A Genetical View of Cardiovascular Disease

The Lewis A. Conner Memorial Lecture

By Victor A. McKusick, M.D.

The last 10 to 15 years have seen phenomenal advances in genetics. Assuming universality of the basic principles of life, geneticists and biochemists—in recent years it has become increasingly difficult to distinguish the two—have opportunistically attacked the questions of the nature of the gene and how it works in whatever form of life yields its secrets most readily. They have provided us with the dogma of one-cistron-one-polypeptide-chain, or somewhat loosely translated, one-gene-one-protein-unit. A holy trinity—DNA, RNA, and protein—is envisioned. How structural genes—those that determine the make-up of proteins, enzymatic and non-enzymatic—are themselves constituted and how they work has been rather clearly revealed. Still shrouded in obscurity, however, are most of the details of how the genes themselves are controlled. Here is the enigma of differentiation and development. All somatic cells have the same full complement of genes, as far as anyone knows. Why do some genes function only in some tissues or only at some stages? A pile of bricks is not a house. How the structural genes work together in a concerted manner, properly scheduled and integrated, is the leading problem not only of genetics but also of embryology and teratology.

Human genetics and that part of the science concerned with disease, medical genetics, have also developed rapidly in the last 10 to 15 years. Progress is enslaved to techniques—in this case biochemical, cytologic, and statistical. In the last decade we have acquired biochemical methods for analyzing phenotypic variation all the way down to differences in the amino acid sequence of proteins; cytologic methods for scrutinizing the chromosomes of man which, albeit crude, have revealed a myriad of changes completely unknown, although I will not say undreamed of, merely 6 years ago; methods for statistical study, especially in the realm of genetic linkage, by which mapping of man’s chromosome is possible.

By advances in general genetics the understanding of disease has been enhanced. Contrariwise, the close study of disease has contributed to advances in general genetics. The best example, perhaps, is the demonstration that a main function of genes is to specify the

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Table 1

<table>
<thead>
<tr>
<th>Chromosomal Aberrations</th>
<th>Frequency</th>
<th>Heart defect</th>
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</thead>
<tbody>
<tr>
<td>Mongolism Triplo 21</td>
<td>1:600 3/9</td>
<td>AV canal defects</td>
</tr>
<tr>
<td>Turner syndrome XO</td>
<td>1:3,000 9</td>
<td>Coarctation</td>
</tr>
<tr>
<td>Klinefelter syndrome XXY</td>
<td>1:500 3</td>
<td>. . .</td>
</tr>
<tr>
<td>Triple X syndrome XXX</td>
<td>1:800 9</td>
<td>. . .</td>
</tr>
<tr>
<td>Group D1 trisomy Triplo 13-15</td>
<td>1:2,000 3/9</td>
<td>VSD dextroposition</td>
</tr>
<tr>
<td>Group E trisomy Triplo 17</td>
<td>1:1,000 3/9</td>
<td>VSD, PDA</td>
</tr>
</tbody>
</table>

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amino acid sequence, or the primary structure, of proteins. Study of sickle and other variant hemoglobins was largely responsible for this concept. Through its contributions to general genetics, human genetics has established itself as a full partner and as a mature scientific discipline.

The net result of the advances so briefly outlined is that genetics has become the unifying force in biology and medicine that the atomic theory has for a longer time been in physics and chemistry.

My charge, as I interpret it, is to survey, in the limits of time, the status of our comprehension of genetic factors in cardiovascular disease. What impact have advances in genetics had, and what are they likely to have, on the practice of cardiology?

In 1959 I wrote as follows:

An analysis of the role of genes in determining disorders of any system tends to divide naturally into two parts. First, there are less commonly occurring disorders in which a single mutant gene is primarily responsible for derangement in structure and function of the system under study or a part thereof.

A second large category in which analysis of genetic factors is in order comprises the common diseases of the system. These are often diseases of multifactorial causation; in many the etiologies and pathogenetic mechanisms are as yet incompletely worked out; however, acquired or environmental factors seem from existing evidence to be of paramount importance. Nonetheless, genetic factors in determining susceptibility and in modifying the behavior of the disease are evident in some.

Because of the discoveries that were first being reported at the time this was written, one now can add chromosomal aberrations as a third recognizable category of genetic disorders of the cardiovascular system. Even though in the majority of instances they are not inherited, at least not in the usual sense of the word, most are potentially heritable and at any rate they all concern change in the genetic material.

**Chromosomal Aberrations**

The best known of the chromosomal aberrations (table 1) are triplo-21 Mongolism,
the XO Turner syndrome, and the XXY Klinefelter syndrome. Cardiovascular malformation is an important feature of the first two, as it is also of the two less familiar but by no means excessively rare autosomal trisomies: that involving a chromosome of group 13-15 and that involving either chromosome 17 or 18.

In the Turner syndrome (fig. 1), coarctation of the aorta is the most frequent cardiovascular complication, but pulmonary stenosis occurs in some. A majority of these cases have one chromosome too few, there being only one sex chromosome, an X. They are referred to as XO.

Hypertension without coarctation occurs in a certain proportion of cases. Although vascular malformation in the kidney is suspected, it is not always easily demonstrated. Angiomata occur in the bowel in the Turner syndrome and are the basis of gastrointestinal hemorrhages in some of these patients. Lymphedema is a peripheral vascular feature of the Turner syndrome (fig. 2).

Requiring further study are two related categories in which features of the Turner syndrome, including short stature, lymphedema, and congenital heart disease occur.

The Turner syndrome. At birth, C. L. (581730) had edema of the dorsum of both feet and both hands, as well as redundant skin of the neck. Most of the edema gradually subsided over a period of a few weeks although slight edema was still present in the left hand at the age of 3½ years. She is chromatin negative with an XO sex chromosome constitution.

