J. med. Genet. (1968). **5**, 9.

Hyperlipidaemic Xanthomatosis

II: Mode of Inheritance in 55 Families with Essential Hyperlipidaemia and Xanthomatosis

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Xanthomata of the skin were first described in the English literature by Addison and Gull in 1851, and their hereditary nature was indicated by Hutchinson in 1871. Pick and Pinkus in 1909 (quoted by Harlan, Graham, and Estes, 1966) first described their association with raised plasma lipids. Familial hyperlipidaemia is not uncommon, but in spite of the relatively large number of reported pedigrees the mode of inheritance of the phenotypes is still uncertain. The heterogeneity of the metabolic disorders associated with familial hyperlipidaemia has been one source of confusion. Recently, Fredrickson and Lees (1965, 1966) have distinguished at least five distinct varieties of hyperlipidaemia on the basis of the lipoprotein pattern, and there is a suggestion that others may emerge. Many previous studies of the inheritance of this condition are based solely on the level of serum cholesterol values in the family, thus failing to differentiate between individual varieties of hyperlipidaemia. Furthermore, there has been understandable difficulty in establishing the best criteria to discriminate between 'affected' and 'normal' individuals within families.

Familial hypercholesterolaemic xanthomatosis, or hyperbetalipoproteinaemia Fredrickson type II, the commonest familial hyperlipidaemia, is usually attributed to an autosomal dominant trait with regular expression; the heterozygote being hypercholesterolaemic from childhood and developing xanthomata in adult life and having an increased risk of ischaemic heart disease (Kornerup, 1948; Piper and Orrild, 1956; Wheeler and Sprague, 1953; Epstein, Block, Hand, and Francis, 1959; Adlersberg, Schaefer, Steinberg, and Wang, 1954; Leonard, 1956). Others (Wilkinson, Hand, and Fliegelman, 1948; Boas, Parets, and Adlersberg (1948); Adlersberg, 1951; Hirschhorn and Wilkinson, 1959) hold that heterozygotes have a moderate hypercholesterolaemia only and that those with marked hypercholesterolaemia, xanthomata, and early onset ischaemic heart disease are homozygous for the gene concerned. More recently (Wheeler, 1957; Adlersberg and Schaefer, 1959; Harlan *et al.*, 1966; Khachadurian, 1964), it has been increasingly clear that heterozygotes for the gene or genes concerned have hypercholesterolaemia, may develop xanthomata with increasing age, and often have early onset ischaemic heart disease, but that in addition it is probable (Epstein *et al.*, 1959) that homozygotes occur with more extreme hypercholesterolaemia, earlier and more extensive development of xanthomata, and perhaps earlier onset ischaemic heart disease.

Familial hypercholesterolaemic xanthomatosis associated with hypertriglyceridaemia is characterized by increases of both the serum cholesterol and triglycerides with xanthomata. This group probably forms a heterogeneous group corresponding mainly to Fredrickson and Lees Type III, but may also include some patients with Types IV and V hyperlipoproteinaemia. Although this variety of hyperlipidaemia occurs in families, the distribution of affected subjects is not that of a trait expressed in single dosage of an abnormal gene (Fredrickson, Levy, and Lees, 1967).

Fat-induced hypertriglyceridaemia, corresponding to Fredrickson Type I hyperlipoproteinaemia, is characterized by high concentration of chylomicrons in serum, absence or deficiency of lipoprotein lipase, bouts of abdominal colic, and eruptive xanthomata usually presenting in infancy.

The purpose of this study is to examine further the inheritance of hyperlipidaemic xanthomatosis classifying the index patients into three groups.

Received July 7, 1967.

Group A: pure hypercholesterolaemic xanthomatosis. *Group B:* mixed hypercholesterolaemic xanthomatosis associated with hypertriglyceridaemia. *Group C:* fat-induced hypertriglyceridaemia.

Subjects and Methods

The families of 55 index patients with hyperlipidaemia were investigated. Of these 32 had familial hypercholesterolaemic xanthomatosis, 21 had familial hypercholesterolaemic xanthomatosis associated with hypertriglyceridaemia, and 2 had fat-induced hypertriglyceridaemia.

Index Patients and their Relatives. The patients were the same 33 men and 20 women investigated in Part I (Slack and Nevin, 1968). In addition, 2 children with fat-induced hypertriglyceridaemia were included; one was a patient at Great Ormond Street Children's Hospital and the other at the Westminster Children's Hospital. Patients were asked to invite the co-operation of as many living, close relatives as possible. There were 210 living first degree relatives. Of these, 107 were examined clinically, and fasting venous blood samples were obtained either at home or in hospital. A further 102 first degree relatives were dead, and for these, death certificates were obtained on all but 3 (see Part I). In addition, 41 second or third degree relatives and 31 spouses of patients and relatives were examined clinically, and fasting venous blood samples were obtained.

The 53 adult index patients were divided into Groups A and B by consideration of their cholesterol and triglyceride levels before treatment was begun (see Part I). All these patients had primary xanthomatosis and cholesterol levels over 325 mg./100 ml. If the serum or plasma was described as 'clear' or if triglyceride levels were less than 200 mg./100 ml., the patients were considered to have hypercholesterolaemic xanthomatosis, and were ascribed to Group A. If the serum was described as 'lipaemic' or if fasting triglycerides were greater than 200 mg./100 ml., the index patients were considered to have hypercholesterolaemia associated with hypertriglyceridaemia and were ascribed to Group B.

The 2 child index patients with fat-induced hypertriglyceridaemia were considered separately in Group C.

Appendices I and II show details of the families examined and the actual levels of cholesterol and triglyceride in the index patients are shown in Appendix III.

Controls. The controls were spouses of the patients, colleagues, relatives, and friends of the authors. There were 86 men and 78 women between the ages of 15 and 60. None was aware of having any serious illness. No clinical examination was carried out.

Blood Lipid Levels. Venous blood was drawn from relatives of the patients and controls after an overnight fast. Total cholesterol levels were determined by the method of Schoenheimer and Sperry (1934), omitting the stage of digitonin precipitation. Triglyceride levels were measured by the method of Van Handel and Zilversmit (1957). Hospital records were used to obtain cholesterol and triglyceride values for relatives from whom specimens were unobtainable because of death or long distance, or to establish pre-treatment levels on relatives who were already under treatment. Levels obtained from hospital records have been placed in brackets in Appendix III, since these measurements were necessarily performed by various methods which were usually not specified.

Causes of Death in First Degree Relatives. Death certificates were obtained for as many dead first degree relatives as possible. Each was classified according to the Registrar General's Classification of Certificates at the time of issue (see Part I).

RESULTS

I: Plasma Lipid Levels

(a) Controls

Cholesterol. Plasma cholesterol levels were measured on 65 male and 51 female controls between 15 and 60 years of age. When the fasting cholesterol levels in the control group were plotted against age for men and women, it was apparent that cholesterol levels increased with age in both sexes, and the increase appeared to be linear between the ages 15 and 60. For male controls, the coefficient of linear regression with age was 1·22 mg./100 ml. per year, between the ages of 15 and 60. This differs significantly from zero ($t = 2{\cdot}54$, $p < 0{\cdot}02 > 0{\cdot}01$). The mean age for male controls was 39·80 years. The scatter of values by age for men and the regression lines are shown in Fig. 1a. The mean plasma cholesterol for men was 223·26 mg./100 ml., with an over-all standard deviation of $\pm 53{\cdot}06$ mg./100 ml. about the mean and $\pm 50{\cdot}52$ mg./100 ml. about the regression line.

The coefficient of linear regression of cholesterol with age for female controls was 1·5 mg./100 ml. per year between the ages of 15 and 60; this differs significantly from zero ($t = 3{\cdot}17$; $p < 0{\cdot}01 > 0{\cdot}001$). The mean age for female controls was 36·94 years. The scatter of values by age for women and the regression line are shown in Fig. 1b. The mean plasma cholesterol for these women was 221·35 mg./100 ml., with a standard deviation of $\pm 46{\cdot}95$ mg./100 ml. about the mean and $\pm 42{\cdot}64$ about the regression line.

The cholesterol levels for all controls were then corrected for age, sex, and standard deviation. Female levels were corrected to their equivalent at 40 years, using the coefficient of linear regression for age for females. The corrected mean for female

