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Familial cardiomyopathies

RICHARD EMANUEL

WE must first define the condition we are going to discuss. The best definition was put forward by Professor John Goodwin and his colleagues some years ago. They suggested that 'a cardiomyopathy was a subacute or a chronic disorder of the heart muscle of unknown or obscure aetiology, often associated with endocardial and sometimes pericardial involvement, but not atherosclerotic in origin'. The cases I intend to discuss are the idiopathic group, i.e. those due to such conditions as amyloid, sarcoid, and collagen disease have been excluded. We have also excluded all cases where there was any suggestion of an alcoholic history and also those where there was a previous illness which could have been viral. It is in this context that I use the term 'idiopathic cardiomyopathy'. The familial nature of this disease was first noted by William Evans in 1947 and reported to the British Cardiac Society in that year. Since then many familial cases have been described and some authors have postulated a dominant inheritance in a few families.

The current study was started in October 1967 and was planned to examine the mode of inheritance in this disease. Material was pooled from The National Heart Hospital, Hammersmith Hospital and The Middlesex Hospital and many people from these centres have taken part. In addition, over seventy physicians in the United Kingdom and abroad have helped to examine patients. Index cases were only accepted when the diagnosis of idiopathic cardiomyopathy was confirmed by cardiac catheterization and left ventricular angiography, operative findings or necropsy data. Many also had coronary arteriography. We eventually collected ninety-seven cases which were acceptable. In the first instance Mrs K. O'Brien, my research assistant, visited each of the propositi, preferably in their own homes and with their help drew up a family pedigree. These ninety-seven families consisted of 617 first-degree relatives.

TABLE 1. Details of 617 first-degree relatives who formed the basis of the study

		Examined	Unexamined
Parents	194	177 (91%)	17
Siblings	295	264 (89%)	31
Children	128	117 (91%)	11
Totals	617	558 (90%)	59

Examination of the first-degree relatives was arranged at the parent hospital wherever possible and included a physical examination, electrocardiogram, and chest radiograph. The results of examination, the electrocardiogram, and chest radiograph were then sent to me. There were a number of cases, particularly children, where the diagnosis of idiopathic cardiomyopathy was uncertain and where cardiac catheterization was not justified. These have been put in a separate group and referred to as 'possible or doubtful cardiomyopathy'. The material obtained, which formed the basis of this study, is shown in Table 1 and owing to Mrs O'Brien's painstaking work over the past 4 years, we have been able to get acceptable data on 90% of the first-degree relatives. In living relatives we only accepted the diagnosis of cardiomyopathy if the physical findings, electrocardiogram and chest radiograph were all compatible and in those who had died the diagnosis was not entertained unless there was firm evidence from previous hospital records, a necropsy report, or operation findings. Sudden death alone without corroborative evidence was not considered adequate for the diagnosis of idiopathic cardiomyopathy.

TABLE 2. The familial incidence of idiopathic cardiomyopathy in the ninety-seven families studied

	Familial	Doubtful	Non-familial
Hypertrophic	23	12	41
Congestive	5	2	14
Totals	28 (29%)	14 (14%)	55 (57%)

Table 2 shows the results of our first analysis. Twenty-eight of our ninety-seven families had more than one affected member. The propositus in twenty-three of the familial cases presented the clinical picture of 'hypertrophic cardiomyopathy' and, much to our surprise, five showed the 'congestive' form. From this analysis we consider the minimal familial incidence in this series is 29% and if the doubtful cases were included, 43%. These figures are rather higher than those previously reported, probably due to the fact that 90% of the first-degree relatives had been examined. Previous genetic analyses have stopped at this point, but after discussion with Ronald Withers he suggested we should look at our material in a different way and examine the matings which had produced our

propositi. Amongst our ninety-seven index cases there were sixty-seven in which neither parent was affected. In a further twelve, one parent was affected, and in one instance both parents were affected. In eight instances one parent had been diagnosed as 'possible cardiomyopathy' and in nine cases we had been unable to examine one of the parents. These two groups were excluded from further analysis, as was the family with two affected parents, because of the limited data.

If we postulate the condition could be inherited as an autosomal dominant gene, this would account for the twelve families in which one parent was clinically affected and the other normal. Although the affected parent could be homozygous for the dominant gene, they were more likely to be heterozygous for it and this assumption was made. In this case half the children (the propositus and his siblings) should be affected. In all the family studies, however, there was at least one affected person, the propositus. Such truncate selection introduces a bias from the expected one-in-two and increases the apparent frequency of affected persons. Professor C. A. B. Smith has constructed tables of this type of analysis and we have used them throughout this study. Table 3 shows the analysis of the twelve families in which the propositus was the product of the mating between one affected and one unaffected parent. The number of observed cases of cardiomyopathy (24) did not differ significantly from the expected (24·3) Thus, we conclude in these twelve cases the disease was inherited as an autosomal dominant.

