MIKAMO LECTURES

GENETICS AND CARDIOVASCULAR DISEASE — 1981

VICTOR A. MCKUSICK, M.D.

IN October, 1963 I gave the Lewis A. Conner Lecture at the annual meeting of the American Heart Association in Los Angeles. The title of that Conner Lecture was "A Genetical View of Cardiovascular Disease." Having selected the same topic for this lecture to the Japanese Circulation Society I found it useful to look back at the published form of the lecture¹ and give thought to how understanding of the role of genetics in cardiology has advanced in the last 17–18 years. (A useful review of this subject was provided by Goldstein⁵ in Braunwald's *Heart Disease*.)

At the outset, in 1963, I spoke of the phenomenal advances in genetics that had been seen in the previous 10 to 15 years. Perhaps more than we might have expected at that time, these advances have continued, indeed accelerated, since 1963. Progress during the recent period includes: "banding" techniques for chromosome study permitting unique identification of each chromosome (1969); recombinant DNA techniques and restriction enzyme analysis for studying variation at the level of the human DNA itself; somatic cell hybridization techniques for mapping the chromosomes of man with, by 1976, at least one gene assigned to each of man's 24 chromosomes²; the use of cultured skin fibroblasts for the study of inborn errors of metabolism *in vitro*. When I gave my lecture in 1963, lysosomal storage diseases (e.g., Hurler syndrome) and receptor diseases (e.g., familial hypercholesterolemia) were not, as such, yet part of our ken or vocabulary.

In that Conner Lecture I pointed out that in analyzing the role of genes in the disorders of a

given system it is useful to divide those disorders into three categories: those disorders which are predominantly due to a single mutant gene, those which appear to be multifactorial in nature, and those which are due to microscopically evident aberrations of the chromosomes. This division is somewhat arbitrary because it is the rare mendelian disease that is not influenced in its expression by other genes in the individual and by environmental factors. Moreover, small chromosomal aberrations have been found to underlie some disorders which in the particular family under study or in other families show a mendelian pattern of inheritance. For example, I am thinking of retinoblastoma and deletion of the 14q14 band. Furthermore, as methods for studying the chromosomes at the level of the DNA itself have come along, we find that small deletions underlie some "single gene" (mendelian) disorders. I am thinking, for example, of the several forms of hereditary persistence of fetal hemoglobin and of several forms of thalassemia. Finally, in the case of multifactorial disorders (which include some of the common disorders such as coronary artery disease and hypertension) the definition of single genes with relatively major effects have been possible, as I will recount shortly.

In clinical practice we have seen since 1963 important advances such as prenatal diagnosis by the study of fetal tissues obtained by amniocentesis (1965) and we have seen the widespread use of cultured cells for the diagnosis and study of human disorders. Genetic nosology, that is, the classification, or more particularly the delineation, of distinct mendelian disorders, has progressed greatly. This is illustrated by the

William Osler Professor and Chairman, Department of Medicine, Johns Hopkins University School of Medicine, Physician-in-Chief, Johns Hopkins Hospital, Baltimore, Maryland, 21205, U.S.A.

growth of my catalogs of mendelian traits,³ published in first edition in 1966 and in fifth edition in 1978, and maintained on an on-going basis by computer methods.

Three principles stand out as particularly important to genetic nosology and to the practice of medicine: pleiotropism, genetic heterogeneity and variability. *Pleiotropism* refers to multiple effects of a single gene resulting in a syndrome, i.e., the more or less consistent concurrence of separate manifestations. The reason pleiotropism is such an important principle in clinical medicine is that some of the manifestations of a single gene may be externally evident features and therefore represent a valuable clue to the presence of, or liability to, serious internal disease.

Genetic heterogeneity means that two or more different genetic defects may result in one or nearly the same clinical disorder. It has been a recurrent theme in the study of genetic disease in the last quarter century that what appeared at first to be a single disorder on close scrutiny turned out to be two or more separate and distinct entities. The Marfan syndrome and homocystinuria⁴ are a pair of disorders that illustrate genetic heterogeneity nicely. Genetic heterogeneity is important to clinical medicine because of the differences in prognosis, genetic counseling and management of the separate disorders.

