GENETICS IN CARDIOLOGY

GENETICS IN CONGENITAL HEART DISEASE

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INTRODUCTION

During the past two decades tremendous advances have been made in the diagnosis and treatment of congenital heart disease. While congenital heart disease has always been common, prior to the early 1940's it excited little interest since nothing could be done for the affected individual anyway and the prognosis was usually poor. All of this, of course, has changed. Whole new specialities, such as pediatric cardiology, cardiovascular surgery and radiology have been created to deal with the problem of congenital heart disease.

While previously only very few types of congenital heart disease such as atrial septal defect, patent ductus arteriosus and coarctation of the aorta were compatible with life for any length of time, allowing affected individuals to reach reproductive age, we now see many other types of defects, including quite complex and previously very lethal ones, being corrected surgically. Presumably most of these individuals will now reach an age at which they will produce children of their own. As with other congenital anomalies, the possibility of genetic transmission exists and one may, and should, raise the question as to what we are doing. Are we promoting an increase both relative and absolute in the number of individuals with congenital heart disease.

It is, therefore, not surprising that recently interest in the pathogenesis and etiology of congenital heart disease has increased considerably. Ideally, of course, the ultimate goal in medicine is not to treat diseases but to prevent them from occurring. Usually this means that we have to find out first what their etiology is.

In the etiology of congenital heart disease both genetic and environmental factors have received much attention. The well documented occurrence of cardiac anomalies in families clearly indicates that genetic factors must play a role. It is equally clear that environmental factors, or teratogens in the broad sense, such as drugs, maternal infection and others may in some cases be the dominant or only etiologic agent responsible. What then is the relative importance of each of these two factors? In the case of man, prevention would appear to be much easier to accomplish if environmental factors were dominant, always assuming, of course, that we could find out what the offending agent or agents were. In animals the reverse obviously is true. One simply disposes of any individuals who have malformations unless it happens to be one which, for one reason or another, is considered to be desirable.

ENVIRONMENTAL FACTORS

Cardiac and other anomalies have been produced in animals for many years. Changes in the ratios between the various components of respired air such as lowering of the oxygen content, for example in high altitude situations, or artificially raising the carbon dioxide content, dyes and other toxic substances, vitamin deficiency, cytotoxic agents and even mechanical interference with cardiac development all have produced anomalies including those of the heart. Generally the anomaly produced is rather non-specific, rarely does a particular type of insult produce a specific type of malformation and the time in development at which a teratogen is allowed to exert its influence appears to be more important than its actual nature.

In man the thalidomide disaster and the discovery that rubella infection of the mother during the early months of pregnancy causes anomalies in the baby in a high, percentage of cases, have clearly demonstrated that environmental factors can be of the utmost importance in producing malformations. Such obvious environmental causes for congenital heart disease are, however, rare, more often than not we are forced to conclude from available data in the analysis of cases that some environmental factor or factors must have played a part but we really at present don't know much about their exact nature. We do know that we are doing our level best to increase the number of environmental factors at an increasingly faster rate, thereby making things ever more difficult and complex for ourselves. I am, of course, referring to our changing way of life, to food additives, air and water pollution, etc.

GENETIC FACTORS

Epidemiologic information on the etiology of congenital heart disease in animals is limited. Only recently has interest in the subject shown a significant increase and have useful data become available for analysis. Relatively high incidences of ventricular septal defect have been reported in some inbred strains of chickens[1] and rats[2], and it has been found that pigs seem to have an unusually high incidence of subvalvar aortic stenosis[3].

The recent work by Detweiler[4] of the University of Pennsylvania Veterinary School and particularly that by Don Patterson[5-8] of the same institution on the incidence of congenital heart disease in certain inbred strains of purebred dogs is most exciting, not only from the point of view of genetics, but also the pathogenesis of a number of types of congenital heart disease. Even relatively simple epidemiologic studies on animals such as dogs have demonstrated that congenital heart disease is more common in purebred strains and that certain types of anomalies predominate in certain breeds, for example, patent ductus arteriosus in poodles, right aortic arch in German shepherds, tetralogy-like defects in Keeshonden and pulmonic stenosis in beagles. This clearly indicates that genetic factors do play a significant role in the etiology of congenital heart disease.

