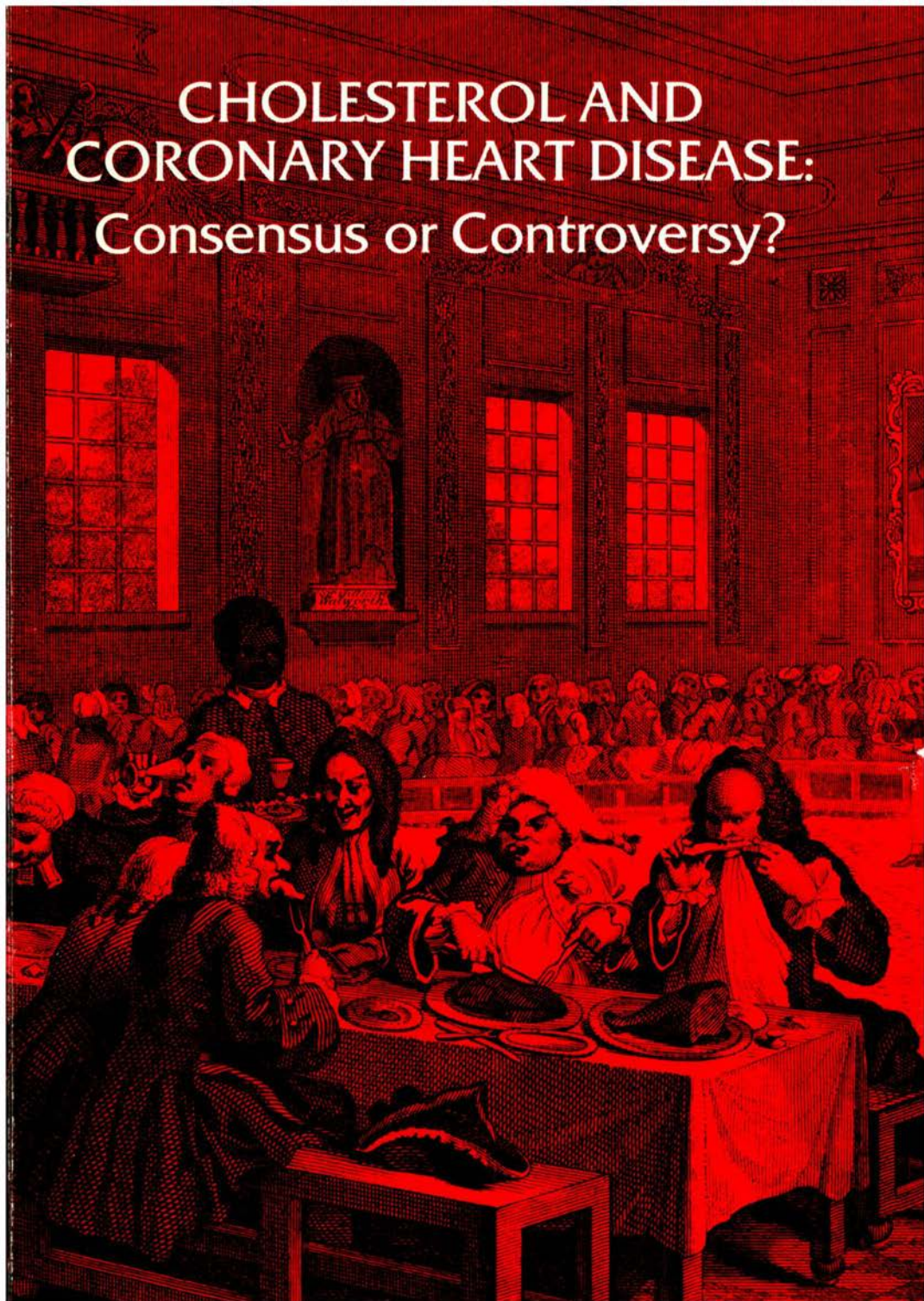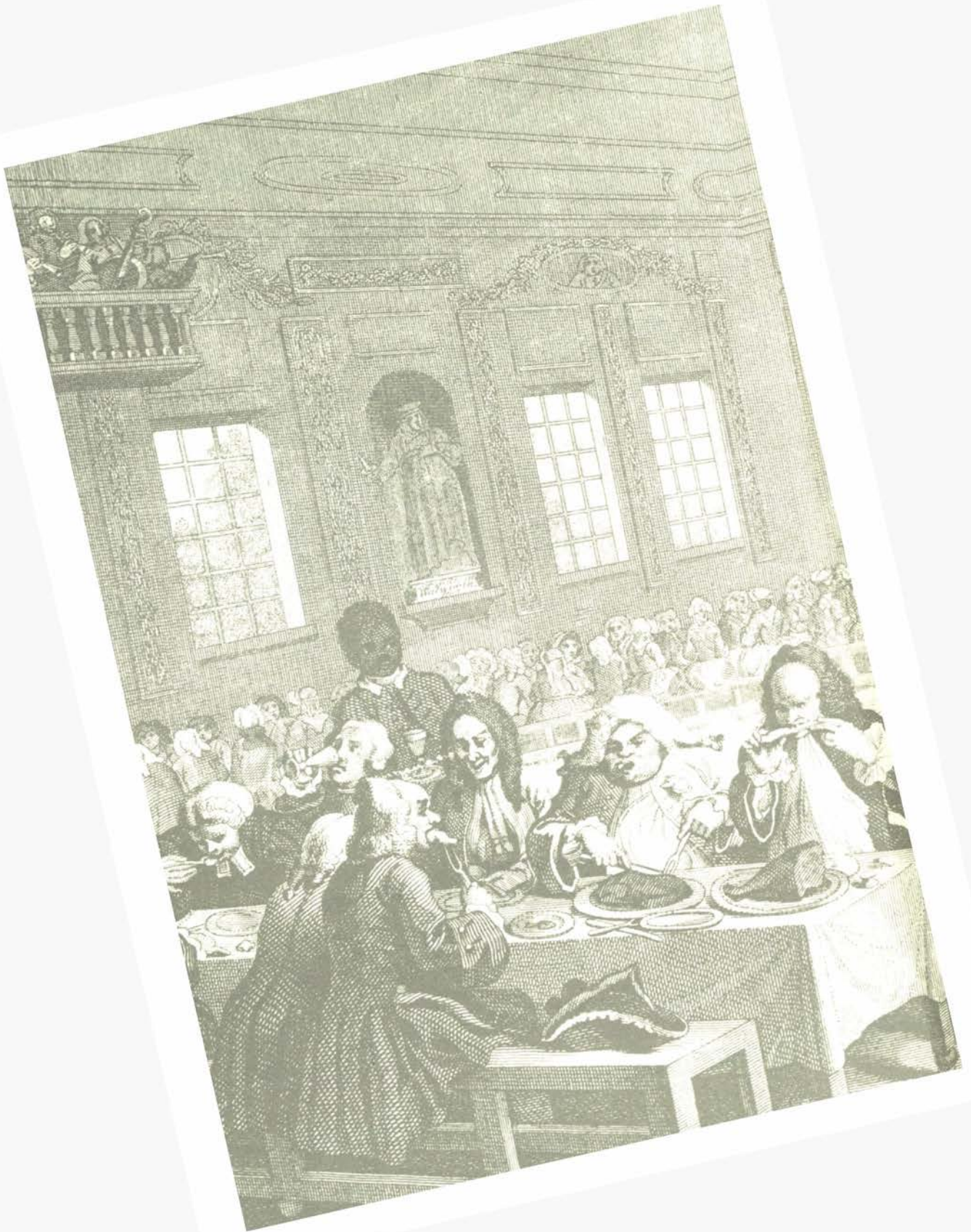# CHOLESTEROL AND CORONARY HEART DISEASE:
Consensus or Controversy?

