined by the Ellis-Bundick method in 500 subjects. *B*, Most young children under 5 years of age show at least 90-degree mobility. In the groups of intermediate age the incidence is appreciably greater in women. *C*, Female subjects show higher grades of mobility. (From Ellis, F. A., and Bundick, W. R.: A.M.A. Arch. Dermat. **74**:22, 1956.)

Although no quantitative study of the subject has been made, there is a clinical impression that Negroes are more loose-jointed than whites.

Blue sclerae are not uncommon in E-D,[6,24] and presence of this feature cannot be taken as evidence of associated osteogenesis imperfecta. Biering and Iverson[108] have reported a more convincing case of association of the two connective tissue disorders. There was no familial history of manifestations of osteogenesis imperfecta, but in the father's line there was joint and skin hyperextensibility. The description[50,74,126] of associated dolichostenomelia (long, thin extremities as in the Marfan syndrome) cannot be taken as evidence that E-D and the Marfan syndrome coincided in those patients, since no ectopia lentis was detected and no unequivocal cases of the Marfan disease in other members of the family were described.

At least three seemingly bona fide instances of coincident E-D and pseudoxanthoma elasticum have been described.[14,59,65] In Cottini's patient[14] there were angioid streaks and lesions of the skin of the neck characteristic of pseudoxanthoma elasticum (see Chapter 6) and, in addition, cigarette paper scars of the elbows and knees and hyperextensible skin and joints characteristic of E-D. The pseudoxanthoma elasticum, which appears to be a recessive trait, was not transmitted to a daughter who suffered from acrocyanosis or a son who had hyperextensible skin and joints, hernia, and varices of the leg veins. The 22-year-old woman described by Pelbois and Rollier[65] consulted them because of the cosmetically undesirable lesions of pseudoxanthoma elasticum involving the skin of the neck and other areas of flexure. As well as angioid streaks of the fundus (characteristic of pseudoxanthoma), the patient had multiple cicatrices indicative of cutaneous fragility, striking cutaneous hyperelasticity, and articular hypermobility. The parents were first cousins, a fact significant in the appearance of the recessive trait, pseudoxanthoma. The parents were themselves unaffected by pseudoxanthoma, although a maternal aunt of the patient was affected. As for E-D, the patient's mother displayed features of this syndrome and had probably transmitted it as a dominant trait to her daughter. These are then examples of accidental coincidence of the two syndromes, one behaving as a dominant and one as a recessive trait.

There is a distinct, although less well defined, entity to which the name cutis laxa can be specifically applied.[140] The unusual patient described by Rossbach[131] in 1885 was probably in this category; in his discussion he also mentioned what was probably a true case of E-D and, in fact, the same case described later by Kopp.[44] In cutis laxa the skin hangs in inelastic folds (see references 115 and 140 for striking illustrations). Associated pulmonary emphysema, resulting in death, has been described in an infant with cutis laxa.[111] Some of the cases may be acquired, being secondary probably to inflammation, whereas others are congenital. Some of of the latter group may have a genetic basis. Carney and Nomland[110] described a patient with pronounced looseness of the skin, prolapse of the uterus, relaxed abdomen, and such pronounced redundancy of the skin over the eyes that she had to suspend it with cellophane tape to see. The skin in pseudoxanthoma elasticum acquires the character of cutis laxa in extreme cases (Fig. 77, p. 219). Cutis laxa (also called dermatochalasia and chalasoderma) in association with a form of dysostosis is discussed on page 315.

In one patient, 61 years old,[58] E-D coexisted with muscular atrophy of the Aran-Duchenne type (amyotrophic lateral sclerosis). I find it impossible to agree with the authors[58] that an etiologic connection between the two conditions existed. In one of my cases, Oppenheim's disease (amyotonia congenita)[120a] was the original diagnosis when the patient was first seen at the age of 4 years. Abnormality of creatine metabolism was reported in one patient,[68] and in another[66] there was coincident parathyroid tumor with osteitis fibrosa cystica. After correction of the hyperparathyroidism surgically, it appeared that the joint laxity, particularly the scoliosis, and the fragility of the skin decreased.

The Bonnevie-Ullrich-Turner syndrome[128] often has hyperelasticity of joints and skin as a feature. Furthermore, the skin of the hands may be loose and wrinkled as an aftermath of the lymphedema that is frequently present in the first

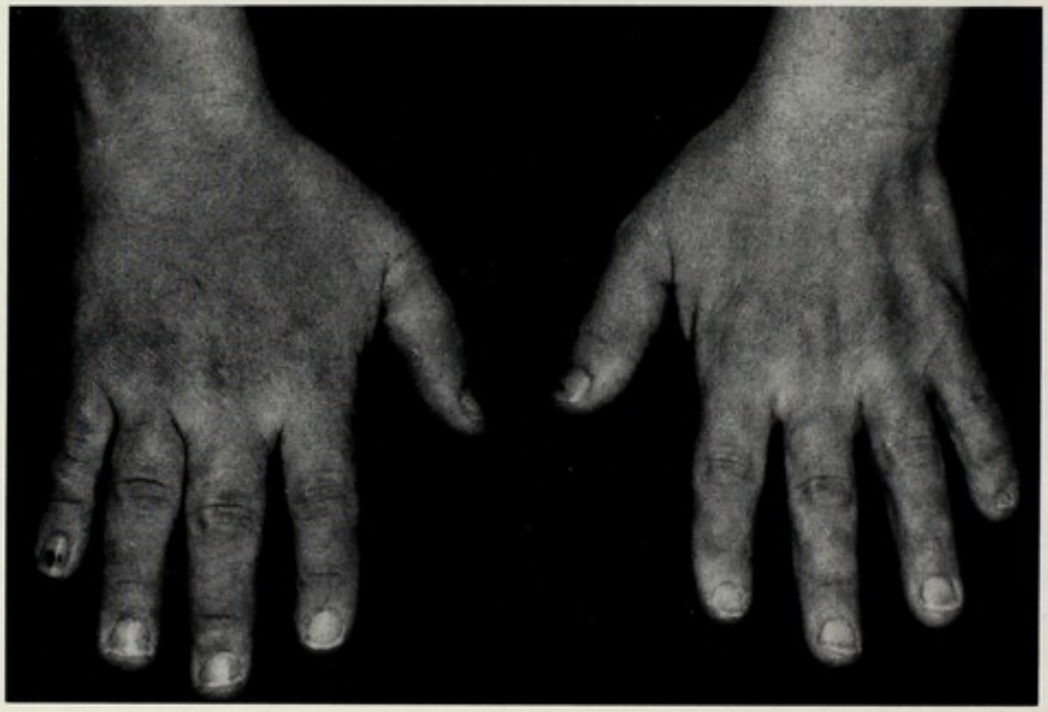


Fig. 59. The hands in a case of Turner syndrome (gonadal dysgenesis), with webbed neck, dwarfism, and coarctation of the aorta (M. H., 270068). The hands are short with the same loose, coarse-grained skin as in E-D. Compare with Fig. 53*C*. However, loose-jointedness is not present in most cases of the Turner syndrome.

year or so after birth. (More characteristic features are dwarfism, webbing of the neck, cubitus valgus, gonadal dysgenesis, and female phenotype with male genotype). Rossi and his colleagues[77,142] have emphasized the similar features. Rossi and Angst[77] write as follows: "The Ehlers-Danlos syndrome sufficiently closely resembles the pterygium syndrome that the former should be considered a forerunner of the latter." Although it is probably far-fetched to presume any fundamental relationship, the possibility of diagnostic confusion cannot be disputed.

Interesting physiologic studies of skin elasticity and tensile strength have been done in recent years.[18,19,37,46,60,75,99] Skin elasticity can be measured with the "pinchmeter" of Olmsted and his associates[136] or the elastometer of Schade or by the simple although subjective method of Ellis and Bundick[115]: The skin of

the dorsum of the wrist is elevated between the forefinger and thumb and relative elasticity estimated. Normal elasticity is indicated by 2+, reduced elasticity by 1+, and increased elasticity by 3+. Scleroderma on this scale is 0 and full-blown E-D, 4+. Rollhäuser[75] found least tensible strength in the skin of infants under 3 months (about 0.25 kg. per square millimeter); more in adults (about 1.6 kg. per square millimeter) and yet more in aged individuals (over 2.0 kg. per square millimeter). With aging, furthermore, skin became progressively less extensible. These observations may explain the tendency for the cutaneous fragility and extensibility in E-D to become less striking as the affected individual ages. Rollhäuser[75] studied the skin tensile strength of a 35-year-old man with E-D and found it to be very low (0.34 kg. per square millimeter). It is of interest that this worker found parallel changes in the tensile strength and extensibility of tendons, suggesting that the properties measured in the skin may be constitutional and generalized. Wenzel[99] found lesser tensile strength in female skin and made important observations indicating reduction in the strength of the skin in normal pregnancy and in Cushing's syndrome. In connection with the latter condition, it is noteworthy that the fragility of the skin and easy bruisability are rather similar in E-D and in Cushing's syndrome.[47] However, in all likelihood, the similarity is only superficial.

Measures of joint elasticity and other characteristics such as plasticity and viscosity will be valuable in the study of E-D. Promising progress in the quantitation of loose-jointedness has been made by Wright and Johns.[152]

Surgery in the Ehlers-Danlos syndrome has often been accompanied by wound dehiscence[63,124] (Figs. 51*A* and 51*B*). The tissues may be strikingly friable and hold sutures poorly. Hemostasis may be a problem. With particular care Ricketson[139] was able to repair a large flaplike wound of the right shin; the scars of the other shin were removed and likewise replaced by a split-thickness graft with excellent results.

Almost always the skin and joint changes in E-D are evident from an early age. However, Jacobs[124] described a patient in whom the manifestations seemed quite clearly to appear first at the age of 29 years. Although the patient had been a pugilist, no friability of the skin had been noted earlier. A brother was also affected.

SUMMARY

On the basis of eleven kinships containing at least one previously unreported case of the Ehlers-Danlos syndrome, and on the basis of the cases reported in the literature, the cardinal manifestations of the syndrome can be said to be hyperelasticity and abnormal fragility of the skin and hyperextensibility of joints. Other cutaneous and skeletal manifestations which are an integral part of the syndrome are discussed, as well as ocular and internal manifestations.

It is suggested that dissecting aneurysm of the aorta may be a complication of this connective tissue disorder as well as of the Marfan syndrome. Diaphragmatic and other types of hernia and gastrointestinal diverticula occur fairly often. Fragility of the bowel with spontaneous rupture may be a feature. Conventional types of congenital heart disease and congenital anomalies of the kidney have been observed. Involvement of the collagenous skeletal structures and valves of the heart

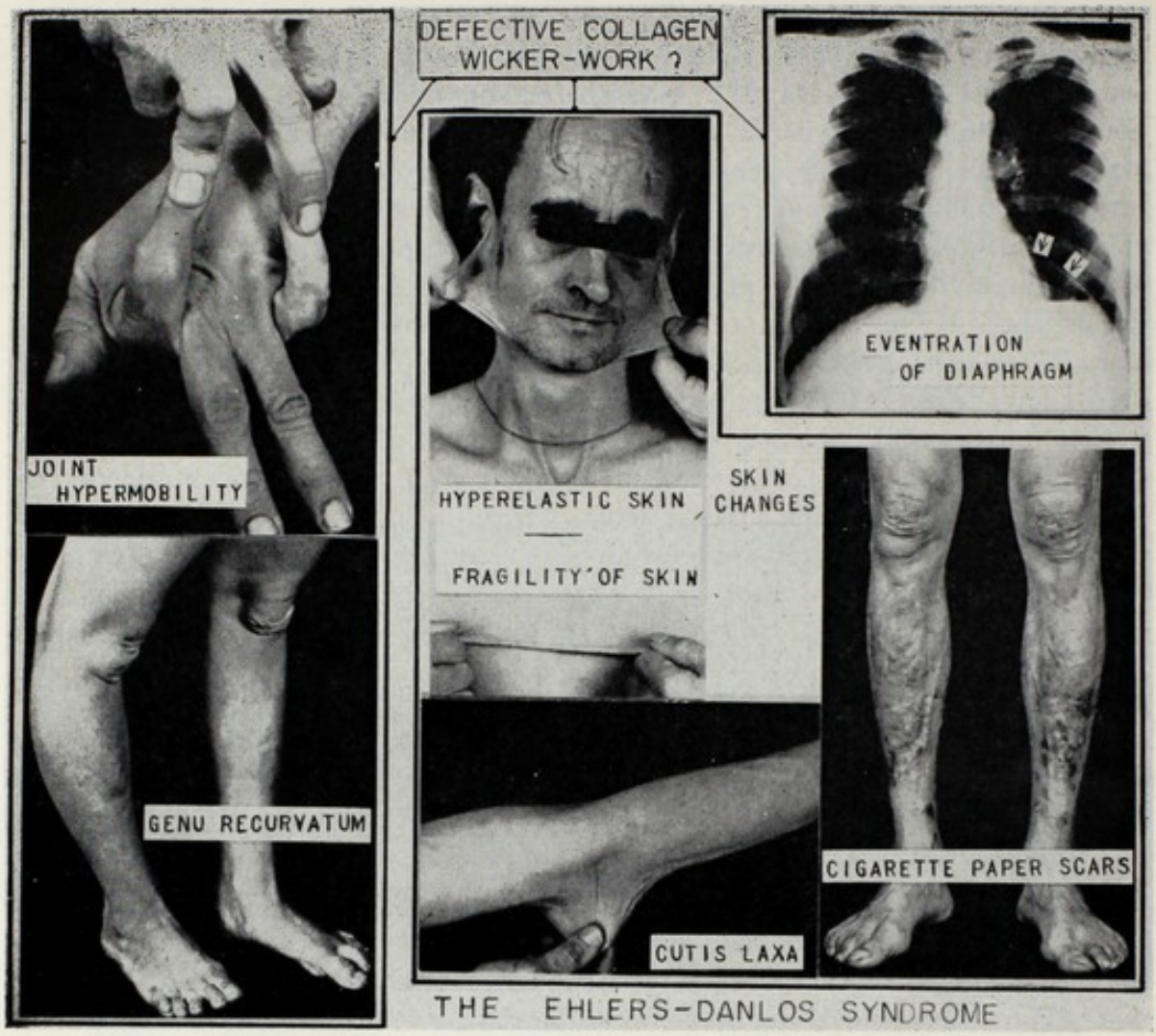


Fig. 60. A composite pictoral presentation of the several manifestations of E-D, related to the defect postulated by Jansen.[86]

is suggested but cannot be considered proved as a primary and integral feature. Rupture of the lung with mediastinal emphysema and/or pneumothorax appears to occur with increased incidence.

Tentatively the basic defect is considered to involve organization of collagen bundles into an intermeshing network.

The disorder is probably inherited as a simple autosomal dominant.

REFERENCES

1. Barber, H. S., Fiddes, J., and Benians, T. H. C.: The Syndrome of Ehlers-Danlos, Brit. J. Dermat. **53**:97, 1941.
2. Benjamin, B., and Weiner, H.: Syndrome of Cutaneous Fragility and Hyperelasticity and Articular Hyperlaxity, Am. J. Dis. Child. **65**:247, 1943.
3. Bloom, W.: Studies on Fibers in Tissue Culture. II. The Development of Elastic Fibers in Cultures of Embryonic Heart and Aorta, Arch. exper. Zellforsch. **9**:6, 1929.
4. Bolam, R. M.: A Case of Ehlers-Danlos Syndrome, Brit. J. Dermat. **50**:174, 1938.
5. Bonnet, P.: Les manifestations oculaires de la maladie d'Ehlers-Danlos, Bull., Soc. opht. France **1**:211, 1953.
6. Bossu, A., and Lambréchts: Manifestations oculaires du syndrome d'Ehlers-Danlos, Ann. ocul. **187**:227, 1954.
7. Brombart, M., Coupatez, G., and Laurent, Y.: Contribution à l'étude de l'étiologie de la hernie hiatale et de la diverticulose du tube digestif; un cas de maladie d'Ehlers-

Danlos associée à une hernie hiatale, un diverticule de l'estomac, un diverticule duodénal, une diverticulose colique et une anémie sidéropénique, Arch. mal. app. digest. **41**:413, 1952.
8. Brown, A.: Ehlers-Danlos Syndrome; Description of 3 Cases, Glasgow M. J. **27**:7, 1946.
9. Brown, A., and Stock, V. F.: Dermatorrhexis; Report of a Case, Am. J. Dis. Child. **54**:956, 1937.
10. Burrows, A.: Epidermolysis Bullosa With Cutis Hyperelastica, Proc. Roy. Soc. Med. **25**:1319, 1932.
11. Burrows, A., and Turnbull, H. M.: Cutis Hyperelastica (Ehlers-Danlos Syndrome), Brit. J. Dermat. **50**:648, 1938.
12. Chakraborty, A. N., Banerjee, A. K., and Ghosh, S.: Ehlers-Danlos Syndrome (Cutis Hyperelastica), J. Indian M. A. **23**:344, 1954.
13. Coe, M., and Silver, S. H.: Ehlers-Danlos Syndrome (Cutis Hyperelastica), Am. J. Dis. Child. **59**:129, 1940.
14. Cottini, G. B.: Association des syndromes de Groenblad-Strandberg et d'Ehlers-Danlos dans le même sujet, Acta dermat.-venereol. **29**:544, 1949.
15. Danlos, M.: Un cas de cutis laxa avec tumeurs par contusion chronique des coudes et des genoux (xanthome juvenile pseudo-diabetique de M. M. Hallopeau et Mace de Lépinay), Bull. Soc. franç dermat. et syph. **19**:70, 1908.
16. Debré, R., and Semelaigne, G.: A propos de la maladie d'Ehlers chez le nourrisson, Bull. mém. Soc. méd. hop. Paris **57**:849, 1936.
17. Debré, R., Marie J., and Seringe, P.: "Cutis laxa" avec dystrophie osseuse, Bull. mém. Soc. Méd. Hôp. Paris **61**:1038, 1937.
18. Dick, J. C.: The Tension and Resistance to Stretching of Human Skin and Other Membranes, With Results From a Series of Normal and Edematous Cases, J. Physiol. **112**:102, 1951.
19. Doerks, G.: Zur klinischen Prüfung der Hautdehnung, Arch. Kinderh. **136**:1, 1949.
20. Dorsch, H. H.: Ueber das Ehlers-Danlos-Syndrom, Veröffentlichung eines Falles bei einem Zwillingskind, Kinderärztl. Praxis **21**:49, 1953.
21. Dreyfus, G., Weill, J., Martineau, J., and Mathivat, A.: Un cas de maladie d'Ehlers-Danlos, Bull. mém. Soc. méd. hôp. Paris **52**:1463, 1936.
22. Du Bois: Cutis Laxa (Abstract), Zentralblat f. Haut-u. Geschlechtskr. **35**:52, 1931.
23. Du Mesnil: Beitrag zur Anatomie und Aetiologie bestimmter Hautkrankheiten, Diss., Wurzburg, 1880. (Cited by Unna.[88])
24. Durham, D. G.: Cutis Hyperelastica (Ehlers-Danlos Syndrome) With Blue Scleras, Microcornea, and Glaucoma, Arch. Ophth. **49**:220, 1953.
25. Ehlers, E.: Cutis laxa, Neigung zu Haemorrhagien in der Haut, Lockerung mehrerer Artikulationen, Dermat. Ztschr. **8**:173, 1901.
26. Freeman, J. T.: Ehlers-Danlos Syndrome, Am. J. Dis. Child. **79**:1049, 1950.
27. Froelich, H.: Fibrodysplasia elastica generalisata (Cutis laxa) und Nervensystem, Nervenarzt **20**:366, 1949.
28. Gadrat, J., and Bazex, A.: Sur le syndrome d'Ehlers-Danlos, Ann. dermat. et syph. **78**:430, 1951.
29. Gilbert, A., Villaret, M., and Bosviel, G.: Sur un cas d'hyperélasticité congénitale des ligaments articulaires et de la peau, Bull. mém. Soc. méd. hôp. Paris **59**:303, 1925.
30. Glass, H. B.: Personal communication.
31. Gore, I.: Dissecting Aneurysm of the Aorta in Persons Under Forty Years of Age, A.M.A. Arch. Path. **55**:1, 1953.
32. Gore, I., and Seiwert, V. S.: Dissecting Aneurysm of the Aorta; Pathologic Aspects; an Analysis of 85 Fatal Cases, A.M.A. Arch. Path. **53**:121, 1952.
33. Gould, G. M., and Pyle, W. L.: Anomalies and Curiosities of Medicine, Philadelphia, 1897, W. B. Saunders Co., p. 217.
34. Hallopeau and de Lépinay, M.: Sur un cas de xanthoma tubéreaux et de tumeurs juveniles offrant les charactères du xanthome diabetique, Bull. Soc. franç dermat. et syph. **17**:283, 1906.
35. Holt, J. F.: The Ehlers-Danlos Syndrome, Am. J. Roentgenol. **55**:420, 1946.
36 Jansen, L. H.: The Structure of the Connective Tissue, an Explanation of the Symptoms of the Ehlers-Danlos Syndrome, Dermatologica **110**:108, 1955.
37. Jochims, J.: Elastometrie an Kindern bei wechselnder Hautdehnung, Arch. Kinderh. **135**:228, 1948.
38. Johnson, S. A. M., and Falls, H. F.: Ehlers-Danlos Syndrome; a Clinical and Genetic Study, Arch. Dermat. & Syph. **60**:82, 1949.
39. Kalz, F.: Cutis laxa als Symptom allgemeiner Stützgewebsschwäche, Arch. Dermat. u. Syph. **171**:155, 1935.
40. Kanof, A.: Ehlers-Danlos Syndrome. Report of a Case With Suggestion of Possible Causal Mechanism, A.M.A. J. Dis. Child. **83**:197, 1952.
41. Katz, I., and Steiner, K.: Ehlers-Danlos Syndrome With Ectopic Bone Formation, Radiology **65**:352, 1955.
42. Key, J. A.: Hypermobility of Joints as a Sex-linked Hereditary Characteristic, J.A.M.A. **88**:1710, 1927.

43. King-Louis, F. J.: Two Cases of Ehlers-Danlos Syndrome, Proc. Roy. Soc. Med. **39**:135, 1946.
44. Kopp: Demonstration zweier Fälle von "Cutis laxa," München. med. Wchnschr. **35**:259, 1888.
45. Korting, G. W., and Gottron, E.: Cutis Laxa, Arch. Dermat. u. Syph. **193**:14, 1951.
46. Kuk, E., and Kvorning, S. A.: Quantitative Measurements of the Elastic Properties of the Skin and Subcutaneous Tissue in Young Adults and Old Individuals, J. Gerontol. **4**:273, 1949.
47. Laane, C. L.: Cushing's Syndrome Associated With Obliterative Arterial Disease and Multiple Subcutaneous Nodules (Ehlers-Danlos Syndrome?), Acta med. scandinav. **148**:323, 1954.
48. Launay, C.: Syndrome d'Ehlers-Danlos chez un garcon de onze ans, associé à une arriération mentale, Bull. mém. Soc. méd. hôp. Paris **56**:709, 1941.
49. Le Coulant, P.: Hyperelasticité cutanée et articulaire avec fragilité anormale de la peau et tumeurs molluscoides, chez un enfant de treize ans (syndrome d'Ehlers-Danlos), Gaz. hebd. sci. méd. Bordeaux **29**:1934.
50. Lienhart, O.: La maladie d'Ehlers-Danlos. Etude clinique, anatomo-pathologique et génetique, Thesis de Nancy, 1945 (No. 30).
51. Littré, E.: Oeuvres complètes d'Hippocrate, Paris, 1840, J.-B. Baillière, vol. 2. pp. 67-83.
52. Margarot, J., Deneze, P., and Coll de Carrera: Hyperlaxité cutanèe et articulaire (syndrome de Danlos) existant chez trois membres d'une même famille, Bull. Soc. franç dermat. et syph. **40**:277, 1933.
53. Maximow, A.: Development of Argyrophile and Collagenous Fibers in Tissue Culture, Proc. Soc. Exper. Biol. & Med. **25**:437, 1928.
54. Méténier, P.: A propos d'un cas familial de maladie d'Ehlers-Danlos, Thése d'Alger, 1939, No. 55.
55. Miguet, A.: Le syndrome d'Ehlers-Danlos, Thése, Paris, 1933, Louis Arnette.
56. Mounier-Kuhn, P., and Meyer, L.: Méga-organes (oesophage, trachée, colon), syndromes de Mickulicz et d'Ehlers-Danlos chez une hérédo-syphilitique, Bull. mém. Soc. méd. hôp. Lyon, Nov. 9, 1943.
57. Murray, J. E., and Tyars, M. E.: A Case of Ehlers-Danlos Syndrome, Brit. M. J. **1**:974, 1940.
58. Nicaud, P., Lafitte, A., and Buhot, S.: Syndrome d'Ehlers-Danlos fruste associé à une atrophie musculaire du type Aran-Duchenne, Bull. mém. Soc. méd. hôp. Paris, Mar. 10, 1944.
59. Noto, P.: Cited by Pelbois and Rollier.[65]
60. Ona, C. K., and Cowdry, E. V.: Aging of Elastic Tissue in Human Skin, J. Gerontol. **5**:203, 1950.
61. Orlandi, O. V., and Rodrigues, Y. T.: Ehlers-Danlos Syndrome; Capillary Microscopy in Cases, Pediatria (Rio) **17**:189, 1952.
62. Ormsby, O. S., and Tobin, W. W.: Cutis Hyperelastica; Case Report, Arch. Dermat. & Syph. **38**:828, 1938.
63. Packer, B. D., and Blades, J. F.: Dermatorrhexis; a Case Report; the So-called Ehlers-Danlos Syndrome, Virginia M. Month. **81**:21, 1954.
64. Pautrier, M.: Note histologique sur un cas de cutis elastica, avec pesudotumeurs aux genoux et aux coudes, presenté par M. Danlos, Bull. Soc. franç dermat. et syph. **19**:72, 1908.
65. Pelbois, F., and Rollier, F.: Association d'un syndrome d'Ehlers-Danlos et d'un syndrome de Groenblad-Strandberg, Bull. Soc. franç dermat. et syph. **59**:141, 1952.
66. Perreau, P., Bangas, J., and Lecuit, P.: Osteitis fibro-kystique atypique et syndrome d'Ehlers-Danlos. Lesion parathyroidienne, Bull. mém. Soc. méd. hôp. Paris **57**:135, 1941.
67. Péyri: Un cas de syndrome d'Ehlers-Danlos, probablement d'origine syphilitique, Bull. Soc. franç dermat. et syph. **44**:1744, 1937.
68. Pittinos, G. E.: Ehlers-Danlos Syndrome With Disturbance of Creatine Metabolism, J. Pediat. **19**:85, 1941.
69. Poumeau-Delille, G., and Soulié, P.: Un cas d'hyperlaxité cutanee et articulaire avec cicatrices atrophique et pseudo-tumeurs molluscoides (syndrome d'Ehlers-Danlos), Bull. mém. Soc. méd. hôp. Paris **50**:593, 1934.
70. Pray, L. G.: Cutis Elastica (Dermatorrhexis, Ehlers-Danlos Syndrome), Am. J. Dis. Child. **75**:702, 1948.
71. Raybaud, A., and Guidoni, P.: Hyperlaxité ligamentaire et cutanée; trouble du métabolisme calcique; maladie d'Ehlers-Danlos, Bull. mém. Soc. méd. hôp. Paris **54**:738, 1938.
72. Ringrose, E. J., Nowlan, F. B., and Perry, H.: Ehlers-Danlos Syndrome; Report of a Case, Arch. Dermat. & Syph. **62**:443, 1950.
73. Rocher, H. L.: Une nouvelle dysmorphose articulaire congénitale: laxité articulaire congénitale multiple, In *Livre jubilaire d'Henri Hartmann,* Paris, 1932, Masson et Cie.
74. Roederer, C.: Syndrome d'Ehlers-Danlos atypique coincidant avec une dolichosténomélie, Arch. franç pédiat. **8**:192, 1951.

75. Rollhäuser, H.: Die Zugfestigkeit der menschlichen Haut, Gegenbaurs morphol. Jahrb. **90**:249, 1950.
76. Ronchese, F.: Dermatorrhexis With Dermatochalasis and Arthrochalasis (the So-called Ehlers-Danlos Syndrome); Additional Data on a Case Reported 12 Years Previously, Rhode Island M. J. **32**:80, 1949.
77. Rossi, E., and Angst, H.: Das Danlos-Ehlers Syndrome, Helvet. paediat. acta **6**:245, 1951.
78. Samuel, M. A., Schwartz, M. L., and Meister, M. M.: The Ehlers-Danlos Syndrome, U.S. Armed Forces M. J. **4**:737, 1953.
79. Schaper, G.: Familiäres Vorkommen von Ehlers-Danlos Syndrome; ein Beitrag zur Klinik und Pathogenese, Ztschr. Kinderh. **70**:504, 1952.
80. Shapiro, S. K.: A Case of Meekrin-Ehlers-Danlos Syndrome With Neurologic Manifestations, J. Nerv. & Ment. Dis. **115**:64, 1952.
81. Shaw, A. B., and Hopkins, P.: A Case of a Boy, Aged Seven, Showing (a) Double-Jointedness, (b) Dermatolysis ("Elastic Skin") With Great Friability of the Skin and Excessive Tendency to Bruising, and (c) Multiple Subcutaneous Tumours on the Limbs (Fibromata, Neuronomata), Proc. Roy. Soc. Med. (Clin. Sec.) **6**:20, 1913.
82. Smith, C. H.: Dermatorrhexis (Ehlers-Danlos Syndrome), J. Pediat. **14**:632. 1939.
83. Stillians, A. W., and Zakon, S. J.: Cutis Laxa (Cutis Hyperelastica), Arch. Dermat. & Syph. **35**:342, 1937.
84. Stuart, A. M.: Three Cases Exhibiting the Ehlers-Danlos Syndrome, Proc. Roy. Soc. Med. **30**:984, 1937.
85. Sturkie, P. D.: Hypermobile Joints in All Descendants for Two Generations, J. Hered. **32**:232, 1941.
86. Sullivan, J. D.: The Danlos-Ehlers Syndrome; Report of Case With Transient Paralysis of Vocal Cord, Arch. Neurol & Psychiat. **47**:316, 1942.
87. Sutro, C. J.: Hypermobility of Bones Due to "Overlengthened" Capsular and Ligamentous Tissues; Cause for Recurrent Intra-articular Effusions, Surgery **21**:67, 1947.
88. Taylor, F. R.: The Meekrin-Ehlers-Danlos Syndrome, Urol. & Cutan. Rev. **47**:378, 1943.
89. Thomas, C., Cordier, J., and Algan, B.: Une étiologie nouvelle du syndrome de luxation spontanée des cristallins: la maladie d'Ehlers-Danlos, Bull. Soc. Belge d'ophtal. **100**:375, 1952.
90. Thomas, C., Cordier, J., and Algan, B.: Les altérations oculaires de la maladie d'Ehlers-Danlos, Arch. opht. **14**:691, 1954.
91. Tobias, N.: Danlos Syndrome Associated With Congenital Lipomatosis, Arch. Dermat. & Syph. **30**:540, 1934; Ibid. **40**:135, 1939.
92. Tunbridge, R. E., Tattersall, R. N., Hall, D. A., Astbury, W. T., and Reed, R.: The Fibrous Structure of Normal and Abnormal Human Skin. Clin. Sc. **11**:315, 1952.
93. Unna, P. G.: The Histopathology of the Diseases of the Skin. Translated from the German with the assistance of the author by N. Walker, New York, 1896, The Macmillan Co., pp. 984-988.
94. van Meekeren, J. A.: De dilatabilitate extraordinaria cutis, chap. 32, Observationes Medico-Chirugicae, Amsterdam, 1682.
95. Vissian, L., and Rovinski, J.: Syndrome d'Ehlers-Danlos chez quatre membres d'une même famille, Bull. Soc. franç. dermat. et syph. **62**:62, 1955.
96. Wallach, E. A., and Berkhart, E. F.: Ehlers-Danlos Snydrome Associated With Tetralogy of Fallot, Arch. Dermat. & Syph. **61**:750, 1950.
97. Weber, F. P., and Aitken, J. K.: Nature of the Subcutaneous Spherules in Some Cases of Ehlers-Danlos Syndrome, Lancet **1**:198, 1938.
98. Weill, J., and Martineau, J.: A propos d'un cas de maladie d'Ehlers-Danlos. Étude anatomoclinique et biologique, Bull. Soc. franç dermat. et syph. **44**:99, 1937.
99. Wenzel, H. G.: Untersuchen über die Dehnbarkeit und Zerreissbarkeit der Haut, Zentralbl. allg. Path. **85**:117, 1949.
100. Whitney, L. F.: Inheritance of Double Jointedness in Thumb, J. Hered. **23**:425, 1932.
101. Wiener, K.: Gummihaut (Cutis laxa) mit dominant Vererbung, Arch. Dermat. u. Syph. **148**:599, 1925.
102. Williams, A. W.: Cutix laxa, Monatsschr. f. prakt. Dermat. **14**:490, 1892.
103. Adams, F.: The Genuine Works of Hippocrates, New York, 1891, William Wood & Co.; Airs, Waters, and Places, paragraphs 20 and 22, vol. 1, pp. 176-178.
104. Agostini, A.: Cited by Jansen.[127]
105. Angst, H.: Das Ehlers-Danlos Syndrom, Diss., Zürich, 1951. Cited by Jansen.[127]
106. Banga, I., and Baló, J.: Elastin and Elastase, Nature **171**:44, 1953.
107. Bernard, J., Bassett, A., and Duperrat: Syndrome defragilité cutanée avec hémorragies multiples, Bull. Soc. franç. dermat. et syph. **61**:486, 1954.
108. Biering, A., and Iverson, T.: Osteogenesis Imperfecta Associated With Ehlers-Danlos Syndrome, Acta paediat. **44**:279, 1955.
109. Burton, A. C.: Relation of Structure to Function of the Tissues of the Wall of Blood Vessels, Physiol. Rev. **34**:619, 1954.
110. Carney, R. J., and Nomland, R.: Acquired Loose Skin (Chalazoderma): Report of a Case, Arch. Dermat. & Syph. **56**:794, 1947.

111. Christiaens, L., Marchant-Alphant, A., and Fovet, A.: Emphysème congénital et cutis laxa, Presse méd. **62**:1799, 1954.
112. Cockshott, W. P., and Omololu, A.: Familial Congenital Posterior Dislocation of Both Radial Heads, J. Bone & Joint Surg. **40-B**:483, 1958.
113. Corcelle and Fourcade: Maladie de Ehlers-Danlos et strabisme, Bull. soc. opht. France **10**:931, 1956.
114. Dick, J. C.: Observations on the Elastic Tissue of the Skin With a Note on the Reticular Layer at the Junction of the Dermis and Epidermis, J. Anat. **81**:201, 1947.
115. Ellis, F. A., and Bundick, W. R.: Cutaneous Elasticity and Hyperelasticity, A.M.A. Arch. Dermat. **74**:22, 1956.
116. Fleming, J. W.: The Ehlers-Danlos Syndrome, J. Florida M. A. **42**:290, 1955.
117. François, P., Woillez, M., Warrot, and Maillet, P.: Maladie d'Ehlers-Danlos avec anévrysme artério-veineux intra-crânien, Bull. Soc. opht. France No. 5:392, 1955.
118. Frick, P. G., and Krakchuk. J. D.: Studies of Hemostasis in the Ehlers-Danlos Syndrome, J. Invest. Dermat. **26**:453, 1956.
119. Fritchey, J. A., and Greenbaum, S. S.: Two Cases of Ehlers-Danlos Syndrome, Arch. Dermat. **42**:742, 1940.
120. Geldmacher, M.: Ein Fall von Dystrophia adiposa generalisata mit Cutis laxa und hochgradiger Vulnerabilität der Haut, Inaug. Diss., Bonn, 1921. Cited by Jansen.[127]
120a. Greenfield, J. G., Cornman, T., and Shy, G. M.: The Prognostic Value of the Muscle Biopsy in the "Floppy Child." Brain **81**:461, 1958.
121. Hall, D. A., Keech, M. K., Reed, R., Saxl, H., Tunbridge, R. E., and Wood, M. J.: Collagen and Elastin in Connective Tissue, J. Gerontol. **10**:388, 1955.
122. Hass, J., and Hass, R.: Arthrochalasis Multiplex Congenita, J. Bone & Joint Surg. **40-A**:663, 1958.
123. Husebye, K. C.: Tre familiäere tilfelle av Ehlers-Danlos syndrom, Tidsskr. norske laegefor. **72**:185, 1952.
124. Jacobs, P. H.: Ehlers-Danlos Syndrome: Report of a Case With Onset at Age 29, A.M.A. Arch. Dermat. **76**:460, 1957.
125. Jaeger, H.: Syndrome d'Ehlers-Danlos (deux cas familiaux), Dermatologica **100**:330, 1950.
126. Jansen, L. H.: Le mode de transmission de la maladie d'Ehlers-Danlos, J. Génét. hum. **4**:204, 1955.
127. Jansen, L. H.: De Ziekte van Ehlers en Danlos, Uitgeverij Excelsior 's-Gravenhage, 1954.
128. Lamy, M., and Frézal, J.: Le syndrome de Bonnevie-Ullrich et ses rapports avec le syndrome de Turner, Analecta genetica, vol. 6 (International Symposium, Turin, 1957).
129. Leider, M.: Forme Fruste of Ehlers-Danlos Syndrome. Urol. & Cutan. Rev. **53**:222, 1949.
130. Levy-Coblentz, G.: Radio-ulnar Synostosis, Bull. Soc. franç. dermat. et syph. **39**:1252, 1932.
131. Lewitus, Z.: Ehlers-Danlos Syndrome; Report of Two Cases With Hypophyseal Dysfunction, A.M.A. Arch. Dermat. **73**:158, 1956.
132. MacCollum, D. W.: The Lop Ear, J.A.M.A. **110**:1427, 1938.
133. McEvitt, W. G.: The Problem of the Protruding Ear, Plast. & Reconstruct. Surg. **2**:480, 1947.
133a. McKusick, V. A.: Hereditary Disorders of Connective Tissue, Bull. New York Acad. Med. **35**:143, 1959.
134. Mories, A.: An Investigation Into the Ehlers-Danlos Syndrome, Edinburgh Thesis, 1954.
135. Nicod, M.: Un cas de syndrome d'Ehlers-Danlos, Ann. paediat. **167**:358, 1946.
136. Olmsted, F., Page, I. H., and Corcoran, A. C.: A Device for Objective Clinical Measurement of Cutaneous Elasticity; a "Pinchmeter," Am. J. M. Sc. **222**:73, 1951.
137. Ota, M., and Yasuda, T.: Erster Fall von "Syndrome d'Ehlers-Danlos" in Japan, Zentralbl. f. Haut- u. Geschlechtskr. **66**:120, 1941.
138. Pascher, F.: Ehlers-Danlos Syndrome, Arch. Dermat. & Syph. **67**:214, 1953.
139. Ricketson, G.: The Behavior of Skin Grafts and Donor Sites in a Case of Ehlers-Danlos Syndrome, Plast. & Reconstruct. Surg. **20**:32, 1957.
139a. Robertson, J. A., Eddy, W. A., and Vossler, A. J.: Spontaneous Perforation of the Cecum Without Mechanical Obstruction; Review of Literature and Case Report, Am. J. Surg. **96**:446, 1958.
140. Robinson, H. M., Jr., and Ellis, F. A.: Cutis laxa, A.M.A. Arch. Dermat. **77**:656, 1958.
141. Ross, M., and Donneief, A. S.: Chest Surgery in the Presence of Cutis Hyperelastica (Ehlers-Danlos Syndrome), New York J. Med. **57**:2256, 1957.
142. Rossi, E., and Caflisch, A.: Le syndrome du pterygium. Status Bonnevie-Ullrich, dystrophia brevicolli congenita, syndrome de Turner et arthromyodysplasia congenita, Helvet. paediat. acta **6**:119, 1951.
143. Saemundsson, J.: Ehlers-Danlos Syndrome; a Congenital Mesenchymal Disorder, Acta med. scandinav. (supp. 312) **154**:399, 1956.
144. Sodeman, W. A., and Burch, G. E.: Skin Elasticity in Scleroderma, Am. Heart J. **17**:21, 1939.

145. Stucke, K.: Ueber das elastische Verhalten der Achillessehne im Belastungsversuch, Arch. klin. Chir. **265**:579, 1950.
146. Summer, G. K.: The Ehlers-Danlos Syndrome; a Review of the Literature and Report of a Case With a Subgaleal Hematoma and Bell's Palsy, A.M.A. J. Dis. Child. **91**:419, 1956.
147. Thurmon, F. M.: Ehlers-Danlos Syndrome, A.M.A. Arch. Dermat. **40**:120, 1939.
148. Tschernogobow, A.: Cutis laxa. (Presentation at first meeting of Moscow Dermatologic and Venereologic Society, Nov. 13, 1891.) Mhft. Prakt. Derm. **14**:76, 1892.
149. Tschernogobow, A.: Ein Fall von Cutis laxa. Protokoly Moskowskawo wenerologitscheskawo i dermatologitscheskawo Obtschestwa, vol. 1, p. 23. Quoted in Jahresb. d. ges. Med. **27**:562, 1892.
150. Villegas, R., and Albornoz, R.: Posibles mecanismos causales del sindrome de Ehlers-Danlos, Acta med. Venezolana **4**: 1956.
151. Weiss, R. S.: Danlos' Syndrome, A.M.A. Arch. Dermat. **40**:137, 1939.
152. Wright, V., and Johns, R. J.: The Quantitative Measurement of Joint Stiffness (abstract), J. Clin. Invest. **38**:1056, 1959.

5. OSTEOGENESIS IMPERFECTA

HISTORICAL NOTE

IT HAS BEEN suggested[101,167] that an early case of osteogenesis imperfecta was that of Ivar the Boneless, the mastermind behind the Scandinavian invasion of England in the last quarter of the ninth century. He is said to have had cartilage where bones should have been. He could not walk on his legs and was carried into battle on shields. Complete verification of the diagnosis is impossible because so much poetic glorification enshrouds any remaining records and Ivar's skeleton is no longer available for study, having been dug up and burned by William the Conqueror. A study of Ivar's descendants turned up no cases of osteogenesis imperfecta or other bone disease.

The recorded history of the development of knowledge of this disease is given in Table 4. Isolated cases were reported even before Ekman, from as early as 1678.[101]

The terms that have been applied to this syndrome are numerous and include, to mention a few, osteogenesis imperfecta (Vrolik[121]), mollities ossium (Ormerod[88]), fragilitas ossium (Gurlt[58]), and osteopsathyrosis idiopathica (Lobstein[75]). To complicate matters further, the disease is called *la maladie de Lobstein* in the French-speaking portion of the medical world; Eddowes' syndrome (brittle bones and blue sclerae); van der Hoeve's syndrome (brittle bones, blue sclerae, and deafness); and Vrolik's disease (osteogenesis imperfecta congenita). Looser[76] suggested the terms osteogenesis imperfecta congenita (OIC) and osteogenesis imperfecta tarda (OIT).

CLINICAL MANIFESTATIONS

Over one hundred kinships with at least one affected member have been identified in the records of the Johns Hopkins Hospital, the Children's Hospital School, and the Kernan Hospital for Crippled Children, Baltimore, Maryland.

The clinical aspects of osteogenesis imperfecta will be discussed under the headings of skeletal, ocular, cutaneous, otologic, and internal. The osseous manifestations greatly outweigh the others in significance.

Clinically two varieties of OI have been distinguished. In so-called osteogenesis imperfecta congenita, the disease is so severe that the relatively minor

Table 4. Landmarks in the History of Osteogenesis Imperfecta

1788 O. J. Ekman.[152] In medical doctrate thesis at Uppsala, described "osteomalacia congenita" in three generations. (See Seedorff[101] for an extensive translation of Ekman's Latin thesis.)

1831 Edmund Axmann,[135] Wertheim, Germany. Described the disease in himself and his brothers, Paul and Anton. Made reference to the occurrence of articular dislocations and and blue sclerotics. One of the brothers had been reported by Strack in 1807.[206a]

1833 J. C. Lobstein (1777-1838), gynecologist and pathologist, Strasbourg. Wrote about adult form of the disease in his textbook of morbid anatomy.[75]

1849 Willem Vrolik (1801-1863), Dutch anatomist. Described disease in newborn infant.[121] See Fig. 61.

1859 Edward Latham Ormerod, Brighton, England. Early description of case of 68-year-old woman only 39½ inches tall. Disease was passed to a son and a daughter. The skeleton, in the Royal College of Surgeons, London, is reproduced in Bell's monograph.[16] Use of term "mollities ossium."

1862-1865 Ernest Julius Gurlt[58] (1825-1899), Professor of Surgery, Berlin. Use of term "fragilitas ossium."

1889 H. Stilling,[206] Strasbourg. Histologic studies.

1896 John Spurway,[107] Tring, England. Described blue sclerotics with fragility of bones.

1897 M. B. Schmidt,[198] Strasbourg. Proposed fundamental identity of the disease in adults and newborn infants.

1900 Alfred Eddowes,[49] London. Described blue sclerotics. Suggested that OI is generalized hypoplasia of mesenchyme.

1903 Leslie Buchanan,[20] Glasgow. Demonstrated that blue sclerotics due to thinness of sclera. Fractures, deafness, or familial incidence not mentioned in his "A. M'C—, a girl aet. 9 years."

1906 E. Looser,[76] Heidelberg. Defended identity of disease in adult and newborn infant. Proposed terms osteogenesis imperfecta congenita (OIC) and osteogenesis imperfecta tarda (OIT).

1912 Charles A. Adair-Dighton,[1] Liverpool. Described deafness.

1918 J. van der Hoeve (Groningen) and A. de Kleyn (Utrecht).[118] Emphasized brittle bones, blue sclerae, and deafness as a syndrome.

1920 K. H. Bauer,[11,12] Breslau. Provided histologic support for view that OI is a "hypoplasia mesenchymialis." Described dental histology.

1919, 1922 E. Ruttin,[97,98] Vienna. Described otosclerotic nature of the deafness in OI.

1928 Julia Bell,[16] of the Galton Laboratory, London. Described dominant pattern of inheritance, especially of blue sclerotics, on basis of large number of pedigrees.

traumata to which the fetus is exposed in utero produce numerous fractures. The victim is usually born dead or survives only a short time. The cranium is soft and membranous. Short clumsy extremities suggest achondroplasia (Fig. 62). In the second variety, so-called osteogenesis imperfecta tarda (or tardiva), the manifestations are so mild that blue sclerae may be the only manifestation and fractures may occur only late in life or not at all. Seedorff[101] further divides osteogenesis imperfecta tarda into levis and gravis types. In the latter, the first fractures are likely to occur when the patient is an infant. In the former, the fractures occur only considerably later.

The above are artificial distinctions based only on the particularly wide variability of clinical expression in this disorder of connective tissue. OI congenita and OI tarda are fundamentally one and the same disease, the only basis for distinction being that the cases in the two groups are at opposite ends of the bell-shaped curve of expressivity. The foundation for this statement lies in the facts (1) that the two varieties of the disease sometimes occur in different members of the same family[88,101,138,149,157,168,186,193,197,203,216]; (2) that there is a continuous spectrum of expressivity through the two major varieties; and (3) that the histologic anatomy of the two varieties is qualitatively identical.[45,46,47,76]

On the basis mainly of radiologic changes, Fairbanks[44] distinguishes a "thick bone type," a "slender bone type," and a form he calls osteogenesis imperfecta

cystica (Figs. 73*A*-73*C*). These, like the antenatal and postnatal distinction which he makes, probably have no basis so far as difference in the fundamental defect is concerned. During prepubertal years a patient may demonstrate an evolution from the "slender bone type" to the cystic type or the "thick bone type."

In summary, *all the several clinical pictures which are referred to in this communication, and which go by separate names in many instances, are one and the same disease which has wide systemic manifestations and an exceedingly great range of clinical severity (expressivity).*

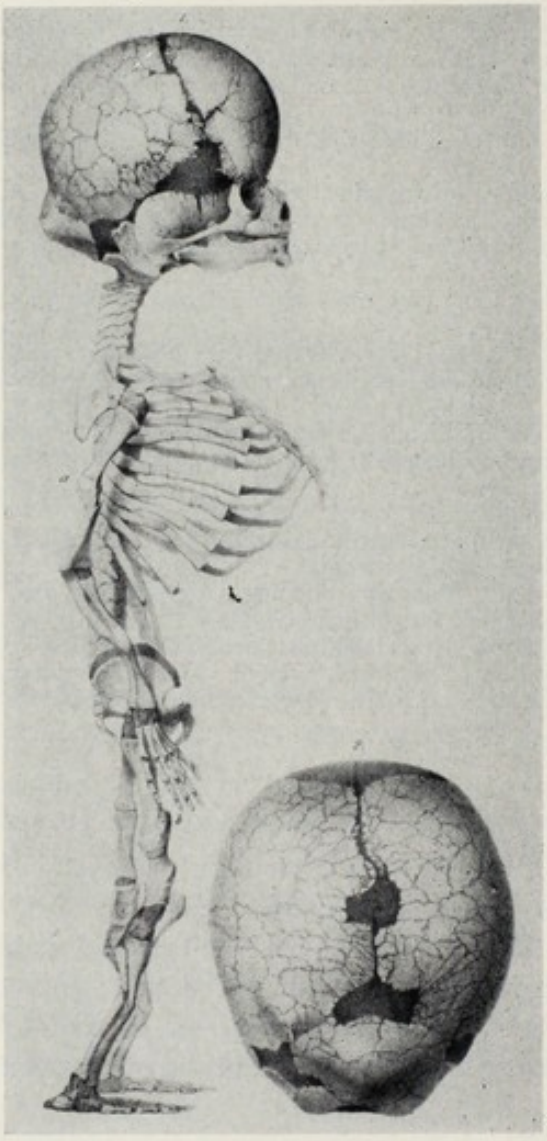


Fig. 61. Skeleton in osteogenesis imperfecta. Note the multiple Wormian bones of the caput membranaceum. (From Vrolik, W.: Tabulae ad illustrandam embryogenesim hominis et mammalium, tam naturalem quam abnormem, Amstelodami, 1849.)

The Musculoskeletal System.[20] As will be seen later, osteogenesis imperfecta is a hereditary defect of the bone matrix. Calcification of what bone matrix is formed probably proceeds normally. Osteogenesis imperfecta is then a form of hereditary osteoporosis inasmuch as osteoporosis is defined as a deficiency in the formation (or an acceleration of the breakdown) of bone matrix. This is an important consideration in the understanding of some of the clinical manifestations of the disease and in its rational therapy. For example, in later life, particularly

if few fractures have occurred, the disease may masquerade as postmenopausal osteoporosis; immobilization is as bad for OI as it is for other forms of osteoporosis.

Caput membranaceum and micromelia ("tiny extremities") are the characteristics of OIC (Figs. 61 to 65). The limbs are described as bowed on the chest and abdomen at birth. If the patient survives, the bowing is likely to persist. Chondrodystrophia fetalis (achondroplasia) is often misdiagnosed. By x-ray examination (see Figs. 63*B*, 63*C*, 64*A*, and 64*B*) the skull is likely to show a mosaic pattern as a result of the presence of numerous Wormian bones.[96] This mosaic phenomenon was very striking in the case described and illustrated by Vrolik in

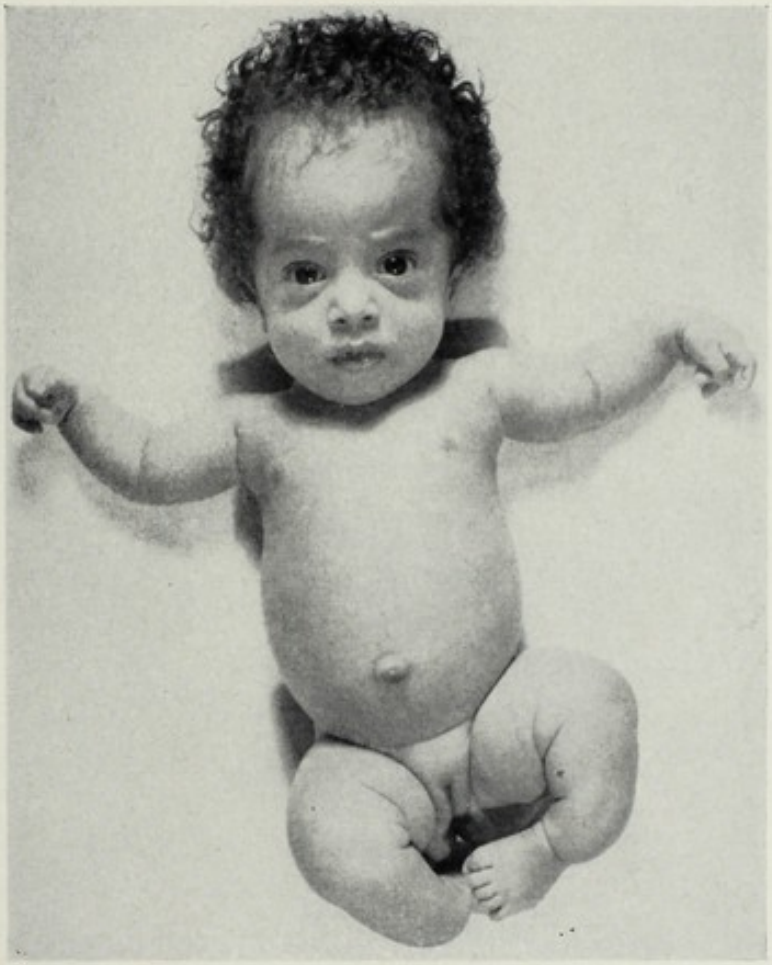


Fig. 62. P. D. (A42000), 3 months old, an instance of so-called osteogenesis imperfecta congenita. Micromelia is striking. The head appears disproportionately large. Numerous fractures were demonstrated immediately after birth. The patient was referred with the diagnosis of chondrodystrophia fetalis, however. The skull bones were described as "crumbly" on palpation. The parents and the parents' families were normal. By the age of 1 year there were evidences of well-advanced hydrocephalus. Death occurred at the age of 38 months.

1849.[121] (See Fig. 61.) (This was the first case to which the name osteogenesis imperfecta was given.) Caffey states that the mosaic phenomenon occurs in only two conditions: osteogenesis imperfecta and cleidocranial dysostosis (see Fig. 43 of reference 28 and compare with Figs. 64*A* and 64*B* here). The mosaic pattern persists throughout life. The patient whose skull was studied anatomically by Ruth[96] was variously estimated to be 46 to 55 years old. The diagnosis of OIC has been made at times in utero by means of x-ray films[38,422] (Figs. 65*A* and 65*B*). In this form, OI is a lethal or sublethal trait. Death is usually the result of intercranial

hemorrhage and other injury since the calvarium offers little protection during delivery and later. Beading of the ribs by calluses is often misinterpreted as a ricketic rosary. Progressive hydrocephalus often occurs in OIC (see Figs. 62 and 65*B*).

In OIT, the triviality of the trauma which may cause fracture is well known: fracture of the forearm in whittling or throwing a chip, of the phalanges in writing, of the femora when another person sits on the patient's lap[109] or when the patient stretches out in bed. Apert[6] called these patients "les hommes de verre." In one family severely affected children were referred to, appropriately, as "china dolls." (R. Y., B.C.H. 143029).

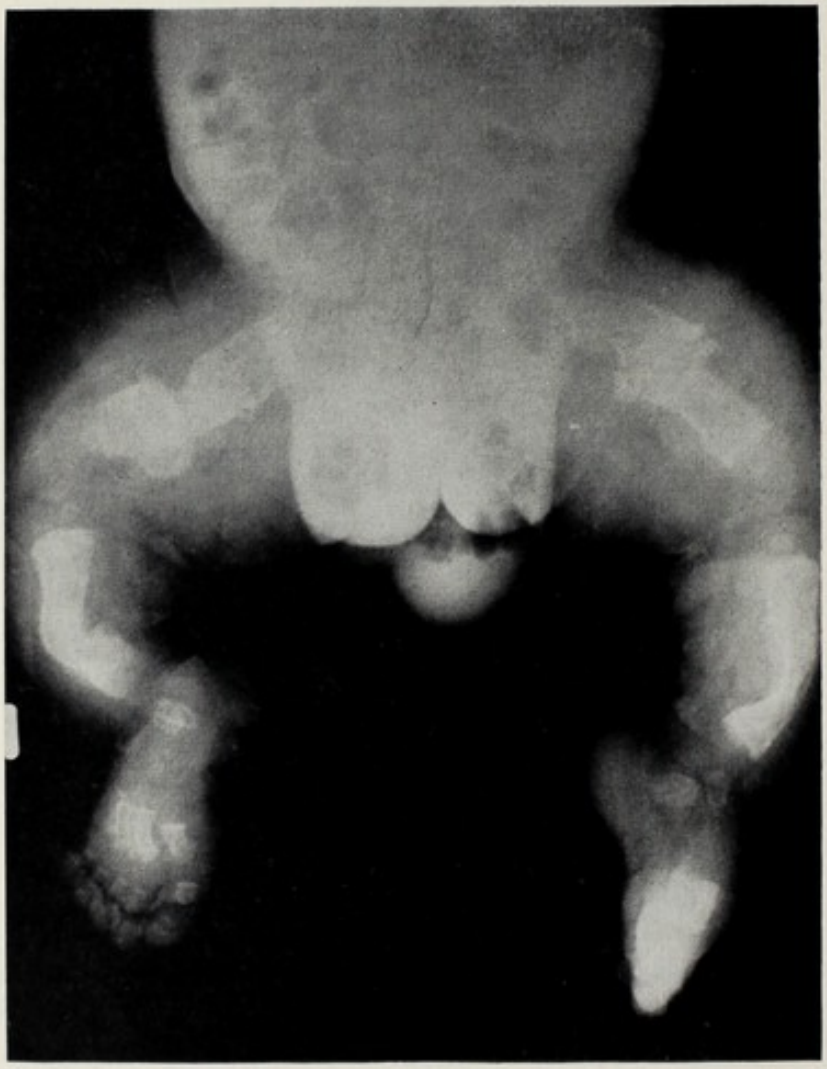


Fig. 63*A*.

Figs. 63*A*-63*C*. "Congenital" osteogenesis imperfecta in K. K. (A95443), 2½ weeks of age. *A*, Multiple fractures, bowing of the extremities, and bilateral inguinal hernias are evident. *B* and *C*, Demonstration of multiple Wormian bones in the caput membranaceum. (*A* and *B*, From McKusick, V. A.: Hereditary Disorders of Connective Tissue, Bull. New York Acad. Med. **35**:143, 1959.)

Sudden muscle pulls may fracture bones: the olecranon, for instance, has been pulled off by the triceps muscle in swimming[1] or even less strenuous exercise. Relatively little pain tends to accompany the fracture, due probably to the facts that there is minimal soft tissue trauma and that the patients become accustomed to

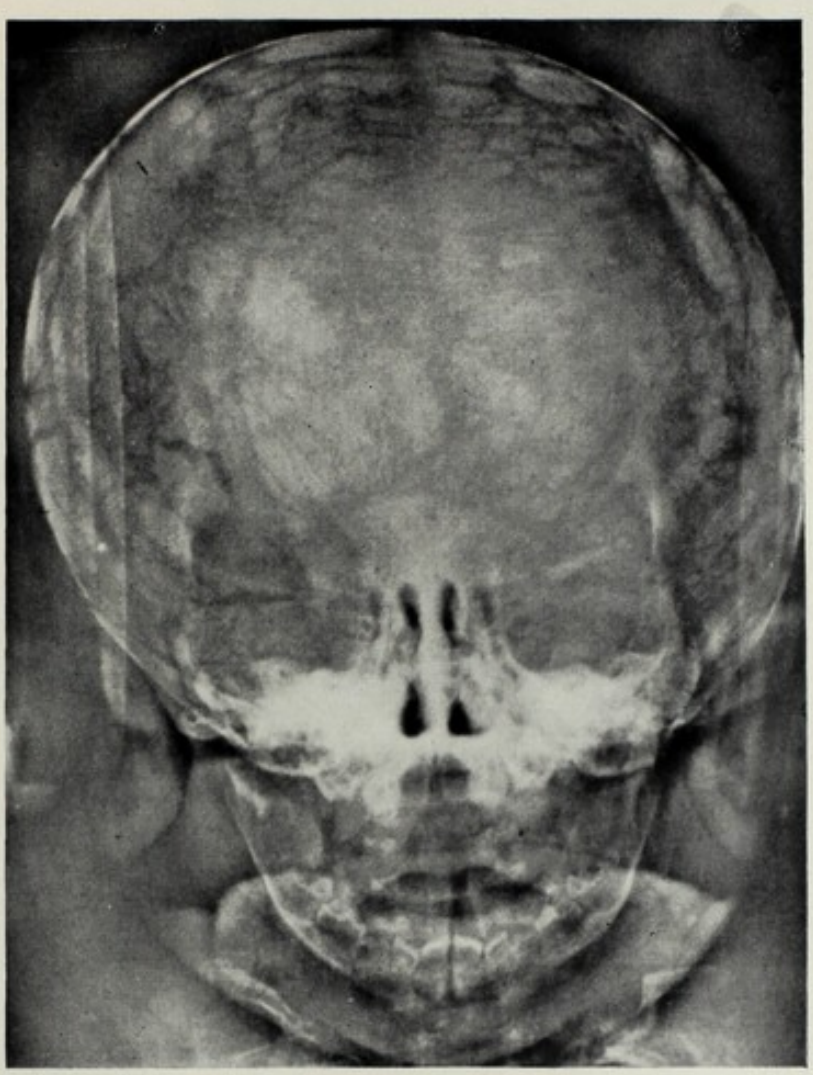


Fig. 63*B*.

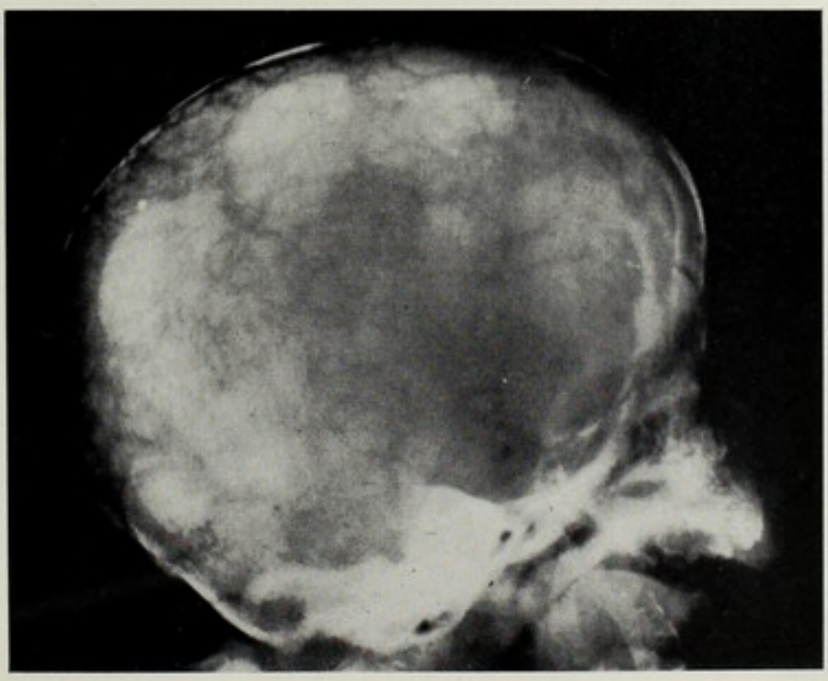


Fig. 63*C*.

Figs. 63*B* and 63*C*. For legend see opposite page.

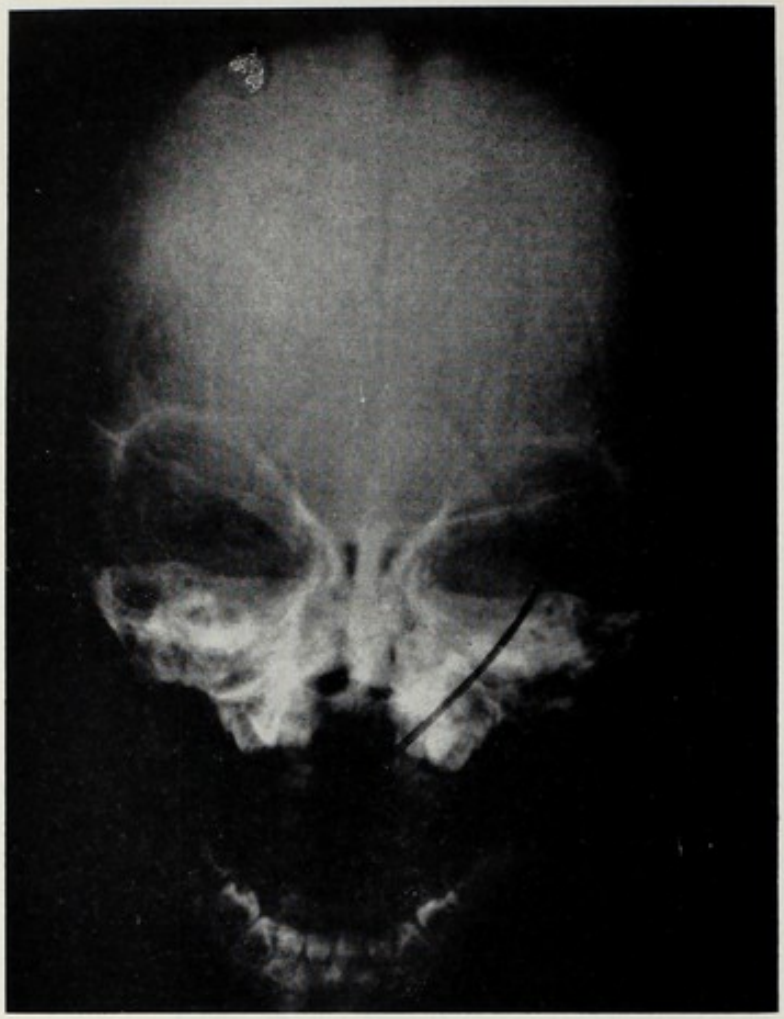


Fig. 64*A*.

Figs. 64*A* and 64*B*. W. B. (A79352), 2-month-old white male. Radiographic views (*A* and *B*) of the skull in a case of osteogenesis imperfecta congenita, showing a mosaic of Wormian bones and the thin calvarium characteristic of so-called *caput membranaceum*.

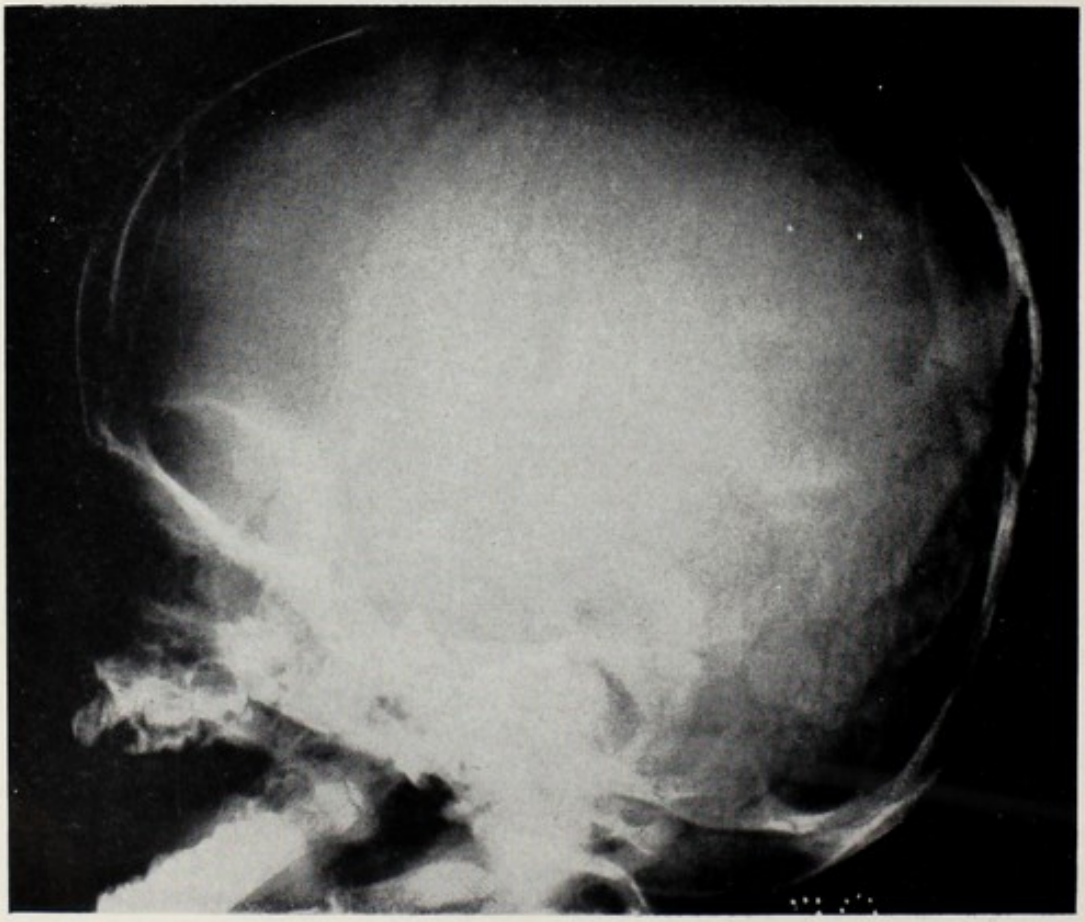


Fig. 64*B*.

the frequent fractures. Occasionally they learn to set their own fractures.[122] The fractures appear to heal with normal speed, but occasionally the callus is so large (see Fig. 73*A*) as to suggest osteosarcoma.[1,44,73,101,113] However, unlike Paget's disease, malignant degeneration is not recognized as a definite complication of this disease, although bone neoplasms have been described.[68,128] Patients (e.g., J. B., in Figs. 70*A* and 70*B*) are sometimes operated upon for suspected osteosarcoma.[73] At times overgrowth of bone occurs without evident fracture, and exostosis-like abnormalities develop. (Wide hypertrophic scars occur at the sites of surgical operations such as laparotomy.[99] These may be fundamentally analogous

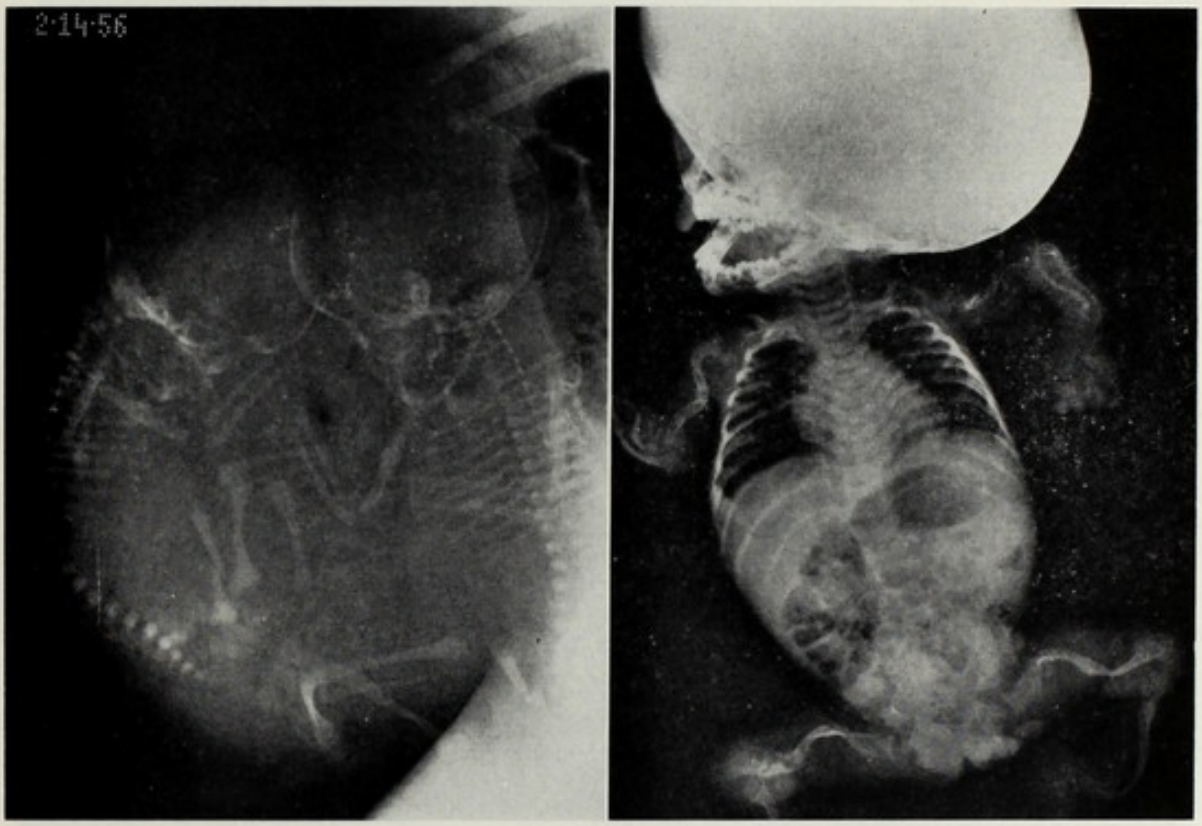


Fig. 65*A*. Fig. 65*B*.

Figs. 65*A* and 65*B*. Presumedly monozygotic twins with osteogenesis imperfecta congenita diagnosed in utero. The mother (M. B., B.C.H. 209850), father, and an only sibling show no stigmata of OI. The mother was admitted to the hospital on Feb. 13, 1956, because of irregular labor pains. The abdomen was very large and tense. X-ray film (Fig. 65*A*) revealed twins in breech presentation, facing each other in boxing position. Both fetuses showed multiple fractures in various stages of healing. Delivery was spontaneous. The baby born second lived for thirty-three days. Autopsy revealed the characteristic changes of OI. There was a patent ductus arteriosus and mild hydrocephalus. The first-born twin lived for twenty-seven months. From the first the head was large and soft. Progressive enlargement occurred, so that the proportions indicated in Fig. 65*B* were attained. The sclerae were never impressively blue.

to the hypertrophic callus formation.) Functionally awkward pseudoarthroses may develop. Pseudoarthrosis of the tibia or other bones may be the presenting manifestation[151,179] (S. E., H.L.H. A18674). (Neurofibromatosis[148] is another hereditary disorder in which pseudoarthrosis occurs.) The development of numerous Wormian bones in the occiptal area of the skull[96] is a similar phenomenon seen particularly in the "congenital" form of the disease. In the series studied at this hospital, one cannot corroborate, in adults at least, the impression[10] that fracture of the neck of the femur is uncommon as compared with other types of osteoporosis. (See,

Figs. 66*A*-66*C*. Severely affected 14-year-old male (J. L., 757361). The family history reveals no similar manifestations. Two other children are normal. The father had cleft palate and harelip. The infant was born by vertex presentation. At birth the left thigh showed a swelling which was later found to be a fracture of the femur with callus formation. The mother estimated that about 107 fractures had occurred, all with minimal trauma at the most. The sclerae are not blue, and there is no deafness. The teeth are small and widely spaced, with translucent enamel. The entire body is covered with nevi, but there were no palpable subcutaneous neurofibromata and no definite café-au-lait spots. The skeletal deformity is adequately described by the photographs and the x-ray films. Calcium, phosphorus, and acid phosphatase of serum were normal. The alkaline phosphatase was 13.7 Bodansky units. Multiple osteotomies with stabilization by metal plates and medullary bars.

A, General view. *B*, Anteroposterior view of both legs. *C*, Lateral view of both legs.

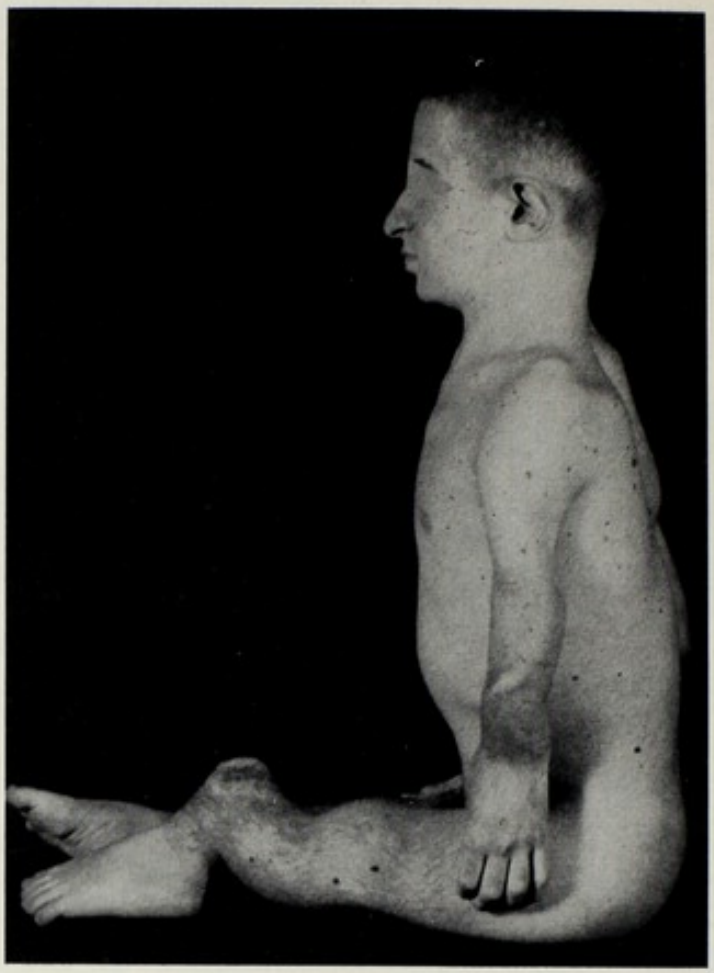


Fig. 66*A*.

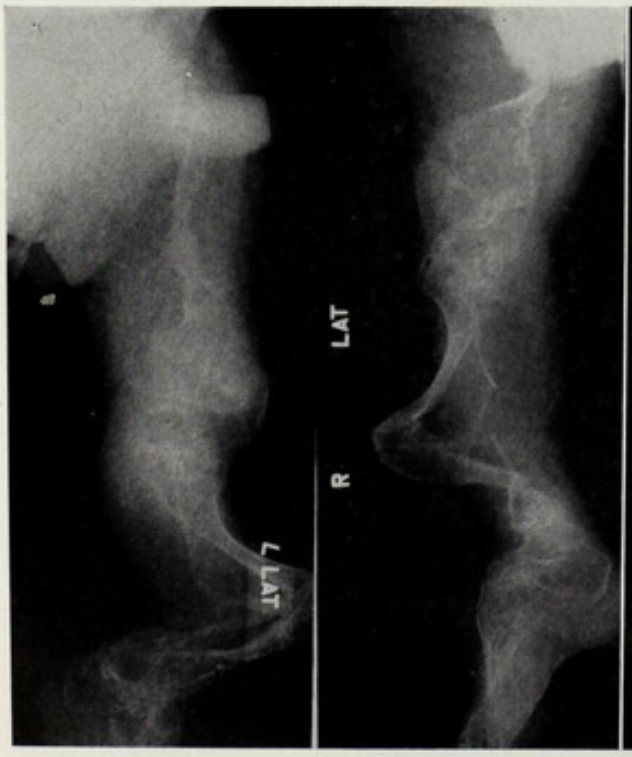


Fig. 66*B*.

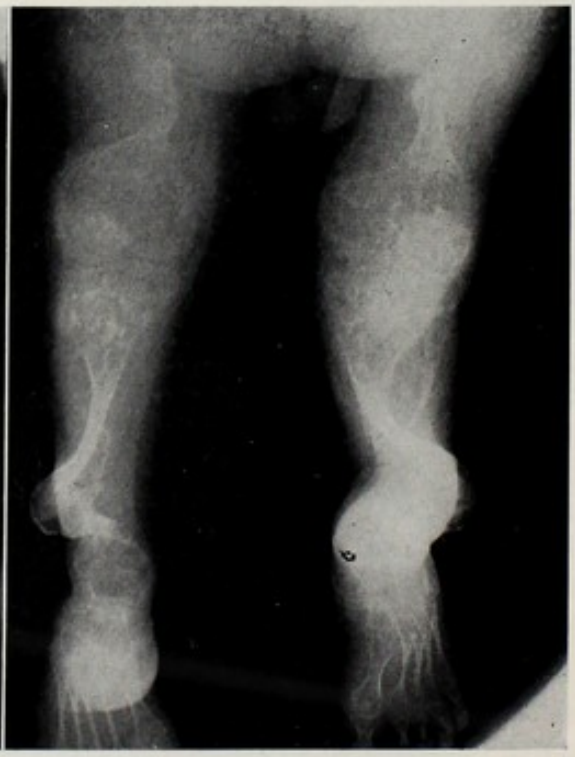


Fig. 66*C*.

for example, patient G. I., Fig. 71.) There is no sex difference in the severity of the fragilitas ossium.