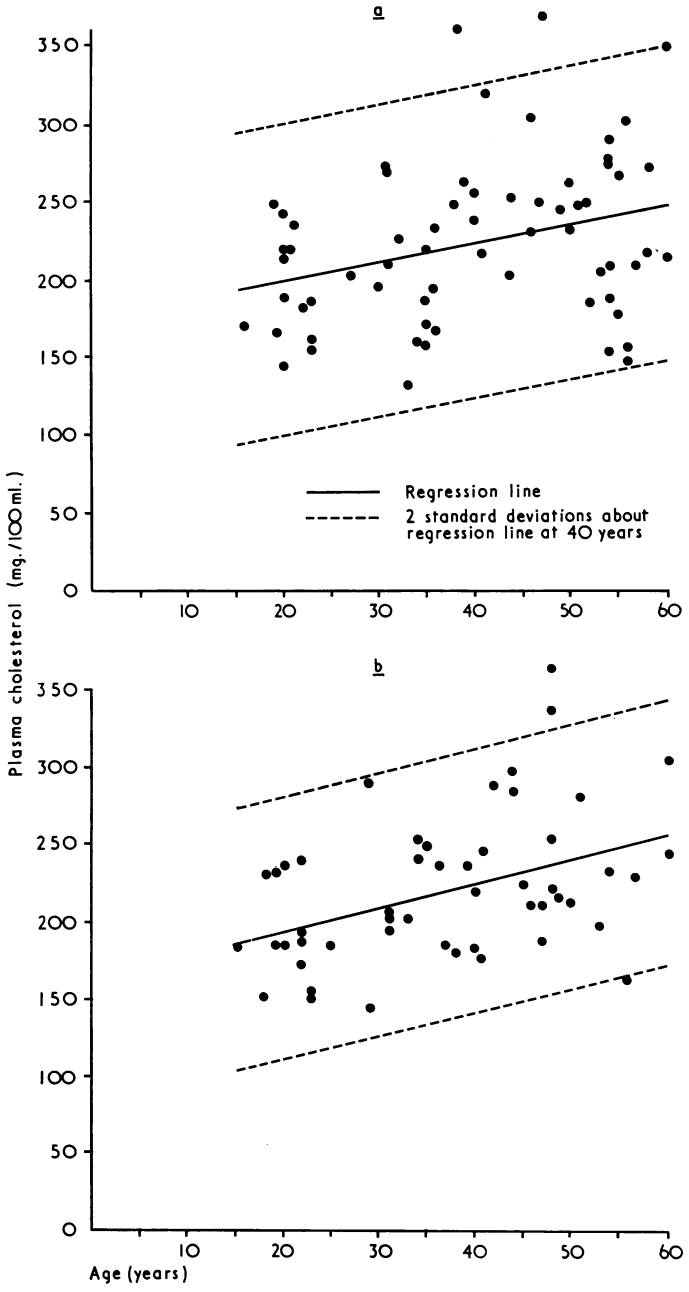

FIG. 1. Plasma cholesterol levels in (a) male controls, and (b) female controls, and regression lines showing variation with age.

controls was 226·06 mg./100 ml., with a standard deviation of ±42·64 mg./100 ml.

Male levels were similarly corrected to their equivalent at 40 years, then the deviation from the male mean at 40 was corrected for the difference in standard deviation in the sexes by the ratio of the female to the male standard deviation from the regression line, and the product was added to the mean for female controls at 40 years. The corrected mean and standard deviation for male controls

TABLE I

PLASMA CHOLESTEROL LEVELS (mg./100 ml.) IN CONTROLS

	No.	Mean Age (yr.)	Mean Cholesterol Level (mg./100 ml.)	Standard Deviation	Coeff. Lin. Regression Ch/Age	Mean Corrected to 40	Standard Deviation	Mean and S.E. Corrected to ♀ 40	Standard Deviation
♂ Controls	65	39·80	223·26	±53·06	1·22	223·51	±50·52	226·06	±42·64
♀ Controls	51	36·94	221·35	±46·95	1·5	226·06	±42·64		
All Controls	116							226·06 ± 2·09	±42·46

was therefore also 226·06 ± 42·64 mg./100 ml. Table I shows the results and corrected results of cholesterol levels in the controls.

A distribution curve of control levels, corrected to the equivalent figure in females age 40, was plotted (see Table III, Fig. 3a and 4a). The curve was close to normal, but slightly positively skewed. 4·31% and not the expected 2·4% had levels more than 2 standard deviations above the mean, a corrected value of 310·98 mg./100 ml.

Triglyceride. Plasma triglyceride levels were measured in 82 male and 75 female controls between 15 and 60 years of age. When these triglyceride levels were plotted against age for men and women, it was apparent that triglyceride levels also increased with age in both sexes, and the increase appeared to be linear between 15 and 60. For male controls, the coefficient of linear regression of the triglycerides with age was 1·34 mg./100 ml. per year between the ages of 15 and 60. This differs significantly from zero ($t = 2{\cdot}965$; $p < 0{\cdot}01 > 0{\cdot}001$). The mean age for male controls was 40·69 and their mean plasma triglyceride level was 106·84 mg./100 ml., with a standard deviation of ± 58·91 mg./100 ml. about the mean, and ± 53·64 mg./100 ml. about the regression line. The scatter of values by age and the regression line for men appear in Fig. 2a.

The coefficient of linear regression of triglycerides with age for female controls was 0·75 mg./100 ml. per year between the ages of 15 and 60. This differs significantly from zero ($t = 2{\cdot}73$; $p < 0{\cdot}01 > 0{\cdot}001$). The mean age for female controls was 36·71 years and the mean plasma triglyceride for women was 69·71 mg./100 ml., with a standard deviation of ± 31·00 mg./100 ml. about the mean and ± 29·53 mg./100 ml. about the regression line. The scatter of values for women and the regression line appear in Fig. 2b. The distribution is notably different from the distribution for men.

The triglyceride levels for all controls were corrected to the equivalent for a female age 40 years, using the method described for correction of cholesterol levels, and a distribution curve of these corrected control levels was plotted (see Table III, Fig. 3b and 4b). The corrected female mean was 71·63 mg./100 ml., with a standard deviation of ± 29·53 mg./100 ml., and the corrected male mean was therefore the same.

The curve of the corrected values showed a near normal distribution. The corrected mean for controls was 71·63 mg./100 ml., with a standard deviation of ± 29·44. Table II shows the results and corrected results of triglyceride levels in the controls.

(b) **Index Patients.** The distribution of corrected cholesterol and triglyceride levels in index patients divided into Groups A and B is shown in Table III, Fig. 3 and 4.

By definition, all these patients had uncorrected cholesterol levels over 325 mg./100 ml. with or without uncorrected triglyceride levels over 200 mg./100 ml., but in many cases only cholesterol levels were available from hospital records before treatment was begun. As a result, all patients had xanthomata with raised cholesterol levels and some in addition had raised triglycerides. It is notable that no patient had high triglyceride levels without raised cholesterol. This may be because of the high proportion of cases in

TABLE II

PLASMA TRIGLYCERIDE LEVELS (mg./100 ml.) IN CONTROLS

	No.	Mean Age (yr.)	Mean Triglyceride Level (mg./100 ml.)	Standard Deviation	Coeff. Lin. Regression Tg./Age	Mean and S.E. Corrected to 40	Standard Deviation	Mean and S.E. Corrected to ♀ 40	Standard Deviation
♂ Controls	82	40·69	106·84	±58·91	1·34	104·99 ± 5·92	±53·64	71·63	±29·53
♀ Controls	75	36·71	69·71	±31·00	0·75	71·63 ± 3·41	±29·53		
All Controls	157							71·63 ± 2·35	±29·44

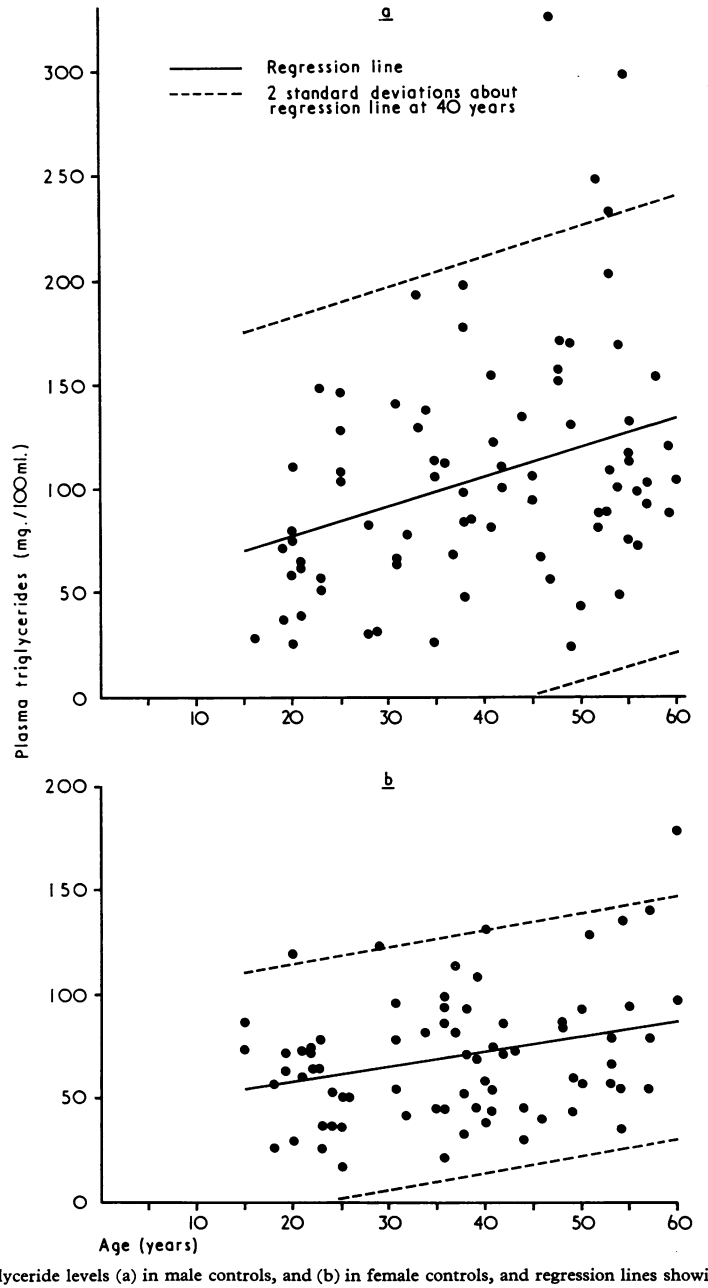

FIG. 2. Plasma triglyceride levels (a) in male controls, and (b) in female controls, and regression lines showing variation with age.

which triglycerides were not recorded, but may also be because very high triglyceride levels associated with xanthomata are seldom found without associated hypercholesterolaemia.

Cholesterol and triglyceride levels of index patients with their mean age and corrected levels are shown in Tables IV and V.