CHOLESTEROL AND CORONARY HEART DISEASE:
Consensus or Controversy?

Bernie J O'Brien
with a foreword by
Professor Anthony Winder

Office of Health Economics

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ACKNOWLEDGEMENTS

THE AUTHOR

Bernie O'Brien has recently been appointed an assistant professor in the Department of Clinical Epidemiology and Biostatistics at McMaster University in Canada and remains an associate research fellow of the Health Economics Research Group at Brunel University in the UK, where he wrote this paper.

FOREWORD

The severe expression of cardiovascular and particularly coronary heart disease in the UK is a proper cause for concern. Analysis of its associations clearly shows the multifactorial – some would say uninterpretable – background to that expression. It is also clear that most of those clinically affected are perceived to have several unfavourable associations, within which however levels of cholesterol stand out. The crucial arguments turn on what follows from that association.

Many in the UK see the North American preoccupation with cholesterol as naive, with overemphasis on that single pathogenic influence and unreasonable expectations of the potential benefits of intervention. All the central issues of concern are addressed in this penetrating and topical report.

The North American interest in cholesterol and cholesterol testing was aroused by professional concern and then facilitated by commercial interest, but it is now overwhelmingly a popular campaign. It may well be that similar alliances drive this campaign in Britain, but developing interests in cholesterol screening and management here are not supported with any balancing new resources, even in the private sector where income generated through screening does not generally flow into patient management. This fundamental difference from the North American situation has both properly and of necessity sharpened perceptions here of selectivity, cost and cost-effectiveness. Thus selective screening is perceived as more efficient, although except for those who have had the good fortune to survive a cardiovascular event, identification of those at high risk is not well founded. Intervention on the basis of the diet-heart hypothesis is also largely untested, mainly because we just do not have the necessary professional skill resource to do so. The cost and other resource implications of diet only, diet first or drug only policies are considerable. It is also necessary to define any risks involved, and whether they relate to having a low cholesterol, lowering a raised cholesterol, or how that lowering is achieved.

This report illuminates the options open to health care planners in tackling the relationship between cholesterol and coronary heart disease. It further emphasises that to make no response also has its costs and disadvantages.

A F Winder
Royal Free Hospital
March 1991

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1. INTRODUCTION

Coronary Heart Disease (CHD) remains the leading cause of death in the UK and the developed world. As illustrated in Figure 1, in 1989 CHD accounted for 150,794 deaths in England and Wales, being 26 per cent of annual mortality from all causes (Office of Population Censuses and Surveys, 1990). Nearly two thirds of all CHD deaths are due to heart attacks or acute myocardial infarction (AMI) where sustained loss of blood supply to the heart muscle results from occlusion of one or more of the coronary arteries. The risk of CHD mortality increases with age and is higher among men; nearly one in three deaths in men aged 55-74 years in 1989 were due to CHD. The annual burden on health service resources for treating the disease has previously been estimated by the Office of Health Economics at around £500m (Office of Health Economics, 1990).