Figure 2

Figure 3

Top. Mongolism in a 14-year-old boy who shows characteristically short stature and typical eyes, facies, flat occiput, stubby hands with brachymesophalangy of the fifth digit, poor circulation with cutis marmorata and loose-jointness (in the ankles, for example). Bottom. Karyotype showing trisomy of chromosome 21. A different arrangement is used here than in the other karyotypes.
One category is represented by female patients with the same facial characteristics, low-set ears, low hair line, short stature, and lymphedema as in the Turner syndrome and with congenital heart malformations such as pulmonary stenosis, but with normal sexual development and function. Suspicions of mosaicism exist in some of these. (Becker and his colleagues have described a patient who had somatic stigmata of the Turner syndrome but normal sexual function; some XO and some normal XX cells were found.) Patients in the second category are commonly referred to as “male Turner’s”; puzzling is the occurrence of a normal male karyotype and a male phenotype in connection with many other features indicative of the Turner syndrome, including congenital heart disease.

Thirty-five per cent or more of newborn Mongoloid idiots (fig. 3) have congenital heart disease, most often a defect of the atrioventricular canal. Congenital heart dis-

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**Figure 4**

Trisomy 13-15 (D1 trisomy). This newborn female infant of a 39-year-old mother (A.S., 975712) weighing 2,355 Gm. showed microcephaly, anophthalmos, malformation of the ears, nose and brain, extra finger on the left, and high ventricular septal defect. The brain showed absence of the longitudinal sulcus and complete failure of lobar differentiation. The nasal canal was a mere pinpoint single opening. An extra long acrocentric chromosome (in group 13-15) is found in the karyotype.
ease is a leading cause of death, which in about 60 per cent of cases occurs before the age of 10 years. A major discovery of the last few years was the demonstration of extra chromosomal material, considered to be chromosome 21, consistently in cases of Mongolism.

The presence of an extra chromosome in group D (13-15) is accompanied\(^6\) by drastic malformations of the eye, brain, and hand and with ventricular septal defect and dextroposition of the heart (fig. 4).

The presence of an extra group E chromosome, whether 17 or 18 is debated, is accompanied\(^7\) by similarly drastic effects but a different pattern of malformations (fig. 5). Ventricular septal defect\(^8\) and large patent ductus arteriosus are the usual cardiac lesions.

The heart in the complexity of its development seems to rival the central nervous system. Both organs are prone to be thrown out of kilter with chromosomal aberrations. That the XXX and XXY syndromes do not have an increased frequency of cardiovascular anomaly may be related (1) to the relative genetic emptiness of the Y chromosome and (2) to the compensatory mechanisms that have developed during evolution to neutralize the effects of extra X chromosomes.\(^9\) The puzzle is why the XO female with the same number of active X chromosomes\(^9\) as the normal XY male and normal XX female should have serious somatic abnormalities.

Of course, coarctation, patent ductus arteriosus, and ventricular septal defect occur frequently, indeed usually, with no demon-

Figure 5

Trisomy 17-18 (E trisomy). This Negro female infant (B.G.D. 981022), born to a 26-year-old mother and 39-year-old father, lived only 12 days. The malformations included satyr ear and small left palpebral fissure, contracture of the fingers with arachnodactyly, rocker-bottom feet, patent ductus arteriosus, atrial and ventricular septal defects, pelvic kidney on right, and double ureter on left.
strable chromosomal aberration. Unfortunately I cannot report that these experiences with chromosomal aberrations have shed light on pathogenetic mechanisms in the usual situation.

**Single Gene Disorders**

All the chromosomal aberrations producing cardiovascular abnormality have extensive noncardiac effects as well. No chromosomal aberration producing isolated cardiac effects has, to my knowledge, been convincingly identified. One would not expect that a chromosomal aberration detectable with our relatively gross technics would produce changes limited to the cardiovascular system.

A similar situation obtains with the single-gene disorders of the cardiovascular system: almost all have extracardiac manifestations—a circumstance fortunate for the diagnostician.

The list of such disorders (table 2) is now rather long. It includes heritable disorders of connective tissue, most particularly the Marfan syndrome, pseudoaxanthoma elasticum, and the Hurler syndrome, but also in the Ehlers-Danlos syndrome, in osteogenesis imperfecta and in mucopolysaccharidoses other than the Hurler syndrome, cardiovascular involvement has come to clinical attention. The importance of connective tissue to the structural integrity of the cardiovascular system is proved—although no proof is really required—by the consequences of these heritable disorders of connective tissue.

The aortic complications of the Marfan syndrome, an autosomal dominant disorder, are too well known to require particular comment (fig. 6). Much, however, remains to be learned about this intriguing disorder, most important, the nature of the basic defect.

**Table 2**

*Single Gene Mutants with Cardiovascular Involvement (a Partial List)*

<table>
<thead>
<tr>
<th>Class</th>
<th>Example</th>
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<tbody>
<tr>
<td>I. Heritable disorders of connective tissue</td>
<td>Marfan syndrome, Pseudoaxanthoma elasticum, Hurler syndrome</td>
</tr>
<tr>
<td>II. Neurologic and muscular disorders</td>
<td>Friedreich's ataxia, Riley-Day familial dysautonomia</td>
</tr>
<tr>
<td>III. Phacomatoses</td>
<td>Neurofibromatosis, von Hippel-Lindau syndrome</td>
</tr>
<tr>
<td>IV. Inborn errors of metabolism</td>
<td>Glycogen-storage disease, especially Type III, Adrenal hyperplasia, Osteogenesis imperfecta</td>
</tr>
<tr>
<td>V. Vascular malformations</td>
<td>Osler-Rendu-Weber hereditary hemorrhagic telangiectasia, Hereditary lymphedema (Milroy type, Meige type)</td>
</tr>
<tr>
<td>VI. Complex syndromes with malformations of heart</td>
<td>Kartagener's syndrome, Holt-Oram syndrome</td>
</tr>
<tr>
<td>VII. Miscellaneous</td>
<td>Werner syndrome, Hemachromatosis, Congenital deafness, electrocardiographic changes, sudden death, Pheochromocytoma, apparently isolated, Pheochromocytoma in multiple endocrine adenomatosis, Disturbances of rhythm or conduction, Pulmonary hypertension, Familial amyloidosis</td>
</tr>
</tbody>
</table>

| Two other mucopolysaccharidoses | Duchenne muscular dystrophy, Myotonic dystrophy, Refsum's disease, Tuberous sclerosis |

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The Marfan syndrome has as cardinal features changes in the eye, especially ectopia lentis; in the skeletal system, especially excessive length of the tubular bones; and in the cardiovascular system, especially the aortic media leading to diffuse aneurysm or dissecting aneurysm. Although the precise nature of the basic defect is not known, some unitary disorder of connective tissue is undoubtedly involved.

