GENETICS OF CORONARY HEART DISEASE

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The genetics of a disease implies the study of the pattern of its inheritance. This may be definable on Mendelian lines and ideally should be attributable to the presence of an abnormal gene or possibly group of genes. There are some difficulties in this approach in a disease which appears to have a number of factors contributing to its basic pathology and to its clinical expression as overt coronary heart disease. It is evident that both environmental and genetic factors are involved and except for the relatively rare disorder of familial xanthomatosis, clear separation of these factors has not been achieved.

Some idea of the complexity of the situation emerges from recent advances in our understanding of the inheritance of hypertension, a major coronary risk factor which is polygenically determined and greatly influenced by the environment. Our knowledge of the inheritance of hypercholesterolaemia is less complete. In the recent series described by Patterson and Slack (1972) the type-2 disorder, due to a single gene of large effect, was responsible for hypercholesterolaemia in a minority of patients but in the majority hypercholesterolaemia was multifactorially determined. The mode of inheritance of familial type-4 hyperlipoproteinaemia which also appears to be associated with coronary disease is less well understood. Stone and Levy (1972) described it as a Mendelian dominant trait with delayed expression and penetrance. However, it is clear that the clinical expression of the type-4 pattern is frequently dependent on environmental factors resulting in obesity.

Despite the complexities of the problem there is good evidence that coronary disease runs in families. Gertler and White (1954) studied family histories of 97 male patients with coronary heart disease and found that 37% of the fathers of this group had died from coronary heart disease as compared with 19% of fathers in the control group. There was no significant differences between the mothers of the coronary group and the controls (10% and 8%) respectively.

Thomas and Cohen (1955) studied family histories in 266 medical students and found that susceptibility is greatest if both parents are affected and least if neither is. Harvald and Hauge (1963) found that the concordance rate for coronary heart disease in monozygotic twins was not significantly greater than in dizygotic twins. Rose (1964) reported familial characteristics in 75 survivors of cardiac infarction and 75 matched controls. Among the parents of index males there was a nearly threefold excess mortality from ischaemic heart disease. Within the index group the familial cases showed significant clustering. Slack and Evans (1966) in a major study of 121 men and 96 women with ischaemic heart disease compared the causes of death of their male and female relatives with the relatives of a male and female control group. The risk of death from coronary heart disease was 2·5 to 7 times greater in the relatives of patients with coronary disease than in the controls. Heritability was calculated at 60% for men and 70% for women so that the increased risk was partly genetic and partly environmental. Familial concentration was most marked in patients with hypercholesterolaemic xanthomatosis and also in diabetic families. Deutscher, Ostrander and Epstein (1970) reported that the younger men in the Tecumseh population were at much greater risk of dying from coronary heart disease when both parents had died of the disease. They also pointed out that high risk individuals had higher serum cholesterol levels and that diabetes was commoner in younger men whose fathers had died from premature coronary disease.

For 6 years we have been carrying out a diet-heart study on men under 60 with coronary disease. We present here data on the incidence of coronary heart disease in the parents of 491 of these men. Seventy of the propositi were aged between 30 and 40 years and the coronary experience of the parents has been compared with that of two normal control groups of the same age. The family history of the young coronary subjects has also been compared with that of 214 patients in the 41-50 age group and 207 in the 51-60 age group. Emphasis is placed on the younger coronary subjects, firstly because previous workers have not always separated them to the same degree from the older age groups and secondly, because it is likely that those who develop the disease early in life will show most clearly the factors with a stronger genetic component.

Table 1 shows the general characteristics of the young coronary propositi compared with control group A who were 70 healthy young men in Sydney and Control group B who were 281 young males included in the 1966 Busselton survey in Western Australia. We are grateful to Dr. Michael McCall and Mr. Norman Stenhouse for the use of their data for this group. The age of the three groups was similar. There was no difference of consequence in their systolic or diastolic blood pressures (Blacket *et al*, 1973). The serum cholesterol was higher in the coronary group than in either of the two normal control groups ($P<0·001$ in each case).

Table II shows the fate of the fathers of the coronary propositi aged 30-40 compared with the fathers of control group A. Death implies death from any cause. Twenty-nine were alive with a mean age of 69 years and 39 were dead with a mean age at death of 58·9 years. In the 69 control group fathers, the proportions were reversed, 40 being alive (mean age 64·7 years) and 29 dead (mean age at death 57·3 years). The differences are suggestive but not statistically significant.

