Hyperlipidaemic Xanthomatosis

I: Increased Risk of Death from Ischaemic Heart Disease in First Degree Relatives of 53 Patients with Essential Hyperlipidaemia and Xanthomatosis

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Relatives of young patients with ischaemic heart disease have a substantially increased risk of early death from ischaemic heart disease (Slack and Evans, 1966), and family aggregations of death from ischaemic heart disease were noted especially amongst the few patients with essential hyperlipidaemia. Morris, Kagan, Pattison, Gardner, and Raffle (1966) have called attention to the value of raised plasma cholesterol levels in predicting susceptibility to ischaemic heart disease in middle age, and Albrink, Meigs, and Man (1961) have demonstrated an association of early onset ischaemic heart disease with raised triglyceride levels. The risks of early death from ischaemic heart disease are known to be high in patients with essential hyperlipidaemia associated with xanthomatosis (Muller, 1938; Piper and Orrild, 1956; Guravich, 1959; Epstein, Block, Hand, and Francis, 1959), and as the condition seems to be genetically determined (Wheeler and Sprague, 1953; Leonard, 1956; Khachadurian, 1964) there is good reason to suppose that the relatives of these patients may also show an increased risk of death from ischaemic heart disease. Family concentrations have been reported, but clearly not all families with hyperlipidaemia run the same high risk of death from ischaemic heart disease (Harlan, Graham, and Estes, 1966). Exact information as to the risks of death from ischaemic heart disease amongst relatives of patients with essential hyperlipidaemia is lacking, and accordingly a study has been undertaken to estimate these risks, and to identify the families in which the risk is high. The risks of death from ischaemic heart disease in all first degree relatives of the index patients have been

calculated. The risks are not uniform and clearly vary with the type of lipid disturbance in the index patient.

Subjects and Methods

Fifty-three patients with xanthomata associated with raised total fasting plasma lipids have been studied. All were free from any known disease predisposing to hyperlipidaemia, such as diabetes mellitus, cirrhosis of the liver, or myxoedema, at the time of diagnosis.

Index Patients. The patients were 33 adult men and 20 adult women who had attended London hospitals* with essential hyperlipidaemia and xanthomatosis. Twenty-nine (22 male and 7 female) patients presented with xanthomata; 22 (9 male and 13 female) patients with ischaemic heart disease and xanthomata; and 2 male patients with intermittent claudication and xanthomata. Three male patients developed diabetes mellitus after essential hyperlipidaemic xanthomatosis had been diagnosed (see Appendix IIA, families 2, 12, and 15).† Two male patients were dead when traced. Their families were traced and have been included in the series (Appendix IA, 11 and 15).

Family Histories. Pedigrees were drawn up to include all first degree relatives. All adult deaths were verified from death certificates where possible and details of previous illnesses obtained from hospital records. Death certificates of three first degree relatives could not be traced; one of these (Appendix IIA, 2) was accepted as a death due to ischaemic heart disease from the description given by the patient. Five relatives were omitted altogether from the study because there was insufficient evidence about their dates of birth or death.

* Westminster Hospital, 20; Middlesex Hospital, 10; St. Bartholomew's Hospital, 9; The London Hospital, 7; The National Heart Hospital, 4; Edgware General Hospital, 1; St. Mary's Hospital, 2.

† The appendices have been grouped together at the end of Part II of this study on pp. 23-28.

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Relatives reported to be alive with ischaemic heart disease were noted, and confirmation was obtained in all but one (Appendix IA, 2), from hospital records or by clinical examination and cardiography.

Classification of Death Certificates. Death certificates were classified by the criteria in use at the time of death by reference to the International Lists of Causes of Death (1929 to the present).

Life Tables. Tables showing 'years at risk' were constructed by the method described by Slack and Evans (1966). Adult sons and daughters of the index patients were included in the same way as brothers and sisters. From these tables the expected number of deaths (E) amongst relatives was compared with the observed number of deaths (O) in each age-group. The ratio of observed to expected number of deaths (O/E) was calculated.