Pure breeds in dogs resemble genetic isolates, comparable in other animals with Darwin's finches or in man with, for example, the Amish in which most individuals in a certain community are descended from a few ancestors. In general the interpretation of epidemiologic data from most genetic isolates is complicated because of the strong tendency for them to be also geographic isolates, sharing a common environment as well. In the dog we have the unusual situation that while a breed is a genetic isolate in the true sense, the members of most breeds live in environments as diverse as those of their human masters. This tends to randomize environmental factors and, therefore, the apparent predisposition of certain breeds to specific cardiovascular defects is most readily explained by a non-random distribution of genetic determinants among the breed.

Further studies carried out by Patterson and coworkers[9] involving matings within a breed resulted in

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observations which superficially appeared to be consistent with autosomal dominant inheritance and were initially interpreted as such. However, further analysis of the data showed that they were inconsistent with any simple genetic interpretation and were more in keeping with transmission as a threshold or quasi-continuous trait as it has been called by Grüneberg[10]. Such threshold traits are more or less discrete phenotypic traits which depend upon differences at multiple gene loci and often are influenced by environmental factors, to which polygenic traits are notoriously susceptible. In contrast to polygenic traits which show continuous variation at their phenotypic level such as short stature, threshold traits are usually considered as being present or absent. Edwards[11] has pointed out that the model of a single gene with a variable penetrance may yield numerical results that are difficult to distinguish from those of the true classic continuous model. If the penetrance is assumed to vary with modifying genes in the genetic background the concept of a single gene with penetrance approaches the true quasicontinuous model as other genes in the genetic background have an increasing influence on its expression. While hereditary patent ductus arteriosus in Patterson's[9] studies showed a superficial resemblance to simple dominant inheritance, it can also be explained by the polygenic threshold model when it is understood that the liability of an individual to develop a threshold trait may lie in any position with respect to the threshold at which phenotypic discontinuity occurs. When an affected animal whose liability lies above the threshold is mated to a normal animal, a proportion of their off-spring approximating 50% may fall above the threshold, depending upon the heritability of the trait, and the position of both parents' liabilities with respect to the threshold. It is also possible for the pattern of transmission of threshold traits to simulate simple recessive inheritance. If the parents are themselves clinically unaffected but their liabilities to the trait lie near the threshold the mean liability of their off-spring will be shifted to the right of the general population and some proportion may fall above the threshold. If that proportion happens to be near 25%, the trait will appear to be inherited as a simple recessive in those families. An increase in incidence of a trait with inbreeding, that is consaguinity, is well known as a feature of simple recessive inheritance, but it is no less characteristic of threshold traits since the multiple genes responsible may be concentrated by the same process. It is interesting to note that the incidence of congenital heart disease in purebred dogs as a group of about 9 per 1,000, is about the same as is seen in man.

GENETICS AND CONGENITAL HEART DISEASE IN MAN

As Dr. Emanuel[12] has pointed out in his paper in 1970, the study of human genetics is difficult because, believe it or not, man is not prolific and takes an awful long time to reach reproductive age and to complete a generation. Furthermore, breeding experiments are, of course, not possible. Man's great interest in his own species has led to an accumulation of data far greater than is available for animals. While analysis of such data of necessity have to be carried out in a retrospective fashion, they have proved to be useful allowing us to reach certain, at least tentative conclusions. In addition, nature in some cases has carried out experiments which are useful in the study of human genetics.