By x-ray examination all bones have thin cortices, and the long bones usually have a slender shaft with rather abrupt widening as the epiphysis is approached. There are instances, as Fairbanks[43,44] has indicated, in which the shaft of the long bones is thick, and yet others in which a cystic appearance is presented on the x-ray film (Fig. 73*B*).

Fig. 67. Seedorff[101] appears to have been responsible for first suggesting that Lautrec had osteogenesis imperfecta. All known facts and photographs such as this are consistent with the diagnosis.[183]

As in other types of osteoporosis, "codfish" or "hourglass" vertebrae develop as a result of the biconcave deformity produced by the pressure of the normally elastic nucleus pulposus on the abnormally soft bone of the vertebral body (Figs. 72*A* and 72*B*). Furthermore, "schmorlsches Knötchen," actual herniations of the nucleus pulposus into the substance of the vertebral body, may occur. (Schmorl's nodes derive their eponym from G. Schmorl who also did a classical study of Paget's disease of bone [see Chapter 8].)

Characteristically the adults have short legs as compared with the upper part of the body. The shortness of the lower extremities is due in part to bowing and to fractures in the shafts of the long bones but is also due in considerable degree to interference with growth by multiple microfractures at the epiphyseal ends of the bones. The short legs with trunk of normal size is unforgettably illustrated by Henri de Toulouse-Lautrec (1864-1901), French painter (Fig. 67). To play Lautrec in the motion picture *Moulin Rouge,* José Ferrer walked about on his knees. This feature may lead to the misdiagnosis of achondroplastic dwarfism (see

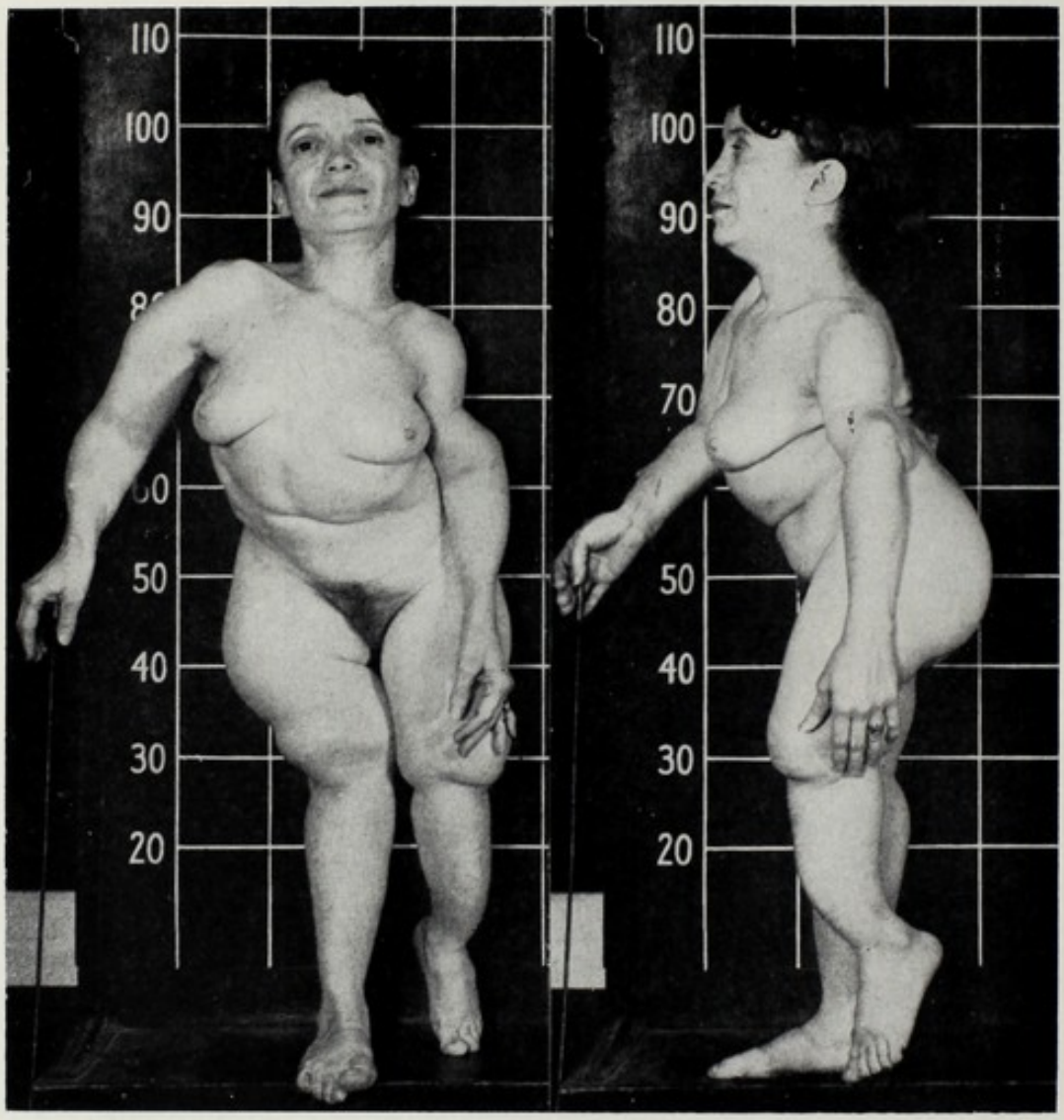


Fig. 68. Osteogenesis imperfecta in K. C. (673043), 35 years of age. Innumerable fractures have occurred, the first having been recognized at the age of 9 months. The sclerae are blue; hearing is intact. The patient is scarcely taller than a 4-year-old child. She has never walked and is carried about by a husky female friend. There are pseudoarthroses of the left humerus and left tibia. Of two pregnancies, one was terminated for therapeutic reasons and the other ended in spontaneous abortion. (From McKusick, V. A.: Hereditary Disorders of Connective Tissue, Bull. New York Acad. Med. **35**:143, 1959.)

p. 205). One patient (Fig. 71), now 56 years old, "is scarcely taller than a 3-year-old child." Marked bowing of the legs often results in a scissors-gait. By x-ray examination the femurs often assume a shepherd's crook appearance.

Anterior bowing of the tibiae, producing sabre shins, is a frequent occurrence. Gross deformities, which resemble somewhat those of Marfan's syndrome, such as kyphoscoliosis, koilosternia (pectus excavatum), and pigeon breast, are not uncommon. Arachnodactyly also has been described by several writers.[41,71,90,101] It must be remembered that arachnodactyly is a symptom, not a disease; that its presence does not indicate the coexistence of Marfan's disease. Unequivocal, or at least less equivocal, manifestations of the latter disease, such as ectopia lentis and involvement of the aortic media, have, with rare exceptions,[15] not been reported with osteogenesis imperfecta.

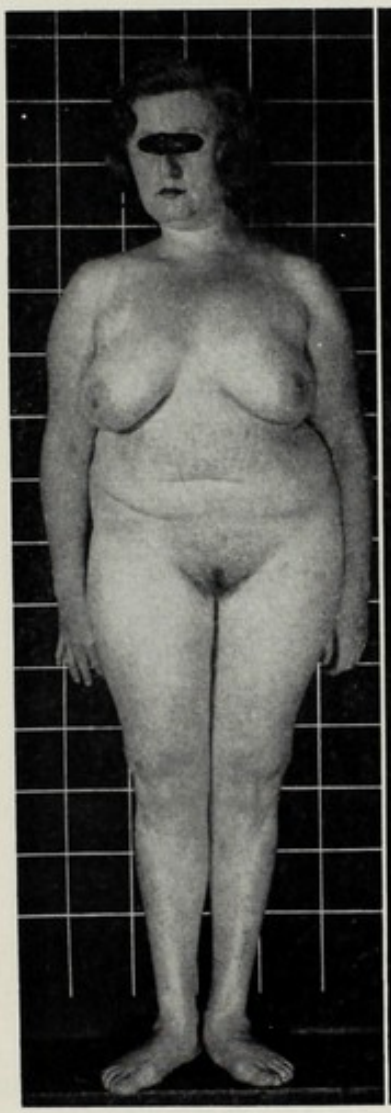


Fig. 69*A*.

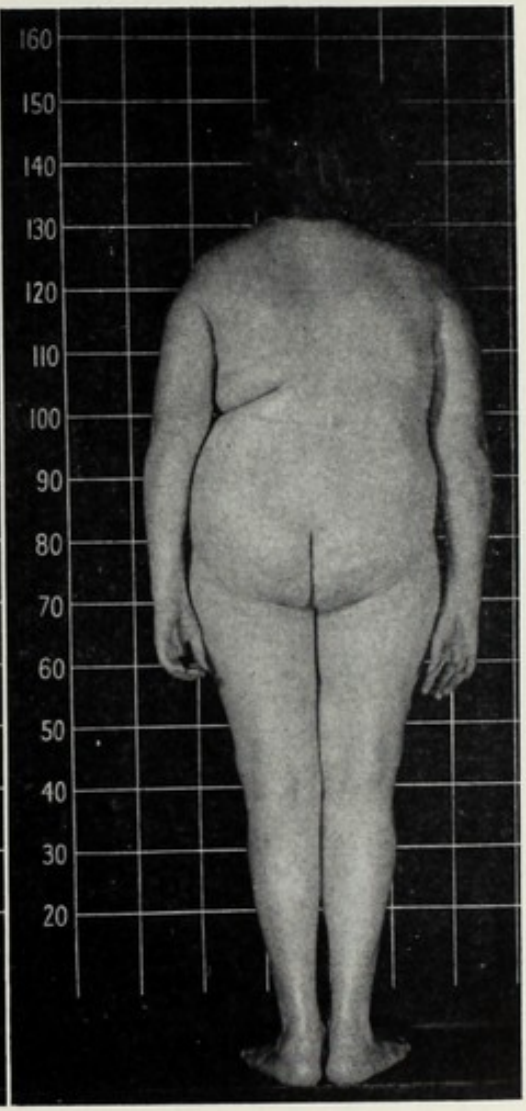


Fig. 69*B*.

Figs. 69*A*-69*C*. J. G. (149692), 43 years old. In *A*, note the bulging calvarium with triangular facies. Flat feet and kyphoscoliosis are also evident in *A* and *B*. The x-ray film in *C* reveals the complex spinal deformity present in this patient. The bones are more radiolucent than is normal. The sclerae are deeply blue. Deafness has been present since at least the age of 25 years and tinnitus has often been distressing. Scoliosis was first noted at the age of 13 years, and since the age of 16 years back pain has been a major complaint. The patient is, in general, loose-jointed with flat feet; the head of the humerus was dislocated on one occasion when she was thrown from a bicycle at the age of 7 years. A ganglion on the right wrist was described at one time. X-ray film of the skull shows characteristic decrease in the vertical dimension. A diastolic murmur at the left sternal border remains unexplained. An amazing feature of this case of undoubted osteogenesis imperfecta is the fact that *no* fractures have occurred in spite of appreciable trauma on several occasions.

The back is usually round, and the thorax has a characteristic conical or beehive shape (see x-ray films). The face is usually triangular, due largely to the bulging calvarium and faciocranial disproportion. The forehead is broad and domed and the temporal areas are overhanging. The "temporal bulge"[37] and the "overhanging occiput"[41] (Fig. 71) are characteristic. The victims have trouble getting hats large enough to fit them. As a result of the bulging calvarium, the ears tend to be displaced outward and to point downward. On skull x-ray film the inferosuperior dimension is reduced. This, together with the "occiptal overhang," the frontal bossing, and the platybasia which may be present in severe cases, results in a mushroom appearance of the skull on lateral x-ray examination. Apert[6] referred to

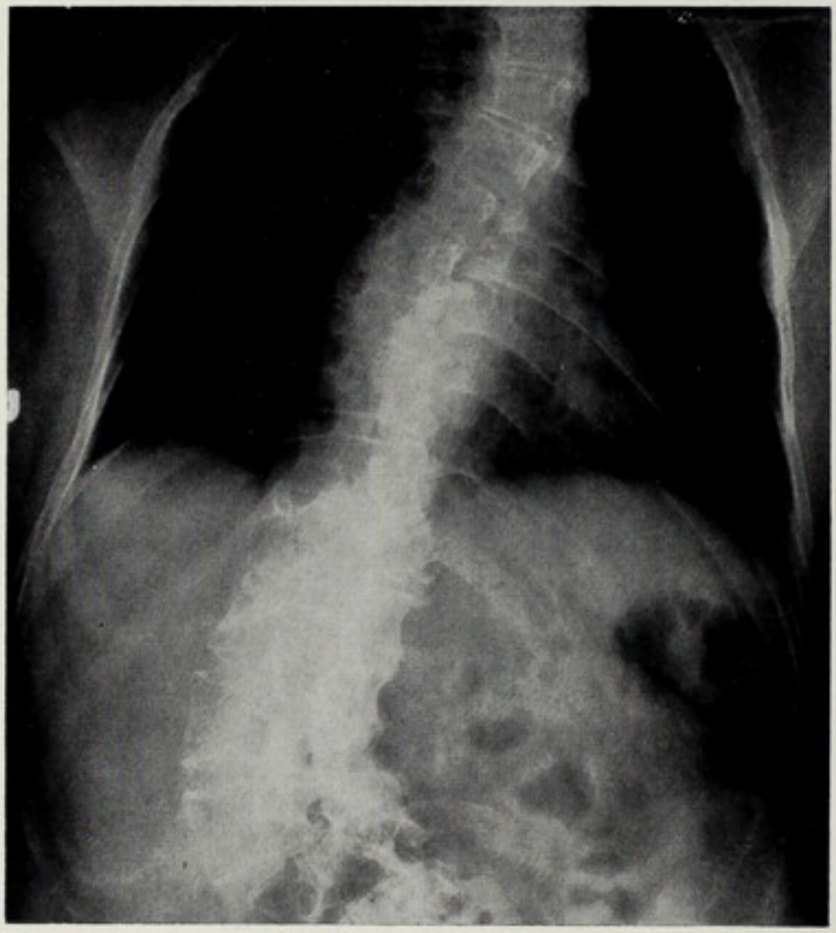


Fig. 69*C*. For legend see preceding page.

the skull as "crâne en rebord," and Nielsen[190] used the analogy "soldier's helmet," or "helmet head." In general, as with so many other hereditary disorders victims of this disease tend to resemble each other closely, even though they are quite unrelated. The facies and skeletal proportions are so characteristic that one can usually recognize the victims from a photograph, a feature useful in pedigree investigations.[101]

Because of pelvic deformity, successful termination of pregnancy may be a serious problem.[175]

By x-ray the bones are more radiolucent than normal. When x-ray films are taken at times when no fractures are present, the skeleton may, at the most, be described as only very "porotic."[177] In fact, the x-ray films may show no definite ab-

normality, and it may be concluded that the findings do not justify the diagnosis of OI. In severe cases the cortex is thin, and gross deformities, such as are shown in Figs. 73*A* to 73*C*, are demonstrated. Bone age is proportionate to chronologic age.

The teeth are particularly susceptible to caries, are easily broken like the bones, hold fillings poorly, and, although normally shaped, may have an abnormal amber, yellowish brown, or translucent bluish gray coloration.[119] Both deciduous

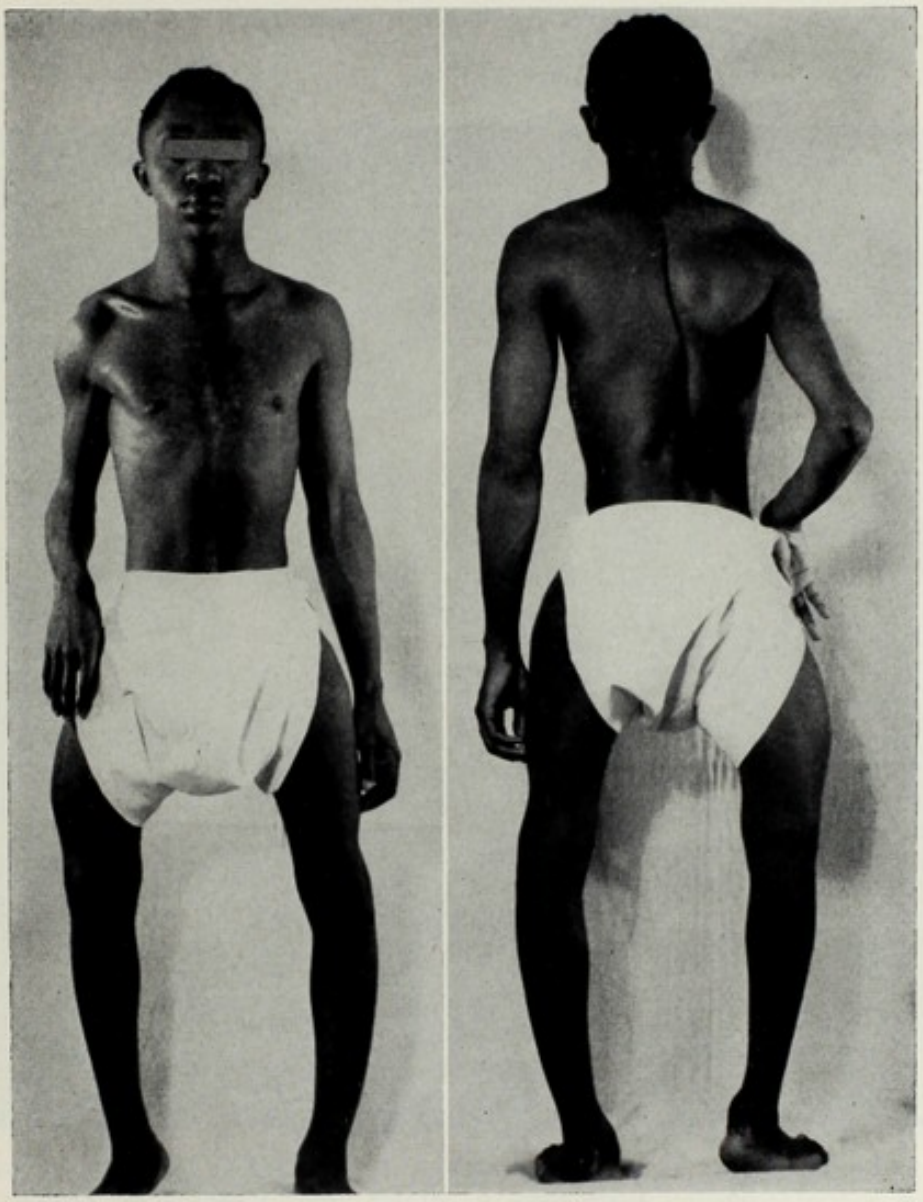


Fig. 70*A*. Fig. 70*B*.

Figs. 70*A* and 70*B*. J. B. (459707), 21 years old. Bowed deformities of the extremities, flat feet, and moderately bulging skull are evident. As a result of the bulging skull, the ears point forward and downward. Beginning at the age of 8 years the patient has had a total of approximately thirteen fractures with no decrease in the incidence of these at puberty. The sclerae are deeply blue.

and permanent teeth may show this peculiarity. Witkop[213] states that the teeth which erupt first, e.g., the lower incisors, are the ones most affected. On x-ray examination the teeth are likely to show no pulp canal. Often during drilling, the patient feels no pain, only vibration. One patient (S. W., 782036) stated that although

his teeth had always been embarrassingly yellow, they were unusually hard to drilling. Inspection revealed a good state of repair. Although most of each tooth was yellowish, the tip of each incisor was slightly translucent and blue. The lamina dura, as in acquired types of osteoporosis, remains intact. The enamel is thought to be fundamentally normal[14] and the abnormality is thought to reside in the dentine. This prompted Roberts and Schour[91] to suggest the name *dentinogenesis imperfecta** for the dental aspect of this disease rather than the terms *hereditary opalescent dentine* or *hereditary hypoplasia of the dentine,* which had been used before. Pedigrees in which this was presumably an isolated anomaly inherited as a

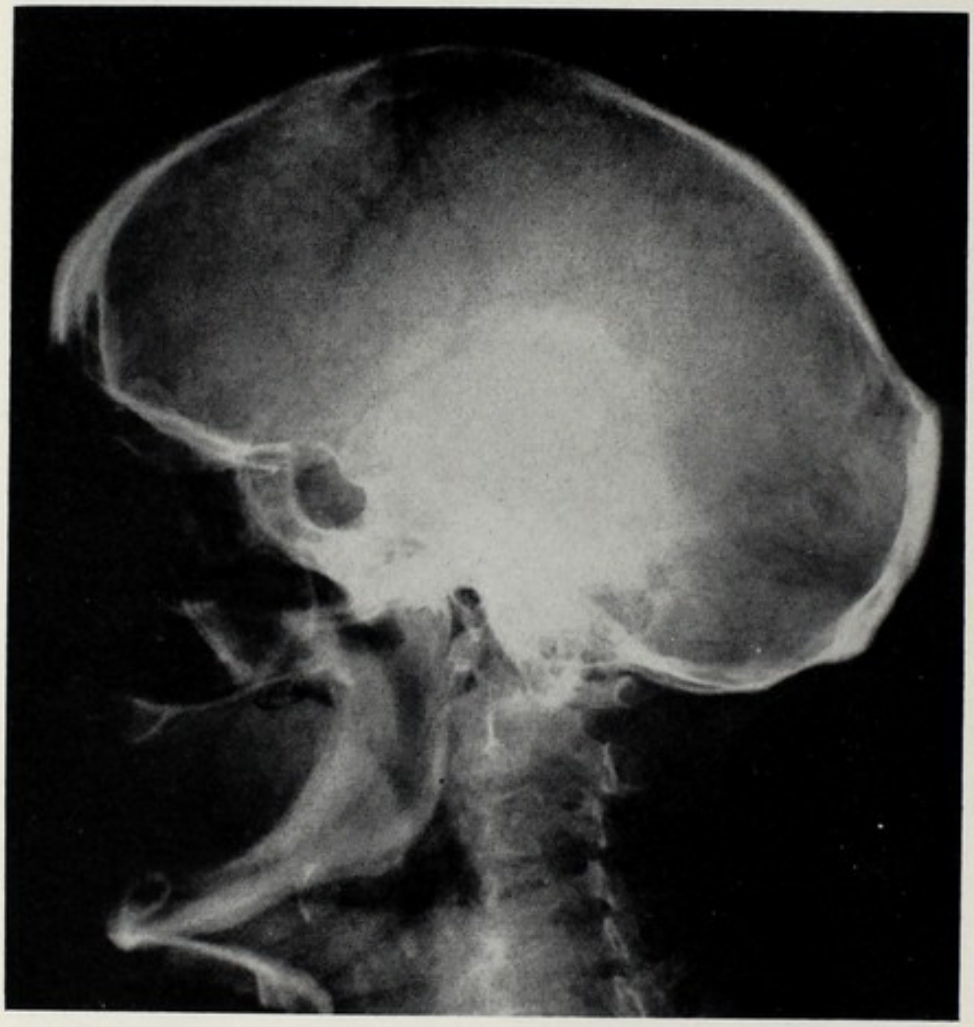


Fig. 71. "Overhanging occiput" with decrease in the vertical dimension is demonstrated by the skull of this 51-year-old patient (G. I., 587372). She is edentulous. Definite platybasia was judged to be present. The patient has deeply blue sclerae and has had a large number of fractures dating from birth and resulting in marked deformity. She is scarcely taller than a 3-year-old child. Deafness of conduction type dates from the age of 13 years following pertussis, and there has been intermittent tinnitus. She has had weakness of the left quadriceps muscle group, with absence of the left knee kick and anesthesia about the left knee, resulting presumably from a compression fracture of the lumbar spine.

dominant are described.[66,130,172] Some of these pedigrees are undoubtedly instances of the generalized disease, osteogenesis imperfecta, in which the dental manifestations dominate overwhelmingly. Roberts and Schour[91] were able to trace a family

**Odontogenesis imperfecta* is a less specific term inasmuch as the first portion refers to both enamel and dentine.

back five generations to 1763. The dental abnormality was very striking and was inherited as a strict dominant. Of forty-five individuals in five generations, twenty-two were affected. The authors made reference to other evidences of a mesenchymal defect. Wide variability in the manifestations of dentinogenesis imperfecta in individuals heterozygous for the dominant gene has been thought[180] to be responsible for reports of several dentine dysplasias as separate clinical entities.

To be differentiated from odontogenesis imperfecta is the hereditary abnormality of enamel production which results in discoloration of the teeth somewhat similar to that with OI. Known to me is a family in Maine with brown teeth traceable to a male ancestor who was born in 1805 and whose parents, of uncertain dental

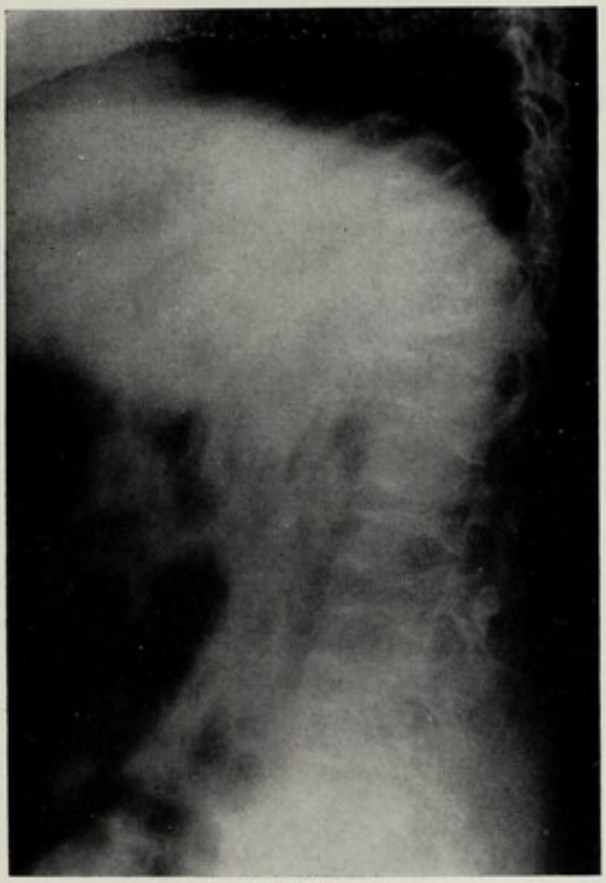


Fig. 72*A*.

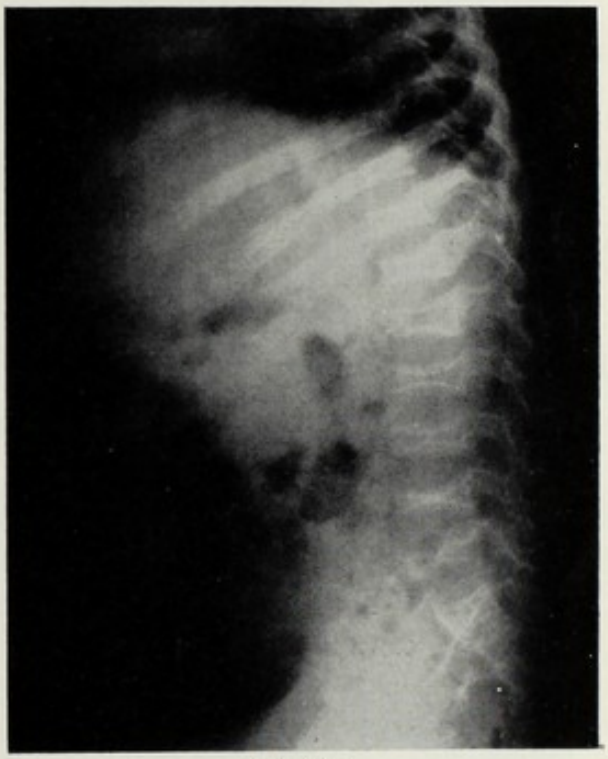


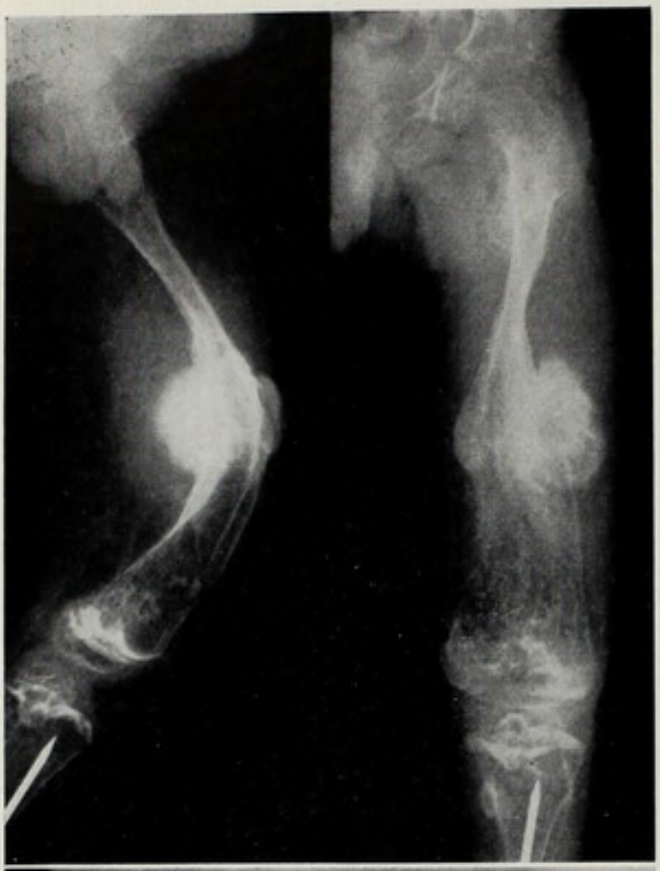
Fig. 72*B*.

Figs. 72*A* and 72*B*. Lateral views of the spine in two patients with codfish vertebrae.
Fig. 72*A*. Patient, J. L. L. (Children's Hosp. Sch.), 13 years of age.
Fig. 72*B*. Patient H. R. (Children's Hosp. Sch.), 2 years of age. The marked change, called platyspondylisis,[215] is shown.

status, immigrated from England. A detailed investigation of this family L. was included in the report of Weinmann and associates.[210] Two types of hereditary abnormality of enamel formation (amyelogenesis imperfecta) are recognized: an inadequate production of enamel substrate and a subnormal calcification of enamel. Clinical points helpful in differentiating the two varieties have been outlined.[210]

The joints are characteristically excessively mobile[18,59,62,101] in this condition, just as in the Marfan syndrome and the Ehlers-Danlos syndrome. It is said[101] that this characteristic is at times so striking that the subject can perform as a contortionist. The basis is in part the presence of weak, stretched tendons and joint capsules and in part the deformity and maladaptation of the bony surfaces of the joints. In one reported case,[140] the patient won prizes as a gymnast; his reper-

Fig. 73*A*.



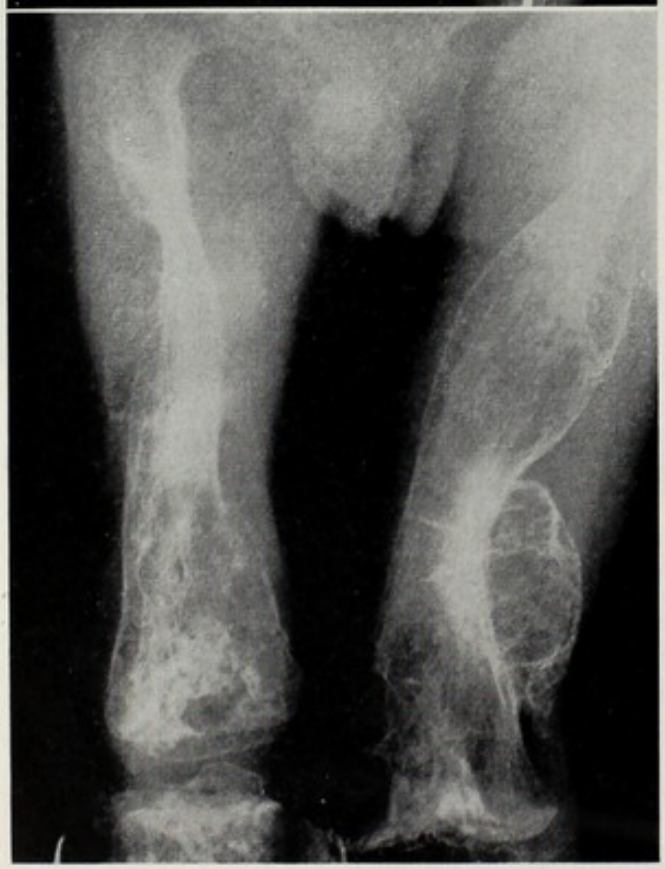


Fig. 73*B*.

Fig. 73*C*.

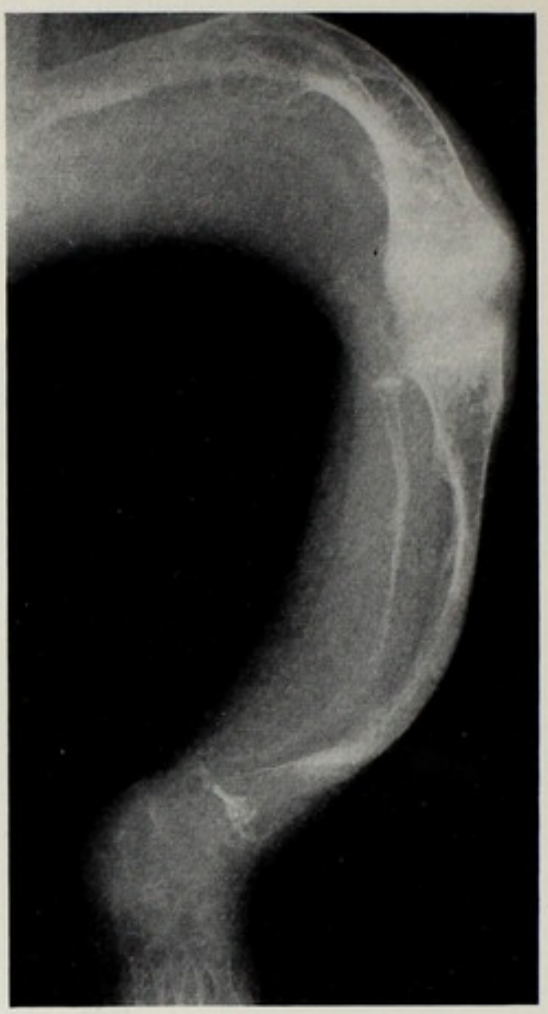


Fig. 73*A*. Frontal and lateral views of femur showing hypertrophic callus.

Fig. 73*B*. Pseudocystic changes.

Fig. 73*C*. Marked curvature of a leg due to bowing both in the femur and in the tibia and fibula.

toire included the ability to put his feet into his trouser pockets. Pseudoarthroses may have been present. Grossly, Key[72] described the Achilles tendon in one patient as the "diameter of a lead pencil (0.6 cm.) and translucent in appearance, there being a striking absence of the dense white fibrous tissue usually seen." From the standpoint of histology and of pathologic involvement in a number of diseases, the sclera bears many resemblances to tendon.[51]

Rupture of the inferior patellar tendon may follow exertion with more forceful quadriceps activity than usual.[78,109] This accident occurred in at least four patients in our series (E. Z., H.L.H. 81588; K. Y., J.H.H. 594806; R. C., U.M.H. 40485; E. R. J.H.H. 602544). Habitual dislocation of joints,[9,15,25,64,111,115] or of the patella,[50] pes planus, and pseudoclubfoot[101] are frequent occurrences. In at least two patients (H.L.H. 19845; A94292) bilateral clubfoot was thought to be present at birth. The reason for confusion is evident from Fig. 62. The father of one of our patients (J. B., 541962), himself a victim of OI, has suffered from recurrent dislocation of the shoulder. The articular laxity probably exposes the victim to falls which are so likely to result in fracture.

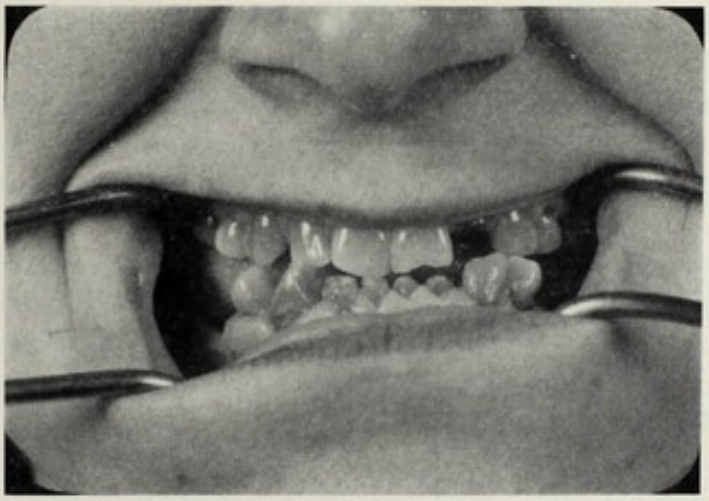


Fig. 74. Teeth in M. W., 32-year-old female with fragilitas ossium, blue sclerotics, and mild deafness. One of her two children (D. W., 736452) has OI. However, five siblings, both parents, and all other relatives are apparently unaffected. The stunting and discoloration of the lower incisor teeth are well demonstrated.

Wyllie and Schlesinger[214] reported two cases in children whose mothers consulted them because of the child's tardiness in walking. No fractures had occurred; at least none had been recognized. The presenting complaint, a not unusual one for OI, was apparently due to difficulty in fixing the joints for walking. The diagnosis of OI was based on the occurrence of clear cases in the family and of supporting radiologic changes in the patients. In one of our patients (R. F., J.H.H. 194765) there was such loose-jointedness and tardiness in walking and sitting that flaccid diplegia was suspected for a time.

Scoliosis may develop as a result of laxity of ligaments as well as of vertebral osteoporosis (Fig. 68). The spinal deformity is often extreme. Pain in the back is frequent in these patients. As in the Marfan syndrome, muscular hypotonia and underdevelopment has been emphasized by several writers.[7,8,35] As in the Marfan syndrome, these features are quite clearly secondary to the anomalies of the tendons and joints and to general debility with reduced muscular activity.

The fibrous skeleton of the muscles may be defective, but there is no evidence that the muscle cell itself is at fault. At times, in children (N. T., A46910), enlargement and weakness of the limbs have suggested pseudohypertrophic muscular dystrophy.

Hernia occurs with high incidence in these patients (see Pedigree 603 in reference 16), as with all the other hereditary connective tissue disorders under discussion, except pseudoxanthoma elasticum. The infant with OIC, shown in Figs. 63*A* to 63*C*, clearly demonstrates the combination of multiple fractures and bilateral scrotal hernias. Cryptorchidism may occur in the males in association with inguinal hernia (E. J. W., S.B.G. 6914).

The Eye. Blue sclerotics constitute the ocular hallmark of this syndrome. The color of the sclera is described at times as robin's egg blue, at times as slate blue. "Wedgwood blue" is another vivid description. Of the manifestations of this disease, blue sclerotics are the most frequent. Occasionally they are absent in unmistakable instances of the syndrome. This is not surprising since a high degree of variability in severity (expressivity) of this manifestation is to be expected, and overlap with the curve of normal distribution is likely to occur. Impressively blue sclerae are not infrequently encountered in persons free from all other stigmata of this syndrome.

Often the part of the sclera immediately around the cornea is whiter, resulting in the so-called "Saturn's ring." There is probably some increased risk of traumatic perforation of the sclera, a complication which occurred in Buchanan's historic case.[26]

Embryotoxon, a congenital opacity in the periphery of the cornea, sometimes called arcus juvenilis, is very frequent.[24,89,92,117,132] By slit lamp the cornea is measurably thinner than normal.[132] Hypermetropia appears to be significantly frequent.[1,2,36,111,112] Chorioretinitis, probably on an independently inherited basis, was reported by Colden.[33]

Other clinical manifestations probably closely related to the same defect of scleral connective tissue are keratoconus,[8,15,26,39] megalocornea,[39] and maculae corneae.[120] Keratoconus was present in one of our patients (E. Z., H.L.H. 81588). Behr's patient[15] had ectopia lentis. Premature arcus senilis is described.[120] However, this may have been merely the embryotoxon mentioned above. In two cases observed at this hospital[78] glaucoma has been present. In one, it was discovered soon after birth (R. F., 194765) and has been termed congenital; in the other (H. J., 428403), the right eye was rendered blind (phthisis bulbi), presumably by glaucoma, at the age of about 20 years, and the other eye later was affected by so-called chronic, wide-angle glaucoma. There are a few reports of associated glaucoma in the literature.[115,129]

The Skin. The skin in this condition is characteristically thin and translucent. It may resemble prematurely the atrophic skin of the aged. Healing of skin wounds has been found, by study of surgical incisions in these patients, to result in wider scars than usual.[97] Subcutaneous hemorrhages tend to occur after minor injuries,[29] and tests of capillary fragility may be positive.[101,202]* Macular atrophy of the skin is described by Blegvad and Haxthausen.[21] This may be comparable to the spotty blueness of the sclera in some instances.[120]

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*See page 198 for a discussion of hemorrhagic disease in OI.

The Ear.[23,34] Deafness is the least constant of the major features of OI.[143] Although the histologic patterns may be distinct, the clinical[19,20,25,32,49,97,112,115,118] pattern of the deafness which accompanies this syndrome differs in no respect from that of otosclerosis. Stenvers[110] demonstrated that characteristic sclerosis of the petrous portion of the temporal bone can be detected radiologically even before the impairment of hearing has its onset; and, of course, these changes may be present but not so located as to cause deafness. Deafness may have its onset in the teens, often begins during pregnancy.[48,101] In Nager's patient,[83] hearing loss had its onset at the age of 9 years. As with otosclerosis of other origin, two types, a common stapes-ankylosing variety and a rarer cochlear type, have been described alone or in combination. Therefore, there may be either conduction or nerve type hearing loss.[52] Fenestration operation[173] has been performed in two patients with good results by Shambaugh[102] and in one with indifferent results by Watkyn-Thomas.[125] As with other types of otosclerosis, middle-ear infection aggravates the hearing loss; and deafness may begin in pregnancy. There has been described[110] an interesting blueness of the tympanic membrane, analogous to the blue sclerotics so far as indicating thinness of the structure is concerned. The patient may complain of almost constant tinnitus for long periods and of attacks of vertigo. Labyrinthine disease uncomplicated by deafness has been described.[52,120] Leicher and Haas[183a] described patients who had no dizziness and only mild difficulty walking in the dark, but little or no response to vestibule-stimulating maneuvers.

Internal Manifestations. As for cardiovascular involvement, Sundberg[114] and Johansson[69] have described calcification of large peripheral arteries in victims of OIC. In one of our cases of OIC (557774; aut. 22803) in which there was neonatal death, necropsy revealed calcification of pulmonary and cerebral arteries. Arteries in the limbs were not studied histologically. Although Bauer[13] and Kaul[176] described changes in the connective tissue elements of the arterial wall, others have not been impressed with these. Lobeck,[74] Colden,[33] and Voorhoeve[120] described premature arteriosclerosis. Congenital heart disease was present in one patient.[120] Hass[61] described heart disease in several members of a kinship. From the descriptions of one of the members of that pedigree, rheumatic heart disease seems to have been present in that individual. In general, the heart disease was probably unrelated to the OI. Severe aortic regurgitation of obscure etiology was present in one patient with OI seen at the Johns Hopkins Hospital when he was 16 years old (G. S., J.H.H. U45942).

In one of my patients (J. G., 149692), with severe S-type rotary scoliosis (Figs. 69*A* to 69*C*), a faint diastolic murmur has been heard to the left of the sternum and there is a borderline increase in systemic arterial pulse pressure. Whether this sound represents regurgitation at the aortic or the pulmonic valve or possibly has an extracardiac origin is unclear.

The severe spinal deformity may be followed by kyphoscoliotic cor pulmonale (e.g., C. B., 242806). Premature emphysema is frequent.

There are no pathognomonic chemical changes in the blood. Significant abnormalities of calcium and phosphorus do not occur. Alkaline phosphatase activity is often increased as a result of multiple healing fractures. We have been unable to corroborate the report[160] that serum acid phosphatase activity is significantly increased in this disease.

Siegel and his co-workers[202] have described a 25-year-old man with OI and hemorrhagic diathesis manifested by epistaxes, hemoptyses, easy bruisability, and prolonged bleeding time. The Rumpel-Leede test was positive. A defect of the platelet was demonstrated by means of the thromboplastin generation test. There were multiple cases of OI in the family, but the only one of these available for study, a sister, did not show the abnormality. The authors suggested that the hemorrhagic diathesis was of the type described by Glanzmann[164] in 1918 as thrombasthenia. The cause of the capillary fragility was not clear. It was corrected by cortisone; however, this can be a nonspecific effect. Gautier and Guinard-Daniol[159] described a 13½-month-old patient with OI in whom defective clot retraction was demonstrated. The mother had blue sclerae with bone disease, abnormal prothrombin consumption test, and impaired clot retraction. The last two tests were also impaired in the father. Siegel and his co-workers[202] suggest that these two mesenchymal defects (OI and platelet defect) are related and not simply coincidental.

Neurologic symptoms, particularly those of platybasia and of spinal cord compression, occur occasionally but are usually submerged by the other types of incapacitation from which these patients suffer. Backache and leg pains, which may have an element of nerve-root compression in their causation, are of frequent occurrence. Neurologic deficits attributable to this are less frequent. As with idiopathic varieties of platybasia (basilar impression), as well as that due to other bone-softening diseases such as Paget's disease, rickets, hyperparathyroidism, and sarcoid, four types of neurologic involvement should be sought[87]: (1) internal hydrocephalus; (2) bilateral, progressive cerebellar disturbance; (3) interference with the function of the lower cranial nerves; and (4) signs of spinal cord compression at the level of the foramen magnum. The impingement of the odontoid process of the axis on the brain stem is responsible for many of these manifestations.

Two methods are used to detect platybasia radiologically: Chamberlain's line (from the posterior end of the hard palate to the posterior lip of the foramen magnum), normally lies above the entirety of the cervical spine.[30] Such is not the case in platybasia. According to Bull's index,[27] the plane of the axis is normally parallel to that of the hard palate, whereas, in platybasia, the two planes make an acute angle with each other.

Bell[16] pictures the skeleton of a 12-year-old boy with marked skeletal changes of OI and with hydrocephalus. The skeleton is in the museum of the Royal College of Surgeons in London. Hydrocephalus developed in several of our patients with osteogenesis imperfecta congenita (see Figs. 62 and 65*B*).

Occasionally patients with OI have retarded intellect (e.g., S. V., H.L.H. 75237; R. F., 194765). Although arrested hydrocephalus may be the basis in some cases, others probably represent mere coincidence of OI and mental retardation on another basis.

Summary of Clinical Manifestations. Bell[16] provides entirely credible figures for the incidence of the several manifestations: among adult individuals "with blue sclerotics approximately 60 per cent have an associated liability to fracture, approximately 60 per cent have an associated otosclerosis, and 44 per cent suffer from all three defects." These values might be higher were it possible to eliminate those cases with hereditary blue sclerae on some other basis. It has not been established that blue sclerae can occur on an independent, genetically distinct

basis and as an isolated anomaly. (They do occur with others of the hereditary disorders of connective tissue.) However, such seems likely from experience with similar situations.

INCIDENCE AND INHERITANCE

Among the five disorders under principal discussion in this book, osteogenesis imperfecta vies with the Marfan syndrome for first place as to incidence. It was relatively easy to accumulate over one hundred apparently unrelated propositi for purposes of this study.* Between 1920 and 1940 forty cases of OI were seen at the Mayo Clinic.[142] Of these, eleven had a story of the disease in other members of the family. Almost half of those with positive family histories had otosclerosis, whereas deafness occurred in only about one-sixth of those without a positive family history.

There is no peculiar racial distribution of OI, cases having been described in Jews[78] and American Negroes,[56,78,124] and in natives of Japan,[70,84] China,[31] India,[60] Egypt,[7,8] and Russia,[123] as well as all Western European countries.

The evidence is overwhelming that the disease is inherited as an autosomal dominant. Bell[16] found such to be the case for blue sclerotics in seventy-three kinships with a total of 463 affected persons. In an analysis of eighty-nine families with 1,000 individuals, of whom 515 were affected, Fuss[53] demonstrated autosomal dominance for the syndrome of bone fragility and blue sclerotics. One of the best-studied pedigrees is that of a family of the Eastern Shore of Maryland, reported by Hills and McLanahan.[63] Twenty-seven of fifty-one members of five generations were affected. A number of other pedigrees with affected persons in five successive generations have been published.[146,178]

Seedorff,[101] after studying fifty-five kinships with 180 affected individuals, constructed a complicated schema based on the theories that (1) each component of the syndrome is the result of a separate gene and (2) three separate genes control the bone fragility, mutation in one, two, or three being responsible, respectively, for OIT levis, OIT gravis, and OIC. This complex schema is untenable because of the arguments against a multiple-gene basis of hereditary syndromes (see Chapter 1) and because of the probability on clinical and histopathologic grounds that the three arbitrarily designated states are in fact different grades of severity of the same disorder of connective tissue.

Frequently the statement appears[63,165] that the so-called congenital form of the disease probably is not inherited in many instances or is inherited in a different manner (e.g., as a recessive) than the other forms.† Many of such instances—severely affected stillborn children of normal parents—may be de novo mutations. I am not aware of the occurrence of two such offspring from parents who were indubitably normal. (Obviously, identical twins with OIC[153,211] [Fig. 65*A*] are not a contradiction to this statement. Occurrence of the disorder in identical twins is evidence of the genetic basis of the "congenital" form of OI. Furthermore, the probable absence of increased parental consanquinity is against the view that OIC

*Patients from Baltimore or Maryland and patients who have been seen at some time at Johns Hopkins Hospital have been reported in several previous publications.[45,46,47,63,95,104]

†A comparable question exists in connection with congenital cystic disease of the kidneys, a disorder in which two forms may truly exist: a congenital form, which proves fatal very early in life, and a late form, with average age of death at about 50 years.[150]

is recessive. Even if the parents had to be considered normal by every gauge, suspicion of subtle abnormality would remain. When a severely affected offspring from very mildly affected parents is encountered, there is the possibility that both parents are heterozygous and the child homozygous.[181]

Seedorff[101] thought from the cases in the literature and from his own cases that OIC occurred much more frequently in females. Among his seven cases of OIC, only one was male. This might be construed as evidence that OIC is a distinct entity. In our own experience, however, defining as OIC any case in which abnormality referrable to the skeleton was described at birth, the sex ratio does not deviate significantly from one.

There have been advocates for the view that there is an entity called osteopsathyrosis idiopathica of Lobstein distinct from the triad of blue sclerotics, deafness, and fragilitas ossium.[171,184] Some permit deafness in patients of the presumedly distinct osteopsathyrosis group but insist that the main differentiating feature is the absence of blue sclerotics. Holcomb[171] wrote as follows: "In the Davis family, whose history I have investigated, the tendency to break bones with abnormal frequency, especially in childhood, occurred in a number of persons in five generations of the family, but in no case was there the slightest indication of the blue sclera or progressive deafness."* This type of evidence does not necessarily indicate that a separate entity is involved, since it is clear that in a given family individual components of a syndrome may display considerable independence in penetrance and expressivity. An alternative possibility is the existence of multiple alleles.

In surveying the genetics of OI, Herndon[170] writes as follows: "In my opinion we do not have sufficient critical information to permit us to distinguish between the possibilities of (1) a minority of cases representing the homozygous state of a different or possibly the same gene; (2) a mutation rate for a dominant gene that is quite high in relation to the number of clinically recognized cases, but not necessarily high in terms of mutant genes per generation; (3) a considerable reduction in penetrance of a dominant gene, with the rate of penetrance probably being different in different family groups, modified either by unrecognized environmental factors or possibly by modifying genes; (4) any possible combination of the first three factors."† These are some of the same factors as are discussed in connection with the "cause" of "sporadic" cases of hereditary disease on pages 26 and 27.

Twins, both of whom were affected by OIC, were described by Schultze.[200] The report is of further note because the father had blue sclerae and deafness but no apparent fragility of the bones; support for the identity of OIC and OIT is, therefore, provided.

Bell[16] found, in tabulating reported cases of bone fragility with blue sclerae on the one hand, and cases of bone fragility alone, on the other, a seemingly highly significant difference in sex incidence and mode of inheritance (whether through mother or father) in the two groups. Although the explanation for a bias, if such was the case, is not apparent, the use of published data rather than those accumulated in a uniform manner by the researcher himself is beset with such

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*From Holcomb, D. Y.: J. Hered. **22**:105, 1931.

†From Herndon, C. N.: Clin. Orthop. **8**:132, 1956.

pitfalls that it is doubtful that one is justified in concluding, and Bell does not so conclude, that a fundamental difference is involved. On the basis of other experience, it is entirely likely that blue sclerotics and fragilitas ossium of otherwise indistinguishable character can occur as isolated, heritable anomalies genetically distinct from osteogenesis imperfecta. It is, of course, well known that otosclerosis clinically identical with that of osteogenesis imperfecta occurs even more commonly as an isolated anomaly than as part of this syndrome. Otosclerosis occurs, furthermore, as one component of a syndrome comprised also of congenital total color blindness.[187] This is a situation somewhat comparable to that involved in the ectopia lentis of the Marfan syndrome: the manifestations may occur alone or as part of a complex syndrome.

Consanguinity is not impressively frequent in the pedigrees of OI. In the motion picture *Moulin Rouge,* the screen biography of Toulouse-Lautrec, the country physician, recognizing the boy's malady as one which is frequently hereditary, points out to the parents that they are first cousins. Actually it is likely that the consanguinity had nothing to do with the son's condition unless both parents carried the disease in very mild form so that there was a chance for the son to have the trait in "double dose," i.e., homozygous form. It is not known that either parent had any stigma of OI. A comparable situation is described by Liber,[184] who reported on the offspring of a marriage of first-cousin children of first-cousin parents. The proband had bone disease and deafness. The mother "was short and squat, had a large skull, and was and apparently always had been almost totally deaf." A child of the proband had multiple fractures. Thus the consanguinity probably played no role. On the other hand, Komai and his associates[181] made reference to the consanguineous mating of two individuals, with only blue sclerotics resulting in a child with the full-blown syndrome.

"Skipped generations" have been described[146,171,216] in well-studied families. Because of the exceedingly wide range of expressivity it is not surprising if manifestations in fundamentally affected persons are at times too mild to be recognized clinically.

Even with the excellent system for indexing hereditary diseases in Denmark, Seedorff[101] concluded that one is not justified in attempting to calculate the mutation rate for this anomaly. Furthermore, Seedorff could find no conclusive evidence that the parents of patients with osteogenesis imperfecta tend to be older, as seems to be the case in chondrodystrophic dwarfism.[82] In his group of cases of OIT, Seedorff[101] concluded that these individuals are 1.4 times more productive of children than their normal siblings. So far as perpetuating the disease is concerned, each affected individual produced, on the average, 0.75 affected children. If it were not for constantly occurring new cases on the basis of mutation, the disease would in time disappear. Seedorff estimated that in Denmark one infant with OIC is born each year.

Komai and his associates[181] attempted a crude estimate of the mutation rate in OI, assuming that all cases of OIC represent new dominant mutation, that the female preponderance in OIC is genuine, that four out of five affected male fetuses die before birth, whereas none of the affected female fetuses die in utero, and finally that the frequency of OIC is about 2 per 100,000 births. OIC cases represent by this estimate a mutation rate of 1.67×10^{-5} per gene per generation. There is also

no reproduction in the severe form of OI tarda, which, according to Seedorff, is 2.14 times as frequent as OIC. In addition, the reduced effective fertility of late cases would bring the total estimate of mutation rate to about 4×10^{-5} per gene per generation.

PATHOLOGY[67]

Histologically, the cortical layer of the bones and the trabeculae of the spongiosa are thin. The periosteum may appear normal, but some have reported reduction in the number of subperiosteal osteoblasts. A peculiar, basophilic, periodic-acid-and-Schiff-positive material has been found in place of osteoid. In other tissue, only argyrophilic reticulin fibers and no mature collagen are demonstrated. Histochemically, phosphatase activity is not demonstrably disturbed, epiphyseal cartilage appears to be completely normal,[46] and invasion of the regularly arranged cartilage cell columns by capillaries is normal. The metaphysis shows calcified cartilage but no true bone or osteoid. This calcified cartilage tends to fracture and fragment. Organic bone matrix fails to be deposited and in its stead a peculiar basophilic material makes its appearance. As stated above, the material stains with periodic acid and leucofuchsin and, furthermore, is argyrophilic. Follis[45] suggests that it may represent immature bone matrix in the manner that reticulin, which it resembles in its staining properties, may represent immature collagen.

Swedish workers using recently developed biophysical techniques demonstrated disorganization of the collagen matrix.[17,42] The specific techniques which they employed were microradiography, polarized light microscopy, and x-ray diffraction. Their findings are by no means inconsistent with those of Follis: ". . . in osteogenesis imperfecta the compact bone has a quite abnormal distribution of mineral salts and arrangement of organic fibers. . . . The immature fibrillar bone normally seen in the foetus and newborn infant resembles in several ways the tissue found in osteogenesis imperfecta. Normally this primary bone tissue is rapidly replaced by secondary bone after birth, but in osteogenesis imperfecta this secondary bone tissue is not found."*

Osteoblasts and osteoclasts are usually present in normal numbers. Chemically, calcium and phosphorus are present in the bones in a normal ratio; the total content of bone salts is reduced, however.

In the skin, Follis[47] found absence of normal adult collagen fibers and substitution by argyrophilic fibers with other properties of reticulin. The shrinkage temperature of the skin was normal, however.

In the eye, decreased thickness of the sclera has been described as early as 1841 by v. Ammon[5] and more recently by Buchanan,[26] Casanovas,[29] and Follis,[46] but normal thickness was found by Bronson[25] and Voigt.[122] Ruedemann[95] has found histologic changes in cornea and sclera fundamentally identical to those described by Follis[46] in the corium. Clearly, the blue coloration is the result of the brown-pigmented choroid showing through the thin sclera.[127]

In sections of the teeth, "clodlike" calcification of quite abnormal type is seen. Rushton[94] showed that peripheral pulp cells produce "precollagenous" argyrophilic fibers but that these are not converted into collagen except in the immediate

*From Engfeldt, B., Engstrom, A., and Zetterstrom, R.: J. Bone & Joint Surg. **36-B**:654, 1954.

vicinity of blood vessels. These observations are in complete agreement with those of Follis, in bone, skin, and sclera.

Histologically the changes in the ear in osteogenesis imperfecta are quite distinct from those of otosclerosis, despite the close clinical similarities, according to the studies made by Ruttin,[98] Gimplinger,[55] and others. Others[83] maintain that, although the changes in the bone of the labyrinthine capsules are admittedly distinctive, deafness does not develop unless there is present histologically typical otosclerosis. It is my impression that the precise pathogenetic relationship of deafness to the rest of this syndrome is in the main unknown.

THE FUNDAMENTAL DEFECT

A generalized mesenchymal defect has been assumed for several decades. The recent histologic investigations of Follis (described above) appear to indicate that the fundamental difficulty may be in the maturation of collagen beyond the reticulin fiber stage. (This assumes that one can subscribe without reservation to the view that reticulin fibers are immature collagen fibers.[77] Even if this is not the case, it can be stated that the collagen fibers in OI are abnormal and resemble reticulin fibers in many respects.) So far as the bones are concerned, the disease must be considered a disorder of osteoblastic activity. Normal chondroblastic activity is suggested by the fact that growth and development of cartilage are normal.

It has been claimed by Seedorff[101] that a condition in cattle called anosteoplasia congenita[65] is an identical disorder. Coop[147] writes as follows: "Osteogenesis imperfecta is a condition recognized with increased frequency in cats during the last eight years, especially in the Siamese and Burmese breeds." Study of such animals could be very useful to the understanding of the disease in man. That the disease behaves as an autosomal recessive in cats[171a,171b] is not necessarily an indication that its basic nature is different from that of the disease in man. Hereditary spherocytosis in mice is recessive and in man is dominant; the biochemical defect may be identical.[188] Calkins and his associates[142a] observed a disorder resembling osteogenesis imperfecta in the standard French poodle and in the Norwegian elkhound. The frequency of fractures diminished at puberty. Clinical differences from the disease in man were attributed to early weight bearing and rapid leg growth in dogs. A reduction in the net rate of collagen formation seemed to be present.

Giordano[163] in Milan, Italy, has been studying histochemical enzymatic reactions in OI.

Although such a suggestion must remain speculative at this stage, one wonders if there may not be synthesized, in osteogenesis imperfecta and possibly in some others of the hereditary disorders of connective tissue, an atypical species of fibrous connective tissue protein. Do the amino acid sequences of collagen, in OI, differ from those in the "normal" by a single amino acid substitution, comparable to the recently demonstrated differences in several of the hemoglobin variants?

MISCELLANEOUS CONSIDERATIONS

In general, a decrease in the incidence of fractures is observed after puberty[142] with, possibly, an increase in this incidence after the menopause. The father of one

of my patients (C. B., 351637) had numerous fractures up to the age of 16 years but thereafter was well enough that he served in the Navy for several years! Both sexes show the improvement at puberty. Both clinical experience in man[4] and experimental evidence from animals[54] indicate an important role of sex hormones in the normal formation of bone matrix. This hormonal influence may explain in large part the observations cited above; increased vigilance on the part of the patient may be in part responsible for the improvement after puberty.

Estrogens and testosterone are worthy of more extensive trial in these patients.[93] Certainly it is important to avoid the superimposition of postmenopausal osteoporosis on the osteoporosis of this heritable disease.[81] Nonmasculinizing forms of androgens[57] might be a boon. Sex hormones are said[147] to be beneficial in osteogenesis imperfecta of cats. Serum albumin, which seems to be a percursor for bone matrix, is beneficial when administered to patients with certain acquired varieties of osteoporosis.[3] It apparently has not been used in osteogenesis imperfecta. Strontium has also not been tested,[103] with the exception of one study[22] in which the author thought the results were favorable and rendered further study worth while. As one might expect, all manner of medications have been employed for this distressing and long-standing disorder, for example, thymus extract.[100] Furthermore, because of difficulties in evaluating results, the variable course of the disease, and wishful thinking on the part of physicians and patient, enthusiastic reports have at times been forthcoming.

Unless quite by accident some efficacious therapeutic measure is discovered, no definitive progress in the therapy of OI can be anticipated until the precise reason for the failure of normal development and/or maturation of collagen is understood. Only then can measures directed at correcting the specific deficit be devised. There is every reason to anticipate that the biochemical defect in hereditary disorders such as this will be precisely defined in the future. Optimism in regard to possibilities of correcting or modifying the basic defect is justified.

Osteogenesis imperfecta and the Marfan syndrome were thought to be present in the same patient, by at least two authors (references 111 and 112 in Marfan section). Although arachnodactyly may have been present, it is not certain that the specific entity of the Marfan syndrome was also present. Fromm and his colleagues[156] and Weil[209] described precocious menarche, blue sclerae, multiple fractures, and irregular cutaneous pigmentation—many of the features of Albright's polyostotic fibrous dysplasia. Although Fromm referred to it as osteogenesis imperfecta, it seems doubtful that this was fundamentally the same disease as that to which we have applied the designation OI in a rather specific manner in this discussion.

As in acquired forms of osteoporosis it is highly important to avoid immobilization of the patient because of the further depletion of bone matrix occasioned thereby. It is doubtful that a high intake of calcium, phosphorus, and vitamin D is helpful, and the combination of these with immobilization may have dire effects: C. B. (J.H.H. 242806) developed large bladder stones and a Proteus infection of the urinary tract after immobilization for eleven weeks in a cast and a "bone-building diet" which included several quarts of milk a day and added calcium and vitamin D. The pinning and plating of fractures have much to recommend them because they reduce the necessity for immobilization.

Osteotomies and related procedures of orthopedic surgery are employed to correct deformities. Fixation by an intramedullary rod has also been recommended.[79,134]

In severely affected women, pregnancy is not to be encouraged, not only because of the 50 per cent chance of the child's being affected but also because of adverse effects of the pregnant and the parturient[85] state on the skeleton. Deafness from otosclerosis often begins or is aggravated during pregnancy. (Some, e.g., Nager,[189] doubt a relationship, however.) Because of the pelvic deformities of the disease, delivery may be mechanically very difficult.[150] One patient[78] has fractured her coccyx with each of the deliveries. There is a strikingly high incidence of breech presentation in cases of OIC born of normal mothers.

Because of inactivity it is easy for victims of this disease to become obese. Obviously, this is to be avoided. In young patients, Fröhlich's syndrome is sometimes suspected without basis.

Achondroplasia is a frequent misdiagnosis in these patients. Confusion may occur at birth (see Fig. 62) or in later life. The patient described by Ruth[96] was diagnosed as having achondroplasia because of the big head and short limbs. At the age of about 50 years he was selling papers from a wheel chair. In a patient 53 years old (I. L., Sinai 70327), it was concluded as follows: "In regard to the developmental anomaly of this patient: I believe he is an achondroplastic dwarf with typically well-built torso and relatively short spindly legs."

OI, a hereditary form of osteoporosis, is accompanied by blue sclerae. In other forms of osteoporosis, such as Cushing's syndrome, prolonged administration of adrenal steroids, and senile (or postmenopausal) osteoporosis, it is likely that the connective tissue defect is more extensive than merely involving the organic matrix. I have in isolated instances (e.g., M. H., 738167) been impressed with the occurence of blue sclerae in senile osteoporosis.

Vaughn[208] noted an increase in the blueness of the sclerae in a case of OI, with episodes of stress such as fractures. This observation, as well as the declining frequency of fractures at puberty (and possible increase after the menopause) may represent an interaction of hormonal effects with the hereditary disorder of connective tissue.

Blue sclerotics can, of course, not as a rule be used as the only criterion for the diagnosis of OI. Evaluation is especially difficult in children, who normally have bluish sclerae.

It is of interest that an Osteogenesis Imperfecta Foundation has been established under the laws of the state of Texas, with headquarters in Fort Worth.*

SUMMARY AND CONCLUSIONS

Osteogenesis imperfecta is a generalized disorder of connective tissue involving, in addition to bone, the skin, ligaments, tendons, fascia, sclera, and inner ear. Although the most frequent functionally important manifestations are brittle bones and deafness, blue sclerae are a dramatic feature, and thin skin, loose-jointedness, and hernia occur as manifestations of a single basic defect.

An exceptionally wide range of expressivity has resulted in the description of several different syndromes, all of which may be but different expressions of a single type of connective tissue disorder, inherited as a Mendelian autosomal dominant.

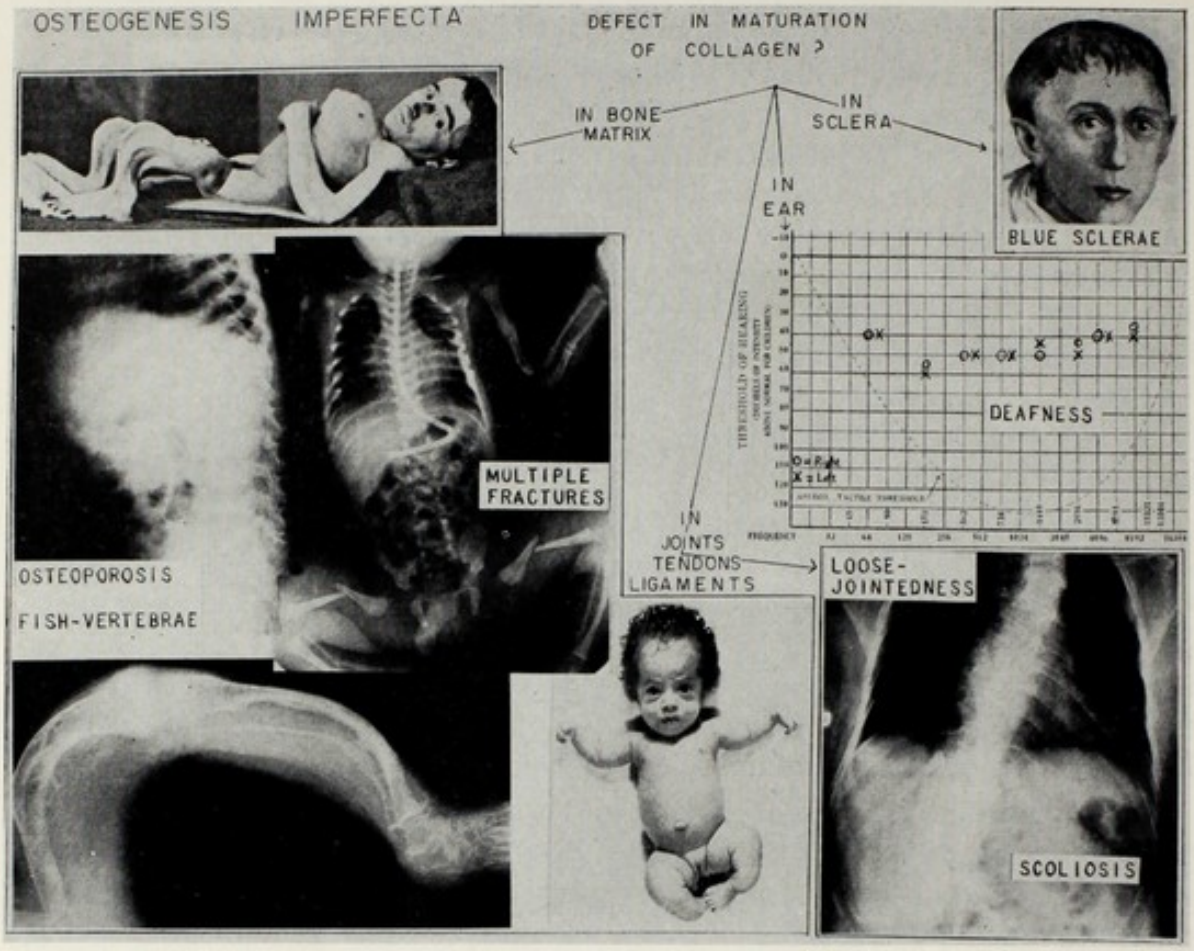


Fig. 75. A pictorial pedigree of causes.

Studies to date are most consistent with the view that the basic defect is one which involves either the maturation of the collagen fiber beyond the stage of the argyrophilic, reticulin fiber or the synthesis of a different species of collagen with tinctorial resemblance to reticulin.

REFERENCES

1. Adair-Dighton, C. A.: Four Generations of Blue Sclerotics, Ophthalmoscope **10**:188, 1912.
2. Alexander, J. B.: Fragilitas Ossium Associated With Blue Sclerotics in Four Generations, Brit. M. J. **1**:677, 1922.
3. Albright, F., Bartter, F. C., Dempsey, E. F., Forbes, A. P., Henneman, P. H., and Reifenstein, E. C., Jr.: Serum Albumin and Bone Matrix, Macy Conferences, Metabolic Interrelations With Special Reference to Calcium, New York, 1953.
4. Albright, F., and Reifenstein, E. C., Jr.: The Parathyroid Glands and Metabolic Bone Disease, Selected Studies, Baltimore, 1948, Williams & Wilkins Co., p. 150.
5. v. Ammon, F. A.: Klinische Darstellungen der angeborenen Krankheiten und Bildungsfehler des menschlichen Auges, Berlin, 1841, G. Reimer, p. 73.
6. Apert, E.: Les hommes de verre, Presse méd. **36**:805, 1928.
7. Attiah, M. A. H.: Blue Sclerotics, Bull. Ophth. Soc. Egypt **26**:96, 1933.
8. Attiah, M. A. H., and Sobhy, M.: Blue Sclerotics, Bull. Ophth. Soc. Egypt. **24**:67, 1931.
9. Bantz, W.: Ueber einen Fall von Osteogenesis imperfecta tarda mit gleichzeitiger habitueller Schultergelenksluxation beiderseits, Zentralbl. f. Chir. **68**:1726, 1941.
10. Bratter, F. C., and Bauer, W.: Fragilitas Ossium; *In* Cecil and Loeb: Textbook of Medicine, ed. 9, Philadelphia, 1955, W. B. Saunders Co., p. 1447.
11. Bauer, K. H.: Ueber Osteogenesis imperfecta, Deutsche Ztschr. Chir. **154**:166, 1920.

*Address: 101 Westchester House, Fort Worth, Texas.

12. Bauer, K. H.: Ueber Identität und Wesen der sogenannten Osteopsathyrosis idiopathica und Osteogenesis imperfecta, Deutsche Ztschr. Chir. **160**:289, 1920.
13. Bauer, K. H.: Erbkonstitutionelle "Systemerkrankungen" und Mesenchym, Klin. Wchnschr. **2**:624, 1923.
14. Becks, H.: Histologic Study of Tooth Structure in Osteogenesis Imperfecta, Dent. Cosmos **73**:737, 1931.
15. Behr, C.: Keratokonus, blaue Sklera, habituelle Luxationen, Monatsbl. f. Augenh. **1**:281, 1913.
16. Bell, J.: Blue Sclerotics and Fragility of Bone. Treasury of Human Inheritance., vol. II, part III, Cambridge and London, 1928, University of London, Cambridge University Press.
17. Bergman, G., and Engfeldt, B.: Studies on Mineralized Dental Tissues. IV. Biophysical Studies in Osteogenesis Imperfecta, Acta path. et microbiol. scandinav. **35**:537, 1954.
18. Bert, J. M.: Les formes de transition entre les syndromes familiaux de fragilité osseuse (type Lobstein) et de grande hyperlaxité-ligamentaire (type Morquio), Presse méd. **50**:290, 1942.
19. Bigler, M.: Ueber das gleichzeitige Vorkommen von Osteopsathyrose und blauer Verfärbung der Skleren bei Otosklerose, Ztschr. f. Hals-Nasen-u. Ohrenh. **5**:233, 1923.
20. Blencke, A.: Ueber das gemeinsame Vorkommen von Knochenbrüchigkeit mit blauen Skleren und Schwerhörigkeit, Ztschr. f. orth. Chir. **45**:406, 1924.
21. Blegvad, O., and Haxthausen, H.: Blue Sclerotics and Brittle Bones, With Macular Atrophy of the Skin and Zonular Cataract, Brit. M. J. **2**:1071, 1921.
22. Breuer, J.: Zur Therapie der Osteopsathyrosis mit blauen Skleren, Deutsche med. Wchnschr. **56**:1735, 1930.
23. Brickley, D. W.: Otosclerosis and Blue Scleras, Arch. Otolaryng. **46**:230, 1947.
24. Broca, A., and Herbinet: De l'osteopsathyrosis ou fragilité osseuse dite essentielle, Rev. Chir. **77**:284, 1905.
25. Bronson, E.: On Fragilitas Ossium and Its Association With Blue Sclerotics and Otosclerosis, Edinburgh M. J. **18**:240, 1917.
26. Buchanan, L.: Case of Congenital Maldevelopment of the Cornea and Sclerotic, Tr. Ophth. Soc. U. Kingdom **23**:267, 1903.
27. Bull, J.: Paget's Disease of the Skull With Platybasia, Proc. Roy. Soc. Med. **40**:85, 1946.
28. Caffey, J.: Pediatric X-ray Diagnosis, ed. 2, Chicago, 1950, Year Book Publishers, Inc., p. 41.
29. Casanovas, J.: Blue Scleras and Fragilitas Ossium, Arch. ophth. hispano-amer. **34**:133, 1934.
30. Chamberlain, W. E.: Basilar Impression (Platybasia). A Bizarre Developmental Anomaly of the Occiptal Bone and Upper Cervical Spine With Striking and Misleading Neurologic Manifestations, Yale J. Biol. & Med. **11**:487, 1939.
31. Chu, H. I., Liu, S. H., Chen, K. C., Yü, T. F., Su, C. C., Wang, C. W., and Cheng, T. Y.: Osteogenesis Imperfecta. II. Observations on the Effect of Vitamins C and D, and Thyroid and Pituitary Preparations on the Calcium, Phosphorus and Nitrogen Metabolism With a Report of Bone Analysis, Chinese M. J. (Suppl.) **3**:539, 1940.
32. Cleminson, F. J.: Otosclerosis Associated With Blue Sclerotics and Osteogenesis Imperfecta, Proc. Roy. Soc. Med. **20**:471, 1927.
33. Colden, C.: Blaue Skleren mit eigenartigem ophthalmoskopischen Befund, Klin. Monatsbl. Augenh. **74**:360, 1925.
34. Committee on Otosclerosis, American Otological Society: Otosclerosis; a Résumé of the Literature to July, 1928, New York, 1929, Paul B. Hoeber, Inc.
35. Cornil, L. Berthier, J., and Sild, A.: Sur l'adjonction à osteopsathyrose hereditaire de deux nouveaux signes: tympans bleus et amyotrophie diffuse, Rev. neurol. **67**:89, 1937.
36. Conlon, F. A.: Blue Sclerotics; a Note Upon Associated Otosclerosis, Am. J. Ophth. **1** (series 3) :726, 1918.
37. Crooks, J.: Two Unusual Examples of Osteogenesis Imperfecta, Brit. M. J. **1**:705, 1932.
38. Danelius, G.: Osteogenesis imperfecta intrauterin diagnostiziert, Arch. f. Gynäk. **154**:160, 1933.
39. Dessof, J.: Blue Sclerotics, Fragile Bones and Deafness, Arch. Ophth. **12**:60, 1934.
40. Eddowes, A.: Dark Sclerotics and Fragilitas Ossium, Brit. M. J. **2**:222, 1900.
41. Ellis, R. W. B.: Four Cases of Fragilitas Ossium and Blue Sclerotics, Proc. Roy. Soc. Med. (Sect. Dis. Child.) **24**:1054, 1931.
42. Engfeldt, B.., Engstrom, A., and Zetterstrom, R.: Biophysical Studies of the Bone Tissue in Osteogenesis Imperfecta, J. Bone & Joint Surg. **36-B**:654, 1954.
43. Fairbanks, H. A. T., and Baker, S. L.: Hyperplastic Callus Formation With or Without Evidence of Fracture in Osteogenesis Imperfecta With Account of the Histology, Brit. J. Surg. **36**:1, 1948.
44. Fairbanks, Sir Thomas: An Atlas of General Affections of the Skeleton, Baltimore, 1951, Williams & Wilkins Co.
45. Follis, R. H., Jr.: Histochemical Studies on Cartilage and Bone. III. Osteogenesis Imperfecta, Bull. Johns Hopkins Hosp. **93**:386, 1953.

