

and more common side effects, such as headache or urinary retention, are not life threatening, our data should result in more widespread use of spinal or epidural anaesthesia.

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Contributors: AR had the original idea for this study. All authors contributed actively to the protocol. NW and AR performed all searching for trials and AM, SS, and GS abstracted the data. NW and TC carried out all data analysis. AR, NW, AM, TC, and SS wrote the first draft of the paper and HK, AvZ, DS, MF, and SM made revisions. AR will act as guarantor for the paper.

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## Outcome of case finding among relatives of patients with known heterozygous familial hypercholesterolaemia

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### Abstract

**Objectives** To assess the feasibility of detecting new cases of heterozygous familial hypercholesterolaemia by using a nurse led genetic register.

**Design** Case finding among relatives of patients with familial hypercholesterolaemia.

**Setting** Two lipid clinics in central and south Manchester.

**Subjects** 259 (137 men and 122 women) probands and 285 first degree relatives.

**Results** Of the 200 first degree relatives tested, 121 (60%) had inherited familial hypercholesterolaemia. The newly diagnosed patients were younger than the probands and were generally detected before they had clinically overt atherosclerosis. Concentrations of serum cholesterol were, respectively, 8.4 (1.7 SD) mmol/l and 8.1 (1.9 SD) mmol/l in affected men and women and 5.6 (1.0 SD) mmol/l and 5.6 (1.1 SD) mmol/l in unaffected men and women. Screening for risk factors as recommended in recent guidelines for coronary heart disease prevention would have failed to identify most of the affected relatives in whom hypertension, diabetes mellitus, cigarette smoking, and obesity were uncommon.

**Conclusions** By performing cholesterol tests on 200 relatives, 121 new patients with familial

hypercholesterolaemia were discovered. Because 1 in 500 people in the United Kingdom are affected by this condition, to detect a similar number by population screening over 60 000 tests would be required, and only a few of these patients would have been detected had cholesterol testing been restricted to those with other risk factors for coronary heart disease. A case exists for organising a genetic register approach, linking lipid clinics nationally.

### Introduction

Familial hypercholesterolaemia in its heterozygous form occurs in around 1 in 500 people in Europe and North America, making it the most common potentially lethal genetic disorder. The characteristic clinical syndrome in adulthood comprises an increased serum cholesterol concentration, tendon xanthomas, and premature coronary heart disease, the median age of onset for coronary heart disease being around 50 years in men and 59 in women.<sup>1,2</sup> Statin treatment and the opportunity for prompt access to cardiological services for patients with familial hypercholesterolaemia seem to have improved survival.<sup>3</sup> In trials using coronary angiography, cholesterol lowering treatment is at least as effective in patients with familial hypercholesterolaemia as it is in other types of

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patients with coronary disease.<sup>1</sup> Most of the potential 100 000 patients with familial hypercholesterolaemia in the United Kingdom are probably undiagnosed, because only a small proportion attend lipid clinics.<sup>4</sup> The same is also likely to be true in other countries.<sup>5</sup> Often the clinical syndrome of familial hypercholesterolaemia is due to a mutation of the low density lipoprotein receptor. However, genetic testing is not currently a feasible means of establishing the diagnosis, except perhaps under special circumstances.<sup>6-9</sup>

It is generally agreed that screening the population for high cholesterol concentrations should be undertaken only as part of a multifactorial approach for the detection of people with a high coronary risk so that cholesterol lowering and antihypertensive treatments can be used in the most cost effective way.<sup>10</sup> Familial hypercholesterolaemia, however, seems to be a condition in which a single risk factor (high cholesterol from birth) often leads to an absolute coronary risk in the range for statin treatment well before middle age.<sup>1 3</sup> We aimed to assess the possibility of using a genetic register method to diagnose new cases of familial hypercholesterolaemia, which has the potential to be adopted nationally.

## Participants and methods

Probands aged 18 years or over attending two adjacent lipid clinics (Manchester Royal Infirmary and University Hospital of South Manchester) for the first time between 1987 and 1998 were identified if serum cholesterol concentrations exceeded 7.5 mmol/l (or low density lipoprotein cholesterol concentrations exceeded 4.9 mmol/l) with tendon xanthomas present in the patient or in first degree or second degree relatives.<sup>11</sup>

Nurses were trained to identify corneal arcus, xanthelasma, and tendon xanthomas and to administer a questionnaire to probands and their first degree relatives that inquired about the presence of other risk factors for coronary and cardiovascular disease already evident. A detailed family history was recorded for the probands. The risk factors recorded were hypertension, cigarette smoking, diabetes mellitus, coronary heart disease, previous diagnosis of stroke, and the possible presence of intermittent claudication.