Recent years have seen a rapid growth in scientific knowledge about the cause of the disease, its diagnosis and treatment. Patients at risk of heart attacks, usually due to the gradual narrowing of the arteries caused by the growth of lesions known as atheromas, can have coronary arteries bypassed by surgery or re-opened by angioplasty where a small balloon catheter is inflated at the site of the arterial stenosis or narrowing. Greater knowledge also exists about the role of thrombosis in the causation of infarcts where a blood clot may cause an artery (possibly already narrowed due to atherosclerosis) to become blocked. The mortality rate for those who do sustain a myocardial infarction has been markedly reduced by a new generation of thrombolytic drugs – such as tissue plasminogen activator and streptokinase – which act to dissolve the blood clot causing the coronary blockage (Rapaport, 1989). Clinical trials in

Figure 1 **All cause and CHD mortality for England and Wales 1989**

Source: OPCS Monitor DH2, June 1990
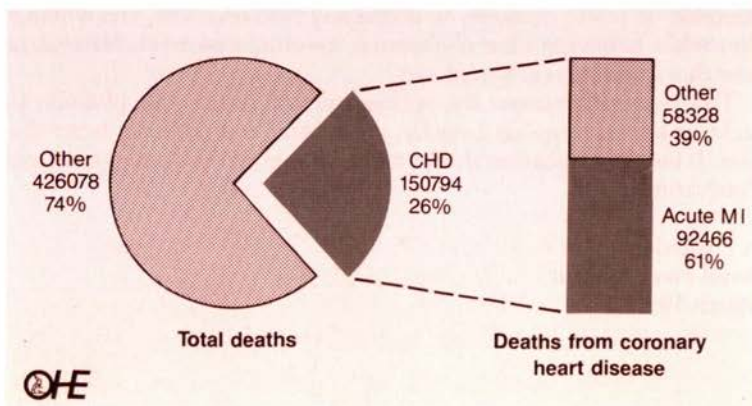
Figure 2 **CHD mortality (rates/100,000) in men aged 35-74 years (age-adjusted)**

Mortality per 100,000

Scotland
Finland
England & Wales
Sweden
USA
Italy
France
Japan

Year
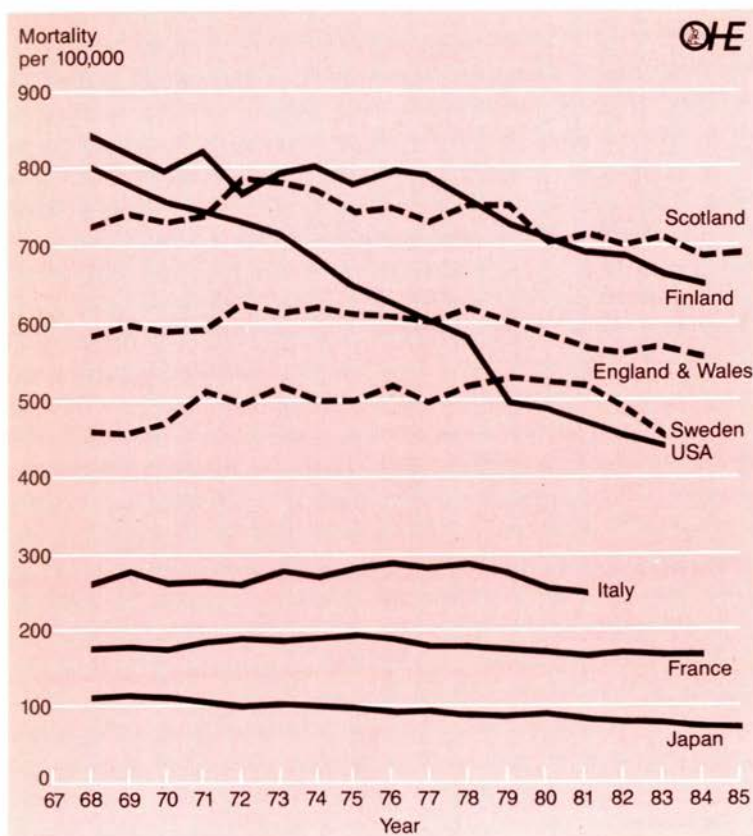
thrombolysis (the 'dissolving' of such blood clots) also led to the discovery that the anti-platelet effects of aspirin taken after infarct offer good secondary prevention from further infarcts (Fuster *et al* 1989).

Despite these advances in the treatment of CHD a long-standing health policy debate hinges on the fact that treating the symptoms and consequences of CHD is a costly response to a disease that may be largely preventable. The international CHD mortality data presented in Figures 2 and 3 are compelling evidence that population CHD incidence can be drastically reduced in a relatively short period. Countries such as the USA lead the international league table of CHD prevention with nearly a 50 per cent reduction in age-standardised death rates among males in