Congenital heart disease is extremely common in individuals with chromosomal anomalies. The cardiac defect in these patients, however, is only one of many other abnormalities present and in many cases may be a relatively unimportant part of the whole clinical picture. The best known and most common of the syndromes associated with **autosomal** chromosomal abnormalities is Down's syndrome. In this condition there is an extra $\neq 21$ chromosome and the patients present themselves with a very characteristic clinical picture with which you are all familiar. About half of these affected individuals have congenital heart disease, most commonly either some type of endocardial cushion defect or a ventricular septal defect. The most common true cyanotic malformation in Down's syndrome is tetralogy of Fallot or a combination of endocardial cushion defect with the outflow tract malformation as seen in tetralogy of Fallot.

Less common are the syndromes associated with either an extra chromosome in the 13-15 group or 17-18 group, the D and E trisomies. Congenital heart disease is almost invariably present but since the multiple associated developmental abnormalities are very severe in these two types of autosomal trisomies survival beyond infancy is rare. The cardiac malformations seen are usually multiple and consist of ventricular septal defect, patent ductus arteriosus, certain forms of dextrocardia and others.

Congenital cardiac defects may also occur in individuals with abnormalities of the **sex chromosome.** The most outstanding and best known example is Turner's syndrome. In the classical form of this syndrome, one of the sex chromosomes is lacking. there is monosomy X and congenital heart disease occurs in approximately 20% of these individuals. The most common anomalies are coarctation of the aorta and congenital aortic valve stenosis. Phenotypically the individuals with classical Turner's syndrome are female. More recently certain variants of the syndrome have been reported in which many of the stigmata of Turner's syndrome such as short stature, webbed neck, cubitus valgus, etc., are present but in whom no chromosomal anomaly is present and the phenotype is male. The name of Jackie Noonan, pediatric cardiologist in Kentucky, has been associated with this syndrome which at one time was also often referred to as male Turner's syndrome. It is interesting that the cardiovascular lesion present in this variant tends to involve the right side of the heart, that is, pulmonary valvar stenosis and pulmonary artery coarctations are present in about 30% of the cases.

There are a host of other syndromes not associated with gross abnormalities of the chromosomes in which cardiovascular lesions are common. All of these syndromes are uncommon and include, to name just a few, Marfan's syndrome, Friedreich's ataxia, dystrophia myotonica, Ellis-van Creveld syndrome, Holt-Oram syndrome, Hurler's syndrome and a sex-linked recessive form of the latter referred to as Hunter's syndrome. These syndromes appear to show an autosomal dominant or recessive pattern of inheritance.

All of these syndromes in whom cardiac lesions are common, with or without chromosomal aberrations represent only a small percentage of the total number of patients with congenital heart disease. In the great majority of instances, congenital heart disease is present as an isolated or nearly isolated anomaly and systematic studies have shown that in this majority no single or simple mode of inheritance can be found. A dominant mode of inheritance has been reported in a few instances of familially occurring atrial septal defect at the fossa ovalis such as those reported by Zuckerman et al.[13] and more recently by Zetterqvist et al[14] Shokeir[15] in 1971 reported on five families in which hypoplastic left heart syndrome was found in 13 individuals. The pattern of transmission in these families was thought to be consistent with an autosomal recessive mode of inheritance and consaquinity could be clearly demonstrated among the parents of the probands in three of the reported sib-ships. While in the very few instances of this sort, simple autosomal or recessive inheritance cannot be excluded with certainty, they could also be explained by the polygenic threshold model as described by Patterson in his dogs. Careful analysis of familial aggregates and individual pedigrees have led to the hypothesis of multifactorial in-