Table III shows the causes of death of the fathers at all ages. Of the 39 dead fathers in the coronary group, 30 had died of vascular disease. Twenty six had fatal coronary disease and 4 other vascular diseases such as stroke or peripheral vascular disease. In the control group 19 of 29 fathers had died of vascular disease, 12 of these being coronary deaths. Deaths from non-vascular disease were similar in the two groups. The results demonstrate a significant preponderance of deaths from coronary disease in the coronary fathers.

So far, we have looked at the mortality experience at all paternal ages. Table IV shows the situation in the fathers at the age of 60. Forty three of the 68 coronary fathers were alive and 25 were dead. In the control group, 52 fathers were alive and 17 had died. Twenty of the 25 coronary fathers had died from coronary disease in contrast to only 4 of the 17 dead in the control group. Total cardiovascular mortality by age 60 was 22 in the coronary group as compared with 9 in the control group. Eight fathers of the control group had died of other diseases compared with 3 in the coronary group.

Table V shows the total incidence of coronary disease both fatal and non-fatal in the fathers by age 60. Twenty four of the coronary fathers and only 6 of the control fathers had experienced coronary disease by this age. The mean age at death of the fathers was 54 and 56 years in the coronary and control groups respectively.

The maternal family history was examined on the same basis (Table VI). The total mortality of the mothers of the coronary subjects (23 out of 69) was greater than that of the mothers of controls (9 out of 68) and the difference was statistically significant at the 1:100 level.

In Table VII the causes of death of the mothers are presented. The differing mortality experience of mothers of coronary subjects was clearly due to their higher incidence of coronary and other vascular diseases. Thus 14 of the coronary group mothers had died of coronary disease, as compared with one of the control group mothers. The total deaths from all vascular disease were 16 in the coronary group and only 2 in the control group. Non vascular deaths were equal in the two groups.

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TABLE I

COMPARISON OF GENERAL CHARACTERISTICS OF PROPOSITI
MEANS ± STANDARD DEVIATION

	Coronary Group	Control A	Control B
NUMBER	70	70	281
AGE AT INTERVIEW	36·9 ± 2·9	34·8 ± 3·3	30 - 39
SYSTOLIC B.P.	132·4 ± 17·9	131·2 ± 16·5	139·0 ± 17·2
DIASTOLIC B.P.	87·0 ± 11·8	83·9 ± 12·0	77·0 ± 11·2
CHOLESTEROL	308 ± 100 (p<0·001)	227 ± 40	244 ± 42

TABLE II

FATHERS

Fate of Fathers		Coronary Group		Control Group A		Total
ALIVE		29 (34·3)		40 (34·7)		69
	Age		69 ± 6·5		64 ± 5·3	
DEAD		39 (33·7)		29 (34·3)		68
	Age		58·9 ± 12·1		57·3 ± 13·6	
TOTAL		68		69		137

In this and subsequent tables, numbers in parenthesis are those expected assuming the null hypothesis.
X2, df 1 = 3·22, 0·1>P>0·05.

TABLE III

FATHERS—CAUSES OF DEATH—ALL AGES

Fate of Fathers	Coronary Group		Control Group A		Total
ALIVE	29 (34·2)		40 (34·8)		69
DEAD CHD	24		12		36
DEAD CHD COMPLICATING OVD	2 (18·9)		0 (19·1)		2
DEAD OVD ALONE	4 (5·4)		7 (5·6)		11
TOTAL DEATHS ALL VASCULAR DISEASE		30 (24·3)		19 (24·7)	49
DEAD NON VASCULAR DISEASE	9 (9·4)		10 (9·6)		19
TOTAL	68		69		137

CHD = Myocardial infarction, angina pectoris, sudden death
OVD = Other vascular disease—i.e. stroke, hypertension, peripheral vascular disease X2, df3 = 7·93, P<0·05

TABLE IV

FATHERS—SITUATION AT AGE 60

Fate of Fathers	Coronary Group		Age		Control Group		Age		Total
Alive	43 (47·2)		—		52 (47·8)		—		95
Dead CHD / Dead CHD Complicating OVD	20 (11·9)		53·5		4 (12·1)		56·4		24
Dead OVD Alone	2 (3·5)		52·0		5 (3·5)		53·9		7
Total Deaths all Vascular Disease		22 (15·4)		53·4		9 (15·6)		55·0	31
Dead Non Vascular Disease	3 (5·5)		41·7		8 (5·5)	44·6			11
TOTAL	68				69				137

