Genetics and Counseling in Cardiovascular Diseases

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PREFACE AND ACKNOWLEDGMENTS

THIS volume was completed during sabbatical at the University of California School of Public Health at Berkeley and represents a summary and synthesis of fifteen years of investigations. It is clearly unbalanced in content, reflecting a major concern with congenital heart diseases and only the awakening of interests in coronary heart disease, rheumatic fever, and hypertension. Thus it represents a watershed in the professional commitment of the senior author to understanding the causes of various cardiovascular diseases. Perhaps, over the next decade, enough information will have been accumulated to require another volume (written during a future sabbatical?) that will treat, in appropriate detail, one or more of the three important areas of cardiovascular disease, which received such modest attention in this presentation. Without completely abandoning etiologic studies of congenital heart diseases, the major thrust of our research is shifting towards genetic and epidemiologic approaches to coronary heart disease.

We wish to thank the Regents and administration of the University of Colorado School of Medicine and The Children's Hospital of Denver for permitting this period of self-renewal so necessary to academic pursuits. And our thanks go to all the many colleagues at the University of California, Berkeley for their generous support during this year. Particularly we wish to thank Doctor Helen Wallace for providing us the opportunity to work on this and other projects in Berkeley.

Our gratitude must also be expressed to our cardiology trainees over the past six years in Denver from whom, in all candor, we learned more than we taught: Doctors Jill Morriss, Vincent Miles, Randall Lortscher, Richard Swensson, Richard Karsh, Mary Smothermon, Gary Way, Warren Toews, Robert McGrath, Richard Readinger, Robin Winkler, Edward

Hargus, and James Wiggins. Four of these have continued on in Denver and are now valued co-workers as are Doctors Robert Wolfe, Richard Hawes and Leslie Kelminson. They have all been involved in the care of many of the patients who are described in these pages.

The bulk of the data collection and preparation must be credited to our staff: Joy Weishuhn Ingram, Marilyn Peterson McCann, Agnes Fountain, Ann Perinchief, Jené Daniel, Sue Gregory, Janet Blu, Michelle Harwayne, and volunteers from the Junior League of Denver. Financial support for the personal research that is presented in this monograph has come from many sources: The National Foundation; The National Heart and Lung Institute; The National Institute of Child Health and Human Development; The American Heart Association; The Colorado, Texas, and Wisconsin Heart Associations; The Junior League of Denver; and The Vida Francis Ellison Trust.

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GENETICS AND COUNSELING IN CARDIOVASCULAR DISEASES

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Chapter 1

OVERVIEW

CARDIOVASCULAR diseases are familial. Although there is a great deal to learn about many of these disorders, we feel that the present state of knowledge now justifies the presentation of data bearing on the subject. If we succeed, there should be, in this one reference, the information that the primary physician requires to answer the frequent questions he receives about the causes and chances for familial recurrence of a given cardiovascular disease. There should also be sufficient data to satisfy the genetic counselor as well as the cardiologist with specific interests in the etiology of cardiovascular diseases.

The familial nature of each of the four broad categories of cardiovascular disease has been appreciated for varying lengths of time. Perhaps Morgagni[1] in 1769 was the first to describe the familial occurrence of vascular disease when he described apparent strokes in two generations of a family.

The familial aspect of coronary heart disease with xanthomatosis first appeared in English literature by Fagge,[2] in 1873. That coronary heart disease, as such, without the emphasis on the sentinel abnormality of familial xanthomatosis, could recur in families was appreciated not by a physician but by the poet Matthew Arnold. While visiting the United States in 1887, he experienced his first attack of angina pectoris and wrote to a friend, "I began to think that my time was really coming to an end. I had so much pain in my chest, the sign of a malady which had suddenly struck down in middle life, long before they came to my present age, both my father and my grandfather."[3] Matthew Arnold lived with chest pain for less than a year before he died on April 15, 1888. One of his biographers disclosed amazingly little scholarship when he described the cause of Arnold's death as "heart failure . . . sudden and quite

unexpected." It was unexpected, to all but Matthew Arnold himself. Sir William Osler called attention in 1897 to the Arnold family in discussing the possible genetic features of coronary heart disease. Through successive editions of Levine's widely used textbook, *Clinical Heart Disease,* heredity has been stressed as "the most important etiologic factor."