In pseudoxanthoma elasticum (fig. 7) characteristic skin changes and angiod streaks of the fundus are combined with vascular changes. The basis of gastrointestinal hemorrhages lies in changes in submucosal vessels. We passed through a period when collagen was suspected as the weak link in this disease, but further observations of the last few years have compelled us to return to the view that the elastic fiber is the seat of the primary defect. Pseudoxanthoma elasticum is inherited as an autosomal recessive. The changes in peripheral arteries are noteworthy. Brachial arteriograms (fig. 8) show striking and unique changes. Occlusion of both the radial and the ulnar arteries occurs in some cases with little or no manifestations of ischemia, probably because the process develops slowly and compensatory dilatation of the interosseous arteries occurs. I had presumed earlier that intimal atherosclerosis secondary to medial damage is responsible for peripheral occlusive disease in pseudoxanthoma. Such is not the case, or not the whole.
story. Biopsy of an occluded artery of the arm (fig. 8) shows a delicate intima; a scarred and swollen media occludes the lumen. The changes in the media are comparable to those in the elevated lesions of the skin.

In the Ehlers-Danlos syndrome (fig. 9) rupture of great vessels, usually a large

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**Figure 7**

*Pseudoxanthoma elasticum is characterized by changes in the skin; in the eye, especially angioid streaks; and in the blood vessels, which may lead to gastrointestinal hemorrhage and other complications. The primary fault seems to involve elastic tissue.*

**Figure 8**

*Peripheral arterial disease in pseudoxanthoma elasticum. Brachial arteriograms, even in young patients, such as this 31-year-old person, show drastic occlusive changes. Abundant collateral vessels account for the usual absence of ischemic symptoms in the hand. Biopsy of an occluded radial artery shows delicate intima and marked medial thickening. The cleft in the area of the external elastic lamella is an artifact but appears to have occurred at the site of degenerative elastic fiber changes.*

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The Ehlers-Danlos syndrome is characterized by changes mainly in the joints, which are hyperextensible, and in the skin, which is abnormally stretchable, fragile, and bruiseable. In addition, however, internal abnormalities such as gastrointestinal diverticula, spontaneous rupture of the bowel, and spontaneous rupture of great vessels have been observed.

branch of the aorta, occasionally the aorta itself, must now be counted among the rare but integral features. Frangility of the skin, bruiseability, dehiscence of surgical wounds, tissues with low tensile strength vividly compared to “wet blotting paper” are well-known features of this syndrome, which is inherited as an autosomal dominant. The great vessels are similarly deficient in tensile strength. The best explanation that anyone has been able to suggest is that the collagen bundles are woven together in abnormally loose and insecure mesh (fig. 10).

The Hurler syndrome (fig. 11) is a genetic disturbance of mucopolysaccharide metabolism. Excessive amounts of mucopolysaccharide are excreted in the urine and deposit-ed at various sites including the vascular intima. Figure 12 shows the heart of a 5-year-old boy. The coronary arteries are thickened and cord-like with heavy intimal deposits. Pseudo-atherosclerosis of marked degree occurred also in the aorta and in the pulmonary artery. For a number of years two distinct forms of mucopolysaccharidosis of the Hurler type have been recognized: one inherited as an autosomal recessive and one inherited as an X-linked recessive. By combined clinical, genetic, and biochemical analysis three other mucopolysaccharidoses can now be distinguished (table 3). I will not attempt to go over these types in detail. (Note, however, that the mucopolysaccharidoses are comparable to the glycogen-storage diseases in
which at least six distinct varieties can be distinguished on clinical and biochemical grounds.) Aortic regurgitation is a feature of mucopolysaccharidoses IV and V.

Mucopolysaccharidosis IV has been called the Morquio-Ullrich syndrome because severe skeletal features of the Morquio type, especially flat vertebrae, are associated with diffuse clouding of the cornea (fig. 13). Biochemically also this is a distinct entity. The mucopolysaccharide keratosulfate is excreted in the urine in large amounts. The inheritance is autosomal recessive (fig. 13). By the time they reach their teens all these patients are likely to have aortic regurgitation. The anatomic change responsible for aortic leak is not yet known.

Mucopolysaccharidosis V is illustrated (fig. 14) by a 47-year-old attorney whose sister is identically affected. Stiff joints, especially those of the hands and feet, clouding of the cornea which is most dense peripherally, a characteristic broad-mouthed facies, and little or no impairment of intellect are features. Aortic regurgitation, again of unknown anatomic basis, is present, developing as early as 7 years in one patient. Some of the patients described by Scheie and his colleagues probably had this type of disorder.

Single gene mutations with cardiovascular effects also include neurologic and muscular disorders, such as Friedreich's ataxia (fig. 15), Riley-Day familial dysautonomia, myotonic dystrophy (fig. 16) and Duchenne muscular dystrophy. In the X-linked Duchenne pseudohypertrophic muscular dystrophy (fig. 17) the myocardium suffers from the same biochemical defect as does skeletal muscle.

