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.

We thank all trialists who confirmed data and provided additional information for the overview. We also thank Iain Chalmers, Rory Collins, Mike Davis, Konrad Jamrozik, John McCall, Tom Pedersen, John Rigg, and Charles Warlow for their helpful comments and Gary Whitlock, Xin-Hua Zhang, Philippa Day, and Valentine Kratsos for help with translating papers.

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.

Funding: Health Research Council of New Zealand and Astra Pain, New Zealand. NW undertook this research during the tenure of a training fellowship from the Health Research Council of New Zealand. AR is a senior research fellow of the National Heart Foundation of New Zealand.

Competing interests: HK has received fees for consulting and speaking at meetings from AstraZeneca.

9 Go A. Cardiac outcomes after regional or general anaesthesia: do we have the answer? Anesthesiology 1996;84:1-2.
Patients with coronary disease. 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. The same is also likely to be true in other countries. 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.

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. 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. 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.

Nurses were trained to identify corneal arcus, xanthelasmas, 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 χ² test whenever appropriate. We considered probabilities ≤0.05 as significant.

Results

Compliance of probands and availability of relatives

Of 282 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, 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.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Probands (n=122)</th>
<th>Affected (n=37)</th>
<th>Unaffected (n=85)</th>
<th>Probands (n=75)</th>
<th>Affected (n=19)</th>
<th>Unaffected (n=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) age</td>
<td>45.0 (11.4)</td>
<td>45.1 (11.4)</td>
<td>44.9 (11.4)</td>
<td>44.0 (11.4)</td>
<td>44.1 (11.4)</td>
<td>43.9 (11.4)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.2 (4.7)</td>
<td>25.3 (4.7)</td>
<td>25.1 (5.1)</td>
<td>25.2 (5.1)</td>
<td>25.1 (5.1)</td>
<td>25.2 (5.1)</td>
</tr>
<tr>
<td>Serum cholesterol (mmol/l)</td>
<td>8.5 (8.1)</td>
<td>8.5 (8.1)</td>
<td>8.5 (8.1)</td>
<td>8.5 (8.1)</td>
<td>8.5 (8.1)</td>
<td>8.5 (8.1)</td>
</tr>
<tr>
<td>Median (interquartile range)</td>
<td>1.67 (1.11-2.30)</td>
<td>1.67 (1.11-2.30)</td>
<td>1.67 (1.11-2.30)</td>
<td>1.67 (1.11-2.30)</td>
<td>1.67 (1.11-2.30)</td>
<td>1.67 (1.11-2.30)</td>
</tr>
<tr>
<td>Serum low density lipoprotein</td>
<td>6.0 (5.6 to 6.4)</td>
<td>6.0 (5.6 to 6.4)</td>
<td>6.0 (5.6 to 6.4)</td>
<td>6.0 (5.6 to 6.4)</td>
<td>6.0 (5.6 to 6.4)</td>
<td>6.0 (5.6 to 6.4)</td>
</tr>
<tr>
<td>Apolipoprotein B (g/l)</td>
<td>1.24 (1.13 to 1.35)</td>
<td>1.24 (1.13 to 1.35)</td>
<td>1.24 (1.13 to 1.35)</td>
<td>1.24 (1.13 to 1.35)</td>
<td>1.24 (1.13 to 1.35)</td>
<td>1.24 (1.13 to 1.35)</td>
</tr>
<tr>
<td>Median (interquartile range)</td>
<td>21 (14 to 28)</td>
<td>21 (14 to 28)</td>
<td>21 (14 to 28)</td>
<td>21 (14 to 28)</td>
<td>21 (14 to 28)</td>
<td>21 (14 to 28)</td>
</tr>
<tr>
<td>Intermittent claudication</td>
<td>12 (7 to 19)</td>
<td>12 (7 to 19)</td>
<td>12 (7 to 19)</td>
<td>12 (7 to 19)</td>
<td>12 (7 to 19)</td>
<td>12 (7 to 19)</td>
</tr>
<tr>
<td>Coronary artery bypass grafting</td>
<td>27 (19 to 35)</td>
<td>27 (19 to 35)</td>
<td>27 (19 to 35)</td>
<td>27 (19 to 35)</td>
<td>27 (19 to 35)</td>
<td>27 (19 to 35)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>44 (35 to 53)</td>
<td>44 (35 to 53)</td>
<td>44 (35 to 53)</td>
<td>44 (35 to 53)</td>
<td>44 (35 to 53)</td>
<td>44 (35 to 53)</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>13 (8 to 20)</td>
<td>13 (8 to 20)</td>
<td>13 (8 to 20)</td>
<td>13 (8 to 20)</td>
<td>13 (8 to 20)</td>
<td>13 (8 to 20)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2 (0 to 12)</td>
<td>2 (0 to 12)</td>
<td>2 (0 to 12)</td>
<td>2 (0 to 12)</td>
<td>2 (0 to 12)</td>
<td>2 (0 to 12)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>&lt;1 (0 to 4)</td>
<td>&lt;1 (0 to 4)</td>
<td>&lt;1 (0 to 4)</td>
<td>&lt;1 (0 to 4)</td>
<td>&lt;1 (0 to 4)</td>
<td>&lt;1 (0 to 4)</td>
</tr>
<tr>
<td>Angina</td>
<td>21 (14 to 28)</td>
<td>21 (14 to 28)</td>
<td>21 (14 to 28)</td>
<td>21 (14 to 28)</td>
<td>21 (14 to 28)</td>
<td>21 (14 to 28)</td>
</tr>
<tr>
<td>Mucocutaneous infarction</td>
<td>18 (12 to 25)</td>
<td>18 (12 to 25)</td>
<td>18 (12 to 25)</td>
<td>18 (12 to 25)</td>
<td>18 (12 to 25)</td>
<td>18 (12 to 25)</td>
</tr>
<tr>
<td>Coronary heart disease†</td>
<td>33 (25 to 45)</td>
<td>33 (25 to 45)</td>
<td>33 (25 to 45)</td>
<td>33 (25 to 45)</td>
<td>33 (25 to 45)</td>
<td>33 (25 to 45)</td>
</tr>
<tr>
<td>Stroke</td>
<td>27 (19 to 35)</td>
<td>27 (19 to 35)</td>
<td>27 (19 to 35)</td>
<td>27 (19 to 35)</td>
<td>27 (19 to 35)</td>
<td>27 (19 to 35)</td>
</tr>
<tr>
<td>Statin</td>
<td>25 (18 to 34)</td>
<td>25 (18 to 34)</td>
<td>25 (18 to 34)</td>
<td>25 (18 to 34)</td>
<td>25 (18 to 34)</td>
<td>25 (18 to 34)</td>
</tr>
</tbody>
</table>