Variability refers to the fact that one and the same gene may have rather different effects when it occurs in individuals of different genetic constitution. The variability that we see between brothers with the Marfan syndrome is a good illustration. Such variability is no stranger to the clinician. Learning medicine is to a large extent learning to cope with variability. If *Mycobacterium tuberculosis* in every individual produced precisely the same clinical picture and this were the case with all etiologic agents, learning medicine would be child's play, relatively speaking.

Chromosomal Aberrations

Looking at my discussion of this area in 1963, it comes to attention that we now have a much clearer understanding of that group of cases that bear phenotypic similarities to the Turner syndrome and were tentatively referred to in 1963 as male Turner syndrome, female pseudo-Turner syndrome, Turner phenotype with normal karyotype, etc. We even have an eponym for this entity (or category), Noonan syndrome,⁷ and

now understand that this is an autosomal dominant trait. We know that the cardiovascular malformations are most often right-sided, e.g., pulmonary stenosis, rather than left-sided as in the case of the Turner syndrome.

The new banding techniques for the study of chromosomes have permitted the identification of series of cases of a particular aberration in "pure culture." Then, a clinical delineation can be achieved which in some instances permits diagnosis on phenotypic grounds alone.

Single Gene Disorders

When I look at Table 2 of my 1963 paper it becomes evident that our understanding of the disorders listed there and our recognition of additional ones have advanced considerably. To the heritable disorders of connective tissue⁴ with cardiovascular involvement, homocystinuria and alkaptonuria have been added and the list of mucopolysaccharidoses has been greatly extended and sharpened up.⁶

In the list of "neurologic and muscular disorders" we would now add the several forms of periodic paralysis, e.g., the hypokalemic form,⁸ and the Emery type of X-linked muscular dystrophy with contractures.⁹

In connection with the phacomatoses, we now recognize pheochromocytoma as a manifestation of two forms of multiple endocrine neoplasia, i.e., the forms with amyloid producing medullary carcinoma of the thyroid without (MEN II) or with (MEN III) multiple mucosal neuromas.^{10,11} We have acquired since 1963 an acronym for the cells involved in this category of disease, namely, the APUD (amine precursor uptake and decarboxylase) system.

In the category of inborn errors of metabolism affecting the cardiovascular system we can now add the variety of glycogen storage disease type II that is known as adult maltase deficiency which appears to be allelic to the common childhood ailment and affects skeletal and cardiac muscle conspicuously and predominantly.¹²

In the area of vascular malformations we might now include ataxia-telangiectasia¹³ and arteriohepatic dysplasia,¹⁴ and we now recognize additional forms of hereditary lymphedema such as that associated with cholestasis¹⁵ as an autosomal recessive trait and that associated with distichiasis and spinal arachnoid cysts¹⁶ as an autosomal dominant trait.

In connection with complex syndromes with malformations of the heart fascinating develop-

ments have come along in connection with the autosomal recessive Kartagener syndrome which is now known to result from an abnormality of dynein in cilia and sperm. The Kartagener syndrome turns¹⁷ out to be a form of immotile cilia syndrome. The bronchiectasis and sinusitis that characterize it are now known to be due to inadequate toilet of the tracheobronchial tree and sinuses because of immotile cilia, and male infertility and perhaps female subfertility have been recognized as other features of this disorder, again due to immotile cilia (or sperm). Even though the matter is not completely understood, the experience with this syndrome indicates the importance of a specific class of cellular protein in the normal rotation of the viscera during embryogenesis. Here is a marvelous and all-too-rare example of the delineation of the molecular defect in a congenital malformation. It appears that some persons homozygous for the Kartagener gene may escape dextrocardia; the mutant gene seems to eradicate obligatory levorotation so that in about half of homozygotes rotation is to the right and about half it is to the left.¹⁷

Fanconi's anemia, an autosomal recessive, is now known to fall in the category of chromosome breakage syndromes.¹⁸