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Figure 3 **Changes in age-standardised death rates for coronary heart disease: males 1970-1985**
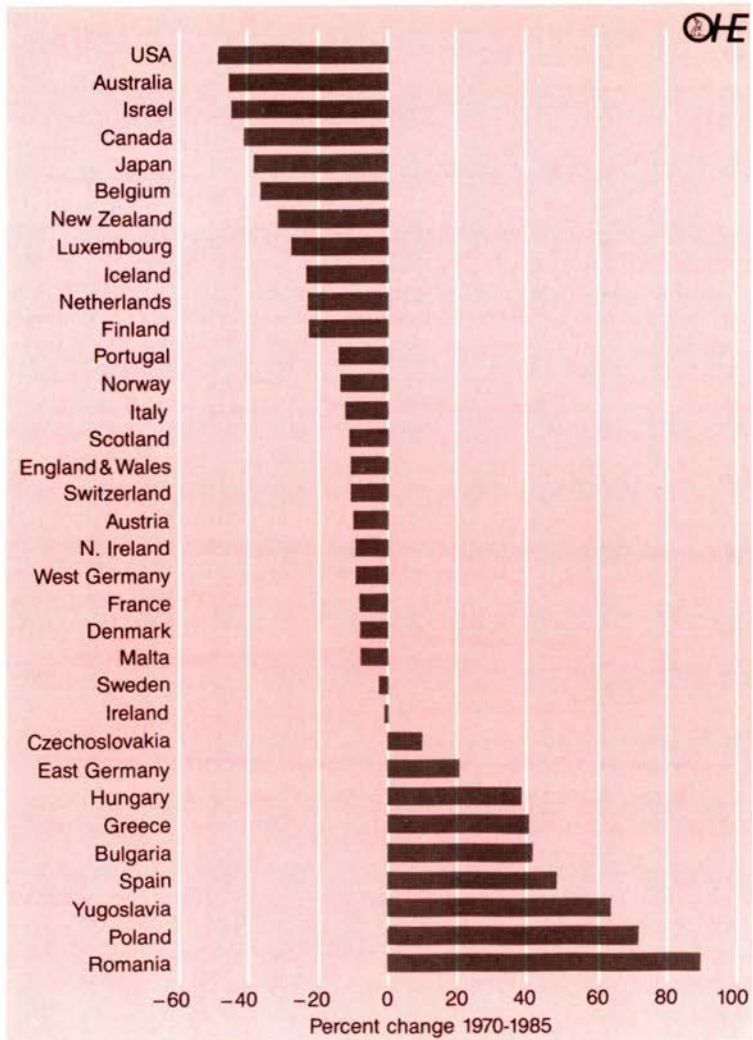
Source: Uemera and Pisa (1988)

the period 1970-85. In the same 15-year period the mortality rate among men in England and Wales also fell, but only by 11 per cent. In contrast, a number of countries in Eastern Europe such as Romania and Czechoslovakia have experienced marked increases in CHD mortality rates.

Given only a modest rate of decline, countries such as Scotland, England and Wales now have some of the highest rates of CHD mortality in the world. Such relatively poor international performance in CHD prevention provided the starting point for recent critical appraisal by the National Audit Office (NAO) (1989) and the Committee of Public Accounts (1989), the latter stating that '. . . we deplore the generally poor performance by Great Britain in reducing coronary heart disease mortality rates' (paragraph 20).

Central to the NAO policy analysis was the epidemiological premise that '. . . it is now widely recognised that the premature onset of coronary heart disease could be reduced significantly if people adopted healthier lifestyles'. Specifically, the three main risk factors which need to be targeted in policies aimed at preventing CHD are well known and generally agreed upon:

- *Blood pressure:* the higher the pressure the greater the risk;
- *Blood cholesterol:* the greater the concentration the greater the risk;
- *Cigarette smoking:* the greater the amount smoked the greater the risk.

This report is about blood cholesterol as a major risk factor for CHD. As Shaper (1988) has stated 'the evidence that the serum total cholesterol level is the most important single factor in determining the risk of CHD in individuals is considerable, if not overwhelming' (page 24). Similarly Grundy (1986) concludes that our understanding of cholesterol in the aetiology of CHD has reached a new era and that 'the evidence relating plasma cholesterol levels to atherosclerosis and CHD has become so strong as to leave little doubt of the aetiologic connection'.

There are three broad reasons for focusing on cholesterol in this report:

(i) a number of recent intervention studies have demonstrated that lowering blood cholesterol, either by diet or drugs, can reduce the incidence of CHD (e.g. Lipid Research Clinics Program, 1984). In the USA this has resulted in clinical policies for the treatment of hypercholesterolaemia being put forward at a Consensus Development Conference (National Institutes of Health, 1984) and the establishment of a National Cholesterol Education Programme. Similar clinical policy statements have been issued on this side of the Atlantic by the European Atherosclerosis Society (1988) and the British Hyperlipidemia Association (Shepherd *et al*, 1987).

If the published algorithms and guidelines are adopted as clinical policy then the health care implications are far-reaching. If all persons with blood cholesterol greater than 6.5 mmol/L were placed on a specific lipid-lowering diet then about 25 per cent of the population would be

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advised to adopt a cholesterol-lowering diet and about 5 per cent would receive active therapy of a supervised diet with perhaps 1-2 per cent being on long-term drug therapy (Mann et al, 1988; Winder, 1990 personal communication). In view of the significance of such proposals it is important to appraise critically the epidemiological evidence they are based upon – particularly since there is disagreement between these consensus statements as to what level of blood cholesterol warrants intervention with diet and/or drugs (Langer et al, 1989).