(c) First Degree Relatives of Index Patients

Cholesterol. The distribution of corrected cholesterol levels for first degree relatives of index patients with familial hypercholesterolaemic xanthomatosis (Group A) and index patients with hypercholesterolaemic xanthomatosis with hypertriglyceridaemia (Group B) were each compared

TABLE III

DISTRIBUTION OF LIPID LEVELS IN PATIENTS AND FIRST DEGREE RELATIVES

Plasma Lipid Levels (mg./100 ml.)	Cholesterol					Triglycerides				
	Controls	Group A		Group B		Controls	Group A		Group B	
		I.Ps.	Rels.	I.Ps.	Rels.		I.Ps.	Rels.	I.Ps.	Rels.
0–24						4	1			
25						38	5	15		1
50						53	5	16		9
75						39	9	15		6
100						15	9	9		7
125	2				1	5	1	1	1	1
150	6				2	2		1		3
175	25		8		4	1	1		2	
200	31		7		9			1		1
225	22		6		4				2	
250	17		5		4				1	1
275	6		4		2			1	1	2
300	4	1	4	3	1				2	
325	3	3	5	1	1				2	
350		6	6	3	1					
375		1	10	2	2					
400		3	6	3					1	
425		5	3	2	1				1	
450		9	3	3						
500		2	3	3					1	
550				1	1				1	
600		1	2							
700										
800		1	1						2	
900									1	
1000										
2000+									1	

separately with the distribution of the controls (Fig. 3a and 4a). Each was inspected for bimodality. In 73 first degree relatives of the Group A patients there is a strong suggestion of bimodality with approximately equal numbers in the two distributions, or even trimodality to include the 3 outliers with levels above 600 mg./100 ml. in the distribution of cholesterol levels. In the 33 first degree relatives of Group B patients there is also a suggestion of biomodality, but here the numbers in the deviant group are clearly smaller.

There does not seem to be any satisfactory formal test for bimodality (C. A. B. Smith, personal communication 1967); the nearest approach is from Haldane (1952). The best point of overlap of the two distributions in the relations of Group A patients appears to be in the region of 310 mg./100 ml.; it so happens that this is also close to the point (310·98) 2

TABLE IV

PLASMA CHOLESTEROL LEVELS (mg./100 ml.) IN INDEX PATIENTS AND FIRST DEGREE RELATIVES

	No.	Mean	Mean and S.E. Corrected to ♀ 40	Standard Deviation	Difference from Controls
Group A index patients	32	473·33	442·71		
Group B index patients	21	456·48	421·0		
First degree relatives Group A patients	73		340·80 ± 22·71	± 194·18	$t = 2·80$ $p < ·001$
First degree relatives Group B patients	33		258·04 ± 16·37	± 94·13	$t = 2·80$ $p < ·01 > ·001$

TABLE V

PLASMA TRIGLYCERIDE LEVELS (mg./100 ml.) IN INDEX PATIENTS AND FIRST DEGREE RELATIVES

	No.	Mean Age (yr.)	Mean	Mean and S.E. Corrected to ♀ 40	Standard Deviation	Difference from Controls
Group A index patients	27	49·96	103·04	81·22		
Group B index patients	19	46·79	823·32	517·60		
First degree relatives Group A patients	59			80·79 ± 5·5	± 42·40	$t = 1·79$ not sig.
First degree relatives Group B patients	31			115·97 ± 12·16	± 67·49	$t = 5·09$ $p < 0·001$

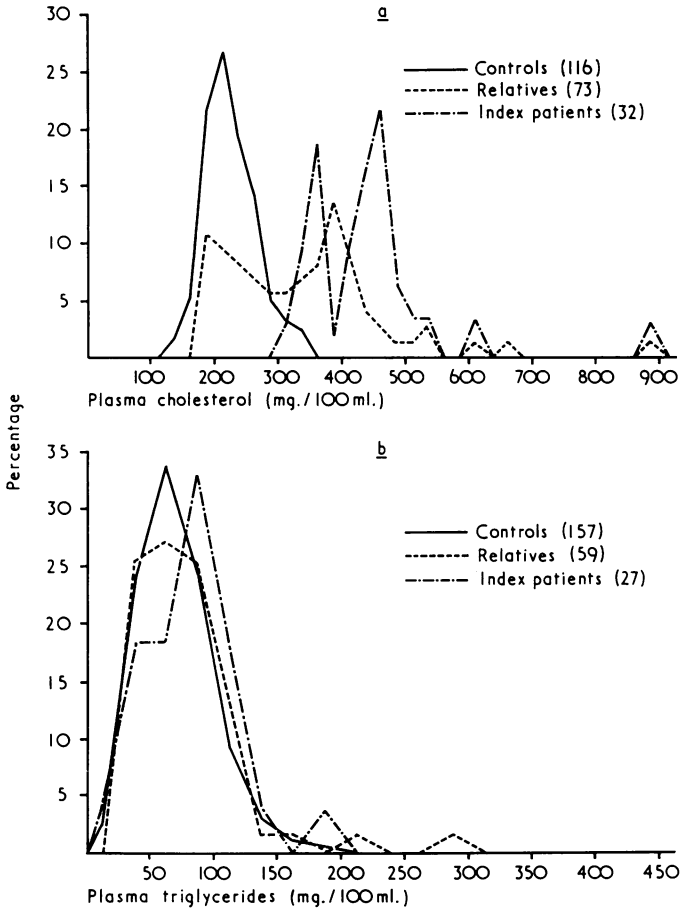

FIG. 3. Distribution of (a) corrected plasma cholesterol and (b) corrected plasma triglycerides, in controls and first degree relatives of patients with familial hypercholesterolaemic xanthomatosis.

standard deviations above the corrected mean for the control series.

The mean corrected cholesterol level in the relatives of patients from Group A was 340·80 (±22·71) mg./100 ml., 114·74 mg. above that of the controls. The difference is significant ($t=7·64$; $p<0·001$). The mean corrected cholesterol level in the relatives of patients from Group B was 258·04 (±16·37) mg./100 ml., 31·98 mg. above that of the controls. The difference is significant ($t=2·80$; $p<0·01>0·001$).

After consideration of the distribution of corrected cholesterol levels in patients and controls a corrected cholesterol level of 310·98 mg. or 2 standard deviations above the mean for controls was selected, admittedly somewhat arbitrarily, as the upper limit to distinguish normal from hypercholesterolaemic individuals.

Triglycerides. The distribution of corrected triglyceride levels for first degree relatives of index patients with familial hypercholesterolaemic xanthomatosis (Group A), and index patients with hypercholesterolaemic xanthomatosis associated with hypertriglyceridaemia (Group B) were each compared separately with the distribution in the controls (Fig. 3b and 4b). Each was inspected for bimodality. There is no real evidence of disturbance of triglyceride levels among the 59 first degree relatives of patients from Group A; there are in fact just two values outside the range of the controls. The distribution curve of triglyceride levels among the 31 first degree relatives of patients from Group B is suggestive of an over-all shift to the right with perhaps bimodality.

The mean corrected triglyceride levels in the relatives of patients from Group A was 80·79±5·5

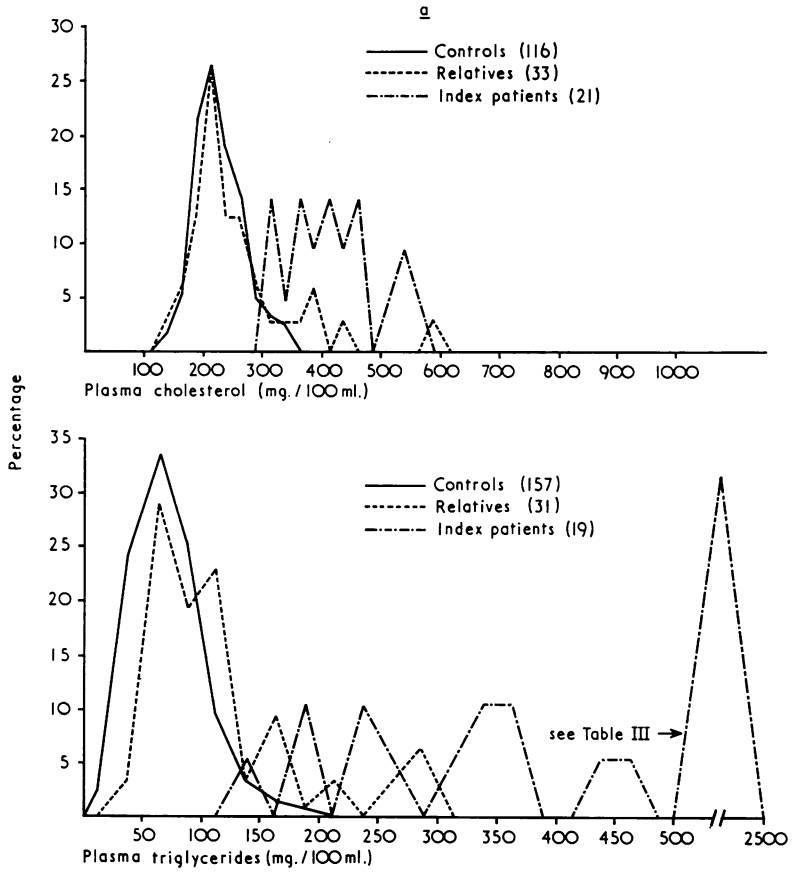

FIG. 4. Distribution of (a) corrected plasma cholesterol and (b) corrected plasma triglycerides in controls and first degree relatives of patients with familial hypercholesterolaemic xanthomatosis with hypertriglyceridaemia.

mg./100 ml., the corrected control mean being 71·63 ± 3·26 mg./100 ml. The difference between these means is not significant (t = 1·79).