First degree relatives were sent a personalised, standard letter explaining the reason for suspecting that they might have familial hypercholesterolaemia, its importance, and the method of diagnosis. They were invited to visit either the Manchester Royal Infirmary or their general practice to complete a questionnaire, have the clinical features of familial hypercholesterolaemia assessed with the help of an information pack containing coloured photographs of xanthomas, and have a blood sample taken and sent to the Manchester Royal Infirmary.

The results of the relatives' blood tests for serum cholesterol concentrations were sent to the general practitioners with a letter explaining why the test had been done and the importance of the result. The location of the nearest lipid clinic was provided when the test gave a positive result. General practitioners also had the option of treating newly diagnosed patients

themselves, with advice, if requested. Relatives with newly diagnosed familial hypercholesterolaemia were sent a letter indicating that their cholesterol concentration was increased and suggesting that they make an appointment to see their general practitioner. Counseling was also available by telephone. Relatives not inheriting familial hypercholesterolaemia were also informed.

The research ethics committees at both hospitals considered that the register was an extension of usual clinical practice.

Concentrations of serum cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, triglycerides, serum apolipoprotein B, and serum Lp(a) lipoprotein were determined using standard methods.

*Statistics*—We used Student's *t* test, the Mann-Whitney U test, and the  $\chi^2$  test whenever appropriate. We considered probabilities  $\leq 0.05$  as significant.

## Results

### Compliance of probands and availability of relatives

Of 262 probands identified, all but three agreed to participate. Thus 259 (99%) (137 men and 122 women) provided details of their family tree. Of these, 216 (83%) had at least one living first degree relative, the total number of whom was estimated to be 285. Of these, 205 (72%) were tested. Of the 80 not tested, 25 were already known to have familial hypercholesterolaemia, 26 considered themselves to live too far away, 18 refused to participate, six agreed but did not attend, and five were infirm. In 26% of cases more than one relative of a proband was tested.

### Detection of new cases

Of the 205 relatives tested, the results for cholesterol concentration were available in 200, of whom 121 (60%; 46 men and 75 women) proved positive (heterozygotes by definition). Male probands were less likely to provide a cooperative relative than were female probands: 137 male probands yielded 46 new cases, whereas 122 female probands produced 75 new cases ( $P < 0.0005$ ).

### Clinical characteristics of probands and relatives

Tendon xanthomas were present in 91% of male and 87% of female probands, whereas only 26% of the newly diagnosed men and 19% of the newly diagnosed women possessed them. Further clinical features of probands, affected relatives, and unaffected relatives are given in table 1.

Cardiovascular disease was significantly more common in probands than it was in newly diagnosed affected relatives and in unaffected relatives, particularly coronary heart disease (table 2). A low prevalence of cardiovascular risk factors was found apart from increased concentrations of cholesterol in either the probands or their newly diagnosed relatives (table 2). Serum cholesterol concentrations would thus be unlikely to be measured in newly diagnosed relatives in the United Kingdom except in those with overt coronary heart disease. Furthermore, the average coronary risk in the newly diagnosed relatives, according to the Framingham risk equation on which the UK, American, and European guidelines are based,<sup>10</sup> was

**Table 1** Age, body mass index, physical signs, and concentrations of lipids and lipoproteins in familial hypercholesterolaemia probands and their affected and unaffected relatives. Values in parentheses are 95% confidence intervals unless stated otherwise