**Table 3**

<table>
<thead>
<tr>
<th>MPS</th>
<th>Clinical</th>
<th>Genetic</th>
<th>Biochemical</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (Hurler syndrome)</td>
<td>Clouding of cornea</td>
<td>Autosomal</td>
<td>Ch S-B</td>
</tr>
<tr>
<td></td>
<td>Grave manifestations</td>
<td>recessive</td>
<td>Heparitin S</td>
</tr>
<tr>
<td>II (Hunter syndrome)</td>
<td>No clouding of cornea</td>
<td>X-linked</td>
<td>Ch S-B</td>
</tr>
<tr>
<td></td>
<td>Course milder than I</td>
<td>recessive</td>
<td>Heparitin S</td>
</tr>
<tr>
<td>III (Sanfillipo syndrome)</td>
<td>Mild somatic, severe CNS effects</td>
<td>Autosomal</td>
<td>Heparitin S</td>
</tr>
<tr>
<td>IV (Morquio-Ullrich syndrome)</td>
<td>Typical bone changes</td>
<td>Autosomal</td>
<td>Keratosulfate</td>
</tr>
<tr>
<td></td>
<td>Cloudy cornea</td>
<td>recessive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intellect +/-</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aortic regurgitation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V (Scheie's syndrome)</td>
<td>Stiff joints</td>
<td>Autosomal</td>
<td>Ch S-B</td>
</tr>
<tr>
<td></td>
<td>Typical facies</td>
<td>recessive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cloudy cornea</td>
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<tr>
<td></td>
<td>Intellect +/-</td>
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<tr>
<td></td>
<td>Aortic regurgitation</td>
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**Normal. E.-D. Syndrome.**

*Figure 10*

*Schematic representation of Jansen's theory of the nature of the connective-tissue derangement in the Ehlers-Danlos syndrome.*

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Although many of these cases arise by new mutation occurring in the X chromosome which the mother gives the affected boy, in some families the mutation occurred in the more remote past and a pattern typical of X-linked recessive inheritance (fig. 17) is observed.

Also included among the single mutations with cardiovascular effects are the phacomatoses such as the von Hippel-Lindau syndrome (fig. 18) and neurofibromatosis (both of which have associated pheochromocytoma in some cases) and tuberous sclerosis. In the last condition (fig. 19) changes in the skin and in the brain are accompanied by rhabdomyomas—tumors of the myocardium, which appear white because of their glycogen content.

The list includes inborn errors of metabolism, notably glycogen-storage disease of the heart and the hypertensive form of adrenal hyperplasia.

Included are disorders of vasculature, arterial, venous and lymphatic: Osler-Rendu-Weber hereditary hemorrhagic telangiectasis and hereditary lymphedema. In figure 20 are shown hereditary telangiectases at a characteristic site and pulmonary arteriovenous fistulas in one such patient. Over half of pulmonary arteriovenous fistulas occurs as a

**Figure 11**

The Hurler syndrome, of which at least three distinct forms exist, is the result of genetic derangement of mucopolysaccharide metabolism. The clinical features are shown here in composite. The patients are examples of MPS I (the girl) and MPS II (the man).
In the last disorder (fig. 22) manifestations suggesting premature ageing include cataracts, sclerodermatous changes in the skin, prematurely gray hair, and diabetes mellitus.\textsuperscript{19} Amputation of the legs is often necessary, in part because of peripheral vascular disease. Calcific aortic stenosis occurs frequently. The inheritance is autosomal recessive.

In most or all of these syndromes the reason the manifestations are multiple and diverse is that the normal gene which underwent mutation determines a substance or process with widespread significance to the body’s economy. All the manifestations result from a \textit{single} mutant gene. As far as we know, none of these syndromes is the result of close linkage, that is, close situation on the same chromosome, of several genes, each determining a separate feature of the syndrome. Evidence of the operation of a single mutant gene is inescapable when a unitary defect accounting for all features can be demonstrated, as in the glycogen-storage diseases. Although not yet discovered, a unitary defect is assumed also in conditions such as Friedreich’s ataxia and tuberous sclerosis.

One can cite at least four examples of what may be single mutants in which the effects seem to be limited to the heart: endocardial fibroelastosis,\textsuperscript{20} idiopathic familial myocardiopathy,\textsuperscript{21} muscular subaortic stenosis, and supravalvular aortic stenosis. In all of these, non-familial cases also occur and probably have a different etiology. Close study in some shows features distinguishing the familial from the sporadic form. The upper part of figure 23 shows the heart in an elderly woman whose grandson and possibly other relatives had the same lesion, supravalvular aortic stenosis.\textsuperscript{22} No extra-cardiovascular peculiarity was detected. On the other hand, the identical cardiovascular lesion occurs in sporadic (i.e., non-familial) cases but here is associated\textsuperscript{23} with typical facies, small head size, and mental defect (fig. 23, lower).

Muscular subaortic stenosis\textsuperscript{24} is part of more general ventricular hypertrophy, elec-
trocardiographic and auscultatory signs of which, including a conspicuous atrial heart sound, antedate signs of outflow obstruction. In some cases the right ventricle is obstructed as well as the left—further reason that subaortic stenosis is a poor designation. Let's call it hereditary ventricular hypertrophy. It is inherited as a mendelian dominant, as demonstrated in the Negro family studied by two of my colleagues (fig. 24). Individual II 2 appears to represent a "skipped generation"; however, she must carry the gene and may manifest it later. Simple inheritance must indicate a single and pinpointable biochemical defect, which I am confident will be detected in the not distant future. Therefore we may learn much about the mecha-

* The female who is next to the oldest sibling in generation II is the person indicated as II 2.