The mean corrected triglyceride level of the first degree relatives of patients from Group B was 115 ± 12·16 mg./100 ml., which is 44·34 mg./100 ml. greater than the controls; the difference is highly significant (t = 5·09; p < 0·001).

After consideration of the distribution of corrected triglyceride levels in patients and controls, a corrected triglyceride level of 130·51 mg./100 ml. or 2 standard deviations above the corrected mean for controls was again rather arbitrarily selected as the upper limit to distinguish normal from hypertriglyceridaemic individuals.

II: Patterns of Inheritance

Classification of Relatives of Index Patients as 'Affected' or 'Unaffected'. In examining the patterns within families, the criteria used to classify relatives of index patients of Group A as 'affected' were: the presence of xanthomata, including xanthelasma palpebrarum and/or a corrected cholesterol level greater than 310·98 mg./100 ml. All other relatives were classified as 'unaffected'.

The criteria for classifying relatives of index patients of Group B as affected were: the presence of xanthomata including xanthelasma palpebrarum and/or a corrected cholesterol level greater than 310·98 mg./100 ml. in association with a corrected triglyceride level greater than 130·51 mg./100 ml. All other relatives were classified as 'unaffected'.

Living relatives. The index patients had 226 living first degree relatives, and of these 111 were examined. The distribution of 'affected' and 'unaffected' living relatives of the two groups of index patients are shown in Tables VI, VII, and VIII.

TABLE VI

FAMILY PATTERNS IN LIVING FIRST DEGREE RELATIVES OF PATIENTS WITH FAMILIAL HYPERCHOLESTEROLAEMIC XANTHOMATOSIS

	Total	Alive	Examined	Affected	Normal
Male index patients (16)					
Fathers	16	4	1	0	1
Brothers	26	20	9	3	6
Sons	10	10	6	3	3
Total male relatives	52	34	16	6	10
Mothers	16	5	3	0	3
Sisters	20	17	6	3	3
Daughters	13	13	10	6	4
Total female relatives	49	35	19	9	10
Total	101	69	35	15	20
Female index patients (16)					
Fathers	14	3	3	1	2
Brothers	29	18	6	6	0
Sons	6	6	4	1	3
Total male relatives	49	27	13	8	5
Mothers	16	3	2	2	0
Sisters	23	18	10	8	2
Daughters	8	8	7	4	3
Total female relatives	47	29	19	14	5
Total	96	56	32	22	10
Grand total	197	125	67	37	30

TABLE VII

FAMILY PATTERNS IN LIVING FIRST DEGREE RELATIVES OF PATIENTS WITH FAMILIAL HYPERCHOLESTEROLAEMIC XANTHOMATOSIS WITH HYPERTRIGLYCERIDAEMIA

	No.	Alive	Examined	Affected	Not Affected
Male patients (17)					
Fathers	16	7	4	2	2
Brothers	15	15	4	1	3
Sons	5	5	5	0	5
Total male relatives	36	27	13	3	10
Mothers	16	10	4	1	3
Sisters	12	12	4	0	4
Daughters	11	11	6	0	6
Total female relatives	39	33	14	1	13
Total	75	60	27	4	23
Female patients (4)					
Fathers	3	0	0	0	0
Brothers	6	1	0	0	0
Sons	1	1	0	0	0
Total male relatives	10	2	0	0	0
Mothers	4	0	0	0	0
Sisters	12	9	3	1	2
Daughters	5	5	1	0	1
Total female relatives	21	14	4	1	3
Total	31	16	4	1	3
Grand total	106	76	31	5	26

Dead relatives. The index patients had 102 first degree relatives who had died in adult life, and for these 99 death certificates were obtained and classified (see Part I). Hospital records were consulted where possible, in order to obtain additional information about these relatives. Information about dead first degree relatives of index patients in the two groups is shown in Tables IX and X.

Familial Hypercholesterolaemic Xanthomatosis (Group A). Sixteen male patients from Group A had 101 first degree relatives of whom 69 were living. Thirty-five of these were examined and 15 were classed as 'affected' by the criteria given above. Sixteen female index patients from Group A had 96 first degree relatives of whom 56 were alive. Thirty-two of these were investigated and 22 were classed as 'affected', including 1 sister (IA14 Si 1916) who had xanthomata, with a corrected cholesterol level of 289 mg./100 ml. Thus, amongst the 67 living first degree relatives investigated, 37 were considered to be 'affected' and 30 were 'unaffected'.

In several families (Appendix I*A5, 9, 11, 15, and I*B7, 13, and 14), it was also possible to examine the children of affected sibs (Table VIII). Four affected brothers and 3 affected sisters had 13 children. Out of 11 children examined, 4 had

TABLE VIII

CHILDREN OF AFFECTED FIRST DEGREE RELATIVES OF PATIENTS WITH FAMILIAL HYPERCHOLESTEROLAEMIC XANTHOMATOSIS

	Total Number	Number Alive	Number Examined	Number Affected	Number Normal
Children of affected brothers of index patients (4)					
Males	2	2	2	0	2
Females	5	5	5	3	2
Total	7	7	7	3	4
Children of affected sisters of index patients (3)					
Females	6	6	4	1	3
Children of affected daughter of index patient					
Male	1	1	1	1	0
Female	1	1	1	0	1
Total	2	2	2	1	1
Grand total	15	15	13	5	8

TABLE IX

DEAD FIRST DEGREE RELATIVES OF PATIENTS WITH FAMILIAL HYPERCHOLESTEROLAEMIC XANTHOMATOSIS

	No.	Dead	Early Death from I H D	Known Hyperlipidaemic Xanthomatosis	Unrelated
Male patients					
Fathers	16	12	0	2	10
Brothers	26	6	2	2	2
Sons	10	—	—	—	—
Total male relatives	52	18	2	4	12
Mothers	16	11	0	2	9
Sisters	20	3	0	1	2
Daughters	13	—	—	—	—
Total female relatives	49	14	0	3	11
Total	101	32	2	7	23
Female patients					
Fathers	14	11	1	1	9
Brothers	29	11	3	4	4
Sons	6	—	—	—	—
Total male relatives	49	22	4	5	13
Mothers	16	13	4	2	7
Sisters	23	5	1	2	2
Daughters	8	—	—	—	—
Total female relatives	47	18	5	4	9
Total	96	40	9	9	22
Grand total	197	72	11	16	45

TABLE X

DEAD FIRST DEGREE RELATIVES OF PATIENTS WITH FAMILIAL HYPERCHOLESTEROLAEMIC XANTHOMATOSIS WITH HYPERTRIGLYCERIDAEMIA

	Total	Dead	Early Death from I H D (R.G. 420·1)	Known Hyperlipidaemic Xanthomatosis	Unrelated
Male patients (17)					
Fathers	16	9	0	1	8
Brothers	15	0	0	0	0
Sons	5	0	0	0	0
Total male relatives	36	9	0	1	8
Mothers	16	6	2	0	4
Sisters	12	0	0	0	0
Daughters	11	0	0	0	0
Total female relatives	39	6	2	0	4
Total	75	15	2	1	12
Female patients (4)					
Fathers	3	3	0	0	3
Brothers	6	5	0	0	5
Sons	1	0	0	0	0
Total male relatives	10	8	0	0	8
Mothers	4	4	0	0	4
Sisters	12	3	0	1	2
Daughters	5	0	0	0	0
Total female relatives	21	7	0	1	6
Total	31	15	0	1	14
Grand total	106	30	2	2	26

hypercholesterolaemia and one also exhibited xanthomatosis, while 7 were unaffected. In one family (Appendix I*A6) an affected daughter of a male index patient had two children, one of whom was 'affected'. None of the 13 children of unaffected sibs of index patients was 'affected' and none of the 5 children of these children was affected.

From a total of 197 first degree relatives of Group A index patients who reached adult life, 72 had died, see Table IX. Examination of the causes of death from death certificates and hospital records of these relatives showed that 7 female and 9 male relatives were known to have had hyperlipidaemic xanthomatosis. In addition, 5 female relatives had died before the age of 55, each with a death certificate classified in the Registrar General's categories 94 or 420·1.

Familial Hypercholesterolaemic Xanthomatosis with Hypertriglyceridaemia (Group B). Seventeen male patients from Group B had 75 first degree relatives of whom 60 were alive (Table VII). Twenty-seven of these were examined and 4 were found to be 'affected'. Of these, 1 father (Appendix II A9) had xanthelasma palpebrarum without hyperlipidaemia; his corrected cholesterol level was 293·66 mg./100 ml., and his corrected triglyceride level was 63·49 mg./100 ml. The 4 female patients had 31 first degree relatives; 4 were examined of whom 1 was 'affected' and 3 were 'unaffected'.

One affected brother (Appendix II* A12), whose wife had a corrected cholesterol level of 324 mg./100 ml. had one son who was examined but showed no sign of hypercholesterolaemia or hypertriglyceridaemia. None of the 9 children of normal sibs examined had hyperlipidaemia or xanthomata.

From a total of 106 first degree relatives of Group B index patients who reached adult life, 30 had died (see Table X). Hospital records confirmed that 2 had died with hyperlipidaemic xanthomatosis and ischaemic heart disease and, in addition, 2 female relatives had died before the age of 65, with death certificates classified in the Registrar General's categories 94 and 420·1.