(ii) the rapid pace of innovation in biotechnology means that general practitioners can now measure blood cholesterol using simple desk-top analysers. The availability of such devices has prompted debate on whether mass population testing of blood cholesterol is desirable (Smith et al, 1989; Tunstall-Pedoe, 1989). This topic has also been the subject of a consensus conference in the UK (Kings Fund Forum, 1989). Should the UK government launch national education programmes similar to those in the US where consumers were urged to 'know your (cholesterol) number'? Or should we rely upon the judgement of the medical profession to decide in each individual case who should have their cholesterol tested? An expert committee convened by the government – the Standing Medical Advisory Committee (SMAC) – issued a consultative document in May 1990 which recommends opportunistic screening for elevated blood cholesterol in general practice and concludes that selecting patients for testing and treatment based on pre-existing CHD risk factors can be cost-effective. The arguments for and against testing are discussed in the present report.

(iii) the prospect of large numbers of the population on cholesterol-lowering drugs and/or diets has generated concern about the high personal and public costs of cholesterol therapy. Given the scarcity of health care resources it is important to evaluate the cost-effectiveness of treatment or public health programmes designed to lower blood cholesterol. Are the new generation of cholesterol-lowering drugs – Hmg CoA reductase inhibitors (e.g. simvastatin) – more cost-effective than existing drug therapies such as bile acid sequestrants (e.g. cholestyramine)? More generally, what evidence is there that drug therapy is more or less cost-effective than diet or modification of other risk factors such as hypertension or smoking?

The overall aim of this report is to review the evidence and arguments concerning blood cholesterol as a CHD risk factor. While it is apparent that a consensus is emerging within the medical and scientific community concerning the importance of lowering blood cholesterol to prevent CHD, there remains confusion and controversy about the appropriate action that government, health care professionals and the public should be taking.

2. WHAT IS CHOLESTEROL?

Cholesterol is a steroid alcohol found in animal fats and oils, bile, blood, brain tissue, milk, egg yolk, myelin sheaths of nerve fibres, liver, kidneys and adrenal glands. Most of the body's cholesterol is synthesised in the liver and it is a precursor of bile acids (hence *chole* from the Greek for bile) and steroid hormones. Cholesterol is vital to human life and every cell in the body can manufacture it. The outer membrane of each cell incorporates cholesterol compounds which play an important role in regulating what may enter and exit the cell.

An important distinction is that between plasma (or serum) cholesterol in the blood and dietary cholesterol. It is the level of cholesterol in the blood which is a risk factor for atherosclerosis and coronary heart disease. In many people the quantity of cholesterol in the diet does not markedly influence the serum cholesterol concentration in the blood. Cholesterol in the blood is reported as a concentration (millimoles per litre) and is usually measured from blood serum or blood plasma. If blood plasma is used then it is customary to use ethylenediaminetetracetic acid (EDTA) as an anticoagulant and results should be multiplied by 1.03 to arrive at the serum equivalent (National Cholesterol Education Programme, 1988). Given the small difference in the two measurement standards the discussion in this report will refer to blood cholesterol and only distinguish plasma and serum where necessary.

Cholesterol binds to particular proteins to form lipoproteins; it is the relationship between various categories of lipoproteins and the formation of atherosclerotic plaques in the coronary arteries which has been the subject of intense research and controversy in recent years. The various plasma lipoproteins are defined and explained in Box 1 from Lewis *et al* (1989). In summary, the plasma lipids such as cholesterol and triglyceride are poorly soluble and they are transported through the body as lipoproteins which are water soluble particles. Of the five classes of lipoproteins it is known that 60-70 per cent of plasma cholesterol is transported as Low Density Lipoproteins (LDL) and 20-30 per cent as High Density Lipoproteins (HDL).

LDL pick up cholesterol from ingested fats and from cells that produce it in the body and deliver it to cells in blood vessels and muscles; LDL levels can be reduced by limiting dietary intake of saturated fat and cholesterol. In contrast, HDL promotes the removal of excess cholesterol from cells (a 'reverse transport' mechanism) and is thought to be beneficial rather than harmful. HDL levels may be reduced, and the 'clearing' of cholesterol impaired, due to smoking, obesity and lack of exercise. Although the exact mechanism is still not well understood there is evidence from a number of prospective studies that HDL is a protective factor for CHD which is independent from other risk factors (for a recent review see Betteridge, 1989).

In addition to its role as a factor in determining CHD risk, the mea-

surement of HDL cholesterol permits the calculation of plasma low density lipoprotein (LDL) cholesterol by the Friedewald formula: LDL = total cholesterol − HDL − triglycerides/2.19.

An important scientific breakthrough, fundamental to the understanding of how plasma cholesterol levels can be controlled, was made by Nobel prize winners Joseph Goldstein and Michael Brown in 1985. In their study of lipoprotein metabolism they discovered cell-surface receptors for LDL and established that control of LDL receptors in the liver –


Box 1 The Plasma Lipoproteins

The plasma lipids are poorly soluble; hence they are transported in lipoproteins which are water-soluble particles that are secreted into plasma by the liver and/or small intestine. Lipoproteins contain cholesterol, triglyceride and phospholipids, and one or more specialized proteins called apolipoproteins.

There are five classes of lipoproteins:

• **Chylomicrons** are the largest of the lipoproteins and are rich in triglyceride. They are produced by the intestinal epithelium during absorption of dietary fat. They enter the general circulation via the thoracic duct where they are degraded to chylomicron remnants by the enzyme lipoprotein lipase (which lines the capillary endothelium, especially in muscle and adipose tissue). Much of the fat they contain is taken up by these tissues. Remnants are rapidly taken up by the liver. In health, chylomicrons are present in plasma after a fat-containing meal but not in the fasted state.