Figure 13
The Morquio-Ullrich syndrome (MPS IV). Brothers J.G. (1063746) and M.G. (1063747) are 15 and 5 years old, respectively. They have characteristic skeletal deformity in severe form: knock-knees, hip disease, flat vertebrae, pigeon breast, short neck, inability to extend the elbows fully, half-crouching stance. Intelligence is unaffected. Aortic regurgitation is present in the older brother. The cornea shows diffuse, ground-glass clouding. The pedigree of another family (R.H., C.H. 7164) with three brothers affected with this syndrome illustrates occurrence of this autosomal recessive disorder in the offspring of a consanguineous (1½ cousin) marriage.
The Scheie syndrome (MPS V). M.McC. (1050314), age 46 years, demonstrates the “broad-mouthed facies”, stiff joints, excessive body hair and corneal clouding characteristic of this newly recognized mucopolysaccharidosis. The corneal clouding is most dense peripherally. Aortic regurgitation is present in this patient. Intelligence is not impaired.
nism of ventricular hypertrophy in more commonplace situations. This is, of course, one of the important uses to which these rare experiments of nature can be put.

**Common Forms of Cardiovascular Disease**

Although individually rare, the disorders discussed to this point comprise, in the aggregate, a significant (although small) part of cardiologic practice. In these conditions the genetic basis is quite clear, either in terms of a microscopically discernible change in the chromosomes or in terms of a point mutation, a single gene change, as inferred from the mode of transmission of the condition in families. But we are left with the four garden varieties of cardiovascular disease, in each of which genetic factors seem to play some role. These are essential hypertension, coronary artery disease (and atherosclerosis in general), acute rheumatic fever (and its cardiac effects), and congenital heart disease.

Proof of a significant genetic factor in some of these is difficult to assemble. Even if heredity is accepted as a proven factor, the genetics is not amenable to straightforward analysis as in the case of the disorders discussed earlier. I will try to say only enough to put this area of investigation into proper perspective in relation to the others. If I appear to give the common diseases short shift considering their importance, it is because of limitations of time and the complexity of study in this area.

The genetic component of common forms of cardiovascular disease would seem to be polygenic—many genes are involved in etiology and pathogenesis—just as many collaborating genes are involved in normal variables such as stature and intelligence. But environmental factors, themselves multiple, are also involved, so that these conditions are in the broadest sense multifactorial.

_Figure 15_

_Friedreich’s ataxia, Scoliosis and cardiomegaly are demonstrated. The electrocardiogram shows striking but nonspecific T-wave changes. Histologically the myocardium shows extensive and diffuse fibrosis._

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That both genetic and environmental factors are involved deserves emphasis. No disease is exclusively genetic and few, if any, are wholly environmental. All disease constitutes a spectrum as to the relative impor-

**Figure 16**
Myotonic dystrophy. Typical hollow temples, myopathic facies, and temporal recession of the hair line are demonstrated. Below are shown the myopathic responses to percussion of the biceps and thenar muscles.

**Figure 17**
X-linked muscular dystrophy (pseudohypertrophic, or Duchenne type). Pseudohypertrophy of the calf muscles is shown. Family with muscular dystrophy showing typical pedigree pattern of an X-linked recessive.

tance of genetic and environmental factors in pathogenesis (fig. 25). Toward one end are predominantly genetic disorders such as galactosemia and phenylketonuria, but these are not at the extreme end because an environmental factor, namely, the composition of the diet, can profoundly influence the disease. At the other, the environmental end of the spectrum, are located infectious diseases, but again not at the extreme end because twin studies in man and numerous studies in experimental animals indicate that resistance to infectious disease is genetically determined to a significant degree.
The von Hippel-Lindau syndrome with pheochromocytoma. Top. Dilated tortuous retinal veins and an angioma are demonstrated in the right eye of V.B. (634120), from whom a cerebellar hemangioblastoma was removed. The mother had the same condition and the maternal grandfather was probably also affected. Bottom. L.M.S. died at age 24 years of subarachnoid hemorrhage from hemangioma of the medulla. Paroxysmal hypertension caused by pheochromocytoma of the right adrenal gland undoubtedly contributed to her demise. A sister, the mother, and more remote relatives on the mother's side also had von Hippel-Lindau's disease. The relation of the pheochromocytoma to the adrenal gland is shown (left). The histology of the tumor (center) and the peculiar but characteristic appearance of the periaortal fat (right) indicating that the pheochromocytoma had been secreting are shown.

In the case of essential hypertension, a polemic has raged as to whether it is inherited as a simple mendelian dominant or whether blood pressure is a continuous, multifactorial variable-like stature.20 (Interestingly neither party in the polemic has for a minute questioned that essential hypertension is hereditary to a significant, indeed predominant, degree.) As I intimated earlier, I find the polygenic argument rather more plausible. But even if we are utterly convinced of the polygenic basis of blood pressure, both high and low, it is still worthwhile to seek individual gene-determined differences important to blood pressure level, such as that postulated by Mendlowitz27 and that implicit in the work of Wood.28 True, the chances of finding an important isolatable gene-determined defect in essential hypertension is greater if the monogenic thesis is correct.

Most clinicians and indeed the lay public have an impression that susceptibility to coronary artery disease runs in families and can cite instances of multiple brothers, or of fathers and sons,21 who succumbed at a relatively early age. In many, no particular derangement of lipid metabolism is discernible. Some of these familial examples are undoubtedly the expected coincidence in families of several cases of a common condition. The question is whether there is anything more than

* Familial aggregation for hypertensive toxemia of pregnancy has been studied by several groups.29, 30

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this. Considering how fixed the clinical impression of familial aggregation has become, the difficulties in proving it are surprising.32–35

It may be worthwhile to review briefly the approaches available for attacking the tough question of how important genetic factors are in coronary artery disease, and indeed in any common disease (table 4).

Familial aggregation is a sine qua non for any genetic hypothesis. However, since such aggregation may be related to peculiar social practices within some families and not to genes shared in common by relatives, it does not prove the genetic hypothesis.