heritance. Our understanding of this mode of inheritance has been developed through the basic work of Wright,[16] Grüneberg[10] and its application to human genetics by Penrose,[17] Edwards,[11] Carter[18] and more recently by Nora[1290]. The hypothesis of multifactorial inheritance has been stated by Nora as follows: "congenital heart diseases are a heterogenous category of developmental anomalies, representing in most cases the multifactorial inheritance of threshold characters the expression of which is the product of a genetic and environmental interaction", or to put it in somewhat more simpler terms: congenital heart diseases are not all one disease, there is a hereditary predisposition determined by many genes and an environmental trigger acts on the predisposed individual to push him over a threshold from normal development to abnormal development. One may postulate that at one end of the spectrum (in a relatively small number of families) there is no hereditary predisposition to congenital heart disease, e.g., ventricular septal defect, and in this type of family no environmental trigger can make congenital heart disease manifest. A second type of family, encompassing the great majority of people, does have a certain predisposition of variable but usually low risk. It takes the action of an environmental trigger in this type of family to produce congenital heart disease. Finally, there is the type of family (fortunately, at least at the present time, again a minority), in which the predisposition to congenital heart disease is so great that even without significant environmental trigger the risk of occurrence of congenital heart disease is high and almost all of the offspring may be affected.

Twin studies provide another means of testing the presence or absence of genetic factors and the etiology of congenital heart disease. If single mutant genes were responsible for cardiac lesions which are not part of a single mutant gene syndrome, both members of identical twin pairs would have the disease in 100% of the cases and the frequency of concordance in non-identical twin pairs should be the same as the frequency of concordance in siblings, that is about 50% concordance for dominants and 25% for recessives. Twin studies have shown, however, that while the concordance in identical twins is five times as great as in non-identical twins, it falls far short of the 100% expected in single mutant gene inheritance. It also falls far short of the 25% expected for a recessive mode of inheritance. As Nora has pointed out, the findings in twins are exactly those which would be predicted in multifactorial inheritance.

We can conclude from all of this then that a single mutant gene type of Mendelian inheritance or chromosomal aberrations only account for a small percentage of cases with congenital heart disease seen in practice. The great majority of cases can best be explained by a multifactorial mode of inheritance, both in animals and in man. Characteristically such diseases are common, show familiar aggregates, have a recurrence rate in sibs of from 1 to 5%, are susceptable to environmental influences and are found much more commonly in both members of identical twins than in non-identical twins. Edwards has calculated that threshold traits inherited through multifactorial inheritance appear in the first degree relatives, that is siblings and parents of affected individuals with a frequency approximating the square root of the population frequency. That is, if the frequency of a congenital anomaly is 1 in 100, or 1% of the population, it should be found in 1 out of 10, or 10% of siblings. The empirical risk of such common cardiac anomalies as ventricular septal defect, patent ductus arteriosus, tetralogy of Fallot, atrial septal defect, pulmonic stenosis and others has been fairly well established. The recurrence risk in siblings arrived at by obtaining the square root of the population frequency for any given defect shows amazing agreement with that arrived at empirically. For example, the observed risk in ventricular septal defect has been found to be 4.4%, whereas the calculated expected recurrence risk was found to be 5%. This figure was arrived at as follows: approximately 1% of children born in the United States have congenital heart defects. Pediatric congenital heart registries show that about 25% of congenital heart lesions are ventricular septal defects, therefore, 25% of 1% is .25% for the incidence of ventricular septal defect. The square root of .0025 is .05 or 5%.

The general finding is that common defects recur with a higher frequency, as high as 4.4% for ventricular septal defect, and that uncommon lesions recur with lower frequency, for example in the order of 1%. Therefore, without any tables at all, cardiologists, in counselling families need only know that the range of recurrence risk is from 1 to 4.4% depending upon how common the defect is. It must be kept in mind, however, that these are the risks to the next child to be born if there is only one affected first degree relative. The risk is much higher if there are more than one affected first degree relative.

What happens then when those individuals who have been operated upon now are allowed to reach reproductive age and have children of their own? At present we can only give preliminary answers. There is no question but that the frequency of congenital heart disease in future generations will increase, the risk being similar to that seen for first degree relatives as in siblings. It seems obvious that marriage of two patients with congenital heart disease should be discouraged, but this, of course, will not always be possible.

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