Blood Lipid Levels. Venous blood was drawn after an overnight fast from each index patient at the time of entering the study. Lipid levels before treatment were obtained from hospital records. Total plasma cholesterol was determined by the method of Schoenheimer and Sperry (1934), omitting the stage of digitonin precipitation. Total plasma triglycerides were measured by the method of Van Handel and Zilversmit (1957). All hypercholesterolaemic patients had a cholesterol level greater than 325 mg./100 ml. and were considered to be hypertriglyceridaemic when fasting triglyceride levels were more than 200 mg./100 ml. These levels were arbitrarily selected as upper limits after consideration of our own laboratory controls. They are consistent with other studies (Schaefer, Adlersberg, and Steinberg, 1958; Carlson, 1960; Fredrickson and Lees, 1966; Mills and Wilkinson, 1966). Thirteen patients undergoing treatment for hyperlipidaemia had plasma lipid levels below these values at the time of the study, and for these patients the lipid levels before treatment were accepted from hospital records. Two patients (Appendix IIA, 2 and 13) were recorded in hospital records as having 'lipaemic' serum, with cholesterol levels 360 mg. and 610 mg./100 ml., respectively, before treatment, and were accordingly classified as having hypercholesterolaemic xanthomatosis with hypertriglyceridaemia. By these criteria, 32 patients had essential hypercholesterolaemic xanthomatosis and 21 had hypercholesterolaemic xanthomatosis associated with hypertriglyceridaemia.

Results

Table I shows the clinical presentation of the 53 index patients and the classification of these patients into the two biochemical groups depending on the levels of total plasma cholesterol and triglycerides. Thirty-two patients (16 male and 16 female) had hypercholesterolaemic xanthomatosis, of whom 12 presented with xanthomata only, 19 with ischaemic heart disease and xanthomata, and 1 with intermittent claudication and xanthomata.

TABLE I
CLINICAL PRESENTATION OF 53 INDEX PATIENTS
WITH ESSENTIAL HYPERLIPIDAEMIA AND
XANTHOMATOSIS

Index Patients	Clinical Presentation		
	Xantho- matosis	Xantho- matosis and Ischaemic Heart Disease	Xantho- matosis and Inter- mittent Claudi- cation
<i>Hypercholesterolaemic xanthomatosis</i>			
Male (16)	7	8	1
Female (16)	5	11	—
Total (32)	12	19	1
<i>Hypercholesterolaemic xanthomatosis with hypertriglyceridaemia</i>			
Male (17)	15	1	1
Female (4)	2	2	—
Total (21)	17	3	1

Twenty-one index patients (17 male and 4 female) had essential hypercholesterolaemic xanthomatosis with hypertriglyceridaemia, of whom 17 presented with xanthomata only, 3 with ischaemic heart disease, and 1 with intermittent claudication.

Risks of Death from Ischaemic Heart Disease in Relatives. Table II shows the risks of death from ischaemic heart disease amongst the

TABLE II
SUMMARY OF RISKS OF DEATH FROM ISCHAEMIC
HEART DISEASE (REGISTRAR GENERAL'S CATE-
GORIES 420 AND 94) IN RELATIVES OF PATIENTS
WITH ESSENTIAL HYPERLIPIDAEMIA AND
XANTHOMATOSIS

Age of Relative at Death from Ischaemic Heart Disease	Relatives of Male Patients			
	Years at Risk	O	E	O/E
Male relatives				
20-54	897	3	0.44	6.82
55 and over	377	5	2.33	2.15
Female relatives				
20-64	1119	3	0.31	9.68*
65 and over	152	2	0.92	2.17
	Relatives of Female Patients			
	Years at Risk	O	E	O/E
Male relatives				
20-54	707	8	0.38	21.05**
55 and over	238	3	1.34	2.24
Female relatives				
20-64	1080	6	0.36	16.67**
65 and over	114	4	0.54	7.41*