Rheumatic fever as a familial disease was first appreciated by Cheadle[4] in 1889. In the 1930s familial clusters of different cardiovascular diseases were being recognized, but it was Wilson and Schweitzer[5] who were the first to attempt a formal genetic analysis of one of these disorders. In 1937 they proposed that susceptibility to rheumatic fever was best explained by inheritance of a single autosomal recessive gene.

As early as 1931, Coburn suggested a streptococcal etiology, but, even in the 1950s, there were those who were not prepared to fully embrace this concept. Reviewing the older literature on the genetics of rheumatic fever is a lesson in humility for all of us who try to understand the genetic and environmental contributions to disease. The cornerstone in today's approach to rheumatic fever is the prompt treatment of beta-hemolytic group A streptococcal infections in those who have not had rheumatic fever, and the prevention of subsequent streptococcal infections in those who have had the disease (through lifetime antibiotic prophylaxis). But there is clearly a genetic aspect to rheumatic fever and this will be discussed further in the chapter on that subject.

The last major category of cardiovascular disease to attract genetic investigators was congenital heart disease. Kindreds with more than one individual with a congenital heart disease appeared sporadically in the literature before the first systematic studies were undertaken in the 1950s. These early studies were impeded by the state of the art, since there were significant limitations in the knowledge of diagnosis of congenital heart disease in the living patient. Also, sometimes methods were employed which were unsuited for informative studies of this problem, e.g. mailed questionnaires. Technical advances in other areas have made possible the more revealing etiologic studies from the 1960s to the present day.

Figure 1-1 is an attempt to place four major categories of cardiovascular disease in the continuum between the poles of heredity and environment. It is obvious that the interaction between these two poles is great. There are relatively small percentages of affected individuals in any category whose disease is exclusively attributable to either the effects of heredity or environment. Congenital heart disease (CHD) and atherosclerosis are visualized as peaking in the middle of the continuum, with CHD having a wider range of genetic contribution and atherosclerosis a wider range of environmental effects. Hypertension is still rather inadequately studied, but individual blood pressure levels are under strong genetic influence with susceptibility to environmental triggers. Rheumatic fever requires a beta-hemolytic streptococcal infection, no matter what the strength of the genetic predisposition. The genetic-environmental interaction in Figure 1-1 is a way we may look at these diseases today. It is subject to updating, if not drastic revision, as new information becomes available.

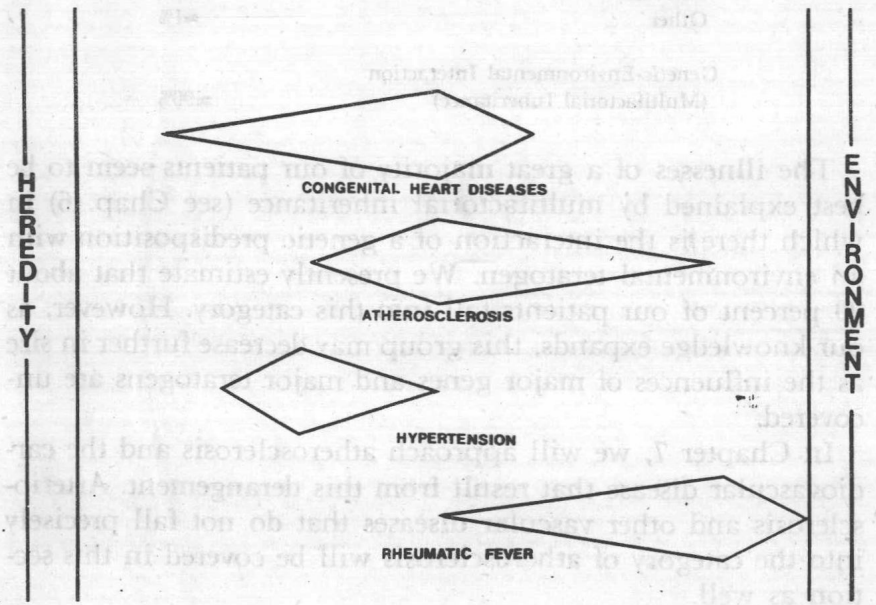

Figure 1-1. The continuum between the poles of heredity and environment for the four major categories of cardiovascular disease.