In my classification of 1963, as given in Table 2, I had a "miscellaneous" category, as all classifications based on incomplete understanding must have. Our understanding of hemochromatosis has been greatly clarified by genetic studies demonstrating the close linkage of a hemochromatosis gene locus to HLA.¹⁹ Previous difficulties in understanding the genetics of hemochromatosis illustrate the problems that plague the student of diseases that are clinically of late onset or reduced penetrance. Because hemochromatosis is basically a disorder of iron handling and the pathology results from iron overload, females have an escape valve in the form of menstruation and rarely express the disorder, and in males the progressive accumulation of iron to the point of pathologic effects requires time.

In addition to the syndrome of congenital deafness, electrocardiographic changes and sudden death (which goes by the eponyms of Jervell and Lange-Nielsen), we now recognize the Ward-Romano syndrome,²⁰ which has two of the same characteristics, i.e., prolonged QT and vulnerability to ventricular fibrillation, but lacks the deafness.

Today we would list under *Miscellaneous* the

cardiomyopathies. Whether the disorder variously referred to as asymmetric septal hypertrophy, idiopathic hypertrophic subaortic stenosis,²¹ etc., should be included as a cardiomyopathy or as a congenital malformation is problematic. The collagenoma-cardiomyopathy-hypogonadism syndrome falls into the cardiomyopathy category.²²

Now we would also have a separate category for the Barlow syndrome (also known as mitral valve prolapse, click-murmur syndrome, or floppy mitral valve syndrome). Perhaps it should be listed as a heritable disorder of connective tissue. It occurs in both primary and symptomatic varieties; the Barlow syndrome is frequent in the Marfan syndrome, the Ehlers-Danlos syndrome and osteogenesis imperfecta, but it also occurs in a familial distribution apparently *sui generis*.²³ There is an ophthalmoplegia-mitral prolapse syndrome.²⁴

Myxoma of the atrium has been observed on a familial basis and in some cases has been associated with pigmentary cutaneous changes. The LEOPARD syndrome is the designation suggested by Robert Gorlin²⁵ for a syndrome that includes lentigines, deafness and various other manifestations. The cardiac abnormalities have been various. *Progressive cardiomyopathic lentiginosis* was the designation suggested by Polani and Moynahan.²⁶ This is a category that requires sorting out.

In the case of the Marfan syndrome echocardiography has provided a marvelous way to evaluate the root of the aorta and the mitral valve. It has both diagnostic and follow-up value. Two modalities of treatment in the Marfan syndrome were introduced in the late 1960's. One is the use of hormonal induction of puberty, particularly in girls with the Marfan syndrome, in order to prevent excessive growth and to carry the girl rapidly through the period of maximal risk for development of scoliosis. The second modality of management relates to the aortic complications and consists of the use of the beta-adrenergic blocker propranolol to reduce abruptness of ventricular ejection and, therefore, reduce the pounding of the ventricle on the defective ascending aorta. Undoubtedly the chronotropic (i.e., bradycardic) and hypotensive effects of propranolol are beneficial as well. We have the impression that propranolol is effective in staying progressive dilatation of the aorta; however, the results of a controlled study are not yet all in and certain it is that some patients who are seemingly adequately treated with propranolol require

surgery. Surgery itself has improved greatly in terms of reduced early mortality and effectiveness of the repair. The technique now presently practiced by our surgical colleagues involves replacing the ascending aorta with a composite graft, i.e., a prosthetic aortic tube into the proximal end of which a prosthetic valve is sewn. The coronary arteries are transplanted to the tube and the dilated aorta is wrapped around the tube.

The rationale of propranolol in the Marfan syndrome is based on the following:

1. Aortic rupture and aortic regurgitation do not occur "out of the blue" but develop against a background of progressive dilatation of the ascending aorta.
2. Dilatation of the aorta is not congenital as a rule, although the weakness in the aorta is present from the first.
3. Experience in animal models, particularly turkeys who are subject to aortic rupture, suggests that reduction of dp/dt is the main reason for the beneficial effect of reserpine and propranolol, not reduction in blood pressure.