Significance ** = $p < 0.001$
* = $p < 0.01$

TABLE III

SUMMARY OF RISKS OF DEATH FROM ISCHAEMIC HEART DISEASE (REGISTRAR GENERAL'S CATEGORIES 420 AND 94) IN RELATIVES OF PATIENTS WITH FAMILIAL HYPERCHOLESTEROLAEMIC XANTHOMATOSIS

Age of Relatives at Death from Ischaemic Heart Disease	Relatives of Male Patients			
	Years at Risk	O	E	O/E
Male relatives				
20-54	519	3	0.25	12.0*
55 and over	248	4	1.48	2.70
Female relatives				
20-64	607	2	0.15	13.33*
65 and over	96	2	0.53	3.77
	Relatives of Female Patients			
	Years at Risk	O	E	O/E
Male relatives				
20-54	595	8	0.32	25.00**
55 and over	186	2	1.09	1.83
Female relatives				
20-64	755	6	0.24	25.00**
65 and over	84	3	0.45	6.66

Significance ** = $p < 0.001$
 * = $p < 0.01$

first degree relatives of the 53 patients with essential hyperlipidaemia and xanthomatosis. From the 'years at risk' and from the risks of death in the general population in the appropriate secular period, the number of deaths expected amongst the relatives can be compared with the number of deaths

TABLE IV

SUMMARY OF RISKS OF DEATH FROM ISCHAEMIC HEART DISEASE (REGISTRAR GENERAL'S CATEGORIES 420 AND 94) IN RELATIVES OF PATIENTS WITH FAMILIAL HYPERCHOLESTEROLAEMIC XANTHOMATOSIS WITH HYPERTRIGLYCERIDAEMIA

Age of Relatives at Death from Ischaemic Heart Disease	Relatives of Male Patients			
	Years at Risk	O	E	O/E
Male relatives				
20-54	405	0	0.21	—
55 and over	136	1	0.90	1.11
Female relatives				
20-64	542	1	0.18	5.55
65 and over	56	0	0.39	—
	Relatives of Female Patients			
	Years at Risk	O	E	O/E
Male relatives				
20-54	112	0	0.06	—
55 and over	52	1	0.25	4.00
Female relatives				
20-64	325	0	0.12	—
65 and over	30	1	0.09	11.11

observed. The male and female relatives were divided into 'younger' and 'older' age-groups at 55 and 65 years, respectively.

The increased risk of death amongst the 'younger' male relatives and the 'younger' female relatives of the male patients is 6½-fold and 9½-fold, respectively. The latter increase is significant ($p < 0.01$). The 'younger' male relatives and the 'younger' female relatives of the female patients show a 21-fold and a 16½-fold increased risk of death from ischaemic heart disease. Both these increases are significant ($p < 0.001$).

Smaller increases of risk were observed amongst the 'older' relatives of the index patients, but only the 7-fold increased risk of death amongst the 'older' female relatives of the female patients is significant ($p < 0.01$).

Families of patients with hypercholesterolaemic xanthomatosis considered separately show a substantially increased risk of death from ischaemic heart disease amongst the first degree relatives (Table III). Male patients' 'younger' male relatives show a 12-fold increase in risk of early death from ischaemic heart disease ($p < 0.01$) and their 'younger' female relatives a 13-fold increase ($p < 0.01$). Female patients' 'younger' male and female relatives both show a 25-fold increase in risk ($p < 0.001$).

Amongst the 'older' male and female relatives of the male and female patients, smaller increases of risk are observed but none are significant.

Families of patients with hypercholesterolaemic xanthomatosis associated with hypertriglyceridaemia show no significant increase in risk amongst any group of relatives of either male or female patients (Table IV). The observed number of deaths is too small to draw any definite conclusion. The over-all increase in risk to all relatives is very small (1.82) and is not significant.