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Table 1-I summarizes the current experience in our clinic with the etiologic evaluation of congenital cardiovascular disease. About 8 percent of our patients have genetic factors which are of such major importance that the environmental contribution is of little consequence. Presently, about 2 percent have an environmental etiology that strongly outweighs the genetic contribution. This 2 percent may vary significantly under special circumstances, such as during rubella or thalidomide epidemics.

TABLE 1-I

ETIOLOGIC BASIS OF CONGENITAL HEART DISEASE

Primarily Genetic Factors	
Chromosomal	5%
Single Mutant Gene	3%
Primarily Environmental Factors	
Rubella	≈1%
Other	≈1%
Genetic-Environmental Interaction (Multifactorial Inheritance)	≈90%

The illnesses of a great majority of our patients seem to be best explained by multifactorial inheritance (see Chap. 6) in which there is the interaction of a genetic predisposition with an environmental teratogen. We presently estimate that about 90 percent of our patients fall into this category. However, as our knowledge expands, this group may decrease further in size as the influences of major genes and major teratogens are uncovered.

In Chapter 7, we will approach atherosclerosis and the cardiovascular disease that result from this derangement. Arteriosclerosis and other vascular diseases that do not fall precisely into the category of atherosclerosis will be covered in this section as well.

The complex interactions producing atherosclerotic cardiovascular disease defy reduction to simplistic figures. But this

does not deter the authors from offering a simplistic figure of their own (Fig. 7-1). How much easier would be the task of prevention if major gene effects and major environmental effects separated cleanly! It appears that some people may tolerate high cholesterol, high fats, cigarettes and stress with impunity, and others cannot. The goal is to identify those with high genetic risk. Chapter 7, instead of providing answers, will indicate more about possible directions for study.

A chapter dealing with the genetics of hypertension and rheumatic fever is brief for good reasons. There is much to be learned about the genetics of hypertension and the role of genetic counseling in this area. As for rheumatic fever, the emphasis is justifiably on the environmental contribution, and the genetics of predisposition to rheumatic fever is far from clear.

There are alternative ways to present the genetic information necessary for counseling. One standard and highly acceptable way is to present a formal review of the literature, complete with tables of the different findings of many individual investigators. This would give appropriate credit to the sizable number of workers in this area and would permit comparison of results from each group, including our own. It would also yield a volume considerably larger than the present one.

Investigators such as McKusick in the United States, Fuhrmann in Germany and Zetterquist in Sweden have invested a great amount of their creative energies in studying the causes of cardiovascular diseases. The list could justifiably be expanded to credit many hundreds of geneticists, cardiologists, teratologists, and epidemiologists — basic scientists and clinicians — for their major contributions, but the names of most of these individuals may not even be referenced in this monograph. This is not because of lack of admiration for their achievements, but because we are striving for brevity. Our goal is not to provide an exhaustive *Handbuch* but rather a convenient handbook.

Major reliance for data will thus be our own published and unpublished observations. However, no one group has a large enough series to eliminate bias adequately, so we will combine data and strive for a consensus between what we have found

and what others have described, without giving detailed comparisons. The end product is simply what we personally use in counseling.

The authors of this monograph are clinicians, so we do not think of the genetics of cardiovascular disease in the abstract. Our goal is the prevention of cardiovascular diseases. Identification of *risks* and *patients at risk* is a first step.

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Chapter 2

CONGENITAL HEART DISEASE: CHROMOSOMAL ANOMALIES

BEFORE the chromosomal anomaly was recognized in certain common clinical syndromes, such as Turner syndrome and Down syndrome, it was appreciated that an important feature of these syndromes was congenital heart disease. When a discovery as important as the method for clinical study of the human chromosome complement became available to investigators, there was a flurry of activity to explore the limits of the new methodology. After some of the common syndromes were defined, it was thought that nonsyndromic, discrete cardiac malformations might also be found in association with gross chromosomal aberrations. This was not to be the case. However, the newer banding techniques have not been fully exploited in this connection. While it is unlikely that such an association (in the absence of other abnormalities) will be disclosed, the possibility has not been entirely excluded.