In the case of the mucopolysaccharidoses the classification has been greatly expanded.⁶ Here cell culture work has been of paramount importance. The specific lysosomal enzymes that are defective in the several forms of mucopolysaccharidosis are those that are involved in the degradation of various mucopolysaccharidoses particularly dermatan sulfate, heparin sulfate and keratan sulfate. In 1963 we did not even know that these were lysosomal storage diseases. Our thinking was then still bogged down along lines of excessive synthesis of mucopolysaccharide rather than thinking in terms of a degradative defect. Even the terminology we then used for the mucopolysaccharides now seems archaic.

The classification of the mucopolysaccharidoses which was presented in a table in the 1963 lecture required subsequent expansion and modification. It turned out that there are no fewer than four forms of the Sanfilippo syndrome. It turned out that the MPS V of the 1963 classification, known eponymically as the Scheie syndrome, is a mild variant of the Hurler syndrome. The same enzyme is deficient in both conditions, namely alpha-L-iduronidase.

We now refer to MPS IV as simply the Morquio syndrome and there are subtypes of it. An MPS VI with major cardiovascular involvement and an MPS VII are now known. MPS VI

known also as the Maroteaux-Lamy syndrome, is characterized by severe somatic features with minimal CNS involvement including absent mental retardation. Two or three presumably allelic forms occur. Familial aortic valve disease has been observed in the mildest forms of MPS VI²⁷; aortic valve disease actually occurs in all forms.

The Hunter syndrome also has several presumably allelic varieties. We at first thought that these were two in number, a severe and mild form but as we scrutinize more cases it would appear that severity describes a continuum and there are probably more than merely two allelic varieties.

The Hurler-like conditions include I cell disease and pseudo-Hurler polydystrophy.²⁸ Both of these were defined, for the most part, in the late 1960's, after the 1963 paper. Their elucidation indicates that they involve deficiency of multiple lysosomal enzymes. The group is referred to as the mucopolipidoses (abbreviated ML), I cell disease being ML II and pseudo-Hurler polydystrophy being ML III. The relationship between the two is, at this point, not entirely clear. Cell fusion studies indicate that some ML II cases and some ML III cases are in the same complementation group; they do not cross-connect. They are presumably allelic variants. The defect in both disorders is deficiency of an enzyme normally involved in addition of a phosphomannose sidechain that serves as a recognition marker on many acid hydrolases necessary for requestration of these hydrolases in lysosomes. ML II has no enzyme; ML III has residual enzyme activity explaining the milder phenotype.

An interesting development in relation to hereditary hemorrhagic telangiectasia is the use of non-surgical methods for closing the pulmonary AV fistulas.²⁹ My colleagues, Dr. Robert White and Dr. Peter Terry, use small balloons introduced into segmental pulmonary arteries by venous catheterization techniques, to occlude the fistulas selectively.

The fetal hypercalcemia syndrome and supra-valvular aortic stenosis are coming into sharper focus. Now the prevailing concept, to which I subscribe, is that we are dealing here with an autosomal dominant disorder which might with historic justification be referred to as the Williams-Beuren syndrome.³⁰ As is notorious for autosomal dominant disorders, great case-to-case variability is observed even among affected

members of the same family. Cardiovascular involvement is not present in all cases nor do all cases have the characteristic elfin facies or mental retardation.

Common Forms of Cardiovascular Disease

In the 1963 lecture, these were listed as four: essential hypertension, coronary artery disease (and atherosclerosis in general), acute rheumatic fever (and its cardiac effects) and congenital heart disease. In any of these multifactorial disorders great usefulness accrues from the demonstration of a discrete defect, the genetics of which can be studied in families, twin series, and racial groups, even though that defect may be only one element in the complex nexus of causality that underlies the disorder. An abnormality of sodium-potassium exchange across the cell membrane, amenable to study in red cells, may fulfill that requirement in the case of essential hypertension.³¹⁻³³

In the case of coronary artery disease and atherosclerosis, definition of the LDL-receptor defect in familial hypercholesterolemia has been an exciting development. The genius of Goldstein and Brown,³⁴ who provided us with this information, lay in (1) studying the disorder in cultured fibroblasts and (2) studying the homozygote who could be expected to have the most striking and least ambiguous changes.