• The liver secretes endogenously-produced triglyceride into the circulation in very **low density lipoproteins** (VLDL). These are degraded by lipoprotein lipase to **intermediate density lipoproteins** (IDL), i.e. 'VLDL remnants'. In turn IDL is in part converted in the liver to *low density lipoproteins* (LDL). LDL and probably IDL are major sources of the cholesterol that accumulates in atherosclerotic plaques.

• Approximately 60-70 per cent of the cholesterol of plasma is transported in LDL. Increased concentration of LDL-cholesterol in plasma, due to oversynthesis or diminished catabolism, manifests as an increase in plasma cholesterol level, and is causally related to atherosclerosis.

• LDL receptors at the surface of cells are important in the uptake of this lipoprotein, and in regulating the cholesterol content of cells and of plasma. Control of hepatic LDL receptors by diet, hormones and drugs influences LDL-cholesterol concentrations in plasma, thereby affecting the risk of atherosclerosis.

• **High density lipoproteins** (HDL) usually contain 20-30 per cent of the plasma cholesterol. HDL-cholesterol levels are inversely correlated with risk of CHD. HDL, or a sub-class of this lipoprotein, plays a poorly-defined but important role in removing cholesterol from peripheral tissues, including the arterial wall.

Source: Lewis *et al* (1989)

Figure 4 **Pathways of lipoprotein metabolism**
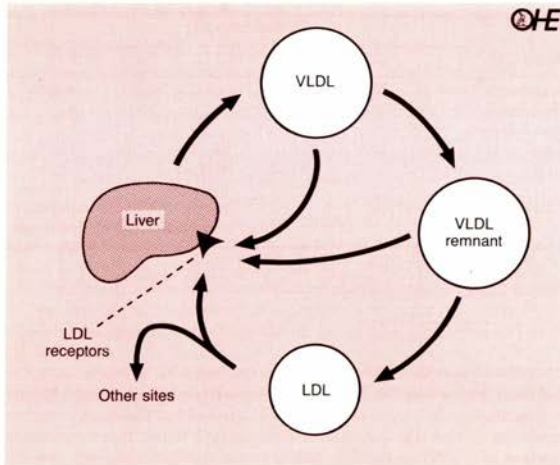
with diet, hormones or drugs – can influence LDL-cholesterol concentrations and the risk of atherosclerosis. The pathways of lipoprotein metabolism are illustrated in Figure 4 and the key role of LDL receptor cells in the liver is apparent.

Reduced clearance of LDL results in an excess of these lipoproteins which are high in cholesterol. One reason for LDL receptors malfunctioning is genetic. Familial hypercholesterolaemia (FH) is an inherited condition where one (heterozygous) or both (homozygous) parental genes for LDL receptors are abnormal. These conditions result in over production and impaired clearance of LDLs and premature atherosclerosis as described above. FH is a genetic condition which is inherited by only 0.2 per cent of the population (Tunstall-Pedoe, 1989), but it results in cholesterol levels which are two to four times normal.

Familial hypercholesterolaemia is only one of a range of general lipid disorders or dyslipidaemias. The biochemical classification system for

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Table 1 **Classification (Fredrickson) and characteristics of dyslipidaemias**

Plasma lipid	Fredrickson type:					
	I	IIa	IIb	III	IV	V
Triglyceride	+++	N	++	++	++	+++
Cholesterol	+	++	++	+	N/+	+
Lipoproteins raised	Chylo-microns	LDL	LDL VLDL	VLDL remnants, chylo-micron remnants	VLDL	VLDL, chylo-microns and their remnants

N = Normal, + = mildly raised, ++ = moderately raised,
+++ = severely raised concentrations, LDL = Low density lipoprotein,
VLDL = Very low density lipoprotein.

Source: O'Connor *et al* (1990)

dyslipidaemias is the WHO/Fredrickson system which has six categories and these are outlined in Table 1. The term hyperlipidaemia can be used to describe conditions of raised lipids in general but the most prevalent condition is type IIa – common ('polygenic') hypercholesterolaemia. Lewis *et al* (1989) report that this is by far the most frequent cause of cholesterol levels exceeding 5.2 mmol/L. The cause is thought to be a mixture of genetic, dietary and environmental factors. Given that this is the most common primary cause of elevated blood cholesterol much of the debate concerning the measurement and management of cholesterol relates to this category.

3. ELEVATED BLOOD CHOLESTEROL AS A CHD RISK FACTOR

In order to prevent CHD or reduce its incidence it is necessary to determine what causes the disease. From a historical or international perspective it is clear that heart disease can be classed as a preventable disease associated with affluence (McKeown, 1979). Such a classification points the finger of causation in the direction of life-styles. The wealth that nations acquire permit populations to adopt 'unhealthy' life-styles in relation to eating, drinking, smoking, lack of exercise and so on. But the translation of causation theories into successful prevention policies requires precise quantification of which specific factors increase, and by how much, the risk of CHD. The risk factors for CHD are presented in Table 2. While age and sex are important predisposing risk factors for CHD (i.e. older males are generally more at risk) many of the prevention and treatment policy questions are concerned with the major risk factors that are modifiable, namely smoking, raised blood pressure and blood cholesterol.