Chromosomal syndromes of small deletions and partial trisomies have proliferated at a rapid rate during the past five years because of banding techniques, which represent another major advance in karyotyping. The uncommon syndromes are still inadequately described from the cardiovascular point of view, and the cardiovascular problems in the common syndromes are so well known that we must reach a compromise concerning the selection of information to be presented. The *first* point is that, at this stage of our knowledge, when we think of a chromosomal disorder in the etiology of a congenital heart lesion, we should *think of a syndrome*. There should clearly be other manifestations of maldevelopment. If it is a common syndrome, the clinician should recognize it, be able to name it and be prepared to find the cardiovascular abnormalities most often reported. If it is uncommon, but the pattern of anomalies leads

one to suspect a chromosomal disorder, then, of course, a karyotype will be required. From the point of view of counseling, direct familial transmission of chromosomal anomalies producing congenital heart defects (plus other syndromic features) is relatively rare. However, isochromosomes, translocations, ring chromosomes and structural abnormalities will be accompanied by variable increases in familial recurrence risk. It is understood that the counseling must relate to the karyotype, so we will not repeat for each chromosomal anomaly that there is increased risk in the presence of translocation, etc.

Because familial recurrence is uncommon does not mean that there is no value in clinical genetics to correctly diagnose chromosomal syndromes with associated congenital cardiovascular diseases. The more a physician knows about what his patient has (or is likely to have), the more effective will be his management, including that aspect of the art of medicine which Hippocrates called the highest: prognosis. It is also imperative to have a sound, clinical and laboratory basis for presenting the best approximation of recurrence risk in the counseling situation.

Table 2-I summarizes what the authors know about the occurrence of cardiovascular disease in chromosomal disorders responsible for the great majority of cases of such association. The frequency of associated heart disease ranges from as high as 99+ percent in 18 trisomy to a minimal, if any, increase in Klinefelter syndrome. The three defects found most often in each syndrome are listed in order, if this is known. It will be appreciated that the cardiovascular abnormalities most frequently found in the general population are usually the most common in the autosomal anomalies as well. Aberrations of the X chromosome, on the other hand, are accompanied by a malformation more commonly found in males in a syndrome which has an absence of an X chromosome (Turner syndrome); however, a malformation more common to females is found when there is an excess of X chromosomes, such as in the XXXXY syndrome.

A detailed discussion of all of the clinical features of each of the chromosomal syndromes is not within the purview of this

TABLE 2-I[28]

CONGENITAL HEART DISEASES (CHD) IN SELECTED CHROMOSOMAL ABERRATIONS

Population Studied	*Incidence of CHD*	*Most Common Lesions* 1	2	3
General population	1%	VSD	PDA	ASD
21 trisomy	50%	VSD or AV canal	ASD	PDA
18 trisomy	99+%	VSD	PDA	PS
13 trisomy	90%	VSD	PDA	Dex
22 trisomy	67%	ASD	VSD	PDA
22 partial trisomy (cat-eye)	40%	complex TAPVR	VSD	ASD
4p-	≈40%	ASD	VSD	PDA
5p- (cri-du-chat)	≈20%	VSD	PDA	ASD
8 trisomy (mosaic)	≈50%	VSD	ASD	PDA
9 trisomy (mosaic)	>50%	VSD	coarc	DORV
13q-	≈25%	VSD		
+14q-	>50%	PDA	ASD	Tet
18q-	<50%	VSD		
XO Turner	35%	coarc	AS	ASD
XXXXY	14%	PDA	ASD	ARCA

ARCA = anomalous right coronary artery
Dex = dextroversion
DORV = double outlet right ventricle
VSD = ventricular septal defect
PDA = patent ductus arteriosus
ASD = atrial septal defect
TAPVR = total anomalous pulmonary venous return

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