Fat-induced Hypertriglyceridaemia (Group C). The families of two children with fat-induced hypertriglyceridaemia were examined (Pedigrees

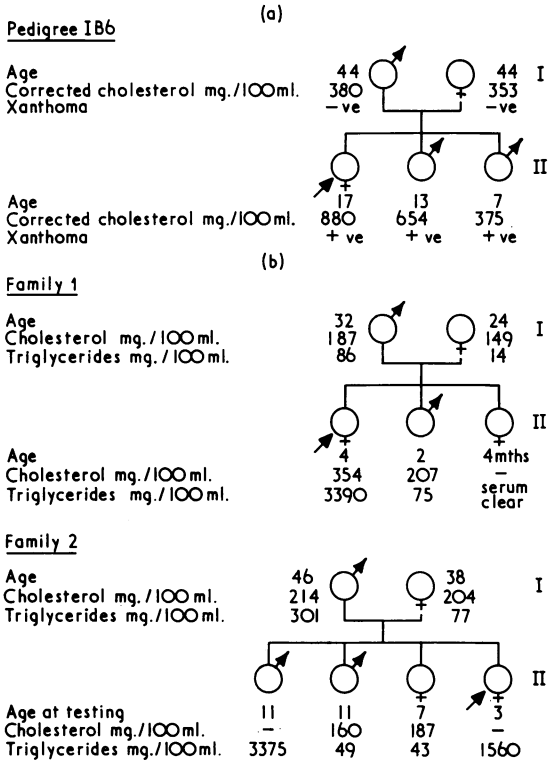

FIG. 5. (a) Pedigree of family of index patient with hypercholesterolaemic xanthomatosis. (b) Pedigrees of families of patients with fat-induced hypertriglyceridaemia.

Fig. 5, Families 1 and 2). Both index patients presented in infancy with 'bouts of colic' and eruptive xanthomatosis. Five living sibs of these families were examined and one was 'affected'. All four parents were studied and one mother (Family 1) had moderate hypertriglyceridaemia on one occasion, but on a second occasion the level was normal. The father in Family 2 had moderate hypertriglyceridaemia on both occasions on which he was tested.

Other Considerations.

Consanguinity. The parents of two unrelated patients were first cousins (see Appendix I A9 and I B14). Both index patients had hypercholesterolaemic xanthomatosis.

Diabetes Mellitus. No patient with hypercholesterolaemic xanthomatosis had diabetes mellitus. Three male index patients (Appendix II A2, 3, and 15) developed diabetes after the diagnosis of hyperlipidaemic xanthomatosis had been made. By definition, no patient was included in the series who developed diabetes before hyperlipidaemic xanthomatosis was diagnosed. Two mothers (Appendix I A9 and 14), 1 father (Appendix I A12), and 1 sister (Appendix I B12) of patients with hypercholesterolaemic xanthomatosis were known to have diabetes mellitus. Two mothers (Appendix II A9 and 14) and 2 brothers (Appendix II A14 and 15) of index patients with hypercholesterolaemic xanthomatosis with hypertriglyceridaemia were known to have diabetes mellitus.

DISCUSSION

The difficulty in establishing the mode of inheritance in familial hyperlipidaemia has arisen from both the failure to discriminate between different types of hyperlipidaemia and from the difficulties of distinguishing 'affected' from 'unaffected' relatives in susceptible families.

The tentative selection of 2 standard deviations above the control means as the upper limit of normal to distinguish 'affected' from 'unaffected' relatives is supported by the findings that of 34 hypercholesterolaemic relatives of patients with hypercholesterolaemic xanthomatosis, 13 had xanthomata while only 1 normocholesterolaemic

relative had xanthomata (Appendix I A14 Si 1916). Among the relatives of index patients with hypercholesterolaemic xanthomatosis associated with hypertriglyceridaemia, 10 were found to be hyperlipidaemic, and of these 3 had xanthomata while 1 relative had xanthomata with lipid levels within 'normal' limits (Appendix II A9).

The findings of the cholesterol and triglyceride levels in the relatives of the patients in the three groups strongly suggests that the families in the three groups should be considered separately. Contrary to the suggestion by Adlersberg and Schaefer (1959), there is no real tendency for first degree relatives of patients in one group to have plasma lipid levels characteristic of any other group. Possible exceptions are seen in Group A families I B8 and I B13, where the index patients had hypercholesterolaemic xanthomatosis with no increase of triglyceride, while each had one relative with both cholesterol and triglycerides raised as well as a relative with hypercholesterolaemia alone. In family II A8, one daughter of a Group B male index patient had marked hypercholesterolaemia without hypertriglyceridaemia but the wife of this patient had a corrected cholesterol level of 308·5 mg./100 ml. (high but not abnormal by our criteria), and so might be responsible for her daughter's abnormality. In family II B4 (Group B), one relative had hypercholesterolaemia without hypertriglyceridaemia.

Genetics of Hypercholesterolaemic Xanthomatosis

The distribution of cholesterol levels in first degree relatives fits very well with the hypothesis that a single mutant gene is responsible for the hypercholesterolaemia. The distribution strongly suggests bimodality with approximately equal numbers of relatives affected and unaffected. The family patterns within families classing living relatives as 'affected' and 'unaffected' by cholesterol levels were entirely consistent with a dominant mutant gene effect except in family I A16 where both parents were alive and had normal lipid levels. The increased risk of death from ischaemic heart disease among first degree relatives is also compatible with this hypothesis (Part I, Slack and Nevin).

Our findings support the view expressed by Wilkinson *et al.* (1948), Piper and Orrild (1956), Epstein *et al.* (1959), Khachadurian (1964), and Harlan *et al.* (1966), that the heterozygotes for the mutant gene have hypercholesterolaemia, may develop xanthoma with increasing age, and often have early onset of ischaemic heart disease.

We found only 1 family, I B6, in which 2 affected individuals were probably homozygous for the mutant gene. The parents in the family had no xanthomata but both had raised plasma cholesterol levels. Two of the 3 children had very marked hypercholesterolaemia with extensive xanthomata in the 2nd decade while the third had only a moderate increase in cholesterol and had developed no xanthoma by 7 years of age, suggesting that he was a heterozygote like his parents. The probably homozygous sib constitutes one of the three extreme deviants on the cholesterol distribution. The pedigree of family I B6 is shown in Fig. 5.

There was no clear evidence of homozygosity in the 2 index patients or their 2 affected sibs born of first cousin marriages (I A9 and I B14).

Two other first degree relatives with very high levels are shown in Appendix III, I A14 and I B11. In family I A14, the sister born in 1910 had a corrected cholesterol level of 871·0 mg./100 ml., and in family I B11 the sister born in 1910 had a corrected cholesterol level of 615·0 mg./100 ml. There is nothing to suggest homozygosity in these two cases though it cannot be excluded. In family I A14, the father was still alive at 84 and the onset of xanthomata in the sister with the high level of cholesterol was in middle life. In family I B11, the father lived to 85 and died of senile dementia. Xanthoma did not develop in the sister with very high cholesterol until the 5th decade.

One other relative, an only daughter of the brother of an index patient, I*B7, who was a second degree relative and does not therefore appear on the distribution chart, had a corrected cholesterol of 721 mg./100 ml. and onset of xanthoma in the second decade. Her father died from ischaemic heart disease at 44 years and had xanthoma but her mother had a normal cholesterol level (corrected cholesterol 185 mg./100 ml.) and no xanthomata.

Two patients developed xanthomata in the first decade of life. One child of an index patient, I B12, F, 1956, with a corrected cholesterol level 437·5 mg./100 ml. had xanthomata at 4 years, but these have since disappeared with treatment. Her cholesterol level lay near the mean of the cholesterol distribution for affected first degree relatives. Unfortunately, her father was not willing to be tested. The other, an index patient I B1, was recorded as having small xanthomata 'the size of a millet seed' at Great Ormond Street Children's Hospital at 8 years. At that time, her cholesterol level was recorded as 498 mg./100 ml. She is now 59 years and has a corrected cholesterol level of 427·20 mg./100 ml. and developed symptoms and electrocardiographic signs of ischaemic heart disease for the first time this year.

The indications are then that heterozygotes may overlap homozygotes both in the high range of cholesterol levels and in the early onset of xanthomatosis, but that the homozygotes are perhaps most readily distinguished by the early onset of extensive xanthomata.

Genetics of Hypercholesterolaemic Xanthomatosis Associated with Hypertriglyceridaemia

The distributions of corrected cholesterol and triglyceride levels in the first degree relatives of the index patients of Group B are shown in Table III and Fig. 4a and b. Both family patterns and the lipid distributions among the relatives of Group B differ considerably from the family patterns and the lipid distributions among the relatives in Group A. Inheritance is clearly not compatible with determination in all cases by a single dominant mutant gene. If there is bimodality in the distribution of either triglyceride or cholesterol levels among the relatives of Group B, the proportion of relatives in the deviant distribution is less than half. The family patterns within families classifying living relatives as 'affected' or 'unaffected' by the presence of abnormal triglyceride and cholesterol levels or xanthomata is equally incompatible with inheritance through a single dominant gene effect, since only 5 out of 31 are classified as 'affected'. The risks of early death from ischaemic heart disease in first degree relatives of Group B patients differ considerably from those in Group A (see Part I), though whether this is due to a fundamental difference in the lipid disturbance or to a different pattern of inheritance in the 2 groups is not yet clear.

When the cholesterol and triglyceride levels of the relatives of patients in Group B are considered separately, the majority of relatives have a cholesterol distribution very similar to that in the controls, but there is a significant minority (7 in 33) with a corrected cholesterol level greater than 310 mg./100 ml. The majority of relatives appear to have a triglyceride distribution shifted to the right of the majority of controls with, in addition, a significant minority (7 in 31) with substantially higher levels. The shift of the main group to the right is probably a real one since even if the 7 relatives in the deviant group are removed, the mean corrected triglyceride level is $85{\cdot}45 \pm 4{\cdot}9$ mg./100 ml., which is significantly higher than that of the controls, $t = 2{\cdot}163$ $p < 0{\cdot}05$.