	Men			Women		
	Probands (n=137)	Relatives		Probands (n=122)	Relatives	
		Affected (n=46)	Unaffected (n=37)		Affected (n=75)	Unaffected (n=42)
Mean (SD) age	45.0 (11.4)	34.5 (14.8)***	26.7 (13.2)***	48.9 (12.6)	38.2 (18.5)***	36.7 (16.2)***
Body mass index (kg/m <sup>2</sup> )	25.2 (24.7 to 25.7)	25.1 (23.9 to 26.3)	24.8 (23.5 to 26.1)	24.6 (24.0 to 25.3)	23.6 (22.3 to 24.9)	24.6 (22.9 to 26.3)
Corneal arcus (%)	49 (41 to 58)	17 (8 to 31)***	3 (0 to 14)***	49 (40 to 58)	17 (10 to 28)***	2 (0 to 13)***
Xanthelasma (%)	21 (14 to 28)	2 (0 to 12)***	0 (0 to 9)***	25 (18 to 34)	16 (9 to 26)***	0 (0 to 8)***
Tendon xanthomas (%)	91 (83 to 99)	26 (14 to 41)***	0 (0 to 9)***	87 (81 to 93)	19 (11 to 29)***	0 (0 to 8)***
Serum cholesterol (mmol/l)	8.5 (8.1 to 8.9)	8.4 (7.9 to 8.9)	5.6 (5.3 to 5.9)***	8.8 (8.3 to 9.3)	8.1 (7.7 to 8.5)	5.6 (5.3 to 5.9)***
Median (interquartile range) serum triglyceride (mmol/l)	1.67 (1.11-2.30)	1.75 (1.00-2.61)	1.20 (0.87-1.67)	1.09 (0.83-1.56)	1.02 (0.76-1.52)	1.02 (0.71-1.41)
Serum low density lipoprotein cholesterol (mmol/l)	6.0 (5.6 to 6.4)	5.3 (4.9 to 5.8)	3.1 (2.8 to 3.4)***	5.5 (5.1 to 5.9)	6.0 (5.6 to 6.4)	3.2 (3.0 to 3.5)***
Serum high density lipoprotein cholesterol (mmol/l)	1.24 (1.13 to 1.35)	1.23 (1.11 to 1.35)	1.53 (1.36 to 1.70)**	1.59 (1.50 to 1.68)	1.45 (1.36 to 1.54)	1.54 (1.38 to 1.70)
Apolipoprotein B (g/l)	1.44 (1.38 to 1.50)	1.45 (1.32 to 1.58)	0.94 (0.85 to 1.03)***	1.51 (1.42 to 1.60)	1.48 (1.38 to 1.58)	0.92 (0.85 to 0.99)***
Median (interquartile range) Lp(a) lipoprotein (g/l)	0.29 (0.119-0.735)	0.148 (0.064-0.562)*	0.086 (0.038-0.353)**	0.479 (0.196-0.821)	0.202 (0.067-0.441)***	0.086 (0.053-0.386)**

\*P<0.05, \*\*P<0.01, \*\*\*P<0.005 compared with probands.

6% over 10 years for men and 3% over 10 years for women.

## Discussion

The investigation indicated that a genetic register based on 262 probands with familial hypercholesterolaemia attending a lipid clinic could identify 121 new cases. Heterozygous familial hypercholesterolaemia affects around 1 in 500 of the general population. Thus to attempt to identify 121 new cases by universal population screening for high serum cholesterol concentrations would require more than 60 000 cholesterol tests, whereas only 200 tests were necessary in the present study. Selective screening for high cholesterol concentrations by confining cholesterol testing to patients in whom other cardiovascular risk factors or coronary heart disease are present would have missed all of the cases identified in our investigation, with the exception of a small proportion with established coronary heart disease or hypertension. Applying a similar method in other lipid clinics nationally would give access to new probands and could lead to a considerable increase in

the number of known heterozygotes for familial hypercholesterolaemia.

The typical male and female heterozygote discovered in the present investigation would seem to have a coronary risk of only 6% or 3%, respectively, over the next 10 years, if calculated according to the Framingham risk equation on which current guidelines for coronary prevention are based,<sup>10</sup> whereas it is known from other investigations that they would be likely to develop clinical coronary heart disease at a similar age to their probands,<sup>2</sup> which means their true risk is several times greater. The discovery of increased cholesterol concentrations in a heterozygote for familial hypercholesterolaemia therefore is not likely to lead to appropriate treatment unless the clinician assessing the importance of the finding is aware that the patient has familial hypercholesterolaemia rather than polygenic hypercholesterolaemia. Our strategy ensures that this is the case.

The finding that male probands were less likely to provide an affected relative than were female probands was probably because men were less likely to provide sufficient details for a relative to be traced, perhaps

**Table 2** Prevalence of major cardiovascular risk factors and diseases among probands with familial hypercholesterolaemia and their affected and unaffected relatives. Values are percentages (95% confidence intervals)