46. Follis, R. H., Jr.: Osteogenesis Imperfecta Congenita; a Connective Tissue Diathesis, J. Pediat. **41**:713, 1952.
47. Follis, R. H., Jr.: Maldevelopment of the Corium in the Osteogenesis Imperfecta Syndrome, Bull. Johns Hopkins Hosp. **93**:225, 1953.
48. Fraser, I.: Fragilitas Ossium Tarda, Brit. J. Surg. **22**:231, 1934.
49. Fraser, J. S.: Otosclerosis Associated With Fragilitas Ossium and Blue Sclerotics; Clinical Report of 3 Cases, Proc. Roy. Soc. Med. **12**:126, 1918.
50. Freytag, G. T.: Ueber blaue Sklera und Knochenbrüchigkeit, Klin. Monatsbl. Augenh. **66**:507, 1921.
51. Friedenwald, J. S., and others: Ophthalmic Pathology: An Atlas and Textbook, Philadelphia, 1952, W. B. Saunders Co.
52. Friedberg, C. K.: Zur Kenntnis des vererbbaren Syndroms: Abnorme Knochenbrüchigkeit, blaue Skleren und Schwerhörigkeit, Klin. Wchnschr. **10**:830, 1931.
53. Fuss, H.: Die erbliche Osteopsathyrosis, Deutsche Ztschr. Chir. **245**:279, 1935.
54. Gardner, W. V., and Pfeiffer, C. A.: Influence of Estrogens and Androgens on the Skeletal System, Physiol. Rev. **23**:139, 1954.
55. Gimplinger, E.: Blauer Verfärbung der Skleren und Herderkrankung der Labyrinthkapsel, Ztschr. f. Hals-Nasen-u. Ohrenh. **13**:345, 1925.
56. Gleich, M.: Osteogenesis Imperfecta Tarda; Report of 4 Cases in One Family, New York J. Med. **30**:850, 1930.
57. Gordan, G. S., Eisenberg, E., Moon, H. D., and Sakamoto, W.: Methylandrostenediol, a Protein Anabolic Steroid With Little Androgenic Activity, J. Clin. Endocrinol. **11**:209, 1951.
58. Gurlt, E.: Handbuch der Lehre von den Knochenbruchen, Berlin, 1862-1865, Bd. I, pp. 147-154.
59. Gutzeit, R.: Ueber blaue Sklera und Knochenbrüchigkeit, Klin. Monatsb. Augenh. **68**:771, 1922.
60. Harnett, W. L.: Two Cases of Osteogenesis Imperfecta With Blue Sclerotics in Natives of India, Brit. J. Surg. **22**:269, 1934.
61. Hass, J.: Zur Kenntnis der Osteopsathyrosis idiopathica, Med. Klin. **15**:1112, 1919.
62. Hilgenfeldt: Beitrag zum Krankheitsbilde der idiopatischen abnormen Knochenbrüchigkeit, Deutsche Ztschr. Chir. **238**:431, 1933.
63. Hills, R. G., and McLanahan, S.: Brittle Bones and Blue Scleras in Five Generations, Arch. Int. Med. **59**:41, 1937.
64. Hunter, D.: A Case of Osteogenesis Imperfecta, Lancet **1**:9, 1927.
65. Inderbitzin, A.: Ueber Anosteoplasia congenita beim Kalbe, Virchows Arch. path. Anat. **269**:665, 1928.
66. Ivancie, G. P.: Dentinogenesis Imperfecta, Oral. Surg. **7**:984, 1954.
67. Jeckeln, E.: Systemgebundene mesenchymale Erschöpfung. Eine neue Begriffsfassung der Osteogenesis imperfecta, Virchows Arch. path. Anat. **280**:351, 1931.
68. Jewell, F. C., and Lofstrom, L. E.: Osteogenic Sarcoma Occurring in Fragilitas Ossium, Radiology **34**:741, 1940.
69. Johansson, S.: Ein Fall von Osteogenesis imperfecta mit verbreiteten Gefassverkalkungen, Acta Radiol. **1**:17, 1921-1922.
70. Katsu, Y.: An Instance of Osteogenesis Imperfecta Congenita, Jap. J. Obst. **16**:171, 1933.
71. Kersley, G. D.: Fragilitas Ossium and Allied Conditions, St. Barth. Hosp. Rep. **68**:159, 1935.
72. Key, J. A.: Brittle Bones and Blue Sclerae (Hereditary Hypoplasia of the Mesenchyme), Arch. Surg. **13**:523, 1926.
73. Kidd, F.: Case for Diagnosis: Imperfect Osteogenesis? Proc. Roy. Soc. Med. **4** (Clin. Sec.) :106, 1911.
74. Lobeck, H.: Ein Beitrag zur Osteogenesis imperfecta, Frankfurt A. M. 1938, Diss., p. 32. Cited by Seedorff.[101]
75. Lobstein, J.G.C.F.M.: Lehrbuch der pathologischen Anatomie, Stuttgart, 1835, Bd. II, p. 179.
76. Looser, E.: Zur Kenntnis der Osteogenesis imperfecta congenita et tarda, Mitt. Grenzgeb. Med. u. Chir. **15**:161, 1906.
77. McKinney, R.: Studies on Fibres in Tissue Cultures. III. The Development of Reticulum Into Collagenous Fibers in Cultures of Adult Rabbit Lymph Nodes, Arch. exper. Zellforsch. **9**:14, 1929.
78. McKusick, V. A.: Unpublished observations.
79. Messinger, A. L., and Teal, F.: Intramedullary Nailing for Correction of Deformity in Osteogenesis Imperfecta, Clin. Orthop. **1**:221, 1955.
80. Milne, M. D., Stanbury, S. W., and Thomson, A. E.: Observations on Fanconi Syndrome and Renal Hyperchloraemic Acidosis in Adults, Quart. J. Med. **21**:61, 1952.
81. Moldamer, M.: Senile Osteoporosis. The Physiological Basis of Treatment, Arch. Int. Med. **96**:202, 1955.
82. Mørsch, E. T.: Chondrodystrophic Dwarfs in Denmark. In Opera ex domo biologiae hereditariae humanae Universitatis Hafniensis, Copenhagen, 1941, E. Munksgaard, vol. 3.

83. Nager, F. R.: Otosklerose bei infantiler Osteopsathyrosis und Blaufärbung der Skleren, Schweiz. med. Wchnschr. **51**:660, 1921.
84. Naita, S.: Klinische und histologische Untersuchungen des Zahngewebes bei Osteogenesis imperfecta, etc., Mitt. med. Fakült. Kais. Univ. Kyushu, Fukuoka. **9**:97, 1924. Ref. Zentralbl. f. Kinderh. **18**:822, 1925.
85. Nordin, B. E., and Roper, A.: Post-pregnancy Osteoporosis; a Syndrome? Lancet **1**:431, 1955.
86. Noyes, F. B.: Hereditary Anomaly in Structure of Dentin (abstract), J. Dent. Res. **15**:154, 1935.
87. O'Connell, J. E. A., and Turner, J. W. A.: Basilar Impression of the Skull, Brain **73**:405, 1950.
88. Ormerod, E. L.: An Account of a Case of Mollities Ossium, Brit. M. J. **2**:735, 1859.
89. Peters, A.: Blaue Sklera und Knochenbrüchigkeit, Klin. Monatsbl. Augenh. **51**:594, 1913.
90. Rennert, H., and Popella, E.: Abortive Fälle von Osteopsathyrose mit Marfan-Symptomatik, Med. Monatsschr. **9**:106, 1955.
91. Roberts, E., and Schour, I.: Hereditary Opalescent Dentine—Dentinogenesis Imperfecta, Am. J. Orthodontics **25**:267, 1939.
92. Rolleston, J. D.: Inherited Syphilis and Blue Sclerotics, Ophthalmoscope **9**:321, 1911.
93. Ropes, M. W., Rossmeisl, E. C., and Bauer, W.: The Effect of Estrin Medication in Osteogenesis Imperfecta, Conference on Metabolic Aspects of Convalescence, Tr. 14th Meeting, Josiah Macy, Jr., Foundation, New York, 1946, p. 87.
94. Rushton, M. A.: The Structure of the Teeth in a Late Case of Osteogenesis Imperfecta, J. Path. & Bact. **48**:591, 1939.
95. Ruedemann, A. D., Jr.: Osteogenesis Imperfecta Congenita and Blue Sclerotics: a Clinico-pathologic Study, A.M.A. Arch. Ophth. **49**:6, 1953.
96. Ruth E. B.: Osteogenesis Imperfecta. Anatomic Study of a Case, Arch. Path. **36**:211, 1943.
97. Ruttin, E.: Ohrbefund bei Osteopsathyrose, Monatschr. Ohrenh. **53**:305, 1919.
98. Ruttin, E.: Osteopsathyrose und Otosklerose, Ztschr. f. Hals-, Nasen- u. Ohrenh. **3**:263, 1922.
99. Scott, D., and Stiris, G.: Osteogenesis Imperfecta Tarda. A Study of Three Families With Special Reference to Scar Formation, Acta med. scandinav. **145**:237, 1953.
100. Second, E. W., Wilder, R. M., and Henderson, M. S.: Osteogenesis Imperfecta Tarda (Osteopsathyrosis) Treated With Thymus Extract (Hanson), Proc. Staff Meet. Mayo Clin. **11**:1, 1936.
101. Seedorff, K. S.: Osteogenesis Imperfecta. A Study of Clinical Features and Hereditary Based on 55 Danish Families Comprising 180 Affected Persons, Copenhagen, 1949, Ejnar Munksgaard.
102. Shambaugh, G. E., Jr.: Fenestration Operation for Otosclerosis; Experimental Investigations and Clinical Observations in 2,100 Operations Over Period of 10 Years, Acta Oto-laryng. (supp. 79) pp. 1-101, 1949.
103. Shorr, E., and Carter, A. C.: The Usefulness of Strontium as an Adjuvant to Calcium in the Remineralization of the Skeleton in Man, Bull. Hosp. Joint Dis. **13**:59, 1952.
104. Simsky: Blue Sclerotics, Fragility of the Bones and Deafness, Am. J. Ophth. **9**:844, 1926.
105. Smith, O. N., and Mitchell, J. M.: The Serum Phosphatase in Osteogenesis Imperfecta, Am. J. M. Sc. **190**:765, 1935.
106. Snapper, I.: Medical Clinics on Bone Diseases, ed. 2, New York, 1949, Interscience Publishers.
107. Spurway, J.: Hereditary Tendency to Fracture, Brit. M. J. **2**:844, 1896.
108. Stapes, P. P., Jr., and Riva, H. L.: Maternal Osteogenesis Imperfecta; Report of Two Cases in Sisters, Obst. & Gynec. **4**:557, 1954.
109. Stein, F. H.: Nogen tilfaelder av osteopsathyrosis idiopathica med nedarvning i 4 led, Tidskr. norsk. Laegeforen. **47**:557, 1927. Cited by Seedorff.[101]
110. Stenvers, H. W.: Röntgenologische Bemerkungen zur vorhergehenden Arbeit von J. van der Hoeve und A. de Kleyn, Arch. f. Ophth. **95**:94, 1918.
111. Stephenson, S.: Blue Sclerotics, Tr. Ophth. Soc. U. Kingdom **35**:274, 1915.
112. Stobie, W.: The Association of Blue Sclerotics With Brittle Bones and Progressive Deafness, Quart. J. Med. **17**:274, 1924.
113. Strach, E. H.: Hyperplastic Callus Formation in Osteogenesis Imperfecta; Report of a Case and Review of the Literature, J. Bone & Joint Surg. **35-B**:417, 1953.
114. Sundberg, C. G.: Discussion of paper by G. Zander, Nord. Med. **1**:802, 1939. Quoted by Seedorff.[101]
115. Terrien, F., Sainton, P., and Veil, P.: Deux cas de syndrome de Van der Hoeve (oeil bleu; fragilité osseuse; surdité), Arch. d'opht. **44**:293, 1927.
116. Terry, W. I.: Hereditary Osteopsathyrosis, Tr. Am. S. A. **36**:317, 1918.
117. Vallery-Radot, P., and Aris, P.: Osteopsathyrosis Hereditaire, Bull. Soc. pédiat. Paris **22**:291, 1924.
118. van der Hoeve, J., and de Kleyn, A.: Blaue Sclera, Knochenbrüchigkeit und Schwerhörigkeit, Arch. Ophth. **95**:81, 1918.

119. Vander Veer, E. A., and Dickinson, A. M.: Fragilitas Ossium, Ann. Surg. **74**:629, 1921.
120. Voorhoeve, N.: Blue Sclerotics, in Connection With Other Hereditary or Congenital Abnormalities, Lancet **2**:740, 1918.
121. Vrolik, W.: Tabulae ad illustrandam embryogenesim hominis et mammalium, tam naturalem quam abnormem, Amstelodami, 1849.
122. Voigt, O.: Ein Fall von Osteogenesis imperfecta, Freiburg, 1926, Diss. Cited by Seedorff [101]
123. Vyropaer, D.: Cited by Seedorff.[101]
124. Wagoner, G. W.: Idiopathic Osteopsathyrosis, Ann. Surg. **80**:115, 1924.
125. Watkyn-Thomas, F. W.: Diseases of the Throat, Nose and Ear, Springfield, Ill., 1953, Charles C Thomas, Publisher, p. 612.
126. Weber, M.: Osteogenesis Imperfecta Congenita, a Study of Its Histopathogenesis, Arch. Path. **9**:984, 1930.
127. Weinmann, J. P., and Sicher, H.: Bone and Bones, St. Louis, 1947, The C. V. Mosby Co.
128. Werner, R.: Mehrfaches Vorkommen einer Neigung zu Knochenbrüchen und Sarkomentwicklung in einer Familie, Ztschr. Krebsforsch. **32**:40, 1940.
129. Wiechmann, E., and Paal, H.: Zur Klinik der sogenannten blauen Skleren, München. med. Wchnschr. **72**:213, 1925.
130. Wilson, G. W., and Steinbecker, M.: Hereditary Hypoplasia of Dentine, J. Am. Dent. A. **16**:866, 1929.
131. Wilton, A.: Die Skeletveranderungen bei einem Spätfalle von Osteogenesis imperfecta nebst Erorterung der Entstehungsweise unter Berücksicktigung anderer Skeletkrankheiten, Virchows Arch. **283**:778, 1932.
132. Wirth, M.: Blaue Skleren und Knochenbrüchigkeit, Klin. Monatsbl. Augenh. **74**:505, 1925.
133. Wyatt, T. C., and McEachern, T. H.: Congenital Bone Dysplasia (Osteogenesis Imperfecta) Associated With Lesions of Parathyroid Glands, Am. J. Dis. Child. **43**:403, 1932.
134. Anon: Fragilitas Ossium, J.A.M.A. **161**:773, 1956.
135. Axmann, E.: Merkwürdige Fragilität der Knochen ohne dyskrasische Ursache als krankhafte Eigenthümlichkeit dreier Geschwister, Ann. f. d. ges. Heilk. (Karlsruhe) **4**:58, 1831.
136. Baker, S. L.: Hyperplastic Callus Simulating Sarcoma in Two Cases of Fragilitas Ossium, J. Path. & Bact. **58**:609, 1946.
137. Biering, A., and Iversen, T.: Osteogenesis Imperfecta Associated With Ehlers-Danlos Syndrome, Acta paediat. **44**:279, 1955.
138. Bierring, K.: Contribution to the Perception of Osteogenesis Imperfecta Congenita and Osteopsathyrosis Idiopathica as Identical Disorders, Acta chir. scandinav. **70**:481, 1933.
139. Blattner, R. J., Heyes, F., and Robinson, H. B. G.: Osteogenesis Imperfecta and Odontogenesis Imperfecta (Hereditary Opalescent Dentin), J. Dent. Res. **21**:325, 1942.
140. Bonnet, P., and Wertheimer, C.: Un cas d'osteopsathyrose, Bull. Soc. d'opht. de Paris, p. 119, 1935.
141. Bromer, R. S.: Rickets and Infantile Scurvy Occurring in Case of Osteogenesis Imperfecta, Am. J. Roentgenol. **55**:30, 1946.
142. Bryan, R. S., Cain, J. C., and Lipscomb, P. R.: Hereditary Osteogenesis Imperfecta. A Mother and Son With Their Family Tree, Mayo Clin., Proc. Staff Meet. **31**:475, 1956.
142a. Calkins, E., Kahn, D., and Diner, W. A.: Idiopathic Familial Osteoporosis in Dogs; "Osteogenesis Imperfecta," Ann. New York Acad. Sc. **64**:410, 1956.
143. Caniggia, A., Stuart, C., and Guideri, R.: Fragilitas ossium hereditaria tarda (Eckman-Lobstein Disease), Acta med. scandinav., Suppl. **340**:1, 1958.
144. Chont, L. K.: Osteogenesis Imperfecta; Report of 12 Cases, Am. J. Roentgenol. **45**:850, 1941.
145. Cocchi, U.: Hereditary Diseases With Bone Changes; *In* Schinz, H. R.: Roentgen-Diagnostics, New York, 1951, Grune & Stratton, Inc.
146. Conlon, F. A.: Five Generations of Blue Sclerotics and Associated Osteoporosis, Boston M. & S. J. **169**:16, 1913.
147. Coop, M. C.: A Treatment for Osteogenesis Imperfecta in Kittens, J. Am. Vet. M. A. **132**:299, 1958.
148. Crowe, F. W., Schull, W. J., and Neel, J. V.: A Clinical, Pathological and Genetic Study of Multiple Neurofibromatosis, Springfield, Ill., 1956, Charles C Thomas, Publisher, p. 36.
149. Cronental, R.: Ueber die Osteopsathyrosis hereditaria, Deutsches Arch. klin. Med. **174**:228, 1932.
150. Dalgaard, O.: Bilateral Polycystic Disease of the Kidneys, Copenhagen, 1957, Ejnar Munksgaard Forlag.
151. Daubenspeck: Pseudarthrosenbehandlung bei Osteopsathyrosis, Zentralbl. Chir. **67**:370, 1940.
152. Ekman, O. J.: Dissertatio medica descriptionem et casus aliquot osteomalaciae sistens, Upsala, 1788.

153. Faxén, N.: Case of Twins With Osteogenesis Imperfecta, Acta paediat. **14**:251, 1932.
154. See Reference 48.
155. Frerking, H. W., and Zink, O. C.: A Case of Osteogenesis Imperfecta Diagnosed in Utero, Am. J. Roentgenol. **67**:103, 1952.
156. Fromm, G. A., Parisier, H., Roca, J., and Defilippi Novoa, C. A.: Osteogenesis Imperfecta Associated With Cutaneous Pigmentation and Other Congenital Malformations, A.M.A. Am. J. Dis. Child. **96**:344, 1958.
157. Fulconis, H.: La fragilité osseuse congénitale. (Maladie de Durante), Paris, 1939, Masson et Cie.
158. Funk, P.: Beitrag zur Kenntnis der Osteopsathyrose (Typus Lobstein), Schweiz. med. Wchnschr. **70**:473, 1940.
159. Gautier, P., and Guinard-Daniol, J.: Un cas de maladie de Lobstein associée à une thrombasthenie héréditaire et familial de Glanzmann, Bull. et mém. Soc. méd. hôp. Paris **68**:577, 1952.
160. Gebala, A.: Acid Hyperphosphatasia in Three Families With Osteogenesis Imperfecta, Lancet **2**:1084, 1956.
161. Geipert, G.: Beitrag zur Erblichkeit der sog. Osteopsathyrosis, Ztschr. menschl. Vererb.- u. Konstitutionslehre **19**:691, 1936.
162. Gillanders, L. A.: Osteogenesis Imperfecta Diagnosed in Utero, Brit. J. Radiol. **30**:500, 1957.
163. Giordano, A.: Hereditary Diseases of the Osteo-cartilaginous System. Comparative Morphological Basis, Acta genet. **7**:155, 1957.
164. Glanzmann, E.: Hereditäre hämorrhagische Thrombasthenie (ein Beitrag zur Pathologie des Blutplättchen), Jahrb. Kinderheilk. **88**:113, 1918.
165. Glanzmann, E.: Osteogenesis Imperfecta (Typus Vrolik) und Osteopsathyrosis idiopathica (Typus Lobstein), Schweiz. med. Wchnschr. **66**:1122, 1936.
166. Hanhart, E.: Ergebnisse der Erforschung von Erbkrankheiten und Missbildungen in der Schweiz, Arch. Julius Klaus Stiftg. **18**:632, 1943.
167. Hatteland, K.: T. norske Lageforen **77**:75, 1957. Quoted in Brit. M. J. **1**:1172, 1957.
168. Hein, B. J.: Osteogenesis Imperfecta With Multiple Fractures at Birth: an Investigation With Special Reference to Heredity and Blue Sclera, J. Bone & Joint Surg. **10**:243, 1928.
169. Henley, F. A.: A Case of Congenital Osteopsathyrosis With Genealogical Tree of the Family, Brit. M. J. **1**:326, 1942.
170. Herndon, C. N.: Osteogenesis Imperfecta; Some Clinical and Genetic Considerations, Clin. Orthop. **8**:132, 1956
171. Holcomb, D. Y.: A Fragile-Boned Family; Hereditary Fragilitas Ossium, J. Hered. **22**:105, 1931.
171a. Holzworth, J.: Disease Conditions Prominent in Cats, Univ. of Pennsylvania Bull. School of Vet. Med., Veterinary Extension Quart. **58**:101, 1958.
171b. Holzworth, J.: Osteogenesis Imperfecta, Vet. Bull. (Lederle) **15 (no. 2)**:18, 1956.
172. Hursey, R. J., Witkop, C. J., Jr., Miklashek, D., and Sackett, L. M.: Dentinogenesis Imperfecta in a Racial Isolate With Multiple Hereditary Defects, Oral Surg. **9**:641, 1956.
173. Jelnes, K. T.: Osteogenesis Imperfecta and Otosclerosis, Ugesk. laeger **111**:1262, 1949.
174. Joachim, H., and Wasch, M. G.: Fragilitas Ossium in Five Generations, Ann. Int. Med. **7**:853, 1934.
175. Johnson, W. A., and Karrer, M. C.: Osteogenesis Imperfecta in Pregnancy, Report of a Case, Obst. & Gynec. **10**:642, 1957.
176. Kaul, B.: Ein Abortivfall von Osteogenesis imperfecta congenita kombiniert mit Missbildungen der Blutgefasse (Osteoangiogenesis imperfecta), Frankfurt. Ztschr. Path. **53**:289, 1939.
177. Keats, T. E.: Diffuse Thickening of the Calvarium in Osteogenesis Imperfecta, Radiology **69**:408, 1957.
178. Kellogg, C. S.: Osteogenesis Imperfecta; Study of Five Generations, Arch. Int. Med. **80**:358, 1947.
179. Khoo, F. Y.: Congenital Pseudarthrosis of the Tibia and Its Relation to Fragilitas Ossium, Am. J. Dis. Child. **77**:201, 1949.
180. Knaggs, L.: Osteogenesis Imperfecta, Brit. J. Surg. **11**:737, 1924.
181. Komai, T., Kunai, H., and Ozaki, Y.: A Note on the Genetics of Van der Hoeve's Syndrome, With Special Reference to a Large Japanese Kindred, Am. J. Human Genet. **8**:110, 1956.
182. Krabbe, K. H.: La maladie de Henri de Toulouse-Lautrec, Acta psychiat. et neural. scandinav. Suppl. **108**:211, 1956.
183. Lamy, M.: L'infirmité de Toulouse-Lautrec, Presse méd. **64**:249, 1956.
183a. Leicher, H., and Haas, E.: Labyrinthausfall bei Osteopsathyrosis, Ztschr. Laryng. **36**:190, 1957.
184. Liber, B.: Fragilitas ossium, J.A.M.A. **162**:700, 1956.
185. See Reference 76.
186. Lovett, R. W., and Nichols, H.: Osteogenesis Imperfecta. With the Report of a Case With Autopsy and Histological Examination, Brit. M. J. **11**:915, 1906.

187. Macgregor, A. G., and Harrison, R.: Congenital Total Color Blindness Associated With Otosclerosis, Ann. Eugenics **15**:219, 1950.
187a. McKusick, V. G.: Hereditary Disorders of Connective Tissue, Bull. New York Acad. Med. **35**:143, 1959.
188. Motulsky, A., Heustis, R., and Anderson, R.: Hereditary Spherocytosis in Mouse and Man, Acta Genet. et Statist. Med. **6**:240, 1956.
189. Nager, F. R.: Pathology of the Labyrinthine Capsule, and Its Clinical Significance. Nelson Loose-Leaf Medicine of the Ear, New York, 1939, Thomas Nelson & Sons, p. 237.
190. Nielsen, H. E.: Familial Occurrence of Osseus Fragility, Blue Sclera and Deafness, Nord. Med. **15**:2203, 1942.
191. Pelner, L., and Cohen, J. N.: Osteogenesis Imperfecta Tarda, Am. J. Roentgenol. **61**:690, 1949.
192. Posner, A. C., and Goldman, J. A.: A Case of Osteogenesis Imperfecta Congenita Diagnosed in Utero, Am. J. Obst. & Gynec. **73**:1143, 1957.
193. Puppel, E.: Osteogenesis Imperfecta, Monatschr. Geburtsh. u. Gynäk. **82**:269, 1929.
194. Riddell, W. J. B.: A Pedigree of Blue Sclerotics, Brittle Bones and Deafness, With Colour Blindness, Ann. Eugenics **10**:1, 1940.
195. Rieseman, F. R., and Yater, W. M.: Osteogenesis Imperfecta. Its Incidence and Manifestations in Seven Families, Arch. Int. Med. **67**:950, 1941.
196. Rodgers, T. R.: Otosclerosis Associated With Blue Sclerotics and Fragilitas Ossium, Proc. Roy. Soc. Med. **29**:1107, 1936.
197. Rosenbaum, S.: Osteogenesis Imperfecta and Osteopsathyrosis, a Contribution to the Study of Their Identity and Their Pathogenesis, J. Pediat. **25**:161, 1944.
198. Schmidt, M. B.: Die allgemeinen Entwicklüngshemmungen der Knochen, Ergebn. d. allg. Path. u. Path. Anat. **4**:612, 1897.
199. Schulze, C.: Erbbedingte Strukturanomalien menschlicher Zähne, Munich and Berlin, 1956, Urban u. Schwarzenberg.
200. Schultze, F.: Beitrag zur idiopathischen Osteopsathyrose, Arch. klin. Chir. **47**:327, 1894.
201. Shugrue, J. J., Rockwood, R., and Anderson, E. W.: Fragilitas Ossium and Deafness, Arch. Int. Med. **39**:98, 1927.
202. Siegel, B. M., Friedman, I. A., and Schwartz, S. O.: Hemorrhagic Disease in Osteogenesis Imperfecta. Study of Platelet Functional Defect, Am. J. Med. **22**:315, 1957.
203. Simmons, C. C.: Osteogenesis Imperfecta and Idiopathic Fragilitas Ossium, Ann. Surg. **46**:179, 1907.
204. Sisk, J. N.: Fragilitas Ossium in Twins, Wisconsin M. J. **30**:273, 1931.
205. Skaggs, J. W., and Theobald, J. A.: Osteogenesis Imperfecta in a Kitten, J. Am. Vet. Med. A. **130**:450, 1957.
206. Stilling, H.: Osteogenesis Imperfecta, Virchows Arch. **115**:357, 1889.
206a. Strack, E.: Beobachtung von Fragilität der Knochen in der Jugend, ein Beitrag zu der Lehre von den Knochenkrankheiten, J. pract. Arzneyk. u. Wundarzneyk. **25**:163, 1807.
207. Toto, P. D.: Osteogenesis Imperfecta Tarda With Dentinogenesis Imperfecta, Oral Surg. **6**:772, 1953.
208. Vaughn, J. (Richmond): Personal communication.
209. Weil: Pubertas praecox und Knochenbrüchigkeit (abst.), Klin. Wchnschr. **2**:2114, 1922.
210. Weinmann, J. P., Svoboda, J. F., and Woods, R. W.: Hereditary Disturbances of Enamel Formation and Calcification, J. Am. Dent. A. **32**:397, 1945.
211. Welz, W. E., and Lieberman, B. L.: Report of a Case of Osteogenesis Imperfecta in Twins, Am. J. Obst. & Gynec. **14**:49, 1927.
212. Winter, G. R., and Maiocco, P. D.: Osteogenesis Imperfecta and Odontogenesis Imperfecta, Oral Surg. **2**:782, 1949.
213. Witkop, C. (Bethesda, Md.): Personal communication.
214. Wyllie, W. G., and Schlesinger, B.: Osteogenesis Imperfecta Presenting With Delay in Walking, Two Cases, Proc. Roy. Soc. Med. **42**:80, 1949.
215. Zander, G. S. F.: Case of Osteogenesis Imperfecta Tarda With Platyspondylisis, Acta radiol. **21**:53, 1940.
216. Zurhelle, E.: Osteogenesis imperfecta bei Mutter und Kind, Ztschr. Geburtsh. u. Gynäk. **74**:942, 1913.

6. PSEUDOXANTHOMA ELASTICUM

HISTORICAL NOTE

THE first description of the skin changes and the first autopsy report were provided by Balzer[1] in 1884. Because of the yellow and elevated appearance of the skin lesions, the disorder was grouped with the xanthomatoses by Balzer and by Chauffard.[10] The disease was identified as a separate and nonxanthomatous entity by Darier[14] in 1896.

In 1889 Chauffard,* at a meeting of the Société Médicale des Hôpitaux in Paris described a patient destined to occupy a prominent role in the history of this disease. His case was separately reported, during the next fifteen years, by Besnier and Doyon[6]; by Darier,[14] who established the histopathology and offered the name *pseudoxanthoma elasticum* with the alternative *elastorrhexis;* and by Hallopeau and Laffitte,[31] who described dramatic changes in the fundus oculi. The patient's well-documented story is of further interest because it demonstrates the typical features of the syndrome from which he suffered: changes in the skin, repeated massive gastrointestinal hemorrhages, weak peripheral pulses, and failing vision. Chauffard's discription[10] follows†:

> This is a man of thirty-five years. . . . At twenty-four years of age, while doing his military service in New Caledonia, he suffered a large hematemesis. This accident repeated itself several times (at ages twenty-six, thirty-one and thirty-three). This summer he was admitted to the Hôtel Dieu for a hematemesis.
>
> In 1880 L. was discharged and returned to France; and it was shortly afterward, he states, when he noted the beginning of his skin affection. . . . The xanthomatous eruption is comprised of a series of evolving groups, perfectly symmetrical and confined exclusively to the several flexural folds, that is, base of the neck, the two axillary creases, the folds of the elbows, the anterior abdominal wall, especially just below the umbilicus, the two inguinal triangles, the inferior aspect of the penis, around the anus, the two popliteal fossae. . . . The center of the group is formed by an almost confluent agglomeration of intradermal plaques, soft to the touch, projecting to some extent like papules, separated by small folds of skin. Their coloration is rather pale, resembling that of fresh butter or yellow chamois; the size of the largest plaque is scarcely

*Anatole Chauffard (1855-1932), an internist, is better known for his discovery (with Minkowski) of congenital hemolytic icterus (1900) and of the increased fragility of the erythrocytes in this condition (1907).[86]

†Translation mine.

> greater than that of a pea. . . . If one retracts both lips, one sees that the mucosa of the inner aspect is involved. It demonstrates a cluster of small, yellowish intramucosal nodules, resting on a richly vascular background traversed by numerous dilated and tortuous capillaries. . . . In February there developed an unusual phenomenon of which there is today scarely any trace remaining. The peripheral zone of the eruptive groups in the skin were traversed by rather large, violaceous rose networks which were not elevated and formed a congestive halo around the yellow plaques. . . . Today traces of this perinodular hyperemia remain only in the pectoral regions, on the anterior extension of the axillary groups. . . .
>
> The pulse is feeble and compressible and gives with the sphygmometer of Verdin a tension of 650, rather than of 750, the average normal figure.

In August, 1896, at the Third International Dermatologic Congress in London, Darier[14] reported histologic studies on the skin of Chauffard's patient. By 1903, this patient had developed amblyopia; and Hallopeau and Laffitte[31] reported that there was "chorioretinitis of the central region, involving the macula, with secondary atrophy of the optic disc."

Although Hallopeau and Laffitte in 1903 speculated that there might be some connection between the changes in the skin and those in the fundus oculi of Chauffard's patient, it was not until 1929 that the relationship of angioid streaks and pseudoxanthoma elasticum was established by Ester Grönblad,[26] an ophthalmologist, and James Strandberg,[64] a dermatologist, both of Stockholm. Angioid streaks had been described by Doyne[16] in 1889, and the name was assigned by Knapp[41] in 1892. Knapp thought angioid streaks have a vascular basis. Their origin as a result of crazing of Bruch's membrane was first suggested by Kofler[42] in 1917.

Involvement of the peripheral arteries in this syndrome and the physiologic consequences thereof have been studied in the last twenty-five years by Carlborg,[9] Van Embden Andres,[76] Scheie and Freeman,[58] Urbach and Wolfram,[75] Prick,[38,55] Guenther,[27] and Wolff and his associates.[81] Gastrointestinal hemorrhage was emphasized by several of these authors and particularly by Revell and Carey[56] in 1948. Evidence that this disease may be an abnormality of collagen fibers rather than elastic fibers can be attributed largely to Hannay,[32] who used standard histologic techniques, and to Tunbridge and his collaborators,[74] who used electron microscopy.

Pseudoxanthoma elasticum is an objectionable name for this syndrome, since it refers only to its cutaneous aspect, perpetuates the possibility of confusion with the xanthomatoses, and conveys the notion that elastic tissue is unequivocally the defective element. Unfortunately, the only eponym that has been applied to this syndrome at all frequently, Grönblad-Strandberg, is not easily remembered or spoken and has not attained wide use. "PXE" is the abbreviation that will be used frequently in this presentation to refer to the entire syndrome.

CLINICAL MANIFESTATIONS

Clinical expression of PXE is found mainly in three areas: the skin, the eye, and the cardiovascular system. Because of the widespread involvement of the muscular arteries, hemorrhagic symptoms referable to virtually every organ system may occur. The following descriptions are based in part on eighteen cases observed at Johns Hopkins Hospital.

The changes in the skin (Figs. 76*A* and 78*A*) are often not recognizable clinically before the second decade of life or later. The face, neck, axillary folds, cubital

areas, inguinal folds, and periumbilical area are particularly prone to involvement. The skin in the perioral area, including the creases of the skin, another zone of particular wear and tear, is likely to show changes. (It is of note that senile "elastotic degeneration" [v. infra] occurs frequently in the same area, as indicated by the frequency with which this histologic change is seen in specimens of lip carcinoma. Surgical pathologists and skin pathologists become very familiar with senile elastosis because of its frequency in specimens with neoplasms of the skin in older individuals.) The skin becomes thickened and grooved like coarse-grained Moroccan leather. The areas between the grooves, diamond-shaped, rectangular, and polygonal, are elevated and yellowish. *Cutis rhomboidalis nuchae* and *la peau citréine*,

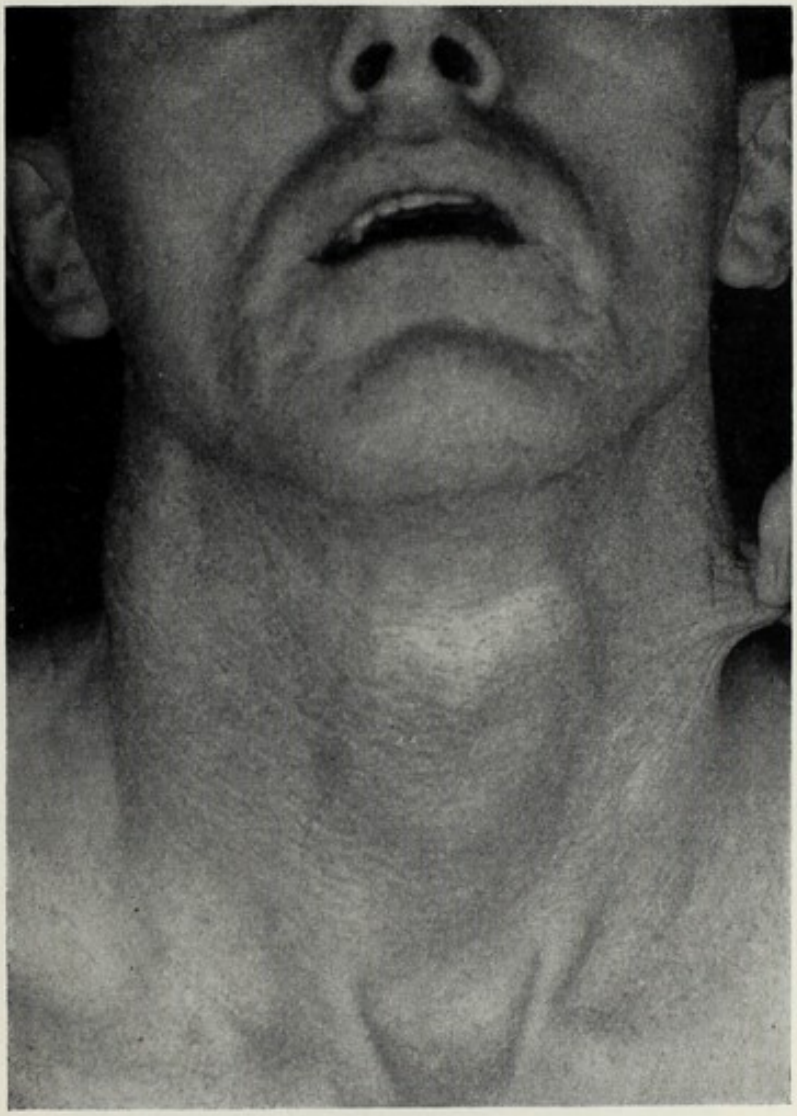


Fig. 76*A*.

Figs. 76*A*-76*G*. C. T. (582989), a 32-year-old man. *A* and *B*, The skin is lax, rigid, and grooved with a yellowish tint. *C*, Angioid streaks and proliferative changes in fundus oculi. *D*, Calcification of deep femoral artery (photograph retouched). *E*, Calcification of posterior tibial artery (photograph retouched). *F*, Histologic changes in the skin. Elastic tissue stain. (×50.) *G*, Same. (×125.) The skin of the neck, axillae, and groin is involved. Both second toes have a congenital flexion deformity ("hammertoe"). Beginning at the age of 30 years, the patient has had a total of about ten massive gastrointestinal hemorrhages necessitating hospitalization and transfusion. No bleeding site has ever been identified. X-ray film of the lungs reveals peculiar nodular densities diffusely distributed throughout both lung fields. (Fig. 76*B*, From McKusick, V. A.: Bull. New York Acad. Med. **35**:143, 1959.)

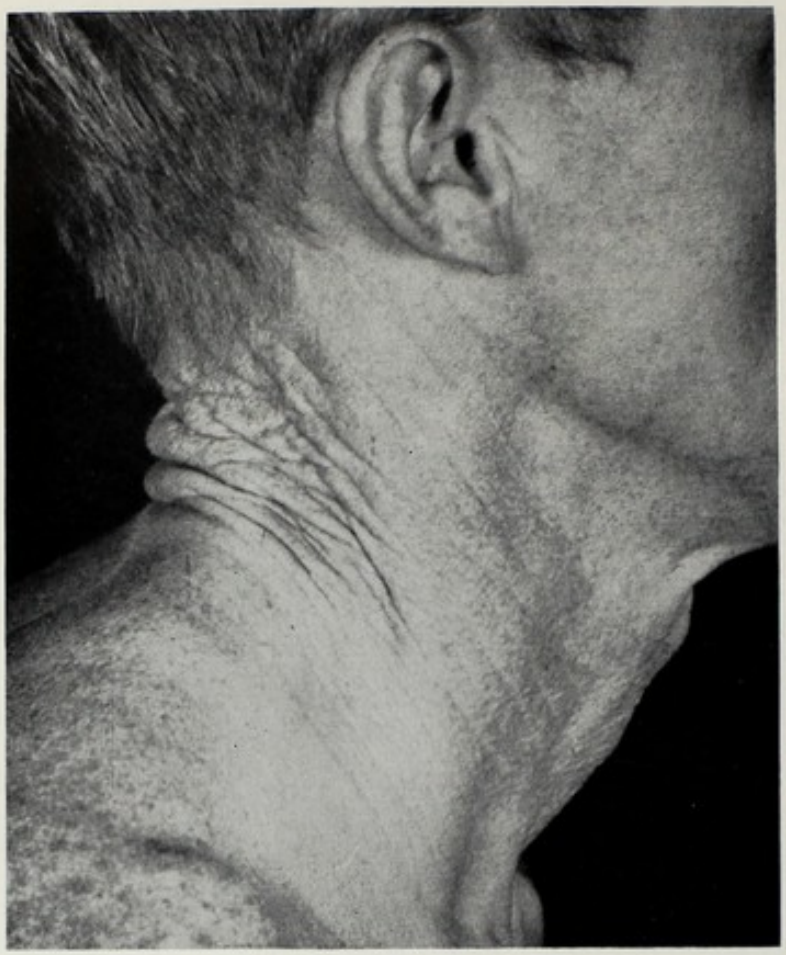


Fig. 76*B*.

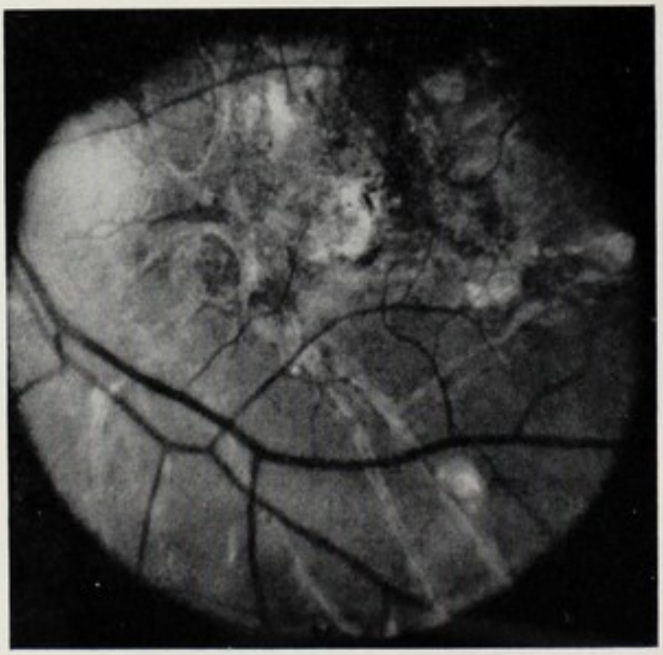


Fig. 76*C*.

Figs. 76*B* and 76*C*. For legend see page 215.

although terms used for conditions distinct from PXE, would often be appropriate for the changes seen in these patients.[67] "Crepelike" is a suggested description.[106] The skin in the involved areas becomes lax, redundant, and relatively inelastic. In girls, and the female is more often affected by this disorder, the cosmetically undesirable changes in the skin, especially that of the neck, are often occasion for consulting medical advice. The soft palate often shows changes grossly and histologically identical to those in the skin[23]; the inner aspect of the lips is a commonly affected mucosal area.[106] At times the mucosa of the rectum and vagina is affected.[9] In some patients the cutaneous changes are exceedingly mild despite advanced ocular and

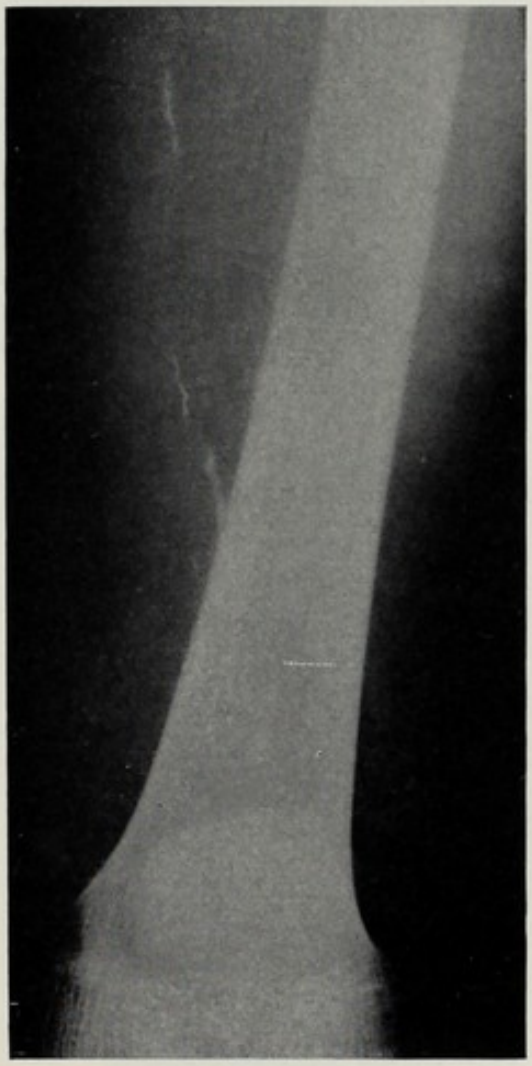


Fig. 76*D*.

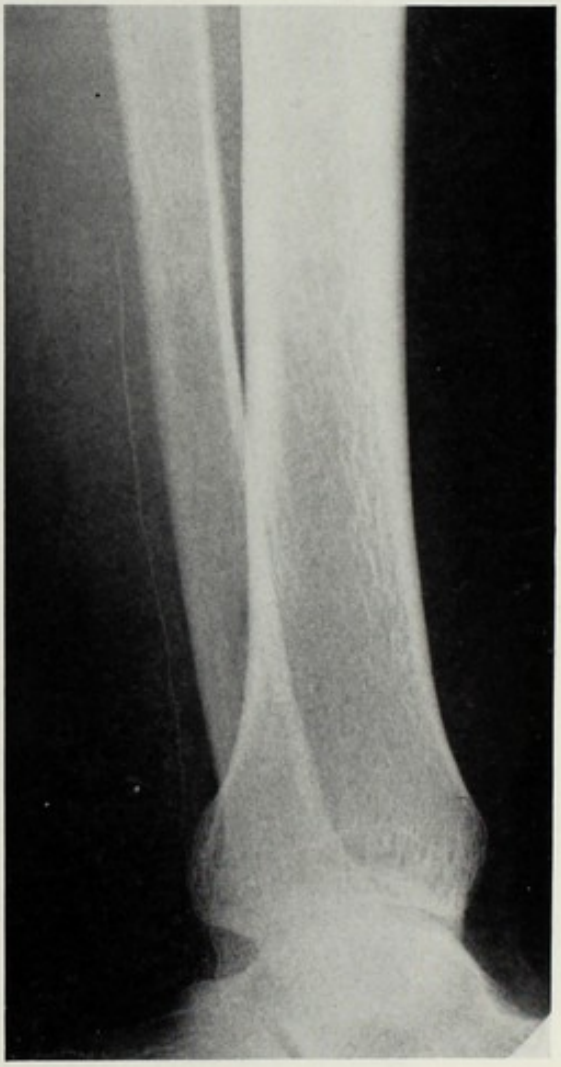


Fig. 76*E*.

Figs. 76*D* and 76*E*. For legend see page 215.

arterial changes (Fig. 78). Van Embden Andres[76] described four patients with only minimal clinical but typical histologic changes in the skin. In two other cases of his, there were no clinically detectable changes in the skin yet there were positive findings on biopsy. Rubbing or stretching of the skin may make the lesions more evident.[106] Extensive calcification of subcutaneous tissues occurs in some cases. Sometimes the patients report expressing "matter" from the nodular lesions of the neck and about the chin. In Gold's case[91] ulceration and drainage of the skin lesions occurred, but this must be very rare.

Fig. 76*F*.

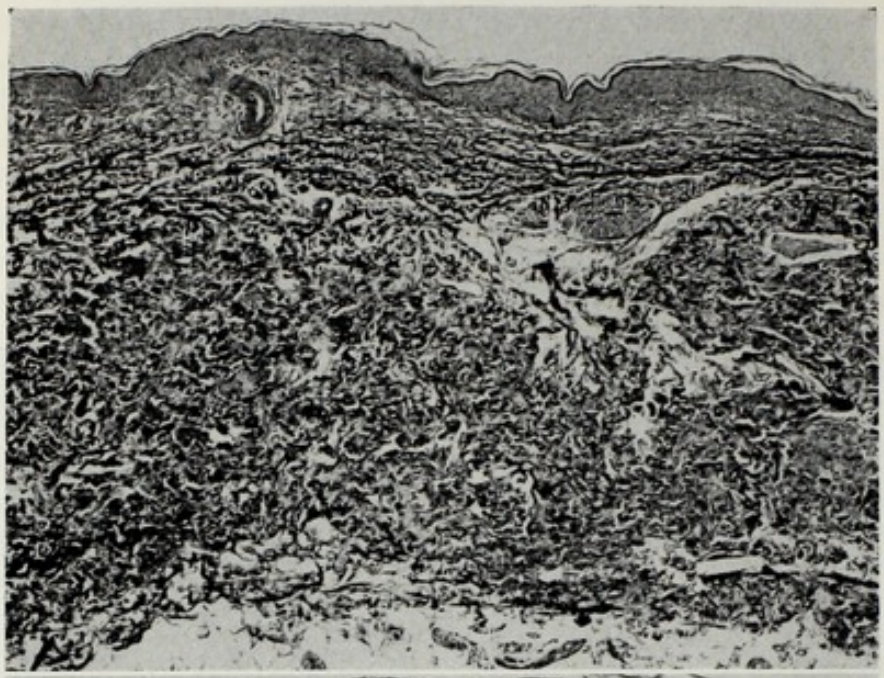


Fig. 76*G*.

Figs. 76*F* and 76*G*. For legend see page 215.

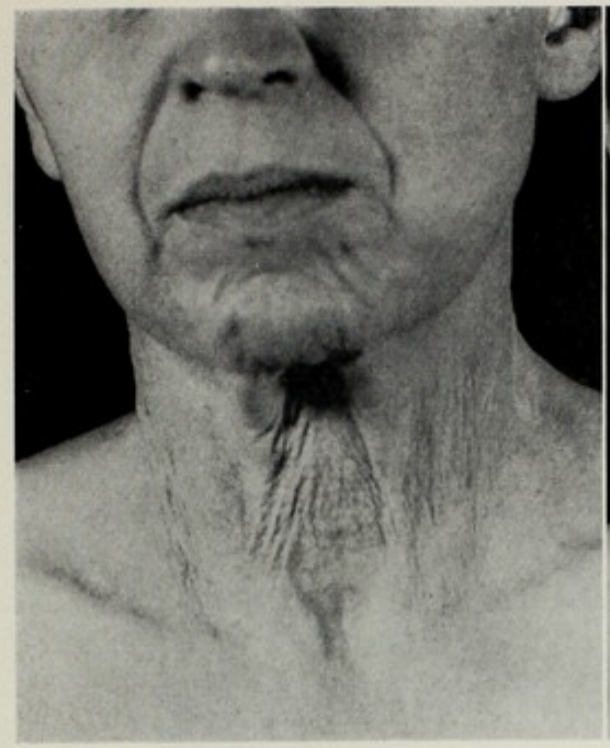


Fig. 77*A*.

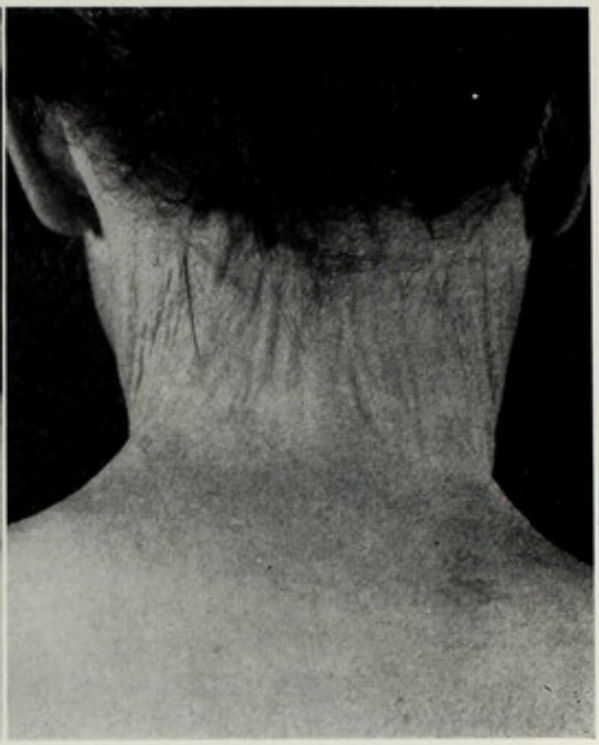


Fig. 77*B*.

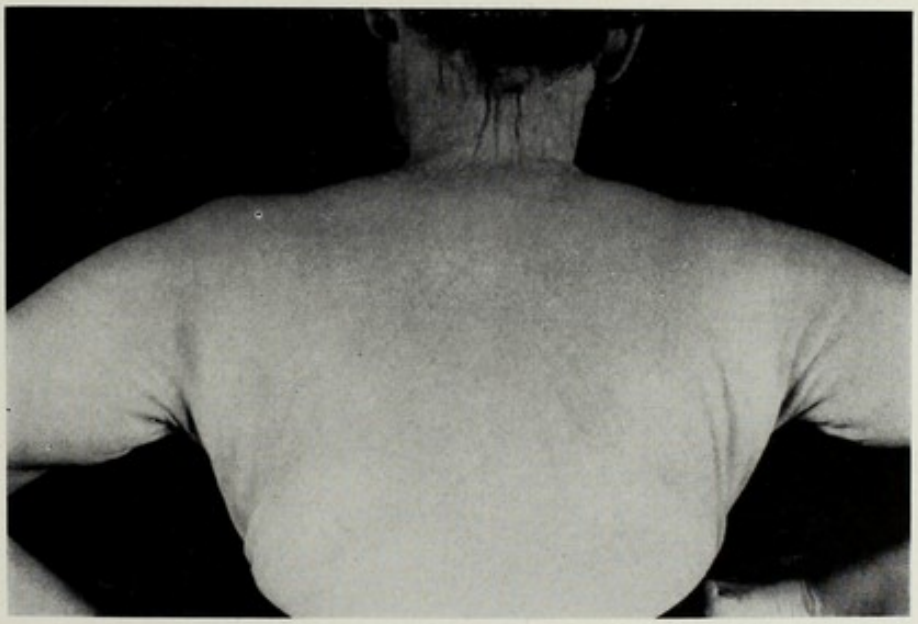


Fig. 77*C*.

Figs. 77*A*-77*F*. D. G. (757275), 48 years of age at the time of study, has extensive cutaneous and mucosal changes and fundus changes. In her early 20's several massive hematemeses occurred, for which gastric resection was performed. It may be significant that the skin changes first appeared after measles at the age of 3 years. No pulses were palpable in the feet. X-ray films showed extensive calcification in the abdominal aorta. In this patient the diagnosis might be suspected from the chest x-ray film, which shows folds of redundant skin in both axillary areas. This patient had congenital short thumbs (short terminal phalanx), probably as an independent hereditary anomaly. Stecher[115] suggested that the abnormality is inherited as a recessive, although other less extensive studies have proposed dominant inheritance.

A and *B*, Changes in the skin of the neck. *C*, The neck and axillae. *D*, The anterior abdominal wall. *E* and *F*, The neck before and after plastic surgical repair.

The characteristic changes in the eye are demonstrated by funduscopic examination and consist of angioid streaking of the fundus (Fig. *76C*). These streaks are brownish or gray and are four or five times wider than veins but resemble vessels in the manner in which they course over the fundus. Proliferative changes occur, with the angioid steaks as points of origin. Hemorrhages from the retinal vessels

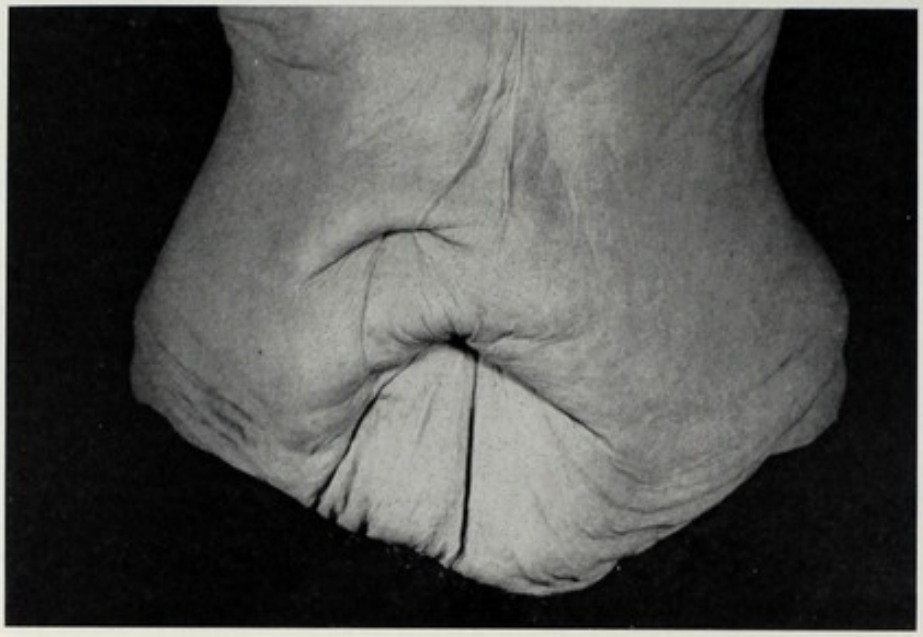


Fig. 77*D*.

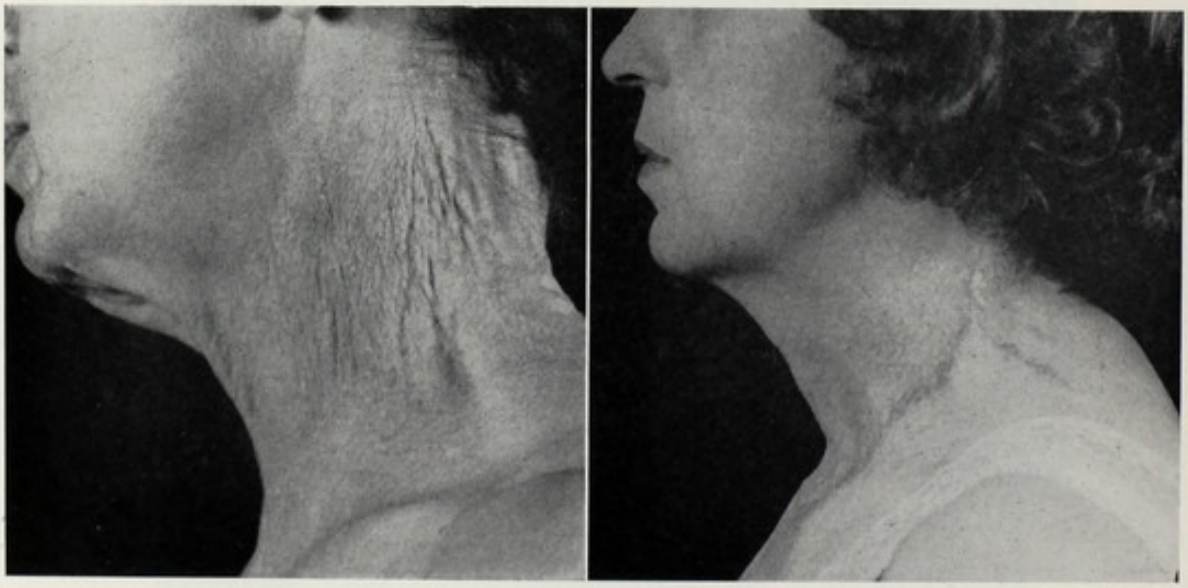


Fig. 77*E*

Fig. 77*F*.

Figs. 77*D*-77*F*. For legend see page 219.

occur both with and without trauma to the eye and are followed by organization. These retinal changes result in loss of vision, which is usually only partial, yet very severe. White or yellowish dots referred to as colloid bodies, or *Drüsen,* are described[81] and were present in the vicinity of the discs in the patient whose skin changes are demonstrated in Fig. 78. The angioid streaks are by no means necessarily

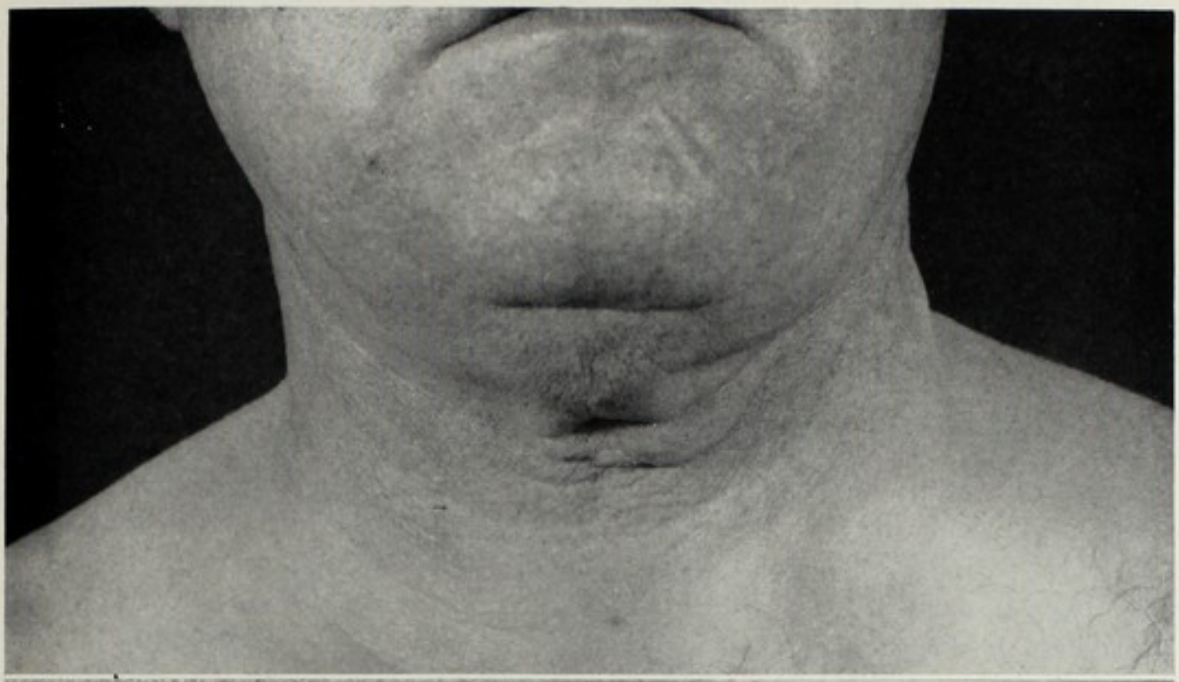


Fig. 78*A*.

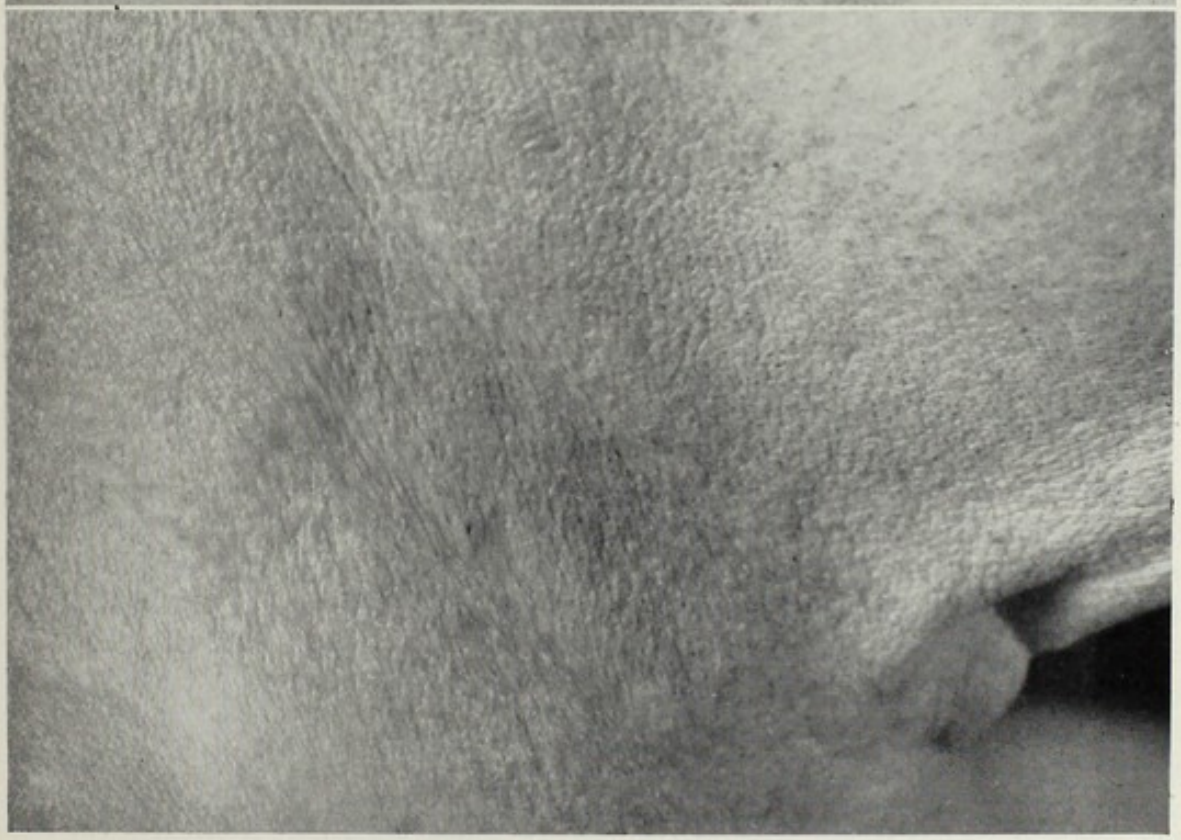


Fig. 78*B*.

Figs. 78*A* and 78*B*. P. J. G. (J.H.H. 721600), 45 years old, had a severe gastrointestinal hemorrhage at the age of 34 years. No basis was discovered and there was no recurrence. He was told at that time that he had hemorrhage in the right eye. For several years, especially in winter, he noted cramping and fatigability of the legs. At the age of 44 years there was onset of progressive failure of vision. There are no similar abnormalities in the family. Examination revealed only minimal changes in the skin of the neck (*A* and *B*). The skin would have been passed as normal were it not for the rest of the clinical picture. The skin elsewhere was normal except possibly for slightly increased looseness in flexure areas. Both fundi showed large areas of old hemorrhage and fibrosis in each macular area, typical angioid streaks, and hyaline bodies near the optic discs. No pulses were palpable in the legs below the femorals. Blood pressure and electrocardiogram were normal. The aorta was moderately tortuous, and serum cholesterol was 335 mg. per cent. (Patient seen through courtesy of Dr. J. R. Krevans.)

present at birth; actually, like the skin changes, they usually develop in the second decade of life or later. Whether trauma plays any contributory role in their pathogenesis is unclear but seems likely. Electroretinography revealed no abnormality in the patient shown in Fig. *77*.[115]

It is important to realize that although angioid streaks are the ocular hallmark of PXE, not infrequently only a less specific central chorioretinitis is present.[5,76] This may have been the case with Chauffard's famous patient.[31] Like the hemorrhages, the central chorioretinitis is a grave threat to vision because of involvement of the macular areas. Anderson[85] described a family in which PXE of the skin was associated with choroidal sclerosis in four males. The choroidal sclerosis alone was present in a fifth male. Short angioid streaks seem evident in certain of the illustrations.

Clinically the arterial involvement is expressed by pulse changes and symptoms of arterial insufficiency in the extremities, by x-ray evidence of premature medial calcification of peripheral arteries, by symptoms of coronary insufficiency, by hemorrhage in one or more of many different areas, and by hypertension.

Weakness or absence of pulses in the extremities is a frequent finding. Fatigability or frank intermittent claudication may occur in the legs. The development of these manifestations by the third decade or earlier and the involvement of the arms as well as the legs aid in the differentiation of these changes from those of ordinary arteriosclerosis. Figs. *76D* and *76E* give examples of arterial calcification which began to develop at least as early as the latter part of the third decade of life. Calcification as early as the age of 9 years has been described[81]; in this child, intermittent claudication, loss of pulsations in the distal arteries of the limbs, calcification of the arteries, and repeated attacks of melena (see below) were present. A brother, 25 years of age, had similar symptoms. Angina pectoris probably occurs more frequently than would be expected in the age groups concerned.

Hemorrhages constitute the major medical problem in most cases of PXE which come to the attention of the internist. Gastrointestinal hemorrhage is common[37] and may be fatal.[29,71] It may occur from a lesion such as peptic ulcer or hiatal hernia, which per se can produce hemorrhage, but in most cases of PXE the source of bleeding is not evident on clinical study. In cases of peptic ulcer, the arterial disease plays a strong contributory role to hemorrhages, similar to that of arteriosclerosis and primary amyloid disease. Superficial ulceration has been discovered by gastroscopy[103] or on gastrectomy.[37] In my own experience, gastrointestinal bleeding in PXE has occurred as early as 18 years of age. In cases of gastrointestinal hemorrhage, the physician should almost automatically look for the skin changes of this syndrome just as one should look for Kayser-Fleischer rings in patients with liver disease, and for cutaneous telangiectasia in these same patients with gastrointestinal hemorrhage. Some patients visit many different clinics, seeking the cause of bleeding. Some have repeated abdominal explorations and repair of some lesion, such as hiatal hernia, which may or may not be incidental. The reports of massive gastrointestinal hemorrhage during pregnancy in three women with PXE[104,120] suggest that pregnancy has an aggravating influence. Nellen and Jacobson[106] noted flushing of the skin lesions with each episode of hematemesis.

In addition to gastrointestinal bleeding, the types of hemorrhage by location include subarachnoid, retinal, renal, uterine,[76] bladder, and nasal. Spontaneous hemarthroses occur.[76] Excessive bleeding from cuts of the skin does not seem

to be a problem, although hemorrhages in the skin lesions have been described,[21,47] Foerster's patient[20] sought medical advice because of purpura on the legs, and later on the left forearm. At the age of 16 years, one of the patients in my series (R. E. H., J.H.H. 193470) had a severe illness diagnosed as "black (hemorrhagic) measles." It is possible that the connective tissue disease was responsible for the hemorrhagic manifestations of the measles. Subarachnoid hemorrhage is commonly a cause of death.

The incidence of hypertension is probably high enough to make it worthy of consideration as a genuine component of this disease syndrome. It may be the result of vascular disease, of the PXE type, in the renal vessels, but this is pure speculation. The occurrence of hypertension is unfortunate because of its aggravating influence on the tendency to hemorrhage. In one patient,[15] 29 years old, intercranial "berry" aneurysm occurred in association with skin changes and angioid streaks. Scheie and Hogan[113] had a similar case. Another patient (E. W., J.H.H. 69818), seen in the past in Johns Hopkins Hospital and twice reported,[34,56] has since died of cerebral hemorrhage at the age of 43 years. Severe hypertension and pronounced albuminuria were persistently present in the last few years of life. Rosenheim[111] tells me of a case of PXE in a teen-ager, with severe hypertension and with calcification of both renal arteries.

Calcification in peripheral arteries (both arms and legs) has been determined radiologically by a number of observers, including Sanbacka-Holström,[57] Zentmayer,[84] Silvers,[60] Silvers and Wolfe,[61] Carlborg,[9] Scheie,[58] and Wolff.[81] Calcification, probably also of vascular location, is sometimes demonstrated in the choroid plexus[76,113] by skull x-ray. It was demonstrated in the siphon of the internal carotid artery in a 30-year-old patient of this series and in reported cases.[84,113] In a 31-year-old European woman living in South Africa, Nellen and Jacobson[106] demonstrated calcification of the coronary arteries radiographically. (Calcification of the falx cerebri and of the pineal was also present.) A 34-year-old brother with skin lesions had coronary thrombosis. Scheie and Hogan[113] described a case of PXE with "bilateral calcified carotid artery aneurysms." Hypercholesterolemia is not a necessary factor in the premature vascular change, although its presence probably exaggerates pathologic alterations. We have one patient (J. C., 279288) with typical cutaneous and fundal changes of PXE and equally typical Leriche syndrome (thrombotic obliteration of the bifurcation of the aorta) for which successful homografting was performed. In another patient, a 48-year-old woman (Fig. 77), there is extensive calcification in the abdominal aorta. Both manifestations may bear no relation to the PXE.

Dilatation of the aorta has been remarked on in several of the cases. This was the case, for instance, in Joffe's 30-year-old patient[35] and in the 35-year-old, normotensive patient of Marchionini and Turgut.[48] Whether this finding bears a direct relationship to the fundamental defect is unclear. Case 9 of Carlborg[9] demonstrated marked dilatation (phlebectasia) of the jugular veins.

Psychiatric disorders seem to occur with abnormally high frequency in these patients. Whether these can be explained on the basis of cerebral vascular changes is difficult to state. Certainly the high incidence of neurologic abnormalities is attributable to the vascular disease and hypertension. The nature of the neurologic abnormalities will not be discussed in detail because they are highly variable, yet

per se not unlike what one customarily encounters with advanced arteriosclerosis and/or hypertension. The unusual feature is the relatively early age at which the neurologic accidents and deterioration occur.

PATHOLOGY

In the skin, the characteristic changes occur in the deeper and middle zones of the corium (Fig. *76F*). Large aggregations of material with the staining property of elastic fibers dominate the field. This material is granular for the most part, but in places rodlike structures more closely resembling fragmented collagen bundles are seen. Tuberculoid areas with giant cells[70,79] occur in the area of degeneration (see Fig. 2-C in reference 7). Calcification of the degenerated material occurs to a pronounced degree. This was established by Finnerud and Nomland,[19] using the von Kossa stain, and by Lobitz and Osterberg,[45] using microincineration. Actual bone formation is claimed.[3]

Most histologic studies of the eye[8,22,29,40,77] have shown basophilia and tears in the lamina elastica of Bruch's membrane; Benedict[4] and Law[43] failed to find these, however. Most observers, furthermore, have found advanced sclerotic changes in the choroidal vessels. When tears are present in Bruch's membrane, scar tissue tends to occupy the breaks or extend through beneath the pigment epithelium.[22] The breaks are probably the site of the streaks seen on funduscopic examination. Basophilia of the lamina elastica is encountered not infrequently in the eyes of older individuals; it occurs more regularly and at a younger age in PXE. Descemet's membrane of the cornea has chemical, physical, and tinctorial resemblances to the lamina elastica of Bruch's membrane. However, clinical or histologic evidence of involvement of the cornea has apparently not been observed in PXE.

Gross and histologic studies of the cardiovascular system are few. In the original case of Balzer,[1] whitish thickening of the endocardium of the right atrium was described, as well as plaques of the same description on the pericardium and on the ventricular endocardium. Histologically, degeneration, thought to involve elastic elements, was demonstrated at these sites and in the walls of the pulmonary alveoli. (I have observed identical findings in one of two autopsied cases described in detail below.) At least three other necropsy cases have been reported in detail in the literature. In Prick's case[38,55] the patient had hypertension and died at the age of 45 years of a cerebrovascular accident. Histologic changes interpreted as degeneration of elastic fibers were described in the coronary, renal, pancreatic, uterine, cutaneous, and mesenteric arteries as well as the splenic trabeculae, hepatic veins, and Bruch's membrane of the eye. In the patient of Urbach and Wolfram,[75] a 49-year-old man, who died with a Korsakoff-type psychosis and who had widening of the aorta, as seen by x-ray examination, identical histologic changes were found in the brachial, cutaneous, and cerebral arteries and in Bruch's membrane. They also described and illustrated histologic changes in the aorta, which are, in my opinion, probably merely those seen in the senile aorta, sometimes even at the age of 49 years. Coffman and Sommers[89a] thought there were specific aortic changes in their patient: Furthermore, these authors attributed valvular disease to PXE; mitral stenosis in one individual was thought to have this basis.

Carlborg[9] recorded autopsy observations made by another physician without

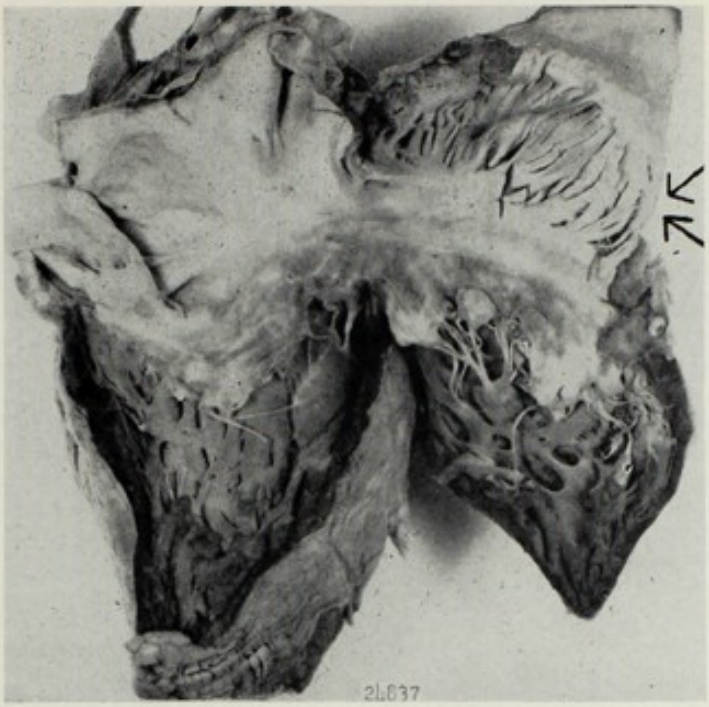


Fig. 79*A*.

Fig. 79*B*.

Fig. 79*A*. The right side of the heart in Case 1. There is an abnormal, pearly thickening of the endocardium, with yellowish, irregularly nodular lesions in the area indicated by the arrows. The latter lesions look not unlike those in the skin.

Fig. 79*B*. Enlarged view of part of heart shown in Fig. 79*A*.

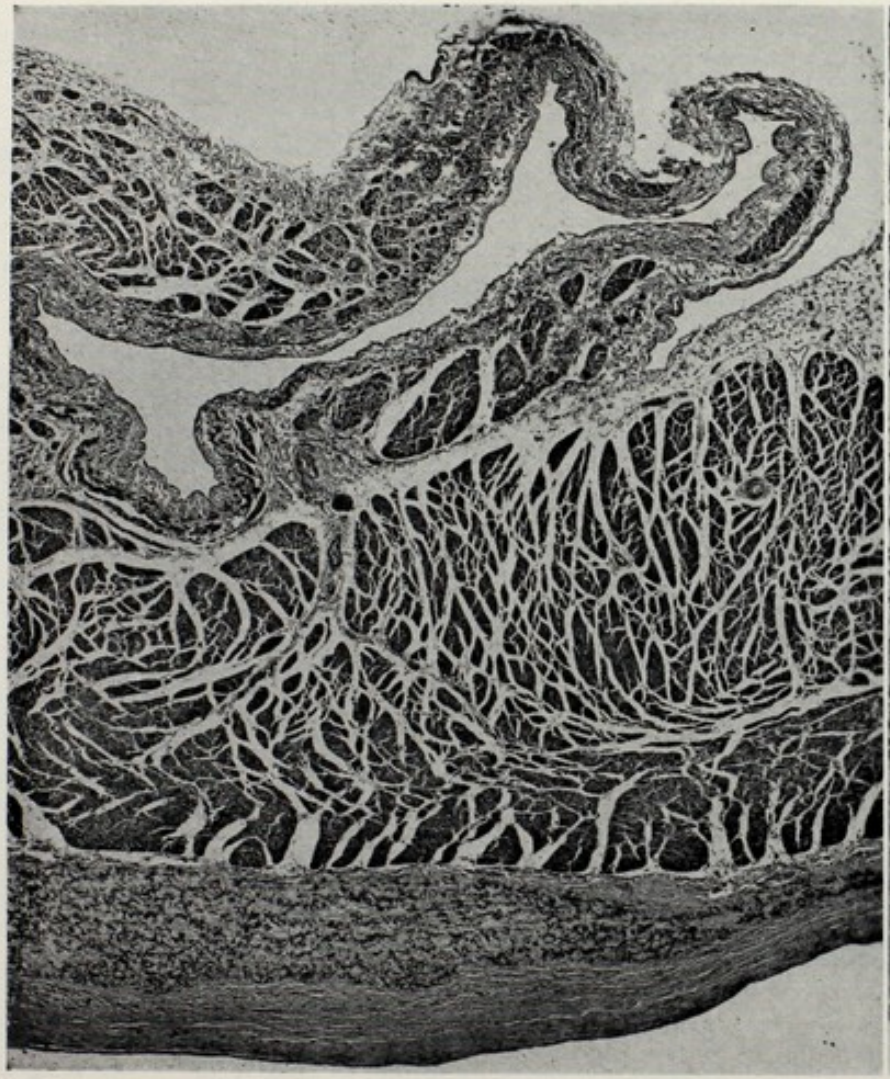


Fig. 79*C*.