We have elucidated another disorder of lipid metabolism that predisposes to precocious atherosclerosis. The rare homozygotes have tuberous and tendinous xanthomas as well as xanthelasmata; precocious atherosclerosis (the proband of our first family was an Amish body who died suddenly at age 13 years); elevated apoB protein of low density lipoprotein; and beta-sitosterolemia (phytosterolemia). The family originally reported with beta-sitosterolemia³⁶ was shown to have the same hyperapolipoproteinemia.³⁵ Heterozygotes are also at increased risk of atherosclerosis; they may not show beta-sitosterolemia but can be recognized by the elevation of apoB in the serum.

Genetic heterogeneity must be kept in mind with multifactorial traits. The Holt-Oram syndrome,³⁷ the Ellis-van Creveld syndrome³⁸ and the syndromes of ASD with prolonged PR interval³⁹ are mendelian forms of atrial septal defect.

Interest in the genetics of acute rheumatic fever has not been great in the last 15 years, perhaps because of decline in the frequency of

the disorder in developed countries through the control of streptococcal infections. I am not aware of studies of HLA in rheumatic fever in parallel to the studies of HLA in other diseases that appear to be in the autoimmune camp, such as SLE. Ankylosing spondylitis⁴⁰ which often shows a mendelian pedigree pattern displays a close association with a specific HLA type, B-27, and Reiter syndrome⁴¹ is also a B-27 related disorder. Both are accompanied by an inflammatory involvement of the root of the aorta leading to aortic regurgitation. We have even seen familial occurrence of giant-cell arteritis⁴² which, of course, involves the aorta and can be the basis of aortic dissection. We also have seen, as have workers here in Japan, familial cases of Takayasu's disease. Association with a particular HLA type in that condition and in Buerger's disease would not be unexpected, I believe, and has indeed been found by studies here in Japan.

In the category of autoimmune disorders, congenital heart block in the offspring of mothers with systemic lupus erythematosus is of extraordinary interest.⁴³ This is not genetic but rather a congenital secondary to maternal autoantibodies that pass the placenta.

The familiarity of hypertensive toxemia of pregnancy has, in the last few years, come in for renewed interest.⁴⁴

The common varieties of congenital malformations of the heart, particularly those that have no non-cardiac associations, are not usually mendelian. There are a few exceptions to this statement. Atrial septal defect with conduction disorder,³⁹ mentioned earlier, occurs as an autosomal dominant.

Genetics and Cardiologic Practice

Increased familiarity with both the principles of genetics and the natural history of genetic disease has had effects on the practice of cardiology. It has sharpened our diagnosis, has improved the accuracy and precision of our counseling of families with all forms of cardiovascular disease and has had important implications in prevention and management. It has permitted the practice of preventive medicine at the level of the family through family planning and through the modification of life style along more healthful lines.

REFERENCES

1. McKUSICK VA: Lewis A. Conner Memorial Lecture: A genetical view of cardiovascular disease. *Circulation* 30: 326, 1964