Twin studies, that is, the comparison of concordance rate (the frequency of “both

Table 4
Approaches for Evaluating Genetic Factors in Common Diseases

<table>
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<tr>
<th>Approach</th>
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<tbody>
<tr>
<td>1. Familial aggregation</td>
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<tr>
<td>2. Twin studies</td>
<td></td>
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Figure 19A

Tuberous sclerosis. Adenoma sebaceum, the main cutaneous manifestation, is demonstrated.

Figure 19B

Tuberous sclerosis. Note the multiple small tumors of the brain. Rhabdomyomata are shown in the myocardium. The tumors are white in contrast to the myocardium because of the content of glycogen. The typical spider cell results from strands of cytoplasm traversing the glycogen-laden cell.
Figure 20A
Rendu-Osler-Weber's hereditary hemorrhagic telangiectasia. The sites shown here are favorite ones for the mucocutaneous lesions.

Figure 20B
Pulmonary arteriovenous fistulas are demonstrated. Ordinary chest x-ray shows little abnormality. Venous angiogram, however, demonstrates multiple arteriovenous communications in the left lower lobe. Dilated vessels were seen on the surface of the lung exposed at operation. The multiple arteriovenous communications are clearly displayed in the resected lobe.
twins affected") in monozygotic vs. dizygotic twins, can give evidence more specifically relevant to the genetic hypothesis.

Since the genetic definition of race must be based on differences in average gene frequencies, comparisons of the prevalence of common disease in different racial groups should provide useful genetic information.

Figure 20C
The pedigree of the family with hereditary telangiectasia and pulmonary fistulas reported by Bergqvist, Hessen, and Hey[^6] redrawn.

Figure 21A
Milroy's lymphedema in three generations. Grandmother, mother, and the three youngest children are affected. The pedigree is shown. The "grandmother," IV 8, may represent a new mutation.
But there is a compelling proviso: if the environmental circumstances are identical. One can never be certain of complete environmental comparability of the races under study. Races are cultural as well as physical entities.

In multifactorial conditions, which most common disorders are, when epidemiologic or laboratory studies suggest that some factor is important—let us say, serum cholesterol in atherosclerosis—then the genetics underlying its variation can be studied by the other methods listed here—intrafamilial similarities, twin studies, ethnic comparisons.

I have next listed blood-group-and-disease association because the approach is closely akin to component analysis. In component analysis one demonstrates first that a given variable is a significant component of etiology and then assays how important genetic factors are to it. Contrariwise, in the case of blood-group-and-disease association one takes a well-established, clear-cut mendelizing genetic variable and determines whether it is a pathogenetic component as indicated by association. Of course, other genetic markers such as serum protein types (e.g., the haptoglobins) can be used in such studies. The fact that there is an association between blood group O and peptic ulcer indicates that the genetic make-up of the person at the ABO blood group locus is one factor in the pathogenesis of this multifactorial ailment, peptic ulcer. Like syndromal relationship, association has nothing to do with genetic linkage—close location of two loci on the same chromosome; it has its basis in some physiological peculiarity—of the type O person, for example, which renders him slightly but definitely (about 40 per cent) more vulnerable to peptic ulcer than the non-O person.

In the sixth place, if one has in animals a disorder seemingly analogous to that in man, pathogenetic factors and their genetics may be analyzable in a way relevant to the understanding of the human disease. The pigeons with atherosclerosis at Bowman-Gray are of interest for this reason, as are also the studies of the genetics of cardiovascular disease in animals by Detweiler and others in the veterinary field.

In the case of some rare disturbances of lipid metabolism, the operation of a single gene or gene pair in producing coronary artery disease is discernible. If time permitted, I could go into detail concerning the xanthomatous hyperlipidemic states in which a single gene seems involved and in which intimal xanthomata of the coronary arteries lead to death even in childhood.

In rheumatic fever demonstrating the role of the streptococcus did not destroy the plausibility that genetic factors are important in susceptibility. Solely on the basis of experience with susceptibility to infectious disease in animals, one would not consider it likely that the genetics is simple mendelian, however."

* There may be a blood group-and-disease association involving rheumatic fever.37

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By congenital malformations of the heart, I refer to the garden varieties—septal defects, valvular stenoses, Fallot’s tetralogy, etc. Congenital merely means, of course, “present at birth.” It has no denotation of etiology. Many hereditary disorders are not congenital. For example, in the Marfan syndrome aortic aneurysm is not present at birth and therefore not congenital. Huntington’s chorea and Wilson’s disease are hereditary but not congenital. To be sure, the fundamental fault is present at birth. Conversely, conditions can be congenital and not conspicuously genetic, witness two clear examples of environmentally induced malformations: those of rubella and those of thalidomide. Actually the term “congenital malformation” is something of a pleonasm; it is difficult to think of any malformation that is not congenital.

Currently, malformations represent one of
the three or four major challenges to medical science. Consideration of genetic factors in the causation of cardiovascular malformations must take into account the following epidemiologic features which they share with the total group:

1. The incidence of congenital malformations taken as a whole is essentially the same in all races of man.

2. However, the incidence of specific malformations varies widely from one race to another. Prime examples are the relatively high frequency of polydactyly and of preauricular fistula in Africans and the low frequency of anencephaly and meningomyelocele in Africans as compared with Caucasians. Comparable racial differences probably exist for cardiovascular malformations grouped together or specified as to type.

3. Combined malformations occur much more frequently than would be expected on the basis of chance coincidence. It is not surprising that pathogenetic mechanisms should be shared in common by several malformations. Parenthetically speaking, information useful in cardiovascular diagnosis and in the total care of the patient can come from statistical inquiry into what specific malformations occur together with increased frequency. As Jonathan Hutchinson put it: "We must analyse, and seek to interpret partnerships in disease."

Figure 23
Supravalvular aortic stenosis. Top. The specimen in a 70-year-old patient with the familial form of the disease. Bottom. Typical facies in the sporadic form of the disease (M.H., 938013, age 8 years).

Figure 24
Hereditary ventricular hypertrophy. Muscular subaortic stenosis and other manifestations of hereditary ventricular hypertrophy have been demonstrated or suspected in this extensively studied Negro family.