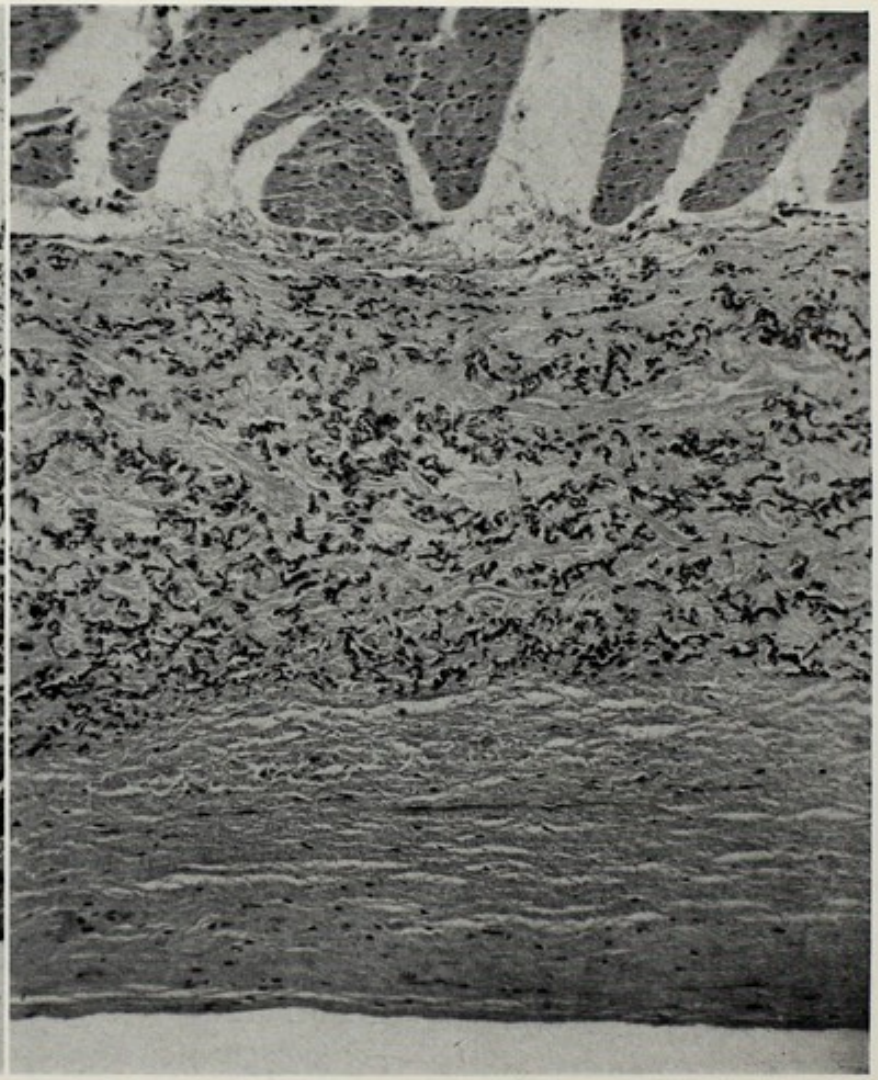


Fig. 79*D*.

Fig. 79*C*. Case 1 (cont'd). Wall of right atrium. (×25; hematoxylin and eosin stain.) On the endocardial surface (below) one of the opaque, elevated plaques is seen in section. On the epicardial surface a branch of a cardiac vein is seen.

Fig. 79*D*. Enlarged view of one part of the field in Fig. 79*C*. (×100; hematoxylin and eosin stain.) Striking similarity to the changes in the skin is evident (see Figs. 76*F* and 76*G*).

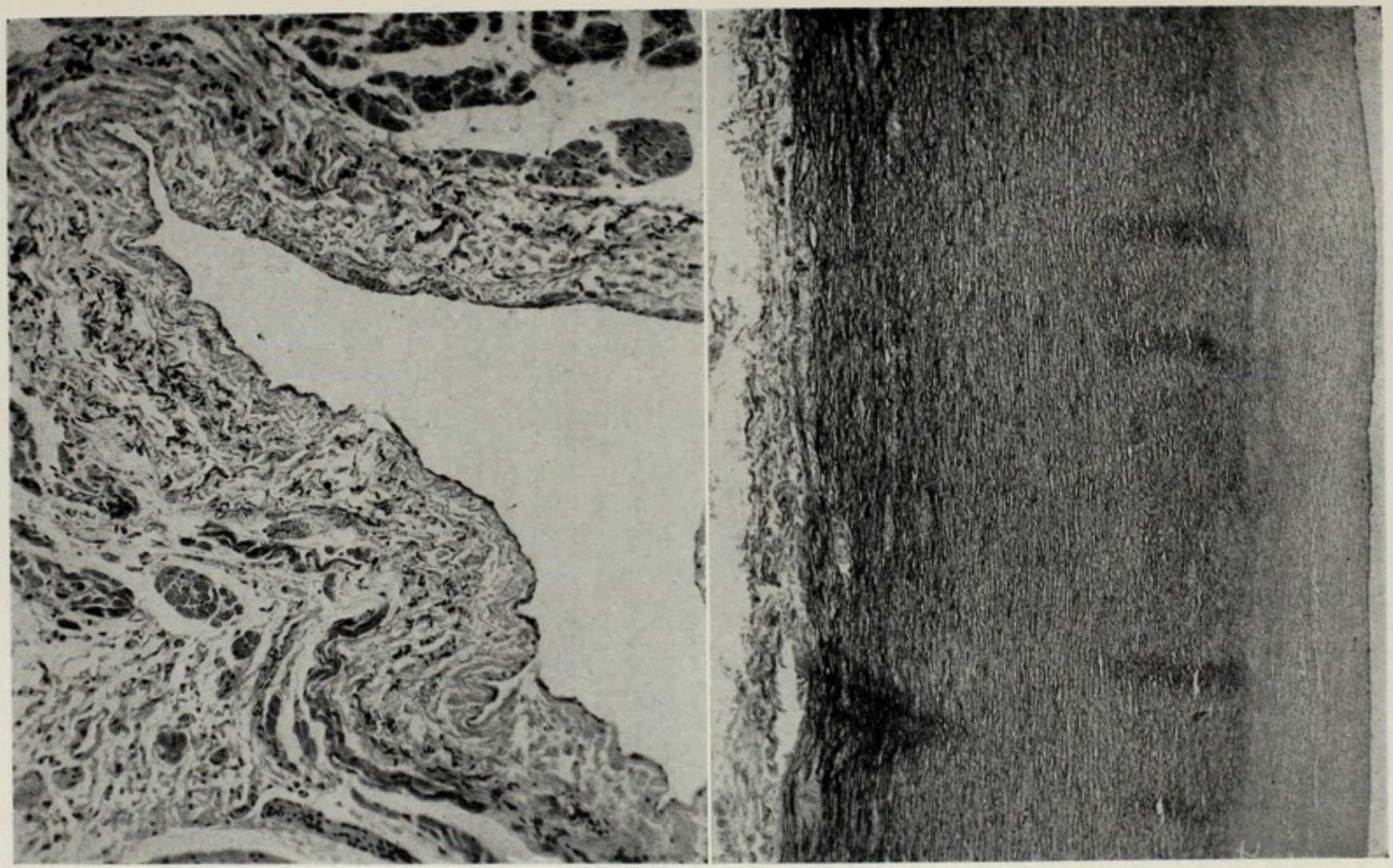


Fig. 79*E*.

Fig. 79*F*.

Fig. 79*E*. Case 1 (cont'd). Enlarged view of another part of the field in Fig. 79*C* to show the changes in the wall of the vein, which again are identical to those in the skin and endocardium. (×100; hematoxylin and eosin stain.)

Fig. 79*F*. Elastic fiber stain of aorta. (×50.) The intima (on right) is thickened but the media shows no striking disorganization.

particular knowledge of, or attention to, this syndrome. Klein[40] also reported an autopsied case. Two other autopsied cases are described in full below.

In the original case, Balzer[1] described degenerative changes involving presumably the elastic fibers in the walls of the pulmonary alveoli. However, the patient was a 49-year-old stonemason, who died of extensive pulmonary tuberculosis. This may have been responsible for any changes observed in the lungs. Furthermore, in the autopsied cases of Prick[55] and Urbach,[75] no abnormality of pulmonary elastic tissue was found. One can only speculate about the possible basis of a miliary mottling of one lung field described in the x-ray examination of one patient[81] and observed in both lung fields of one of my patients (C. T., J.H.H. 582989). It is possible that repeated small interstitial hemorrhages with resultant hemosiderosis are responsible. Calcification in small vessels is another possible explanation. In this same patient, there are no evidences of pulmonary hypertension, and studies of pulmonary function show no definite abnormality. In patients studied by Van Embden Andres,[76] no abnormality of residual air volume, maximum breathing capacity, and vital capacity was discovered.

In the thyroid arteries removed during thyroidectomy there were described[38] abnormalities of the type seen in small coronary arteries in the first autopsied case below. Scheie and Freeman[58] biopsied the ulnar artery in one case and described "elastic tissue degeneration" with compensatory muscular hypertrophy. Without illustration, Kaplan and Hartman[37] described degeneration of elastic elements, especially internal elastic lamella, in the vessels of the stomach removed in a 23-year-old white woman because of gastrointestinal bleeding. Beadlike microaneurysms were also present. Woo and Chandler[120] report similar findings. In one case of Revell and Carey[56] there were changes demonstrated in the peritonsillar tissues.

Many of the patients have advanced and premature arterial changes indistinguishable from ordinary atherosclerosis and arteriosclerosis. It is not legitimate to argue that these are not integral components of PXE. PXE sets the stage for the development of these changes, unusually early in life and in unusually severe degree.

If PXE is truly a dystrophy of collagen (viz. seq.), it seems a bit peculiar that the collagen matrix of bone does not participate in the basic abnormality of this syndrome. The occasional association of Paget's disease of bone with PXE is the only suggestion of bone involvement.

THE BASIC DEFECT

Whether PXE is a dystrophy of elastic fibers or of collagen fibers has been much debated. Certainly the degenerate material which develops in the skin has certain tinctorial characteristics of elastic fibers.

The evidence that PXE is an abiotrophy of collagenous rather than elastic fibers is as follows[32,76]: (1) Normally the skin contains relatively few elastic fibers. Elastin makes up only about 2 per cent of the dry weight of skin.[18] Collagen, on the other hand, constitutes about 72 per cent. The few elastic fibers present are concentrated immediately beneath the epidermis, and serve, according to one view,[18] a principal function of attaching the epidermis to the corium. (A defect in these fibers[68] may be responsible for the lesions of epidermolysis bullosa. This point is moot, however.) The lesions of PXE are located in the deeper layers of

the corium and are more extensive than can be accounted for on the basis of the normal amount of elastic fibers in the skin. The skin of the soles and palms is more liberally supplied with elastic fibers, but PXE lesions do not occur there ordinarily. (2) The arteries predominantly involved are the so-called muscular arteries, the media of which contains collagenous fibers but little elastic tissue. (3) The tunica elastica interna of these vessels (except in one report[37]) remains intact. (4) Except for their orceinophilia, most of the abnormal fibers resemble collagen fibers more than elastic fibers, because of their width. (5) Electron microscopic studies[74] reveal that the dystrophic fibers, although abnormal in other respects, have the characteristic 640 Å. periodicity of collagen. It appears, then, that in PXE the collagen may undergo dystrophic chemical or physicochemical changes, with resulting acquisition of the tinctorial characteristics of elastic fibers. (6) There has been no acceptable clinical or pathologic evidence of abnormality arising from a defect of elastic tissue in the lungs.

Gillman and his co-workers[24] make important observations on what appears to be a rather widely occurring phenomenon. This they term "elastotic degeneration of collagen fibers." Irradiation, trauma, and aging (Fig. 80) appear to be responsible. In addition to degeneration of existing collagen fibers, the authors admit the possibility that there may be a disturbance of formation of new collagen fibers, resulting in simulation of elastic fibers. By means of a battery of many staining procedures the authors showed that there are distinct differences between "normal" elastic fibers of skin and arteries and "elastotically degenerated" collagen fibers at the same site. Although no studies of PXE were made, the important observations of the South African group are probably pertinent in connection with this hereditary syndrome: "elastotic degeneration" of collagen can occur on either an acquired or a hereditary basis. In both, fragmentation and calcification occur. Gillman and his colleagues[24] maintain that Mallory's phosphotungstic acid-hemotoxylin stain differentiates the presumed degenerated collagen of PXE from normal elastic fibers.

Tunbridge and his co-workers[74] noted that enzymatic digestion of skin increases "elastic staining" and results in an increase in amorphous material. Keech and Reed,[96] working in the same group, using electron microscopy, conclude that by a variety of means, physical, chemical, and enzymatic, one can produce so-called "moth-eaten" fibers (MEF) from either collagenous or elastic fibers, that MEF represent an intermediate form, and finally that "collagen and elastin are not two separate and distinct entities but are probably intimately associated in vivo."

The view that collagen is the source of the degenerated material has been challenged and the earlier "elastic theory" defended by Rodnan and his associates[110] and Moran and Lansing,[105] who in histochemical studies, studies by elastase digestion and microincineration, and examinations by fluorescence and electron microscopy concluded that there is a striking resemblance to elastic tissue in the following respects: brilliant autofluorescence, lack of periodicity in ultrastructure, lability to elastase, inhibition of affinity for elastic tissue dyes following methylation, and strong proclivity to calcium incrustation.

Findlay[18] reported that the enzyme elastase removes the degenerate material from sections of skin from PXE patients. An earlier objection was that elastase is not entirely specific, e.g., it is said[30] to dissolve mucoproteins, behaving, therefore, fundamentally as a mucase. Furthermore, other studies[2] with elastase indicate some

effects on normal collagen. More recently elastase has been purified, and it has been demonstrated[102,112] that elastase digestion is relatively specific for elastic tissue.

The argument that insufficient elastic fiber is normally present to account for the relatively large amount of degenerate material is disputed by Moran and Lansing,[105] who feel that there are sufficient elastic fibers in the deeper layers of the corium and further suggest that proliferation of elastic fibers may occur in this disease. They point to the occurrence of macrophages and giant cells[70,107] as a characteristic more of degenerate elastic fiber than of collagen. A similar reaction in

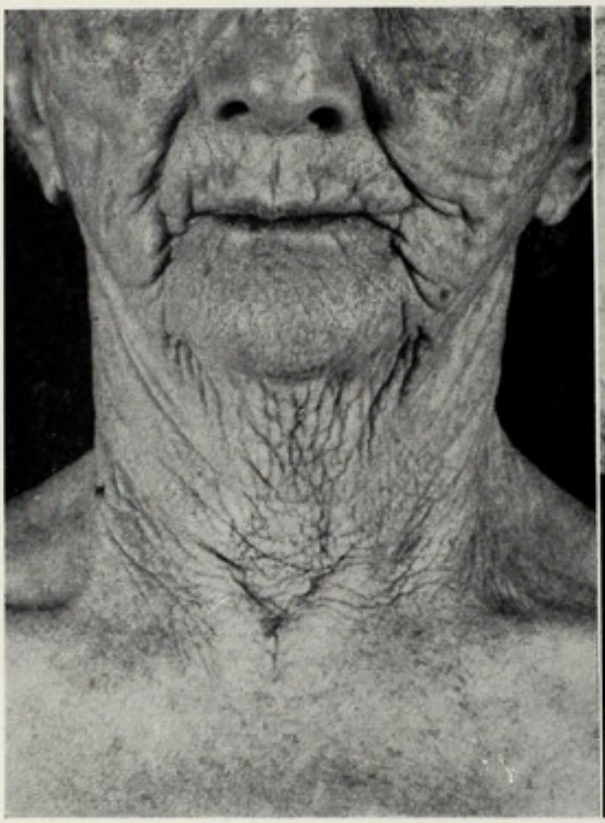


Fig. 80*A*.

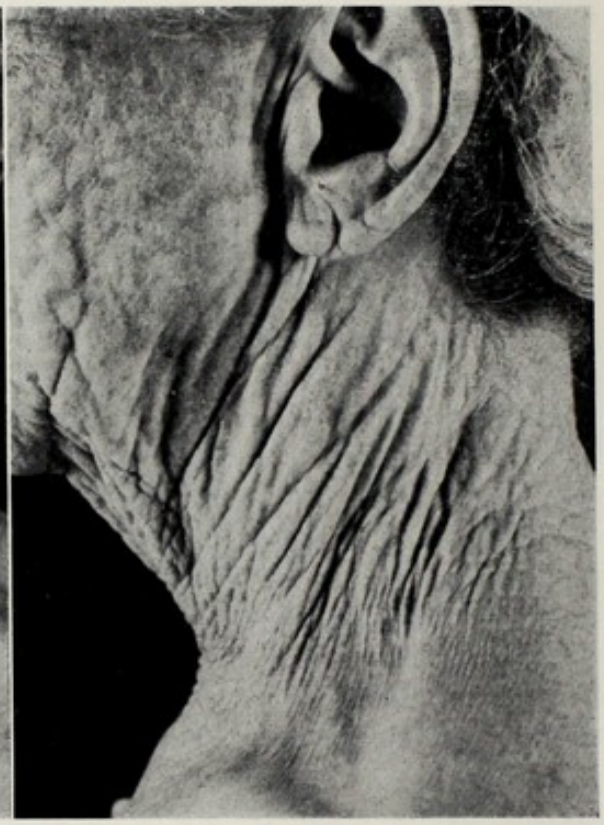


Fig. 80*B*.

Figs. 80*A*-80*F*. Senile elastosis. A. H. (775457), 73-year-old female, was admitted because of bleeding from the lower bowel. The changes in the skin resemble those of PXE but differ in the relative absence of changes in the axillae (Fig. 80*D*). The changes on the hands Fig. 80*C*) are more striking than those usually seen in PXE. There were no angioid streaks in the fundi, and the peripheral arteries showed very little calcification. The histologic appearance (Figs. 80*E* and 80*F*) probably is distinct from that in PXE. Note that there is very little granular material. In Fig. 80*E* is presented the results of hematoxylin and eosin stain of the skin biopsy. Note the broad ribbons of connective tissue fibers, suggesting fragmented collagen. In Fig. 80*F* is presented the orcein stain of the same tissue. Both are at ×100 magnification. The cause of the lower bowel bleeding has not been identified.

the lung, presumably to degenerated elastic tissue, described by Walford and Kaplan,[118] was referred to by Moran and Lansing.

Moran and Lansing[105] state that there is "a definite increase in collagenous tissue in the involved areas." They suggest that it would be easy, under these circumstances, to conclude that all fibers had the electron microscopic characteristics of collagen, simply through inaccurate selection of the fields of study.

Potentially very important observations have been made by Weidman and

associates,[78] Pautrier,[52] and Lever[44]: young asymptomatic individuals may show in the skin abundant, irregularly branching, thick, nonfragmented fibers with the tinctorial characteristics of elastic fibers. The implication has been that these are individuals who would subsequently develop typical PXE and/or are members of kinship containing other definite cases. However, to my knowledge, this implication has not been established except possibly in one patient of Van Embden Andres,[76] who had central chorioretinitis of the type seen in PXE, and by skin biopsy "hyperplasia of elastic fibers without elastorrhexis." If it is further confirmed that these individuals with what Weidman calls "juvenile elastoma" are indeed instances of

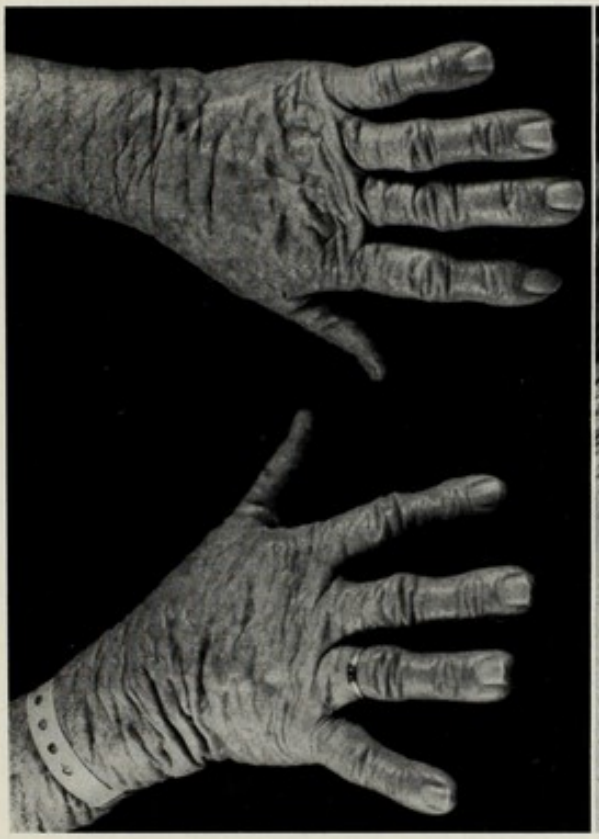


Fig. 80*C*.

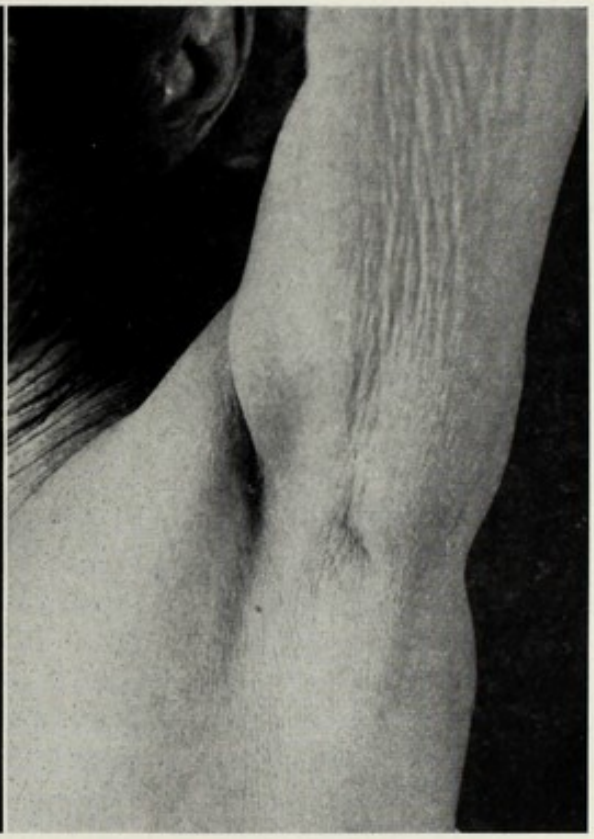


Fig. 80*D*.

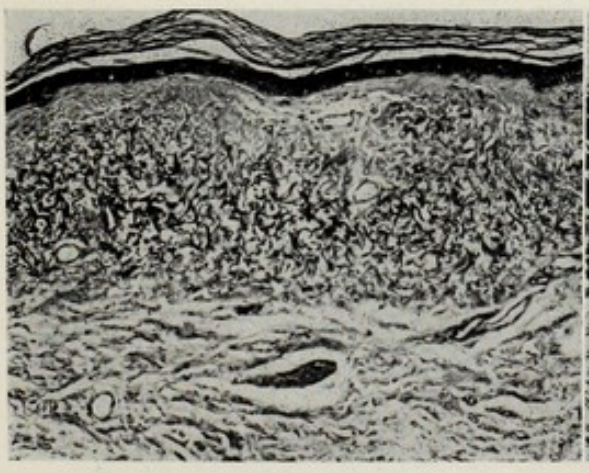


Fig. 80*E*.

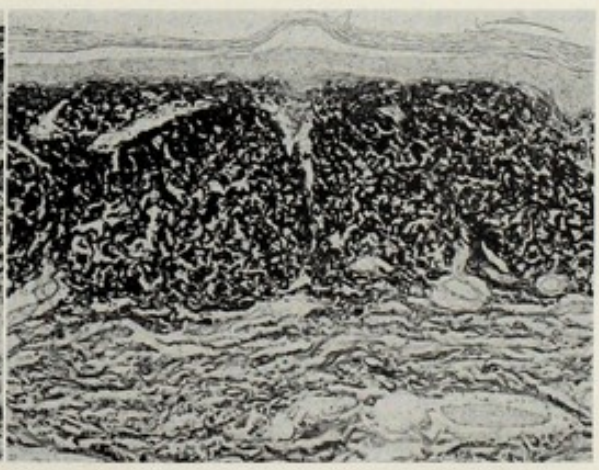


Fig. 80*F*.

Figs. 80*C*-80*F*. For legend see opposite page.

predegeneration PXE, it would mean that a quite unique type of connective tissue fiber is produced in these persons and undergoes degeneration with physiologic stresses. It would mean, furthermore, that the efforts to relate the basic defect to collagen or to elastica is pointless. I find it difficult to believe that these cases of Weidman and others are related to PXE, mainly because there should be identifiable, in one and the same individual, areas of as yet nondegenerate "elastoma" and other areas of typical PXE.

The pathogenesis of the angioid streaks is unsettled.[13] The theory propounded by Kofler[42] in 1917 is that breaks in Bruch's membrane explain this finding. After reviewing the matter, Cowper[13] recently concluded that the original view (that the primary difficulty is a degeneration and sclerosis of the choroidal arteries with secondary changes in the retina and in Bruch's membrane) seems more consistent with the known facts.

Whatever the element of connective tissue basically affected, certain it is that the clinical behavior is that of an abiotrophy. The predominant involvement of areas of the skin exposed to maximum wear and tear, such as flexion folds, belt line,[5] pressure points, etc., is striking. Szymanski and Caro[65] describe a lesion at a site of trauma. It is remarkable that no clinical or pathologic changes in the joints have been encountered. (Gold[91] described Still's disease in a child with PXE, but the association may have been a coincidence.)

INCIDENCE AND INHERITANCE

PXE probably occurs quite generally without particular racial distribution. The two autopsied patients at Johns Hopkins Hospital (see below) were both Negroes and at least one other Negro patient with PXE has been seen here (J. C., 279288). In addition to being described in natives of many European countries including Turkey,[48] it has been observed in Japanese.[50]

Some indication of the incidence of PXE is provided by the fact that 125 cases of associated skin and fundus changes and sixty-eight cases of skin changes alone had been described previous to 1940.[67]

There can be no doubt of the hereditary nature of PXE. However, the genetics of PXE is not firmly established. Part of the difficulty resides in the fact that manifestations appear only more or less late in life. Furthermore, the changes are often subtle (see Fig. 78). Finally, the ocular changes may be asymptomatic and require special examination for demonstration.

Touraine[71,72] found forty-six families with more than one affected person—a total of 104 persons. Inheritance as an autosomal recessive is suggested but by no means proved by the occurrence of multiple cases in individual sibships and by the rarity of its occurrence in successive generations.[33,48,62] For example, Rodnan and his associates[110] did skin biopsy studies in three affected siblings (sisters 35 and 49 years, brother 47 years of age) and four unaffected members of three generations of the same family. Biopsies in both parents of the affected sibs were normal. In 1941, Scholz[59] could find reports of eighteen cases of angioid streaks in which one or more siblings were similarly affected; in four cases the parental union was consanguineous. In the case of the skin changes, consanguinity was noted in the two sisters reported by Throne and Goodman[69]; the parents were first cousins. Up to 1933, Cockayne[12] could find reports of five kinships which contained multiple cases

and in which the status of full sibships was given. In these families there were thirteen affected and twelve normal persons. In eight families containing more than one affected person, there were four males and thirteen females affected. In general, a preponderance of females affected by this syndrome has been noted. (In my own group of eighteen patients, ten are female.) Touraine[71-73] counted fifty-two women among seventy-three cases of the skin changes; among ninety-two cases of both eye and skin changes there were also fifty-two women. Thus, in a total group of 165 cases, 104 were women. Cockayne[12] concluded: "This condition will almost certainly prove to be recessive to the normal, and partially sex-limited to the female." The ratio of about 1:1 of affected to unaffected sibs rather than the 1:3 ratio expected of a recessive trait may be in part an artefact of ascertainment: many sibships which, so far as the genetic make-up of the parents was concerned, might have had an affected individual, did not because the sibship was too small for the one-in-four probability to express itself; on the other hand, only sibships which contained an affected member were recognizable and included in the tabulation.

Témine,[67] writing in 1940, pointed to reports in the literature of the occurrence of this disorder in a parent and offspring seven times and in three successive generations twice. Since 1940 there has been at least one report[51] of direct transmission. Occasional descriptions of affection in successive generations is not necessarily proof of dominant inheritance. The experience with alkaptonuria, of which both recessive and dominant forms have been thought to exist, has taught us caution in the interpretation of fragmentary pedigree data. The marriage of an individual with the homozygous state of a recessive trait to a heterozygous carrier may, of course, result in affected children. A few decades ago when the frequency of consanguineous marriages was appreciably greater the world over and when isolates were commonplace, the occurrence of pedigrees suggesting dominant inheritance was, as one might expect, relatively frequent.

Multiple cases occurred in a single sibship twenty-four times. Parental consanguinity was noted in at least six reports and was specifically stated to be absent in seven. A brother, a sister, and their maternal aunt were reported by Jones and his co-workers[36] as affected.

The series of twenty patients studied personally by Van Embden Andres[76] is of interest. Of these patients thirteen were male. Fourteen families were represented. More than one sib was affected in at least four of these families. There was no example of the disease in successive generations of one family. Consanguinity was present in the case of three of the fourteen pairs of parents. Hartung[92] reported on PXE in the children of a consanguineous mating. Furthermore, two close relatives showed minor change in the fundi in the form of irregular coloration. Minor changes should be sought in persons who may be heterozygotes.

In the family reported by Anderson[85] one sibship consisted of four brothers, all affected, and one sister unaffected. A male first cousin was also affected; his only sib, a sister, was normal. The two sibships with affected members were the offspring of sisters. In discussing the pedigree, Harold Falls of Ann Arbor raised the question of inheritance as a sex-linked recessive. The fundus picture was predominantly that of choroidal sclerosis.

In summary, it must be pointed out that there may be more than one genotype of what phenotypically is PXE. However, the most commonly occurring type is inherited as an autosomal recessive with partial limitation to the female.

MISCELLANEOUS CONSIDERATIONS

There is no definitive treatment for this disorder. Tocopherol (vitamin E) was said[63] to effect dramatic improvement in the skin and eyes of one patient. Others[87] also claim improvement. No beneficial effect was observed in one patient studied. Good cosmetic effects have been reported by plastic surgeons,[11,54] who have removed the loose, excess skin around the neck, which may be distressingly unsightly, especially in women. Fig. 77 demonstrates a patient in whom plastic surgery was performed.

It seems conceivable that a funduscopic picture indistinguishable from that of the angioid streaks seen with PXE may occur on other bases than this particular genetic one. For example, angioid streaks are encountered in association with Paget's disease. However, PXE is the most common basis for the finding. Scholz[59] stated that, previous to 1941, 59 per cent of 139 cases of streaks had the skin condition. On the other hand, in a series collected from the literature, Goedbloed[25] found fifty-seven cases with skin involvement among sixty-seven with streaks, and Sanbacka-Holström[57] found eighty-seven out of one hundred cases. Although angioid streaks may occur with either PXE or Paget's disease, there are, to my knowledge, only two adequately described instances of the occurrence of changes in the skin, fundus, oculi, and bones of the same individual. Woodcock[82] described a 54-year-old white man with bilateral angioid streaks, skin changes of PXE in the axillae, and Paget's disease as manifested by cephalic enlargement, bowing of the legs, spontaneous fractures, renal calculi, and characteristic radiologic changes. Sanbacka-Holström[57] refers in passing to such a patient, and there are loose references to the coincidence of the three manifestations in textbooks and reviews. Shaffer and his colleagues[114] have described a 58-year-old woman with angioid streaks and evidences of Paget's disease from the age of 40 years. The only skin lesion was an "elliptical lemon-yellow plaque 1.0 cm. long on the left posterior axillary fold." The histology was typical of PXE. One sister had mild Paget's disease. Dr. David Paton[107a] tells me of two patients he has studied in which there is association of PXE skin changes, angioid streaks, calcification in peripheral vessels, and Paget's disease of bone.

There may be reason (see Chapter 8) to think that there is no fundamental relationship between PXE and at least one common variety of Paget's disease. One reason is that Paget's disease usually behaves like an autosomal dominant. Furthermore, it is more frequent in men.

Reduced pulse wave velocity in the vessels of the extremities was found in the great majority of cases of PXE,[9,76] and the pulse wave was of reduced amplitude and plateau configuration. There may be a loss of the dicrotic notch. The peak tends to be attained more slowly than is normal.[88,114] Bäfverstedt and Lund[88] found these changes in a 9-year-old child with well-developed cutaneous changes but no angioid streaks. Of particular significance is the fact that arteriography revealed no abnormality; the striking changes observed must be attributed to changes in the media, since there was not, as there is in many of the older patients, obstructing atherosclerotic lesions to provide a possible alternative explanation.

Clinically, the skin changes in senile elastosis (Fig. 80) are somewhat similar to those of PXE. The conclusion of Percival and his associates[53] was that this too is a dystrophy of collagen rather than of elastic fibers. Histologically, however,

senile elastosis is characterized by a diffuse involvement in the superficial parts of the corium, less marked basophilia to hematoxylin and eosin stain, the absence of involvement in more or less circumscribed areas of any one section, and, finally, the usual lack of fragmentation of the dystrophic fibers into granular material. I know of no evidence of a hereditary background in senile elastosis. It may represent a breakdown of basically normal collagen occurring as a result of acquired factors but occurring along lines somewhat similar to that by which genetically weak collagen breaks down under much less stringent stresses.

CASE REPORTS, WITH AUTOPSY OBSERVATIONS

CASE 1. R. K. (J.H.H. 156572), a Negro man, born in 1891, died in 1954 from accidental mercury poisoning.

The family history was largely unknown. He had no children.

About 1932 the patient was found to have a positive serologic test for syphilis, and treatment with arsenicals, mercury, and bismuth was given at another hospital where he had gone because of failing vision. He was first seen at this hospital in 1938 because of continuing dimming of vision. He had worn spectacles for about six years with no apparent staying of the visual failure in spite of several changes. Bilaterally the entire macular area was the site of atrophy and scarring. The vessels were normal. Running out from each disc in all directions were wide, branching, brownish streaks. About the neck he was noted to have many linear 4 or 5 mm. yellowish papules about 1 mm. thick. These were arranged parallel to the clavicle and coalesced in many areas to form short streaks several centimeters in length. The diagnosis of PXE with angioid streaks was made and confirmed by skin biopsy (Skin Path. No. 9606). On general examination the patient was noted to have an arcus senilis bilaterally. The blood pressure was 170/90 mm. Hg. No pulse changes or circulatory abnormality in the legs or elsewhere was detected by history or examination.

The patient was visited in his home several times late in 1953 but refused to come to the hospital for investigation of the connective tissue disorder. He was now almost completely blind. For many years he had been suffering from intermittent swelling and pain of the proximal interphalangeal joints. He had also had much pain in the tibial and calf areas as well as the knees. He had developed ulcerations of the pretibial area and made a practice of soaking these with bichloride of mercury solution. He took Dolcin, a proprietary analgesic, for his aches and pains. Several years previously he had been told that he had diabetes mellitus.

About 6 A.M. on Jan. 11, 1954, the patient went to take Dolcin tablets for relief of pains in both shins and, because of his faulty vision, took three tablets of bichloride of mercury instead. He first noted burning of his mouth and thereafter pain in the mid-epigastrium, accompanied by the vomiting first of a large amount of clear yellow fluid and later of bright red blood of unknown quantity. Severe peristent bloody diarrhea followed. He was seen by his family physician, who could record no blood pressure and sent him to the hospital, where he arrived about eight hours after the accidental ingestion of mercury.

The patient had been noted to be easily confused in recent years, and therefore the exact details of the history of the final days of life are not entirely certain.

Physical examination revealed the skin of the neck, axillae, inguinal areas, and anterior abdominal wall to be nodular and leathery. It was strikingly inelastic, but this may have been in part the result of dehydration. All interphalangeal joints showed fusiform enlargement, and nodules were located around the knuckles. The heart showed a loud blowing apical systolic murmur and rather numerous extrasystoles. Femoral pulses were present, but none could be felt in the popliteal fossae or feet. There were two large depigmented scars with some unhealed and scabbed areas on both pretibial prominences.

The patient was virtually anuric throughout his hospital stay and died on the sixth hospital day. The diagnosis of mercury poisoning was corroborated by the finding of 6 mg. Hg^{++} per 20 ml. of stomach fluid taken at admission. Death occurred despite the use of BAL and supportive measures.

Autopsy (No. 24837) was performed ten hours after death by Dr. H. M. Hill. (In spite of the delay, fibroblasts grew out in tissue culture from explants of skin and of aortic adventitia.) The body weighed 50 kilograms and measured 168 cm. in length. The changes in the skin and joints and the juxtarticular nodules were observed as during the clinical examination.

The heart weighed 325 grams and did not appear to be enlarged. A most impressive finding was thickening of the endocardium of the right atrium. This was somewhat yellowish, and over the trabecular ridges there were perculiar nodular thickenings. The posterior leaflet of the tricuspid valve had a smooth, thickened, firm, rolled edge without excrescenses. The aortic leaflet of the mitral valve was similarly thickened at the edge, and there was marked calcific change at its attachment. The coronary ostia were normal, but everywhere the coronary arteries were exceedingly sclerotic and calcified, with reduction of their caliber to little more than a pin point.

The aorta was of normal caliber, with only minimal atherosclerosis in the abdominal portion and normal elasticity by gross test. There were marked calcification and narrowing of the femoral, popliteal, and posterior tibial arteries. These changes were particularly striking at areas of bending, such as in the popliteal fossae. The posterior tibial arteries were exceedingly beaded. The vessels at the base of the brain were sclerotic. Grossly and histologically there were characteristic changes of mercury poisoning in the kidney and gastrointestinal tract.

Histologically, the corium, the sclera, and the subendocardial area of the right atrium showed the same changes which have been frequently described previously in the skin of patients with PXE. Faintly basophilic (by hematoxylin and eosin stain), fragmented material was concentrated most heavily in the mid-dermis. Present in great abundance in the clinically involved areas and present sparsely elsewhere, it had the tinctorial characteristics of elastic tissue. The popliteal and coronary arteries showed marked medial and intimal sclerosis and calcification. As demonstrated in Fig. 79*C*, branches of the coronary sinus near the right atrium showed changes in the media comparable to those in the atrial endocardium and corium. Small arteries showed similar changes.

Comment. Of particular interest are the histologic changes in the endocardium of the right atrium and in the sclera. Neither site normally demonstrates more than a very sparse distribution of elastic fibers. The deforming arthropathy is likewise of special note. The manifestation has not been commented on previously in cases of PXE. Unfortunately, no histologic studies of either joint structures or juxtarticular nodules were performed.

Case 2. C. J. (J.H.H. 292168), a Negro woman, born in 1896, was seen here on several occasions in 1943 and died at the hospital on Jan. 1, 1944.

Her mother died of a stroke at the age of 48 years. The patient had four brothers: two died in childhood, one shortly after discharge from the Army in World War I, and one was living and well. The patient had sixteen children, of whom seven were living in 1943. No other instance of PXE was known to have occurred in the family. However, the family has not been traced and studied with this point specifically in mind.

The patient's eyesight had always been poor but had become worse in the last year of life. She noted tarry stools on several occasions and complained at times of epigastric burning. Early in 1943 she developed anginal symptoms for the first time.

Examinations revealed a blood pressure of 190/110 mm. Hg. There was evidence of marked weight loss (about 50 pounds in one year). The skin everywhere was very loose, due in part to PXE. The neck veins were full and dilated but not the arm veins. The heart was enlarged to the left anterior axillary line. The patient was so debilitated that carcinoma was suspected. Directly above the umbilicus there was a plaque of smooth skin containing small, hard, elevated nodular areas. Histologically (Skin Path. No. 5157) there were changes typical of PXE. The fundi showed no angioid streaking, but there were fairly marked hypertensive and sclerotic changes in the arteries, many hemorrhages, and in the macula area many yellow shiny plaques.

Total serum protein was 8.3 Gm. per cent, of which 5.5 Gm. per cent was globulin. Hemoglobin was 10.5 Gm. per cent. Electrocardiogram revealed left axis deviation, left ventricular strain pattern, and prolonged A-V conduction. On chest x-ray examination, calcification in superficial vessels in the left axilla was demonstrated. The aorta was dilated and tortuous. On

barium swallow the esophagus was relaxed and tortuous. Gastric analysis revealed normal acidity.

After four months away from the hospital, during which time she had become steadily weaker, the patient was brought back to the hospital with massive leg edema and ascites and with Cheyne-Stokes breathing. She died two hours later.

Autopsy (No. 18717) revealed marked generalized arteriosclerosis, arteriosclerotic and arteriolosclerotic nephritis with Kimmelstiel-Wilson type lesions of glomeruli, and coronary sclerosis with myocardial scarring. In addition, there were tuberculous peritonitis and caseous obstruction of the thoracic duct with chylous ascites. The aorta was atheromatous, with a few ulcerations.

Comment. Hyperglobulinemia was probably due to tuberculosis. It was of interest that Kimmelstiel-Wilson lesions occurred in this nondiabetic individual. In general, premature and severe arteriosclerosis dominated the clinical picture and the findings at autopsy. What relation there may have been between the skin changes and the vascular disease is unclear. In general, however, this patient demonstrates the early and rapidly progressive dissolution of the vascular system characteristic of patients with PXE.

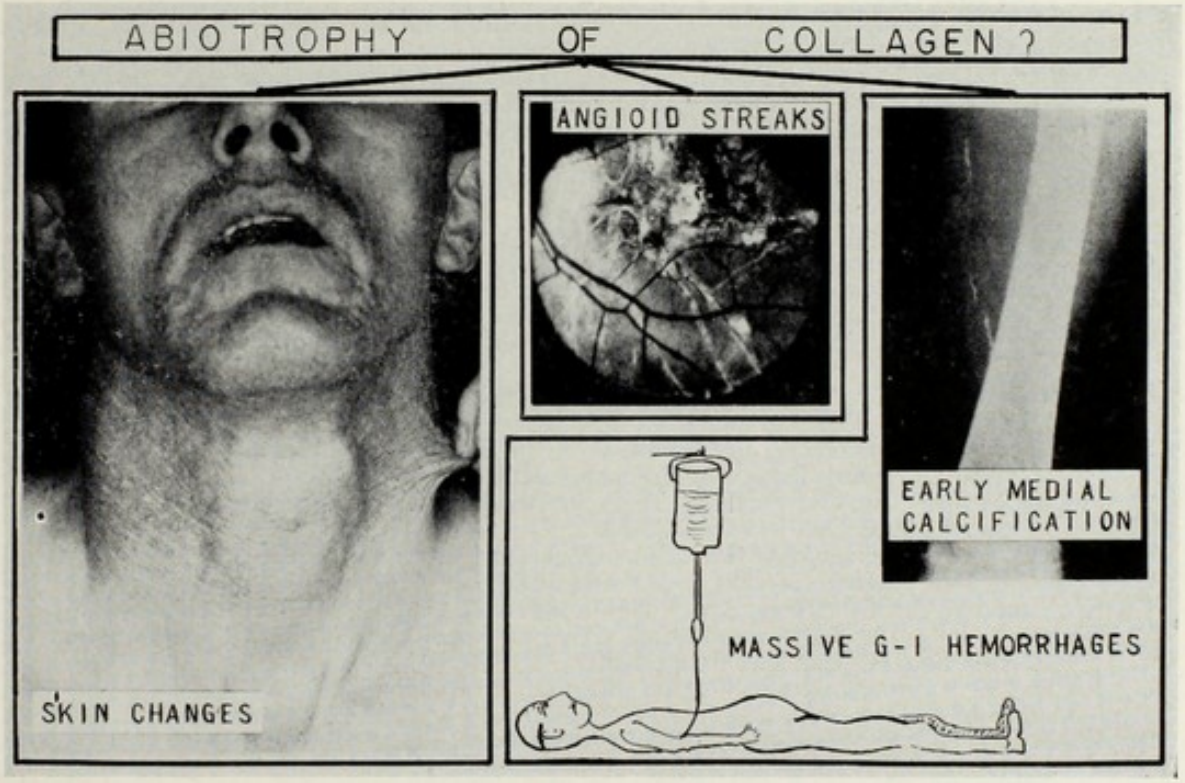


Fig. 81. Pedigree of causes in PXE.

SUMMARY AND CONCLUSIONS

The clinical manifestations of pseudoxanthoma elasticum include (1) characteristic skin changes, occurring especially in areas of wear and tear; (2) angioid streaks of the fundus oculi; and (3) hemorrhage, symptoms of ischemia, and hypertension, resulting from arterial degeneration. Gastrointestinal hemorrhage is the complication of most importance to the internist.

Evidence on the nature of the basic defect is reviewed, and it is concluded that collagen is most suspect as being primarily involved in this abnormality which behaves as an abiotrophy. However, the subject cannot be considered closed.

Descriptions of two autopsied cases are added to the meager information available on the state of tissues other than the skin and eye. In one case, changes completely unique to PXE were demonstrated in the endocardium of the right atrium and in the coronary vessels. Both cases had advanced atherosclerosis and arteriosclerosis.

This disorder is most often inherited as an autosomal recessive. Partial sex limitation appears to result in its occurrence in females more frequently than in males.

REFERENCES

1. Balzer, F.: Récherches sur les charactères anatomiques du xanthelasma, Arch. de physiol. **4** (3rd ser.) :65, 1884.
2. Banga, I.: Thermal Contraction of Collagen and Its Dissolution With Elastase, Nature **172**:1099, 1953.
3. Beeson, B. B.: Pseudoxanthoma Elasticum (Darier) Associated With Formation of Bone, Arch. Dermat. & Syph. **34**:729, 1936.
4. Benedict, W. L.: The Pathology of Angioid Streaks in the Fundus Oculi, J.A.M.A. **109**:475, 1937.
5. Benedict, W. L., and Montgomery, H.: Pseudoxanthoma Elasticum and Angioid Streaks, Am. J. Ophth. **18**:205, 1935.
6. Besnier, E., and Doyon, P. A. A.: Annotations et appendices en traité des maladies de la Peau, de Kaposi, ed. 2, 1891, p. 336. Cited by Darier.[14]
7. Bronner, A.: Considérations sur la syndrome de Groenblad et Strandberg, Bull. Soc. franç. dermat. et syph. **61**:78, 1954.
8. Böck, J.: Zur Klinik und Anatomie der gefässähnlichen Streifen im Augenhintergrund, Ztschr. Augenh. **95**:1, 1938.
9. Carlborg, U.: Study of Circulatory Disturbances, Pulse Wave Velocity and Pressure Pulses in Larger Arteries in Cases of Pseudoxanthoma Elasticum and Angioid Streaks. A Contribution to the Knowledge of the Function of the Elastic Tissue and the Smooth Muscles in Larger Arteries, Acta med. scandinav. Supp. **151**:1-209, 1944.
10. Chauffard, A.: Xanthélasma disséminé et symétrique sans insuffisance hépatique, Bull. Soc. méd. Hôp. Paris **6** (ser. 3) :412, 1889.
11. Chikelair, G. F.: Pseudoxanthoma Elasticum Treated Surgically, Plast. & Reconstruct. Surg. **12**:152, 1953.
12. Cockayne, E. A.: Inherited Abnormalities of the Skin and Its Appendages, London, 1933, Oxford University Press and Humphrey Milford, pp. 319-321.
13. Cowper, A. R.: Angioid Streaks; Tears in Bruch's Membrane or Pigmented Choroidal Vessels? Arch. Ophth. **51**:762, 1954.
14. Darier, J.: Pseudoxanthoma Elasticum, Monatschr. f. prakt. Dermat. **23**:609, 1896.
15. Dixon, J. M.: Angioid Streaks and Pseudoxanthoma Elasticum With Aneurysm of the Internal Carotid Artery, Am. J. Ophth. **34**:1322, 1951.
16. Doyne, R. W.: Choroidal and Retinal Changes; the Result of Blows on the Eyes, Tr. Ophth. Soc. U. Kingdom. **9**:129, 1889.
17. Felsher, Z.: Collagen, Reticulin, and Elastin; *In* Rothman, S.: Physiology and Biochemistry of the Skin, Chicago, 1954, University of Chicago Press, chap. 17, p. 391 ff.
18. Findlay, G. H.: On Elastosis and the Elastic Dystrophies of the Skin, Brit. J. Dermat. & Syph. **66**:16, 1954.
19. Finnerud, C. W., and Nomland, R.: Pseudoxanthoma Elasticum; Proof of Calcification of Elastic Tissue; Occurrence With and Without Angioid Streaks of the Retina, Arch. Dermat. & Syph. **35**:653, 1937.
20. Foerster, O. H.: Transactions of the Dermatological Conference of the Mississippi Valley, Arch. Dermat. & Syph. **30**:280, 1934.
21. Franceschetti, A., and Roulet, E. L.: Le syndrome de Groenbald et Strandberg (stries angioides de la rétine et pseudoxanthome élastique) et ses rapport avec les affections du mésenchyme, Arch. d'opht. **53**:401, 1936.
22. Friedenwald, J. S., and others: Ophthalmic Pathology; an Atlas and Textbook, Philadelphia, 1952, W. B. Saunders Co.
23. Giesen, H.: Beitrag zur Kasuistik des Pseudoxanthoma elasticum, Inaugural Dissertation, Erlangen, 1936.
24. Gillman, T., Penn, J., Bronks, D., and Roux, M.: Abnormal Elastic Fibers; Appearance in Cutaneous Carcinoma, Irradiation Injuries, and Arterial and Other Degenerative Connective Tissue Lesions in Man, Arch. Path. **59**:733, 1955.
25. Goedbloed, J.: Syndrome of Groenblad and Strandberg; Angioid Streaks in the Fundus Oculi, Associated With Pseudoxanthoma Elasticum, Arch. Ophth. **19**:1, 1938.

26. Grönblad, E.: Angioid Streaks—Pseudoxanthoma Elasticum; vorläufige Mitteilung, Acta ophth. **7**:329, 1929.
27. Guenther, E.: Untersuchen über den Pulsverlauf in der grösseren distalen Arterien der Extremitäten in einigen Fällen von Pseudoxanthoma elasticum cum angioid streaks (Grönblad-Strandbergs Syndrom), Acta med. scandinav. **123**:482, 1946.
28. Haber, H.: Histological Report on a Case Shown by Dr. Fenner at the Royal Society of Medicine, Proc. Roy. Soc. Med. (Sect. Derm.) **42**:136, 1949.
29. Hagedoorn, A.: Angioid Streaks, Arch. Ophth. **21**:746, 935, 1939.
30. Hall, D. A., Reed, R., and Tunbridge, R. E.: Structure of Elastic Tissue, Nature **170**:264, 1952.
31. Hallopeau and Laffitte: Nouvelle note sur un cas de pseudo-xanthome élastique, Ann. de dermat. et syph., Paris **4**:595, 1903.
32. Hannay, P. W.: Some Clinical and Histopathological Notes on Pseudoxanthoma Elasticum, Brit. J. Dermat. **63**:92, 1951.
33. Hubler, W. R.: Two Cases of Pseudoxanthoma Elasticum, Arch. Dermat. & Syph. **50**:51, 1944.
34. Jacoby, M. W.: Pseudoxanthoma Elasticum and Angioid Streaks; Report of a Case, Arch. Ophth. **11**:828, 1934.
35. Joffe, R., and Joffe, M.: Zur Aetiologie des Pseudoxanthoma elasticum (Darier), Arch. Dermat. u. Syph. **165**:713, 1932.
36. Jones, J. W., Alden, H. S., and Bishop, E. L.: Pseudoxanthoma Elasticum. Report of Five Cases Illustrating Its Association With Angioid Streaks of the Retina, Arch. Dermat. & Syph. **27**:423, 1933.
37. Kaplan, L., and Hartman, S. W.: Elastica Disease; Case of Grönblad-Strandberg Syndrome With Gastrointestinal Hemorrhage, Arch. Int. Med. **94**:489, 1954.
38. Kat, W., and Prick, J. J. G.: A Case of Pseudoxanthoma Elasticum With Anatomicopathological Irregularities of the Thyroid Arteries, Psychiat. en neurol. bl. (Amsterdam) **44**:417, 1940.
39. Kissmeyer, A., and With, C.: Clinical and Histological Studies on the Pathological Changes in the Elastic Tissue of the Skin, Brit. J. Dermat. **34**:175, 1922.
40. Klein, B. A.: Angioid Streaks; a Clinical and Histopathologic Study, Am. J. Ophth. **30**:955, 1947.
41. Knapp, H.: On the Formation of Dark Angioid Streaks as an Unusual Metamorphosis of Retinal Hemorrhage, Arch. Ophth. **21**:289, 1892.
42. Kofler, A.: Beiträge zur Kenntnis der Angioid Streakes (Knapp), Arch. Augenh. **82**:134, 1917.
43. Law, F. W.: A Contribution to the Pathology of Angioid Streaks, Tr. Ophth. Soc. U. Kingdom **58**:191, 1938.
44. Lever, W. F.: Histopathology of the Skin, ed. 2, Philadelphia, 1949, J. B. Lippincott Co., p. 56.
45. Lobitz, W., and Osterberg, A. E.: Pseudoxanthoma Elasticum; Microincineration, J. Invest. Dermat. **15**:297, 1950.
46. Lynch, F. W.: Elastic Tissue in Fetal Skin, Arch. Dermat. & Syph. **29**:57, 1934.
47. Marchesani, O., and Wirz, F.: Die Pigment-streifenerkrankung der Netzhaut—das Pseudoxanthoma elasticum der Haut—eine Systemerkrankung, Arch. Augenh. **104**:522, 1931.
48. Marchionini, A., and Turgut, K.: Ueber Pseudoxanthoma elasticum hereditarium, Dermat. Wchnschr. **114**:145, 1942.
49. Morrison, W. H.: Osteitis Derformans With Angioid Streaks, Arch. Ophth. **26**:79, 1941.
50. Ohno, T.: Ueber Pseudoxanthoma elasticum und dessen Histologie, Arch. Dermat. u. Syph. **149**:420, 1925.
51. Osborn, R. A., and Olivo, M. A.: Pseudoxanthoma Elasticum in Mother and Daughter, Arch. Dermat. & Syph. **63**:661, 1951.
52. Pautrier, L. M.: À propos de deux affections d'élastine du revêtement cutané, témoins d'affections généralisées de l'élastine de tout l'organisme, Arch. belges dermat. et syph. **4**:259, 1948.
53. Percival, G. H., Hannay, P. W., and Duthie, D. A.: Fibrous Changes in the Dermis, With Special Reference to Senile Elastosis, Brit. J. Dermat. **61**:269, 1949.
54. Pickrell, K. L., Kelley, J. W., and Marzoni, F. A.: The Plastic Surgical Treatment of Pseudoxanthoma Elasticum, Plast. & Reconstruct. Surg. **3**:700, 1948.
55. Prick, J. J. G.: Pontine pseudobulbar-paralyse bei Pseudoxanthoma elasticum. Eine clinische anatomische Studie, Doctral treatise, Maastricht, 1938.
56. Revell, S. T. R., Jr., and Carey, T. N.: Pseudoxanthoma Elasticum as a Disseminated Disease, South. M. J. **41**:782, 1948.
57. Sanbacka-Holström, I.: Das Grönblad-Strandbergische Syndrome. Pseudoxanthoma elasticum—angioid streaks—Gefässveränderungen, Acta dermat.-venereol. **20**:684, 1939.
58. Scheie, H. G., and Freeman, N. E.: Vascular Disease Associated With Angioid Streaks of the Retina and Pseudoxanthoma Elasticum, Arch. Ophth. **35**:3, 1946.
59. Scholz, R. O.: Angioid Streaks, Arch. Ophth. **26**:677, 1941.
60. Silvers, S.: Pseudoxanthoma Elasticum With Angioid Streaks of Retina, Arch. Dermat. & Syph. **42**:155, 1940.

61. Silvers, S. H., and Wolfe, H. E.: Pseudoxanthoma Elasticum With Angioid Streaks. The Syndrome of Groenblad and Strandberg, Arch. Dermat. & Syph. **45**:1142, 1942.
62. Stegmaier, O. C.: Pseudoxanthoma Elasticum Assoicated With Angioid Streaks of the Retina, Arch. Dermat. & Syph. **70**:530, 1954.
63. Stout, O. M.: Pseudoxanthoma Elasticum With Retinal Angioid Streaking, Decidely Improved on Tocopherol Therapy, Arch. Dermat. & Syph. **63**:510, 1951.
64. Strandberg, J.: Pseudoxanthoma Elasticum, Zentralbl. Haut u. Geschlechtskr. **31**:689, 1929.
65. Szymanski, F. J., and Caro, M. R.: Pseudoxanthoma Elasticum. Review of Its Relationship to Internal Diseases and Report of an Unusual Case, Arch. Dermat. **71**:184, 1955.
66. Tannenhein, V.: Zur Kenntnis des Pseudoxanthoma elasticum (Darier), Wien. klin. Wchnschr. **14**:1038, 1901.
67. Témine, P.: Contribution à l'étude de l'élastorrhexie systématisée, Paris thesis, Paris, 1940, Jouve & Cie.
68. Terry, T. S.: Angioid Streaks and Osteitis Deformans, Tr. Am. Ophth. Soc. **32**:555, 1934.
69. Throne, B., and Goodman, H.: Pseudoxanthoma Elasticum, Arch. Dermat. & Syph. **6**:419, 1921.
70. Tominaga, B., Harada, S., and Hashimoto, T.: A Case of Pseudoxanthoma Elasticum With Tuberculoid Granulation Tissue, Arch. Dermat. & Syph. **30**:864, 1934.
71. Touraine, A.: L'elastorrhexie systématisée, Bull. Soc. franç dermat. et syph. **47**:255, 1940.
72. Touraine, A.: L'élastorrhexie systématisée, Presse méd. **49**:361, 1941.
73. Touraine, A., and James: Pseudoxanthome élastique (élastorrhexis), Bull. Soc. franç. dermat. et syph. **47**:217, 1940.
74. Tunbridge, R. E., Tattersall, R. N., Hall, D. A., Astbury, W. T., and Reed, R.: The Fibrous Structure of Normal and Abnormal Skin, Clin. Sc. **11**:315, 1952.
75. Urbach, E., and Wolfram, S.: Ueber Veränderungen des elasticum Geweses bei einem autoptisch untersuchten Falle von Groenblad-Strandbergschen Syndrome, Arch. Dermat. u. Syph. **176**:167, 1938.
76. Van Embden Andres, G. H.: Afwijkingen, aan de inwendige organen bij Pseudoxanthoma Elasticum en Angioide Strepen, Groningen, 1952.
77. Verhoeff, F. H.: Histological Findings in a Case of Angioid Streaks, Brit. J. Ophth. **32**:531, 1948.
78. Weidman, F. D., Anderson, N. P., and Ayres, S.: Juvenile Elastoma, Arch. Dermat. & Syph. **28**:183, 1933.
79. Welti, M. H.: Pseudoxanthoma elasticum (Darier) in Verbindung mit einer tuberculoiden Granulationsbildung, Arch. Dermat. u. Syph. **163**:427, 1931.
80. Wilmer, W. H.: Atlas Fundus Oculi, New York, 1934, The Macmillan Co., plate 92.
81. Wolff, H. H., Stokes, J., and Schlesinger, B.: Vascular Abnormalities Associated With Pseudoxanthoma Elasticum, A.M.A. Arch. Dis. Childhood. **27**:82, 1952.
82. Woodcock, C. W.: Transactions of the Cleveland Dermatological Society, Arch. Dermat. & Syph. **65**:623, 1952.
83. Woringer, F.: Sur deux aspects histologiques différents de pseudoxanthome elastique, Bull. Soc. franç. dermat. et syph. **61**:80, 1954.
84. Zentmayer, W.: Angioid Streaks of the Fundus Oculi Observed Over a Period of Thirty-six Years; Report of a Case, Arch. Ophth. **35**:541, 1946.
85. Anderson, B.: Familial Central and Peripapillary Choroidal Sclerosis Associated With Familial Pseudoxanthoma Elasticum, Tr. Am. Ophth. Soc. **46**:326, 1948.
86. Anon.: Obituary of A. Chauffard, Bull. de la soc. franç. d'hist. de la méd. **26**:402, 1932.
87. Ayres, S., Jr.: Discussion of Paper of Shaffer et al.,[114] Arch. Dermat. & Syph. **76**:632, 1957.
88. Bäfverstedt, B., and Lund, F.: Pseudoxanthoma Elasticum and Vascular Disturbances With Special Reference to a Case in a Nine-Year-Old Child, Acta dermat.-venereol. **35**:438, 1955.
89. Burton, D., Hall, D. A., Keech, M. K., Reed, R., Sax, H., Tunbridge, R. E., and Wood, M. J.: Apparent Transformation of Collagen Fibrils Into Elastin, Nature **176**:966, 1955.
89a. Coffman, J. D., and Sommers, S. C.: Familial Pseudoxanthoma Elasticum and Valvular Heart Disease, Circulation **19**:242, 1959.
90. Fontan, P., Méraud, A., and Pfister, R.: Syndrome de Groenblad-Strandberg, Bull. Soc. franç. dermat. et syph. **62**:101, 1955.
91. Gold, S. C.: Still's Disease With Pseudoxanthoma Elasticum, Proc. Roy. Soc. Med. **50**:473, 1957.
92. Hartung, H.: Ueber familiäre angioide Pigmentstreifenbildung des Augenhintergrundes, Klin. Monatsbl. Augenh. **88**:43, 1932.
93. Hermann, H.: Das Grönblad-Strandberg-Syndrom in erbbiologischer Betrachtung, Ztschr. Haut. u. Geschlkr. **20**:314, 1956.

94. Hoffman, D.: Kardiovasculäre Erkrankungen beim Strandberg-Grönblad-Syndrom, Ztschr. menschl. Vererb.-u. Konstitutionslehre **33**:389, 1956.
95. Kaplan, L., and Hartman, S. W.: Elastica Disease. Case of Grönblad-Strandberg Syndrome With Gastrointestinal Hemorrhage, A.M.A. Arch. Int. Med. **94**:489, 1954.
96. Keech, M. K., and Reed, R.: Enzymatic Elucidation of the Relationship Between Collagen and Elastin; an Electron-Microscopic Study, Ann. Rheumat. Dis. **16**:35, 1957.
97. Keech, M. K., Reed, R., and Wood, M. J.: Further Observations on the Transformation of Collagen Fibrils Into "Elastin" and Electron-Microscopic Studies, J. Path. & Bact. **71**:477, 1956.
98. Kennedy, C. B.: Discussion of Paper of Shaffer, et al.,[114] Arch. Dermat. & Syph. **76**:631, 1957.
99. Kupfer, C.: Personal communication.
100. Lee, M. M. C.: Physical and Structural Age Changes in Human Skin, Anat. Rec. **129**:473, 1957.
101. Levy, G., and Brewer, R. L.: Pseudoxanthoma Elasticum. Report of a Case, Am. J. Med. **26**:157, 1959.
102. Lewis, U. J., Williams, D. E., and Brink, N. G.: Pancreatic Elastase; Purification, Properties and Function, J. Biol. Chem. **222**:705, 1956.
103. Loria, P. R., Kennedy, C. B., Freeman, J. A., and Herrington, V. M.: Pseudoxanthoma Elasticum (Groenblad-Strandberg Syndrome). A Clinical, Light- and Electron-Microscope Study, Arch. Dermat. & Syph. **76**:609, 1957.
104. McCaughey, R. S., Alexander, L. C., and Morrish, J. A.: The Grönblad-Strandberg Syndrome. A Report of Three Cases Presenting With Massive Gastrointestinal Hemorrhage During Pregnancy, Gastroenterology **31**:156, 1956.
104a. McKusick, V. A.: Hereditary Disorders of Connective Tissue, Bull. New York Acad. Med. **35**:143, 1959.
105. Moran, T. J., and Lansing, A. I.: Studies on the Nature of the Abnormal Fibers in Pseudoxanthoma Elasticum, A.M.A. Arch. Path. **65**:688, 1958.
106. Nellen, M., and Jacobson, M.: Pseudoxanthoma Elasticum (Grönblad-Strandberg Disease) With Coronary Artery Calcification, S. Africa M. J. **32**:649, 1958.
107. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, ed. 8, Philadelphia, 1954, Lea & Febiger, p. 747.
107a. Paton, D.: Personal communication.
108. Reinerston, R. P., and Farber, E. M.: Pseudoxanthoma Elasticum With Gastrointestinal Bleeding, California Med. **83**:94, 1955.
109. Rizzuli, A. B.: Angioid Streaks With PXE; a Case Followed With Fundus Photography Over a Period of 27 Years, Am. J. Ophth. **40**:387, 1955.
110. Rodnan, G. P., Fisher, E. R., and Warren, J. E.: Pseudoxanthoma Elasticum: Clinical Findings and Identification of the Anatomic Defect (abstract), Clin. Res. **6**:236, 1958.
111. Rosenheim, M. (London): Personal communication.
112. Rosenthal, T. B., and Lansing, A. I.: Isolation and Assay of Elastase From Pancreatin (abstract), Anat. Rec. **124**:356, 1956.
113. Scheie, H. G., and Hogan, T. F., Jr.: Angioid Streaks and Generalized Arterial Disease, Arch. Ophth. **57**:855, 1957.
114. Shaffer, B., Copelan, H. W., and Beerman, H.: Pseudoxanthoma Elasticum. A Cutaneous Manifestation of a Systemic Disease. Report of a Case of Paget's Disease and a Case of Calcinosis With Arteriosclerosis as Manifestations of This Syndrome, Arch. Dermat. & Syph. **76**:622, 1957.
115. Stecher, R. M.: The Physical Characteristics and Heredity of Short Thumbs, Acta genet. et. statist. med. **7**:217, 1957.
116. Storsteen, K. A., and Janes, J. M.: Arteriography and Vascular Studies in Paget's Disease of the Bone, J.A.M.A. **154**:472, 1954.
117. Teller, H., and Vester, G.: Elektronenmikroskopiche Untersuchungsergebnisse an der kollagenen Interzellularsubstanz des Koriums beim Pseudoxanthoma elasticum, Dermat. Wchnschr. **136**:1373, 1957.
118. Walford, R. L., and Kaplan, L.: Pulmonary Fibrosis and Giant-Cell Reaction With Altered Elastic Tissue; Endogenous "Pneumoconiosis," A.M.A. Arch. Path. **63**:75, 1957.
119. Winer, L. H.: Elastic Fibers in Unusual Dermatoses, Arch. Dermat. & Syph. **71**:338, 1955.
120. Woo, J. C., Jr., and Chandler, F. W.: Pseudoxanthoma Elasticum With Gastric Hemorrhage. Report of a Case, Ann. Int. Med. **49**:215, 1958.

7. THE HURLER SYNDROME

HISTORICAL NOTE

THE DISORDER which is now called, among other names, the Hurler syndrome, is said by Henderson[48] to have been recognized in three siblings by John Thompson of Edinburgh between about 1900 and 1913. Berkhan's case,[128] reported in 1907, may have been the Hurler syndrome. The first definitive description was that of Charles H. Hunter* whose report appeared in the *Proceedings of the Royal Society of Medicine* in 1917, while he was serving in England as a major in the Canadian Army Medical Corps. This beautifully detailed and descriptive report concerned two brothers, 10 and 8 years of age, respectively, who were admitted to the Winnipeg General Hospital in 1915. The habitus was typically dwarfed. There were deafness, widely spaced teeth, short neck, protuberant abdomen with hepatosplenomegaly, inguinal hernias, short, broad, thick, stiff hands, semiflexed knees, and noisy respiration. The elder boy had cardiomegaly and "a distinct diastolic murmur audible in the third and fourth left interspaces close to the sternum . . .; at the apex, a systolic murmur was conducted towards the axilla." Twelve illustrations, including many x-ray films demonstrating typical changes (such as "shoe-shaped" sella), were presented by Hunter. The boys appeared to be normally intelligent; clouding of the cornea was not observed; the spine was straight with loss of the normal contour, but there was no gibbus. We have been able to obtain follow-up information (Fig. 82).

In 1919 Gertrud Hurler of Munich[56] published cases at the suggestion of Professor Meinhard von Pfaundler,[88] who was chief of the University Clinic of Pediatrics and who had presented two patients with this syndrome to the Munich Society for Pediatrics on June 27 of the same year. The patients of Hurler and Pfaundler were infants; gibbus was present, as were corneal clouding and retardation of intellect.

It is surprising that Hunter's beautiful publication received, compared to Hurler's, relatively little attention. Subsequently, even in the English-speaking medical world, it was principally Hurler's paper that was referred to and the

*Hunter was later Professor of Medicine in the University of Manitoba, Winnipeg. He died March 18, 1955, at the age of 82 years (Canad. M. A. J. **72**:712, 1955).

Fig. 82*A*.

Fig. 82*B*.

Figs. 82*A* and 82*B*. Previously unpublished photographs of the patients Hunter described in 1917.[55] The younger brother (G. B. C., born 1907) died in 1918 of pneumonia, and the elder one (R. W. C., born in 1904) died in 1920 of "dropsy." The youngest sibling (Fig. 82*A*) was apparently unaffected. The characteristic facies and "claw hands" are evident. These brothers are thought to have had the sex-linked recessive form of the Hurler syndrome. (Photographs and follow-up information courtesy Dr. Nancy Gemmell and Dr. L. G. Bell, University of Manitoba, Winnipeg.)

names of Hurler and Pfaundler that became most firmly associated with the syndrome. (A similar situation exists in connection with the Morquio syndrome which was described in England by Brailsford slightly earlier than by Morquio of Montevideo.)

The first case from the United States was that reported by Putnam and Pelkan[164] in 1925 under the title "Scaphocephaly With Malformations of the Skeleton and Other Tissues." The nosography of the Hurler syndrome has now advanced to the point where the limits of the syndrome and its several clinical and pathologic features are reasonably well described, although mildly affected persons are still difficult to identify with certainty except by chemical test (see p. 276). A tabular survey of the cases reported up to 1950 has been presented by Jervis.[63] Emanuel[36] estimated that over 200 cases had been reported by 1954.

Many different names have been suggested for this syndrome. Husler[57] suggested "dysostosis multiplex." Ellis and his co-workers,[34] Cockayne[17] and other English authors used the term gargoylism.* Washington[117] suggested lipochondrodystrophy, believing this to be a disorder of lipid metabolism. This is the term used by the *Cumulative Index Medicus.* However, it is probably a misnomer, as indicated by recent evidence bearing on the basic defect of the disease (see below). This is another instance demonstrating the desirability of using noncommital terms in connection with these syndromes in which the basic defect is as yet unknown. Consistent with my practice with other syndromes discussed in this book, an eponymous designation, *the Hurler syndrome,* has been used here. Equally acceptable are the names of Pfaundler and of Hunter, which are sometimes associated with this condition.

In spite of Hunter's claim to priority, Hurler's name is selected for use because it is the eponym most firmly established in the literature. It is, after all, merely a symbol to indicate a clinical sydrome which is incompletely understood. Although there is some suggestion that what Hunter and Hurler described were genetically and clinically distinct entities *(v. seq.),* it is preferable to consider all these cases one syndrome, the Hurler syndrome, until the basic defect is more accurately known and methods for distinguishing precisely the possible subgroups of the syndrome are available.

In 1952, Brante[11] classified the Hurler syndrome as a mucopolysaccharidosis. The development of views about the basic nature of this disease is discussed below in the section dealing with that particular aspect.

CLINICAL MANIFESTATIONS

The clinical description provided here is based on the findings in twenty patients with the Hurler syndrome seen at the Johns Hopkins Hospital and at the Rosewood State Training School, Owings Mills, Maryland.

The cardinal features of this syndrome are disproportionate dwarfism with a characteristic, grotesque skeletal deformity, limitation of joint motion, deafness,

*This seems an unnecessarily cruel term in view of the fact that the intellect may be little impaired and survival to adulthood is not infrequent. It is scarcely a diagnosis that can be cited to a parent, for example. Families sometimes raise legitimate objections to such statements (all too frequent in the literature) as these: "He is a typical gargoyle"; "there are three gargoyles in this family."

hepatosplenomegaly, cardiac abnormality (either from the outset or developing with the passage of years), clouding of the cornea, and mental retardation. The last two features need not be present, especially in the earlier stages.

The patient frequently appears normal at birth but, with the passage of the first year (a "symptom-free interval"), becomes manifestly abnormal. The lines along which development occurs in these patients is so similar from patient to patient that, as in the Marfan syndrome, myotonic dystrophy, Mongolism, and other conditions, the patients, even though unrelated, tend to resemble each other more than their unaffected siblings.

The head is large and bulging, often with prominent scalp veins in the case of small children. The bridge of the nose is flattened, creating a saddle appearance. The tip of the nose is broad with wide nostrils. Hypertelorism is usual. The skull is often scaphocephalic,* i.e., shaped like the keel of a boat, seemingly as a result of premature closure of the sagittal and metopic sutures with hyperostosis in those areas. This hyperostosis often creates a longitudinal (sagittal) ridge which may cross the forehead. Radiologic changes in the sella turcica in the form of unusual length and shallowness and an anterior "pocketing" (Figs. 85*C* and 86*C*) are striking and virtually pathognomonic. This type of sella is called "shoe-shaped" by Ullrich,[111] who found in other cases a shallow "shell-shaped" or a deeper "bowl-shaped" fossa.

The lips are large and patulous. These, with the apathetic facies, the open mouth, and frequently enlarged tongue, may lead to a false diagnosis of cretinism. In general, the facial features are coarse and ugly. The teeth are usually small, stubby, widely spaced, and malformed. In many of the cases there is hypertrophy both of the bony alveolar ridges and of the overlying gums.[22] An actual bone cyst of the alveolar ridge was present in one of Caffey's cases.[14] Chronic "rhinitis" with noisy mouth breathing is virtually universal in this group of patients. X-ray films of the facial bones usually show marked deformities which are probably responsible for the nasal manifestations. On lateral view of the skull, it can often be seen that a mass of adenoid tissue in the nasopharynx is narrowing or obliterating the normal air shadow.

The neck is exceedingly short, and the thorax, on which the head appears to rest directly, is deformed. There is usually a flaring of the lower rib cage, probably due in part to the hepatosplenomegaly. Kyphosis with gibbus in the lower thoracic and upper lumbar area is likely to be present. Myelograms in one case revealed partial obstruction of the spinal canal at the level of the gibbus. Radiologic examination usually shows a wedge-shaped deformity of the body of the vertebrae with an anterior hooklike projection, so-called beaking of the vertebrae. In some instances there appears to be anterior herniation of the nucleus pulposus with pressure atrophy of the upper anterior margin of the subjacent vertebral body (usually the second lumbar). This atrophy may be the mechanism of the anterior hook in some cases (see Figs. 83*C* and 88*E* and reference 14). The gibbus is often the first observed abnormality. When the infant begins to sit, he is likely to assume a posture like a cat's in sitting (Fig. 83*B*), the "cat-back deformity."

*There is usually no difficulty in distinguishing the Hurler syndrome from the specific conditions given the generic names *acrocephaly* and *scaphocephaly*,[87] although in the earlier days of the nosography of Hurler's syndrome such confusion did occur.[61]

The hands are usually broad, with stubby fingers.[102] The fifth fingers are often bent radially, and, in general, there is likely to be at least partial flexion contracture of the fingers as well as of the larger joints. The terminal phalangeal bones are often hypoplastic by x-ray examination and this is evident clinically. Clawhand is present in most patients more than a few years old (see Figs. 82, 86, and 88). This deformity results from stiffening of the phalangeal joints, with inability of full extension.

Limitation in extensibility of joints is usually striking.[56] This feature may be due in part to deformity of the joint surfaces but more likely to changes in the

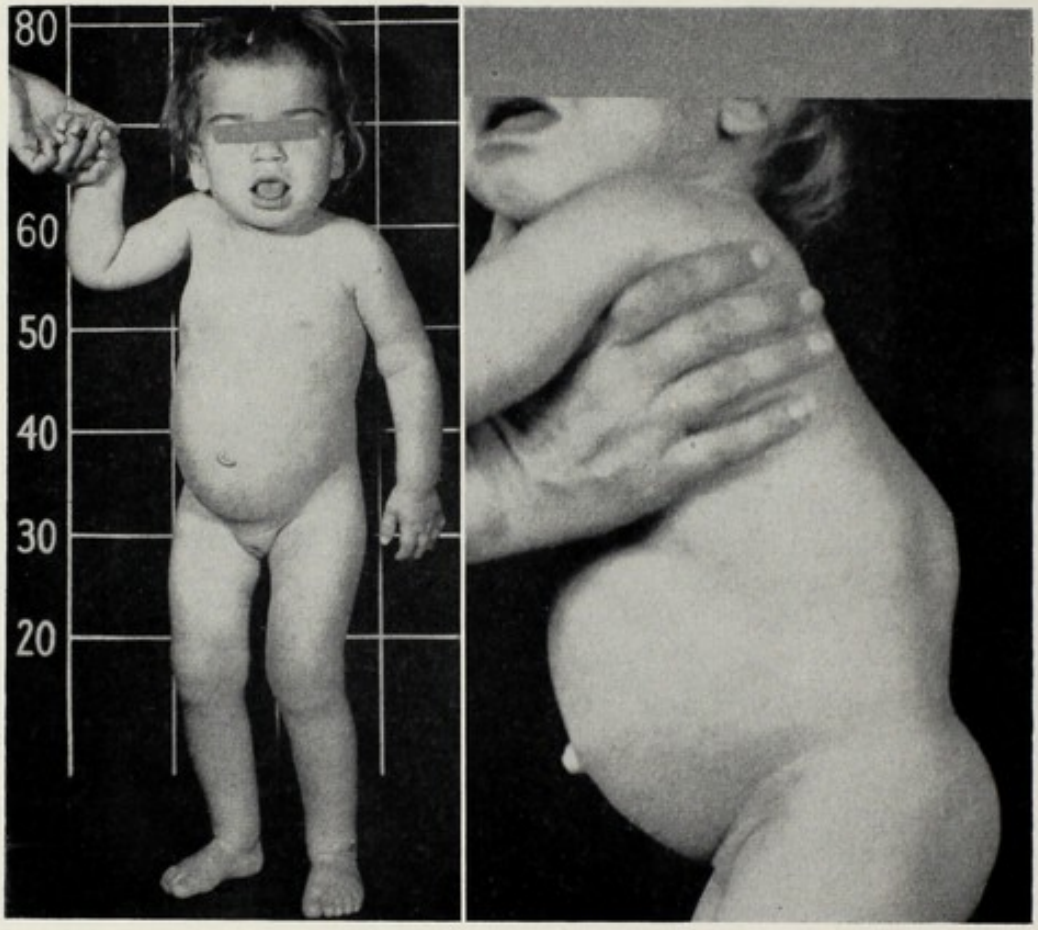


Fig. 83*A*. Fig. 83*B*.

Figs. 83*A*-83*C*. Thirty-four-month-old child (S. S., B3747). The child is mentally retarded. The liver and spleen are enlarged, the corneas cloudy, and the teeth short, abnormally formed, and late in appearing. The fingers show flexion contractures as do other joints to a slight extent. There is constant nasal congestion so that the patient is a mouth-breather. Most of these features are evident in Fig. 83*A*. In Fig. 83*B* the lower dorsal, upper lumbar gibbus is evident. The skeletal basis for this appearance is shown by the x-ray film of the spine in Fig. 83*C*. Note the lumbar kyphos, beaking of the lumbar vertebrae, the sabre-shaped ribs, and hepatosplenomegaly.

tendons and ligaments surrounding the joints. As a result, the patients often find it necessary to walk on their toes, especially if they have been in bed a good deal. A deformity of the wrist may superficially suggest rickets. However, the stiff joints (along with many other features) help distinguish the Hurler syndrome[52]; the joints in rickets are more limber than normal. The limitation of motion of joints seems to extend to the thorax, which often is relatively fixed in position.[36]

In addition to the radiologic changes already described in the skull and in the vertebral column, the bones of the extremities are abnormal in appearance. Caffey[14] pointed out that metaphyseal changes are minimal and that the predominant change involves the diaphysis. The tubular bones show a swelling of the shaft due to expansion of the medullary cavity. The cortex may be thinned. Changes tend to be more striking in the bones of the arms than in those of the legs. A curious narrowing of the proximal third of the femora to a caliber less than half normal has been noted.[14] The phalangeal bones, for example, are short and misshapened (Fig. 85*C*). The ribs are characteristically broad, sabre-shaped, or spatulate (Figs. 85*A* and 89).

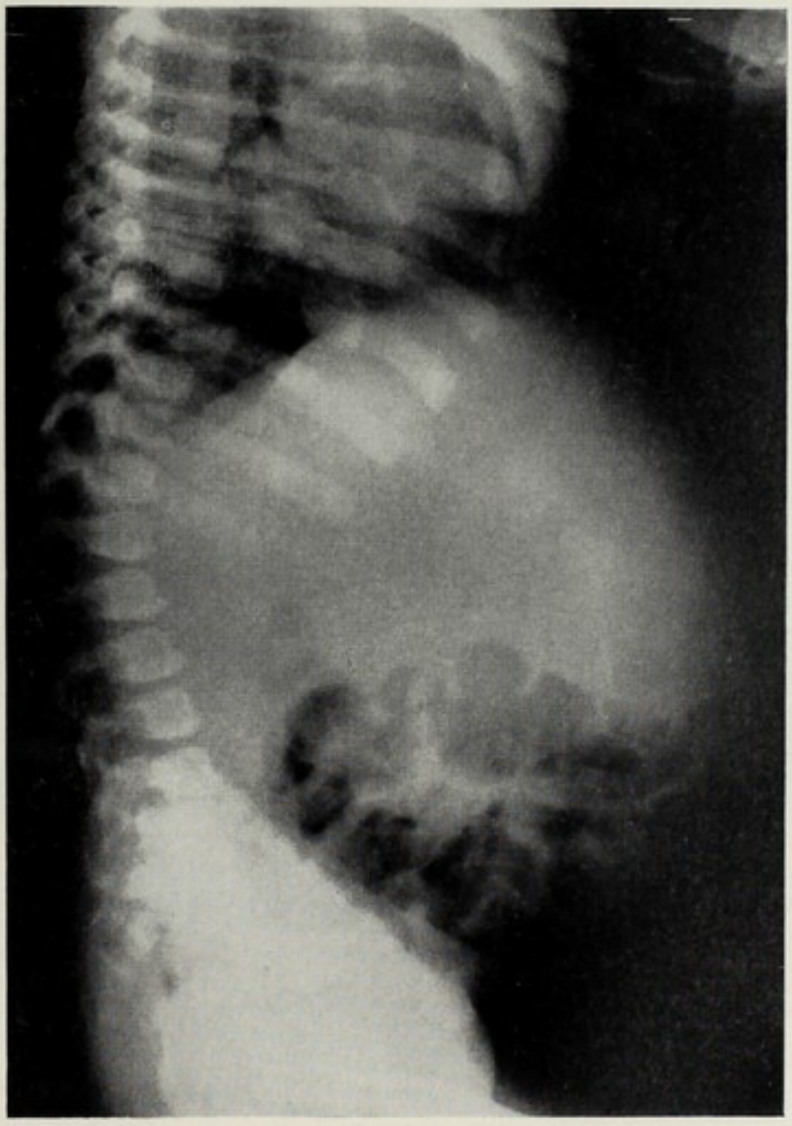


Fig. 83*C*. For legend see opposite page.