The lipid levels in the deviant individuals either for cholesterol or triglycerides are shown in Table XI.

It will be seen that 4 of these relatives had high levels for both cholesterol and triglycerides; of these, 2 had xanthomata, 4 had high triglycerides alone, and 2 had raised cholesterol alone, while 1 has raised cholesterol but no triglyceride level is available. Only the first 4 relatives mentioned, together with 1 other with xanthomata but normal lipid levels, have been classed as clearly exhibiting the same disorder as the index patient. The daughter (Appendix II A8), with raised cholesterol alone, has been mentioned above.

There is no simple interpretation of the lipid distributions or of the family patterns in this group. The most economical explanation perhaps would be that in about half the index patients genetic factors play little part in determining the hyperlipidaemia whereas in the other half, a mutant gene (not necessarily the same in each family) is concerned. A better hypothesis perhaps is that most of the index patients in Group B represent the extreme right hand end of the skew in triglyceride levels in the normal population, having developed xanthomata by virtue of the duration and intensity of their hyperlipidaemia. Their first degree relatives then show a similar but less marked shift to the right. It is perhaps still necessary to assume that the outliers in the relatives' distribution represent a rare abnormal group determined by single dominant genes which have produced the abnormality in the index patient. This hypothesis has been suggested by Harlan *et al.* (1966) in their classification of hyperlipidaemia.

Whatever the explanation for the lack of frankly abnormal first degree relatives of the Group B index patients, their numerical deficiency may well account for some of the lack of risk of early death from ischaemic heart disease among these relatives compared with the first degree relatives of index patients in Group A. (Part I, Slack and Nevin.) The future

TABLE XI

DETAILS OF FIRST DEGREE RELATIVES OF GROUP B INDEX PATIENTS WITH 'HYPERLIPIDAEMIA'

Appendix No.	Relative	Corrected Cholesterol (mg./100 ml.)	Corrected Triglyceride (mg./100 ml.)
II A4	Fa.	313·91	295·26
II A7	Mo.	338	209
II A7	So.	216·21	143·47
II A8	Fa.	211·13	288·84
II A8	Si.	240	253
II A8	Da.	597·5	73·75
II A12	Br.‡	363·04	172·71
II B2	Si.	442	—
II B3	Si.‡	393	151
II B3	Si.	386	123

‡ Indicates presence of xanthomata.

health of the abnormal relatives of patients in Group B must be followed closely to assess their risks of early ischaemic heart disease. There is some indication that even the affected relatives may not run a greatly increased risk of early death from ischaemic heart disease, since only 7 out of 21 index patients have clinical signs of ischaemic heart disease, while 20 out of 29 index patients in Group A have already developed ischaemic heart disease and 3 of the 20 have already died of the condition. There is, however, no real difference in mean cholesterol levels in the index patients of the 2 groups.

The index patients must be further divided by more detailed metabolic studies to eliminate as far as possible the heterogeneity of the group. Among this group, a few families contribute a large proportion of hyperlipidaemic relatives (II A7 and 8, II B3) and more detailed investigation of their lipid abnormalities may reveal more clearly specific inherited abnormalities that are not present in other index patients.

Genetics of Fat-induced Hypertriglyceridaemia

The families of the two index patients with fat-induced hypertriglyceridaemia support previous suggestions that the condition is recessively inherited with occasional minimal manifestations of hypertriglyceridaemia in the heterozygote.

SUMMARY

Fifty-five index patients with essential hyperlipidaemic xanthomatosis have been divided by their cholesterol and triglyceride levels into 3 groups. *Group A:* pure hypercholesterolaemic xanthomatosis (32); *Group B:* mixed hypercholesterolaemic xanthomatosis associated with hypertriglyceridaemia (21); *Group C:* fat-induced hypertriglyceridaemia (2).

The mode of inheritance of the lipid abnormalities has been investigated among the relatives of the patients by: (a) investigation of cholesterol and triglyceride levels and the presence of xanthomata among the living relatives of patients; (b) causes of death of relatives.

Relatives of index patients with hypercholesterolaemic xanthomatosis show a bimodal distribution of age and sex adjusted cholesterol levels which differs significantly from the distribution among controls. They show little difference from controls in corrected triglyceride levels. There is an increased risk of early death from ischaemic heart disease among these relatives. Inheritance of the lipid abnormality appears to be by a single autosomal dominant gene. Expression in the heterozygote appears to be an increase in cholesterol with or without the appearance of xanthomata in middle life and is associated with an increased risk of early death from ischaemic heart disease. Expression in the rare homozygotes encountered seems to overlap the heterozygote in raised cholesterol levels, but may be characterized by more extensive xanthomata in childhood.

Relatives of index patients with mixed hypercholesterolaemic xanthomatosis associated with hypertriglyceridaemia show no clear bimodal distribution of either cholesterol or triglyceride levels. A few relatives show an increase in cholesterol and/or triglycerides and the remainder demonstrate a slight shift to the right in triglyceride levels compared with the control series. Little increased risk of early death from ischaemic heart disease has been demonstrated among the dead relatives. Inheritance in this almost certainly heterogeneous group may be multifactorial with a few distinct autosomal dominant genes playing a part in a minority.

The families of the two index patients with fat-induced hypertriglyceridaemia confirm previous findings that the condition is inherited as an autosomal recessive characteristic with occasional moderate expression in the heterozygous carrier.

We thank Dr. C. O. Carter for his help throughout this study, and Dr. J. C. Leonard for introducing us to the families he reported in 1956. We are grateful to Dr. E. Jepson, Dr. W. Somerville, Dr. P. Borrie, Dr. E. L. McDonald, Dr. W. Brigdon, Dr. V. Wynne, Prof. O. Wolff, and Dr. K. Hugh Jones for allowing us to see their patients, and to the patients and record officers who helped us trace the relatives.

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APPENDICES

Male and female first degree relatives are shown M F; male and female half-sibs m f; maternal and paternal indicated by mat and pat; italic shows relative affected with ischaemic heart disease; * indicates diabetes; | indicates hyperlipidaemia; † indicates xanthomata present; ‡ indicates hyperlipidaemic xanthomatosis; ND indicates death not documented; IE insufficient evidence for use in tables; W indicates war death; RG's category following date of death shows classification of death certificate if death was due to coronary heart disease; Mx indicates male died at x years; [ ] indicate twins; sb indicates stillbirth; NE living relative not examined.

Appendix I

Details of families of index patients with familial hypercholesterolaemic xanthomatosis

Family No.	Propositi Year of Birth	Spouse	Parents		Sibs and Half-sibs	Children
			Mothers	Fathers		
(A)—MALE PATIENTS						
1	*1901*	—	*1866–1952* *420·1*	*1868–1929* *89*		
2	1923	1926	1894NE	*1891NE*		M 1952NE; F 1954
3	1903	IE	1873–1950 451	1869–1956		
4	1928	1933NE	1900	*1900–1966‡*	M 1936‡	F 1965|
5	*1920*	1924	*1886*	*1888–1962* *420·1*	M 1922NE; *F 1924‡*	F 1949|; M 1954|
6	*1909*	1909	1877–1945	1874–1955	M 1901NE: *M 1904–1956* *420·1*	F 1934|; F 1939|
7	1909	1909	1879–1918	1870–1956	F 1913; M 1915	M 1939; M 1944; F 1946
8	1914	—	1879–1963	1863–1947	M 1906–1962; M 1907; F 1917NE	
9	*1915–1966*	1913	1875–1916* (1st cousins)	1873–1946	M 1899; F 1901; *F 1907–1967‡* *420·1*	F 1939|; M 1942; *M 1947|*
10	*1920*	1929	1884NE	*1882–1948†* *94a*	M 1911NE; M 1915NE; F 1926NE	F 1953; F 1956|
11	*1924–1963* *420·1*	—	1892–1945	1892–1948	*M 1912–1952*; F 1918–1964; *420·1* *M 1934–1965|* *420·1*	
12	*1918*	IE	*1884–1953†* *420·1*	*1883–1960** *420·1*	M 1907; (F 3); F 1915NE; F 1919NE	M 1946NE; M 1948NE
13	1921	1916NE	1881–1944	1879–1927	M 1906NE; (M 10); F 1908NE; [M 1921]NE; M 1922NE	F 1957NE
14	1924	—	1886–1946*	1888NE	F 1910‡; F 1912; F 1916†; M 1917; M 1920	
15	*1926–1957* *420·1*	1925NE	*1899–1957†* *420·1*	1899NE	*M 1923–1965‡*; F 1926NE; M 1930NE; *420·1* M 1932NE; M 1934‡; M 1940‡	F 1950NE; M 1951NE; M 1953|; F 1955NE
16	*1917*	1920	1892	1884	F 1913–1941W; F 1914NE; M 1914–1946; F 1923NE; F 1928NE; F 1930NE; M 1932NE; M 1934NE; F 1936NE	F 1946