### 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 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 cases likely to develop clinical coronary heart disease at a similar age to their probands, 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 due to their being under some form of pressure to provide this information.

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

### 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).

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Probands (n=137)</th>
<th>Affected (n=46)</th>
<th>Unaffected (n=91)</th>
<th>Probands (n=122)</th>
<th>Affected (n=75)</th>
<th>Unaffected (n=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>2 (0 to 12)</td>
<td>2 (0 to 12)</td>
<td>2 (0 to 12)</td>
<td>2 (0 to 12)</td>
<td>2 (0 to 12)</td>
<td>2 (0 to 12)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>18 (12 to 25)</td>
<td>18 (12 to 25)</td>
<td>18 (12 to 25)</td>
<td>18 (12 to 25)</td>
<td>18 (12 to 25)</td>
<td>18 (12 to 25)</td>
</tr>
<tr>
<td>Coronary heart disease†</td>
<td>33 (25 to 45)</td>
<td>33 (25 to 45)</td>
<td>33 (25 to 45)</td>
<td>33 (25 to 45)</td>
<td>33 (25 to 45)</td>
<td>33 (25 to 45)</td>
</tr>
<tr>
<td>Stroke</td>
<td>27 (19 to 35)</td>
<td>27 (19 to 35)</td>
<td>27 (19 to 35)</td>
<td>27 (19 to 35)</td>
<td>27 (19 to 35)</td>
<td>27 (19 to 35)</td>
</tr>
<tr>
<td>Statin</td>
<td>25 (18 to 34)</td>
<td>25 (18 to 34)</td>
<td>25 (18 to 34)</td>
<td>25 (18 to 34)</td>
<td>25 (18 to 34)</td>
<td>25 (18 to 34)</td>
</tr>
</tbody>
</table>

*P<0.01, **P<0.001, ***P<0.0001 compared with affected or unaffected relatives (χ² 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%) 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. There are potentially detrimental effects of screening. 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. 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.

We thank Ms C Price for preparing the manuscript and sisters Mary Brady, Pat Lockely, and Morag Ravenscroft for additional nursing support. Copies of the standard letters to relatives and general practitioners are available from PND.

Contributors: PND and DB conceived the study, secured its funding, designed the protocol, and supervised its execution. JM 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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