X2, df3 = 15·23, p<0·01

TABLE V

FATHERS—INCIDENCE OF CHD AT AGE 60

Fate of Fathers	Coronary Group	Age	Control Group A	Age	Total
DEAD WITH CHD	20	53·5	4	56·4	24
ALIVE WITH CHD	4	55·5	2	58·0	6
TOTAL CHD	24		6		30
TOTAL FATHERS	68		69		137

For death from CHD $P<0.001$
For all CHD $P<0.001$

By age 60, 6 of the mothers of the coronary group had died of vascular disease, 5 of them coronaries, but none of the control group mothers had died of these causes (Table VIII). Deaths from other causes were slightly higher in the control group. These differences were not significant on the multiple contingency table. However, as Table IX shows, the total incidence of coronary disease by age 60 was significantly higher in the mothers of the coronary group, but the numbers were small.

Table X summarises the mortality and morbidity experience in both fathers and mothers of coronary and control groups at age 60.

We now compare the coronary experience of fathers and mothers of coronary propositi aged 41-50 and 51-60 with those in the decade 30-40 (Table XI). The survival experience was the same in the three decades but the mortality pattern was different. The fathers of the youngest coron-

TABLE VI

MOTHERS

Fate of Mothers		Coronary Group		Control Group A		Total
ALIVE		46 (52·9)		59 (52·1)		105
DEAD	AGE	23 (16·1)	65·5 ± 5·9	9 (15·9)	63·4 ± 7·0	32
	AGE		59·7 ± 11·7		48·7 ± 13·0	
TOTAL		69		68		137

X2, df 1 = 7·73, $P<0.01$

TABLE VII

MOTHERS—CAUSES OF DEATH—ALL AGES

Fate of Mothers	Coronary Group		Control Group A		Total	
ALIVE	46 (52·9)		59 (52·1)		105	
DEAD CHD	11		1		12	
DEAD CHD COMPLICATING OVD	3 (7·6)		0 (7·4)		3	
DEAD OVD ALONE	2 (1·5)		1 (1·5)		3	
TOTAL DEATHS ALL VASCULAR DISEASE		16 (9·1)		2 (8·9)		18
DEAD NON VASCULAR DISEASE	7 (7·1)		7 (6·9)		14	
TOTAL	69		68		137	

X2, df 3 = 13.08 $P<0.01$

TABLE VIII

MOTHERS, SITUATION AT 60, CAUSES OF DEATH

Fate of Mothers	Coronary Group		Age		Control Group A		Age	Total	
Alive	60 (61·15)		—		62 (60·5)		—	122	
Dead CHD Dead CHD Complicating OVD	5 (2·5)		55		0 (2·5)			5	
Dead OVD Alone	1 (0·5)		58·0		0 (2·5)			1	
Total Deaths all Vascular Disease		6 (3·0)		55·5		0 (3·0)			6
Dead Non Vascular Disease	3 (4·5)		36·0		6 (4·5)		41·2	9	
TOTAL	69				68			137	

X2, df 3 = 7·08 $0.10>p>0.05$

TABLE IX

MOTHERS—INCIDENCE OF CHD AT AGE 60

Fate of Mothers	Coronary Group		Control Group A		Total
		Age		Age	
DEAD WITH CHD	5	55·0	0	—	5
ALIVE WITH CHD	1	60·0	0	—	1
TOTAL CHD	6		0		6
TOTAL MOTHERS	69		68		137

For death from CHD $P<0.05$
For all CHD $P<0.01$

TABLE X

INCIDENCE OF CHD—FATHERS AND MOTHERS AT AGE 60

	Coronary Group			Control Group A			Probability
	Dead	Alive	Total	Dead	Alive	Total	
FATHERS	20	4	24	4	2	6	<0·001
MOTHERS	5	1	6	0	0	0	<0·01

TABLE XI

COMPARISON OF CORONARY HEART DISEASE BY DECADES FATHERS AT AGE 60

Fate of Fathers	30 - 40		41 - 50		51 - 60		Total	
Alive	43 (48·1)		158 (151·4)		145 (146·6)		346	
Dead CHD Dead CHD Complicating OVD	20 (7·4)		15 (23·2)		18 (22·4)		53	
Dead OVD Alone	2 (1·4)		6 (4·4)		2 (4·2)		10	
Total Deaths all Vascular Disease		22 (8·8)		21 (27·6)		20 (26·6)		63
Dead Non Vascular Disease	3 (11·1)		35 (35·0)		42 (33·8)		80	
TOTAL	68		214		207		489	