Continued overleaf

Appendix I *continued*

Family No.	Propositi Year of Birth	Spouse	Parents		Sibs and Half-sibs	Children
			Mothers	Fathers		
(B)—FEMALE PATIENTS						
1	*1915*	—	*1891–1963* *420·1*	1879–1928		
2	*1910*	1913	*1881–1933* *94a*	IE		M 1942|; F 1944‡
3	*1915*	1911	*1892–1948‡* *94a*	*1889*		F 1944; F 1949
4	*1920*	1910	*1897–1965* *420·1*	1899–1963		F 1946|; M 1951
5	*1909*	IE	*1884–1948* *94a*	1883–1914	Mat.f 1920NE	M 1934NE
6	1949	—	1922|	1922|	M 1953‡; M 1959|	
7	1916	IE	1888NE	1885–1956‡ 451	*M 1912–1956‡*; *M 1920‡* *420·1*	F 1943‡; M 1946
8	*1935*	IE	*1909‡*	1907	F 1928; [M 1930‡; F 1930]	
9	1904	IE	1877–1962	*1872–1933* *94a*	M 1902NE; *M 1909–1944*; F 1911|; *M 1916–1956‡* *420·1*	F 1933NE
10	*1904*	IE	1882–1962	IE	*F 1906‡*; Mat.m 1910NE; f 1912NE; m 1914NE; m 1916NE	
11	*1908*	IE	*1875–1925* 89	1875–1960	*M 1897–1955*; M 1898–1930; *420·1* F 1899–1950 F *1903‡*; F *1903‡*	
12	*1916*	1911NE	1874–1916	1866–1939	M 1901NE; *F 1901–1959**; *420·1* M 1903NE *M 1908–1951*; F *1909‡*; *420·1* *M 1916–1951†NE* *420·1*	F 1947; F 1956‡
13	*1909*	1906	*1878–1946* *94a*	1882–1935	*M 1901–1962*; F 1903|; F 1915|; *420·1* *M 1906–1957*; (F 6); [M 0; F 5] *420·1*	(F 14); M 1946
14	*1912*	—	1877–1959 (1st cousins)	1874–1950	(M 18); F 1902NE; F 1904NE; F 1906NE; M 1910NE; M 1916NE; F 1917–1947; F 1919NE; *M 1920–1962‡* *420·1*	
15	1903	—	1873–1949	1870–1945	F 1896NE; M 1897–1948; *M 1899*|; 421·1 M 1902NE; M 1905NE; F *1906–1952*|; *420·1* *F 1907–1954*|; F 1908|; M 1912| *420·1*	
16	*1909*	IE	1887–1960	1885–1954	(M 6); M 1912NE; M 1914NE; [M 1916NE; M 1916NE]; F 1920NE; F 1923NE; M 1925NE; F 1929NE	M 1938NE

Appendix I*

Details known of families of sibs and children of index patients with familial hypercholesterolaemic xanthomatosis

Family No.	Sibs	Sibs' Spouses	Children	Children's Spouses	Children's Children
(A)—MALE PATIENTS					
5	*F 1924‡*	M 1924	F 1950; F 1952|		
6			F 1934| (child of index patient)	M 1932	M 1957|; F 1959
7	M 1915	F 1918	M 1952		
9	M 1899	IE	M 1928		
	F 1901	M 1898–1963	M 1922 F 1924 M 1928	F 1925 F 1930	F 1947; M 1952; F 1954 M 1959; M 1962; F 1964NE
	F 1907–1967‡ *420·1*	IE	F 1939NE; F 1934		
11	F 1918–1964	M 1912	M 1946		
	M 1934–1965| *420·1*	IE	F 1953; F 1958		
15	M 1934‡	F 1944	M 1965; F 1966|		

Continued opposite

Appendix I* *continued*

Family No.	Sibs	Sibs' Spouses	Children	Children's Spouses	Children's Children
(B)—FEMALE PATIENTS					
7	*M 1912–1956‡ 420·1*	F 1918	F 1942‡		
8	F 1928 [F 1930]	IE M 1930	F 1950; M 1953 F 1949; F 1951; M 1955; M 1959; F 1962		
13	F 1915|	M 1914	F 1943NE; F 1950		
14	*M1920–1962‡ 420·1*	IE	F 1944; M 1950		

Appendix II

Details of families of index patients with hypercholesterolaemic xanthomatosis and hypertriglyceridaemia

Family No.	Propositi Year of Birth	Spouse	Parents		Sibs and Half-sibs	Children
			Mothers	Fathers		
(A)—MALE PATIENTS						
1	*1913*	1916NE	1872–1963	1875–1947		F 1953NE
2	*1899**	—	*1876–1939 94ND*	1860–1918ND		
3	1920	1918|	1898NE	*1895*		M 1946; F 1948
4	*1943*	—	1912	*1903*|		
5	1928	1935*NE	1890NE	1900NE	F 1926NE	(M sb)
6	1936	IE	1908NE	*1899–1960 420·1*	M 1934NE	F 1965NE
7	1915	1915	1890|	1889–1961 421·1	M 1911	M 1948|
8	1929	1937	1905	*1907*|	F 1930|	F 1958|; M 1960
9	1934	1936NE	*1904–1963* 420·1*	1903†	[F 1932|; F 1932]	
10	1929	1935	1900	1901–1964	M 1926; [F 1929]	F 1958; F 1963
11	1909	1916	1876–1947	1875–1919	F 1903†NE; F 1906NE	F 1944
12	1908*	1910NE	1887–1958	1887–1962†	M 1916‡; M 1924NE	
13	1922	IE	1888NE	1888NE	F 1910NE; M 1929NE	
14	1923	1926	1899*NE	1897–1927	M 1920†*NE; F 1922NE; M 1926NE	F 1949; M 1957; F 1965NE
15	1923*	—	1890–1952	1889NE	M 1915NE; M 1917*NE; F 1920NE; F 1931NE	
16	1931	IE	1900NE	1899–1958	M 1929NE; M 1933NE; F 1935NE; M 1936NE; M 1939NE	M 1955; F 1957NE; F 1966NE
17	1929	1930NE	IE	IE	M 1925	
(B)—FEMALE PATIENTS						
1	*1899*	1891	1865–1943	1866–1950	F 1896; M 1898–1962	F 1925NE; F 1927; (M 15); (F 18)
2	*1895*	—	1863–1924	1860–1929	M 1894–1956; F 1898–1958; F 1899–1964‡; M 1902–1958	
3	*1908*	1908NE	1870–1935	1875–1936	F 1901NE; F 1903NE; F 1905NE; F 1907NE; F 1910‡; M 1913NE	M 1928NE; F 1930NE; F 1932NE
4	*1902*	IE	*1869–1942 94a*	IE	*M 1899–1955*; F 1892–1950; *420·1* M 1894–1916W; F 1896NE; F 1898|; F 1900NE	F 1933NE

Appendix II*

Details of families of sibs of index patients with hypercholesterolaemic xanthomatosis associated with hypertriglyceridaemia

Family No.	Sibs	Sibs' Spouses	Offspring
(A)—MALE PATIENTS			
7	M 1911	IE	F 1941; M 1949NE
9	[F 1932	M 1932	F 1959; F 1961
	F 1932]	IE	M 1955
10	[F 1929]	IE	F 1953; F 1957
12	M 1916‡	F 1918|	M 1946
17	M 1925	F 1924	M 1956
(B)—FEMALE PATIENTS			
1	M 1898–1962	F 1915	F 1940; F 1944

Appendix III

IP indicates Index patient; other relatives are indicated as follows: Wf: wife; Hd: husband; Si: sister; Dau: daughter; Mo: mother; Fa: father; Br: brother. Information obtained from hospital records in brackets.

Details of families of male patients with familial hypercholesterolaemic xanthomatosis

Appendix	Family No.	Identity	Date of Birth	Age Tested (yr.)	Cholesterol (mg./100 ml.)	Triglycerides (mg./100 ml.)
IA	1	IP	1901	59	(485)	(clear serum)
IA	2	IP	1923	43	460	43
,,	,,	Wf	1926	40	153	57
,,	,,	Dau	1954	12	225	37
IA	3	IP	1903	61	400	58
IA	4	IP	1928	38	448	178
,,	,,	Mo	1900	66	314	86
,,	,,	Fa	1900	60	(440)	—
,,	,,	Br	1936	30	368	158
,,	,,	Dau	1965	9/12	284	—
IA	5	IP	1920	46	517	98
,,	,,	Wf	1924	36	288	94
,,	,,	Mo	1886	80	218	55
,,	,,	Si	1924	42	532	94
,,	,,	Dau	1949	17	288	85
,,	,,	Son	1954	12	415	69
I*A	5	Si hd	1924	42	251	144
,,	,,	Si's dau	1950	16	269	64
,,	,,	Si's dau	1952	14	344	55
IA	6	IP	1909	57	520	122
,,	,,	Wf	1909	57	189	54
,,	,,	Dau	1934	32	380	61
,,	,,	Dau	1939	27	394	71
I*A	6	Dau's hd	1932	34	158	64
,,	,,	Dau's son	1957	9	375	62
,,	,,	Dau's dau	1959	7	248	58
IA	7	IP	1909	57	350	135
,,	,,	Wf	1909	57	229	140
,,	,,	Si	1913	53	300	103
,,	,,	Br	1915	51	242	75
,,	,,	Son	1939	27	210	119
,,	,,	Son	1944	22	243	71
,,	,,	Dau	1946	20	231	74
I*A	7	Br wf	1918	48	221	64
,,	,,	Br son	1952	14	173	36
IA	8	IP	1914	52	450	140
,,	,,	Br	1907	59	245	124
IA	9	IP	1915	51	(410)	—
,,	,,	Wf	1913	53	198	79
,,	,,	Br	1899	67	261	115
,,	,,	Si	1901	65	249	48
,,	,,	Si	1907	59	443	122
,,	,,	Dau	1939	27	325	105
,,	,,	Son	1942	24	274	115
,,	,,	Son	1947	19	412	87
I*A	9	Br's son	1928	38	187	89
,,	,,	Si's son	1922	44	287	85
,,	,,	Si's son's wf	1925	41	185	44
,,	,,	Si's son's dau	1947	19	196	50
,,	,,	Si's son's son	1952	16	209	62
,,	,,	Si's son's dau	1954	14	214	69
,,	,,	Si's dau	1924	42	234	40
,,	,,	Si's son	1928	38	279	152
,,	,,	Si's son's wf	1930	36	201	99
,,	,,	Si's son's son	1959	7	202	81
,,	,,	Si's son's son	1962	4	221	59
,,	,,	Si's dau	1934	32	222	55
IA	10	IP	1920	46	511	120
,,	,,	Wf	1929	37	201	113
,,	,,	Dau	1953	13	162	29
,,	,,	Dau	1956	10	414	44
IA	11	IP	1924	37	(562)	(clear plasma)
,,	,,	Br	1934	29	(430)	—
I*A	11	Si's hd	1912	54	187	49
,,	,,	Si's son	1946	20	156	83
,,	,,	Br's dau	1953	13	187	38
,,	,,	Br's dau	1958	8	144	36
IA	12	IP	1918	48	370	72
,,	,,	Br	1907	51	(310)	—
IA	13	IP	1921	45	492	54
IA	14	IP	1924	42	480	99
,,	,,	Si	1910	56	895	127
,,	,,	Si	1912	54	217	60
,,	,,	Si	1916	50	304	78
,,	,,	Br	1917	49	276	133
,,	,,	Br	1920	46	280	119
IA	15	IP	1926	30	(447)	—
,,	,,	Br	1923	37	(380)	—
,,	,,	Br	1934	32	519	125
,,	,,	Br	1940	26	541	159
,,	,,	Son	1953	4	380	—