Discussion

Ischaemic heart disease is more frequent in families of patients with essential hyperlipidaemic xanthomatosis than in the general population. The present study shows quantitatively a substantially increased risk of death from ischaemic heart disease in the 'younger' relatives of patients with essential hyperlipidaemia and xanthomatosis. The risks are not uniform and when the patients are divided into two chemical groups, those with cholesterol only raised and those with both cholesterol and triglycerides raised, it is clear that the relatives of

patients in the two groups experience a very different risk of early death from ischaemic heart disease.

Among the patients with hypercholesterolaemic xanthomatosis the actual risk over the period of observation to the 'younger' male relatives of the male patients is 1 in 5, to the 'younger' female relatives of the male patients it is 1 in 7, to the 'younger' male relatives of the female patients it is 1 in 2, and to the 'younger' female relatives of the female patients it is 1 in 3. The risks to the relatives of the patients with hypercholesterolaemic xanthomatosis associated with hypertriglyceridaemia are not significantly raised above the general population. If the same increase in risk had applied to the relatives of the patients with hypercholesterolaemic xanthomatosis associated with hypertriglyceridaemia, as was found amongst the relatives of patients with hypercholesterolaemic xanthomatosis, a significant increase would have been expected in the total group of relatives. Expected deaths were 2.2 in the whole group and 14 deaths would be expected if the same increases in risk had operated.

It is notable that 3 first degree relatives of the patients in the whole group died with aortic aneurysm (see Appendix IA, 3; IB, 7; and IIB, 2) and 2 with aortic stenosis (see Appendices IB, 15 and IIA, 7).

Living relatives of the patients demonstrate a similar distribution in incidence of ischaemic heart disease in relatives of the 2 groups. Patients with hypercholesterolaemic xanthomatosis had 120 adult living relatives of whom 11 had ischaemic heart disease confirmed by clinical and electrocardiographic evidence. Patients with hypercholesterolaemic xanthomatosis with hypertriglyceridaemia had 67 adult living relatives of whom only 2 had confirmed ischaemic heart disease. This distribution of ischaemic heart disease amongst the living relatives follows closely the pattern of difference in risk of death from ischaemic heart disease in the 2 groups.

The risk of early death from ischaemic heart disease is high for relatives of patients with hyperlipidaemic xanthomatosis, but the risks depend upon the type of hyperlipidaemia manifest in the index patient. Patients with hypercholesterolaemic xanthomatosis associated with hypertriglyceridaemia presented more frequently with skin lesions than with ischaemic heart disease, indicating less risk amongst the patients themselves, and their relatives appear to carry so little increased risk that rigid preventive measures may prove unjustified. Investigation of the families of more female patients is necessary before firm conclusions should be

drawn. Relatives of patients with hypercholesterolaemic xanthomatosis, however, run such a high risk of early death from ischaemic heart disease that early identification and treatment of affected relatives before the onset of symptoms may be the only way of preventing early death from ischaemic heart disease. If the condition is inherited as a simple autosomal dominant trait (Leonard, 1956; Nevin and Slack, 1968 (Part II of this paper)) only half the first degree relatives of the index patients will be 'at risk', and it is likely that detection of raised cholesterol levels in childhood will identify this moiety.

It is not yet possible to say what proportion of the increased risk to relatives of unselected patients is due to essential hypercholesterolaemic xanthomatosis, and even within this group a few families (Appendix IA, 7, 8, 13, 14 and IB, 6) appear to escape cardiovascular complications.

Summary

There is an increased risk of early death from ischaemic heart disease in first degree relatives of patients with essential hyperlipidaemic xanthomatosis. When the patients are broadly classified by their total plasma cholesterol and triglyceride levels, the risks to the relatives are not uniform.

Relatives of male patients with hypercholesterolaemic xanthomatosis experience an increased risk which is 12-fold amongst the 'younger' male relatives and 13-fold amongst the 'younger' female relatives. All 'younger' relatives of the female patients in this group experience a 25-fold increase in risk.

No significant increase in risk of death from ischaemic heart disease has been demonstrated amongst the relatives of patients with hypercholesterolaemic xanthomatosis associated with hypertriglyceridaemia.

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