Genu valgum, coxa valga, pes planus, talipes equinovarus, and other deformities occur frequently. Hooper's patient[51] was operated upon for talipes equinovarus at the age of 17 years. Deformity of the sternum has been said[58] not to be a feature; however, congenital deformity of one type or another has been seen (Fig. 86).[149] "Funnel chest" was present in one of Hurler's cases[63] and in one of mine.

The abdomen is protuberant, due in part to hepatosplenomegaly, in part to the defect of the supporting tissues. Both liver and spleen may be so large that their lower borders dip into the pelvis. One patient developed pancytopenia and epistaxes, possibly on the basis of hypersplenism.[102] Lindsay[71] described an abnormal hippuric acid test in one patient and, in another, prolonged elevation of galactose in the blood after intravenous injection. The number of patients tested was not stated. Although no systematic study has been made, the impression is

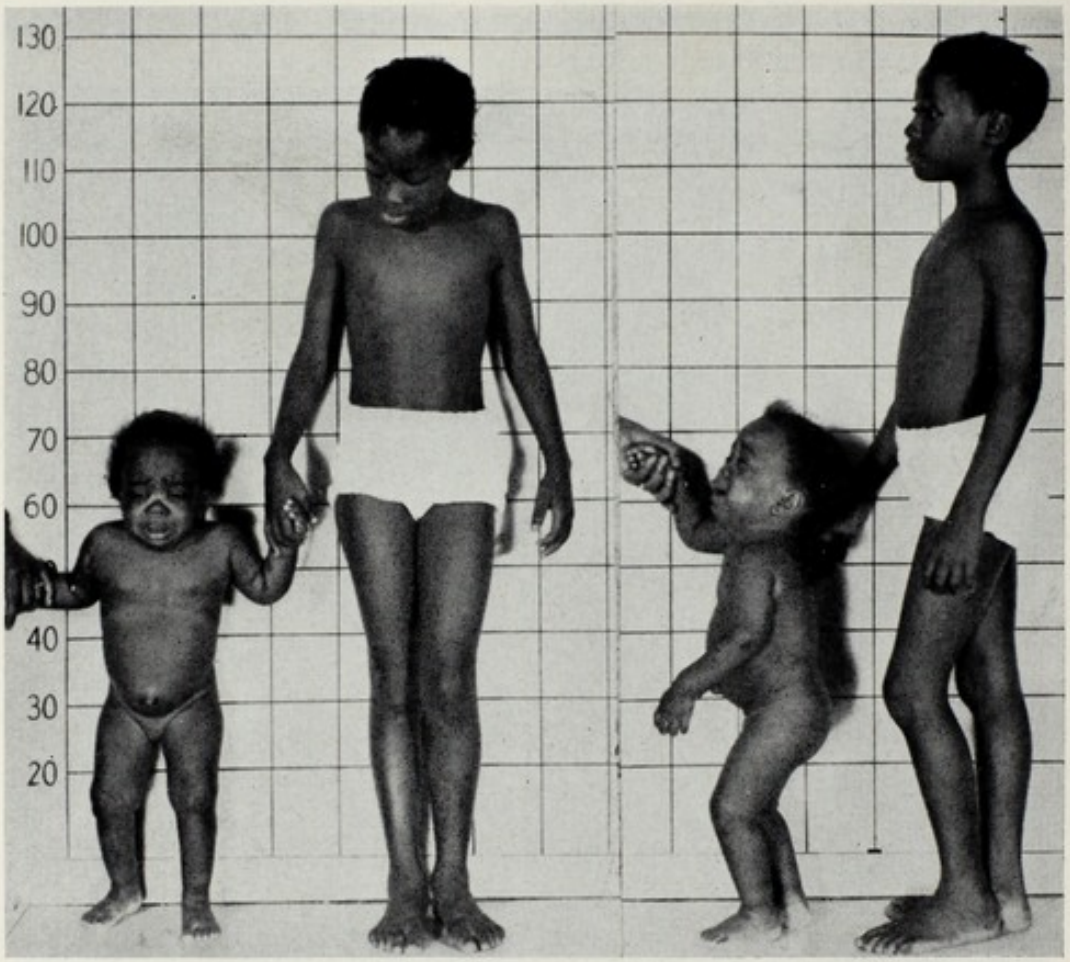


Fig. 84. The Hurler syndrome. On the left of each view: C. D. (B41371), 2½ years of age, is a member of the only Negro family with the Hurler syndrome I have seen. The head is large and the facies characteristic of the Hurler syndrome. The elbows, shoulders, knees, and other joints show reduced mobility, preventing full extension. The hands are short, and the terminal phalanges cannot be fully extended. Both the liver and the spleen are enlarged. Nasal breathing is obstructed by a continuous mucopurulent discharge. Both corneas are clouded. Of six children, three—two boys and this girl—have been affected with the autosomal recessive form of the Hurler syndrome. A normal 8-year-old sister is also shown here. The two other affected children died at the ages of 3 and 4 years. (From McKusick, V. A.: Bull. New York Acad. Med. **35**:143, 1959.)

given that surprisingly little functional impairment results from the marked gross and histologic involvement of the liver. One case of cirrhosis of the liver in a 37-year-old patient with quite typical Hurler's syndrome has been reported by Schwarz and Gagne.[98] Portal hypertension, massive ascites, hematemeses, melena, and death resulted. At necropsy the liver was found to weigh only 900 grams. In a 29-year-old patient[102] with fairly marked hepatosplenomegaly, cephalin flocculation, thymol turbidity, total serum proteins, albumin-globulin ratio,

prothrombin time and Bromsulphalein excertion were all unequivocally normal. Many of the patients in my series have had these same tests with similarly normal findings. Moderate increases in serum cholesterol concentration do seem to occur more often than is normal and may be related to the liver disease.

Diastasis recti and umbilical hernia are almost invariable and inguinal hernia is frequent. Engel[37] described scrotal hernias the size of a child's head. Bilateral hydrocele is also seen.[47]

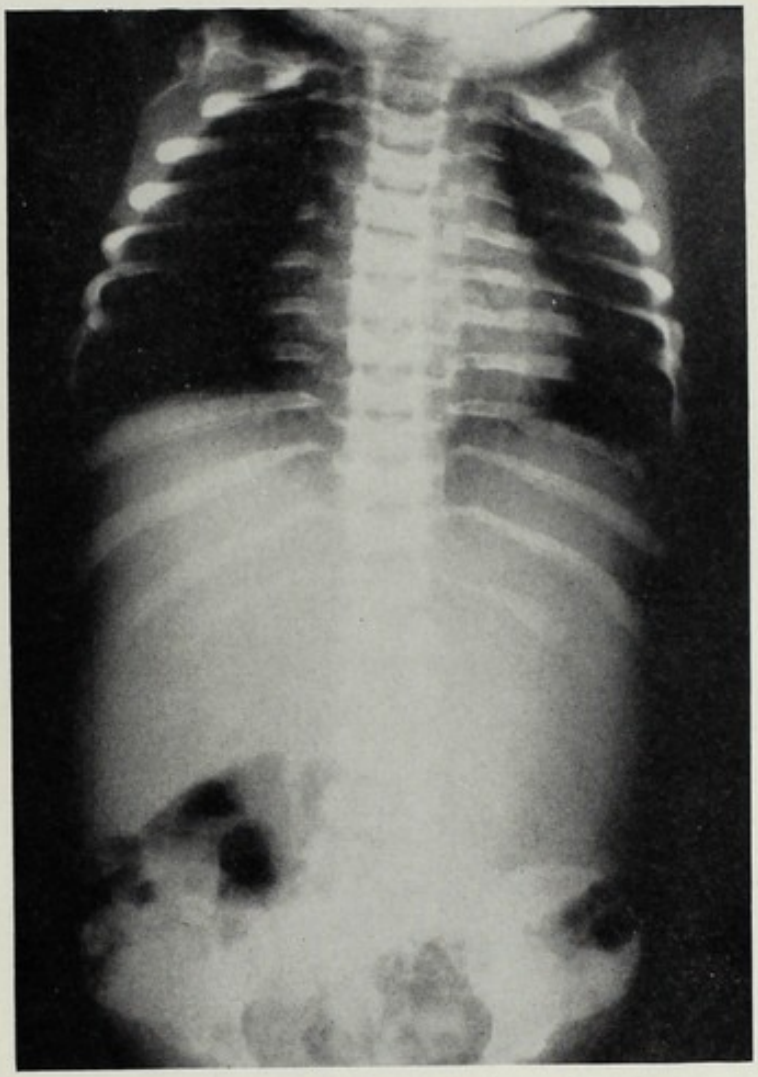


Fig. 85*A*.

Figs. 85*A*-85*C*. Skeletal changes in the Hurler syndrome.
Fig. 85*A*. The lower ribs are unusually broad and spatulous. Note the evidence of hepatosplenomegaly.

Changes in the skin[69] in the form of grooving and either ridged[19] or nodular[1] thickening, especially over the upper arms and thorax, have been described. In two of the reports[1,19] the changes were strikingly similar, especially as to location—"symmetrically distributed in an area of about 6 by 10 cm., extending from the angle of the scapula towards the axillary line." This distribution is probably the characteristic one.[145] In most of the cases the entire surface of the body, both trunk and extremities, is covered by fine, lanugo-like fuzz. In older patients, too, hairiness is quite striking, especially over the arms and hands (Figs. 86*B* and 86*C*).

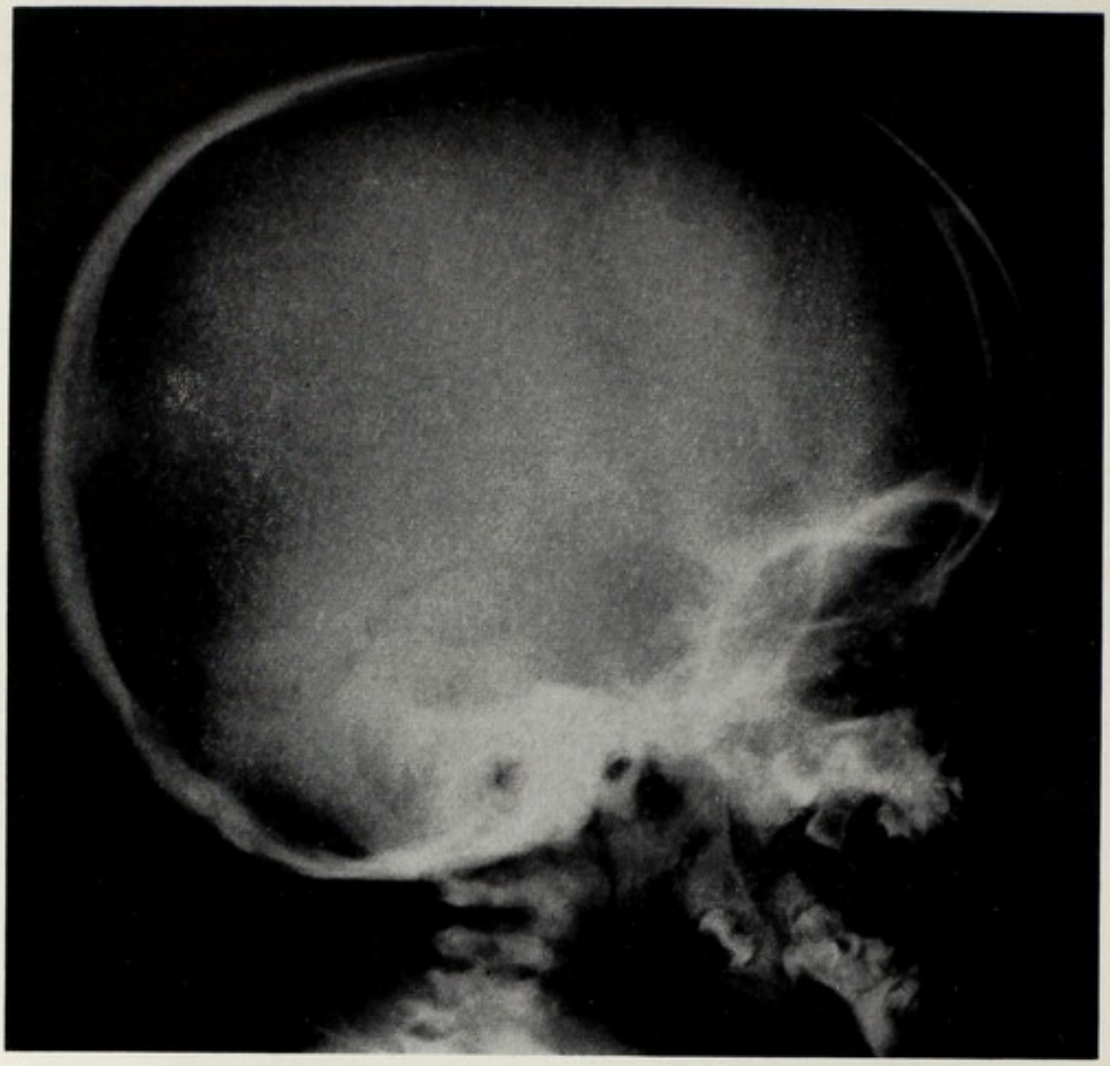


Fig. 85*B*. The anterior pocketing of the sella, "shoe-shaped" sella, is highly characteristic. Furthermore, pronounced abnormality in the region of the paranasal sinuses is evident.

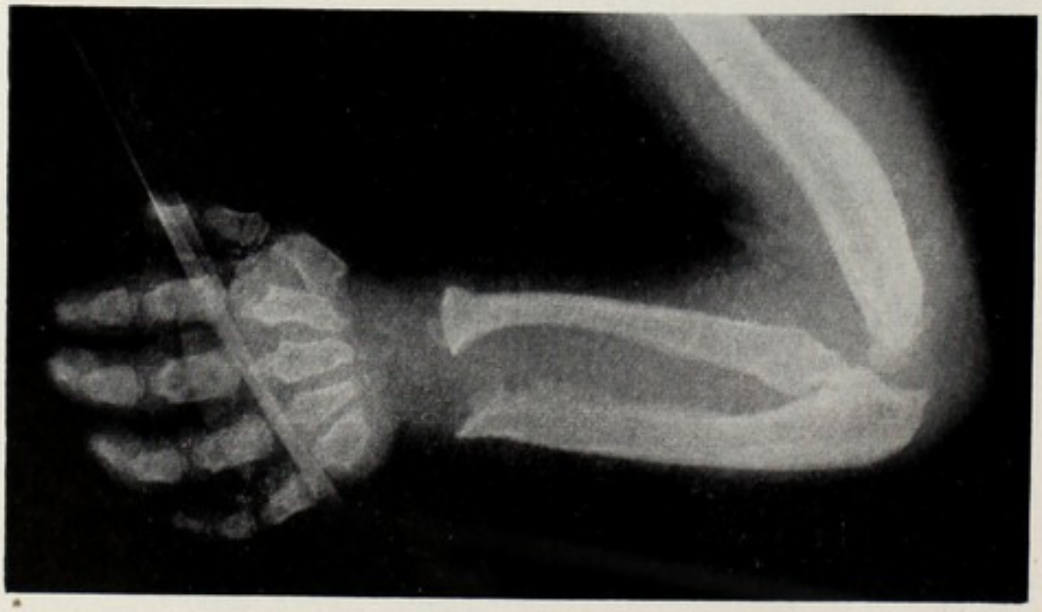


Fig. 85*C*. The long bones of the arm are abnormally short and broad. The bones of the hand are strikingly abnormal in configuration. Again their shape is virtually pathognomonic of the Hurler syndrome.

No consistent endocrine abnormality is clinically detectable, in spite of the histologic evidence of cellular deposits in most glands of internal secretion. Thyroid enlargement without dysfunction has been described and is probably related to the histologic infiltration referred to. Hypoglycemia from hepatic involvement is thought to be a risk but has not actually been demonstrated, to my knowledge. The deformity of the sella turcica is part of the disorder of bone and not a result of enlargement of the pituitary.

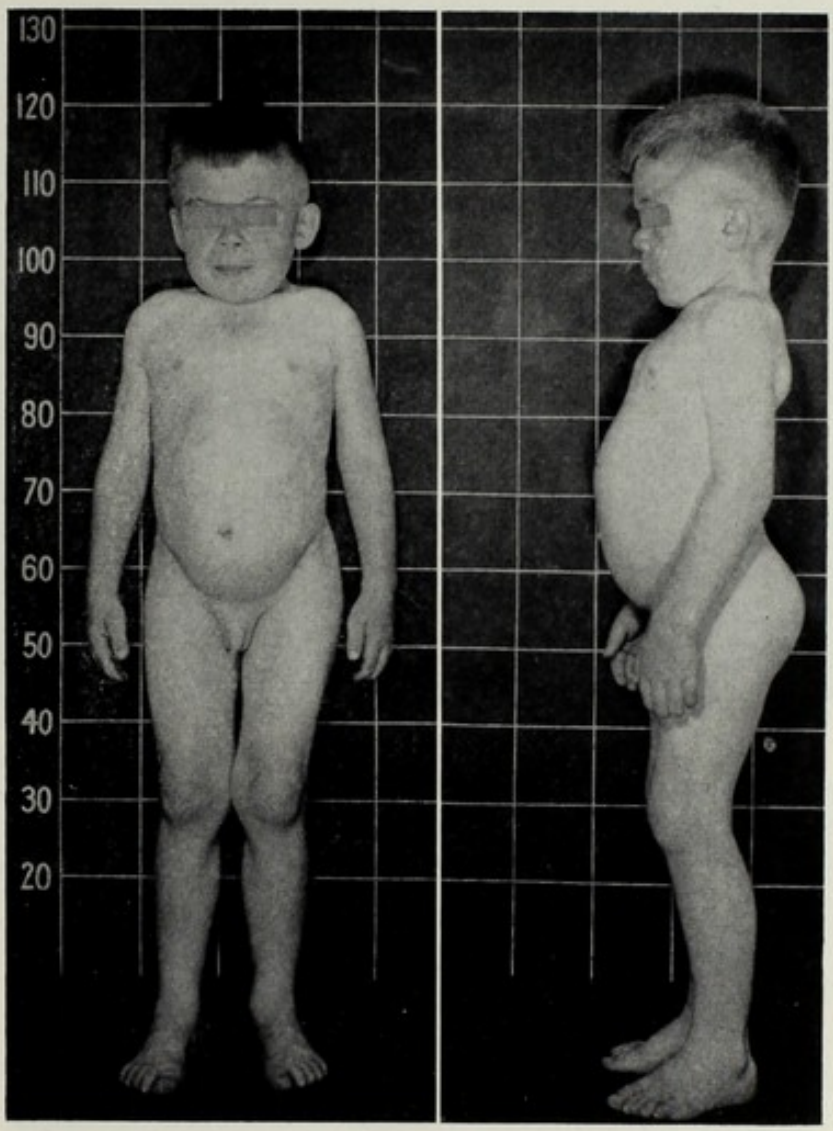


Fig. 86*A*.

Figs. 86*A*-86*H*. Typical case of the Hurler syndrome (I. S. 204375).

Fig. 86*A*. At the age of 10 years.

This patient, 22 years old in Fig. 86*B*, and now 27 years old, has dysostosis multiplex, deafness, "chronic rhinitis," exertional dyspnea, hepatomegaly, restricted joint mobility, hydrocele, and hernia, but no splenomegaly or corneal opacification. Mentality is retarded. The patient graduated from high school because of courtesy promotions. He reads voluminously, especially Ellery Queen novels! No inclusions could be demonstrated in the white cells. The testes are small and soft. However, the patient shaves daily and erections and nocturnal emissions occur. Vision was 20/100 in the right eye, 20/30 in the left. A startling finding was bilateral papilledema, probably long-standing, with "bone corpuscle" pigmentary degeneration of both fundi, especially the right. A peculiar feature has been the subjective response to administration of thyroid extract (see p. 279).

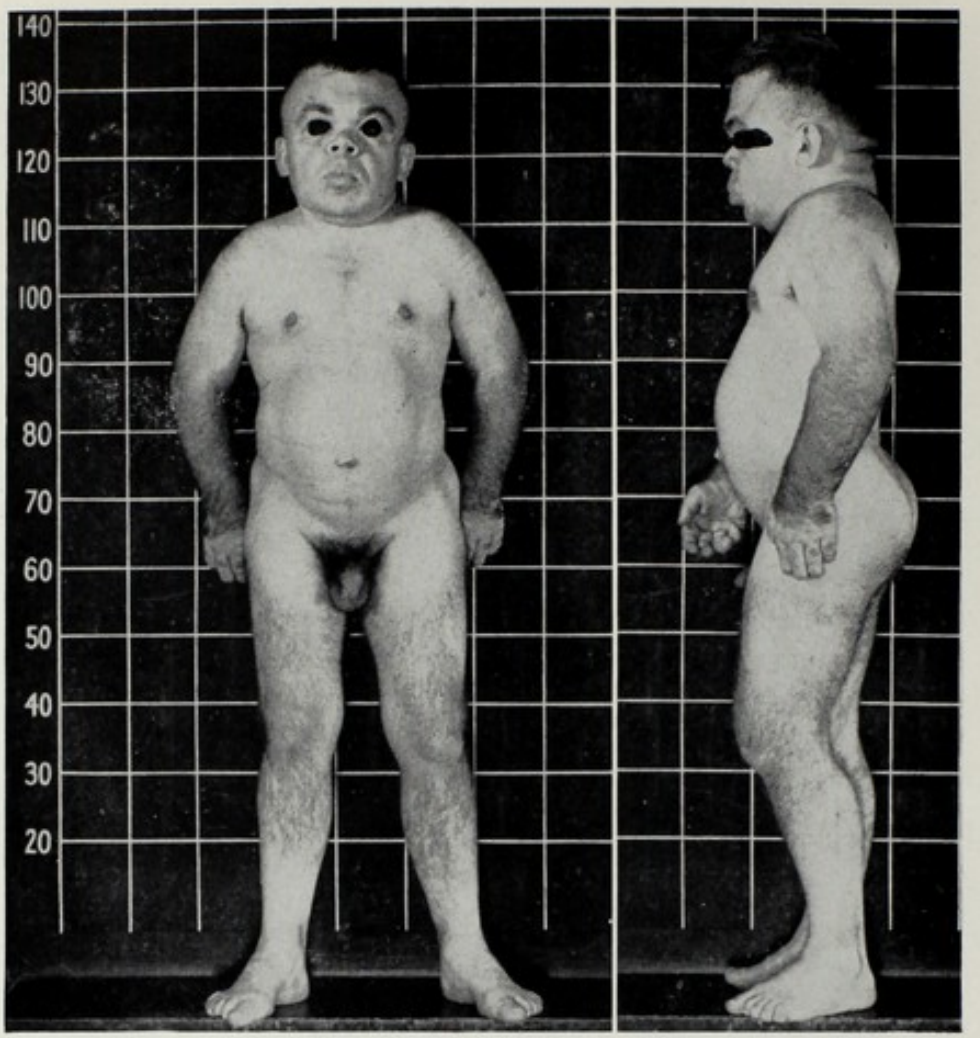


Fig. 86*B*. Fig. 86*C*.

Figs. 86*B* and 86*C*. Same patient as in Fig. 86*A* at the age of 22 years.

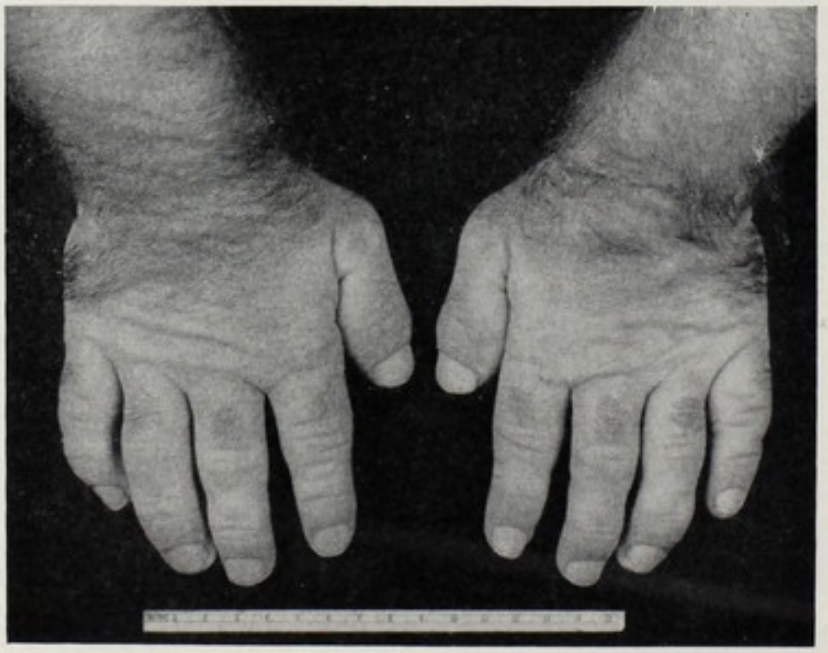


Fig. 86*D*. The hands of patient in Figs. 86*A* to 86*C*.

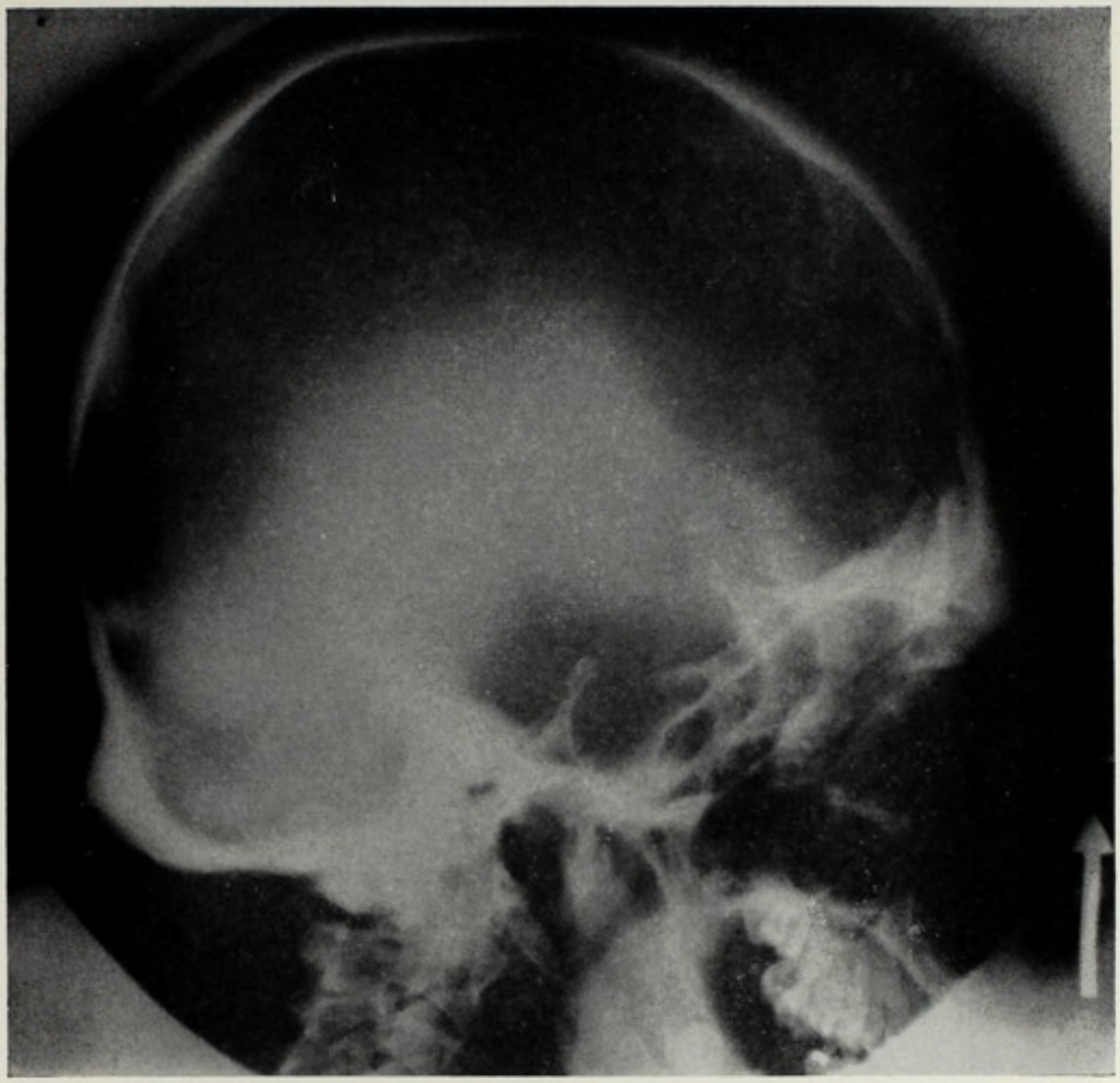


Fig. 86*E*. Lateral radiograph of skull. Characteristic anterior pocketing of the sella is present. There are obvious frontal and occipital areas of hyperostosis. The mastoid air cells are underdeveloped and in general the mastoid is more dense than normal.

Fig. 86*F*. Two uncles of the patient. Both probably had the Hurler syndrome.

Fig. 86*G*. The propositus (on left), 22 years of age, and his unaffected brother (on right), 8 years of age.

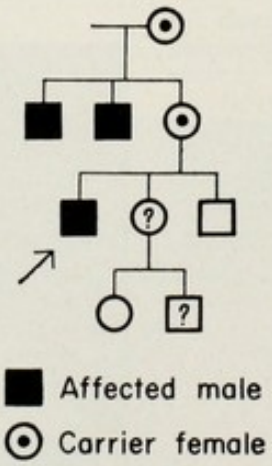


Fig. 86*H*. Pedigree. The propositus is indicated by the arrow.

Two maternal uncles (Fig. 86*E*) had the Hurler syndrome with characteristic skeletal features, deafness, and symptoms of cardiac incompetence. They died at the ages of 12 and 17 years, one having been found dead in bed. The patient's parents are normal and he has two normal siblings. A young nephew of the patient may have the disease; I have not had an opportunity to examine the child but the descriptions are suggestive.

The possible occurrence in four males in three generations is consistent with, and at least mildly indicative of, inheritance of the trait as a sex-linked recessive. Lamy and his associates[151] have also presented a pedigree with affected males in three generations.

Meyer[158] was able to demonstrate relatively large amounts of chondroitin sulfate B and heparitin sulfate in the urine of the propositus. No chemical difference from the autosomal recessive form of the disease was demonstrated by these studies.

Inclusions (Alder bodies) in the polymorphonuclear leukocytes are sometimes found.[90] These are described as being larger than the ordinary granules and tending to take a dark lilac color when stained by the Giemsa-Wright technique. In a number of the patients seen in the hospital, Dr. C. L. Conley has looked for inclusions without success. Although others[9,31] have confirmed Reilly's[90] original observation, the occurrence of leukocytic granules may not be as frequent as often thought.[112] The inclusions have histochemical characteristics, suggesting identity with the material which balloons cells of other parts of the body.[72,125a,156a] The granules are removed by formalin fixation but retained by basic lead acetate.[137] With toluidine blue the inclusions stain metachromatically. No difference in the incidence of leukocytic granules in the two genetic varieties of the Hurler syndrome (see p. 270) have been established with certainty. (Apparently, inclusions may also occur in the leukocytes in glycogen storage disease.[12,116]

Jermain and his colleagues[148a] studied thirteen cases and demonstrated that

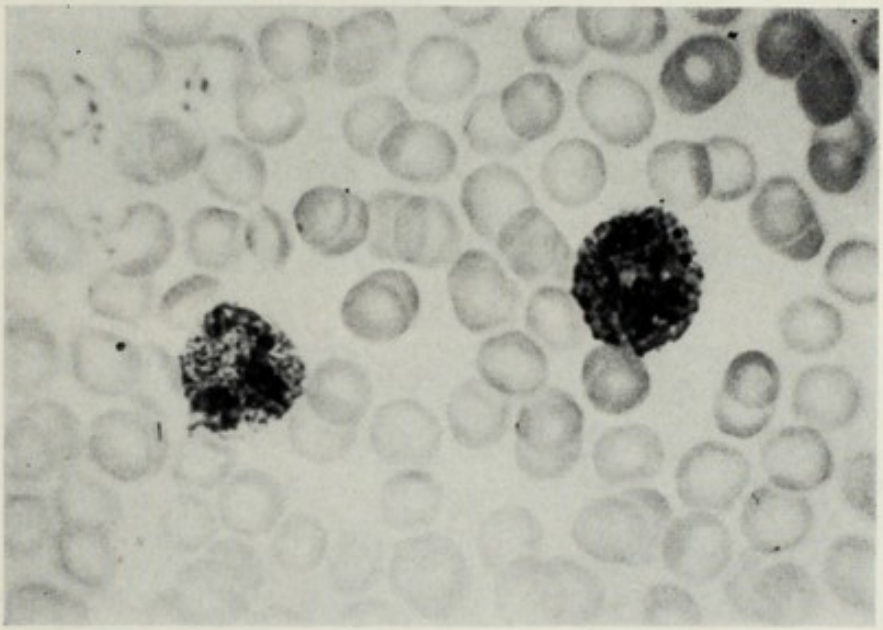


Fig. 87*A*.

Figs. 87*A*-87*C*. Cytoplasmic inclusions in the Hurler syndrome. (Wright-Giemsa stain, ×1,600; reduced ¼.).

A, Peripheral blood. The lighter cell is a polymorphonuclear leukocyte of the type described by Reilly[90] (Type I polymorph). There are small lilac-staining granules of relatively uniform size in the cytoplasm. The darker cell, which superficially resembles a basophil, has large lilac-blue granules of nonuniform size (Type II polymorph).

B, Peripheral blood. Lymphocyte with lilac and blue granules.

C, Bone marrow myelocytes. The darker cell in the center is probably the precursor of the Type II polymorph in the peripheral blood. The other two cells with lilac granules are probably the precursors of the similar cells in the peripheral blood (Type I polymorph).

The patient was a 3½-year-old boy with typical manifestations of the Hurler syndrome. The total white cell count was 17,400 per cubic millimeter with the following differential:

28 per cent Type I polymorph
6 per cent Type II polymorph
55 per cent lymphocytes without granules
9 per cent lymphocytes with granules
2 per cent monocytes

100 per cent

Formalin was found to dissolve the granules. After basic lead acetate fixation the granules were stained by toluidine blue.

(Courtesy Dr. Ralph L. Engle, Jr., New York City.)

cells from the bone marrow showed inclusions consistently, whereas demonstration of inclusion in the cells of the peripheral blood was infrequent. Cells classified as histocytes were especially likely to show inclusions. None was found in presumed heterozygotes, a finding consonant with the failure to find excessive mucopolysaccharide excretion in such persons (p. 270).

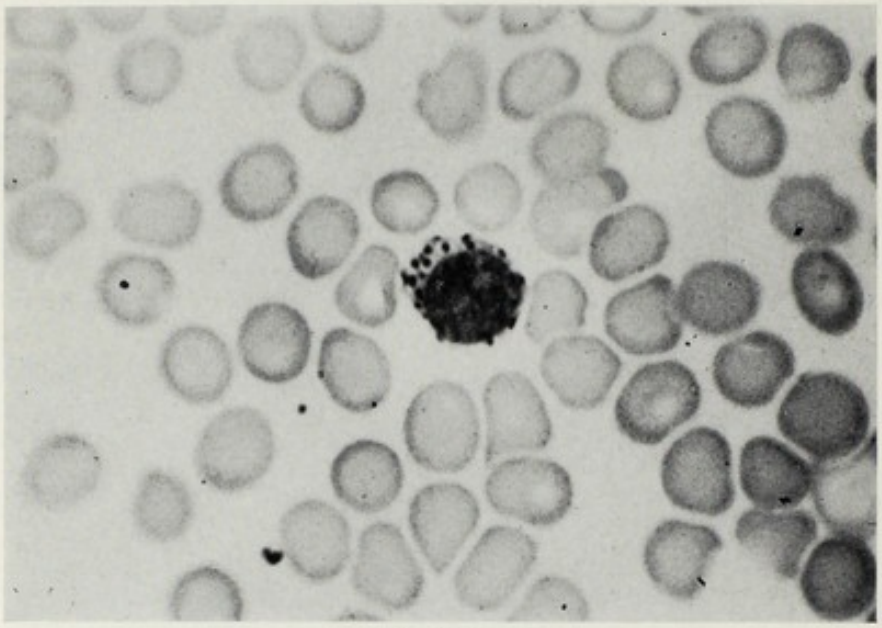


Fig. 87*B*.

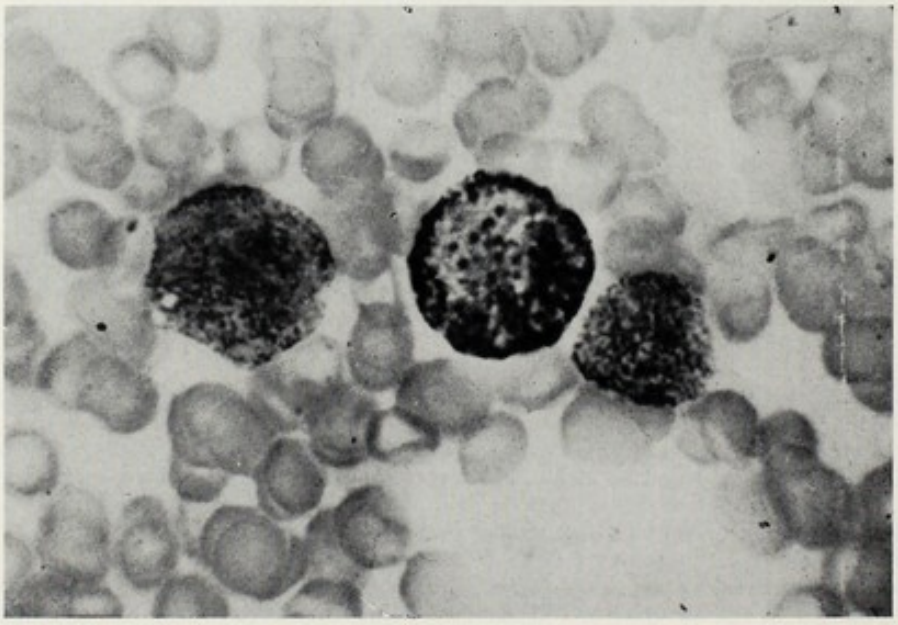


Fig. 87*C*.

Figs. 87*B* and 87*C*. For legend see preceding page.

Although in vitro anticoagulant effects of chondroitin sulfate B has been claimed[134] and although heparitin sulfate, the second mucopolysaccharide found in abundance in cases of the Hurler syndrome (p. 266), resembles heparin in some of its physical properties, hemorrhagic phenomena are not a clinical feature of the Hurler syndrome, and tests of coagulation yield normal results[145a] unless prothrombin synthesis becomes impaired as a result of hepatic dysfunction.

Clouding of the cornea has been described in about 70 per cent of reported cases. The cornea usually has merely a steamy appearance in earlier stages. On inspection this feature is most apparent if light is shined on the cornea from the side.

Ullrich[111] found, up to 1943, fifty-one cases with corneal involvement, eighteen without. Although the number of cases with evidences of corneal involvement is increased by slit-lamp examination, there are certainly some with none. Specifically, corneal opacities are missing in the cases inherited as a sex-liked recessive trait (see p. 270). Among the female cases of the Hurler syndrome, which probably represent a genetically homogeneous group inherited as an autosomal recessive trait, the incidence of corneal opacity is about 90 per cent.[151] Slit-lamp examination reveals that the opacities are located in the medial and deeper layers of the cornea. The epithelium and endothelium are spared. Other ocular abnormalities such as buphthalmos[26] and megalocornea[5,34,63,80] have been described. There may be a retinal element in visual impairment since histopathologic changes in the retina have been described.[72] The occurrence of papilledema in these patients (see Figs. 86 and 88) has suggested hydrocephalus, or at least increased intracranial pressure. Primary involvement of the nerve head by deposits is a possibility which has not been investigated. It is a likely possibility since the course of the "papilledema" is not that characteristic of increased intracranial pressure. The patient shown in Fig. 86 has retained the fundus picture of "papilledema" for at least five years. Optic atrophy was described in two siblings by Davis and Currier.[26]

Mental retardation may be only mild in some cases. Hydrocephalus may occur in severely affected infants.[2,71] Some cases may show simple dilatation of the ventricles secondary to cortical atrophy.[111] There is true internal hydrocephalus in some cases; the ventricular dilatation is too marked to be accounted for on the basis of cortical atrophy alone (Fig. 90*A*). The mental deterioration is likely to be progressive, resembling juvenile amaurotic idiocy in this respect.[63] There may be accompanying neurologic signs such as motor paralysis, increase in muscular tone, and the Babinski sign.

One would presume that the deafness is, in the main, secondary to the bone disease as in osteogenesis imperfecta. In a 24-year-old patient studied by Dr. William G. Hardy of the Johns Hopkins Hearing and Speech Clinic, the deafness was found to be of perceptive type. In a 16-month-old child and a 2-year-old child it was of the conductive type, and in a 3-year-old patient hearing was unimpaired. Because of the deformity of the nasopharynx, these patients probably have more than the average susceptibility to middle-ear infection. Furthermore, the ossicles have shown deformity with limitation of joint motion as in other joints and bones.[120] Therefore, a conductive element in the deafness of some patients is to be expected.

Nasal congestion, noisy mouth breathing, and frequent upper respiratory infections occur in essentially all patients with the Hurler syndrome. The malformation of the facial and nasal bones is probably in large part responsible. Ellis and his associates[34] commented on this feature. Most other writers have also emphasized it and considered malformation of the nasopharynx to be its basis.

In Hunter's historic report[55] he remarked on the occurrence in one of his patients of cardiomegaly and both systolic and diastolic murmurs. As noted on page 243, follow-up suggests that one and possibly both brothers died cardiac deaths

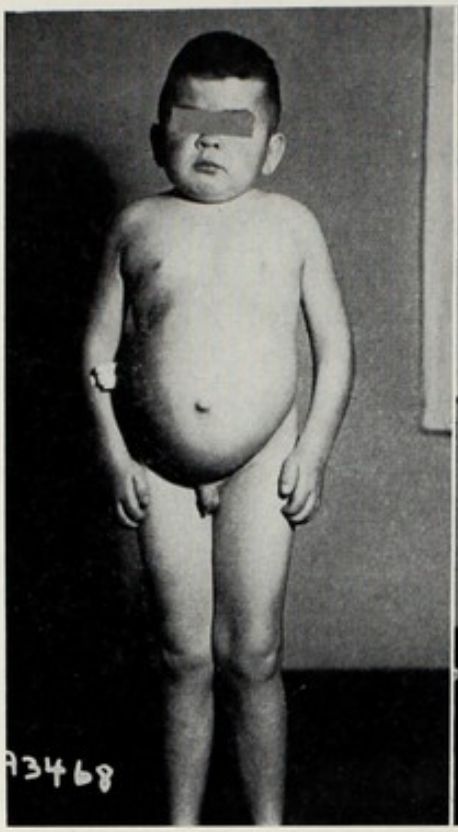


Fig. 88*A*.

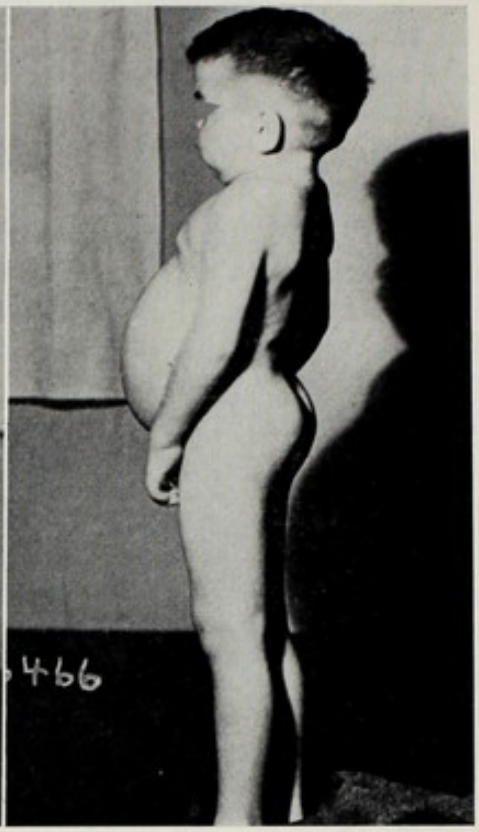


Fig. 88*B*.

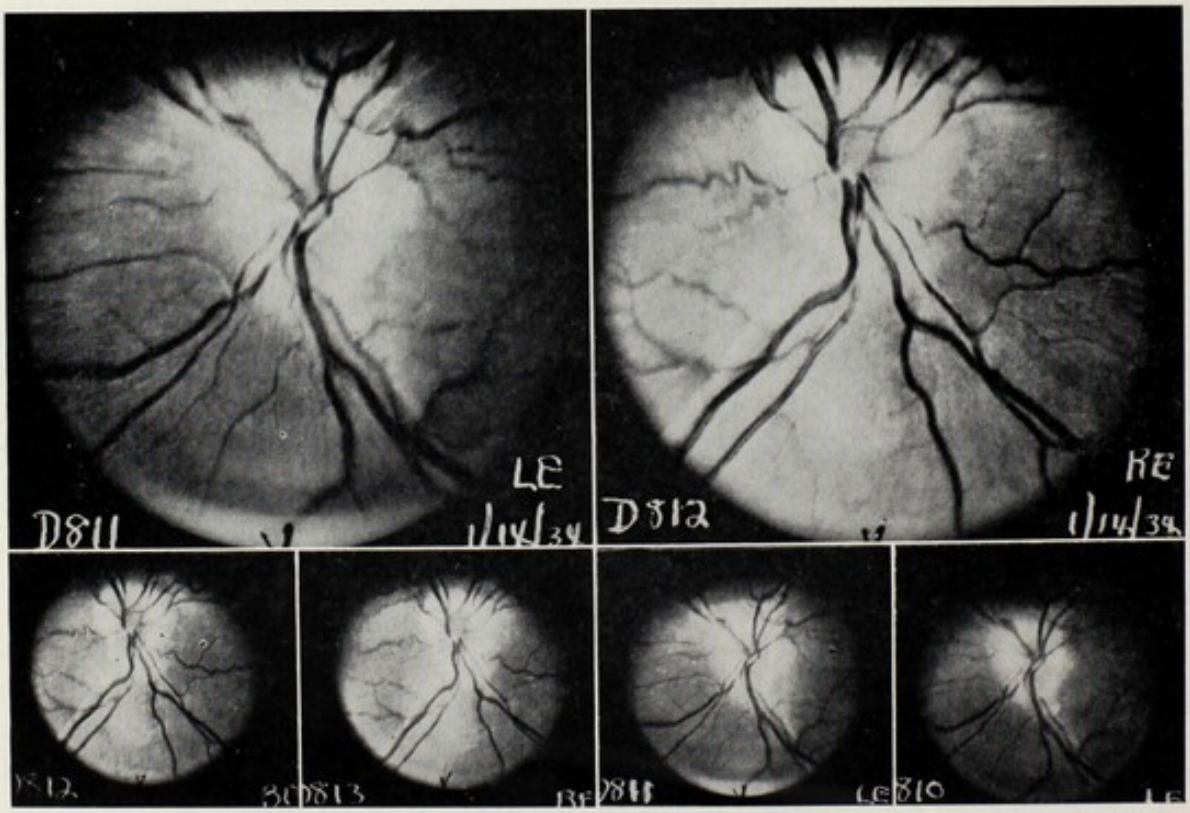


Fig. 88*C*.

Fig. 88*D*.

Figs. 88*A*-88*D*. For legend see opposite page.

at a young age. Murmurs were described also by Meyer and Okner,[80] Engel,[37] and others. Ashby and his co-workers[2] described "congenital heart disease" as the cause of death at 9 years of age in one child and in a 19-year-old patient who died suddenly. Mouth breathing and dyspnea from thoracic deformity and restriction of expansion[36] (which may be very striking), abnormality of the bronchial cartilages, and, finally, frequent attacks of bronchitis make it difficult to dissect out that part of the dyspnea which is on a cardiac basis. The best specific descriptions of the cardiovascular aspects of the Hurler syndrome are those of Lindsay[71] and Emanuel.[36] Emanuel described in two brothers cardiac signs he interpreted as being those of pulmonary hypertension. In one, cardiac catheterization was performed with demonstration of a much elevated pulmonary artery pressure (88/50 mm. Hg). The peripheral arteries of the arms were described as thickened in a 6½-year-old child[72] and there was hypertension (132/100 mm. Hg).

What was interpreted as angina pectoris occurred[22] as early as 4¾ years of age in a child who died at the age of 7 years. The extensive occlusive disease of the coronary arteries discovered at autopsy in this child would suggest that this is the basis of sudden death in many of these patients.

Lindsay[71] stated that systolic murmurs along the left sternal border were so striking in these patients that four of sixteen were suspected of having an interventricular septal defect. There was a similar clinical experience in the group of cases at the Johns Hopkins Hospital. The experience with other heritable disorders of connective tissue, specifically the Marfan and Ehlers-Danlos syndromes, in which cardiac malformations of the conventional types occur with predictably increased frequency, suggests that the same might occur in the Hurler syndrome. Pathologic studies have not corroborated this suspicion (see below). Although some cardiovascular abnormality was present in the great majority of patients who have died, all the changes have been of a specific type, as described later.

Death from "heart failure" (either congestive or coronary artery in type) often occurs before the age of 20 years. Of the patients described by Smith and his associates,[102] one died at the age of 28 years and another was "reasonably well" at 29 years of age. Hooper[51] described a 37-year-old patient who was still living. In two of his other patients, death occurred at 20 and 30 years of age, respectively.

Figs. 88*A*-88*D*. J. M. J. (U53195), 10 years old, was noted to have a short neck and large head at birth, always had frequent colds and trouble breathing because of a "low bridge" of the nose, and had noted limitation of joint movement. However, he had always done well in school and was in the fifth grade. In a school examination he was found to "need glasses," and papilledema was discovered by the ophthalmologist consulted. There had been no headache or vomiting and no impairment of vision so far as the patient was concerned. Examination revealed, in addition to the features obvious in the photographs, the liver to be enlarged 4 cm. below the right costal margin and the spleen 2 cm. below the left; limitation of motion of the elbows, wrists, toes (which were fixed in a position of partial flexion like the fingers), ankles, knees, and spine; height of 44½ inches; papilledema of about 2.5 diopters. Dr. Walter E. Dandy performed ventriculograms which showed "symmetrically dilated ventricles and large third ventricle, aqueduct of Sylvius and fourth ventricle, and air in all the cisternae, including chiasmatis and interpeduncularis, and, curiously, the large main trunks of the subarachnoid spaces but no air in the branches. The main trunks were terminated in large bulbous ends. It was, therefore, communicating hydrocephalus with congenital absence of the terminal branches of the subarachnoid space." (The quotation is from Dr. Dandy's operative note.) Choroid plexectomy was performed in an effort to relieve the hydrocephalus. Histologically, the excised choroid plexus appeared atrophic. The patient died two weeks after operation, of an infectious complication. Autopsy was not performed. This patient resembles closely the one pictured in Fig. 86, who also had papilledema which has, however, not been progressive.

The photographs (Figs. 88*A* and 88*B*) demonstrate the general skeletal changes, prominent abdomen, and claw hands. In Figs. 88*C* and 88*D* is displayed the bilateral papilledema.

The two oldest patients in my series are now 26 and 29 years old (see Fig. 86 for one of these). Beebe and Formel[4] described nine well-documented cases of the Hurler syndrome in one family. Five had died at an age in excess of 40 years. There were four survivors 45, 43, 17, and 14 years of age, respectively.

The following narrative by an intelligent and observing father outlines the evolution of the Hurler syndrome up to the age of about 4 years:

> My impression is that her most difficult period was roughly that of her first to second year. Deafness appeared, so far as we could tell, shortly after her first birthday, becoming complete by about 16 to 18 months of age. Around this time the more pronounced abdominal swelling also began to show, and she was sick much of the time. Nights were very difficult for her and everyone during this time, and until a bit beyond

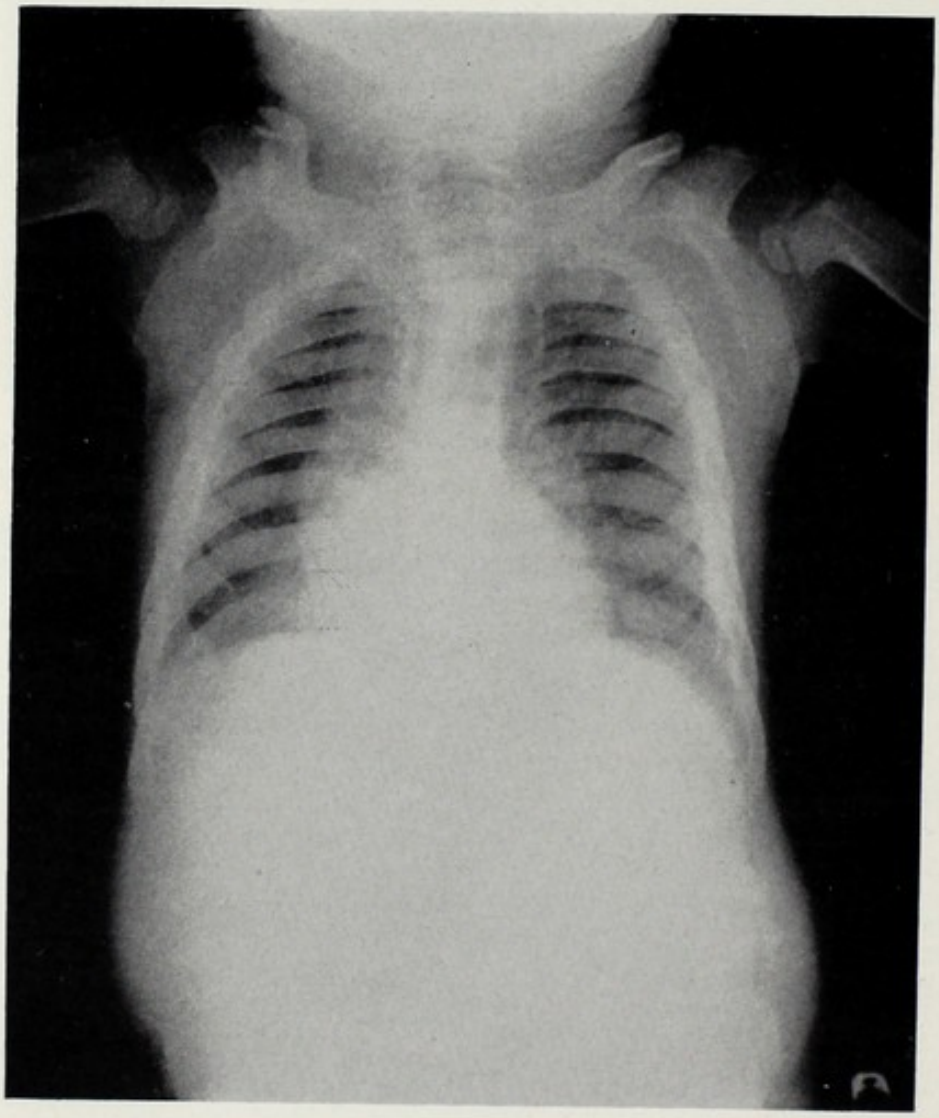


Fig. 89. Chest x-ray film of G. V. D., Jr. (B2188), 4½ years of age. This patient has the Hurler syndrome in entirely typical form. He reached a peak of intellectual development at about 2 years and has deteriorated since then. Gibbus was noted at 1 year. Thick skin, lanugo, "shoe-shaped" sella, and ground-glass corneas are present. Hydrocele and right inguinal hernia were treated surgically at the age of 1½ years.

The central infiltration of the lung fields was present in an unchanged form for at least six months. Tuberculin skin tests are negative. The changes are believed to be the result of chronic bronchitis. However, interstitial pulmonary infiltration as part of the disease and analogous to the infiltrations elsewhere cannot be excluded. The opacification of the upper abdomen by hepatosplenomegaly, the broad ribs, and the abnormality of the proximal ends of the humeri are evident.

2 years of age, she would cry for hours, perhaps in pain. On the other hand, she has seemed to be a bit less sensitive to outside pain than the other children. After the crying spells began to diminish, her personality became more buoyant. During the last year or more, *angelic* would scarcely be too strong a word. She radiates love and affection and thoughtfulness, coupled with a good sense of humor. Her motor skills have kept up remarkably well; she ate with a spoon before 1 year and has kept it up with normal increase in proficiency; she was diaper-trained by about 2½ years and bed-trained by about 3¼ years, with no unusual effort; although the gait is a bit awkward because of underdevelopment of leg muscles and a very large abdomen, she loves to run and dance and slide and swing. Picture books are great favorites; animals are adored, as are dolls and cuddly toys, toward which she is quite maternal. Vision seems still acute, although cloudiness is apparent in the cornea. She dresses and undresses herself as far as her build permits and is almost fastidious about putting away clothes, hanging things up, removing dishes to the sink after eating, etc. (this behavior pronounced since 3 years of age). Simple cutout jigsaw puzzles she handles well. She understands gestures and expressions perfectly and uses them herself for very efficient communication. During April and May of this year (at the age of 3¾ years) she was a day pupil at a nursery school for the deaf. Since September she has been a Monday to Friday boarding pupil at a state institution for deaf children. Here a very capable teacher seems to be making progress with lip reading and vocalization instruction. Other than the direct Hurler's symptoms, her general health has been reasonably good: chickenpox; several periods of respiratory infection each year; and occasional (every six weeks or so?) flash fevers to about 103°F., which are over in a few hours, leaving her worn out for a day. Her teeth have never developed fully, even now being little more than widely separated stumps; however, she can handle, and seems to enjoy, practically any kind of food.

My wife and I feel that, at least until quite recently, her intelligence has been essentially normal. She usually learns new patterns of action, or placement of objects, or play, after only one or two repetitions—unless something arouses the stubbornness, of which she has a powerful streak. She watches the other children playing with close comprehension of their actions and antics, often either joining or copying, nearly always enjoying. She knows all the clothing in the house, often bringing the appropriate items, in proper order, to those of us getting dressed. In driving, she will often back-seat drive, telling me which turns to take by murmurs and gestures, even when we are several miles from home but headed for it. She sets great store on the proper way of doing things! Her sleep is now peaceful, 11 hours a night and usually an hour's nap; even when she is tired her personality holds up cheerfully. When hurt in any way she usually cries but little; however, the offended member *must* be kissed to make the hurt go away.

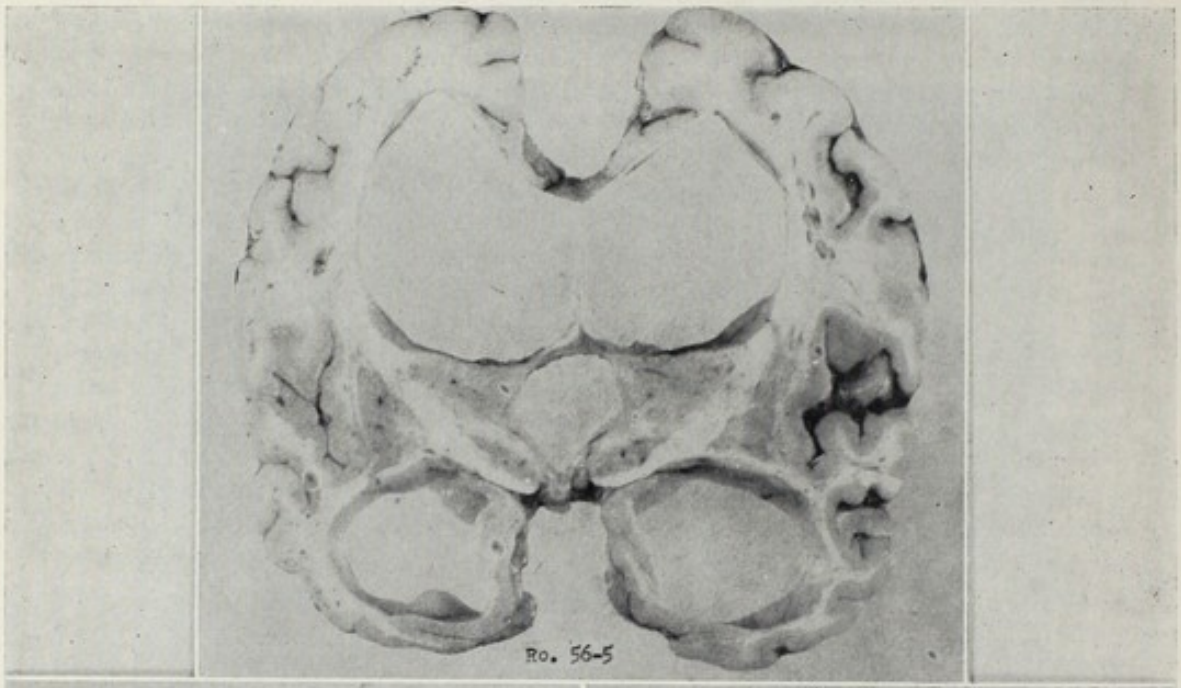
It is possible that her rate of development is slowing down; she is learning, or at least responding, among the slowest members of her eighteen-pupil nursery class. Also, recently there has been pronounced increase in the swelling. Our local pediatrician believes that the liver is almost entirely responsible for the more than double normal girth, and that x-ray treatment might offer her a palliative. Should the swelling become much greater, walking will become extremely difficult. Difficulties with respiratory disease might have been too much for her system already, before modern drugs; except for a couple of summer months, there is a constant nasal discharge of varying rate of flow. Her circulation seems to have its troubles, in that lips and fingernails are often very blue.

PATHOLOGIC CHANGES[38]

About forty autopsies have been reported: many individual case reports,[2,4,30,36,42,49,66,67,68,76,81,96,98,102,105,106,110,111,113,117] two by Jervis,[63] eight by Lindsay and his co-workers,[72] and so on. Jackson[58] and others have reported on biopsies of the liver.

Among other sites, abnormalities have been identified in cartilage, fasciae, tendons, periosteum, blood vessels, heart valves, meninges, and cornea. All of these may contain cells which are thought to be of the fibroblast line and which are distended with large amounts of deposited material. These are appropriately called "clear cells" by Millman and Whittick,[81] but perhaps it would be preferable to use the more specific designation "gargoyle cells."[109] In addition, collagen in many of these areas has been said to look abnormal in a poorly defined way. Collagen fibers are described by some (e.g., reference 71) as swollen, homogeneous,

Fig. 90*A*.



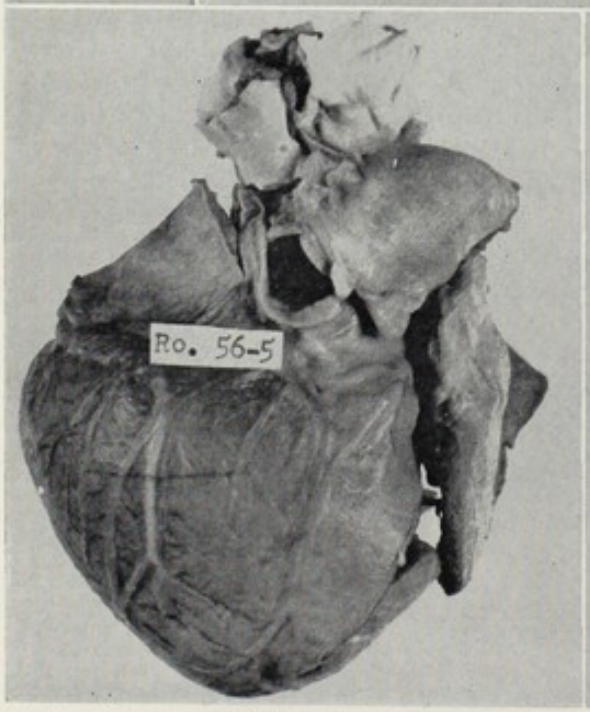
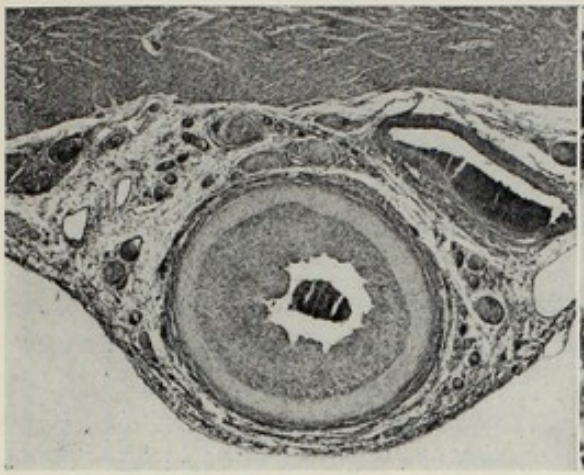


Fig. 90*B*.

Fig. 90*C*.

Figs. 90*A*-90*H*. Case of the Hurler syndrome in 10-year-old male.
Fig. 90*A*. Pronounced hydocephalus. Possible involvement of the meninges is responsible.
Figs. 90*B* and 90*C*. Two views of the heart. The coronaries are obviously thickened.

Fig. 90*D*.



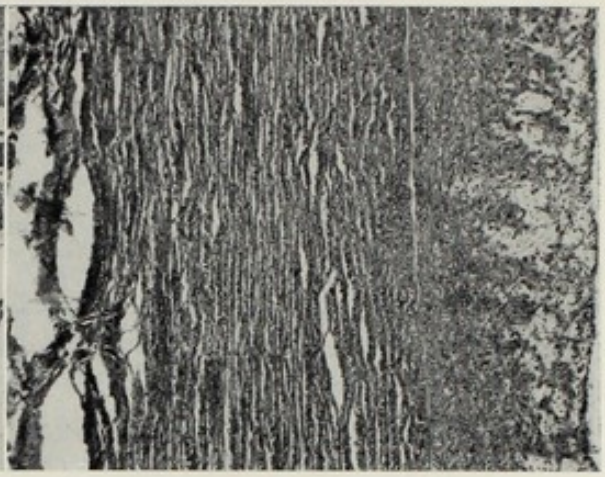


Fig. 90*E*.

Fig. 90*F*.

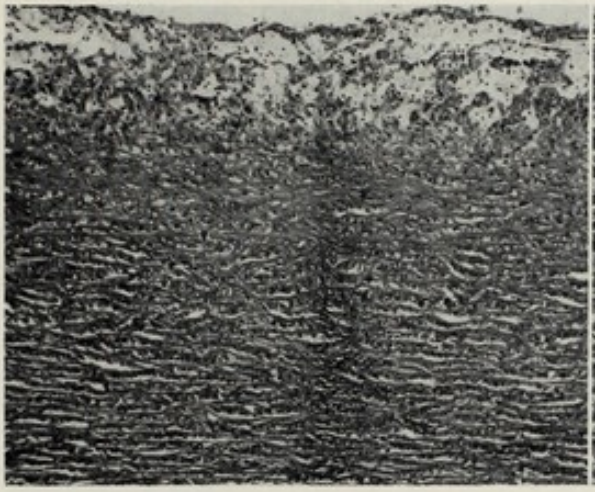


Fig. 90*G*.

Fig. 90*D*. Coronary arteries showing pronounced thickening of intima. (×30; reduced 5/8.)
Fig. 90*E*. Section of pulmonary artery showing enormous thickening of intima. (×67; reduced 5/8).
Fig. 90*F*. Section of aorta showing, in addition to intimal deposit, inclusion-laden connective tissue cells between the elastic lamellae.
Fig. 90*G*. Section of myocardium showing infiltration of connective tissue cells laden with inclusion material. (×100; reduced 5/8.)

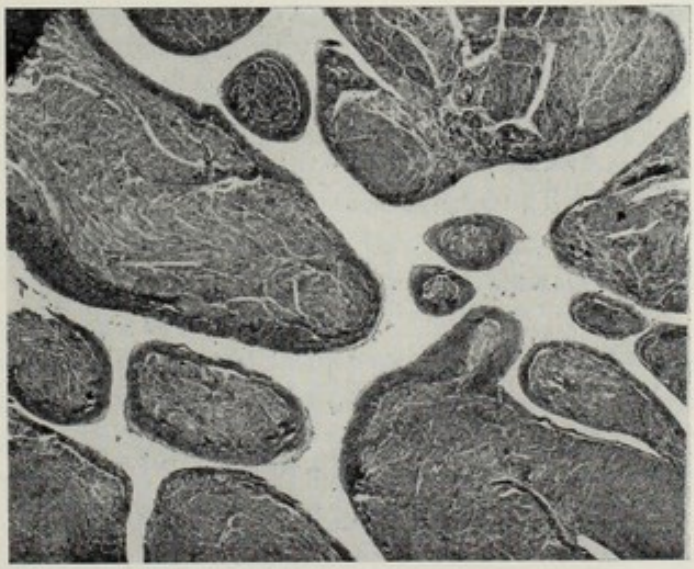


Fig. 90*H*. Endocardial thickening surrounding the carneous trabeculae of the ventricle is evident. (×30; reduced 1/3.)

and lacking in their normal fibrillary characteristics. Material, presumably identical to that in the fibroblasts, balloons the nerve cells of both the central nervous system and the peripheral ganglia, the nerve cells in the nuclear layer of the retina,[72] the Kupffer cells of the liver, the parenchymal cells of the liver, the reticulum cells of the spleen and lymph nodes, and the epithelial cells of several endocrine organs such as the pituitary[68] and testis. Mental retardation and hepatosplenomegaly are explained by these deposits.

Enlargement and vacuolization of the chondrocytes and osteocytes, as well as of the periosteal cells, are described[72,129] and probably are intimately related to the skeletal malformation.

In the heart, in persons dying after a few years of life, the aortic and mitral valves almost invariably have shown some degree of nodular thickening,[36,72] as well as changes in the chordae tendineae.[129] Functionally both stenosis and regurgitation can result. In the case of Smith and his co-workers[102] the histologic picture in the heart valves was dominated by the presence of "gargoyle cells." These have also been seen in the coronary arteries.[72,76,132] Grossly[36] even in young individuals the coronary arteries may "stand out like white cords." Virtually complete occlusion may result from the extensive intimal deposits.[22,27] The aorta[76] and pulmonary artery[36] may show extensive intimal deposits, presumably of the same material as forms the vacuoles of the cells of various organs. The myocardial cells may show marked ballooning by vacuoles (see photomicrograph, reference 6). Patchy thickening of the endocardium and epicardium is described.[36,72,106] Of the peripheral arteries, changes have been described in those of the brain, spleen, pancreas, and kidney, as well as in the mesenteric, carotid, radial, and anterior tibial arteries.

Emanuel[36] was able to find thirty-two autopsy reports in which specific description of the heart was provided in twenty-six. Of these, twenty-two had cardiovascular abnormalities (85 per cent). In fifteen patients the mitral valve was deformed, in nine the aortic, in seven the tricuspid, and in two the pulmonary. In three (including Emanuel's case) all four valves, the epicardium, the endocardium, the corornary arteries, and the aorta and pulmonary artery were involved.[72,106]

It is of note that the order of incidence of involvement of the heart valve—mitral, aortic, tricuspid, pulmonary—is precisely as in rheumatic fever. In both situations there are probably operating at least two prominent factors. The metabolic aberration (in one case acquired, in the other inherited) and the hemodynamic stresses. The peak pressures sustained by the four valves in the position of closure are in the same sequence as the incidence of valve involvement: mitral, 120* mm. Hg; aortic, 80 mm. Hg; tricuspid, 25 mm. Hg; pulmonary, 12 mm. Hg.

A conventional type of congenital malformation of the heart has been thought clinically to be present in three of the patients seen at this hospital. Seemingly, however, no such malformation has been revealed by any of the pathologic studies.

Abnormality of the tracheobronchial cartilages together with that of the upper airways may be responsible for the suceptibility to respiratory infection in these patients. Bronchopneumonia is a frequent cause of death.[63]

Cole and his associates[19] illustrate a histologic section of skin which was in-

*All values are approximations.

terpreted as showing "marked fragmentation of collagen fibers and mucinous degeneration."

Vacuolated cells have been described in Bowman's membrane by Berliner[5] and others. Lindsay and his co-workers[72] described highly metachromatic granules in the cornea.

Multiple abnormalities in the middle and inner ear have been discovered in one twice-reported case.[102,120]

Extensive changes in the leptomeninges were described by Magee.[76] The coincidence of subdural hematoma in his case makes these changes difficult to interpret. However, others report extensive changes in the meninges.[27,42,165] Millman and Whittick[81] found thickening of the leptomeninges over the cerebral hemispheres and "clear cells" histologically. In Njå's[85] Case 2, there was hydrocephalus with "thickened and milky leptomeninges." The hydrocephalus[165] may be the result of interference with drainage produced by the deposits characteristic of the disease.[143] The frequency of hydrocephalus (Fig. 90*A*) has been underestimated. It is probably an important factor in the cerebral impairment in these patients.

Greenfield and his associates[143] describe the central nervous system changes as being predominantly distension of the nerve cells of the cerebral cortex with little or no defect of myelination. A peculiar feature of the Hurler syndrome is "the presence in the centrum semi-oval and medullary cores of the gyri of greatly enlarged perivascular spaces."

Formalin or alcohol dissolves the vacuolar material.[129] Some reported failtures[27,72,105] to stain the material in post-mortem tissues may have their bases in this fact. Dioxane-dinitrophenol fixative has been useful[72] in preserving the deposited material.

Some have reported that the intracellular deposits do take the conventional fat stains.[6,46,110] Most have found that the vacuoles do not stain as fat or stain atypically.[102] Analyses of hepatic and splenic tissue for fat reveal no increase.[49,105,109] The material may stain with periodic acid-Schiff's reagent (PAS) or with Best's carmine. It displays striking metachromasia.[113] Bishton and his colleagues[129] suggest that even if precautions are taken to prevent solution of the material deposited in the liver, one cannot expect satisfactory staining of "heparin-type" polysaccharides by the periodic acid-Schiff technique. They recommend use of toluidine blue as a stain in these cases.

Histochemical studies led Lindsay and his collaborators[72] to suspect that the storage material is glycoprotein. Brante[11] isolated a material, polysaccharide in nature, having 0.9 per cent sulfur, 27 per cent hexosamine, and 26 per cent glucuronic acid, containing no fatty acids by hydrolysis, and representing 10 per cent of the dry weight of the liver. Uzman[113] described two storage materials isolated from the liver and spleen of these patients: (1) a complex polysaccharide containing glucose, galactose, hexosamines, and sulfate, soluble in water and formaldehyde but insoluble in other organic solvents, and staining metachromatically with toluidine blue; (2) a glycolipid soluble in water and ethanol but not in other organic solvents, and containing fatty acids, sphingosine, neuraminic acid, hexuronic acid, hexosamines, glucose, and galactose. These Uzman refers to as fractions P and S, respectively. Stacey and Baker[167] reported the presence of sulfated polysaccharide fractions as well as of nonsulfated fractions, the latter somewhat related to blood group-specific substances. Brown[130] has pro-

posed a possible molecular structure of the material he isolated in large amounts from the liver of patients with the Hurler syndrome and referred to as an oligosaccharide. By his evidence the material is composed exclusively of D-glucosamine and D-glucuronic acid units combined in glycosidic linkage. The material in point may be identical to the type of mucopolysaccharide called heparitin sulfate by Meyer.[157] Meyer and his colleagues[160] found large amounts of heparitin sulfate in the liver of one patient.

Dawson[27] thought that the deposits in the brain consisted of phospholipid, although those elsewhere seemed to be mucopolysaccharide. Uzman[113] did not study brain. Meyer[158] finds that mucopolysaccharide (both chondroitin sulfate B and heparitin sulfate) was deposited in the brain in appreciable amounts.

THE FUNDAMENTAL DEFECT

Straus and his associates[105] thought that this might be a dystrophy of collagen, and Cole and his co-workers[19] also subscribed to this view. These authors based their view mainly on the lack of good evidence of this being a lipid-storage disease and the fact that contractures of joints and hernia occur, as well as skin changes which Cole interpreted as involving primarily collagen.

On the other hand, Ellis and his colleagues[34] considered gargoylism (as they called it) a disorder of lipid metabolism. Washington[117] in his term "lipochondrodystrophy" implied the same theory.

de Lange and his co-workers[29] and Strauss[106] thought the storage material might be a glycogen. Lindsay and his co-workers[72] suggested that the stored material might be a polysaccharide (such as glycogen) or glycoprotein. Brante[11] studied three cases clinically and histologically and came to the conclusion that the Hurler syndrome is a "congenital enzyme disturbance as regards the metabolism of the mucopolysaccharide or of some of its components, or as regards the binding of the mucopolysaccharide to protein, etc." The qualitatively and/or quantitatively abnormal mucopolysaccharide accumulates at various sites, according to the last view.

Uzman[113] takes a slightly different view. He holds that the genetic defect is one concerning the metabolism (i.e., synthesis) of "structural polysaccharides" which are normally important building blocks of connective tissue elements.[41]

Dorfman and Lorincz[135] and Meyer and his associates[160] have found considerable amounts of chondroitin sulfate B and heparitin sulfate in the urine and tissues of patients with the Hurler syndrome—a nice corroboration of the view that this disease is a mucopolysaccharidosis. These polysaccharides have also been identified in the brain.[145] Meyer and his collaborators[160] found large amounts of heparitin sulfate in the liver of a patient, and Stacey and Baker[167] found what was probably the same polysaccharide.

The mucopolysaccharides (chondroitin sulfate B and heparitin sulfate) are probably produced in excess; a defect in removal is less likely. Furthermore, the mucopolysaccharides are, by any evidence yet available, "normal," i.e., they have all the properties of those identified in certain normal tissues. (These mucopolysaccharides are not found in the urine of normal persons.) Meyer and his colleagues[159] point out that the mucopolysaccharides produced by connective tissue in different sites fall into distinct pattterns. Chondroitin sulfate B occurs normally in all connective tissue with the exception of cartilage, bone, and cornea, whereas

heparitin sulfate has been isolated only from lung and aorta (and in large amounts from amyloid liver). It is suggested, therefore, that connective tissue cells each produce only one specific type of product, e.g., cells producing hyaluronic acid cannot produce any of the chondroitin sulfates. Tentatively Meyer and his coworkers[160] propose that the Hurler syndrome is a genetic error in the chemical differentiation of the fibroblasts—"a chemical metaplasia." The excessive production of polysaccharides results in the accumulation of these substances, not only in the connective tissue cells themselves but also in the cells of many organs, and the excretion of large amounts in the urine. The Hurler syndrome is, in this view, both a generalized disorder of connective tissue and a storage disease ("thesaurosis"). Storage of lipid in the brain and deficiency of glycogen in the liver are probably secondary effects of the derangement of normal cellular function produced by the storage.

As pointed out earlier, hydrocephalus from meningeal involvement is undoubtedly a factor in the progressive impairment of intellect. Furthermore, a biochemical mechanism common to connective tissue and brain may be faulty. Just as in phenylketonuria and galactosemia, the details of how the normal biochemical and functional status of the brain is disturbed in the Hurler syndrome are unknown.

It is possible that the corneal involvement is a primary feature of the syndrome and not a secondary feature due to the deposit of an anomalous polysaccharide. The fact that corneal change occurs in only one of the two genetic varieties of the Hurler syndrome, although other seemingly storage phenomena occur in both, suggests that the corneal change is indeed primary. Corneal grafting might settle the question.