(*Continued opposite*)

Appendix III *continued*

Appendix	Family No.	Identity	Date of Birth	Age Tested (yr.)	Cholesterol (mg./100 ml.)	Triglycerides (mg./100 ml.)
I*A	15	Br's wf	1944	22	195	64
,,	,,	Br's son	1965	20/12	166	—
,,	,,	Br's dau	1966	5/12	442	—
IA	16	IP	1917	49	410	115
,,	,,	Wf	1920	46	253	40
,,	,,	Mo	1892	74	269	132
,,	,,	Fa	1884	82	200	83
,,	,,	Dau	1946	20	208	71

Details of families of female patients with familial hypercholesterolaemic xanthomatosis

IB	1	IP	1915	51	630	129
IB	2	IP	1910	56	497	95
,,	,,	Hd	1913	53	275	109
,,	,,	Son	1942	24	355	209
,,	,,	Dau	1944	22	369	92
IB	3	IP	1915	51	545	115
,,	,,	Hd	1911	55	178	113
,,	,,	Fa	1889	77	210	91
,,	,,	Dau	1944	22	195	78
,,	,,	Dau	1949	17	156	152
IB	4	IP	1920	46	353	98
,,	,,	Hd	1910	56	302	99
,,	,,	Dau	1946	20	314	34
,,	,,	Son	1951	15	189	71
IB	5	IP	1909	57	384	37
IB	6	IP	1949	17	846	114
,,	,,	Mo	1922	44	359	47
,,	,,	Fa	1922	44	412	86
,,	,,	Bro	1953	13	703	41
,,	,,	Bro	1959	7	370	—
IB	7	IP	1916	50	476	190
,,	,,	Br	1920	36	518	—
,,	,,	Dau	1943	23	420	74
,,	,,	Son	1946	20	169	34
I*B	7	Br's dau	1942	24	697	147
,,	,,	Br's wf	1918	49	208	66
IB	8	IP	1935	31	359	99
,	,,	Mo	1909	57	462	215
,,	,,	Fa	1907	59	226	61
,,	,,	Si	1928	38	220	72
,,	,,	Br	1930	36	373	179
,,	,,	Si	1930	36	188	75
I*B	,,	Si's dau	1950	16	194	46
,,	,,	Si's son	1953	13	193	54
,,	,,	Si's hd	1930	36	234	43
,,	,,	Si's dau	1949	17	158	76
,,	,,	Si's dau	1951	15	165	50
,,	,,	Si's son	1955	11	165	91
,,	,,	Si's son	1959	7	158	—
,,	,,	Si's dau	1962	4	128	—
IB	9	IP	1904	62	(502)	53
,,	,,	Si	1911	55	370	55
,,	,,	Br	1916	40	(592)	—
IB	10	IP	1904	62	431	108
,,	,,	Si	1906	60	(428)	—
IB	11	IP	1908	58	490	71
,,	,,	Si	1903	60	430	22
,,	,,	Si	1903	61	645	—
IB	12	IP	1916	50	514	96
,,	,,	Si	1909	55	390	—
,,	,,	Dau	1947	19	166	19
,,	,,	Dau	1956	10	400	49
,,	13	IP	1909	57	513	122
,,	,,	Hd	1906	60	212	104
,,	,,	Si	1903	63	429	89
,,	,,	Si	1915	51	340	292
,,	,,	Son	1946	20	219	32
I*B	13	Si's hd	1914	52	249	252
,,	,,	Si's dau	1950	16	178	30
IB	14	IP	1912	54	350	106
,,	,,	Br	1920	42	(410)	—
I*B	14	Br's dau	1944	16	(270)	—
,,	,,	Br's son	1950	10	(170)	—
IB	15	IP	1903	63	480	115
,,	,,	Br	1899	67	380	183
,,	,,	Si	1907	47	(400)	—
,,	,,	Si	1908	58	(358)	—
,,	,,	Br	1912	52	322	63
IB	16	IP	1909	56	(465)	(clear serum)

(*Continued overleaf*)

Appendix III *continued*

Details of families of male patients with familial hypercholesterolaemic xanthomatosis with hypertriglyceridaemia

Appendix	Family No.	Identity	Date of Birth	Age Tested (yr.)	Cholesterol (mg./100 ml.)	Triglycerides (mg./100 ml.)
IIA	1	IP	1913	53	493	408
IIA	2	IP	1899	67	(360)	('lipaemic')
IIA	3	IP	1920	46	404	317
,,	,,	Wf	1918	48	361	85
,,	,,	Fa	1895	71	280	153
,,	,,	Son	1946	20	136	67
,,	,,	Dau	1948	18	150	37
IIA	4	IP	1943	23	368	498
,,	,,	Mo	1912	54	199	90
,,	,,	Fa	1903	63	352	538
IIA	5	IP	1928	38	337	4150
IIA	6	IP	1936	30	433	615
IIA	7	IP	1915	51	518	458
,,	,,	Wf	1915	51	280	128
,,	,,	Mo	1890	76	368	224
,,	,,	Fa	1889	71	(135)	—
,,	,,	Br	1911	55	244	90
,,	,,	Son	1948	18	185	206
II*A	7	Br's dau	1941	25	186	34
IIA	8	IP	1929	37	622	790
,,	,,	Wf	1937	29	292	122
,,	,,	Mo	1905	61	283	101
,,	,,	Fa	1907	59	229	525
,,	,,	Si	1930	36	234	250
,,	,,	Dau	1958	8	560	55
,,	,,	Son	1960	6	196	72
IIA	9	IP	1934	32	476	900
,,	,,	Fa	1903	63	328	117
,,	,,	Si	1932	34	201	170
,,	,,	Si	1932	34	283	76
II*A	9	Si's hd	1932	34	157	189
,,	,,	Si's dau	1959	7	162	83
,,	,,	Si's dau	1961	5	165	52
,,	,,	Si's son	1955	11	180	19
IIA	10	IP	1929	37	500	564
,,	,,	Wf	1935	31	204	95
,,	,	Mo	1900	66	183	59
,,	,,	Br	1926	40	202	69
,,	,,	Si	1929	37	263	106
,,	,,	Dau	1958	8	196	50
,,	,,	Dau	1963	3	182	91
II*A	10	Si's dau	1953	13	169	61
,,	,,	Si's dau	1957	9	187	33
IIA	11	IP	1909	57	530	257
,,	,,	Wf	1916	50	213	93
,,	,,	Dau	1944	22	220	93
IIA	12	IP	1908	58	465	1024
,,	,,	Bro	1916	50	398	302
II*A	12	Br's wf	1918	48	336	96
,,	,,	Br's son	1946	20	207	115
IIA	13	IP	1922	44	(610)	('lipaemic')
IIA	14	IP	1923	43	427	580
,,	,,	Wf	1926	40	182	130
,,	,,	Dau	1949	17	157	79
,,	,,	Son	1957	9	177	44
IIA	15	IP	1923	43	575	1485
IIA	16	IP	1931	35	378	388
,,	,,	Son	1955	11	180	152
IIA	17	IP	1929	37	315	788
,,	,,	Br	1925	41	254	178
II*A	17	Br's wf	1924	42	240	86
,,	,,	Br's son	1956	10	194	55

Details of families of female patients with familial hypercholesterolaemic xanthomatosis with hypertriglyceridaemia

IIB	1	IP	1899	67	545	856
,,	,,	Hd	1891	75	270	142
,,	,,	Si	1896	70	236	133
,,	,,	Dau	1927	39	181	92
II*B	1	Br's wf	1915	49	207	59
,,	,,	Br's dau	1940	26	126	36
,,	,,	Br's dau	1944	22	167	39
IIB	2	IP	1895	71	364	210
,,	,,	Si	1899	64	(472)	—
IIB	3	IP	1908	58	420	380
,,	,,	Si	1910	56	417	163
IIB	4	IP	1902	64	446	975
,,	,,	Si	1898	68	416	138