Figure 25
The spectrum of disease, with regard to the relative significance of genetic and environmental factors in etiology and pathogenesis. The specific location of the entities on the scale is not intended to convey the impression that the relative importance of these two factors has been accurately quantitated.
4. Consanguinity of parents increases the incidence of congenital malformations. This was evident in studies by Neel and his colleagues in Japan, and it was evident for cardiovascular malformations specifically in the study of Lamy and colleagues in Paris.

5. Monozygotic twins show a low concordance rate. The rate should be 100 per cent for an almost strictly genetic disorder. It is 30 to 40 per cent for some malformations such as dislocated hip and hare lip, but for congenital heart disease the concordance rate is very low.

6. The risk of recurrence in a sibling is low—e.g., about 2 per cent for pulmonary stenosis—yet is higher than in the general population by 10-fold or more.44

7. The frequency in parents or offspring of affected persons is about the same as in siblings—a few per cent at the most.

8. Season of birth, sex of the child, maternal age, birth order, and other factors are of demonstrable significance. No simple genetic model will account for these eight features. Fragmentary pedigrees are sometimes observed in which atrial septal defect, patent ductus arteriosus, or other anomaly occurs in multiple family members in a pattern consistent with autosomal dominant or autosomal recessive inheritance.

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Figure 26A


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Figure 26B

Hands and chest x-ray of daughter (R.L., 759999). Both have atrial septal defect.

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The point to keep in mind is that polygenic inheritance, or a pathogenesis which is multifactorial in the broad sense, can simulate Mendelian inheritance. Transmission through several generations and several collateral lines is more convincing evidence of single gene inheritance.

There are several complex syndromes, de-

Figure 27
The Ellis-van Creveld syndrome. A.W. (107557), now age 44 years, is probably the oldest case in the literature. (An affected male discovered in the Amish study is age 58.) The polydactyly and short stature with particular shortening of the distal part of the extremities are evident. The extra finger is rather well formed. Dysplastic fingernails are demonstrated.

Figure 28
Skeletal changes in the Ellis-van Creveld syndrome. In addition to polydactyly, two characteristic skeletal features of this syndrome are shown: Fusion of the hamate and capitate bones. Defect in lateral aspect of proximal end of tibia, producing “knock-knees.”

Figure 29
Single atrium in the Ellis-van Creveld syndrome. In addition to the characteristic polydactyly and distal shortening of the extremities, the patient was found by selective angiocardiology to have single atrium.
The Ellis-van Creveld syndrome occurs with a frequency of about 2 cases per 1,000 living persons and about 5 cases per 1,000 live births (fig. 30). Because of the congenital heart malformation, many cases die young. Thus far, 30 sibships have been identified in which at least one definite case has occurred and the total

determined by single genes, in which some form of heart malformation occurs in all cases or in a significant proportion (table 2). As examples, we might cite the Kartagener syndrome with dextrocardia and the recently recognized Holt-Oram syndrome with atrial septal defect and hand malformation (fig. 26A and B). But I wish to speak particularly of the Ellis-van Creveld syndrome.

Features of the Ellis-van Creveld syndrome include chondrodystrophic dwarfism, polydactyly, dystrophy of the fingernails and teeth, and a peculiar deformity of the upper lip sometimes called “partial hare-lip” (fig. 27). Fusion of the hamate and capitate bones and change in the tibia causing knock-knees are typical (fig. 28). The cardiac lesion 45 is most frequently single atrium (fig. 29).

My pièce de résistance is a kindred which contains about as many cases of the Ellis-van Creveld syndrome as are found in the entire literature. The Old Order Amish represent a religious isolate living mainly in Pennsylvania, Ohio, and Indiana. In the Amish of Lancaster County, Pennsylvania, the Ellis-van Creveld syndrome occurs with a frequency of about 2 cases per 1,000 living persons and about 5 cases per 1,000 live births (fig. 30). Because of the congenital heart malformation, many cases die young. Thus far, 30 sibships have been identified in which at least one definite case has occurred and the total number

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For making possible these studies of the Ellis-van Creveld syndrome in the Amish I am indebted to Miss Janice A. Egeland and to many Lancaster County physicians, especially Drs. David E. Kruser, Robert L. Bauer, Harold E. Stauffer, and Noah K. Mack.

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*On the right, M.S., age 19 years, is 42½ inches tall. The stumps of amputated extra fingers, the dysplastic finger nails, and the short upper lip are evident. N.Z., on the left, age 50 years, has a different type of recessively inherited dwarfism which is also frequent in the Amish, so-called cartilage-hair hypoplasia. The subjects may appear taller than they really are because of the “compact” ear in the background.*
number of identified cases living or dead is at least 49. Related to each other in an intricate way, the cases can in almost all instances be traced back through both parents to one Christian Fisher, born in 1757, who was not affected but has many affected descendants by each of two unrelated wives (fig. 30C-F).

*In the final genealogic analysis it appears that all cases can be traced back through both parents to Samuel King, who immigrated in 1742. Therefore King or his wife is considered more likely to have been the heterozygous carrier who introduced the gene to this population.

Figure 30C-F

Fragmentary pedigrees of selected Amish cases of the Ellis-van Creveld syndrome demonstrating how both parents, in each instance, can be traced back to a common ancestor who may have been a carrier of the recessive gene for this syndrome. The left lower pedigree is of particular interest because an affected male, now age 58 years, married a distant cousin (who presumably is a heterozygote) and has two affected children. The 58-year-old father resembles very closely the patient shown in figure 27.
What is wrong? (Diagnosis) What is going to happen? (Prognosis) What can be done about it? (Treatment). I would add that it is the scientific and social responsibility of the physician always to keep a fourth question in mind: Why did it happen?