2. McKUSICK VA, RUDDLE FH: The status of the gene map of the human chromosomes. *Science* 196: 390, 1977
3. McKUSICK VA: Mendelian Inheritance in Man: Catalogs of Autosomal Dominant, Autosomal Recessive and X-linked Phenotypes (5th ed). Johns Hopkins University Press, Baltimore, 1978
4. McKUSICK VA: Heritable Disorders of Connective Tissue (4th ed). C. V. Mosby Co, St. Louis, 1972
5. GOLDSTEIN JL, BROWN MS: Genetics and Cardiovascular Disease. Chapter 46 In *Heart Disease: A Textbook of Cardiovascular Medicine*, ed by BRAUNWALD E, W. B. Saunders Co, Philadelphia, 1980
6. McKUSICK VA, NEUFELD EF: Mucopolysaccharide Storage Diseases. Chapter 36 In *The Metabolic Basis of Inherited Diseases* (5th ed), ed by STANBURY JB, WYNGAARDEN JB, FREDRICKSON DS, GOLDSTEIN JL, BROWN MS, McGraw-Hill, New York, 1982
7. BAIRD PA, DeJONG BP: Noonan's Syndrome (XX and XY Turner phenotype) in three generations of a family. *J Pediatr* 80: 110, 1972
8. JOHNSEN T: Familial periodic paralysis with hypokalaemia: Experimental and clinical investigations. *Danish Med Bull* 28: 1, 1981
9. EMERY AEH, DREIFUSS FE: Unusual type of benign X-linked muscular dystrophy. *J Neurol Neurosurg Psychiatr* 29: 338, 1966
10. SIPPLE JH: The association of pheochromocytoma with carcinoma of the thyroid gland. *Am J Med* 31: 163, 1961
11. SCHIMKE RN, HARTMANN WH, PROUT TE, RIMOIN DL: Pheochromocytoma, medullary thyroid carcinoma and multiple neuromas. *N Engl J Med* 279: 1, 1968
12. KARPATI G, CARPENTER S, EISEN A, AUBE M, DiMAURO S: The adult form of acid maltase (alpha-1, 4-glucosidase) deficiency. *Ann Neurol* 1: 276, 1977
13. McFARLIN DE, STROBER W, WALDMANN TA: Ataxia-telangiectasia. *Medicine* 51: 281, 1972
14. RIELY CA, COTLIER E, JENSEN PS, KLATSKIN G: Arteriohepatic dysplasia: A benign syndrome of intrahepatic cholestasis with multiple organ involvement. *Ann Intern Med* 91: 520, 1979
15. AAGENAES O: Hereditary recurrent cholestasis with lymphoedema: Two new families. *Acta Paediatr Scand* 63: 465, 1974
16. SCHWARTZ JF, O'BRIEN MS, HOFFMAN JC Jr: Hereditary spinal arachnoid cysts, distichiasis, and lymphedema. *Ann Neurol* 7: 340, 1980
17. MORENO A, MURPHY EA: Inheritance of Kartagener syndrome. *Am J Med Genet* 8: 305, 1981
18. FANCONI G: Familial constitutional panmyelocytopenia, Fanconi's anemia. I. Clinical aspects. *Seminars Hematol* 4: 233, 1966
19. EDWARDS CQ, CARTWRIGHT GE, SKOLNICK MH, AMOS DB: Homozygosity for hemochromatosis: Clinical manifestations. *Ann Intern Med* 93: 519, 1980
20. HASHIBA K: Hereditary QT prolongation syndrome in Japan: Genetic analysis and pathological findings of the conduction system. *Jpn Circul J* 42: 1133, 1978
21. DARSEE JR, HEYMSFIELD SB, NUTTER DO: Hypertrophic cardiomyopathy and human leukocyte antigen linkage: Differentiation of two forms of hypertrophic cardiomyopathy. *N Engl J Med* 300: 877, 1979
22. HENDERSON RR, WHEELER CE Jr, ABELE DC: Familial cutaneous collagenoma. *Arch Derm* 98: 23, 1968
23. SHAPPELL SD, MARSHALL CE, BROWN RE, BRUCE TA: Sudden death and the familial occurrence of mid-systolic click, late systolic murmur syndrome. *Circulation* 48: 1128, 1973
24. DARSEE JR, MIKLOZEK CL, HEYMSFIELD SB, HOPKINS LC Jr, WENGER NK: Mitral valve prolapse and ophthalmoplegia: A progressive, cardioneurologic syndrome. *Am J Med* 92: 735, 1980
25. GORLIN RJ, ANDERSON RC, BLAW ME: Multiple lentigines syndrome: Complex comprising multiple lentigines, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonary stenosis, abnormalities of genitalia, retardation of growth, sensorineural deafness, and autosomal dominant hereditary pattern. *Am J Dis Child* 117: 652, 1969
26. POLANI PE, MOYNAHAN EJ: Progressive cardiomyopathic lentiginosis. *Quart J Med* 41: 205, 1972
27. WILSON CS, MANKIN HT, PLUTH JR: Aortic stenosis and mucopolysaccharidosis. *Ann Intern Med* 92: 496, 1980
28. NEUFELD EL, McKUSICK VA: Chapter 37 In *The Metabolic Basis of Inherited Disease* (5th ed), ed by STANBURY JB, WYNGAARDEN JB, FREDRICKSON DS, GOLDSTEIN JL, BROWN MS, McGraw-Hill, New York, 1982
29. TERRY PB, BARTH KH, KAUFMAN SL, WHITE RI Jr: Balloon embolization for treatment of pulmonary arteriovenous fistulas. *N Engl J Med* 302: 1189, 1980
30. GRIMM T, WESSELHOEFT H: The genetic aspects of Williams-Beuren syndrome and the isolated form of the supravalvular aortic stenosis: Investigation of 128 families. *Z Kardiol* 69: 168, 1980
31. GARAY RP, DAGHER G, PERNOLLET M-G, DEVYNCK M-A, MEYER P: Inherited defect in a Na⁺, K⁺-cotransport system in erythrocytes from essential hypertensive patients. *Nature* 284: 281, 1980
32. PARFREY PS, WRIGHT P, HOLLY JMP, EVANS SJW, CONDON K, VANDENBURG MJ, GOODWIN FJ, LEDINGHAM JM: Blood pressure and hormonal changes following alteration in dietary sodium and potassium in young men with and without a familial predisposition to hypertension. *Lancet* 1: 113, 1981
33. PARKER JC: Hypertension and the red cell (Editorial). *N Engl J Med* 302: 804, 1980
34. GOLDSTEIN JL, BROWN MS: Familial hypercholesterolemia: Pathogenesis of a receptor disease. *Johns Hopkins Med J* 143: 8, 1978
35. KWITEROVICH PO Jr, SMITH HH, CONNOR WE, BACHORIK PS, McKUSICK VA, TENG B, SNIDERMAN AD: Hyperapobetalipoproteinaemia