The manner in which abnormal deposits occur in the intima and elsewhere is reminiscent of the handling in rabbits of methylcellulose and pectin,[53,54] both of which are macromolecular carbohydrates. Hueper[54] observed ballooning of cells in the liver, spleen, kidney, arterial intima, bone marrow, and anterior pituitary when pectin was administered intravenously in rabbits and dogs. However, "no lesion was found in the cerebral parenchyma, the vascular system of the brain or the choroid plexus."

It is probable that the basic defect in the two genotypes of the Hurler syndrome *(v. seq.)* is slightly different. The phenotypic differences would suggest this to be the case. Thus far chemical differences have not been identified.[145a,160]

The clinicopathologic differences between the Hurler syndrome, on the one hand, and the syndromes of Gaucher and of Niemann and Pick, on the other, are suggestive evidence that the storage material in the Hurler syndrome is not lipoid. In neither Gaucher's disease nor Niemann-Pick's disease are the parenchymal cells of epithelial organs involved. (Thannhauser[109] refers to Gaucher's disease as "reticular and histiocytic cerebrosidosis" and to Niemann-Pick's disease as "reticular and histiocytic sphingomyelinosis.") The bone lesions of Gaucher's disease, such as the Erlenmeyer flask deformity of the long bones, result from the involvement of the marrow and not from the implication of fundamental skeletal building blocks as in the Hurler syndrome.

In reference to the skeletal lesions of the Hurler syndrome, it is noteworthy that chondroitin sulfate B and heparitin sulfate have not been identified in normal bone and cartilage (see p. 36).

INCIDENCE AND INHERITANCE

This disorder is more common in males than in females. Prior to the first edition of this book (1956), few cases had been described in Negroes and we had not seen the disease in a Negro. Since then several such cases have been reported,[126,134,138,142,148a,150,169,170] and we have observed a Negro family with three affected members (Fig. 84). The characteristic facies may be more easily overlooked in the Negro child. The syndrome has been reported in Chinese[37,131a] and in Oriental Indians.[144,156]

More often than not, the Hurler syndrome displays features of inheritance consistent with a recessive autosomal trait.[44] Parental consanguinity[8,44] is frequent, and affection of multiple sibs of both sexes without the occurrence of affected individuals in the preceding generation ("familial" characteristics) is often the case. There are no well-documented descriptions of skeletal deformities in close relatives of patients with full-blown cases to suggest that partial expression of the trait in the heterozygous state may occur. Concordance in identical twin sisters has been described.[86] Craig[22] described the disorder in a twin brother and sister. Others[141] have observed discordance in twins who were presumably dizygotic.

In 1952, Jervis[63] reviewed the information on 103 families described in the literature. When the ratio of affected to unaffected sibs was corrected by the method of Bernstein and that of Lenz, statistically significant agreement with the expected 1:3 ratio was obtained. (Jervis did not recognize the possibility of a second genotype, the sex-linked recessive form—see below. If sex is not taken into account, a sex-linked recessive disorder will fulfill satisfactorily certain of the criteria for an autosomal recessive trait: both parents are phenotypically normal and one-fourth of all children are affected. In the group analyzed by Jervis there were ninety-three affected male and fifty-two affected females.) Cousin marriages are *known* to have occurred in eleven of the 103 families and probably actually occurred in more. Using Hogben's formula, Jervis calculated that a 10 per cent consanguinity rate would correspond to a phenotype frequency of 1 in 40,000.

So far as is known, none of these patients has procreated. Some of the patients with milder affection may be capable of reproduction. Because of the statistical unlikelihood of mating with a carrier for the disease trait, unless the mate is a relative, the offspring of an affected person can be expected to be normal but will of necessity be a carrier for the trait if the theory of the recessive inheritance of the Hurler syndrome is correct. Actually the individuals most capable of reproducing are all males who may have the sex-linked variety of the disease *(v. seq.)*. This means that none of their sons would be affected but half the daughters would be carriers.

A seemingly sex-linked form is described in at least nine reports,[4,24,51,74,81,85,120,300] and, of course, there are many other instances in which this theory of inheritance is consonant with the known facts.[19,30,36,55,64,74,75] In these cases the inheritance follows the pattern of a recessive X-chromosome factor, such as hemophilia. Njå[85] suggested that cases without corneal opacity are most likely to show this mode of inheritance. Lamy's analysis[151] corroborates Njå's suggestion. Whereas about ninety per cent of all reported female patients with the Hurler syndrome have cloudy cornea, only about 60 per cent of male patients, especially those reported at a later age, show the sign.

In the fascinating report by Beebe and Formel,[4] nine cases were described occurring in four generations of a family of Dutch extraction which has resided in the Catskill Mountains for about 250 years. Of nineteen males, nine were affected. Of sixteen female siblings of affected males, none was affected. All nine affected males were related through their mothers, who were presumably carriers. Furthermore, they were all descended from a common female ancestor who was almost certainly likewise a carrier or perhaps started the disease (by mutation), just as Queen Victoria probably initiated hemophilia[103] in the royal houses of Europe. Five other females could be identified as carriers by reason of affected brothers and sons. Six females had borne only normal children.

The family described by Beebe and Formel[4] may corroborate Njå's[85] impression that the sex-linked disease is a different entity clinically as well as genotypically. The sex-linked form of the disease may pass unrecognized until the age of 4 to 8 years. Mentation is usually less severely affected. The patients live longer. Finally, there is no corneal involvement. Fig. 86 presents the case of a patient with Hurler's syndrome, probably of the sex-linked variety.

It would seem significant that most of the patients known to have survived beyond the age of 20 years (see above) were male. In Jervis' survey[63] there were 145 cases in which the sex was stated; of these, ninety-three (64 per cent) were male. Of 112 sibships, sixty-five could, by reason of the fact that all affected individuals were male, represent the hypothesized sex-linked variety of the disease. There were twenty-seven sibships with more than one affected individual; of these, twelve had only males affected, four had only females affected, and in eleven both males and females were affected. The average age of the affected individuals in the sibships with more than one affected individual, all males, was 6.65 years. The comparable value for the sibships containing both male and female affected individuals was 10.02 years. Although this appears to contradict the rough impression that the patients with the sex-linked variety of the Hurler syndrome are older when they come to medical attention and when they die, it must be remembered that these collected sibships may contain some in which the trait was inherited as an autosomal recessive; these may weigh down the average.

Again following Jervis'[63] survey the state of the cornea was analyzed in (1) the isolated female cases plus the sibships with affected persons of mixed sex and in (2) the isolated male cases plus the sibships with affected persons all male. In the case of multiple affected sibs all affected persons in that sibship were counted as having cloudy cornea if one was said to show it. In sibships of the first type, the cornea was described in sixty-nine individuals, of whom fifty-one (74 per cent) had corneal clouding. In category 2, the cornea was described in seventy individuals, of whom thirty-nine (55.6 per cent) had corneal clouding.

Parents have been invariably unaffected. The difficulties in distinguisihing autosomal from sex-linked recessive inheritance are well illustrated. It should be pointed out that when the victim of the particular hereditary trait does not procreate, one cannot be certain that the inheritance is as a sex-linked recessive rather than as a sex-limited autosomal recessive.

One may conclude that there are sex-linked and autosomal recessive forms of this disease, the latter being several times more common than the former.* (Lamy

*In one report,[18] dominant inheritance is claimed, however.

and his associates[151] estimate that about one-third of the males and 14 per cent of all patients with the Hurler syndrome have the sex-linked recessive form.) Furthermore, it seems that there may be slight phenotypic differences corresponding to the genotypic differences, as outlined in Table 5.

Table 5

	Autosomal Recessive	*Sex-Linked Recessive*
Corneal clouding	4+	Probably 0
Deafness	1+ to 3+	2+ to 4+
Retardation of intellect	2+ to 4+	± to 2+
Gibbus	2+ to 4+	±
Age of death	Usually under 20 years	Often over 40 years
Reported cases	Majority, e.g., refs. 22, 47, 48, 63, 86, 93	Quite definite examples: refs. 4, 74, 81, 85, 120—likely examples: refs. 19, 30, 36, 55, 64, 74, 75
Personal cases	Probably 14 cases	Probably three pedigrees (see Fig. 86 for one)

If it were not for the confusion it would create, one might, with historic justification, refer to the disorder inherited as an autosomal recessive as the Hurler syndrome, and to that inherited as a sex-linked recessive as the Hunter syndrome (see Historical Note).

No increased urinary excretion of mucopolysaccharide has been found in the parents of patients with the autosomal recessive form of the disease or the mothers of males with the sex-linked recessive form.[145] Nor has any other method for identification of the heterozygous carrier been developed.

DIFFERENTIAL DIAGNOSIS

At least superficially, there are many resemblances betwen the *Hurler syndrome* and the *Brailsford-Morquio syndrome*.[10,82] In fact, it has been claimed that the two syndromes occurred in different members of the same family.[8] Fig. 92 describes an experience which makes me skeptical of such reports. de Rudder[92] has suggested that the Hurler syndrome is merely a combination (through gene linkage) of Morquio's dystostosis with what he calls a "phosphatide diathesis." Actually, as was discussed in Chapter 1, gene linkage probably plays no role in hereditary syndromes. Cases are pointed to in which it appeared that only the "phosphatide diathesis" existed, e.g., by Grebe.[43]

Brailsford-Morquio chondro-osteodystrophy was independently described about 1929 by the two observers[10,82] whose names identify the syndrome. Morquio's name is more commonly associated with the disease than is Brailsford's. The disorder[3,4,9,13,21,23,32,33,35,77,84,89,100,107,118,123] is usually first detected at the age of less than 1 year, when a thoracolumbar kyphos is noted. The disease is characterized by kyphosis and failure of the trunk to grow in length whereas the extremities grow in a more nearly normal manner. The patients are dwarfed. Radiologically the vertebrae display wedge deformities or, more commonly, platyspondyly, i.e., flat vertebrae. In the extremities there may be palpable enlargement of the epiphyses which may superficially suggest rickets, a frequent misdiagnosis. The skull, mentality, corneas, liver, and spleen are usually normal. These normal features and

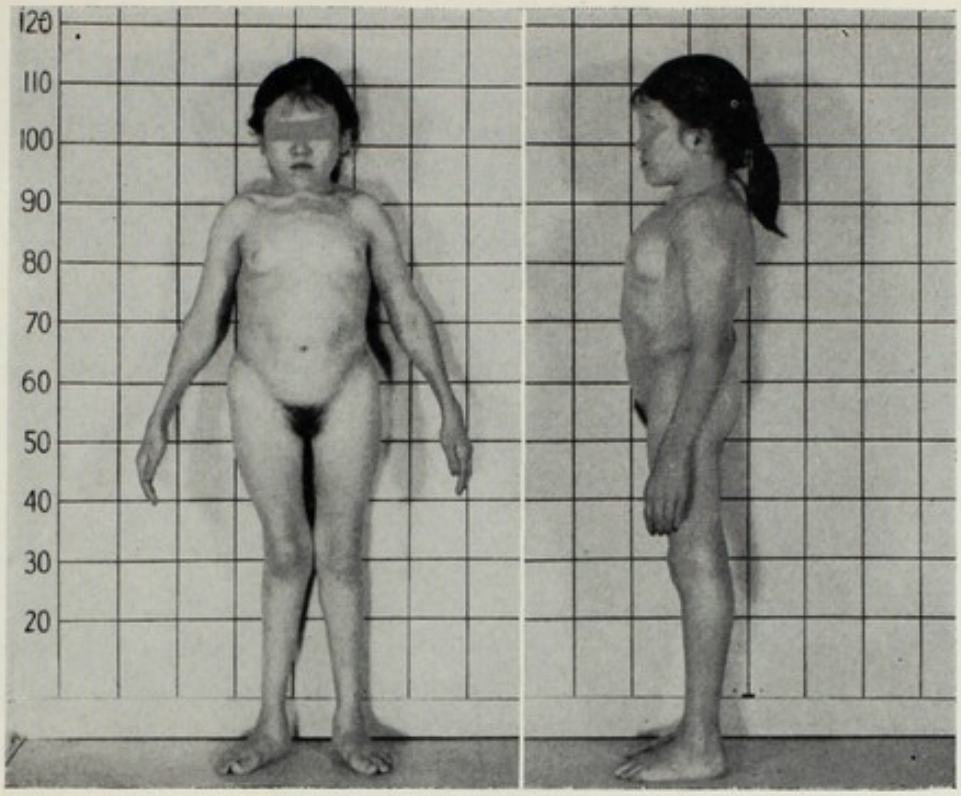


Fig. 91*A*. Fig. 91*B*.

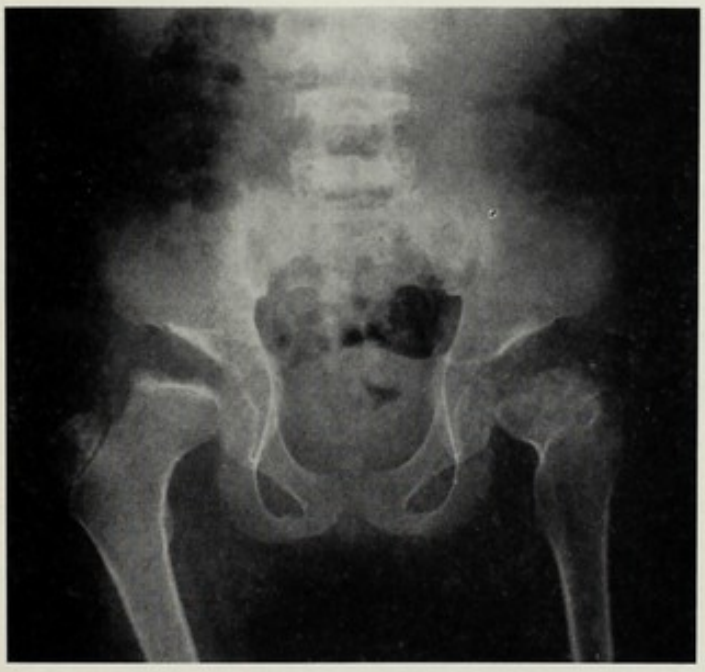


Fig. 91*C*.

Fig. 91*D*.

Figs. 91*A*-91*D*. E. M. (695487), 10 years old, an undoubted example of the precise disorder described by Morquio. Abnormality of growth was first noted by the family at the age of 6 years. Increased diameter of the thorax and genu valgum and increase in the size of the knees and knuckles were noted. The teeth have undergone rapid caries. The patient is alert and above average in intelligence. All joints are hyperextensile. The fourth toes are shorter than the others. The patient's height (Figs. 91*A* and 91*B*) is that of a 5½-year-old child. X-ray films revealed the metacarpals and radii as short and "blocky." The second lumbar vertebra is flame-shaped and posteriorly displaced. Note the pronounced changes, resembling Legg-Perthes' disease, in the heads of the femurs (Fig. 91*C*). (Fig. 91*D* is a tracing of the spine x-ray film.)

The parents are second cousins; they have the same great grandfather. Two siblings of this patient died at the ages of 5 weeks and 9 months of hereditary hyperbilirubinemia, a disease also transmitted as an autosomal recessive.[132a] The parents clearly carry at least two "recessive disease" genes in heterozygous state.

Fig. 92*A*.

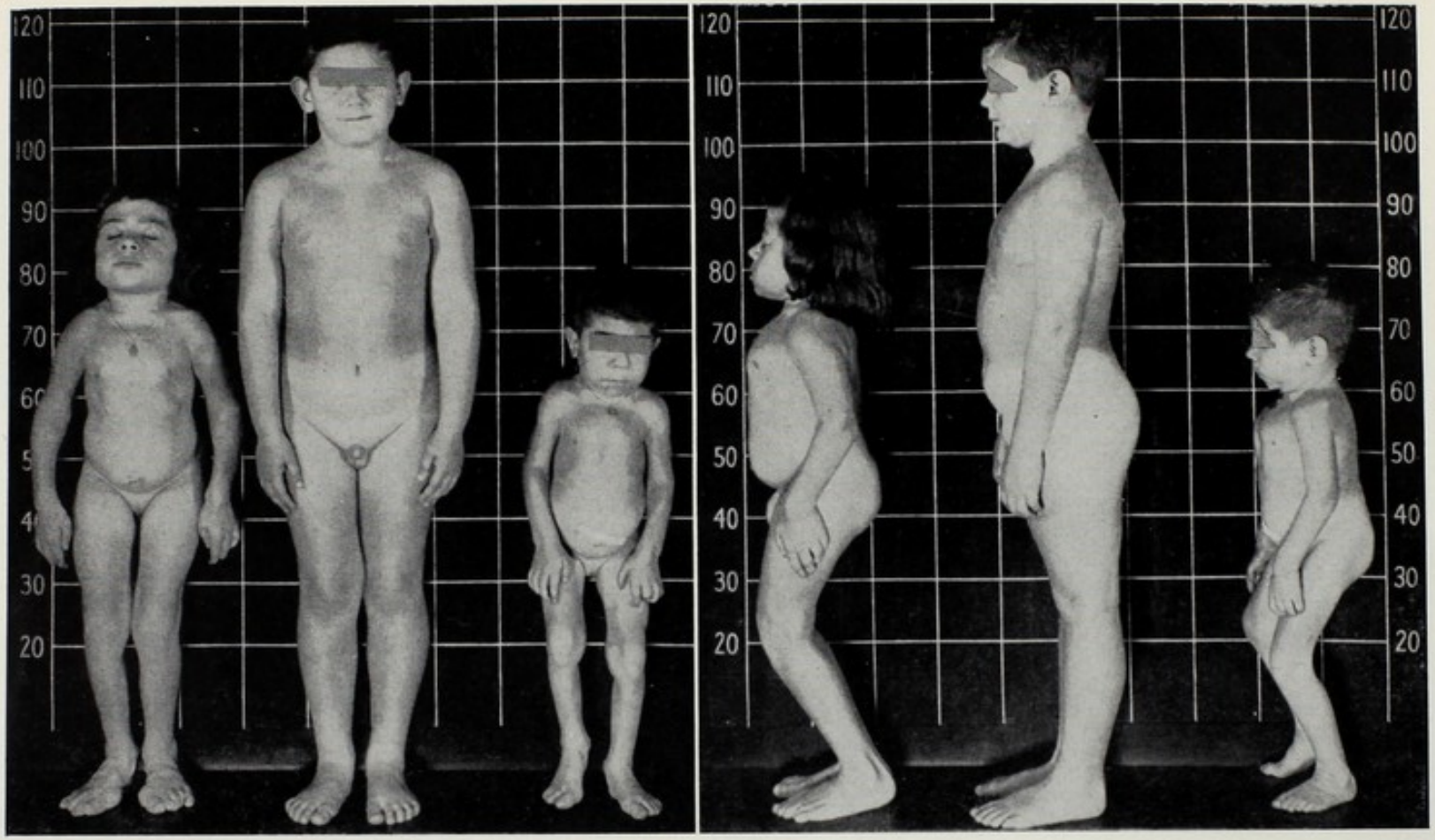


Fig. 92*B*.

Figs. 92*A* and 92*B*. The Morquio syndrome. Three siblings, 12, 6, and 8 years of age, respectively, left to right. The male in the middle, 6 years of age, is normal, as are also two older siblings, 15 and 17 years of age, and the parents.

The two affected siblings appear to have the Morquio syndrome, although some clinical features suggest the Hurler syndrome. Study of the urine in one of them reveals no mucopolysaccharide; hence, the Hurler syndrome is adequately excluded.

Both affected children are markedly dwarfed and have limitation of motion of essentially all joints. Contractures of the fingers (Fig. 92*C*) had their onset at about 18 months. There is no gibbus, but the vertebral bodies show anterior beaking (Fig. 92*E*). Mentality is normal and the children are lively and energetic. Teeth are wide-set, peglike, and susceptible to caries. Both children are somewhat deaf. The affected male has hypospadias; bilateral inguinal hernias with strangulation were repaired surgically at the ages of 1 and 2 years; an umbilical hernia is present. In both affected children there are heart murmurs which are thought to be innocent. The liver and spleen are not enlarged in the affected girl; the liver and spleen are felt 5 and 4 cm., respectively, below the costal margins in the affected male, but this may be largely displacement of the organs. The cornea in both is clear. ECG and EEG are normal.

Follow-up: At the age of 11 years the affected male developed severe pain in the back, complete paralysis below the waist, and fecal and urinary incontinence. X-ray films revealed a marked anterior angulation at the level to T_2, with about 50 per cent spondylolisthesis of T_2 on T_3. Myelogram revealed total block of the spinal canal at that level. Surgical decompression was performed. A serious lack of well-calcified bone was found in the laminae, spinous processes, and vertebral facets, and the fibrocartilage seemed to be of poor grade. The patient died within twenty-four hours of operation, apparently of respiratory distress. Autopsy was not performed.

At the age of 15 years the affected female was essentially unchanged from her status three years before. Catamenia had not occurred. The mother commented repeatedly, over a four-year period of observation, on an objectionable odor associated particularly with the hair of the affected female. Studies of the urine in the affected female demonstrate no abnormal excretion of mucopolysaccharides.

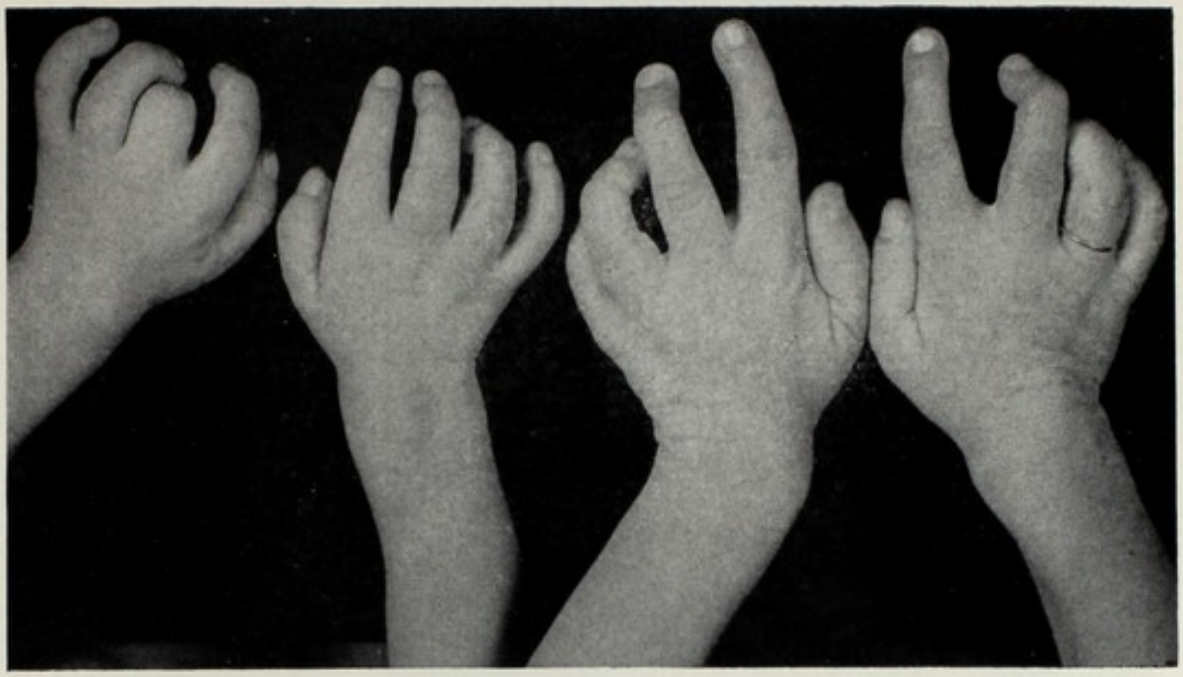


Fig. 92*C*. The fingers are being held in maximum extension possible. Note the contractures.

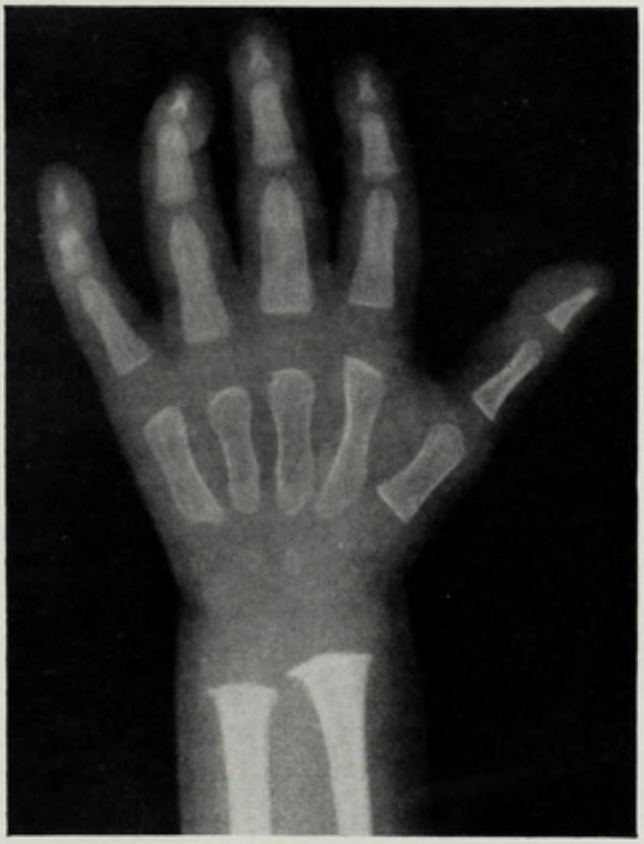


Fig. 92*D*. X-ray film of the hand revealed moderate coarsening of the bones but not as marked changes or the specific change in shape seen in Fig. 85*C*. The contractures seem to be the result of changes in the soft tissues.

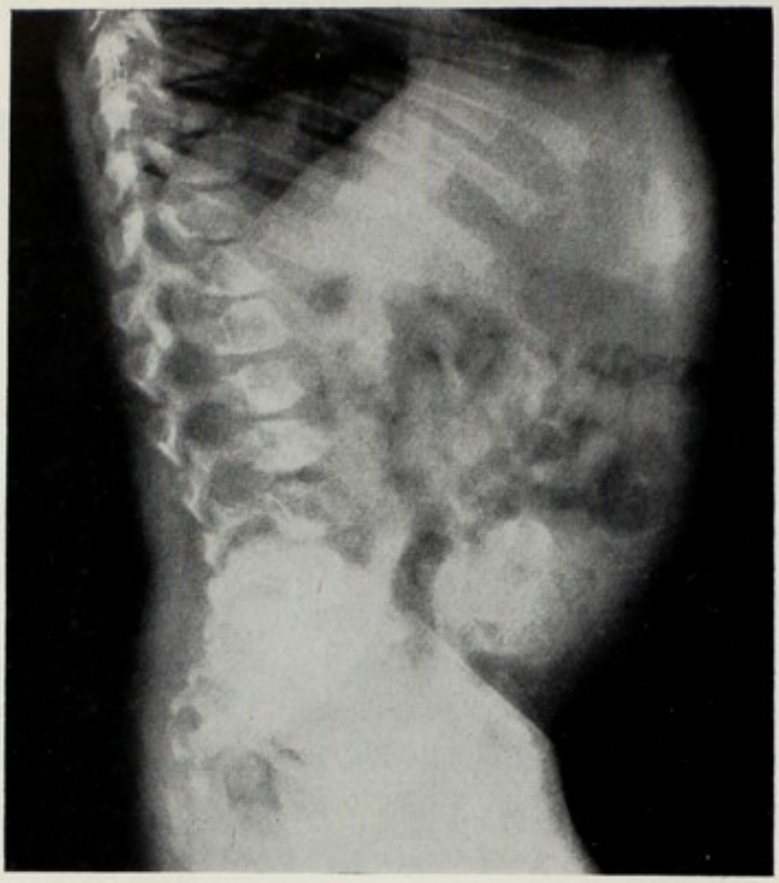


Fig. 92*E*. Lateral view of the spine in affected girl. Note the same sabre-like ribs and beaking of the lower margin of the vertebrae as in Fig. 83*C*.

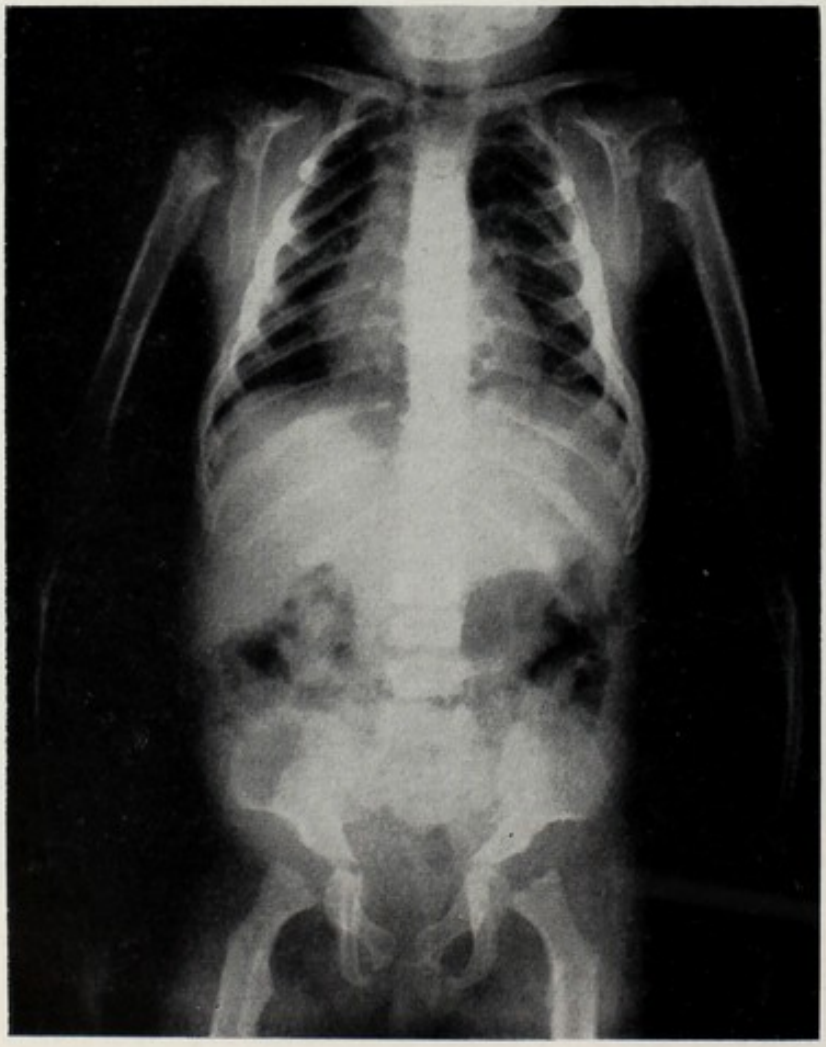


Fig. 92*F*. Frontal view of skeletal system in affected girl. Note the advanced changes in the epiphyses of each femur and humerus.

the relatively minimal affection of the limbs permit differentiation from the Hurler syndrome. In some cases the joints are hypermobile (as described by Morquio), but in others they exhibit limitation of motion. The evidence of a hereditary basis is clear-cut, although the precise mode of inheritance is seeminly variable. The variable inheritance may indicate that a phenotypic similarity leads to classification together of several disorders which are fundamentally distinct. In Jacobsen's very interesting family[59] the disorder was traced through five generations with twenty affected individuals, all male. The genetic behavior was thought to be that of a sex-linked recessive like hemophilia. (Interestingly, two female carriers of the trait had "marked arthritic processes in the hips and ankles.") In other instances inheritance as an autosomal dominant or an autosomal recessive has been hypothesized. Autosomal recessive inheritance as illustrated by the patient in Fig. 91, is probably most frequent.

The difficulties in differentiating the Morquio and the Hurler syndromes are illustrated by the siblings shown in Fig. 92. The difficulties are also well illustrated by the report of Davis and Currier.[26] Although entitled "Morquio's Disease: Report of Two Cases," the patients were described as having striking hepato-

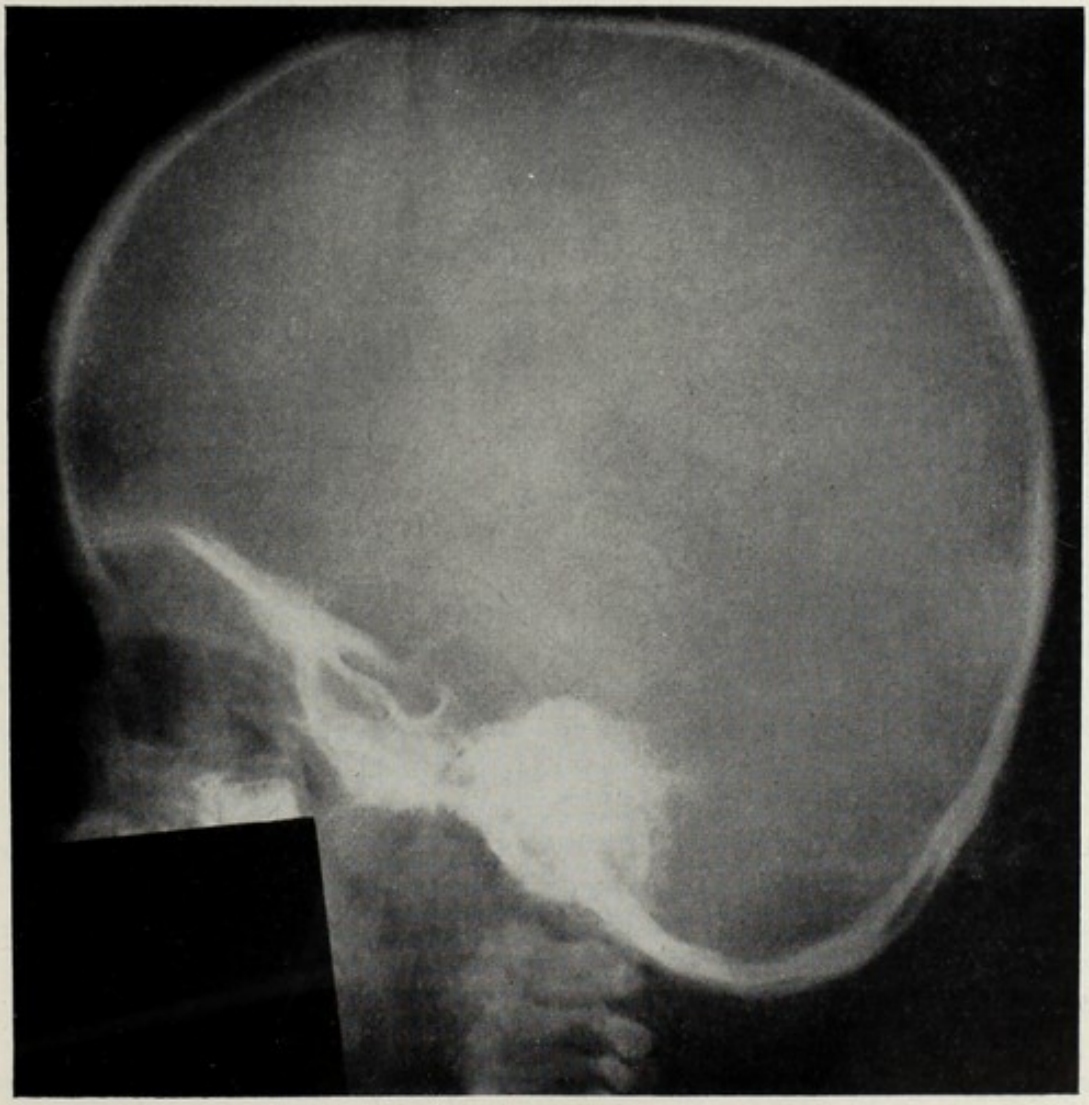


Fig. 92*G*. Note marked anterior pocketing of the sella. Compare with Fig. 86*E*. Clinically there is a ridge running sagittally over the skull (scaphocephaly).

splenomegaly, "shoe-shaped" sella, clawhands, and contractures in other joints. Most subsequent authors have accepted these as cases of the Hurler syndrome. Ruggles[93] applied the label of Morquio's syndrome to the disorder present in three members of a sibship totaling seven. However, the presence of deafness, mental defect, and cloudy cornea makes the Hurler syndrome likely.

A possibly helpful differentiating point is suggested by Garn and Hurme[140] who in three of nine siblings affected by the Morquio syndrome found that the enamel of both the deciduous and permanent teeth was affected, whereas the rest of the tooth seemed normal. The teeth of unaffected siblings were normal. The evidences of enamel defect were thin enamel upon x-ray examination, tendency of the enamel to fracture and flake off, and a dull grayish appearance of the crowns of the teeth.

Specific chemical diagnosis of the Hurler syndrome on the basis of urinary mucopolysaccharides is now available. Furthermore, differentiation of the two genotypes will probably be possible in the future. We have already found assistance from the urinary tests in the positive diagnosis of mild cases of the Hurler syndrome. A simplified screening test has been described by Dorfman[134] and Lorincz.[153] It consists merely of adding five volumes of an acidified bovine serum albumin reagent to one volume of urine; a positive test is indicated by the development of dense white turbidity. Both false negative and false positive tests seem to occur very infrequently.

The following is a simplified "filter paper test" devised by Berry[128a]:

Add 10 and 25 ml. of urine to spots on a small piece of filter paper, using 5 ml. increments and allowing each increment to dry before adding another. Dip papers in toluidine blue reagent for about 45 seconds. Drain. Wash in two separate portions of 10 per cent acetic acid. Urine from patients with the Hurler syndrome gives a purplish reaction; a negative result is light blue. The toluidine blue reagent consists of the following: 1.0 Gm. toluidine blue, 400 ml. acetone, and 100 ml. water.

An alternative toluidine blue reagent is prepared by dissolving 30 mg. of the dye in 100 ml. of Coleman certified buffer solution, pH 2.0. With this reagent staining is done for one minute and the papers are washed in 95 per cent ethanol.

As in the "collagen-vascular" group of acquired connective tissue diseases, there appears to be in the group of chondrodystrophies a clinical spectrum such that one entity blends smoothly into the next and it becomes impossible to say with certainty where one entity leaves off and the next begins. With the "collagen-vascular" group, increasing familiarity has sharpened up the boundaries of the individual entities. It is to be hoped that the nosography of chondrodystrophies will be advanced to a like degree. It is my impression that there are several entirely distinct dysostoses such as Morquio's and Hurler's, and that it is only our ignorance which results in confusion of one with another. Quite the opposite view, namely, that Morquio's syndrome and Hurler's syndrome are clinical variants of what is fundamentally the same disorder, is expressed by Eichenberger.[31]

Reduced joint mobility such as is seen in the Hurler syndrome is a characteristic of *arthrogryposis multiplex congenita.* In fact, in an extensive survey James[60] prefers to use the designation of "multiple congenital articular rigidities," as suggested by Nové-Josserand, rather than the more generally used term pro-

posed by Stern.[104] Subluxation, especially of the hips, may occur in this condition of tight joints, just as it does with the loose-jointedness of the Ehlers-Danlos syndrome. Rigidity of the temporomandibular joint may create a feeding problem in severely affected infants. Ek[136] suggests that bilateral involvement of both the upper and the lower extremities should be a necessary criterion for the diagnosis. The patella may be rudimentary or absent. The subcutaneous tissues are likely to feel thick, doughy, and gelatinous. In general the subcutaneous tissues may be deficient or may be excessive so that the limbs have the appearance of stuffed sausages. The peripheral circulation tends to be poor and the limbs cold. Inguinal hernia occurs as well as congenital anomalies such as hypospadias, cleft palate, cryptorchidism, micrognathia, and mental deficiency. Usually orthopedists are consulted for the joint manifestations. The ages of the patients reported vary from prematurity to 61 years.

From the above brief survey it is evident that there are many features of arthrogryposis, such as the changes in the articular structures and skin and the occurrence of hernia, all from a very early age, which suggest a *heritable* disorder of connective tissue. However, up to 1951 James[60] could find not a single instance of more than one case in the same family. There had been several reports of the disorder in one of twins who appeared to be uniovular.[50,73] These interesting observations cast doubt on both of the two leading theories for the etiology of this condition: (1) an adverse influence of the intrauterine environment; (2) heredity. On the other hand, Ek[136] presents evidence for a significant role of heredity in these cases but emphasizes the frequent occurrence of organic cerebral lesions which may be of primary pathogenetic significance.

Also, to be differentiated from the Hurler syndrome are cleidocranial dysostosis, craniofacial dyostosis of the Crouzon type, Léri's familial pleonosteosis[70,114] (to be described in Chapter 8), and acrocephaly.[88]

The Hurler syndrome was thought to be associated with xanthomatosis and called familial dermo-chondro-corneal dystrophy by François.[40] Rare xanthoma-like lesions were found in the skin in one of my cases (F. M. O'N., Rosewood 4821). Tay-Sachs' disease and the Hurler syndrome bear certain superficial resemblances to each other, and a presumed intermediate form is described by Jervis.[62]

Clinically, cretinism is another frequent misdiagnosis and is often the basis for referral of these cases to endocrinologists. However, the patient with the Hurler syndrome is usually active in his movements and displays normal cutaneous circulation. Tests of thyroid function are usually normal. Bone age is little delayed in the Hurler syndrome and the epiphyseal changes characteristic of cretinism do not occur. Secondary hypothyroidism from involvement of endocrine glands is theoretically possible.

The histologic changes in the brain resemble those of Tay-Sachs' juvenile amaurotic idiocy.[110] The rest of the picture permits differentiation, of course.

Inclusions in the leukocytes said to be indistinguishable from those described in the Hurler syndrome occur as an isolated hereditary trait, the Alder anomaly.[65]

As awareness of, and interest in, the Hurler syndrome increases, we are seeing more cases in which the diagnosis cannot be established or denied with confidence. In two such cases (N. L. H., NIH 7634; D. F., 799359) mental retardation was the predominant feature. Its course was consistent with that in the Hurler syn-

drome, there having been seemingly normal development for about two years and retrogression thereafter. However, the liver and spleen were not enlarged, and the skeletal features were limited to slight beaking of the vertebrae and "chunky" appearance of the ribs and phalangeal bones. Study of the urine for mucopolysaccharides may help in such cases and will, perhaps, push back the frontiers of this disease.

OTHER CONSIDERATIONS

As with the other multifaceted syndromes studied in this series, diverse specialists, such as surgeons (*in re:* hernia), otolaryngologists (*in re:* deafness, rhinitis), ophthalmologists (*in re:* corneal abnormality), psychiatrists (*in re:* mental deficiency), cardiologists (*in re:* cardiac abnormalities), orthopedists (*in re:* skeletal deformity), neurosurgeons (*in re:* increased intracranial pressure), endocrinologists (*in re:* differentiation from cretinism), see these patients for the individual complaints which comprise the total picture.

The nosography of the Hurler syndrome has already begun to follow the pattern of so many other hereditary syndromes: it is at first considered to be largely a pediatric disorder simply because only the most severely affected individuals are identified. These individuals are so severely affected that they are unlikely to survive to adulthood and come to the attention of the internist. Because of the wide variability in expressivity which the student of hereditary disease comes to expect, the occurrence of mildly affected individuals in the adult age group is not surprising. It is entirely reasonable to believe that procreation by these individuals is possible. A 19-year-old patient of Ashby and associates was sexually mature.[2] (The authors stated: "Sexual development exceeds the normal.") Mental capacity may be little restricted: one of the patients of Barr and his co-workers was an agricultural engineer. Ullrich[112] was one of the first to write in detail about the "late form" of the disease, as he called it in contradistinction to the "infantile form." (These are undesirable terms since they may lead to the same confusion that has existed in the case of osteogenesis imperfecta.) He considered it likely that the 47- and 40-year-old patients described by Schmidt in 1938[97] as suffering from "a previously undescribed form of familial degeneration of the cornea in association with osteoarthropathy" and earlier (1927) by Schinz and Furtwängler[95] as "hereditary osteoarthropathy with recessive inheritance," suffered from a mild ("late") form of the Hurler syndrome. Of eleven children of consanguineous parents (first cousins) two daughters had died at the age of 8 and 18 years, respectively. They showed markedly crippling stiffening of their joints. Scharf[94] described a 28-year-old man, Grebe[43] described patients 21, 24, and 30 years old, Hooper[51] had patients 20, 30, and 37 years of age, and Barr and his co-workers[102] had patients 28 and 29 years old. Schwarz and Gagne[98] had a 37-year-old patient who was still living. Zierl[124] reported on a 21-year-old man and Noller[84] on a 43-year-old woman. Cocchi[16] provides two photographs of a patient, one taken when he was 4 years old, the other when he was 22 years. Cole and his associates[19] had a 23-year-old patient.

Hurler[56] stated that mydriasis was unusually marked and prolonged after homatropine but sweating from pilocarpine less than normal.

No definitive treatment for the Hurler syndrome is known. Hurler,[56] in one of her original cases,[58] observed that thyroid extract, while having no measurable effect, produced subjective improvement in the patient. We have observed the same phenomenon (Fig. 86). Large doses of prednisone had no effect on urinary excretion of mucopolysaccharide.[145a]

SUMMARY

In the Hurler syndrome, the charcteristic features are skeletal deformity, limitation of joint motion, hernia, hepatosplenomegaly, cardiac abnormality, corneal opacification, deafness, and mental retardation.

The basic pathology is the distention of cells of many organs with material of two types: a complex polysaccharide and an aglycolipid. The fundamental defect appears to concern either the mucopolysaccharide or "structural polysaccharide" of connective tissue.

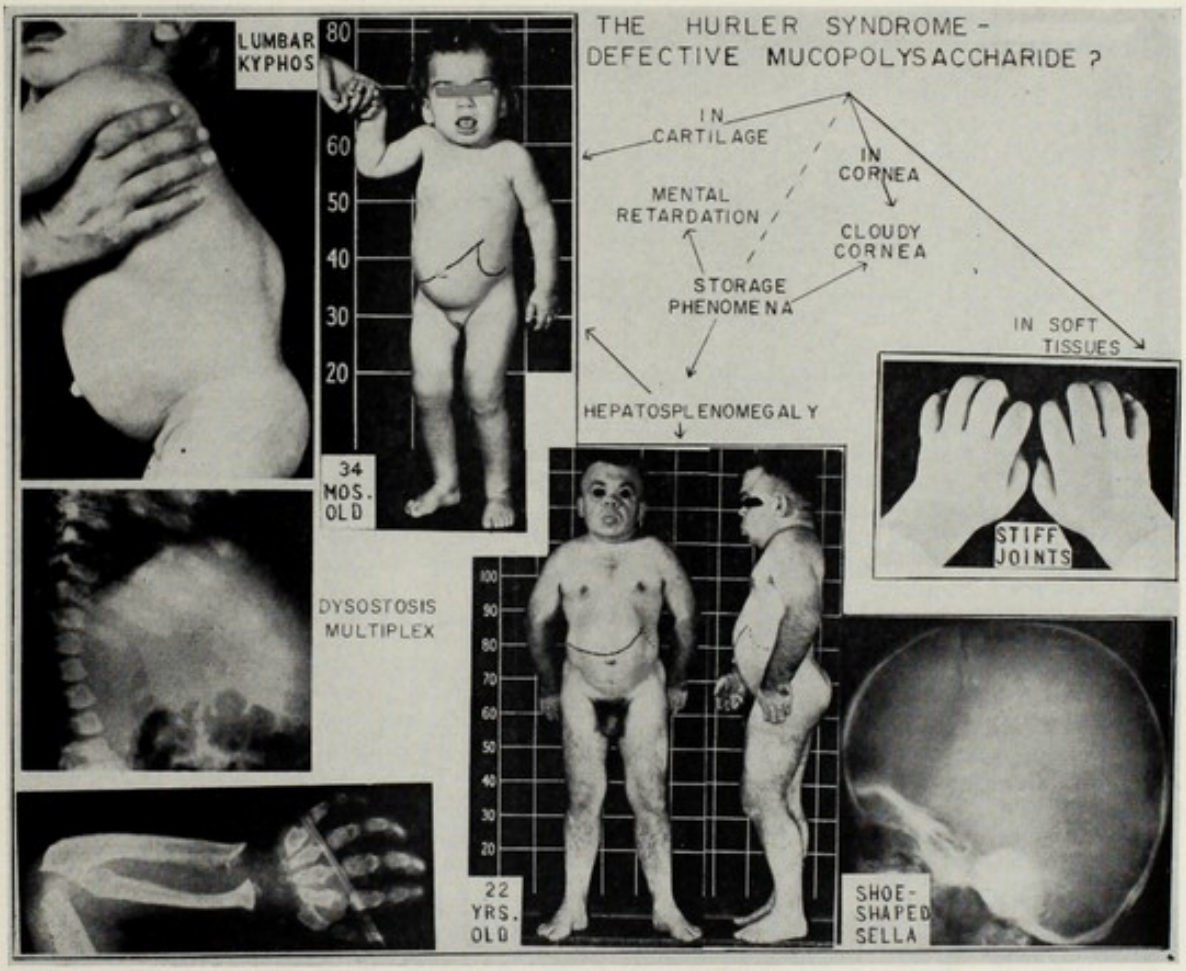


Fig. 93. Pictorial pedigree of causes.

The Hurler syndrome is usually inherited as an autosomal recessive trait, less commonly as a sex-linked (x-linked) recessive. Clinical differences between the two genotypes appear to exist (see Table 5).

Other chondrodystrophies, especially that of Brailsford and Morquio, display many features in common with the Hurler syndrome but are fundamentally distinct entities.

REFERENCES

1. Andersson, B., and Tandberg, O.: Lipochondrodystrophy (Gargoylism, Hurler Syndrome) With Specific Cutaneous Deposits, Acta paediat. **41**:162, 1952.
2. Ashby, W. R., Stewart, R. M., and Watkins, J. H.: Chondro-osteo-dystrophy of the Hurler Type (Gargoylism); a Pathological Study, Brain **60**:149, 1937.
3. Barnett, E. J.: Morquio's Disease, J. Pediat. **2**:65, 1933.
4. Beebe, R. T., and Formel, P. F.: Gargoylism: Sex-Linked Transmission in Nine Males, Tr. Am. Clin. & Climatol. A. **66**:199, 1954.
5. Berliner, M. L.: Lipin Keratitis of Hurler's Syndrome (Gargoylism or Dysostosis Multiplex); Clinical and Pathologic Report, Arch. Ophth. **22**:97, 1939.
6. Bindschedler, J. J.: Polydystrophie du type Hurler chez un frére et une soeur, Bull. Soc. pédiat. de Paris **36**:571, 1938.
7. Binswanger, E., and Ullrich, O.: Ueber die Dysostosis multiplex (Typus Hurler) und ihre Beziehungen zu anderen Konstitutionsanomalien, Ztschr. Kinderh. **54**:699, 1933.
8. Böcker, E.: Zur Erblichkeit der Dysostosis multiplex, Ztschr. Kinderh. **63**:688, 1943.
9. Boldt, L.: Beitrag zur Dysostosis multiplex (von Pfaundler-Hurler). Ztschr. Kinderh. **63**:679, 1943.
10. Brailsford, J. F.: Chondro-osteo-dystrophy, Roentgenographic and Clinical Features of Child With Dislocation of Vertebrae, Am. J. Surg. **7**:404, 1929; The Radiology of Bones and Joints, ed. 5, Baltimore, 1953, Williams & Wilkins Co.
11. Brante, G.: Gargoylism: a Mucopolysaccharidosis, Scandinav. J. Clin. & Lab. Invest. **4**:43, 1952.
12. Bridge, E. M., and Holt, L. E., Jr.: Glycogen Storage Disease; Observations on the Pathologic Physiology of Two Cases of the Hepatic Form of the Disease, J. Pediat. **27**:279, 1945.
13. Brown, D. O.: Morquio's Disease, M. J. Australia **1**:598, 1933.
14. Caffey, J.: Gargoylism (Hunter-Hurler Disease, Dysostosis Multiplex, Lipochondrodystrophy); Prenatal and Neonatal Bone Lesions and Their Early Postnatal Evaluation, Am. J. Roentgenol. **67**:715, 1952.
15. Cocchi, U.: Polytope erbliche enchondrale Dysostosen, Fortschr. Geb. Röntgenstrahlen **72**:435, 1950.
16. Cocchi, U.: Hereditary Diseases With Bone Changes; *In* Schinz, H. R., Boensch, W. E., Friedl, E., and Uehlinger, E.: Roentgen-diagnostics, New York, 1951, Grune & Stratton, Inc., p. 728.
17. Cockayne, E. A.: Gargoylism (Chondro-osteodystrophy, Hepatoplenomegaly, Deafness in Two Brothers), Proc. Roy. Soc. Med. **30**:10, 107, 1936.
18. Cockayne, E. A.: Gargoylism (Chondro-osteodystrophy, Corneal Opacities, Hepatosplenomegaly and Mental Deficiency), Proc. Roy. Soc. Med. **30**:158, 1936.
19. Cole, H. N., Jr., Irving, R. C., Lund, H. Z., Mercer, R. D., and Schneider, R. W.: Gargoylism With Cutaneous Manifestations, Arch. Dermat. & Syph. **66**:371, 1952.
20. Cordes, F. C., and Hogan, J. J.: Dysostosis Multiplex (Hurler's Disease); Lipochondrodystrophy; Gargoylism; Report of Ocular Findings in Five Cases, With a Review of the Literature, Arch. Ophth. **27**:637, 1942.
21. Coward, N. R., and Nemir, R. T.: Familial Osseous Dystrophy (Morquio's Disease), Am. J. Dis. Child. **46**:213, 1933.
22. Craig, W. S.: Gargoylism in a Twin Brother and Sister, Arch. Dis. Childhood **29**:293, 1954.
23. Crawford, T.: Morquio's Disease, Arch. Dis. Childhood **14**:70, 1939.
24. Cunningham, R. C.: A Contribution to the Genetics of Gargoylism, J. Neurol. Neurosurg. & Psychiat. **17**:191, 1954.
25. David, B.: Ueber einen dominanten Erbgang bei einer polytopen enchondralen Dysostose Typ Pfaundler-Hurler, Ztschr. Orthop. **84**:657, 1954.
26. Davis, D. B., and Currier, F. P.: Morquio's Disease. Report of Two Cases, J.A.M.A. **102**:2173, 1934.
27. Dawson, I. M.: The Histology and Histochemistry of Gargoylism, J. Path. & Bact. **67**:587, 1954.
28. Debré, R., Marie, J., and Thieffry, S.: La polydystrophie de Hurler: Le "gargoylisme" d'Ellis (ál'occasion des trois observations nouvelles), Semaine hôp. Paris **22**:309, 1946.
29. de Lange, C., Gerlings, P. G., de Kleyn, A., and Lettinga, T. W.: Some Remarks on Gargoylism, Acta. paediat. **31**:398, 1944.
30. de Lange, C.: Dysostosis Multiplex of the Hurler Type (Gargoylism), Psychiat. en neurol. bl. **1-2**:2, 1942.
31. Eichenberger, K.: Kann die Dysostosis Morquio als selbständiges Krankheilschild vom Gargoylismus abgetrennt werden? Ann. paediat. **182**:107, 1954.
32. Einhorn, N. H., Moore, J. R., Ostrum, H. W., and Rountree, L. G.: Osteochondrodystrophia Deformans (Morquio's Disease). Report of Three Cases, Am. J. Dis. Child. **61**:776, 1941.

33. Einhorn, N. H., Moore, J. R., and Rountree, L. G.: Osteochondrodystrophia deformans (Morquio's Disease). Observations at Autopsy in One Case, Am. J. Dis. Child. **72**:536, 1946.
34. Ellis, R. W. B., Sheldon, W., and Capon, N. B.: Gargoylism (Chondro-osteo-dystrophy, Corneal Opacities, Hepatosplenomegaly and Mental Deficiency), Quart. J. Med. **5**:119, 1936.
35. Ellman, P.: A Rare Primary Osseous Dystrophy, Brit. J. Child. Dis. **30**:188, 1933.
36. Emanuel, R. W.: Gargoylism With Cardiovascular Involvement in Two Brothers. Brit. Heart J. **16**:417, 1954.
37. Engel, D.: Dysostosis Multiplex (Pfaundler-Hurler Syndrome), Two Cases, Arch. Dis. Childhood **14**:217, 1939.
38. Franceschetti, A., and Forni, S.: The Heredo-familial Degenerations of the Cornea, Acta 16th Internatl Cong. Ophth., London, July 17-22, 1950, pp. 157-193.
39. François, J., and Rabaey, M.: Examen histochimique de la dystrophie cornéenne et étude de l'hérédité dans un cas de gargoylisme (maladie de Hurler), Ann. ocul. **185**:784, 1952.
40. François, J.: Dystrophie dermo-chondro-cornéenne familiale, Bull. Acad. roy. de med. de Belgique **14**:135, 1949.
41. Glegg, R. E., Eidinger, D., and Leblond, C. P.: Some Carbohydrate Components of Reticular Fibers, Science **118**:614, 1953.
42. Green, M. A.: Gargoylism (Lipochondrodystrophy), J. Neuropath. & Exper. Neurol. **7**:399, 1948.
43. Grebe, H.: Die Chondrodysplasie, ihre Klinik, Differentialdiagnose und Erbpathologie, Habilitationsschrift, Frankfurt, 1942. Cited by Ullrich.[112]
44. Halperin, S. L., and Curtis, G. M.: The Genetics of Gargoylism, Am. J. Ment. Deficiency **46**:298, 1942.
45. Harvey, R. M.: Hurler-Pfaundler Syndrome (Gargoylism). Review of the Literature With Report of an Additional Case, Am. J. Roentgenol. **48**:732, 1942.
46. Hässler, E.: Die Beziehungen der Hurlerschen Krankheit (Dysostosis multiplex-dysostotische Idiotie-Gargolismus) zum Kretinismus, Monatsschr. Kinderh. **86**:96, 1941.
47. Helmholtz, H. F., and Harrington, E. R.: Syndrome Characterized by Congenital Clouding of the Cornea and by Other Anomalies, Am. J. Dis. Child. **12**:793, 1931.
48. Henderson, J. L.: Gargoylism; Review of Principal Features With Report of Five Cases, Arch. Dis. Childhood **15**:215, 1940.
49. Henderson, J. L., MacGregory, A. R., Thannhauser, S. J., and Holden, R.: Pathology and Biochemistry of Gargoylism; Report of Three Cases With Review of Literature, Arch. Dis. Childhood **27**:230, 1952.
50. Hillman, J. W., and Johnson, J. T. H.: Arthrogryposis Multiplex Congenita in Twins, J. Bone & Joint Surg. **34A**:211, 1952.
51. Hooper, J.M.D.: Unusual Case of Gargoylism, Guy's Hosp. Rep. **101**:222, 1952.
52. Hubeny, M. J., and Delano, R. J.: Dysostosis Multiplex, Am. J. Roentgenol. **46**:336, 1941.
53. Hueper, W. C.: Macromolecular Substances as Pathogenic Agents, Arch. Path. **33**:267, 1942.
54. Hueper, W. C.: Experimental Studies in Cardiovascular Pathology. Pectin Atheromatosis and Thesaurosis in Rabbits and in Dogs, Arch. Path **34**:883, 1942.
55. Hunter, C.: A Rare Disease in Two Brothers, Proc. Roy. Soc. Med. **10**:104, 1917.
56. Hurler, G.: Ueber einen Typ multipler Abartungen, vorwiegend am Skelettsystem, Ztschr. Kinderh. **24**:220, 1919.
57. Husler, J.: Handbuch der Kinderheil, ed 4, vol. 1, p. 651.
58. Jackson, W. P. U.: Clinical Features, Diagnosis and Osseous Lesions of Gargoylism Exemplified in 3 Siblings, Arch. Dis. Childhood **26**:549, 1951.
59. Jacobsen, A. W.: Hereditary Osteochondrodystrophia Deformans. A Family With Twenty Members Affected in Five Generations, J. A. M. A. **113**:121, 1939.
60. James, T.: Multiple Congenital Articular Rigidities: A Review of the Literature With Report of 2 Cases, Edinburgh M. J. **58**:565, 1951.
61. Jelke, H.: Gargoylism; Report of a Case, Ann. paediat. **177**:355, 1951.
62. Jervis, G. A.: Familial Mental Deficiency Akin to Amaurotic Idiocy and Gargoylism, Arch. Neurol. & Psychiat. **47**:943, 1942.
63. Jervis, G. A.: Gargoylism: Study of 10 Cases With Emphasis on the Formes Frustes, A. M. A. Arch. Neurol. & Psyciat. **63**:681, 1950.
64. Jewesbury, R. C., and Spence, J. C.: Two Cases: (1) Oyxcephaly and (2) Acrocephaly, With Other Congenital Deformities, Proc. Roy. Soc. Med. **14**:27, 1921.
65. Jordans, G. H. W.: Hereditary Granulation Anomaly of Leucocytes (Alder), Acta med. scandinav. **129**:348, 1947.
66. Josephy, H.: Lipoidosis of the Brain Combined With Glycogenosis of the Liver, J. Neuropath. & Exper. Neurol. **8**:214, 1949.
67. Kny, W.: Zur Kenntnis der Dysostosis multiplex Typ Pfaundler-Hurler, Ztschr. Kinderh. **63**:366, 1942.
68. Kressler, R. J., and Aegerter, E. E.: Hurler's Syndrome (Gargoylism); Summary of Literature and Report of Case With Autopsy Findings, J. Pediat. **12**:579, 1938.

69. Lausecker, H.: Zur Symptomatologie der Dysostosis multiplex (Pfaundler-Hurler), Hautarzt **5**:538, 1954.
70. Léri, A.: Pléonostéose familiale (Dystostrophie osseuse généraliseé, congénitale et hereditaire, Presse méd. **2**:13, 1922.
71. Lindsay, S.: The Cardiovascular System in Gargoylism, Brit. Heart J. **12**:17, 1950.
72. Lindsay, S., Reilly, W. A., Gotham, Th. J., and Skahen, R.: Gargoylism. II. Study of Pathologic Lesions and Clinical Review of Twelve Cases, Am. J. Dis. Child. **76**:239, 1948.
73. Lipton, E. L., and Morgenstern, S. H.: Arthrogryposis Multiplex Congenita in Identical Twins, Am. J. Dis. Child. **89**:233, 1955.
74. Lundström, R.: Gargoylism; Three Cases, Nord. med. **33**:41, 1947.
75. Lurie, L. A., and Levy, S.: Gargoylism, Am. J. M. Sc. **207**:184, 1944.
76. Magee, K. R.: Leptomeningeal Changes Associated With Lipochondrodystrophy (Gargoylism), Arch. Neurol. & Psychiat. **63**:282, 1950.
77. Meyer, H. F., and Brennemann, J.: A Rare Osseous Dystrophy (Morquio), Am. J. Dis. Child. **43**:123, 1932.
78. Meyer, K., Linker, A., Davidson, E. A., and Weissman, B.: The Mucopolysaccharides of Bovine Cornea, J. Biol. Chem. **205**:611, 1953.
79. Meyer, K.: Chemistry of Ground Substance; *In* Connective Tissue in Health and Disease (G. Asboe-Hansen, ed.), Copenhagen, 1954, Ejnar Munksgarrd, p. 54.
80. Meyer, S. J., and Okner, H. B.: Dysostosis Multiplex With Special Reference to Ocular Findings, Am. J. Ophth. **22**:713, 1939.
81. Millman, G., and Whittick, J. W.: A Sex-Linked Variant of Gargoylism, J. Neurol. Neurosurg. & Psychiat. **15**:253, 1952.
82. Morquio, L.: Sur une forme de dystrophie osseuse familiale, Bull. Soc. pédiat. de Paris **27**:145, 1929.
83. Newell, F. W., and Koistinen, A.: Lipochondrodystrophy (Gargoylism); Pathologic Findings in Five Eyes of Three Patients, Arch. Ophth. **53**:45, 1955.
84. Noller, F.: Dysostosis multiplex (Hurler) und verwandte Krankheitsbilder, Deutsche Ztschr. Chir. **258**:259, 1943.
85. Njå, A.: A Sex-linked Type of Gargoylism, Acta paediat. **33**:267, 1946.
86. Nonne, M.: Familiäres Verkommen (3 Geschwister) einer Kombination von imperfekter Chondrodystrophie mit imperfekten Myxoedema infantile, Deutsche Ztschr. Nervenh. **83**:263, 1925.
87. Park, E. A., and Powers, G. F.: Acrocephaly and Scaphocephaly With Symmetrically Distributed Malformations of the Extremities, Am. J. Dis. Child. **20**:235, 1920.
88. Pfaundler, M.: Demonstrationen über einen Typus kindlicher Dysostose, Jahrb. Kinderh. **92**:420, 1920.
89. Pohl, J. F.: Osteodystrophy (Morquio's Disease): Progressive Kyphosis From Congenital Wedge-Shaped Vertebrae, J. Bone & Joint Surg. **21**:187, 1939.
90. Reilly, W. A.: The Granules in the Leuocytes in Gargoylism, Am. J. Dis. Child. **62**:489, 1941.
91. Rose, J. R., Hawke, W. A., and Brown, A.: Gargoylism, Arch. Dis. Childhood **16**:71, 1941.
92. Rudder, B. de: Über "Phosphatiddiathese" und ihr Verhältnis zur Dysostosis multiplex und Dysostosis Morquio, Ztschr. Kinderh. **63**:407, 1942.
93. Ruggles, H. C.: Dwarfism Due to Disordered Epiphyseal Development, Am. J. Roentgenol. **25**:91, 1931.
94. Scharf, J.: Ein Beitrag zur Kenntnis der Dysostosis multiplex (Hurler) unter besonderer Berücksichtigung der Erbverhältnisse, Gräefes Arch. Ophth. **143**:477, 1941.
95. Schinz, H. R., and Furtwängler, A.: Zur Kenntnis einer hereditären Osteoarthropathie mit rezessivem Erbgang, Deutsche Ztschr. Chir. **207**:398, 1927.
96. Schmidt, M. B.: Die anatomischen Veränderungen des Skeletts bei der Hurlerschen Krankheit, Zentralbl. allg. Path. **79**:113, 1942.
97. Schmidt, R.: Eine bischer nicht beschreibene Form familiäre Horhautentartung in Verbindung mit Osteoarthropathie, Klin. Monatsbl. Augenh. **100**:616, 1938.
98. Schwarz, H., and Gagne, R.: A Case of Gargoylism, Canad. M. A. J. **66**:375, 1952.
99. Sears, H. R., and Maddox, J. K.: A Case of Hurler's Disease, M. J. Australia **1**:488, 1945.
100. Shelling, D. H.: Osteochondrodystrophia Deformans (Morquio's Disease); *In* Brennemann's Practice of Pediatrics, Hagerstown, 1948, W. F. Prior Co., Inc., vol. 4, chap. 29.
101. Slot, G., and Burgess, G. L.: Gargoylism, Proc. Roy. Soc. Med. **31**:1113, 1937.
102. Smith, E. B., Hempelmann, T. C., Moore, S., and Barr, D. P.: Gargoylism (Dysostosis Multiplex): Two Adult Cases With One Autopsy, Ann. Int. Med. **36**:652, 1952.
103. Stern, C.: Principles of Human Genetics, San Francisco, 1950, Freeman, p. 406.
104. Stern, W. G.: Arthrogryposis Multiplex Congenita, J.A.M.A. **81**:1507, 1923.
105. Straus, R., Merliss, R., and Reiser, R.: Gargoylism. Review of the Literature and Report of the Sixth Autopsied Case With Chemical Studies, Am. J. Clin. Path. **17**:671, 1947.
106. Strauss, L.: The Pathology of Gargoylism. Report of a Case and Review of the Literature, Am. J. Path. **24**:855, 1948.

107. Summerfeldt, P., and Brown, A.: Morquio's Disease: Report of Two Cases, Arch. Dis. Childhood **11**:221, 1936.
108. Taylor, H. E.: The Role of Mucopolysaccharides in the Pathogenesis of Intimal Fibrosis and Arteriosclerosis of the Human Aorta, Am. J. Path. **24**:871, 1953.
109. Thannhauser, S.: Lipoidoses: Diseases of the Cellular Lipid Metabolism, New York, 1950, Oxford University Press.
110. Tuthill, C. R.: Juvenile Amaurotic Idiocy, Arch. Neurol & Psychiat. **32**:198, 1934.
111. Ullrich, O.: Die Pfaundler-Hurlersche Krankheit. Ein Beitrag zum Problem pleitroper Genwirkung in der Erbpathologie des Menschen, Ergebn. inn. Med. u. Kinderh. **63**:929, 1943.
112. Ullrich, O., and Wiedemann, H. R.: Zur Frage der konstitutionellen Granulationanomalien der Leukocyten in ihrer Beziehung zu enchondralen Dysostosen, Klin. Wchnschr. **31**:107, 1953.
113. Uzman, L. L.: Chemical Nature of the Storage Substance in Gargoylism, Arch. Path. **60**:308, 1955.
114. Valentin, B.: Pleonosteosis familiaris (Léri); *In* Schwalbe-Gruber; Die Morphologie der Misshildungen des Menschen und der Tiere, III Teil; XVII, p. 502. Jena, Fischer.
115. Veasy, C. A.: Ocular Findings Associated With Dysostosis Multiplex and Morquio's Disease, Arch. Ophth. **25**:557, 1941.
116. Wagner, R.: Glycogen Content of Isolated White Blood Cells in Glycogen Storage Disease, Am. J. Dis. Child. **73**:559, 1947.
117. Washington, J. A.: Lipochondrodystrophy; *In* Brennemann's Practice of Pediatrics, Hagerstown, 1937, W. F. Prior Co., Inc., vol. IV, chap. 30.
118. Whiteside, J. D., and Cholmeley, J. G.: Morquio's Disease; Review of Literature With Description of 4 Cases, Arch. Dis. Childhood **27**:487, 1952.
119. Wolf, H. G.: Zur Frage der Alder-Anomalie der Leukocyten, Ztschr. Kinderh. **75**:27, 1954.
120. Wolff, D.: Microscopic Study of Temporal Bones in Dysostosis Multiplex (Gargoylism), Laryngoscope **52**:218, 1942.
121. Woodin, A. M.: The Corneal Mucopolysaccharide, Biochem. J. **51**:319, 1952.
122. Zeeman, W. P. C.: Gargoylismus, Acta ophth. **20**:40, 1942.
123. Zellweger, H., Giaccai, L., and Firzli, S.: Gargoylism and Morquio's Disease, Am. J. Dis. Child. **84**:421, 1952.
124. Zierl, F.: Ueber Skelettveränderungen bei der juvenilen Form der amaurotischen Idiotie, Ztschr. ges. Neurol. u. Psychiat. **131**:400, 1930.
125. Alder, A. von: Konstitutionell bedingte Granulationsveränderungen der Leucocyten und Knochenveränderungen, Schweiz. med. Wchnschr. **80**:1095, 1950.
125a. Astaldi, G., and Strosselli, E.: Histochemische Untersuchungen an den Leukoblasten und Leukocyten der konstitutionellen Alderschen Anomalie, Schweiz. med. Wchnschr. **88**:989, 1958.
126. Aycock, E. K., and Paul, J. R., Jr.: Gargoylism; a Report of Two Cases in Negroes, J. South Carolina M. A. **53**:128, 1957.
127. Beradinelli, W.: Gargoylisme chez un petit noir, Presse méd. **64**:1757, 1956.
128. Berkhan, O.: Zwei Fälle von Skaphokephalie, Arch. Anthrop. **34**:8, 1907.
128a. Berry, H. K. (Cincinnati): Personal communication.
129. Bishton, R. L., Norman, R. M., and Tingey, A.: The Pathology and Chemistry of a Case of Gargoylism, J. Clin. Path. **9**:305, 1956.
130. Brown, D. H.: Tissue Storage of Mucopolysaccharides in Hürler-Pfaundler's Disease, Proc. Nat. Acad. Sc. **43**:783, 1957.
131. Brown, David H. (St. Louis): Personal communication.
131a. Chou, Yi-Che: Ocular Signs in Gargoylism, Chinese M. J. **78**:130, 1959.
132. Cottier, H.: Infantile kardiovaskuläre Sklerose bei Gargoylismus, Schweiz. Ztschr. allg. Path. **20**:745, 1957.
132a. Crigler, J. F., Jr., and Najjar, V. A.: Congenital Familial Nonhemolytic Jaundice With Kernicterus, Pediatrics **10**:169, 1952.
133. Crome, L.: Epiloia and Endocardial Fibro-elastosis, Arch. Dis. Childhood **29**:136, 1954.
134. Dorfman, A.: Studies on the Biochemistry of Connective Tissue, Pediatrics **22**:576, 1958.
135. Dorfman, A., and Lorincz, A. E.: Occurrence of Urinary Acid Mucopolysaccharides in the Hurler Syndrome, Proc. Nat. Acad. Sc. **43**:443, 1957.
136. Ek. J. I.: Cerebral Lesions in Arthrogryposis Multiplex Congenita, Acta paediat. **47**:302, 1958.
137. Engle, R. L., Jr. (New York City): Personal communication.
138. Epps, R. P., and Scott, R. B.: Gargoylism (Hurler's Syndrome; Lipochondrodystrophy Dysostosis Multiplex); Report of 2 Cases in Negro Children, J. Pediat. **52**:182, 1958.
139. Garn, S. M. (Yellow Springs, O.): Personal communication.
140. Garn, S. M., and Hurme, V. O.: Dental Defects in Three Siblings Afflicted With Morquio's Disease, Brit. Dent. J. **93**:210, 1952.
141. Gasteiger, H., and Liebenam, L.: Beitrag zur Dysostosis multiplex unter besonderer Berüchsichtigung des Augenbefundes, Klin. Monatsbl. Augenh. **99**:333, 1937.
142. Gilbert, E. F., and Guin, G. H.: Gargoylism; a Review Including Two Occurrences in the American Negro, A.M.A. J. Dis. Child. **95**:69, 1958.

143. Greenfield, J. G., and others: Neuropathology, London, 1958, Edward Arnold & Co., p. 468.
144. Griffiths, S. B., and Findlay, M.: Gargoylism: Clinical, Radiological and Haematological Features in Two Siblings, Arch. Dis. Childhood **32**:229, 1958.
145. Grumbach, M. M. (New York City): Personal communication.
145a. Grumbach, M. M., and Meyer, K.: Urinary Excretion and Tissue Storage of Sulfated Mucopolysaccharides in Hurler's Syndrome, A.M.A. J. Dis. Child. **96**:467, 1958.
146. Jacobson, L., Kibel, M. A.: Hurler's Syndrome: A Clinical Report on Two Cases, Central Africa J. Med. **4**:193, 1958.
147. Jelke, H.: Gargoylism. II. Post-mortem Findings in an Earlier Published Case, Ann. paediat. **184**:101, 1955.
148. Kennealy, E. V.: The Occular Manifestations of Gargoylism, Am. J. Ophth. **36**:663, 1953.
148a. Jermain, L. F., Rohn, R. J., and Bond, W. H.: Studies on the Role of the Reticuloendothelial System in Hurler's Disease, Clin. Res. **7**:216, 1959.
149. Kibel, M., and Jacobson, L. (South Rhodesia): Personal communication.
150. Lahey, M. E., Lomas, R. D., and Worth, T. C.: Lipochondrodystrophy (Gargoylism), J. Pediat. **31**:220, 1947.
151. Lamy, M., Maroteaux, P., and Bader, J. P.: Étude génétique du gargoylisme, J. génét. hum. **6**:156, 1957.
152. Lamy, M., Maroteaux, P., and Frezal, J.: Les chondrodystrophies genotypiques. Définition et limites, Semaine hôp. Paris **34**:1675, 1958.
153. Lorincz, A. E. (Chicago): Personal communication.
153a. Lorincz, A. E.: Acid Mucopolysaccharides in the Hurler Syndrome, Fed. Proc. **17**:266, 1958.
154. MacGillivray, R. C.: Gargoylism (Hurler Disease), J. Ment. Sc. **98**:687, 1952.
154a. McKusick, V. A.: Hereditary Disorders of Connective Tissue, Bull. New York Acad. Med. **35**:143, 1959.
155. Maroteaux, P., and Lamy, M.: Les dysplasies spondylo-épiphysaires génotypiques, Semaine hôp. Paris **34**:1685, 1958.
156. Mathur, P. S.: Gargoylism, Ind. J. Pediat. **24**:372, 1957.
156a. Mauri, C., and Soldati, M.: Les caracteristiques cytochimiques des granulations cellulaires de Alder. Definition de la dysostose enchondrale multiple en tant que polysaccharidose, Schweiz. med. Wchnschr. **88**:992, 1958.
157. Meyer, K.: Abstracts of 130th Am. Chem. Soc. Meetings, Sept., 1956, p. 150.
158. Meyer, K (New York City): Personal communication.
159. Meyer, K., Davidson, E., Linker, A., and Hoffman, P.: The Acid Mucopolysaccharides of Connective Tissue, Biochim et. biophys. acta **21**:506, 1956.
160. Meyer, K., Grumbach, M. M., Linker, A., and Hoffman, P.: Excretion of Sulfated Mucopolysaccharides in Gargoylism (Hurler's Syndrome), Proc. Soc. Exper. Biol. & Med. **97**:275, 1958.
161. Meyer, K., Hoffman, P., and Linker, A.: Chondroitin Sulfate B and Heparitin Sulfate (abst.), Ann. Rheumat. Dis. **16**:129, 1957.
162. Naidoo, D.: Gargoylism (Hurler's Disease): Neuropathological Report, J. Ment. Sc. **99**:74, 1953.
163. Nisbet, N. W., and Cupit, B. F.: Gargoylism; Report of a Case, Brit. J. Surg. **41**:404, 1954.
164. Putnam, M. C., and Pelkan, K. F.: Scaphocephaly With Malformations of Skeleton and Other Tissues, Am. J. Dis. Child. **29**:51, 1925.
164a. Rainer, S., and Böök, J. A.: Genetics and Blood Morphology in Amaurotic Idiocy, Lancet **1**:1077, 1958.
165. Russell, D. S.: Observations on the Pathology of Hydrocephalus. Special Report Series, Med. Res. Council, No. 265, London, 1948, p. 52.
166. Sjolin, S., and Skoog, T.: The Clawhand in Gargoylism, Its Pathology and Treatment, Acta paediat. **41**:563, 1952.
167. Stacey, M., and Baker, S. A.: Chemical Analysis of Tissue Polysaccharides, J. Clin. Path. **9**:314, 1956 (appendix to paper of Bishton et al.[129]).
168. Steen, R. E.: A Family Consisting of Three Cases of Hunter's Polydystrophy (Gargoylism) With Cardiac Lesions (abst.), Brit. Heart J. **19**:585, 1957; Hunter's Polydystrophy (Gargoylism) With Cardiac Lesions and Some Formes Frustes, Brit. Heart J. **21**:269, 1959.
169. Strauss, L., and Platt, R.: Endocardial Sclerosis in Infancy Associated With Abnormal Storage (Gargoylism). Report of a Case in an Infant, Age 5 Months, and Review of the Literature, J. Mt. Sinai Hosp., New York **24**:1258, 1957.
170. Thomas, J. E.: Gargoylism in the African: Report of a Case, Central Africa J. Med. **4**: 112, 1958.
171. Uzman, L. L.: Personal communication, March 9, 1956.

8. CONCLUDING COMMENTS

Introduction; Fibrodysplasia Ossificans Progressiva; Osteopoilkilosis; Léri's Pleonosteosis; Paget's Disease of Bone; Other Possible Hereditary and Generalized Disorders of Connective Tissue; The Future in the Study of Heritable Disorders of Connective Tissue; General Summary and Conclusions

A. INTRODUCTION

In addition to the five disorders which have already been discussed and which seem clearly to be generalized and hereditary disorders of connective tissue, other conditions were investigated in a preliminary manner for the propriety of including them in this general group. The disorders so studied can be grouped in the following manner as to the likelihood of their generalized and hereditary character:

I. *More likely*
   1. Fibrodysplasia ossificans progressiva
   2. Osteopoikilosis
   3. Léri's pleonosteosis
   4. Paget's disease of bone
   5. Cutis laxa (not to be confused with the Ehlers-Danlos syndrome)

II. *Less likely*
   1. Localized and limited to one specialized type of connective tissue
      (a) Dupuytren's contracture
      (b) Peyronie's disease
      (c) Group of aseptic necrosis syndromes
   2. Probably limited to one specialized variety of connective tissue (although generalized in that tissue)
      (a) Osteopetrosis
      (b) Achondroplasia

(c) The Morquio-Brailsford syndrome
(d) Lipomatosis
(e) Neurofibromatosis
(f) Keloidosis
(g) Multiple hereditary exostoses
(h) Ollier's enchondromatosis

3. Too generalized (e.g., epithelial as well as connective tissue elements affected)
   (a) Werner's syndrome
   (b) The Ellis-van Creveld syndrome (chondroectodermal dysplasia)
   (c) Hereditary osteodysplasias and arthrodysplasias with dystrophy of the fingernails.
   (d) Chrondrodystrophy with Pelger-Huët anomaly of leukocytes
4. Although generalized and involving connective tissue elements, doubtful that hereditary
   (a) Arthrogryposis multiplex congenita
   (b) Urticaria pigmentosa
5. Mooted whether site of basic defect is elastic fibers of skin, i.e., precise defect unestablished
   (a) Epidermolysis bullosa hereditaria
   (b) Generalized arterial calcification of infancy
6. Connective tissue involved only secondarily in metabolic aberration
   (a) Gout
   (b) Alkaptonuria (ochronosis)

B. FIBRODYSPLASIA OSSIFICANS PROGESSIVA

HISTORICAL NOTE

The name *myositis ossificans progressiva* is said[40] to have been assigned to this condition by von Dusch in 1868. The designation in which fibrositis is substituted for myositis has been used more frequently in recent decades[15,30,45b] since the primary change is in the connective tissues, specifically aponeuroses, fascia and tendons, and the muscles are only secondarily affected. (Rosenstirn[40] suggested "fibrocellulitis.") It is not entirely improper to refer to it as fibrositis since the lesions may appear to be quite inflammatory during early stages. However, "fibrodysplasia," the term suggested by Bauer and Bode,[2] impresses me (as it has Falls[9]) as most valid. "FOP" is the abbreviation which will be used in this discussion.