The “why” and “how” of disease is obviously of central concern to medical genetics, but what of its role in diagnosis, prognosis, and treatment? Genetic information is useful to diagnosis in three ways. Knowledge that single genes produce syndromes and that certain readily discernible signs are clues to specific grave internal disorders, for example, of the cardiovascular system, is one of these. Examples: Ectopia lentis and aneurysm of the aorta; mucocutaneous telangiectases and pulmonary arteriovenous fistulas; neurofibromatosis (café-au-lait spots and tumors) and pheochromocytoma (fig. 31). About 5 per cent of cases of pheochromocytoma have the skin lesions of von Recklinghausen’s neuro-

![Figure 31](image)

**Figure 31**

Phaeochromocytoma in neurofibromatosis. Café-au-lait spots and neurofibromata in E.S. (JHH 468773) from whom a phaeochromocytoma was removed in 1950. Since that time the patient has remained normotensive or at the most mildly hypertensive.

The inheritance, as in cases in the literature, is clearly autosomal recessive. Of the cases reported in the literature 60 per cent have had cardiac malformation. This is probably something of an overestimate. Those cases with the associated cardiac malformation are more likely to come to the attention of pediatricians and other familiar with the syndrome.

**Genetics and Cardiologic Practice**

In closing I wish to say something about the role of genetics in the practice of medicine, and in the practice of cardiology specifically. Bradford Hill, the British biostatistician, made a comment worth quoting. He said the practice of medicine resolves itself into seeking answers to three questions:

Endocardial fibroelastosis in Negro brother and sister. Sister was born in June 1950, died in April 1951 from heart failure. Autopsy showed extensive endocardial fibroelastosis of the left ventricle with mural thrombus formation. Brother was born in December 1951 and died in February 1955. He had several admissions for heart failure. The same diagnostic uncertainty obtained as in the case of the sister, largely because no effort was made to determine the autopsy findings in the case of the sibling. Autopsy showed endocardial fibroelastosis (shown here) and the changes of chronic heart failure.
fibromatosis, a valuable diagnostic clue.* In the second place, the family history and familiarity with the usual familial pattern of a given disorder help in the diagnosis of the given case. Endocardial fibroelastosis \(^{20}\) (Fig. 32) led to death at the age of 10 months in the child of a family of six. When a sibling presented with heart failure, the same diagnosis could be strongly suspected. (In the course of the Amish study to which I made reference a very large family was brought to my attention \(^{1}\) in which six siblings had endocardial fibroelastosis, confirmed at autopsy in most.) In the third place, a study of the chromosomes can aid specific diagnosis in some instances.

In medical genetics prognosis has a different twist than in other areas of medicine because the question, What is going to happen? usually concerns not the person asking the question but his unborn child. "I have had one child with congenital heart disease; what is the chance that another will be affected?" Or, increasingly in recent years, "I have had my congenital heart defect repaired surgically; what is the chance that a child of mine will be affected?" I have shown you examples of simply inherited autosomal dominant traits (for example, hereditary myocardial hypertrophy, hereditary telangiectasia, and Milroy's disease), of autosomal recessive traits (for example, the Ellis-van Creveld syndrome), and of X-linked recessive traits (for example, Duchenne muscular dystrophy). In such conditions the risk of recurrence can be stated with some precision, although there are complicating features which in some specific instances require hedging on the part of the genetic counsellor. I have also pointed out the large group of conditions, mostly common conditions, in which the genetic contribution is complex and ill-understood with environmental factors also importantly involved. Here empiric risk figures are about the best we have. In the third place, we discussed at the outset chromosome aberrations. In these the risk of recurrence is dependent on matters such as parental age and whether the parent has a normal karyotype or is a translocation carrier.

As to the treatment of genetic disorders of the cardiovascular system, reference can be made to xanthomatosis and an analogy drawn to phenylketonuria and galactosemia in which dietary measures offer some benefit. That all disease is to some extent environmentally conditioned or influenced allows room for therapeutic manipulation, admittedly now limited in many instances. Undoubtedly in time we will have means to change drastically the genetic machinery of the cell—not so easily the DNA itself but almost certainly the steps between DNA and the protein it synthesizes. Given, for example, an enzyme molecule which is warped as a result of mutation and which has, let us say, only 2 per cent of the activity of normal enzyme, methods for effecting a 10-fold increase in the amount of the warped enzyme synthesized, through measures directed at the intermediate steps, would raise enzyme activity to 20 per cent of normal and might make the difference between healthy life and death.

It is hoped that sociologic and ethical developments will keep pace with the scientific ones in this sensitive area. At any rate, a gloomy outlook for the future of therapy of genetic disease is not justified. Therapy of infectious disease was pretty gloomy less than a century ago.

**Acknowledgment**

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GENETICS OF CARDIOVASCULAR DISEASE


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"William Harvey, April 17, 1616"

On the solemn occasion of his first taking possession of his chair as professor of anatomy he merely noted in his book (for his private use only) that: "It is plain from the structure of the heart that the blood is passed continuously through the lungs to the aorta as by the two clacks of a water bellows to raise water.

"It is shown by the application of a ligature that the passage of blood is from the arteries into the veins, whence it follows that the movement of the blood is constantly in a circle, and is brought about by the beat of the heart."

The lecture was held on April 17, 1616, in the dissecting room of the College of Physicians and it is probably safe to assume that it must have occasioned amazement, confusion, and in some even scandalized shock. For it was astounding and even unthinkable that everything which had been asserted and been believed with complete confidence for centuries and was thought to have been proved repeatedly by a multitude of able scientists, should fall apart in a heap of errors . . . .

The calendar of these events showed April of the year 1616. It was the year and month in which Harvey first made public his new theory of blood circulation.—TIBOR DOBY, M.D. Discoverers of Blood Circulation. From Aristotle to the Times of Da Vinci and Harvey. New York, Abelard-Schuman, 1963, p. 194.
A Genetical View of Cardiovascular Disease: The Lewis A. Conner Memorial Lecture
VICTOR A. MCKUSICK

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