TABLE 3. Analysis of the twelve families in which the propositus was the product of the mating between one affected and one unaffected parent

No. in sibship	No. of families	Observed no. affected	Expected no. affected	Variance
2	5	6	6·665	1·110
3	1	3	1·714	0·490
4	2	5	4·266	1·564
5	2	5	5·162	2·164
6	1	2	3·048	1·379
7	1	3	3·528	1·667
Totals	12	24	24·383	8·374

$P > 0{\cdot}9$.

Now turning to the sixty-seven families in which neither parent was affected, these could either be accounted for by the sporadic occurrence of the disease or by a recessive pattern of inheritance and we examined the latter possibility. If there was a recessive gene one would expect one in four of the offspring to be affected but, once again, truncate selection occurred as only families with at least one affected person (the propositus) were included, thus producing a bias from the expected one in four. The analysis was carried out according to Smith (Table 4). Except for the sibships of eight children there was good agreement and the observed number of affected individuals did not differ from the expected at the 1% level of significance. We found seventy-five affected children, whereas there should have been 100. I think there are three reasons for this rather low figure. First, we used very strict criteria before the clinical diagnosis of cardiomyopathy was accepted in the first-degree relatives. Secondly, any case diagnosed as 'possible cardiomyopathy' was excluded and thirdly, there was rather a large number of stillbirths and miscarriages in this group (twenty-seven), some of which could well have been cases of cardiomyopathy. If we add in the 'possible cardiomyopathies' the figure of seventy-five increases to eighty-two and if we add the stillbirths and miscarriages to this the total becomes 109, compared with the expected figure of 100.

TABLE 4. Analysis of the sixty-seven families in which the propositus was the product of the mating between two unaffected parents

No. in sibship	No. of families	Observed no. affected	Expected no. affected	Variance	Probability
1	8	8	8·000	0	0
2	23	24	26·289	2·806	>0·1
3	5	6	6·485	1·315	>0·6
4	10	11	14·630	4·200	>0·05
5	6	8	9·834	3·552	>0·3
6	3	3	5·475	2·328	>0·1
7	2	2	4·040	1·940	>0·1
8	4	4	8·892	4·688	>0·01
9	3	6	7·299	4·140	>0·5
10	2	2	5·298	3·184	>0·05
15	1	1	3·801	2·658	>0·05
Totals	67	75	100·043	30·811	>0·01 (10 d. f.)

Examining further the possibility of recessive inheritance, an analysis was made of the families in which the propositus was considered to be a recessive homozygote and had at least one affected child. The assumption made was that the homozygous recessive propositus had mated with a heterozygote carrying the recessive gene (Fig. 1). Under these circumstances 50% of the children should be affected but, once again, the selection was truncate and the data analysed according to Smith. We had seven such families (Table 5) and once again there was good agreement between the observed number of cardiomyopathies and the expected number ($P > 0{\cdot}1$). This gives further evidence that the hypothesis of recessive inheritance is correct for the sixty-seven index cases where neither parent was affected. We have also divided this material into those index cases which presented with hypertrophic cardiomyopathy and those where the disease appeared in its

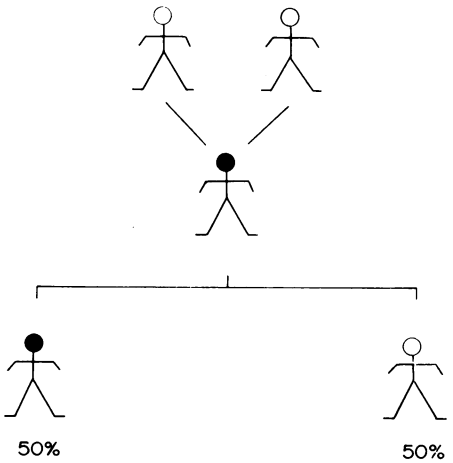

FIG. 1. Analysis of children of recessive propositi.

TABLE 5. Analysis of the seven families of homozygous recessive propositi who had at least one affected child.

No. in sibship	No. of families	Observed no. affected	Expected no. affected	Variance
1	1	1	1·000	0
2	2	2	2·666	0·444
3	3	4	5·142	1·470
6	1	2	3·048	1·379
Totals	7	9	11·856	3·293

$P > 0{\cdot}1$.

congestive form according to Goodwin's criteria. In both clinical groups we were able to demonstrate the presence of dominant and recessive modes of inheritance. The significance of this awaits further analysis as Goodwin has already drawn attention to the difficulty in differentiating between hypertrophic and congestive cases, especially when seen in the terminal stages of the disease, but our data suggest that hypertrophic and congestive forms could be different clinical phases of the same disease. At present we are in the process of comparing the clinical features of the dominant and recessive groups.

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Discussion

PROFESSOR A. P. WATERSON: Thank you very much, Dr Emanuel. This paper is now open for discussion and I am going to exercise my Chairman's right to ask the first question if I may. There seems to be a considerable number of families with very large sibships. Is this in any way relevant or does it reflect a sampling problem? As a corollary to that, is the propositus normally distributed for place in the family?

DR EMANUEL: In answer to your first question, I suspect the high frequency of families with a large sibship is a sampling problem and in answer to the second question, there was nothing special about the birth order of the propositi.