In a review of the subject to which little has since been added, Rosenstirn[40] in 1918 abstracted 119 cases and added his own. The first case may have been described in Guy Patin in 1692. Extraordinarily clear descriptions of the end stages of the disease were provided in the *Philosophical Transactions of the Royal Society of London* in the first half of the eighteenth century by John Freke and others. John Freke (1688-1756), a London surgeon and man of wide culture, was a friend

of Fielding, who mentions him twice in *Tom Jones*. Freke saw his case of FOP at St. Bartholomew's Hospital[245]:

> April 14, 1736, there came a Boy of a healthy Look and 14 Years of Age, to ask of us at the Hospital, what should be done to cure him of many large Swellings on his Back, which began about 3 Years since, and have continued to grow as large on many Parts as a Penny-loaf, particularly on the left side. They arise from all the *vertebre* of the Neck, and reach down to the *Os sacrum;* they likewise arise from every Rib of his Body, and joining together in all Parts of his Back, as the Ramifications of Coral do, they make, as it were, a fixed bony Pair of Bodice.*

Abernethy, Caesar Hawkins, Jonathan Hutchinson,[23] Volkmann, Kronecker, Virchow, Stephen Paget, Rolleston,[39] Garrod, F. Parkes Weber, Eugene L. Opie, and many others added cases. Since Rosenstirn, other reviews have appeared.[29,34,240]

Helferich[20] is generally credited with having first described (in 1879) the important association of microdactyly with FOP. The distinctive type of deformity seen in these cases (monophalangy of the great toe) had been described as an isolated anomaly by Fränkel[19] in 1871.

In 1901 Rolleston[39] expressed the opinion that the disease is a defect of the mesoblast. This was probably one of the earliest statements of this idea. It has been stated by many others since that time. For example, Hirsch and Low-Beer[21] called it an "exceedingly unusual anomaly of the mesenchyme."

CLINICAL MANIFESTATIONS

The onset of the process in the fascia and tendons may be in fetal life[23,30,40] or rarely not until after the age of 20 years.[11,21] Usually, however, evidences of the disorder appear in the early years of life, before the age of 10 years.

Typically, localized swellings appear first in the region of the neck and back and later the limbs. They are sometimes painful. These lumps come and go in a matter of days. Sometimes injury appears to be involved in their inception. The lumps may or may not be attached to deep fascia. Sometimes the tumors are cystic and appear to contain blood. Discharge may occur. At times fever is associated with the development and/or absorption of the tumor. In fact, acute rheumatic fever may be simulated.[41] As the disorder progresses, wryneck deformity may develop. The masseter may also be affected, but the tongue, heart, larynx, diaphragm, and sphincters enjoy immunity from the process. The dorsal aspect of the trunk and the proximal (but usually only the proximal) portions of the extremities may be affected. The plantar and palmar fascia may be involved. At the attachments of fibrous structures to bones it is not uncommon for exostoses to develop—for instance, in the occipital area of the skull or as an anterior calcaneal spur.

Eventually, columns and plates (Figs. 95*B* to 95*D*) of bone replace the tendons, fasciae, and ligaments. The spine may become completely rigid and the victims converted into columns like Lot's wife at Sodom. Koontz'[25] patient "was completely unable to sit down . . . she either had to lie down or stand up. She had enough motion in one of her knee joints so that she could walk with a very halting, mincing step. She was of slight build, weighing very little, and it was simple to carry this plank-like girl around."[26] Fairbank[8] presents drawings of

*From Freke, J.: Phil. Tr. Roy. Soc., London, 1740.

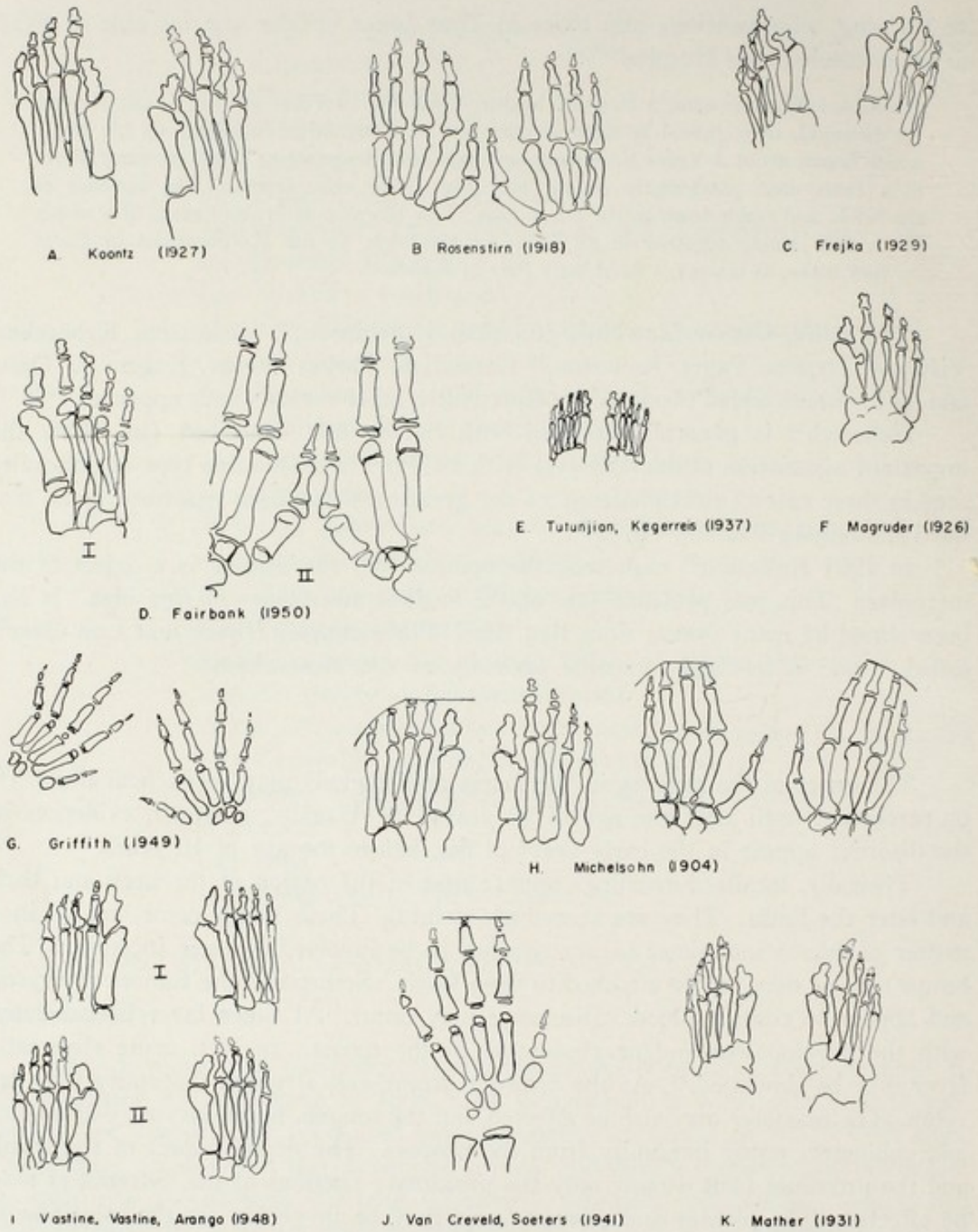


Fig. 94. Tracings of x-ray films of hands and feet in selected reported cases (these are not reproduced to the same scale). *A*, Koontz[25]: Hands little affected. In feet, monophalangic first digit and biphalangic fifth digit. On the right the fourth toe is also biphalangic. There is an exostosis on the right great toe and bone bridge between metatarsals on the left. *B*, Rosenstirn[40]: The short, pointed terminal phalanx of the thumb is typical. The first metacarpal on the left is abnormal in shape. (Frequently the first metacarpal and metatarsal has a disorganized trabecular pattern.) The terminal phalanges of the other digits, especially the second and third, also short and pointed. *C*, Frejka[11]: The fingers were not commented on. The first toe is monophalangic and the others biphalangic at the most. Typical hallux valgus is present. *D*, Fairbank[7]: *I*, 7 years of age. First metatarsal appears to have been lengthened by fusion with the proximal phalanx. The other toes are all biphalangeal. *II*, 10 years of age. The characteristic short, pointed terminal phalanx is seen. There was also microdactyly of the great toes. *E*, Tutunjian and Kegerreis[43]: No comment on the state of the hands. It is interesting to note that monophalangic first toe can be present without microdactyly or hallux valgus. *F*, Magruder[29]:

(Continued on opposite page.)

skeletons showing extensive changes. Often a ridge of bone on the back appears like a handle by which the patient can literally be lifted.[43]

The skin is usually exempt as are the muscles of abdominal wall, perineum, and eye. The heart is not affected. Remissions and exacerbations are characteristic of the disease. Hernias may occur with increased frequency.[40]

In spite of marked involvement, patients have survived to fairly advanced years, e.g., 61 years in Case 73 described by Fairbank.[8] The patient who was 17½ years old when studied by Koontz[25] is still living and reasonably well, although severely disabled, at the age of 51 years.[26]

Obviously, microdactyly can be a valuable diagnostic sign in the earlier stages of the process of ossification or before calcification has appeared. The great toe (Fig. 94) is affected in the great majority of cases, the thumb less frequently (in less than half of cases), and at times other digits. Hallux valgus frequently results and is often what impresses the observer rather than shortening of the digit (Fig. 95*A*). Fairbank[8] states that all the fingers were shortened in two cases. The shortening is the result of change in the phalangeal bones, rarely in the metatarsals. The proximal phalanx may be completely suppressed. A synostosis of the phalanges of the great toe is perhaps the most typical change. Rosenstirn[40] believed that microdactyly is present in all true cases of FOP. Furthermore, the classic review of digital anomalies by Pol[37] indicates that the changes in FOP (see Fig. 94) are in all likelihood unique to this condition and, for practical purposes, absolutely pathognomonic. Clinodactyly, radial curvature of the fifth finger, may occur in these cases.

The only other skeletal change which has been seen at all frequently is an abnormally broad neck of the femora[16,45a] (Figs. 95*B*, 98*F*, and 98*G*). In children the epiphyseal ossification centers may be large for the patient's age (Fig. 98).

Occasionally there is tendency to bruise, with negligible trauma.[16] No defect of coagulation is demonstrable in these instances, however.

REVIEW OF CASES

To my knowledge only seven patients with FOP have been seen in Johns Hopkins Hospital during the past forty years.* All patients are still living. One was reported by Koontz.[25] Two were briefly referred to by Geschickter and Mazeritz.[14] In none of these seven families has another case of FOP been known. All the patients have deformity of the toes and/or fingers. In at least two instances (Cases 1 and 2) digital deformity was also present in other members of the family. One patient (Case 5) did not notice any abnormality until the age of 25 years, when

*Barker's[1] case was probably calcinosis universalis and not FOP.

(Continued from previous page.)

Typical monophalangy of first toe and biphalangy of others. Note exostosis like that in Koontz's patient. *G*, Griffith[16]: Typically short, pointed terminal phalanx of thumbs and of other fingers. Clinically the fifth fingers were curved (clinodactylous). The great toes were monophalangic. *H*, Michelsohn[33]: First toes monophalangic; fifth toes biphalangic. Typical thumbs. *I*, Vastine, Vastine, and Arango[45a]: Identical twins. Monophalangy of first toes. Biphalangy of fourth and fifth toes. *J*, van Creveld and Soeters[41]: 5 years of age. Typical thumb. *K*, Mather[32]: Monophalangic first toe. Biphalangic fifth toe.

It is noteworthy that in the feet of many of the patients in the illustrated cases of FOP, sesamoid bones have been conspicuous by their absence. In their place, projections like exostoses occur, particularly at the distal end of the first metatarsal. It is likely that these "exostoses" are synostoses of sesamoid bones with the metatarsal.

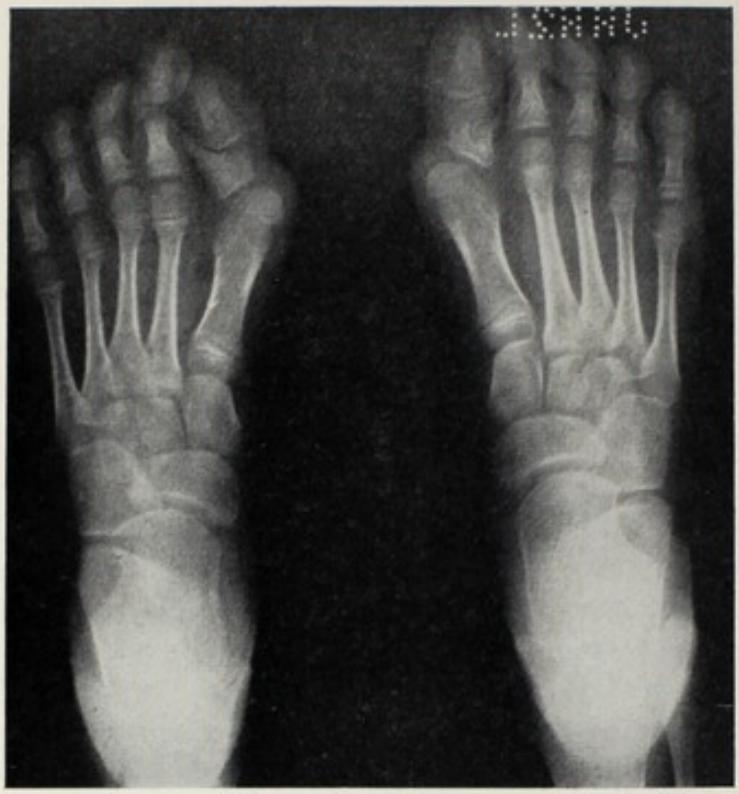


Fig. 95*A*.

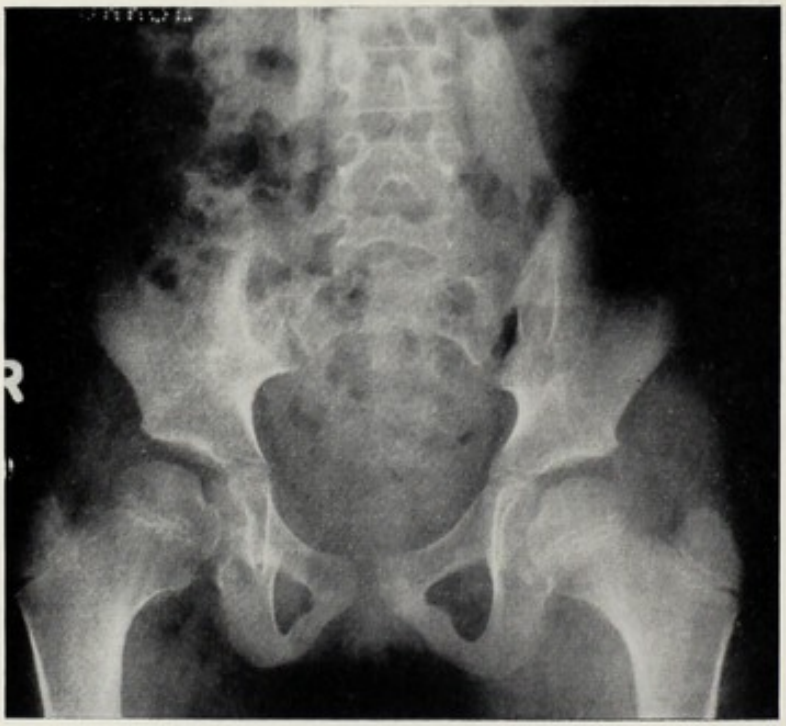


Fig. 95*B*.

Figs. 95*A*-95*D*. X-ray studies in Case 2 of FOP (see text). As demonstrated in Fig. 95*A*, there was distortion of the contour of the distal tip of the first metatarsal and of the proximal phalanges resulting in the hallux valgus deformity seen clinically. It is of note that in this case a normal number of phalangeal bones are present in all the toes. This is, as will be seen from inspection of Fig. 94, the exception; as a rule, monophalangy of the great toes is at least present. It will be interesting to see if synostosis occurs in the future as was observed in to occur in Michelsohn's patient.[33] The hands were normal. As demonstrated in Fig. 95*B*, the neck of the right femur is slightly widened and blunted; immediately adjacent to the epiphyseal line the left femur is normal. Anomalous bone is seen on each side of the lower lumbar spine, especially the left. The ossification in the axillary areas (Fig. 95*C*) has the appearance of cortical bone. In places, it resembled the ribs in contour. At least one false joint was identified. In the lateral view of the lumbar spine (Fig. 95*D*) plates of bone are clearly demonstrated on the back.

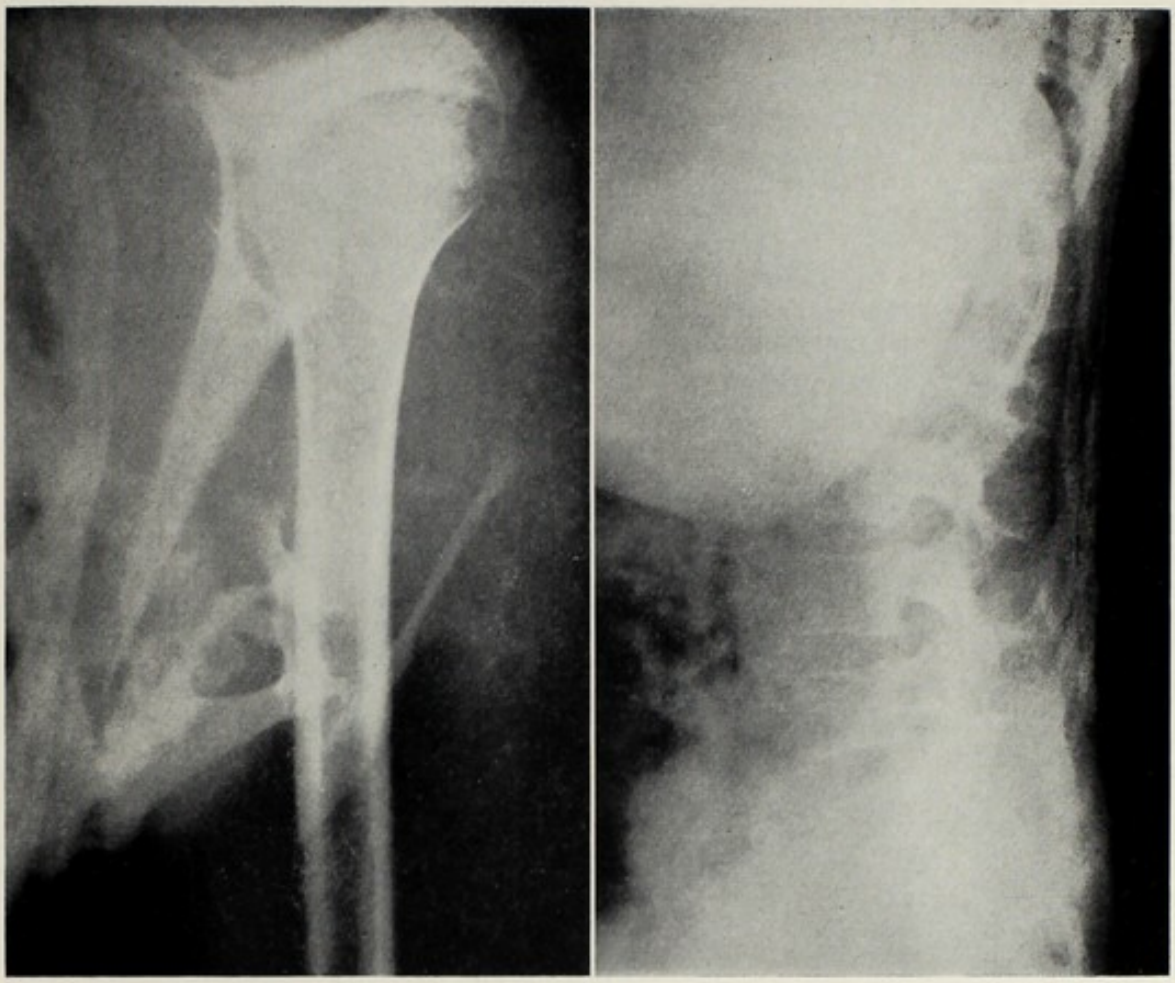


Fig. 95*C*. Fig. 95*D*.

Fig. 95*C* and 95*D*. For legend see opposite page.

lumps appeared above one knee. In another patient (Case 3) torticollis was noted at 1 month of age and advanced FOP was present when he was seen at the age of 16 months. Biopsies have been made in at least the last six patients. There is generally said to be a predominance of males affected; three of the seven are female. Alkaline phosphate determinations are available in three patients and are not in excess of values anticipated for the patient's age.

Abstracts of these seven cases follow:

Case 1. The case of N. J., born in 1908, was reported by Koontz[25] in 1927, with excellent illustrations of the gross appearance and radiologic changes including those of the thumbs and great toes. The maternal grandfather and his two brothers developed late in life what apparently were Dupuytren contractures. A cousin on the maternal side apparently had a deformity of the toes similar to the patient's. The patient's first symptom was stiffness at the age of 9 years. Menstruation never occurred. Both great toes and thumbs were short and malformed. Concentrations of calcium and phosphorus in the blood were normal. I examined the patient in April, 1956. She was then 48 years of age. The disease had progressed slowly but steadily. The jaw was partially fixed, she could not sit, and the arms were in an absolutely fixed position with a minimum of wrist motion present. Using a long-handled fork and standing up, the patient was able to feed herself.

Case 2. B. W. (A85874), a 7½-year-old white girl, has a normal brother and sister. The father had stunting of the great toes similar to the patient's but no other instance of FOP is

known in the family. At 10 months, when the patient began to sit up, the head leaned to the left. At the age of 6½ years, she developed an exostosis on the right knee after trauma. However, she remained apparently well otherwise until the age of about 7 years, when she began to complain of pain in the left side of her neck, and firmness and tenderness was discovered there. Thereafter, swelling and induration developed on the back, abdomen, and shoulder. There was marked limitation of motion of the neck, arms, and spine, and the head was held to the left. Dermatomyositis was the initial diagnosis. See Fig. 95 for x-ray studies of this patient.

Case 3. R. W. (A62462) was found at birth to have hallux valgus and short thumbs. At 1 month the head was noted to be bent to the left and there was a firm mass in the stenomastoid muscle. Thereafter asymmetry of the face developed. Lumps appeared in many areas over the back and scalp. These masses never appeared inflamed. There were, however, frequent

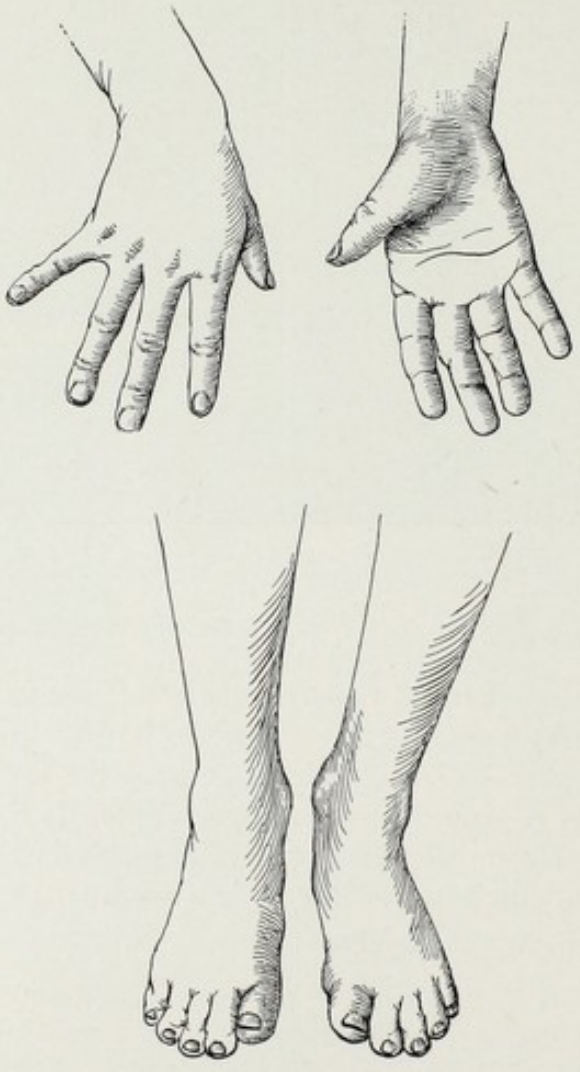


Fig. 96. Drawings of the hands and feet of patient 4 of the FOP series (see text). Microdactlyly of the thumbs and toes is strikingly demonstrated.

bouts of unexplained fever. Examination revealed atrophy of the left side of the face. The sternomastoid muscle on the left was converted into a stony hard mass. The ligamentum nuchae was similarly affected. Extensive involvement about the scapulae (which were attached to the ribs) and the trapezius muscles formed a yoke on the back.

Case 4. V. W. (U52691) has seven siblings, but none has either microdactyly or FOP. She was presumably well until the age of 6 years, when she fell from a swing, striking her back.

Swelling and discoloration resulted. X-ray films at that time revealed "a spider's web on the spine." Thereafter, there was steadily progressive increase in stiffness and limitation of motion of joints. The thumbs and toes had always been small. It is of note that the facial muscles were involved in this case. By the age of 25 years the jaws became locked and the upper teeth had to be removed to permit alimentation. (See Fig. 96 for drawings of this patient.)

Case 5. F. K. (U52689) was well until the age of 25 years, when he developed a "bump" above one knee following trauma. During the following year there were several episodes of soreness and swelling in the left side of the neck with difficulty in swallowing. There are six

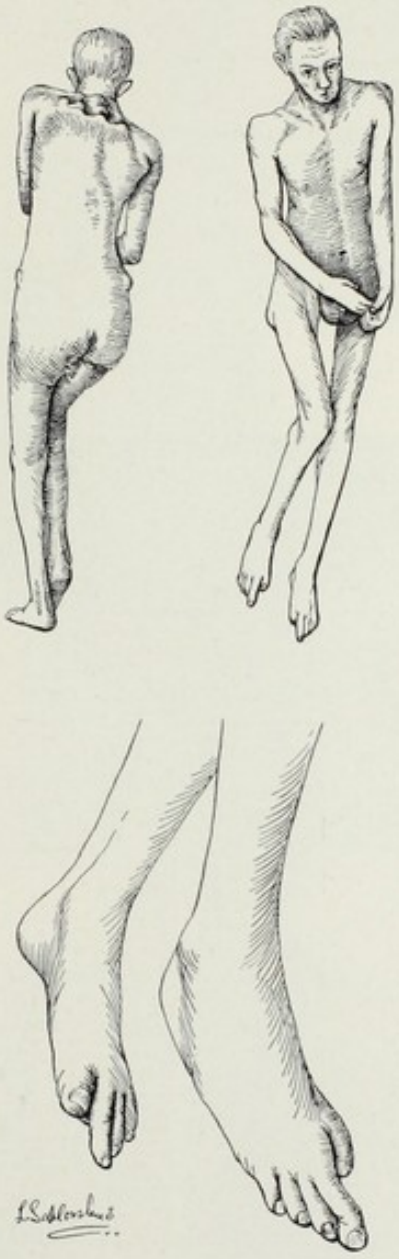


Fig. 97. Drawings of patient 5 of the FOP series (see text). The ridges of bone on the back and the fixedly awkward posture are highly characteristic. Striking microdactyly is also present.

siblings. No other members of the family had microdactyly or ossification. The patient's thumbs were small, with fusion of the interphalangeal and metacarpophalangeal joints. All the terminal phalangeal joints of the second and fourth fingers were fused. Hearing was impaired bilaterally. As long as the patient could remember, he had had restriction of motion of the head, mandible, both shoulders, right elbow, both thumbs, both hips, left knee, left ankle, and toes of the left foot. Supposedly, poliomyelitis affecting mainly the left leg had occurred at 5 years of age, but

suspicion is cast on the diagnosis by later developments. (See Fig. 97 for drawings of this patient.)

Case 6. M. W. (422628) was seen at the age of 14 years, and a diagnosis of calcinosis of the muscles of both hips was rendered. However, in retrospect there can be no question but that FOP was actually present. The boy had always been stiff, and following a blow on the back at the age of 5 years a lump on the left scapula was noted. The mass was biopsied and called sarcoma. The boy was given only three months to live; he is still alive, although disabled, at the age of 27 years. Other lumps appeared and flexion contracture of the hips and right knee gradually developed. The left great toe was short and deformed.

Case 7. P. H. (770577), born Oct. 4, 1951, has, as his first manifestation of FOP, the appearance (in 1954) of transient, nontender "bumps" in the posterior part of the scalp. A biopsy diagnosis of neurofibromatosis was made. The correct diagnosis was made in October, 1956, by which time typical ossifying changes in the aponeuroses of the back had developed. A striking feature at that time was local heat over the involved areas of the back. The thumbs and toes were characteristically short. Two older siblings born in 1947 and 1949 are normal and no definite abnormality has been detected in members of the family. Other features of note include short, broad femoral necks and exostosis-like spurs on the upper end of each tibia at the site of muscle attachments. (See Fig. 98.) Steroid therapy undoubtedly suppresses acute inflammatory phases in this patient. Whether it also will prevent the subsequent ossification remains to be seen.

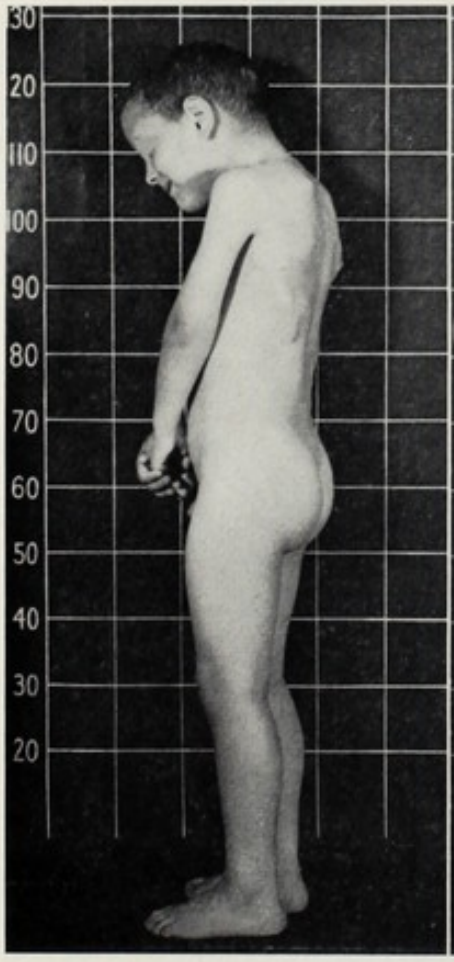


Fig. 98*A*.

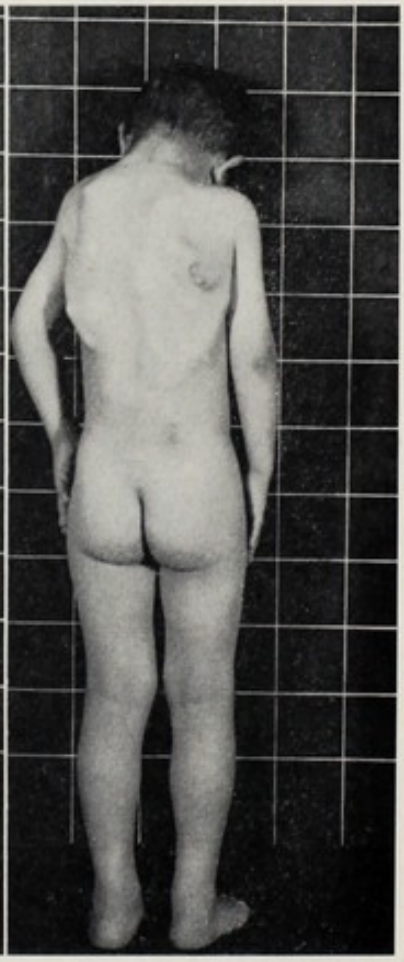


Fig. 98*B*.

Figs. 98*A*-98*H*. Case 7. *A*, Lateral view (June, 1958). *B*, Rear view (June, 1958). *C*, Feet. *D*, X-ray of feet (April, 1957). *E*, Occiput, showing ossified nodule. Note the ossification in the tissues of the posterior part of the neck. *F* and *G*, The neck of the femur is short and broad (1954 and 1957). *H*, Exostoses of the tibias at site of tendon attachment.

Fig. 98*C*.

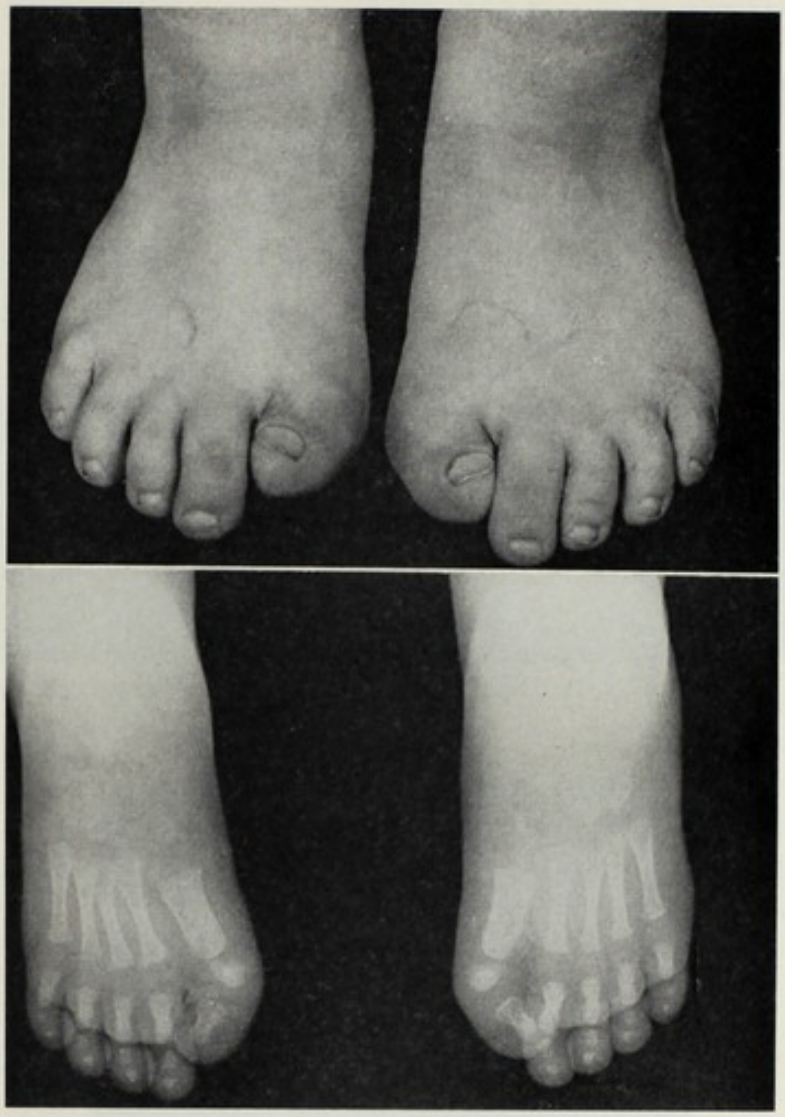


Fig. 98*D*.

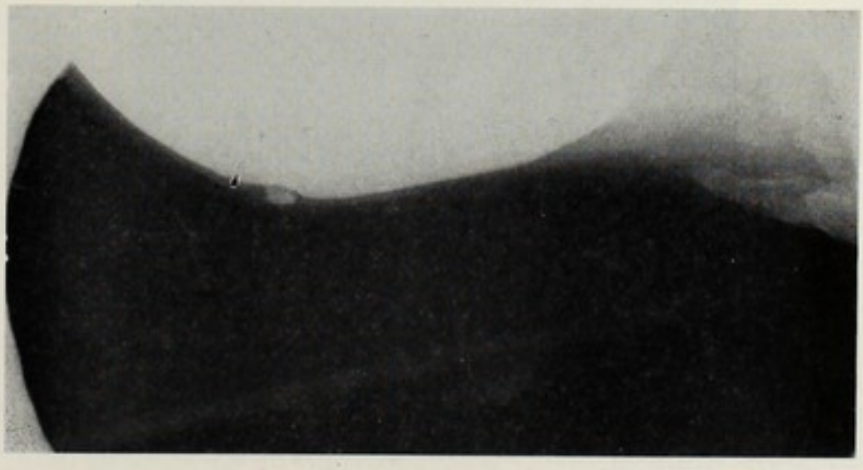


Fig. 98*E*.

Figs. 98*C* to *E*. For legend see opposite page.

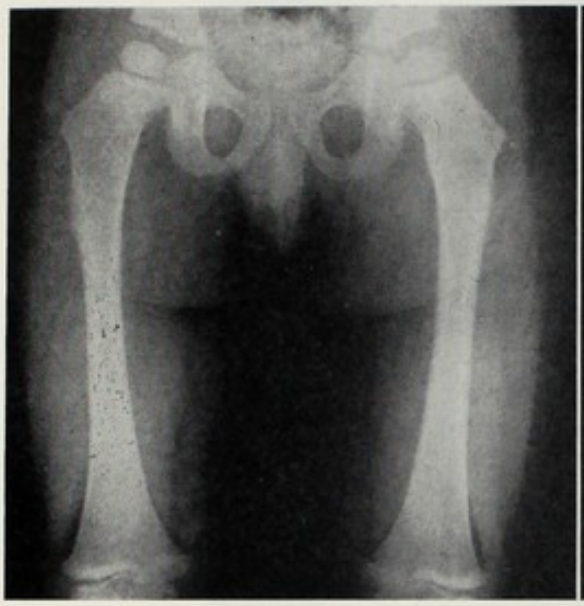


Fig. 98*F*.

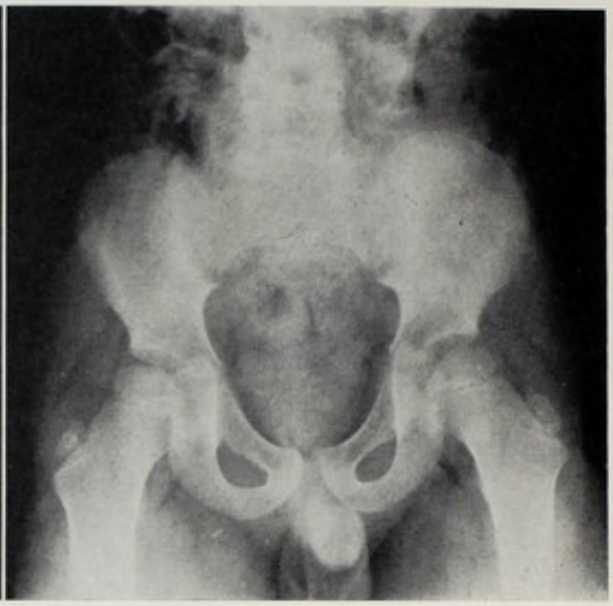


Fig. 98*G*.

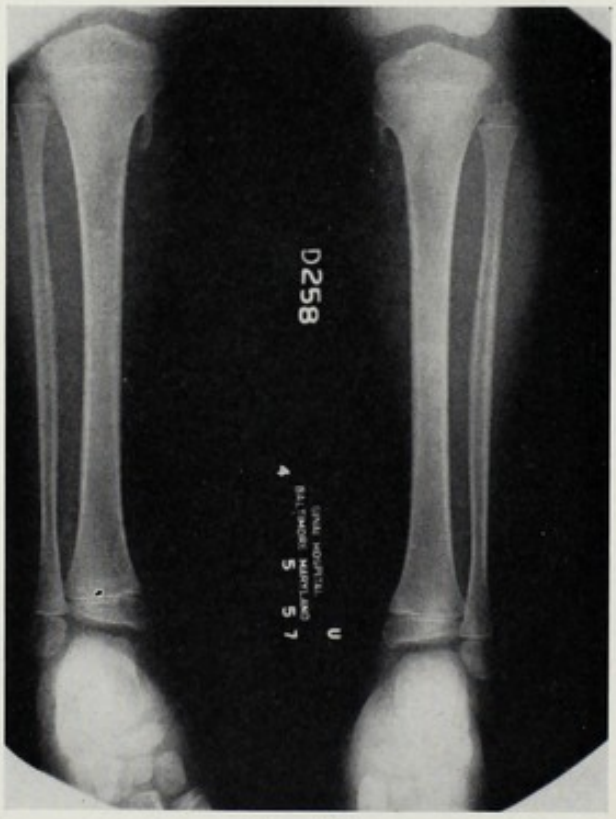


Fig. 98*H*.

Figs. 98*F*-98*H*. For legend see page 294.

INCIDENCE AND INHERITANCE

In 1918 Rosenstirn,[40] in reviewing this disorder, could find 119 cases in the literature. In later reviews[30,34] other cases have been added. The disease is appreciably more frequent in males, in a ratio of 4:1 according to some[41] but 3:2 by the statement of others. In Rosenstirn's collection of cases, 62 per cent were male (sixty-eight male and forty-two female of cases clearly described as to diagnosis and sex).

Sympson[42] reported microdactyly in father and son, with FOP in the son. Drago[6] reported the same situation in a mother and son. Koontz[25] described "contractures of two fingers" in four relatives of the patient. The anomaly apparently developed later in life, however, and may have been Dupuytren's contracture. Burton-Fanning and Vaughan[5] described FOP (the full syndrome) in both father and son. Gaster[13] observed the disorder, including phalangeal deformity in five male members of three generations, three brothers, the father, and paternal grandfather, Vastine and his co-workers[45b] and Eaton and his associates[242] each saw FOP in both of a pair of identical twins. It may be that this disease trait is dominant with a particularly wide range of expressivity. Many of the cases may be new dominant mutations; very few of the patients have children to whom the disease can be transmitted. There seems to be no increase in consanguineous marriages among the parents. Multiple affected sibs, except for identical twins, are rare.

PATHOLOGY

The early histologic changes are not known. Obviously it is these which are of most significance in reference to the basic abnormality. It is clear[17] that the skeletal muscle is fundamentally normal. Geschickter and Maseritz[14] picture cartilage and also "young osteoid tissue surrounded by osteoblasts." The surgical pathologist may find it difficult to distinguish FOP from osteogenic sarcoma. In the case described by Paul[36] both were thought to have been present.

THE BASIC DEFECT

That the fundamental disorder resides in connective tissue seems indisputable. Isolated bone tissue may be found in the skin[40] well removed from muscles. No aberration of calcium metabolism has been demonstrated. In one case (P. H., 770577) ossification began in the galea aponeurotica. The serum transaminase activity was normal during stages of activity of the disease, as manifested by fever, leukocytosis, and local heat. Because of the similarities of behavior to the calcification and ossification which occurs after traumatic and other injury which involves necrosis of tissue, one suspects that this is fundamentally a dystrophy of connective tissue with secondary calcification. Rosenstirn believed that the fundamental defect resides in the small blood vessel and that the initial lesion is a hemorrhage which is followed by organization and ossification.

The observations of Wilkins and his associates[47] are important and point the way to an area for possibly productive investigation by other techniques such as tissue culture of fibroblasts from these patients. Specifically they found a very high level of alkaline phosphatase activity in the areas of heterotopic cartilage and bone formation. The activity was, in fact, higher than in normal rib.

An enigmatic feature of this syndrome has been the association of an anomaly of the conventional congenital type, microdactyly, with the other cardinal component, ectopic ossification, which behaves more like a hereditary weakness of some element of connective tissue. Previously, in discussing the explanation for the association of congenital anomalies of conventional types with hereditary disorders which behave more like abiotrophies, it was proposed that the presence of a basic tissue defect results in an abnormal environment for embryologic development so that specific congenital defects occur predictably with increased incidence. Such may be the case with the microdactyly of FOP. Certainly, a disorder of normally ossified tissues is not too farfetched an association. However, a more straightforward explanation is possible. There is an intriguing set of observations reported by Michelsohn,[33] suggesting that in connection with the abnormality of growth of the first digits in FOP there is no sharp distinction between antenatal and postnatal developments. The patient in question was a 17-year-old girl when seen. In the first months of life the mother noted pronounced shortening and stiffening of the great toes, with no morphologic or functional abnormality of the thumbs. At the age of 7 years when the changes in the muscles were beginning, the thumbs became painfully swollen and later stiff, then ankylosed. By definition the change in the great toes was synostosis and that in the thumbs, ankylosis. However, it may be that the same basic process was operating in both instances. The predominant and usually unique involvement of the first digit may be related to the difference in the growth pattern of the first digit as compared with the others (see pp. 54 and 56).

The malformation of the digits appears to occur in the fairly regular manner of a Mendelian autosomal dominant trait; ossification occurs in less predictable fashion. The factors determining whether ossification will occur in a given case of microdactyly are entirely obscure. Rosenstirn[40] reported that both FOP and microdactyly occurred in a setter dog. It is a pity that breeding and other experiments were not undertaken on this valuable animal.

OTHER CONSIDERATIONS

In the differential diagnosis, calcinosis universalis, dermatomyositis, Weber-Christian's disease, and other conditions must come in for consideration. The picture suggests torticollis in the early stages.[30] Calcinosis universalis is probably basically a "collagen vascular" disease with secondary calcification.[46] It is certainly not a heritable disorder. The patient described by Barker,[1] a Negro male who was for many months on the wards of the Johns Hopkins Hospital, probably had calcinosis universalis and not FOP. Actually there must be very few descriptions of FOP in Negroes.

Beryllium has been used in the treatment of FOP.[43] Since beryllium suppresses alkaline phosphatase activity,[18,24] there might be some rationale for this therapy. This effect of beryllium was, however, unknown in 1937 when it was used; furthermore, its benefit was, at the most, doubtful. Adrenocortical hormones were used in Case 2 and in patients reported in the literature.[28,38] Again, benefit is, at the most, dubious. Somewhat encouraging results in an early and active case were described by Riley and Christie,[38] but no benefit was noted in an old, probably static case. In other instances[2,42] steroids did no good even when given early. They may be helping the boy shown in Fig. 98. X-ray therapy may aggravate the con-

dition. The reader is referred elsewhere (e.g., reference 38) for reviews of the other forms of therapy that have been employed without any particular success.

SUMMARY

The cardinal manifestations of fibrodysplasia ossificans progressiva are microdactyly and progressive ossification of fascia, aponeuroses, and other fibrous structures related to muscles. Microdactyly is always most striking in the thumb and great toes. It probably represents fundamentally the same disorder occurring usually, although not exclusively, during antenatal development. There is usually a synostosis with resulting monophalangic great toe.

This disorder is probably inherited as a Mendelian dominant with irregular penetrance.

C. OSTEOPOIKILOSIS (OSTEO-DERMATO-POIKILOSIS)

Osteopoikilosis, like osteopetrosis, was first described in a definitive manner (earlier references[71] can be found) by the German radiologist, H. Albers-Schönberg (1915).[48] It is sometimes referred to as "spotted bones," an appropriate designation as seen from Fig. 99. "Osteopoikilosis" (variations: "osteopoecilia," "osteopecilia," "osteopoicilosis," "osteopoikilie") is derived from Greek words meaning "mottled bones." The bone lesion is also referred to as "osteitis condensans generalisata" or "osteosclerosis disseminata." Bauer and Bode[2] called it "osteodysplasia enostotica." The skin lesions were first described in 1928 by A. Buschke and Helen Ollendorff[52] (later Curth[57]) as "dermatofibrosis lenticularis disseminata." Osteo-dermato-poikilosis might be a satisfactory designation for the entire syndrome.

Neither the osseous nor the cutaneous lesions are of any known clinical significance whatever. They are usually discovered incidentally, since the bone lesions are asymptomatic and the skin lesions inconspicuous. One reason why the clinican should be familiar with this condition is that he may avoid confusing the condition for osteoblastic metastases to the skeleton.[68]

The bone lesions are circumscribed, round areas of increased bone density, usually less than 1 cm. in diameter, situated particularly at the ends of the bones of the extremities (but not necessarily in the epiphyses) and in the small bones of the feet and wrists (Fig. 101). The lesions may or may not be bilaterally symmetrical. At times the lesions are linear (striate) in distribution.[77] For example, Voorhoeve[75] found vertical striae parallel to the long axis of the bones and as a fan in the wings of the ilia, but no spots, in two children whose father had typical spots and no striae. See Fig. 100 for a demonstration of the distribution of lesions. The skull has been spared in most cases. Bistolfi[49] described involvement of the occipital bone. All three cases of Funstein and Kotschiew[59] had skull involvement and indeed the calvarial lesions dominated the picture in Erbsen's[58] case. In the case of Martinčić[63] unusual involvement of the lumbar spine was present.

As was nicely demonstrated by Funstein and Kotschiew[59] the islands tend, in pronounced cases, to be oriented along the "traction and pressure lines,"[63] especially at points of crossing of these lines.

The skin lesions, always inconspicuous, are most often located on the posterior aspect of the thighs and buttocks, occasionally on the arms and trunk, but never on the face. Their location bears not constant relation to that of the bone lesions, al-

though it is noteworthy that the head is usually affected neither by skin nor by bone lesions. They are closely situated, slightly elevated, whitish yellow, and usually oblong or oval in outline. Like the bone lesions, they have been described as occurring in longitudinal streaks. They are usually about the size of a lentil or pea, from which the name of the skin lesions (dermatofibrosis lenticularis disseminata) is in part derived. Most of the cases of bone lesions that have been subjected to careful inspection have been found to show skin lesions as well. Busch[51] described skin changes in six patients, Buschke and Ollendorff[52] in one and Šváb[72] and Windholz[77] in two each.

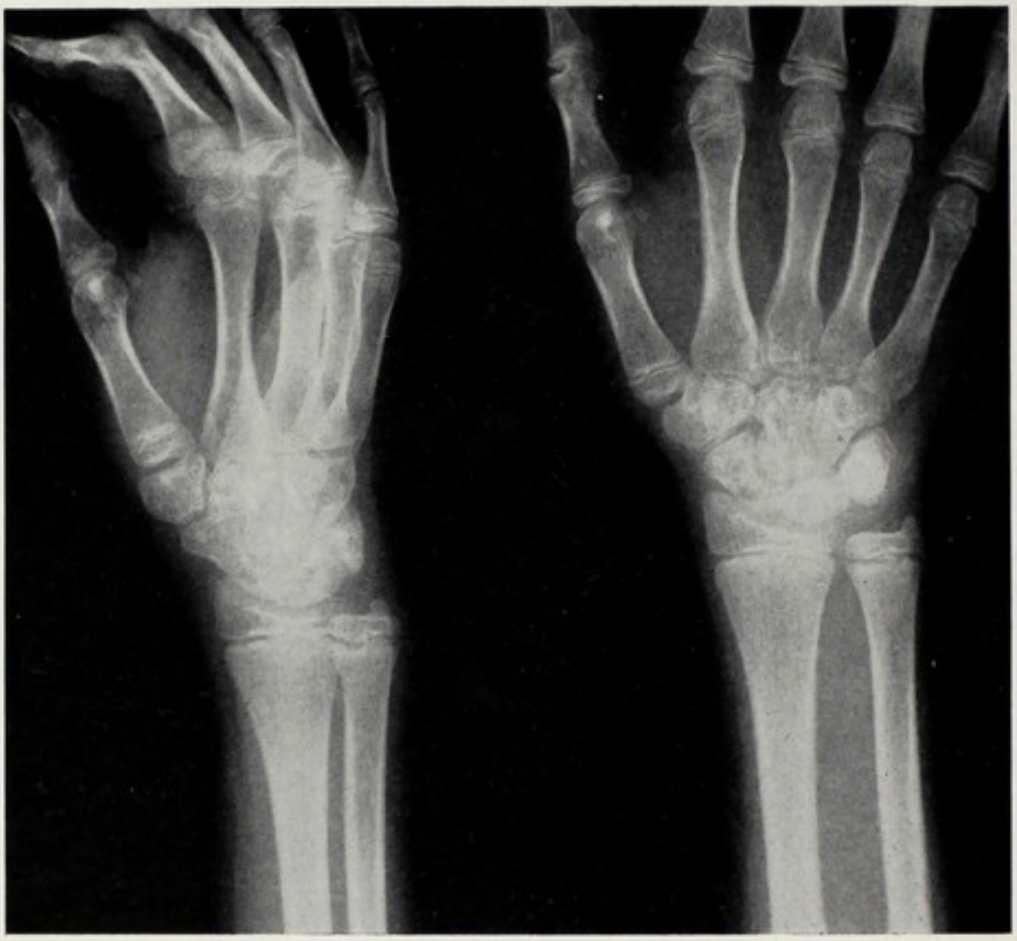


Fig. 99. Typical osteopoikilosis discovered incidently when radiologic studies for a wrist injury were performed (J.H.H. 644704) in a 13-year-old white boy.

Information on the age of appearance and evolution of both the osseous and cutaneous changes is meager. It is clear that lesions may be present at both sites in the first years of life. Furthermore, it appears that once formed, the bone lesions remain static for many years. The longest reported follow-up, seventeen years, was in a female first observed at the age of 14 years.[64]

Keloids may occur with increased frequency in these patients.[57] The only internal medical ramification that has even been suggested is that of fibrous nodules of the peritoneal lining discovered at laparotomy in a 13-year-old patient who complained of severe abdominal pains.[70] It can fairly be stated that this was not a "clear case," however. Grossly the nodules suggested tubercles. Scleroderma beginning at the age of 7 months was described in association with osteopoikilosis

by von Bernuth.[74] However, I doubt seriously that the bone condition described and pictured was the same as that under discussion here. In a case reported by Nichols and Shiflett[64] an obscure generalized skeletal disease was present in addition to osteopoikilosis; the authors thought there was no connection. There were exostoses in the cases of Albers-Schönberg,[48] Risseeuw,[67] and Albronda.[237] Copeman[54] saw

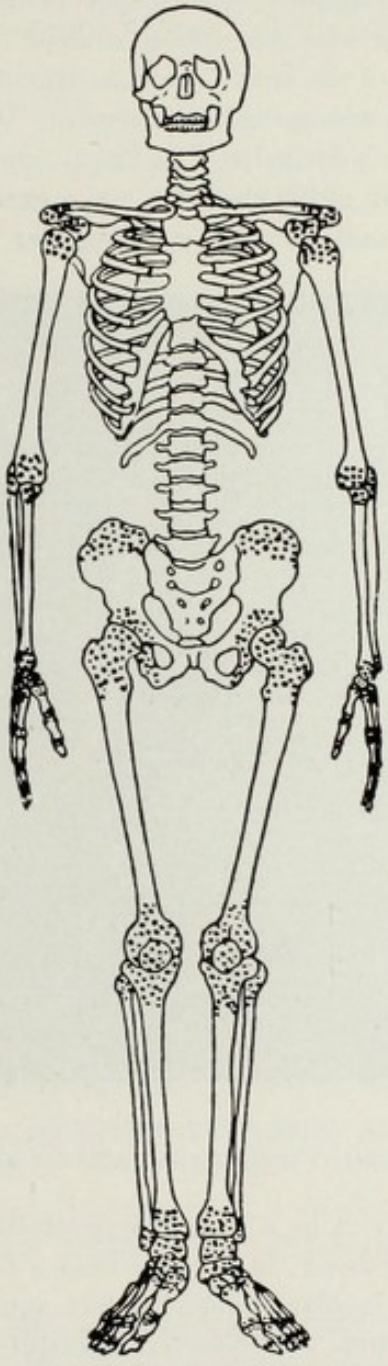


Fig. 100. Typical location of bone lesions in osteopoikilosis.[19]

osteopoikilosis in association with rheumatoid arthritis. In general, one seems justified in considering this situation as incapable of producing symptoms and as prognostically insignificant.

The bone lesions were examined histologically by Schmorl[69] in an 18-year-old boy who died of seemingly unrelated cause. He found that each "island" is a clump of osseous trabeculae which are thicker at the periphery than at the center.

The trabeculae at the center form a complex network with ordinary marrow in the space between. The skin lesions consist of collagenous fibrosis with preservation of the elastic fiber elements.[51,52]

From the point of view of inheritance this disorder behaves as a Mendelian autosomal dominant. Busch[51] found fourteen cases in three generations of one family, and the condition probably extended further back in the ancestry since there were three affected siblings in the first generation studied. Hinson[60] studied it in two generations. In x-ray films of the entire skeleton Bloom[50] found only a single spot in the sister of a patient with widespread involvement. Wilcox[76] saw the bone condition in father and daughter; Voorhoeve,[75] in father, son, and daughter. Risseeuw[67] saw the disorder in a man, six of his children, and a grandson. Albronda[237] saw the bone condition in a woman and one son and daughter; there was no skin change.

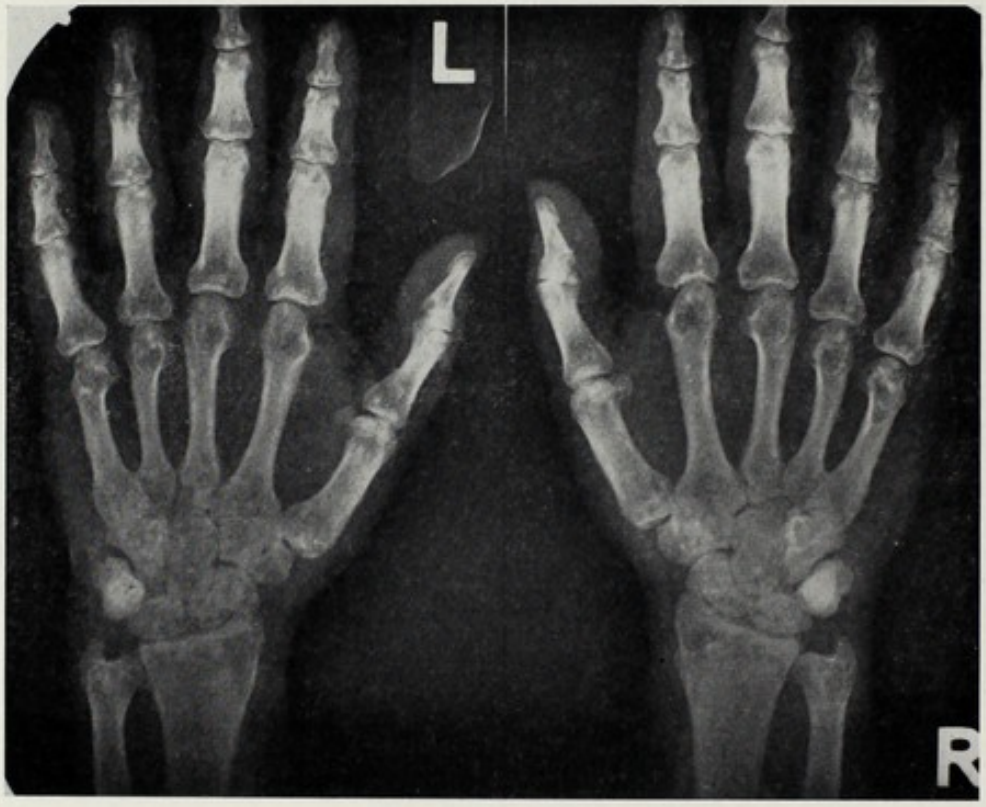


Fig. 101. Osteopoikilosis in M. M. (644555), 47 years of age. Asymptomatic. No skin manifestations. Family not available for study.

The basic defect appears to be a spotty hyperplasia of collagen in the corium and bone matrix. This is, however, little more than a restatement of the histologic findings. What is basically involved in this defect and why there is the peculiar spotty distribution are obscure. Voorhoeve[75] thought the bone lesions arise in cartilage. He based this theory on the fact that in two children he observed striate lesions extending a variable distance into the diaphysis from the epiphyseal line. The relative immunity of the skull and clavicle ("membranous bones") may be supporting evidence for enchondral origin.

In a paper entitled "Follicular Atrophoderma and Pseudopelade Associated With Chondrodystrophia Calcificans Congenita," Curth[56] has written about an interesting familial and almost certainly hereditary disorder involving bone and skin. As indicated in her references to the literature, others have reported cases.

In the case of the skin involvement it may be connective tissue that is primarily affected and not the epidermis. However, studies to date leave the nature of the basic defect in question. It is certainly distinct from osteo-dermato-poikilosis. There is probably no fundamental kinship between so-called "stippled epiphyses" (chondrodystrophia calcificans congenita[55]) and osteopoikilosis. Traub[73] has described mottling of the epiphyses, superficially resembling osteopoikilosis, in cases of pituitary gigantism, and a vaguely similar picture is associated with cretinism.[66]

D. LÉRI'S PLEONOSTEOSIS

In 1921 André Léri,[82] Parisian orthopedist, described a previously unrecognized condition in a 35-year-old man and his children by a second wife, a daughter 4 years and a son 3 weeks of age. The child by his first wife was normal. The disorder was not present at birth and became evident sooner or later in extrauterine life. The father was only 62 inches tall and had short, broad hands and feet with thickened palmar pads and accentuated creases, with limitation of motion in the wrists, elbows, hips, and knees. The toes, and presumably the thumbs as well, were broad and stiff. Fairly numerous cases have since been described in the French literature,[81,83,87,89,90] including one report from Russia[81] and some in the German literature (see reference 85 for list of German reports); there have also been reports in journals of Brazil and Argentina (see reference 91), but there appears to be only one article in British journals[91] and none at all in the periodical American medical literature.

The term "pleonosteosis" suggested by Léri was based on his impression, probably inaccurate, that the basic abnormality is one of excessive ossification.

The clinical characteristics of Léri's pleonosteosis are broadening and deformity of the thumbs and great toes, flexion contractures of the interphalangeal joints, and limitation of motion in other joints, including even those of the spine. A form of "hammertoe" may develop. Mongoloid facies has been described[91] but are by no means an invariable feature (see Case 1 of reference 91). Furthermore, in the majority of cases of mongoloid features, the patients are normally intelligent, e.g., Watson-Jones'[91] patient 2 who was a university graduate. However, there are at least two reports of impairment of the intellect.[86,90]

There is usually semifixed internal rotation of the upper limbs and external rotation of the lower limbs. In general the limbs are short. The joints of the hands in particular may appear to be swollen. The hands are short, square, and thick. Changes in the lower extremities seem to be less striking, but this may be a function of the fact that less intricate movements are required of the feet and ankles.

A complication of the fibrous hyperplasia in the hands and feet can be nerve compression: carpal tunnel syndrome involving the median nerves and Morton's metatarsalgia from involvement of the digital nerves of the feet.

Watson-Jones[91] described the dense fibrous tissue removed from the wrist and consisting essentially of a highly hyperplastic anterior carpal ligament. The specimen consisted of greatly increased, dense collagenous tissue which in portions was actually fibrocartilage. Elastic fibers were conspicuous in their absence. Mucinous material was present, and in tissue removed from the foot, numerous "tissue mast cells" were described.

The fundamental abnormality was thought by Léri to be one of excessive and perhaps precocious ossification of the epiphyses. It seemed more likely to Watson-Jones[91] that the joint deformities are due to capsular contractures, that in general the abnormality resides in the fibrous tissues, and that the "thickening of the bones may be due to periosteal traction at their metaphyseal attachments."

All evidence suggests that pleonosteosis is inherited as a Mendelian autosomal dominant trait.

Although uncommon, Léri's pleonosteosis almost certainly occurs more frequently than the rarity of reports in American publications would suggest. In their monograph *Human Heredity,* Neel and Schull[86] describe a 34-year-old woman with progressive loss of joint mobility and moderately severe contractures beginning in adolescence. Movements of the hands in particular were awkward and clumsy. The mother, 58 years of age, was affected and by this time of life was unable to perform most fine movements of the hands and the rest of the body. A brother of the proposita and a half-brother of her mother were also affected. A feature of all affected persons was a broad thumb. The proposita sought information on whether her two sons would be affected. Since one of them already displayed broad thumbs, the inquirer was advised that a vocation requiring manual dexterity would be inadvisable. Rukavina and colleagues[90a] have reported the family in full.

The nosography of this disorder is far from fully established. Cocchi[78] includes this condition in the group of "polytopic enchondral dysostoses" in which he also includes the Morquio syndrome and the Hurler syndrome. In a detailed clinicopathologic study based on two brothers, Materna[85] described what he called Léri's pleonosteosis, which differs radically from the condition in the four patients reported by Watson-Jones.[91] There was no mention of limitation of joint mobility. The entire skeleton revealed extensive changes with "innumerable microfractures," fish vertebrae, a wedge vertebra, and coarsening and widening of the tubular bone, among other changes. The father was thought to have the same disorder as his two sons. One of the sons died at the age of 42 years of heart failure; no autopsy was performed. In the other, heart disease believed to be rheumatic was discovered at autopsy. This brother had had repair of bilateral inguinal hernias at the age of 14 months.

In the differential diagnosis, the Hurler syndrome and arthritis, either rheumatoid or degenerative, come in for consideration. One would be suspicious that the case thought by Rocher and Pesme[87] to be one of pleonosteosis with corneal opacification was, in fact, one of the Hurler syndrome. Sometimes thoracic outlet syndrome (compression of components of the cervical plexus) is suspected.[91]

E. PAGET'S DISEASE OF BONE

Is Paget's disease of bone a generalized disorder of connective tissue? The evidence that Paget's disease of bone can legitimately be considered a heritable abiotrophy, probably of the collagen matrix of bone, can be summarized in the way indicated below. None of the pieces of evidence is by itself conclusive, but taken together they make a rather convincing argument.

1. The hereditary nature of the process appears to be established. However, it is worth while examining the evidence for this, since one review,[134] which is otherwise comprehensive, makes no mention of the genetic factor in discussing

etiology. In 1889 Paget[129] himself wrote: "I have tried in vain to trace any hereditary tendency to the disease. I have not found it twice in the same family." However, the observations of familial aggregation reported from even before that time (beginning with Pick[131] in 1883) are fairly numerous (see Fig. 102).

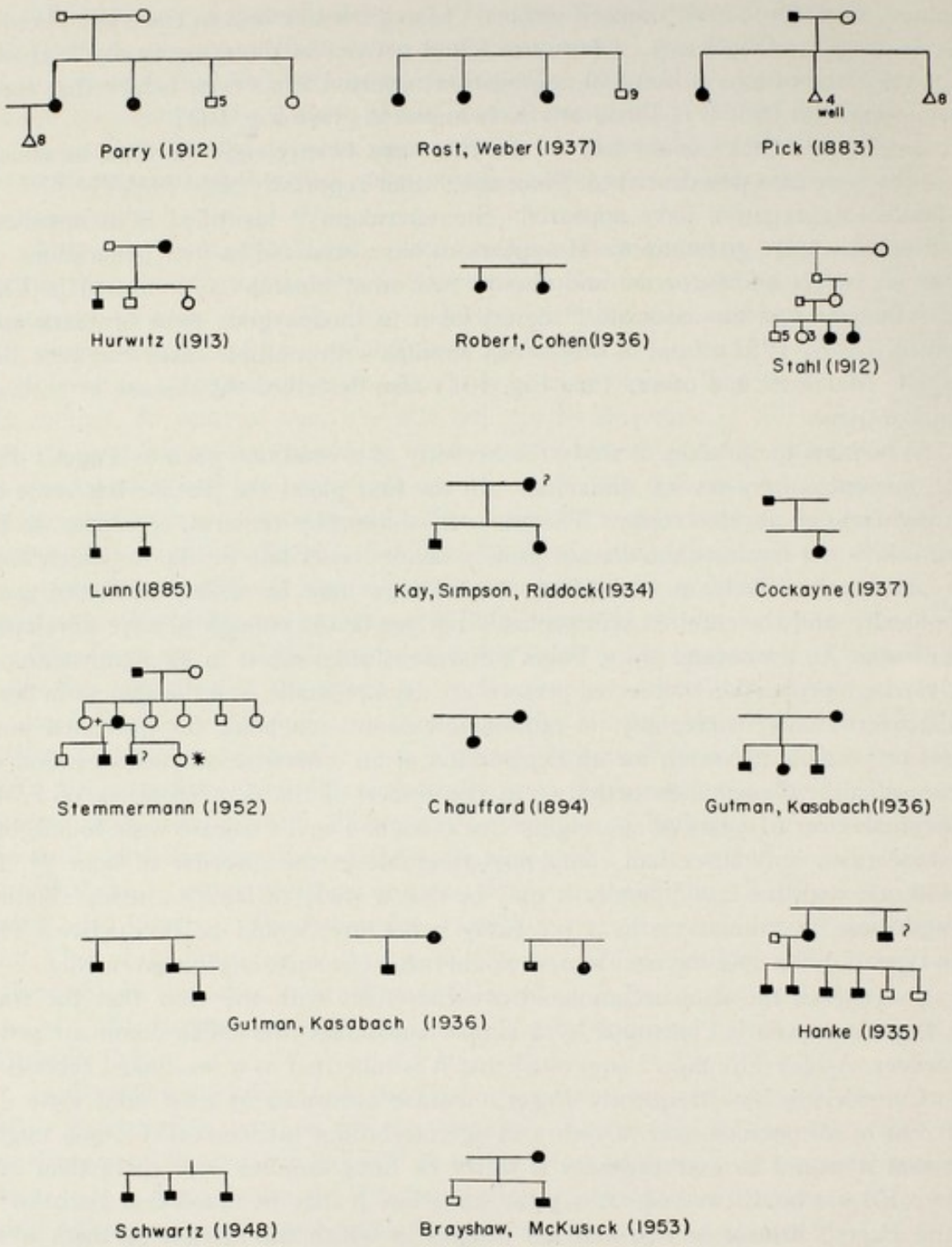
In 1946 Koller[117] could find in the literature twenty-eight families in which more than one case was described. Since then other reports[93,94,100,113,115,122,127,137,143] of familial aggregation have appeared. Stemmermann[143] identified it in members of three successive generations. It appears to have occurred in four generations of a Jewish family known to me and also in two other kinships as indicated in Fig. 102. Aschner and his associates[93] described it in monozygous twin brothers and claimed that by 1952 a total of fifty-seven families with multiple cases had been described. Martin[121] and others (see Fig. 102) also described the disease in both of identical twins.

When one undertakes to study the heredity of a condition such as Paget's disease, one encounters several difficulties. In the first place, the disease has some of the earmarks of an abiotrophy. That it is an abiotrophy remains, of course, to be established. At any rate the disease usually has its onset late in life, by which time the parents are likely to have died, the siblings may be widely scattered geographically, and the children will probably not yet be old enough to have developed the disease. In the second place, Paget's disease is often subtle in its manifestations. A very high proportion of affected persons are asymptomatic, and the change in bone is discovered only incidentally on radiologic examination made for unrelated purposes or possibly in search for an explanation of an otherwise obscure elevation of serum alkaline phosphatase activity. In the course of the detailed study of 7,941 individuals over 61 years of age, eighty-five cases of Paget's disease were found, but of these cases only three had complaints referable to the disorder of bone.[124] In connection with the last difficulty it may be that a study of families, using alkaline phosphatase determinations as a screening procedure, would be productive. The first type of difficulty—the age factor—would not, to be sure, be circumvented.

In general, the data accumulated are consistent with the view that the trait for Paget's disease is controlled by a simple autosomal Mendelian-dominant gene. However, Ashley-Montagu[94] suggested that it is inherited as a sex-linked recessive.

Considering how frequently Paget's disease occurs in at least mild form (3 per cent of all persons over 40 years of age, according to Schmorl[136]), one might say that it would be extraordinary if thirty or forty families with more than one case could *not* be discovered. Along the same line it may be noted that Sabatini[135] found Paget's disease in two married couples in which the marital partners were unrelated. Actually I believe there is a significant familial aggregation of cases. Particularly in the pedigrees with more than two cases is the evidence convincing. The incidence of Paget's disease in the general population is roughly 0.013 per cent.[117] It can be estimated that the chance of two or more cases occurring in the same family by random distribution alone is very slight indeed.

2. Angioid streaks of the retina are associated with only two conditions with any regularity. These are pseudoxanthoma elasticum and Paget's disease of bone.[125,145] Angioid streaks of the fundus of the eye, pseudoxanthoma elasticum in the skin, and Paget's disease in the bones have been observed in the same patient.[150] There may be reasons for believing there is no fundamental relationship between Paget's disease and pseudoxanthoma elasticum: The first may be inherited as a



Figs. 102*A* and 102*B*. Thirty-five pedigrees from the literature and two from the unpublished experience of Brayshaw and McKusick, showing familial aggregation of Paget's disease. Moehlig[122] and Ashley-Montagu[94] and probably others reported Jewish pedigrees. Concordance in identical twins was reported by Koller,[117] by Mozer,[126] and by Dickson, Camp, and Ghormley.[102] In the last instance there was a striking similarity of distribution in the twins, both having, for example, tibial involvement. In the twins observed by Mozer[126] onset of the clinically evident abnormalities occurred at the age of 48 years in both. In Irvine's[113] pedigree the affected male died of a malignant osteoclastoma of the jaw and both daughters had the onset of Paget's disease of the skull and jaw at the age of 18 years. In the pedigree of Brayshaw and McKusick in Fig. 83*B*, the first individual in the second generation, a female (A. H., 511948), had so-called osteitis pubis and changes in the skull compatible with Paget's disease. The alkaline phosphatase, however, was always normal. The other two affected individuals (C. T., 502845; W. T., 620032) had Paget's disease in entirely typical form. These patients were discovered on study of the records of the hospital; if a more detailed study of the family were made, other members would probably be found to be affected.

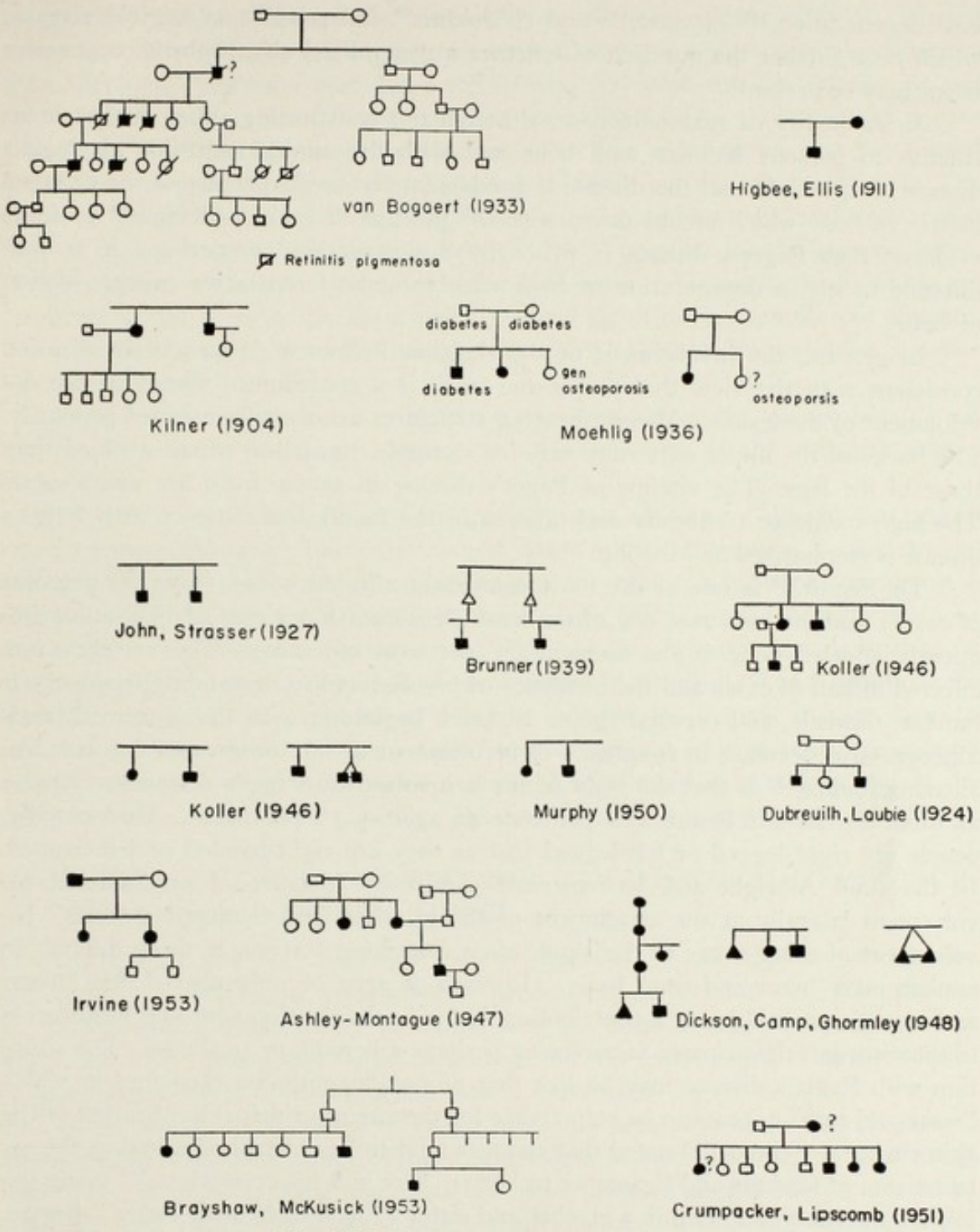


Fig. 102*B*. For legend see opposite page.

Mendelian dominant, the second as a Mendelian recessive; the first occurs more frequently in men, the second in women. (Paget's disease seems to occur more commonly in men but in more severe form in women.)

Although Paget's disease and pseudoxanthoma elasticum may be basically distinct entities, the fact that angioid streaks, which are an integral part of a definite disorder of connective tissue (PXE), occur also in Paget's disease suggests that Paget's disease may likewise be a disorder of connective tissue with abnormalities much more widespread than the bone lesions alone would suggest.

Also in Paget's disease, there occur other ocular abnormalities such as cor-

neal degeneration,[147] cataract,[118] and choroiditis[98] independent of angioid streaks, which raise further the question of whether a generalized abiotrophy of connective tissue may be present.

3. A quality of reasonableness, although not constituting proof, makes it attractive to persons familiar with bone and with the clinical behavior of Paget's disease to speculate that the disease is fundamentally an abiotrophy of the collagen matrix of bone which breaks down with the passage of years. Albright[92] presents evidence that Paget's disease is primarily a destruction or, perhaps it is permissible to say, a degeneration of bone with secondary reparative overproduction of bone.

In general, the involvement of the skeleton follows a pattern of localization consistent with the view that "wear-and-tear" is a contributing factor in the development of the lesions. Weight-bearing structures are usually involved primarily. The bones of the upper extremity are, for example, much less often involved than those of the legs. The victims of Paget's disease in severe form are often obese. The high incidence of obesity and tallness in the families of patients with Paget's disease is emphasized by Moehlig.[122,123]

The femur[136] is one of the most commonly affected bones (over 30 per cent of cases) and the humerus, one of the least (less than 5 per cent).* The most frequently affected bone is the sacrum (57 per cent of cases). The vertebrae are affected in half of cases and the incidence of involvement in descending frequency is lumbar, thoracic, and cervical spine. In brief, beginning with the sacrum there is a progressive decrease in frequency of involvement as one progresses craniad. An amazing finding[136] is that the right femur is involved by Paget's disease over twice as often as the left femur (31 per cent as against 15 per cent). Undoubtedly, people are right-legged or left-legged just as they are right-handed or left-handed. In the skull Albright and Reifenstein[92] picture an instance of predominant involvement laterally at the attachment of the masseter and temporal muscles. Involvement of other areas of the skull, often a striking feature, is more difficult to explain on a "wear-and-tear" basis. However, it must be remembered that "wear-and-tear" is probably only a contributing factor in the development and localization of the disorder, the primary factor being perhaps a hereditary weakness. The situation with Paget's disease may be like that of pseudoxanthoma elasticum in which "wear-and-tear" appears to be responsible for the site of principal localization of the skin changes. Schmorl[136] noted that changes tend to be most pronounced at the attachments of tendons and ligaments to bones. Kay and his co-workers[115] made the important observation that in a brother and sister (Fig. 102*A*) with Paget's disease, both with unilateral involvement of the radius, the left radius was involved in the left-handed individual and the right radius in the right-handed one! This appears to be a nice demonstration of the cooperation of genetic and postnatal factors.