Risk factor	Men			Women		
	Probands (n=137)	Relatives		Probands (n=122)	Relatives	
		Affected (n=46)	Unaffected (n=37)		Affected (n=75)	Unaffected (n=42)
Cigarette smoking	13 (8 to 20)	28 (16 to 43)	6 (1 to 18)	17 (11 to 25)	12 (6 to 22)	19 (9 to 34)
Hypertension	2 (0 to 6)	4 (0 to 12)	6 (1 to 18)	4 (1 to 10)	0 (0 to 5)	0 (0 to 8)
Diabetes mellitus	<1 (0 to 4)	0 (0 to 8)	0 (0 to 9)	<1 (0 to 5)	0 (0 to 5)	0 (0 to 8)
Angina	21 (14 to 28)*	7 (1 to 18)	0 (0 to 9)	17 (11 to 25)*	7 (2 to 15)	2 (0 to 13)
Myocardial infarction	18 (12 to 25)**	4 (0 to 12)	0 (0 to 9)	9 (5 to 16)*	1 (0 to 7)	0 (0 to 8)
Coronary artery bypass grafting	27 (19 to 35)**	7 (1 to 18)	3 (0 to 14)	7 (11 to 25)*	0 (0 to 5)	0 (0 to 8)
Coronary heart disease†	44 (35 to 53)**	11 (4 to 24)	0 (0 to 9)	26 (19 to 35)**	8 (3 to 17)	2 (0 to 13)
Stroke	7 (3 to 13)*	7 (1 to 18)	3 (0 to 14)	6 (2 to 12)*	0 (0 to 5)	0 (0 to 8)
Coronary heart disease or stroke, or both	44 (35 to 53)**	15 (6 to 29)	3 (0 to 14)	28 (21 to 37)**	9 (4 to 18)	2 (0 to 13)
Intermittent claudication‡	12 (7 to 19)*	4 (0 to 12)	0 (0 to 9)	16 (10 to 25)*	11 (5 to 20)	5 (1 to 16)
Cardiovascular disease§	51 (41 to 59)***	20 (9 to 34)	3 (0 to 14)	41 (32 to 50)***	20 (12 to 31)	5 (1 to 16)

\*P<0.01, \*\*P<0.001, \*\*\*P<0.0001 compared with affected or unaffected relatives ( $\chi^2$  test).

†Angina, myocardial infarction, or coronary artery bypass grafting, or a combination of these.

‡Rose questionnaire.

§Coronary heart disease, stroke, or intermittent claudication, or a combination of these.

### What is already known on this topic

Familial hypercholesterolaemia occurs in 1 in 500 people in Europe and North America

High cholesterol concentrations in this group should be treated with statins

### What this study adds

Most relatives of known patients with familial hypercholesterolaemia wanted their cholesterol concentration measured

Most patients were diagnosed before the clinical onset of coronary heart disease

This would rarely have been the case during a screening approach for multiple risk factors

because their wives write the Christmas cards. A possible improvement to the present strategy might therefore be to ensure that wives are, if possible, present when male probands are interviewed.

The high prevalence of cardiovascular disease in probands is likely to be the result of the older age of the probands compared with that of the newly diagnosed relatives, and because their hypercholesterolaemia was discovered as the consequence of presenting with vascular symptoms. The present findings thus suggest that this method of detecting new cases often identifies them before vascular disease is clinically overt which, given the mortality associated with a first myocardial infarction (around 30%<sup>12</sup>) and the subsequent morbidity, is a potentially important advantage.

It has been calculated that the cost per life year gained from cholesterol reduction in familial hypercholesterolaemia is similar to that in patients after acute myocardial infarction, which is generally considered to be highly cost effective: more so, for example, than the cost of a generic thiazide to treat hypertension.<sup>13</sup> There are potentially detrimental effects of screening.<sup>14</sup> Our approach avoids the adverse effects caused by screening of the general population, leading to the discovery of huge numbers of asymptomatic people with more common less severe hypercholesterolaemia in which the health gain from such knowledge may be minimal. Furthermore, our pragmatic approach also avoided the potential psychological harm caused by DNA testing.<sup>8,15</sup> It also ensured that counselling was provided by healthcare workers who had frequent contact with patients with familial hypercholesterolaemia. There are this many potential advantages of the detection of new cases of familial hypercholesterolaemia through established lipid clinics using the genetic register approach reported here.

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carried out most of the patient interviews and counselling. She helped to collate the results with SS, who together with DB, performed the statistical analyses. PND and JPM have clinical responsibility for the probands. MIM was responsible for the biochemical analyses. PND wrote the first draft of the paper after which all authors contributed to the final manuscript. PND and DB will act as guarantors for the paper.

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### Endpiece

#### The Old Man

You think my sons I should be more content,  
Rest on my honoured name, grow old with grace?  
You do not understand how I resent  
The narrow confines of life's too brief space.  
There are so many mountains yet to climb,  
And winding river valleys to explore,  
So much unsavourd poetry and wine,  
Such magnitude of beauty to adore.  
The world is full of fine warm-hearted folk  
And I can never sit beside their fires  
To talk of wonders, eat, and sing and joke—  
I ache with unattainable desires.  
Range far my sons, before you too grow old.  
No—bide with me awhile. The house grows cold.

Walter Phillips Kennedy (1899-1982)

Submitted by W P U Kennedy,  
retired chest physician, Colchester