DR M. BARRY (Ipswich): I can add some information to that of Dr Emanuel and it bears out some of his findings. My investigation was done from a different angle as it

was a field exercise. Some of my cases are included in his study. I had nineteen affected families in which 637 people were examined. In those cases where an apparently unaffected parent produced affected children, the spouse and his and her sibs were investigated. This accounted for an additional 110 people. The sample was good enough, I was assured by the Department of Genetics of the University of Cambridge, for inferences to be drawn. In these families there were fifty-one proven cases of cardiomyopathy including proof by necropsy or operation. In addition, there were fifty probable cases. There were twenty-seven histological confirmations and also seven necropsies in which histological studies were not performed.

Amongst the larger family groups penetrance was 63% and roughly the same for males (62·5%) and females (64%). However, I noticed that in the offspring of an affected mother penetrance was 43%, whereas amongst the offspring of an affected father it was 75%. Applying the sibship method and the Lenz–Hogben test did not lead to completely conclusive results but there was some evidence in favour of an autosomal dominant mode of inheritance.

There also appeared to be an excess of males in affected sibships. The ratio of males to females was 1·5 : 1. This differs from equality, but one must remember that in Suffolk the sex ratio is 1·3 : 1 in any group of families.

DR R. VECHT (Zurich): I would like to ask Dr Emanuel what he considers the frequency of the recessive gene in the general population, for he showed seven families in which the affected relative, a homozygote recessive, mated with a heterozygote who was clinically normal. I think this shows an unexpectedly high frequency for the recessive gene in the normal population and wonder whether this data does not support the view of dominant inheritance with incomplete penetrance?

DR EMANUEL: I shall ask Mr Withers to reply to these very pertinent comments.

MR R. WITHERS (Middlesex Hospital): We are trying to determine the frequency of the recessive gene in the population. Consideration of Dr Vecht's reasons for asking leads to a few remarks on the concept of penetrance. In the medical literature one can find papers where a gene is described as dominant (by which the author means that it goes from an affected parent to an affected child) and yet has low penetrance (by which the author means that it hardly turns up at all). As a geneticist I cannot see the difference between that situation and possible recessive inheritance, so I honestly think it is not very useful to involve the concept of penetrance. What we are dealing with is something to do with primary gene action, about which we know nothing in many of these cases, and the development of the organism subsequent to or consequent on that gene action. In some cases the developmental history allows us to see the effect of gene action while in other cases it does not. Until we know what is the primary gene action and what happens in development there is little point in hiding our ignorance under the concept of penetrance.

If we look at the example referred to we must remember that the sibship of the affected person in Table 5 in fact showed far better agreement with the recessive hypothesis than it did with a dominant hypothesis. In fact the findings were significantly different from those expected on a dominant hypothesis. This means that when we look at the children of such a person we start by having good reasons for postulating that he is a homozygous recessive. Furthermore, if we examine the sibships of such affected people there is a risk rate of about one in twenty-four for affected relatives. If this were due to spontaneous dominant mutation, the mutation rate would be far too high. Therefore, one must not look at the figure in isolation as though it could just possibly be dominant. There is good reason for saying that it is not.

What we are saying is that we have presented evidence that all forms of this sort of cardiomyopathy are inherited —some as a dominant, some as a recessive. (Some should or could even have both genes!) The interesting point is that this means that we should stop looking at what I would call the gross phenotype—the malformed heart and its diagnosis—and start to try to think aetiologically in terms of gene action—in terms of abnormal proteins. Even the wildest biochemical studies on these people might produce results of importance. Our genetical results could suggest that our two genes might work in a biochemical pathway from A to B to C, where a deficiency of C gives rise to cardiomyopathy. Our genes might affect either the A to B step or the B to C step and in either case a deficiency of C would result. Such thinking is familiar to those of you who have examined inborn errors of metabolism. Therefore, I would urge a biochemical investigation of any persons with this condition.

DR W. BRIGDEN (London): I would like to ask Richard Emanuel what is the sex ratio of the affected parents of the propositi? Did you find that more mothers appeared to pass on the disorder than fathers?

DR EMANUEL: In the twelve families where there was an affected parent there were four females to eight males, a sex ratio of female to male of 1 : 2. So in answer to the second part of your question, it appeared that fathers rather than mothers passed on the disease.

DR W. BRIGDEN: Did you find any age or sex difference in those who died from cardiomyopathy?

DR EMANUEL: In our series there were twenty-two patients who died. This, of course, excludes those who succumbed following surgery. Rather conveniently, eleven of these were in families with a dominant inheritance and eleven in families with a recessive inheritance. The age of death did not differ significantly. It was 37 years in the dominant group and 33·2 years in the recessive group. The sex ratio, however, was very different; in the eleven dominant cases there were ten males and one female, and in the eleven recessive cases there were six males and five females. The sample, however, is small, so I do not think too much should be inferred from these figures.

DR W. BRIGDEN: In my own series of familial cases the males seemed to die at a significantly earlier age than the females.

DR EMANUEL: In the twenty-two cases that died there were sixteen males with an average age of death of 33·9 years and six females with an average age of 38·3 years. These figures are not significantly different.