The significance of localized trauma preceding the onset of monostotic Paget's disease is difficult to evaluate (p. 332 of reference 142). The reported cases may represent coincidence.

4. Vascular disease has been thought to occur prematurely and with increased incidence in these patients.[140] This has been thought to be independent of the "high output" heart failure which may occur as a result of the vascular

*The statistics listed here are derived from the classical necropsy study of Schmorl.[136]

peculiarities which functionally resemble arteriovenous fistulae.[104,144] Medial sclerosis of the Mönckeberg's type has been though to occur especially often in these persons. Harrison and Lennox[109] found valvular calcification in 39 per cent of their patients with Paget's disease, an incidence five times that of a control group of comparable age distribution. Vascular calcification may be related merely to the periodic hypercalcemia to which these persons are subjected. The elevation of circulating alkaline phosphatase may contribute. Extraskeletal calcification occurs commonly in these patients,[128,138,148] possibly for the reasons listed, possibly because of an abnormality of connective tissues. Urinary calculi, which are frequent, would seem to be explained by the high urinary excretion of calcium. Salivary calculi, which were identified in twenty of 111 cases,[134] may have a somewhat similar basis.

This fourth bit of evidence is by far the weakest of the points bearing on the possible nature of Paget's disease as an abiotrophy of the collagen matrix of bone.

Hitherto, a principal view of the pathogenesis of Paget's disease has implicated vascular changes. This view would consider that intimately related to the primary defect is the increased vascularity of the bones, which may represent a significant and at times intolerable burden to the heart similar to arteriovenous fistulae,[140] is a problem in hemostasis to surgeons, for instance, the neurosurgeon performing craniotomy in instances of involvement of the skull,[101] and results in the fact that the skin overlying bones severely affected by Paget's disease may be warmer than elsewhere. In the present state of ignorance it is probably at least equally valid to suspect that Paget's disease of bone may be an abiotrophy of the collagen matrix and that the vascular phenomena are secondary developments.

F. OTHER POSSIBLE HEREDITARY AND GENERALIZED DISORDERS OF CONNECTIVE TISSUE

Christiaens and his associates[160] have described (with clinical photographs and autopsy findings) the association of pronounced cutis laxa with bilateral and severe pulmonary emphysema. The latter was the cause of death in the 18-month-old infant. No mechanical factor to account for the emphysema was discovered. A generalized defect of elastic fibers was hypothesized and seemingly found support in the results of histologic studies. The cutis laxa present in this infant was appropriately named as indicated by the photographs which show the skin hanging, from the trunk in particular, in large loose folds. This disorder is not to be confused with either the Ehlers-Danlos syndrome or pseudoxanthoma elasticum; there is no evidence of fundamental alliance with either.

Gout and *ochronosis* (alkaptonuria) might be construed as proper constituents of this general group. Both are hereditary and, in both, connective tissues are conspicuously implicated. However, there is no good evidence that connective tissue is primarily at fault. It is true that in gout there may be a tissue factor to explain some of the peculiar observations such as the following, which suggest that hyperuricemia is not the whole story: (1) Gout does not occur regularly in association with the pronounced hyperuricemia of renal failure, leukemia, or resolving pneumonia. There are suspicions that when gout does occur in these situations the patient is by genetic background fundamentally a gouty person. (2) The solu-

bility product of sodium biurate is not exceeded by the concentrations attained in the serum. Some other local factor must favor precipitation of urate.

In *ochronosis,* there are in the sclera, cartilage, ligaments, joint capsules, and arteries deposits of material which accumulates because of inability of the organism to metabolize phenylalanine and tyrosine beyond the stage of homogentisic acid, which is excreted in the urine.[154,168,185,192] Disabling arthritis and ankylosing spondylitis develop. Calcification of the intervertebral discs is a frequent feature in older

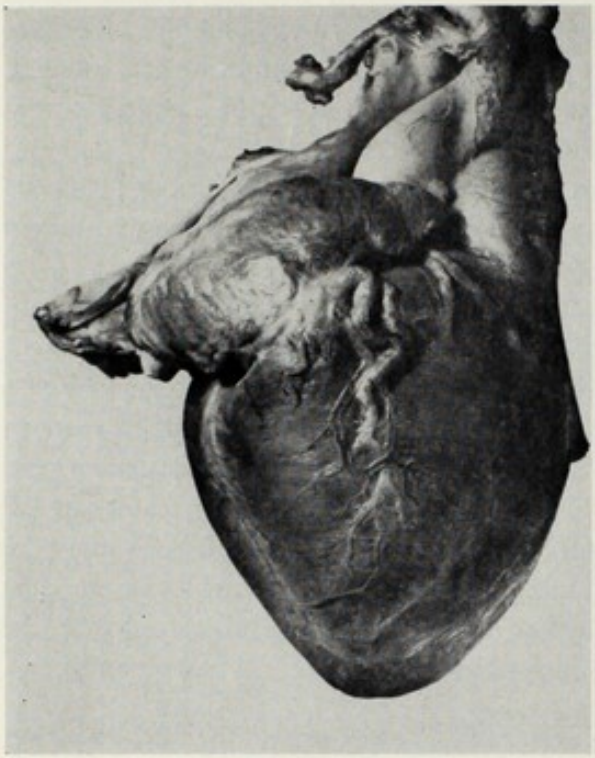


Fig. 103*A*.

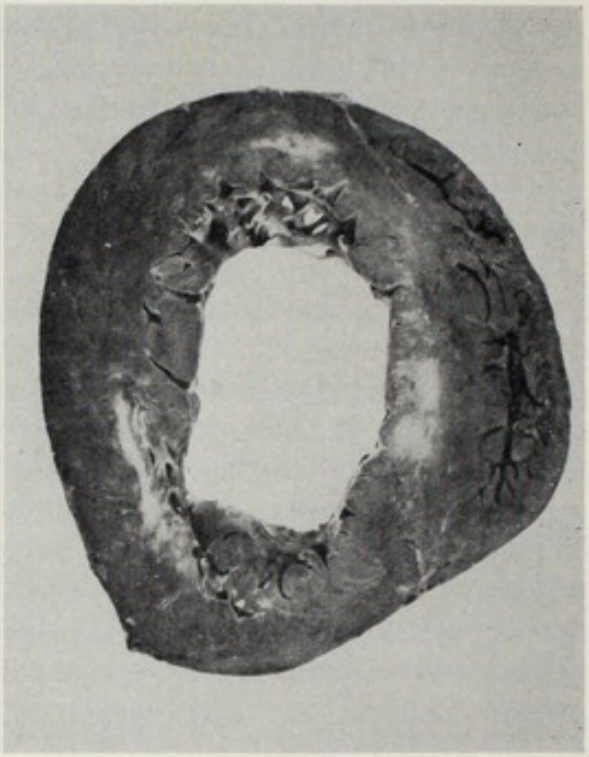


Fig. 103*B*.

Figs. 103*A*-103*G*. Brothers with generalized arterial calcification of infancy.

M. W. died of heart failure at the age of 4 months. Beginning at the age of 3 weeks he appeared to have a respiratory infection, with cough and dyspnea. He was pale and had episodes of sweating. On several occasions he had attacks in which he cried out suddenly and stiffened his body. Peripheral cyanosis, cardiac and hepatic enlargement, and ST segment and T-wave changes in the electrocardiogram were found.

The striking feature was the presence of calcified tortuous coronary arteries (Fig. 103*A*). When the heart was sectioned, evidence of old and recent myocardial infarction was discovered (Fig. 103*B*). Calcification was seen in small arteries of the omentum. Histologically many arteries, including the aorta and pulmonary artery, showed calcification around elastic laminae, which appeared fragmented (Fig. 103*C*). In the outer part of the pulmonary artery, granuloma formation was demonstrated in the area of interruption of the elastic fibers (Fig. 103*D*). The aorta (Fig. 103*E*), stained by the periodic acid-Schiff technique, showed deeply stained margins of abnormal elastic fibers contrasting with the weakly staining edges of normal fibers. In the coronary artery (Fig. 103*F*), after calcium was removed by dilute nitric acid, material staining with periodic acid-Schiff was demonstrated surrounding the elastic lamellae. The association of the calcium deposition with abnormal elastic fibers was demonstrated in the stains of the aorta (Fig. 103*G*) with the von Kossa technique.

The above histologic findings suggest that accumulation of mucopolysaccharide is a consequence of degenerative change in elastic fibers. Similar evidence is available in Erdheim's cystic medial necrosis, in the Marfan syndrome, and in experimental lathyrism. That alteration in the mucopolysaccharide of ground substance is followed by deposition of calcium salts is well recognized. In generalized arterial calcification of infants the "basic defect" may reside in the elastic fibers. Accumulation of mucopolysaccharide and deposition of calcium may be secondary and tertiary phenomena.

C. W., brother of M. W., died at the age of 7 months following an illness identical to that in M. W. Serum calcium concentration and alkaline phosphatase activity were normal. Autopsy revealed widespread arterial calcification and myocardial infarction. (Photographs and information courtesy Dr. Alan L. Williams, Melbourne, Australia.)

individuals.[154] Pigmentation and calcification of the annulus fibrosis mitralis, of the heart valves, and of the arteries occur. Calcific aortic stenosis and severe arteriosclerosis may be integrally related to the metabolic defect.[185]

Generalized arterial calcification of infancy has been noted in multiple sibs[248,250,257] (see Fig. 103). The justification for mentioning it in a discussion of generalized heritable disorders of connective tissue is provided by the evidence

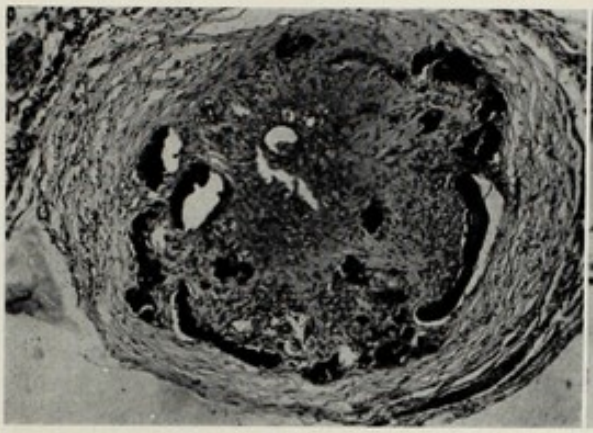


Fig. 103*C*.

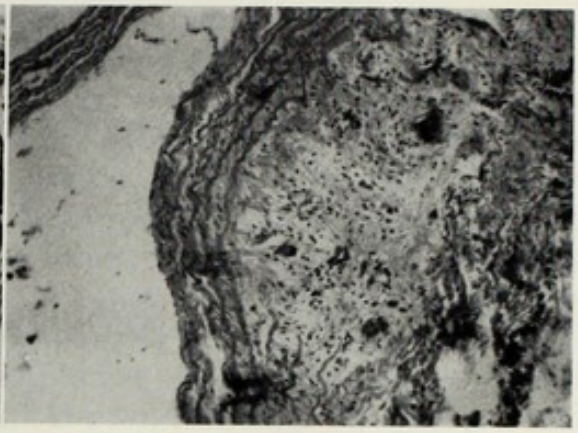


Fig. 103*D*.

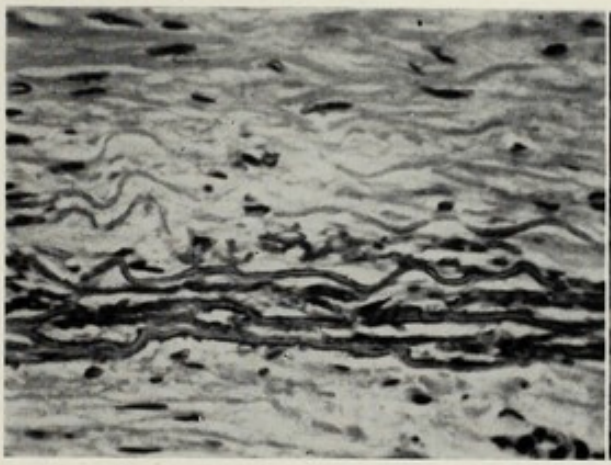


Fig. 103*E*.

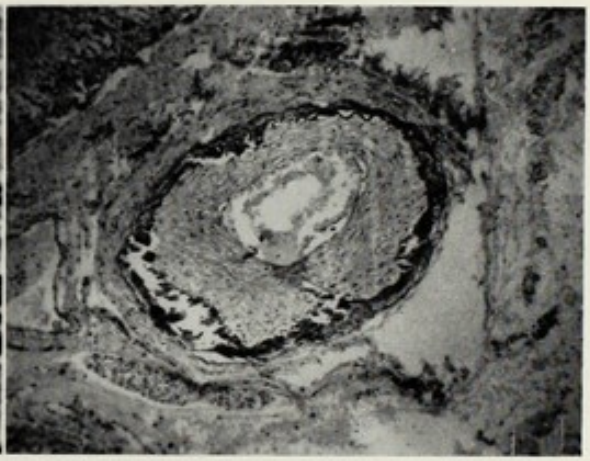


Fig. 103*F*.

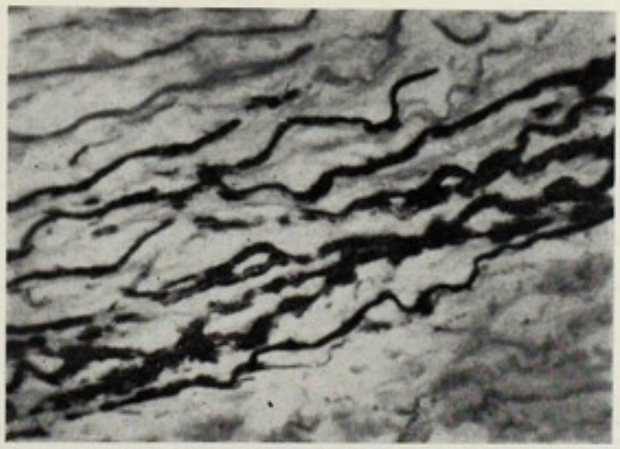


Fig. 103*G*.

Figs. 103*C*-103*G*. For legend see opposite page.

suggesting that fundamentally the disorder is a degeneration of elastic fiber. The calcification shows a remarkable predilection for the internal elastic lamina. Considerable material with the staining properties of mucopolysaccharide accumulates around the elastic laminae.[256] Fine calcium incrustation of the lamina is the minimal lesion. Later the lamina is ruptured and occlusive changes of the intima take place. Death from myocardial infarction usually occurs in the first six months after birth. The clinical diagnosis is suggested by the discovery of calcification in a peripheral vessel in an infant with electrocardiographic evidence of coronary artery disease. Idiopathic infantile hypercalcemia, of which there may be more than one etiologic variety, is probably unrelated; to my knowledge there is not yet evidence of a genetic variety of infantile hypercalcemia.

Osteopetrosis (marble bones; osteosclerosis fragilis generalisata; Albers-Schönberg's* disease), although hereditary and although involving the skeletal system in a generalized fashion, is probably not a generalized disorder of connective tissue of the type under discussion.

This condition is sometimes† inherited as an autosomal recessive trait,[177,179] usually appears very early in life, like osteogenesis imperfecta may be detected in utero, involves the entire skeleton, and may result in such encroachment of the petrified osseous structure on the hematopoietic space of the bone marrow that pancytopenia occurs as the main clinical feature.[155,158,164,179,181,183,186,187,193,194,195,210] Frequently, the disease pursues a less malignant course with, however, a tendency to fracture and to chronic osteomyelitis, especially of the jaw in association with dental infections. The bones are described by some as so hard as to turn the edge of a steel chisel and by others as more like chalk. Usually they are excessively brittle and susceptible to spontaneous fracture. Because of experience with many other progressive disease syndromes of hereditary background, one is not surprised that mild adult cases occur.[158] Repeatedly, hereditary diseases which are at first considered to be only the province of the pediatrician, simply because doctors have learned to recognize only the childhood cases which are the most severe, are found in fact to occur in mild form which does not find clinical expression until later decades or is at least consistent with survival to adulthood. The original patient of Albers-Schönberg[151] was 26 years old and is said to have been living ten years later for re-examination by Reiche. Alexander's[152] patient was 43 years old. The nature of the basic defect is not clear.

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*Albers-Schönberg[151] was one man; this is not a syndrome named for two persons like the Ehlers-Danlos syndrome or the Grönblad-Strandberg syndrome. Care should be taken not to confuse osteopetrosis with osteopoikilosis, which was also first described in a definitive manner by Albers-Schönberg; some writers have evidenced this confusion.

†Clearly there is more than one genetic variety of osteopetrosis. We have done a follow-up study of the family, reported by Ghormley[168a] in 1922, in which the disease occurred in a male born in 1913 and in his father and one paternal uncle. Liability to fractures and to osteomyelitis, especially of the jaw, was the main clinical feature. The uncle died in his 70's, having had chronic osteomyelitis of the mandible starting on the right at age 30 years and on the left at age 55 years. The father was a strong and relatively healthy man despite radiologic evidence of osteopetrosis; he died at 52 years following surgery for peptic ulcer. The proband, the most severely affected of the three, had frequent fractures and developed chronic osteomyelitis of the mandible, bilaterally, at the age of 32 years. In the original report coxa vara was noted; in later years pronounced hip stiffness was bothersome, both in the proband and in his uncle. In spite of his physical incapacitation, the proband became a world's authority on the subject of electrical insulation and was director of the dielectrics research laboratory of a leading university at the time of his death. He died at the age of 45 years from fulminant meningitis, secondary, presumably, to the chronic osteomyelitis.

Multiple enchondromatosis is another heritable and generalized disorder of a specialized variety of connective tissue; in this instance, cartilage. It is usually referred to as Ollier's disease.[162,178,196,198,204] It may be associated with angiomata in the soft tissue—Maffucci's syndrome.[153,159] In Maffucci's syndrome the angiomata may involve the gut.

Like the two conditions just mentioned—osteopetrosis and multiple enchondromatosis—hereditary exostoses,[173,175] which may be confused with enchondromatosis, probably cannot qualify for the group of generalized hereditary disorders of connective tissue because involvement is seemingly limited to a specialized variety of connective tissue. (Even in fibrodysplasia ossificans progressiva this may be the case, fascia and aponeuroses being the specialized connective tissue involved.)

Von Recklinghausen's *neurofibromatosis*[241] is inherited as an autosomal dominant. The histogenesis of the nerve sheath tumors of this disorder is in dispute.[211] If the basic defect resides in the fibroblasts which produce the perineural and endoneural collagen fibers, then this condition might be considered a generalized variety of connective tissue. On the other hand, there is evidence[189] that the parent cell of the von Recklinghausen neurofibroma may be the Schwann cell, which is generally considered a special derivative of the neural crest and not a mesenchymal derivative. The facts that abundant collagen is sometimes present in these tumors and that cells presumed to be of the Schwann cell lineage produce collagen fibers in tissue culture[190] present perplexing problems of general biologic nature as well as problems in the origin of these tumors. It may be that whatever the histogenesis of the nerve sheath tumors, the pigmentary anomalies of the syndrome, the local exaggerations of growth ("elephantiasis nervosum," etc.), the pheochromocytomas in relatively high incidence, scoliosis, and so on can be considered as secondary or tertiary features resulting from the involvement of nerves.

Achondroplasia and *cleidocranial dysostosis*[171] are conditions limited to bone but relatively generalized there. Clark[161] makes the interesting observation that, although there are certain similarities between the two disorders, achondroplasia involves "cartilaginous bones," whereas in cleidocranial dysostosis "membrane bones" are affected.

Clearly there are genetic differences in the tendency to *keloid* formation. Negroes and some Caucasian families are notoriously susceptible.[154a]

Development of knowledge of the basic defect in *primary systemic amyloidosis* will be awaited with interest. Although possibly this diagnosis is applied to more than one basic entity, there is at least one form that is hereditary,[253] being transmitted probably as an autosomal dominant. Preliminary data[251] suggest that the deposited material may be made up of material similar or identical to material normally found in the ground substance of connective tissue. Systemic amyloidosis is not excessively rare. Jones and Frazier[249] in Memphis found it in 2.33 per cent of consecutive autopsies in persons over 20 years of age and 3.47 per cent of those over 50 years of age. They suggested that "amyloid substances may be quite diverse and related to one another only as manifestations of an alteration of a basic extracellular mucopolysaccharide response." Systemic amyloidosis in mice is recessive.[247]

In *urticaria pigmentosa*, the specific pathologic lesion appears to be the accumulation of large numbers of mast cells in the corium and more rarely at other sites such as bone and lung.[162,166] Irritation of the skin lesions results in wheal for-

mation, presumably from the release of histamine from the mast cells. The disease occurs most often in young individuals and usually pursues a self-limited course, disappearing completely at puberty in many cases.

Although the mast cell may legitimately be considered an element of connective tissue, there is very little to indicate that urticaria pigmentosa is hereditary. Cockayne[163] found reports of its occurrence once in two brothers, twice in two sisters, once in three sisters, once in the mother and cousin of an affected child, and once in male uniovular twins. However, the majority of writers have not been impressed by a familial aggregation of cases.

Certain hereditary syndromes display abnormalities of structures other than connective tissues. Such a syndrome is that which goes by Werner's name.[172,197,203,206] The victim of the *Werner syndrome,* which is usually inherited as an autosomal recessive, displays short stature; slender limbs with stocky trunk; scleroderma-like changes, especially in the skin of the extremities, with the development of ulcers over the ankle malleoli, Achilles tendon, heels, and toes, with atrophy of the corium demonstrable microscopically; localized soft tissue calcifications; and, finally, premature arteriosclerosis with Mönckeberg calcification. However, the patients also display premature canities and balding, juvenile cataract,* weak high-pitched voice, atrophy of the epidermis as well as the corium, hypogonadism, osteoporosis, and increased incidence of diabetes mellitus. This is an intriguing disorder as far as definition of the basic defect is concerned. One is reminded of myotonia dystrophica, in which baldness, cataract, and hypogonadism cannot in the present state of ignorance be related to the disorder of muscle.

Epithelial, as well as connective, tissue elements are also involved in the *Ellis-van Creveld syndrome*[157] and in the several varieties of hereditary osteodysplasia and arthrodysplasia which have been reported[176,200,207,210] in association with dystrophy of the fingernails.

In 1928 Pelger and in 1931 Huët, both of the Netherlands, described an anomaly of the nucleus of the leukocyte which in essence consists of a deficiency in segmentation.[208] It was found to be inherited as a dominant. Nachtscheim[191] found the anomaly in one person in 1,000 in the population of Berlin. What ostensibly is the same anomaly occurs in the rabbit, where again it is inherited as a dominant. When two animals affected with the nuclear anomaly are bred, it is found that those offspring which are presumably homozygous for the Pelger-Huët trait demonstrate a severe form of chondrodystrophy.[180,191] The trait is lethal or sublethal in this homozygous form. At least one instance in man of a presumed homozygous form of *Pelger-Huët anomaly* has been reported.[170] Although the change in the leukocyte was more striking than usually seen, no skeletal abnormality was detected. The basis of the relationship between the nuclear anomaly and the chondrodystrophy in the homozygous rabbits is obscure.

In *Dupuytren's contracture*[156,201,205,249a] and in *Peyronie's disease*[199] there is convincing evidence of a hereditary basis. However, the changes are confined to the connective tissue of the palmar fascia and of the corpus cavernosum, respectively.

There are a large number of members of the epiphysitis or *aseptic necrosis* group of disorders in which, more perhaps than in any other area of medicine,

*The internist must keep the Werner syndrome[188] in mind in connection with patients who appear to have a more conventional, acquired variety of scleroderma. Cataracts can be the tip-off to the presence of this hereditary syndrome.

eponyms abound and confound. The following five entities are only a partial enumeration:

Tubercle of tibia	Osgood-Schlatter
Head of femur	Legg-Calvé-Perthes
Spine	Scheuermann
Tarsal scaphoid	Köhler
Semilunar	Kienböck, etc.

All of these probably have a hereditary background, although the evidence in Legg-Perthes' disease is most complete. It is peculiar that each seems to be a distinct genotypic entity. There is, for example, no evidence that more than one of these entities occurs in the same patient or that one member of an affected family has one variety whereas another member has a different variety. Interestingly, Legg-Perthes' disease probably almost never occurs in bona fide form in the pure Negro, although a simulating condition occurs with sickle cell-hemoglobin C disease.[202]

In the case of *epidermolysis bullosa hereditaria* there is a view[167,174,209] of long standing that the basic defect is a deficiency of the elastic fibers of the superficial (papillary) layer of the corium. Normally these fibers are thought by some to bind the epidermis to the corium and their absence has been thought to explain adequately the bullous lesions of this congenital disorder. Others[165,182] have questioned this theory mainly on the basis of a failure to confirm the deficiency of elastic fibers on which the theory was predicated. The mucous membranes of the mouth have been involved, but no specific internal lesions have been described in autopsied cases.[165,182]

For a discussion of the Morquio-Brailsford syndrome and of arthrogryposis multiplex congenita, see the section on the Hurler syndrome.

In Whipple's disease of the bowel[255] the inclusions found in macrophages were thought to be lipoid; hence, the designation "intestinal lipodystrophy." However, Whipple himself[255] recorded the fact that the inclusions do not stain like fat, and others[238,254] have identified the inclusion material as glycoprotein. Furthermore, mesenchymal lesions occur in this disorder. In four twice reported cases,[243,252] the presenting complaint in one was related to arthritis of the right knee, right ankle, and hands. In a second, polyarthritis preceded the onset of diarrhea by several months. Enlargement of mediastinal, axillary, and other lymph nodes may occur.[252,254]

Reported in the literature and occasionally encountered in practice are cases of generalized abnormality suggestive of a disorder of connective tissue but not clearly classifiable in any of the categories discussed in this monograph. Fittke[244] describes such a situation under the title "On an Unusual Form of 'Multiple Congenital Degeneration' (Chalodermia and Dysostosis)." The proband, a 10½-month-old female, had shown, from birth, skin of the entire body, with the exception of the face, which fell in loose redundant folds. On stretching, it returned to its original position very slowly. The skeletal system showed widely persistent fontanels, slight oxycephaly, and dislocation of one hip with flattening of the other acetabulum. There was no known consanguinity, but the family lived in an area of Europe where most persons were related. The mother, 25 years of age, had long been under treatment for "weak knee joints." A first cousin of the proband, 7¾ years of age, showed the same loose skin which was restored only slowly to its original position after

stretching. There was pigeon breast, static scoliosis, and flatfeet. The fontanels did not close until the third year.

G. THE FUTURE IN THE STUDY OF HERITABLE DISORDERS OF CONNECTIVE TISSUE

Undoubtedly, some of the most important problems in connection with these heritable disorders concern pathogenetic (phenogenetic) mechanisms. In the case of each entity here discussed, what information is available has been surveyed. However, our knowledge of the basic defects involved and the links in the pathogenetic chain leading to each of the multiple manifestations is pitifully limited. Snyder[233] expressed well the present direction of interest in genetics:

> In the early days of the study of genetics, the geneticist was content to establish the correlation between the gene in the chromosome and the characteristic in the individual, without raising much question as to the chain of events which connected the two. The attitude was very much like that of the traveler who boards the Miami train in New York confident that he will step out at the Miami station, but actually knowing very little about the physico-chemical principles of the Diesel engine or the intricacies of the switching and signaling systems that will get him there.
>
> Today, however, the question of genic action in the development of finished characters is uppermost in the minds of geneticists, and biochemical genetics is leading the attack on this front.*

Physiologic genetics is the term customarily used for that division of the field concerned with tracing the link between gene and phene. The term is not precisely applicable to the study of mechanisms in disease traits. To be sure, it is often difficult to draw the line between pathologic states and deviations from the physiologic average. However, the term *genetic pathology* is probably a better one for the discipline concerned with the same problems in connection with heritable disease which the physiologic geneticist deals with in the case of traits such as skin color or polydactylism.

Many different technologic approaches to identification of the fundamental biochemical defect in these conditions must be adopted. Electron microscopy has already been applied to the Ehlers-Danlos syndrome[234] and pseudoxanthoma elasticum,[234] but apparently not to OI.[218] Tissue culture of fibroblasts is possibly one of the more promising, although as yet unexplored, techniques for the study of heritable disorders of connective tissue. (In general, tissue culture has been too little used in physiologic genetics.) In vitro fibrogenesis has been investigated with the assistance of light microscopy[214,217,227,229,230] and electron microscopy[232] but not in these diseases. Synthesis of certain of the constituents of the ground substance has also been studied in tissue culture.[224,229] Methods for chemical quantification of collagen production in vitro are available.[223] Tissue culture, or rather organ culture, has been employed in some hereditary developmental anomalies of animals,[216,219,220,221] but except for the studies of Geiger and Garvin[222] on muscle from patients with muscular dystrophy, tissue culture methods have not, to my knowledge, been utilized in the study of hereditary disorders of man.

In connection with the heritable disorders of connective tissue, the first ob-

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*From Snyder, L. H.: Frontiers in Genetics; *In* Frontiers in Medicine; The March of Medicine, 1950, New York, 1951, Columbia University Press.

jective of tissue culture studies should be the in vitro replication of the morphologic abnormalities. In osteogenesis imperfecta and in the Hurler syndrome one can with justification anticipate success in demonstrating morphologic abnormality, in the fibers formed in the first instance, possibly in the fibroblast itself in the second, i.e., the "gargoyle cell" may be demonstrable in culture. It is possible that the fibers produced by fibroblasts from patients with pseudoxanthoma elasticum might be morphologically abnormal or undergo premature deterioration. In the Marfan syndrome and the Ehlers-Danlos syndrome, morphologic abnormality is much less likely to be evident. However, if in the latter condition there is failure to observe excessive production of elastic fibers, then significant negative evidence bearing on the nature of the basic defect will have been provided. Much interest is attached to observations of cultures of fascial fibroblasts from patients with fibrodysplasia ossificans progressiva.

If the initial morphologic studies are consonant with the view that a fibroblast strain growing in the the test tube represents the original donor's disease "in pure culture," then intensive studies should be undertaken of the chemical character of the fibers and ground materials produced by the cells, e.g., amino acid profile of the collagen and elastin. Rate of fibrogenesis must be quantified.

The demonstration that the anomaly in certain hemoglobin variants consists of substitution of one amino acid out of many making up the hemoglobin protein[224a] stimulates speculation about the nature of the fibrous proteins in heritable disorders of connective tissue. It is to be hoped that studies in the near future will explore the possibility, for example, that in osteogenesis imperfecta an anomalous species of collagen is produced which differs in only one amino acid from the collagen in persons free of this disease.

Generalized disorders of connective tissue which satisfy the criteria of these studies seem to be almost completely unknown in animals.[228] Their existence in animals is likely, however. More easily recognized disorders, such as achondroplasia, do occur in many species, and the Pelger-Huët anomaly of leukocytes with associated chrondrodystrophy occurs in the rabbit. As noted in the appropriate sections, conditions in animals resembling OI and FOP in man have been described. The whole body of knowledge about connective tissue and perhaps understanding of the hereditary disorders of connective tissue in man could be greatly enlarged if there were available animal strains containing a mutant gene determining an aberration of connective tissue.

Not only do diverse disciplines have much to offer in the elucidation of pathogenetic mechanisms in these disorders of connective tissue but also, conversely, these heritable disorders per se can be exploited as valuable tools for the investigation of connective tissue in general.

Through the attention of the rheumatologist, the advent of steroid therapy, the increased familiarity with systemic lupus erythematosus and related so-called "collagen diseases"[226] or "connective tissue diseases,"[225] connective tissue has in recent years come into its own as an object of medical interest. As objects of study the heritable disorders of connective tissue have conspicuous advantages over these acquired conditions. The lesion tends to be more selective, i.e., can better be pinpointed to one element of connective tissue. The biochemical lesion is, one would presume, definable in a more clean-cut manner. These hereditary disorders of connective tissue are in themselves of sufficient clinical importance to justify intensive

study of basic pathogenesis. But, in addition, they can be looked upon as tools by use of which much has been, and much more can be, learned about the biology of normal connective tissue and the reactions of connective tissue in acquired disease.

Great interest was stimulated by the discovery by Ponseti and Baird[231] that seed of the sweet pea *(Lathyrus odoratus)* contains a substance (subsequently identified as an aminonitrile) which is a specific toxin for some connective tissue element. This announcement created a stir, in part because of a similarity of the lesions observed in rats to those encountered under some circumstances in man, but more because there seemed here to be a tool for indirectly getting at normal mechanisms in connective tissue. Vitamin C deprivation[235,236] has likewise been and promises to continue to be a useful tool for studying such matters as collagen fibrogenesis and the relation of the ground substance to same. As unitary defects of connective tissue elements, the heritable disorders of connective tissue also represent potentially productive areas for investigation.

I do not intend to create the impression that there is no longer opportunity for studies of this group of disorders on the clinical level.[213] This is by no means the case. The genetics of all of these conditions requires further investigation. Improved means for recognizing mild forms of the several disorders would have some practical usefulness and would increase understanding of the mechanisms of inheritance. Similarly, clinical analyses of the factors responsible for variability in expression of these syndromes could have both practical and theoretical implications of importance. For the benefit of the patients, methods for modifying the clinical expression of the disorders should be sought.

In the case of several of the syndromes, particularly pseudoxanthoma elasticum and the Ehlers-Danlos syndrome, information on internal medical ramifications is still regrettably scanty. Knowledge in this area depends on the continuation of clinical and pathologic observations of the classical type.

In general, the future of study of heritable disorders of connective tissue looks exciting and promises productivity which will have significance far outreaching that relating to the clinical problems presented by these patients.

SOME GENERAL COMMENTS

As to the biology of connective tissue, study of heritable disorders probably underscores more than any other single feature the intimate interrelationship of the several elements of connective tissue—collagen, elastin, and ground substance. The interrelationship is responsible in part for the uncertainty which surrounds attempts at identification of the primary defect in each of these syndromes.

Aside from the fact that the same structures are involved, the behavior of these hereditary disorders of connective tissue is quite distinct from the acquired diseases of connective tissue. One can point to the stiff joints in the Hurler syndrome and to involvement of the base of the aorta in rheumatoid arthritis, but, on the whole, analogies are strained and unconvincing.

H. GENERAL SUMMARY AND CONCLUSIONS

1. In general, the clinical picture of each of the heritable disorders of connective tissue is as specific and predictable as that of other clinical entities; for

example, infectious diseases. There is, of course, a certain amount of variability in clinical expression, such as the physician learns to expect. The clinical manifestations of each syndrome were summarized in tabular form in Chapter 1.

2. The heritable disorders of connective tissue are not congenital malformations in the conventional sense. Certain congenital malformations do seem to occur with increased frequency in association with some of these disorders. It is proposed that during embryogenesis the connective tissue defect sets the stage favorable to the development of the particular malformations. See Chapter 3 on the Marfan syndrome for examples.

3. Pseudoxanthoma elasticum behaves like an abiotrophy, as does also the aortic involvement in the Marfan syndrome. The peculiarities of growth in the Marfan syndrome and the Hurler syndrome are apparently intimately related to the basic defect of connective tissue. Certain features of the Hurler syndrome (specifically those relating to the brain, liver, spleen, and cardiovascular system) partake of the characteristics of a thesaurosis, or "storage" disease. In osteogenesis imperfecta and in the Ehlers-Danlos syndrome there appears to be a defect in the formation of collagen; in the first the defect is relatively early in fibrogenesis, whereas in the second the organization of collagen bundles into the usual meshwork is defective.

4. Many principles of heredity are illustrated by these disorders. Examples of dominant, recessive, and sex-linked inheritance are provided. Phenomena of expressivity and penetrance are displayed.

5. The recognition of the more easily detectable expressions of the basic defect of connective tissue provides clinical clues to the nature of internal disturbances which are less accessible for study. Most dramatic illustrations of this time-honored principle are the association of ectopia lentis with aortic regurgitation in the Marfan syndrome and of angioid streaks of the fundus oculi and characteristic skin changes with massive gastrointestinal hemorrhage in pesudoxanthoma elasticum.

6. The intimate interrelationships of the several elements of connective tissue are indicated by the difficulties in identifying the specific element of connective tissue which is defective in several of these syndromes.

7. The heritable disorders of connective tissue are ripe for major advances in identification of the fundamental biochemical defect.

8. The heritable disorders of connective tissue can be useful tools for the study of the normal biology of connective tissue. Further confirmation is provided for the principle enunciated by Sir Archibald Garrod: The clinical and other investigation of hereditary disorders will shed light on normal developmental and biochemical mechanisms.

REFERENCES

Fibrodysplasia Ossificans Progressiva (FOP)

1. Barker, L. F.: Medical Clinics, Philadelphia, 1922, W. B. Saunders Co.
2. Bauer, K. H., and Bode, W.: Erbpathologie der Stutzgewebe beim Menschen. Erbbiologie und Erbpathologie korperlicher Zustande und Funktionen, Berlin, 1940, Julius Springer, vol. 1, p. 105.
3. Bell, J.: On Hereditary Digital Anomalies. Part I. On Brachydactyly and Synphalangism. The Treasury of Human Inheritance, London, 1951, Cambridge University Press.
4. Brooks, W. D. W.: Calcinosis, Quart. J. Med. **3**:293, 1934.
5. Burton-Fanning, F. W., and Vaughan, A. L.: A Case of Myositis Ossificans, Lancet **2**:849, 1901.

6. Drago, A.: Contributo allo studio della moisite ossificente progressive multipla, Pediatria **27**:715, 1919.
7. Fairbank, H. A. T.: Myositis Ossificans Progressiva, J. Bone & Joint Surg. **32-B**:108, 1950.
8. Fairbank, H. A. T.: An Atlas of General Affections of the Skeleton, Baltimore, 1951, Williams & Wilkins Co.
9. Falls, H. F.: Skeletal System, Including Joints, chap. 14 in Sorsby, A.: Clinical Genetics, St. Louis, 1953, The C. V. Mosby Co., p. 246.
10. Fränkel, B.: Ein Fall von erblicher Difformität, Berl. klin. Wchnschr. **8**:418, 1871.
11. Frejka, B.: Heteropic Ossification and Myositis Ossificans Progressiva, J. Bone & Joint Surg. **11**:157, 1929.
12. Garrod, A. E.: The Initial Stage of Myositis Ossificans, St. Bart. Hosp. Rep. **43**:43, 1907.
13. Gaster, A.: Discussion in Meeting of West London Medico-Chirurgical Society, Oct. 7, 1904, West London M. J. **10**:37, 1905.
14. Geschickter, C. F., and Maseritz, I. H.: Myositis Ossificans, J. Bone & Joint Surg. **20**:661, 1938.
15. Greig, D. M.: Clinical Observations of the Surgical Pathology of Bone, Edinburgh, 1931, Oliver & Boyd, p. 170.
16. Griffith, G.: Progressive Myositis Ossificans; Report of a Case, Arch, Dis. Childhood **24**:71, 1949.
17. Gruber, G. B.: Anmerkungen zur Frage der Weichteilverknockerung, besonders der Myopathia osteoplastica, Virchows Arch. **260**:457, 1926.
18. Gutman, A. B., and Yü, T. F.: A Further Consideration of the Effects of Beryllium Salts on in vitro Calcification of Cartilage. Metabolic Interrelations, Tr. Josiah Macy, Jr. Found. **3**:90, 1950.
19. Guyatt, B. L., Kay, H. D., and Branion, H. D.: Beryllium "Rickets," J. Nutrition **6**:313, 1933.
20. Helferich, H.: Ein Fall von sogenannter Myositis ossificans progressiva, Aerztliches Intelligenz-Blatl. **26**:485, 1879.
21. Hirsch, F., and Löw-Beer, A.: Ueber einen Fall von Myositis ossificans progressiva, Med. Klin. **25**:1661, 1929.
22. Huggins, C. B.: The Formation of Bone Under the Influence of Epithelium of the Alimentary Tract, Arch. Surg. **22**:377, 1931.
23. Hutchinson, J.: Reports of Hospital Practice, M. Times & Gaz. **1**:March 31, 1860.
24. Klemper, F. W., Miller, J. M., and Hill, C. J.: The Inhibition of Alkaline Phosphatase by Beryllium, J. Biol. Chem. **180**:281, 1949.
25. Koontz, A. R.: Myositis Ossificans Progressiva, Am. J. M. Sc. **174**:406, 1927.
26. Koontz, A. R.: Personal communication.
27. Kubler, E.: Neue Gesichtspunkte bei der Beurteilung der Verlaufsformen der Myositis ossificans progressiva, Fortschr. Geb. Röntgenstrahlen **81**:354, 1954.
28. Lockhart, J. D., and Burke, F. G.: Myositis Ossificans Progressiva. Report of a Case Treated With Corticotropin (ACTH), A.M.A. J. Dis. Child. **87**:626, 1954.
29. Magruder, L. F.: Myositis Ossificans Progressiva. Case Report and Review of the Literature, Am. J. Roentgenol. **15**:328, 1926.
30. Mair, W. F.: Myositis Ossificans Progressiva, Edinburgh M. J. **39**:13, 69, 1932.
31. Maudsley, R. H.: Case of Myositis Ossificans Progressiva, Brit. M. J. **1**:954, 1952.
32. Mather, J. H.: Progressive Myositis Ossificans, Brit. J. Radiol. **4**:207, 1931.
33. Michelson, J.: Ein Fall von Myositis ossificans progressiva, Ztschr. f. orthop. Chir. **12**:424, 1904.
34. Nutt, J. J.: Report of a Case of Myositis Ossificans Progressiva, With Bibliography, J. Bone & Joint Surg. **5**:344, 1923.
35. Pack, G. T., and Braund, R. R.: Development of Sarcoma in Myositis Ossificans, J. A. M. A. **119**:776, 1942.
36. Paul, J. R.: A Study of an Unusual Case of Myositis Ossificans, Arch. Surg. **10**:185, 1925.
37. Pol: "Brachydaktylie," "Klinodaktylie," Hyperphangie und ihre Grundlagen. Form und Entstehung der meist unter dem Bild der Brachydaktylie auftreitenden Varietaten, Anomalien und Missbildungen der Hand und des Fusses, Virchows Arch. **299**:388, 1921.
38. Riley, H. D., Jr., and Christie, A.: Myositis Ossificans Progressiva, Pediatrics **8**:753, 1951.
39. Rolleston, H. D.: Progressive Myositis Ossificans With References to Other Developmental Diseases of the Mesoblast, Clin. J. **17**:209, 1901.
40. Rosenstirn, J.: A Contribution to the Study of Myositis Ossificans Progressiva, Ann. Surg. **68**:485, 591, 1918.
41. Ryan, K. J.: Myositis Ossificans Progressiva. Review of the Literature With Report of a Case, J. Pediat. **27**:348, 1945.
42. Sympson, T.: Case of Myositis Ossificans, Brit. M. J. **2**:1026, 1886.
43. Tutunjian, K. H., and Kegerreis, R.: Myositis Ossificans Progressiva With Report of a Case, J. Bone & Joint Surg. **19**:503, 1937.
44. van Creveld, S., and Soeters, J. M.: Progressive Myositis Ossificans, Am. J. Dis. Child. **62**:1000, 1941.

45a. Vastine, J. H., II, Vastine, M. F., and Arango, O.: Genetic Influence on Osseous Development With Particular Reference to the Deposition of Calcium in the Costal Cartilages, Am. J. Roentgenol. **59**:213, 1948.
b. Vastine, J. H., II, Vastine, M. F., and Arango, O.: Myositis Ossificans Progressiva in Homozygotic Twins, Am. J. Roentgenol. **59**:204, 1948.
46. Wheeler, C. E., Curtis, A. C., Cawley, E. P., Grekin, R. H., and Zheutlin, B.: Soft Tissue Calcification, With Special Reference to Its Occurrence in the "Collagen Diseases," Ann. Int. Med. **36**:1050, 1952.
47. Wilkins, W. E., Reagan, E. M., and Carpenter, G. K.: Phosphatase Studies on Biopsy Tissue in Progressive Myositis Ossificans, Am. J. Dis. Child. **49**:1219, 1935.

Osteopoikilosis

48. Albers-Schönberg, H.: Eine seltene bisher nicht bekannte Strukturanomalie des Skelettes, Fortschr. Geb. Röntgenstrahlen **23**:174, 1915.
49. Bistolfi: Cited by Curth.[57]
50. Bloom, A. R.: Osteopoecilia, Am. J. Surg. **22**:239, 1933.
51. Busch, K. F. B.: Familial Disseminated Osteosclerosis, Acta radiol. scandinav. **18**:693, 1937.
52. Buschke, A., and Ollendorff, H.: Ein Fall von Dermatofibrosis lenticularis disseminata und Osteopathia condensans disseminata, Dermat. Wchnschr. **86**:257, 1928.
53. Cocchi, U.: *In* Schinz, H. R., Baensch, W. E., Friedl, E., and Uehlinger, E.: Roentgendiagnostics (J. T. Case, editor of American edition), New York, 1951, Grune & Stratton, Inc., p. 744.
54. Copeman, W. S. C. (ed.): Textbook of Rheumatic Diseases, Edinburgh and London, 1955, E. & S. Livingston, Ltd., p. 307.
55. Coughlin, E. J., Jr., Guare, H. F., and Moskovitz, A. J.: Chondrodystrophia Calcificans Congenita: Case Report With Autopsy, J. Bone Joint Surg. **32-A**:938, 1950.
56. Curth, H. O.: Follicular Atrophoderma and Pseudopelade Associated With Chondrodystrophia Calcificans Congenita, J. Invest. Dermat. **13**:233, 1949.
57. Curth, H. O.: Dermatofibrosis Lenticularis Disseminata and Osteopoikilosis, Arch. Dermat. & Syph. **30**:552,1934.
58. Erbsen, H.: Die Osteopoikilie (Osteopathia condensans disseminata), Ergebn. med. Strahlenforsch. **7**:137, 1936.
59. Funstein, L., and Kotschiew, K.: Ueber die Osteopoikilie, Fortschr. Geb. Röntgenstrahlen **54**:595, 1936.
60. Hinson, A.: Familial Osteopoikilosis, Am. J. Surg. **45**:566, 1939.
61. Jeter, H., and McGehee, C. L.: Osteopoikilosis, J. Bone & Joint Surg. **15**:990, 1933.
62. Koch, J. C.: The Laws of Bone Architecture, Am. J. Anat. **21**:177, 1917.
63. Martinčić, N.: Osteopoikilie (Spotted Bones), Brit. J. Radiol. **25**:612, 1952.
64. Nichols, B. H., and Shiflett, E. L.: Osteopoikilosis. Report of an Unusual Case, Am. J. Roentgenol. **32**:52, 1934.
65. Osgood, E. C.: Polyostotic Fibrous Dysplasia and Osteopathia Condensans Disseminata, Am. J. Roentgenol. **56**:174, 1946.
66. Reilly, W. A., and Smith, F. S.: Stippled Epiphyses With Congenital Hypothyroidism (Cretinoid Epiphyseal Dysgenesis), Am. J. Roentgenol. **40**:675, 1938.
67. Risseeuw, J.: Familiäre Osteopoikilie, Nederl. tijdschr. v. geneesk. **80**:3827, 1936.
68. Ritterhoff, R. G., and Oscherwitz, D.: Osteopoikilosis Associated With Bronchogenic Carcinoma, and Adenocarcinoma of Stomach, Am. J. Roentgenol. **48**:34, 1942.
69. Schmorl, G.: Anatomische Befunde bei einem Fall von Osteopoikilie, Fortschr. Geb. Röntgenstrahlen **44**:1, 1931
70. Steenhuis, D. J.: About a Special Case of Osteitis Condensans Disseminata, Acta radiol. **5**:373, 1926.
71. Stieda, A.: Ueber umschriebene Knockenverdichtungen in Bereich der Substantia im Röntgenbilde, Beitr. klin. Chir. **45**:700, 1905.
72. Šváb, d'Vaclav: À propos de l'ostéopoecilie héréditaire, J. radiol. et electr. **16**:405, 1932.
73. Traub, E.: Epiphyseal Necrosis in Pituitary Gigantism, Arch. Dis. Childhood **14**:203, 1939.
74. von Bernuth, F.: Ueber Sklerodermie, Osteopoikilie und Kalkgicht im Kindesalter, Ztschr. Kinderh. **54**:103, 1932.
75. Voorhoeve, N.: A Hitherto Undescribed Picture of Abnormality of the Skeleton, Acta radiol. **3**:407, 1924.
76. Wilcox, L. R.: Osteopoikilosis (Disseminated Condensing Osteopathy), Am. J. Roentgenol. **27**:580, 1932.
77. Windholz, F.: Ueber familiäre Osteopoikilie und Dermatofibrosis lenticularis disseminata, Fortschr. Geb. Röntgenstrahlen **45**:566, 1932.

Léri's Pleonosteosis

78. Cocchi, U.: Hereditary Diseases With Bone Changes; *In* Schinz, H. R., Baensch, W. E., Friedl, E., and Uehlinger, E.: Roentgen-diagnostics (editor of American edition: J. T. Case), New York, 1951, Grune & Stratton, Inc., vol. 1, pp. 720 ff.

79. Cohen and de Herdt: Pléonostéose familiale, J. Neurol. et Psychiat. **28**:395, 1928.
80. Copeman, W. S. S., editor: Textbook of the Rheumatic Diseases, Edinburgh and London, 1955, E. & S. Livingston, Ltd.
81. Feiguine, E., and Tikhodéeff, S.: Un cas rare d'osteopathie systematisee—un cas de pléonostéose en U. R. S. S., Arch. de méd. d. enf. **35**:654, 1932.
82. Léri, A.: Une maladie congenitale et héréditaire de l'ossification: la pléonostéose familiale, Bull. et mém. Soc. méd. hôp. Paris **45**:1228, 1921.
83. Léri, A.: Sur la plénostéose familiale, Bull. et mém. Soc. méd. hôp. Paris **48**:216, 1924.
84. Léri, A.: Dystrophie osseuse généralisée congénitale et héréditaire: la pléonostéose familiale, Presse méd. **30**:13, 1922.
85. Materna, A.: Zur Pathologie der Pleonosteose (Léri), Beitr. path. Anat. **112**:112, 1952.
86. Neel, J. V., and Schull, W. J.: Human Heredity, Chicago, 1954, University of Chicago Press, p. 309.
87. Rocher, H. L., and Pesme, P.: Un cas de pléonostéose (maladie de Léri) avec cornées opalescentes, J. méd. Bordeaux **123**:121, 1946.
88. Rocher, H. L., and Roudil, G.: La pléonostéose (maladie de Léri), Bordeaux chir. **4**:359, 1932.
89. Rothea, M.: La pléonostéose familiale (maladie d'André Léri), Theses, Paris and Nancy, No. 421.
90. Rouillard, J., and Barreau, P.: Un nouveau cas de pléonostéose héréditaire avec atteintes graves des grosses articulations, Bull. et mém. Soc. méd. hôp. Paris **51**:794, 1927.
90a. Rukavina, J. G., Falls, H. F., Holt, J. F., and Block, W. G.: Léri's Pleonosteosis. A Study of a Family With a Review of the Literature, J. Bone & Joint Surg. **41-A**:397, 1959.
91. Watson-Jones, R.: Léri's pléonostéosis, Carpal Tunnel Compression of the Medial Nerves and Morton's Metatarsalgia, J. Bone & Joint Surg. **31-B**:560, 1949.

Paget's Disease

92. Albright, F., and Reifenstein, E. C., Jr.: The Parathyroid Glands and Metabolic Bone Disease. Selected Studies, Baltimore, 1948, Williams & Wilkins Co., pp. 284-301.
93. Aschner, B. M., Hurst, L. A., and Roizin, L: Genetic Study of Paget's Disease in Monozygotic Twin Brothers, Acta genet. med. et gemel. **1**:67, 1952.
94. Ashley-Montagu, M. F.: Paget's Disease (Osteitis Deformans) and Heredity, Am. J. Human Genet. **1**:94, 1947.
95. Brunner, H.: Zur Pathologie der Ostitis deformans (Paget) des Schlafenbeins, Klin. Wchnschr. **2**:174, 1931.
96. Brunner, W.: Osteodystrophia deformans Paget unter besonderer Berücksichtigung unserer Erfahrungen der letzten 10 Jahre, Deutsche Ztschr. Chir. **52**:585, 1939.
97. Chauffard, A.: Discussion of Paper by Gilles de la Tourette and Marinesco, Bull. mém. Soc. méd. hôp. Paris, **11** (ser. 3):426, 1894.
98. Clegg, J. T.: Paget's Disease With Mental Symptoms and Choroiditis, Lancet **2**:128, 1937.
99. Cockayne, E. A.: Quoted by Rast and Weber.[132]
100. Crumpacker, E. L., and Lipscomb, P. R.: The Familial Incidence of Paget's Disease of Bone (Osteitis Deformans). Report of Occurrence in Three Siblings, M. Clin. North America **35**:1203, 1951.
101. Dandy, W. E.: Personal communication.
102. Dickson, D. D., Camp, J. D., and Ghormley, R. K.: Osteitis Deformans (Paget's Disease of Bone), Radiology **44**:449, 1945.
103. Dubreuilh, W., and Laubie: Maladie osseuse de Paget chez deux frères, Bull. Soc. franç. dermat. **3**:87, 1924.
104. Edholm, O. G., Howarth, S., and McMichael, J.: Heart Failure and Bone Blood Flow in Osteitis Deformans, Clin. Sc. **5**:249, 1945.
105. Faugeron, R.: Essai sur les rapports de la syphilis et de la maladie osseuse de Paget, Thèse de Paris, 1923.
106. Goldenberg, R. R.: The Skeleton in Paget's Disease, Bull. Hosp. Joint Dis. **12**:229, 1951.
107. Gutman, A. B., and Kasabach, H. H.: Paget's Disease (Osteitis Deformans). Analysis of 116 Cases, Am. J. M. Sc. **191**:361, 1936.
108. Hanke, H.: Osteodystrophische Erkankungen und ihre Begrenzung, Deutsche Ztschr. Chir. **245**:641, 1935.
109. Harrison, C. V., and Lennox, B.: Heart Block in Osteitis Deformans, Brit. Heart J. **10**:167, 1948.
110. Higbee, W. S., and Ellis, A. G.: A Case of Osteitis Deformans, J. Med. Res. **24**:43, 1911.
111. Hurwitz, S. H.: Osteitis Deformans, Paget's Disease: A Report of Six Cases, Bull. Johns Hopkins Hosp. **24**:263, 1913.
112. Hurwitz, S. H.: Osteitis Deformans (Paget's Disease), Bull. Johns Hopkins Hosp. **24**:266, 1913.
113. Irvine, R. E.: Familial Paget's Disease With Early Onset, J. Bone & Joint Surg. **35-B**:106, 1953.
114. John, E., and Strasser, U.: Zur Aetiologie, Klinik und Therapie der Ostitis fibrosa deformans (Paget), Deutsche Ztschr. Nervenh. **97**:81, 1927.

115. Kay, H. D., Simpson, S. L., and Riddock, G.: Osteitis Deformans, Arch. Int. Med. **53**:208, 1934.
116. Kilner, J.: Two Cases of Osteitis Deformans in One Family, Lancet **1**:221, 1904.
117. Koller, F.: Ueber die Heredität der Ostitis deformans Paget, Helvet. med. acta **13**:389, 1946.
118. Laederich, L., Mamon, H., and Beuchesne, H.: Un cas de maladie osseuse de Paget avec cataracte de type endocrinien, Bull. et mém. Soc. méd. hôp. Paris **65**:529, 1938.
119. Lambert, R. K.: Paget's Disease With Angioid Streaks of the Retina, Arch. ophth. **22**:106, 1939.
120. Lunn, J. R.: Four Cases of Osteitis Deformans, Tr. Clin. Soc. London **18**:272, 1885.
121. Martin, E.: Considérations sur la maladie de Paget, Helvet. med. acta **14**:319, 1947.
122. Moehlig, R. C.: Osteitis Deformans: Familial Constitutional Hereditary Background as Etiological Factors, J. Michigan M. Soc. **51**:1004, 1027, 1952.
123. Moehlig, R. C.: Paget's Disease (Osteitis Deformans) and Osteoporosis: Similarity of the 2 Conditions as Shown by Familial Background and Glucose Tolerance Studies, Surg. Gynec. & Obst. **62**:815, 1936.
124. Monroe, R. T.: Diseases of Old Age, Cambridge, 1951, Harvard University Press, p. 304.
125. Morrison, W. H.: Osteitis Deformans With Angioid Streaks. Report of a Case, Arch. Ophth. **26**:79, 1941.
126. Mozer, J. J.: Discussion of Koller.[117]
127. Murphy, W.: Osteitis Deformans in a Brother and Sister, M. J. Australia **1**:507, 1950.
128. Narins, L., and Oppenheimer, G. D.: Calcification of Vas Deferens Associated With Paget's Disease of Bone, J. Urol. **67**:2118, 1952.
129. Paget, J.: Remarks on Osteitis Deformans, Illustrated Medical News **2**:181, 1889.
130. Parry, T. W.: A Case of Osteitis Deformans in Which Fracture of a Femur Took Place as the Result of Stooping, Brit. M. J. **1**:879, 1912.
131. Pick: Osteitis Deformans, Lancet **2**:1125, 1883.
132. Rast, H., and Weber, F. P.: Paget's Bone Disease in Three Sisters, Brit. M. J. **1**:918, 1937.
133. Roberts, R. E., and Cohen, M. J.: Osteitis Deformans (Paget's Disease of Bone), Proc. Roy. Soc. Med. **19**:13, 1936.
134. Rosenkrantz, J. A., Wolf, J., and Kaicher, J.: Paget's Disease (Osteitis Deformans); Review of 111 Cases, Arch. Int. Med. **90**:610, 1952.
135. Sabatini, G.: Ostitis fibrosa di Paget in due coppie di coniugi, Minerva med. **39**:607, 1948.
136. Schmorl, G.: Ueber Ostitis deformans Paget, Virchows Arch. **283**:694, 1932.
137. Schwartz, L. A.: Paget's Disease in 3 Male Siblings; Clinical Report, J. Michigan M. Soc. **47**:1244, 1948.
138. Seligman, B., and Nathanson, L.: Metastatic Calcification in the Soft Tissues of the Legs in Osteitis Deformans, Ann. Int. Med. **23**:82, 1945.
139. Smith, S. M.: A Case of Osteitis Deformans in Which the Disease Is Present in Father and Son, Tr. med. Soc. London **28**:224, 1904-1905.
140. Sornberger, C. F., and Smedel, M. I.: Mechanism and Incidence of Cardiovascular Changes in Paget's Disease; Critical Review of Literature With Case Studies, Circulation **6**:711, 1952.
141. Stahl, B. F.: Osteitis Deformans, Paget's Disease, With Reports of Two Cases and Autopsy in One, Am. J. M. Sc. **143**:525, 1912.
142. Stein, I., Stein, R. O., and Beller, M. L.: Living Bone in Health and Disease, Philadelphia, 1955, J. B. Lippincott Co.
143. Stemmermann, W.: Die Ostitis deformans Paget unter Berücksichtigung ihrer Vererbung, Ergebn. inn. Med. **3**(n.s.):185, 1952.
144. Storsteen, K. A., and Jones, N. J.: Arteriography and Vascular Studies in Paget's Disease of Bone, J. A. M. A. **154**:472, 1954.
145. Terry, T. L.: Angioid Streaks and Osteitis Deformans, Tr. Am. Ophth. Soc. **32**:555, 1934.
146. van Bogaert, L.: Ueber eine hereditäre und familiäre Form der Pagetschen Ostitis deformans mit Chorioretinitis pigmentosa, Ztschr. ges. Neur. **147**:327, 1933.
147. von der Heydt, R.: Osteitis Deformans With Pigmented Corneal Degeneration, Am. J. Ophth. **20**:1139, 1937.
148. Wells, H. G., and Holley, S. W.: Metastatic Calcification in Osteitis Deformans, Arch. Path. **34**:435, 1942.
149. Wilton, A.: On the Genesis of Osteitis Deformans (Paget), Acta orthop. scandinav. **24**:30, 1954.
150. Woodcock, C. W.: Transactions of the Cleveland Dermatological Society, Arch. Dermat. & Syph. **65**:623, 1952.

Other Possible Hereditary and Generalized Disorders of Connective Tissue

151. Albers-Schönberg, H.: Eine bisher nicht beschriebene Allgemeinerkrankung des Skelettes im Röntgenbilde, Fortschr. Geb. Röntgenstrahlen **11**:261, 1907.
152. Alexander, W. G.: Report of a Case of So-Called "Marble-Bones" With a Review of the Literature and a Translation of Article, Am. J. Roengenol. **10**:280, 1923.

153. Bean, W. B.: Dyschondroplasia and Hemangiomata (Maffucci's Syndrome) Arch. Int. Med. **95**:767, 1955.
154. Black, R. L., Lowney, J. L., and Duffy, P. M.: Alcaptonuria and Ochronosis. Report of Five Cases Occurring in an American Family, Arch. Int. Med. **93**:75, 1954.
154a. Bloom, D.: Heredity of Keloids, New York J. Med. **56**:511, 1956.
155. Brailsford, J. F.: The Radiology of Bones and Joints, ed. 5, Baltimore, 1953, Williams & Wilkins Co.
156. Bunnell, S.: Surgery of the Hand, Philadelphia, 1948, J. B. Lippincott Co.
157. Caffey, J.: Chondroectodermal Dysplasia (Ellis-van Creveld Disease). Report of Three Cases, Am. J. Roentgenol. **68**:875, 1952.
158. Callender, G. R., Jr., and Migakawa, G.: Osteopetrosis in Adult, Case, J. Bone & Joint Surg. **35-A**:204, 1953.
159. Carleton, A., Elkington, J. St. C., Greenfield, J. G., and Robb-Smith, A.H.T.: Maffucci's Syndrome (Dyschondroplasia With Haemangiomatosis), Quart. J. Med. **35**:203, 1942.
160. Christiaens, L., Marchant-Alphant, A., and Fovet, A: Emphysème congénital et cutis laxa, Presse méd. **62**:1799, 1954.
161. Clark, W. E. LeGros: The Tissues of the Body. An Introduction to the Study of Anatomy, Oxford, 1945, Clarendon Press, p. 69.
162. Clyman, S. G., and Rein, C. R.: Urticaria Pigmentosa Associated With Bone Lesions; Survey, J. Invest. Dermat. **19**:179, 1952.
163. Cockayne, E. A.: Inherited Abnormalities of the Skin and Its Appendages, London, 1933, Oxford University Press, p. 310.
164. Cohen, J.: Osteopetrosis; Case Report, Autopsy Findings and Pathologic Interpretation; Failure of Treatment With Vitamin A, J. Bone & Joint Surg. **33-A**:923, 1951.
165. Craig, H. R.: Epidermolysis Bullosa, Am. J. Dis. Child. **39**:898, 1930.
166. Ellis, J. M.: Systemic Lesions in Urticaria Pigmentosa, Arch. Path. **48**:426, 1949.
167. Engman, M. F., and Mook, W. H.: A Further Contribution to the Study of Elastic Tissue in Epidermolysis Bullosa, J. Cutan. Dis. **28**:275, 1910; Study of Some Cases of Epidermolysis Bullosa With Remarks Upon the Congenital Absence of Elastic Tissue, Ibid. **24**:55, 1906.
168. Galdston, M., Steele, J. M., and Dobriner, K.: Alcaptonuria and Ochronosis, With a Report of Three Patients and Metabolic Studies in Two, Am. J. Med. **13**:432, 1952.
168a. Ghormley, R. K.: A Case of Congenital Osteosclerosis, Bull. Johns Hopkins Hosp. **33**:444, 1922.
169. Grollman, A.: Dyschondroplasia (Hereditary Deforming Chondrodysplasia); *In* Christian, H. A.: Oxford Medicine, New York, 1947, Oxford University Press, vol. 3, pt. 3, p. 487.
170. Haverkamp Begemann, N., and van Lookeren Campagne, A.: Homozygous Form of Pelger-Huët's Nuclear Anomaly in Man, Acta haemat. **7**:295, 1952.
171. Herndon, C. N.: Cleidocranial Dysostosis, Am. J. Human Genet. **3**:314, 1951.
172. Irvin, G. W., and Ward, P. B.: Werner's Syndrome, With a Report of Two Cases, Am. J. Med. **15**:266, 1953.
173. Jaffe, H. L.: Hereditary Multiple Exostoses, Arch. Path. **36**:335, 1943.
174. Kanoky, J. P., and Sulton, R. L.: Epidermolysis Bullosa Congenita (Epidermolysis Bullosa Hereditaria of Köbner), J. A. M. A. **54**:1137, 1910.
175. Keith, Sir A.: The Nature of the Structural Alteration in the Disorder Known as Multiple Exostoses, J. Anat. **54**:101, 1919-1920.
176. Keizer, D. R. R., and Schilder, J. H.: Ectodermal Dysplasia, Achondroplasia, and Congenital Morbus Cordis, Am. J. Dis. Child. **82**:345, 1951.
177. Kelley, C., and Lawlah, J. W.: Albers-Schönberg Disease: A Family Survey, Radiology **47**:507, 1946.
178. Khoo, F. Y., Chang, P. Y., Lee, C. T., and Fan, K. S.: Multiple Cartilaginous Exostoses (Hereditary Deforming Chondrodysplasia), Chinese M. J. **66**:252, 1948.
179. Klein, A.: Zur Frage der Erblichkeit der Marmorknockenkrankheit, Fortschr. Geb. Röntgenstrahlen **76**:366, 1952.
180. Klein, H.: Die Pelger-Anomalie der Leukocyten und die pathologische Anatomie des neugeborenen homozygoten Pelger-Kaninchens. Ein Beitrag zum Formenkries der fetelen Chondrodystrophie, Ztschr. menschl. Vererb.-u. Konstitutionslehre **29**:551, 1949.
181. Kneal, E., and Sante, L. R.: Osteopetrosis (Marble Bones); Report of a Case With Special Reference to Early Roentgenologic and Pathologic Findings, Am. J. Dis. Child. **81**:693, 1951.
182. Lamb, J. H., and Halpert, B.: Epidermolysis Bullosa of the Newborn, Arch. Dermat. & Syph. **55**:369, 1947.
183. Laubmann: Ueber die Knochenstruktur bei Marmorknockenkrankheit, Virchows Arch. **296**:343, 1935.
184. Landauer, W.: Studies on the Creeper Fowl. XII. Size of Body, Organs and Long Bones of Late Homozygous Creeper Embryos, Storrs Agric. Exper. Station, University of Connecticut Bull. No 232, 1939; Also: Studies on Fowl Paralysis. 3. A Condition Resembling Osteopetrosis (Marble Bone) in the Common Fowl, Bull. No. 222, 1938.

185. Lichtenstein, L., and Kaplan, L.: Hereditary Ochronosis; Pathologic Changes Observed in Two Necropsied Cases, Am. J. Path. **30**:99, 1954.
186. Lorey and Reye: Ueber Marmorknockenkrankheit, Fortschr. Geb. Röntgenstrahlen **30**:35, 1923.
187. McCune, D. J., and Bradley, C.: Osteopetrosis (Marble Bones) in an Infant. Review of the Literature and Report of a Case, Am. J. Dis. Child. **48**:949, 1934.
188. Meyer, R. J.: The Medical Significance of Lenticular Opacities (Cataract) Before the Age of Fifty, With Emphasis on Their Occurrence in Systemic Disorders, New England J. Med. **252**:622, 665, 1955.
189. Murray, M. R.: Demonstration of Schwannian Origin of Tumors of the Nerve Sheaths, Arch. Neurol. & Psychiat. **42**:1175, 1939.
190. Murray, M. R., and Stout, A. P.: Characteristics of Human Schwann Cells in Vitro, Anat. Rec. **84**:275, 1942.
191. Nachtscheim, H.: Pelger Anomaly in Man and Rabbit, J. Hered. **41**:131, 1950.
192. Osler, W.: Ochronosis, the Pigmentation of Cartilage, Sclerotics and Skin in Alkaptonuria, Lancet **1**:10, 1904.
193. Pearce, L., and Brown, W. H.: Hereditary Osteopetrosis in the Rabbit, J. Exper. Med. **88**:579, 597, 1928.
194. Pirie, A. H.: The Development of Marble Bone, Am. J. Roentgenol. **24**:147, 1930; Marble Bones, Ibid. **30**:618, 1933.
195. Plotz, M., and Chakales, H. J.: Osteopetrosis (Albers-Schönberg Disease; Marble Bone Disease), New York J. Med. **53**:445, 1953.
196. Potterfield, T. C., and Gonzalez, I.: Ollier's Dyschondroplasia, J. Pediat. **33**:705, 1948.
197. Reed, R., Seville, R. H., and Tattersall, R. N.: Werner's Syndrome, Brit. J. Dermat. **65**:165, 1953.
198. Sanderson, G. H., and Smith, F. S.: Chondrodysplasia (Ollier's Disease), J. Bone & Joint Surg. **20**:61, 1938.
199. Schourup, K.: Plastic Induration of the Penis, Acta radiol. **26**:313, 1945.
200. Senturia, H. R., and Senturia, B. D.: Congenital Absence of Patellae Associated With Arthrodysplasia of Elbows and Dystrophy of Nails, Am. J. Roentgenol. **51**:352, 1944.
201. Skoog, T.: Dupuytren's Contraction With Special Reference to Etiology and Improved Surgical Treatment; Its Occurrence in Epileptics; Note on Knucklepads, Acta chir. scandinav., suppl. 139, 1948.
202. Smith, E. W., and Conley, C. L.: Genetic Variants of Sickle Cell Disease, Bull. Johns Hopkins Hosp. **94**:289, 1954.
203. Smith, R. C., Winer, L. H., and Martel, S.: Werner's Syndrome; Report of Two Cases, Arch. Dermat. **71**:197, 1955.
204. Stocks, P., and Barrington, A.: Hereditary Disorders of Bone Development. Treasury of Human Inheritance, vol. 3, part 1, Diaphysial Aclasia (Multiple Exostoses), Multiple Enchondromatosis, Cleidocranial Dysostosis, London, 1925, Cambridge University Press.
205. Teleky, L.: Dupuytren's Contraction as Occupational Disease, J. Indust. Hyg. & Toxicol. **21**:233, 1939.
206. Thannhauser, S. J.: Werner's Syndrome (Progeria of the Adult) and Rothmund's Syndrome; Two Types of Closely Related Heredofamilial Atrophic Dermatoses With Juvenile Cataracts and Endocrine Features; a Critical Study With Five New Cases, Ann. Int. Med. **23**:559, 1945.
207. Thompson, E. A., Walker, E. T., and Wiens, H. T.: Iliac Horns, Osseous Manifestation of Hereditary Arthrodysplasia Associated With Dystrophy of Fingernails, Radiology **53**:88, 1949.
208. van der Sar, A.: The Pelger-Huët Familial Nuclear Anomaly of the Leucocytes, Am. J. Clin. Path. **15**:544, 1944.
209. Weiss, R. S.: A Case of Epidermolysis Bullosa, Showing Loss of Elastic Tissue in the Apparently Normal Skin, J. Cutan. Dis. **35**:26, 1917.
210. Wildervanck, L. S.: Hereditary Congenital Abnormality of Elbows, Knees and Nails in Five Generations, Acta radiol. **33**:41, 1950.
211. Willis, R. A.: Pathology of Tumours, ed. 2, London and St. Louis, 1953, Butterworth & Co., Ltd., and The C. V. Mosby Co., p. 839.
212. Zwerg, H. G., and Laubmann: Die Albers-Schönbergsche Marmorkrankheit, Ergebn. med. Strahlenforsch. **7**:95, 1936.

The Future in This Field

213. Bauer, K. H., and Bode, W.: Erbpathologie der Stützgewebe beim Menschen. Erbbiologie und Erbpathologie korperlicher Zustande und Funktionen, Berlin, 1940, Julius Springer, vol. 1, p. 105.
214. Bloom, W.: Studies on Fibers in Tissue Culture. II. The Development of Elastic Fibers in Cultures of Embyronic Heart and Aorta, Arch. exper. Zellforsch. **9**:6, 1929.
215. Bollet, A. J., Boas, N. F., and Bunim, J. J.: Synthesis of Hexosamine by Connective Tissue (in Vitro), Science **120**:348, 1954.

216. David, P. R.: Studies on the Creeper Fowl. A Study of the Mode of Action of a Lethal Factor by Explantation Methods, Wilhelm Roux' Arch. Entwicklungsmech. Organ. **135**:521, 1936-1937; Biol. Abst. **11**:No. 17892, 1937.
217. Doljanski, L., and Roulet, F.: Studien über die Entstehung der Bindegewebsfibrille, Virchows Arch. **291**:260, 1933.
218. Engfeldt, B., Engström, A., and Zetterström, R.: Biophysical Studies of Bone Tissue in Osteogenesis Imperfecta, J. Bone & Joint Surg. **36-B**:654, 1954.
219. Ephrussi, B.: The Behaviour in Vitro of Tissues From Lethal Embryos, J. Exper. Zool. **70**:197, 1935.
220. Fell, H. B., and Gruneberg, H.: The Histology and Self-Differentiating Capacity of the Abnormal Cartilage in a New Lethal Mutation in the Rat (Rattus norvegicus), Proc. Roy Soc. London (ser. B) **127**:257, 1939.
221. Fell, H. B., and Landauer, W.: Experiments on Skeletal Growth and Development in Vitro in Relation to the Problem of Avian Phokomelia, Proc. Roy. Soc. London (ser. B) **118**:133, 1935.
222. Geiger, R. S., and Garvin, S. J.: Growth Pattern in Vitro of Skeletal Muscle From Pseudohypertrophic Muscular Dystrophy, Fed. Proc. **14**:55, 1955.
223. Gerarde, H. W., and Jones, M.: The Effect of Cortisone on Collagen Synthesis in Vitro, J. Biol. Chem. **201**:553, 1953.
224. Grossfeld, H., Meyer, K., and Godman, G.: Differentiation of Fibroblasts in Tissue Culture as Determined by Mucopolysaccharide Production (abst.), Anat. Rec. **121**:471, 1955.
224a. Ingram, V. M.: Abnormal Human Haemoglobins. 1. The Comparison and Sickle-Cell Haemoglobins by Finger-Printing, Biochim. et biophys. acta **28**:539, 1958.
225. Kellgren, J. H.: Some Concepts of Rheumatic Disease, Brit. M. J. **1**:1093, 1152, 1952.
226. Klemperer, P.: The Concept of Collagen Diseases, Am. J. Path. **26**:505, 1950.
227. Maximow, A.: Development of Argyrophile and Collagenous Fibers in Tissue Culture, Proc. Soc. Exper. Biol. & Med. **25**:437, 1928.
228. Nachtsheim, H.: Erbpathologie des Stützgewebes der Saugetiere. Erbbiologie und Erbpathologie korperlicher Zustande und Funktionen, Berlin, 1940, Julius Springer, vol. 1, p. 46.
229. Odiette, D.: La fibre élastique dans les cultures de tissus in vitro (deuxième mémoire), J. physiol. et path. gén. **33**:475, 1935.
230. Odiette, D.: La fibre élastique dans les cultures de tissus in vitro. Étude histo-physiopathologique, J. physiol. et path. gén. **32**:715, 1934.
231. Ponseti, I. V., and Baird, W. A.: Scoliosis and Dissecting Aneurysm of the Aorta in Rats Fed With Lathyrus odoratus Seeds, Am. J. Path. **28**:1059, 1952.
232. Porter, K. R., and Vanamee, P.: Observations on the Formation of Connective Tissue Fibers, Proc. Soc. Exper. Biol. & Med. **71**:513, 1949.
233. Snyder, L. H.: Frontiers in Genetics; *In* Frontiers of Medicine: The March of Medicine, 1950, New York, 1951, Columbia University Press, p. 56.
234. Tunbridge, R. E., Tattersall, R. N., Hall, D. A., Astbury, W. T., and Reed, R.: Fibrous Structure of Normal and Abnormal Human Skin, Clin. Sc. **11**:315, 1952.
235. Wolbach, S. B., and Howe, P. R.: Intercellular Substances in Experimental Scorbutus, Arch. Path. **1**:1, 1926.
236. Wolbach, S. B.: Controlled Formation of Collagen and Reticulum. A Study of the Source of Intercellular Substance in Recovery From Experimental Scorbutus, Am. J. Path. (supp.) **9**:689, 1933.
237. Albronda, J.: Familiale Osteopoikilie, Nederl. tijdschr. geneesk. **100**:3533, 1956.
238. Black-Schaffer, B.: The Tinctorial Demonstration of a Glycoprotein in Whipple's Disease, Proc. Soc. Exper. Biol. & Med. **72**:225, 1949.
239. Catzel, P.: Congenital Laxity of the Ligaments With Hypotonia, Arch. Dis. Childhood **30**:387, 1955.
240. Cox, H. L.: Progressive Myositis, Ossificans: Review of the Literature and Report of a Case, North Carolina M. J. **18**:459, 1957.
241. Crowe, F. W., Schull, W. J., and Neel, J. V.: A Clinical, Pathological and Genetic Study of Multiple Neurofibromatosis, Springfield, Ill., 1956, Charles C Thomas, Publisher.
242. Eaton, W. L., Conkling, W. S., and Daeschner, C. W.: Early Myositis Ossificans Progressiva Occurring in Homozygotic Twins; A Clinical and Pathologic Study, J. Pediat. **50**:591, 1957.
243. Eyler, W. R., and Doub, H. P.: Extraintestinal Roentgen Manifestations of Intestinal Lipodystrophy, J. A. M. A. **160**:834, 1956.
244. Fittke, H.: Ueber eine ungewöhnliche Form "multipler Erbabartung" (Chalodermie und Dysostose), Ztschr. Kinderh. **63**:510, 1942.
245. Freke, J.: Phil. Tr. Roy. Soc., London, 1740. Quoted by Ralph H. Major: Classic Descriptions of Disease, With Biographical Sketches of the Authors, ed. 3, Springfield, Ill., 1945, Charles C Thomas, Publisher, p. 304.
246. Grumbach, M. M.: Personal communication, Feb. 28, 1958.
247. Heston, W. E., and Deringer, M. K.: Hereditary Renal Disease and Amyloidosis in Mice, Arch. Path. **46**:49, 1948.

248. Hunt, A. C., and Ley, D. G.: General Arterial Calcification of Infancy, Brit. M. J. **1**:385, 1957.
249. Jones, R. S., and Frazier, D. B.: Primary Cardiovascular Amyloidosis. Its Clinical Manifestations, Pathology and Histogenesis, Arch. Path. **50**:366, 1950.
249a. Kostia, J.: A Dupuytren Contracture Family, Ann. chir. et gynaec. Fenniae **46**:351, 1957.
250. Menten, M. L., and Felteman, G. H.: Coronary Sclerosis in Infancy. Report of Three Autopsied Cases, Two in Siblings, Am. J. Clin. Path. **18**:805, 1948.
251. Meyer, K:. Sulfated Polysaccharides of Connective Tissues, Abst. 130th American Chemical Society Meeting, September, 1956, p. 150.
252. Puite, R. H., and Tesluk, H.: Whipple's Disease, Am. J. Med. **19**:383, 1955.
253. Rukavina, J. G., Block, W. D., Jackson, C. E., Falls, H. F., Carey, J. H., and Curtis, A. C.: Primary Systemic Amyloidosis; A Review and an Experimental, Genetic, and Clinical Study of 29 Cases With Particular Emphasis on the Familial Form, Medicine **35**:239, 1956.
254. Upton, A. C.: Histochemical Investigation of the Mesenchymal Lesions in Whipple's Disease, Am. J. Clin. Path. **22**:755, 1952.
255. Whipple, G. H.: A Hitherto Undescribed Disease Characterized Anatomically by Deposits of Fat and Fatty Acids in the Intestinal and Mesenteric Lymphatic Tissues, Bull. Johns Hopkins Hosp. **18**:382, 1907.
256. Williams, A. L. (Melbourne): Personal communication.
257. Williams, A. L.: The Pathology of Cardiac Failure in Infancy, M.D. thesis, University of Melbourne, 1958.

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