In assessing the validity and importance of risk factors, particularly from epidemiological evidence, it is important to keep a clear distinction

Table 2 **Risk factors for coronary heart disease**

	Characteristic	*Effects on the risk of coronary heart disease*
Principal risk factors	Smoking (cigarettes)	The greater the amount smoked currently, the greater the risk
	Blood pressure	The higher the pressure the greater the risk
	Blood cholesterol	The greater the concentration the greater the risk
Other risk factors	Age	Risk of CHD increases with age
	Sex	Males are more at risk than females
	Diabetes	People with diabetes have a higher risk
	Family history of CHD	Persons with a family history of CHD may be more at risk
	Obesity	Being overweight may increase the risk
	Stress	Stress may increase the risk
	Personality	Some types may be more prone than others
	Physical activity	The less exercise customarily taken, the greater may be the risk

between factors which are associated with the incidence of CHD and factors which are causative. There are many variables associated with the disease which are proxy measures for principal risk factors. For example, given that CHD is a disease of more affluent countries there might be an association between ownership of television sets and the incidence of the disease, but this would be non-causal and merely reflects a degree of societal affluence which has implications for factors such as diet, and smoking which are causally linked to CHD.

Atherosclerosis

To distinguish association from causality it is necessary to have an underlying biological model of the CHD disease process. Atherosclerosis is the primary disease mechanism of CHD which damages the coronary arteries. The term atherosclerosis comes from the Greek *athere*, meaning 'porridge' and *scler* meaning 'hard'. This describes well the process whereby the coronary arteries become narrowed with deposits of fat which develop into atheromas or plaques filled with cholesterol. As a coronary artery becomes narrower due to this process then the flow of blood through the vessel becomes impaired. Reduced blood supply to the heart muscle – the myocardium – initially may cause no problem at rest but during exercise the heart gets inadequate oxygen to metabolise its energy substrates and the accumulation of metabolites causes chest pain (angina). In extreme cases the efficiency of the heart as a pump is compromised first on exercise and later at rest. Ultimately if coronary arteries actually become blocked, which may be precipitated by a thrombosis (blood clot), then a myocardial infarction (heart attack) occurs which can be fatal.

From the involvement of cholesterol in the formation of atheromas it is clear that blood cholesterol is heavily implicated as a causative factor for CHD. Many of the epidemiological studies reviewed in this chapter demonstrate a positive correlation between the concentration of blood cholesterol and the risk of CHD and this association is presumed causative due to the observed atherogenic effect of raised blood cholesterol in prospective autopsy surveys. For example, the data of Solberg and Strong (1983) are illustrated in Figure 5 and demonstrate a linear relationship between the ante-mortem concentration of blood cholesterol and the post-mortem severity of atherosclerosis measured in terms of the percentage of the coronary surface covered with lesions.

But elevated blood cholesterol is not the only CHD risk factor where the underlying biology and evidence of association have indicated a causative relationship. The principal modifiable risk factors in Table 2 are cigarette smoking, raised blood pressure (hypertension) as well as raised blood cholesterol (hypercholesterolaemia).

The distinction between the three principal risk factors and the secondary risk factors such as age, sex, obesity, reduced physical activity and

Figure 5 **Relation of premortem plasma cholesterol level to severity of atherosclerosis at autopsy in prospective study. Atherosclerosis is expressed as percentage of surface of coronary arteries covered with raised atherosclerotic lesion**
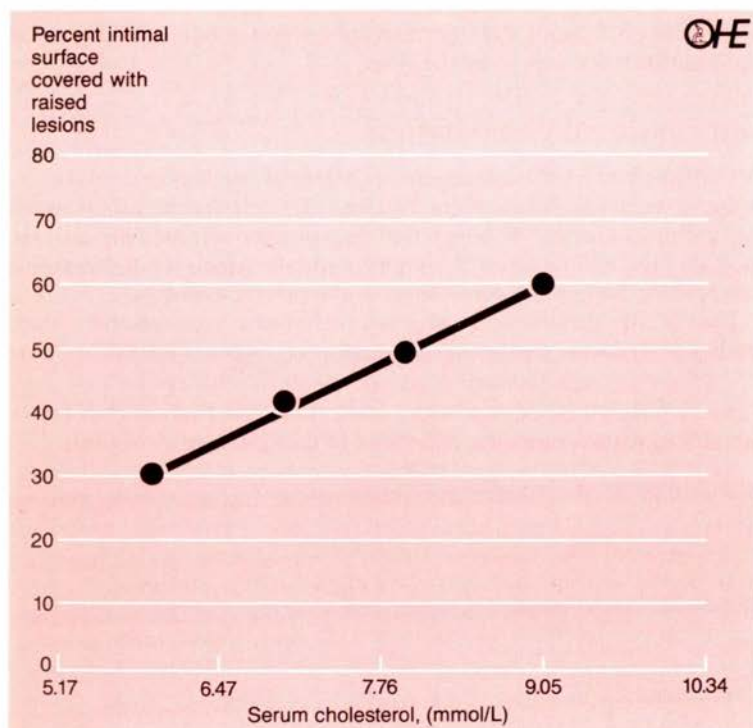
so on, is that the former are independent risk factors whereas the secondary factors generally are not.

For example, obesity is associated with CHD but is not independent of raised blood pressure and blood cholesterol, i.e. obesity is not a risk factor *per se*, only to the extent that it influences the primary risk factors (Shaper *et al*, 1985).