- in two families with xanthomas and phytosterolemia. *Lancet* 1: 466, 1981
36. BHATTACHARYYA AK, CONNOR WE: Beta-sitosterolemia and xanthomatosis: A newly described lipid storage disease in two sisters. *J Clin Invest* 53: 1033, 1974
37. SMITH AT, SACK GHJr, TAYLOR GJ: Holt-Oram syndrome. *J Pediat* 95: 538, 1979
38. McKUSICK VA, EGELAND JA, ELDRIDGE R, KRUSEN DE: Dwarfism in the Amish. I. The Ellis-Van Creveld syndrome. *Bull Johns Hopkins Hosp* 115: 306, 1964
39. PEASE WE, NORDENBERG A, LADDA RL: Genetic counselling in familial atrial septal defect with prolonged atrio-ventricular condition. *Circulation* 53: 759, 1976
40. WOODROW JC, EASTMOND CJ: HLA B-27 and the genetics of ankylosing spondylitis. *Ann Rheum Dis* 37: 504, 1978
41. ARNETT FC, HOCHBERG MC, BIAS WB: Cross-reactive HLA antigens in B27-negative Reiter's syndrome and sacroilitis. *Johns Hopkins Med J* 141: 193, 1977
42. GRANATO JE, ABBEN RP, MAY WS: Familial association of giant cell arteritis. *Arch Intern Med* 141: 115, 1980
43. CHAMEIDES L, TRUEX RC, VETTER V, RASHKIN WJ, GALIOTO FMJr, NOONAN JA: Association of maternal systemic lupus erythematosus with congenital complete heart block. *N Engl J Med* 297: 1204, 1977
44. COOPER DW, LISTON WA: Genetic control of severe pre-eclampsia. *J Med Genet* 16: 409, 1979