X2, df 6 = 36·20. $P<0.001$

TABLE XII

COMPARISON OF CORONARY HEART DISEASE BY DECADES MOTHERS AT AGE 60

Fate of Mothers	30 - 40		41 - 50		51 - 60		Total	
Alive	60 (55·1)		179 (170·8)		155 (165·2)		391	
Dead CHD Dead CHD Complicating OVD	5 (2·4)		9 (7·4)		3 (7·2)		17	
Dead OVD Alone	1 (3·0)		9 (9·2)		11 (8·9)		21	
Total Deaths all Vascular Disease		6 (5·4)		18 (16·6)		14 (16·0)		38
Dead Non Vascular Disease	3 (8·6)		20 (26·6)		38 (25·8)		61	
TOTAL	69		214		207		490	

ary group died predominantly from coronary disease while the fathers of the two older age groups tended to die from non-vascular causes. We have examined the causes of death of the fathers of the two older age groups and find it unlikely that the higher incidence of death from non-vascular causes was attributable to different diagnostic fashions.

Data for mothers at age 60 is shown in Table XII. There was no difference in the total mortality in the three groups. The differences lay principally in the higher incidence of death from non-vascular causes in the 41-50 and particularly in the 51-60 age groups. The excess of deaths from coronary disease in the mothers of the younger age group may have been significant had the numbers been greater.

In Table XIII, the situation at age 60 for the fathers and mothers of the three decade groups is summarised. Men who had experienced coronary disease by the age of 40 showed a three to four times greater incidence of coron-

TABLE XIII

FATHERS AND MOTHERS AT AGE 60 OF 3 CORONARY GROUPS DEATH FROM CORONARY HEART DISEASE

	30 - 40	41 - 50	51 - 60	Total	
Fathers	20	15	18	53	X2, df2 = 28·49 $p<0.001$
Mothers	5	9	3	17	X2, df2 = 5·82 $0.1>p>0.05$
Numbers of Affected Families	24	20	21	65	X2, df2 = 31.28 $p<0.001$

ary disease in the fathers than in the two older age groups. The findings in the mothers were similar but small numbers precluded statistical significance. The number of families affected was also greater in the young coronaries than in the later decades.

SUMMARY AND DISCUSSION

Our data confirm the findings of previous authors that in men with coronary disease before the age of 40 a positive history of coronary disease before the age of 60 in one or both parents is commoner than in the parents of normal controls.

A positive family history in parents by age 60 is also more frequent in the young coronary subjects than in coronary men in the two following decades.

Familial aggregation does not separate genetic and environmental influences. However, the concentration in younger subjects suggests a genetic factor. This may operate independently or alternatively may require environmental influences for its expression. The work of Ancel Keys and his group (1966) supports the likelihood of the environment enhancing a genetic predisposition.

The outstanding feature of young coronary subjects is hyperlipidaemia, particularly hypercholesterolaemia. Our group did not have more arterial hypertension than controls. This was also the experience of Gertler and White (1954). Glucose intolerance is more common in subjects with arterial disease than in the normal population. However frank diabetes mellitus occurred in only 4 of our young coronary subjects and could not be held to be a major factor in coronary disease at this age.

Uric acid levels in excess of 7·0 mg.% were present in 40% of our young coronaries. The incidence of hyperuricaemia was similar in the older age groups. It is not clear whether hyperuricaemia is an independent risk factor or whether it is related to over nutrition with hyperglyceridaemia. There is evidence that gout may also be inherited rather than acquired. It is not known whether there is any link with the inheritance of coronary disease.

We are left with hyperlipidaemia. Dominant inheritance is recognised in the relatively rare familial xanthomatosis with very high serum cholesterol. In these patients serum cholesterol is influenced by environment in only minor degree.

The role of inheritance in the commoner and lesser degrees of hyperlipidaemia is less clear. Environment undoubtedly plays an important part but given a uniform dietetic pattern individual response may well be genetically determined. Data on the resemblance of cholesterol levels in the first degree relatives of coronary and normal propositi under the age of 40 would be of great interest.

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