CHD is a prime candidate for prevention because, unlike some diseases, many of the major risk factors are modifiable. This is particularly true of cigarette smoking but is also true of hypertension and raised blood cholesterol where population or individual strategies to reduce levels using diet or drug therapy can reduce the risk of CHD. It is important to note the distinction between CHD risk in a population and management of CHD risk in an individual. Data for risk factor quantification are gen-

erally determined from population studies and when an individual modifies a risk factor he only alters his personal probability of future CHD events occurring. Hence the data presented in this section relate to averages within statistical distributions and some individuals will always lie in the tails of such distributions – i.e. some hypertensive smokers with high blood cholesterol will live to an old age and not die of CHD, but on average this is unlikely to be the case.

International comparisons

A starting point for the assessment of CHD epidemiology and risk factors is the observation that death rates from CHD vary enormously between and within countries. Although the study of international differences in mortality and risk factor(s) cannot be used to test theories of causality it can provide data on the consistency of the risk relationship.

One of the earliest and most comprehensive international cohort studies of CHD was the *Seven Countries Study* (Keys, 1980). Data were

Figure 6 **Percentage of men with serum cholesterol values over 6.5 mmol/L in seven countries, compared to the CHD incidence rate**
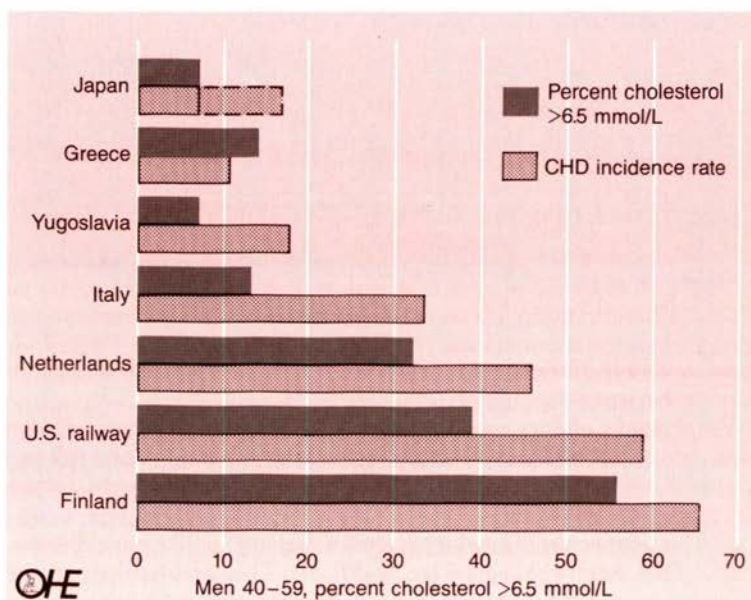
Note: Non-fatal CHD incidence for Japan is not precisely indicated, as the relevant 5-year clinical and ECG records were not independently reviewed at the University of Minnesota centre.

18   *Source:* Keys (1986)

Figure 7 **Ratio of polyunsaturated to saturated fats and incidence of CHD (per 100,000 population per year) in men aged 40-59 in the Seven Countries Study**

Incidence of CHD per 100,000 per year

240

● Finland

200

● USA

160

● Netherlands

120

● Italy

80

Yugoslavia
●

● Corfu

40

● Greece

Japan ●

0

0.1   0.2   0.3   0.4   0.5   0.6   0.7 0.8 0.9 1.0

Ratio of polyunsaturated fats to saturated fats
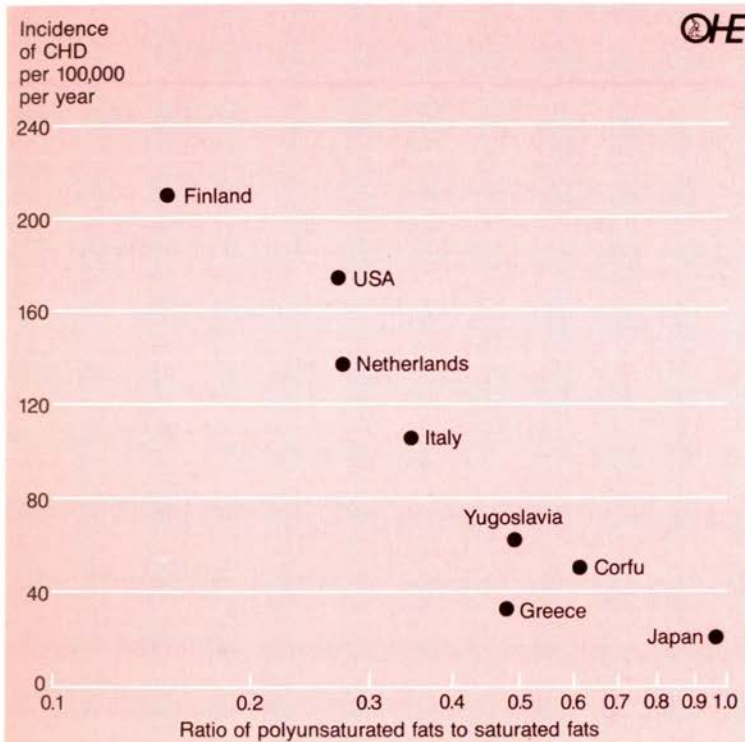
Notes: Greece = Corfu and Crete, but, as data for polyunsaturated fatty acids for Crete were not reliable, data for Corfu by itself are also presented.

Source: Shaper (1977)

obtained on 12,763 men aged 40-59 years in the years 1957-1962. After an initial examination subsequent patterns of CHD incidence were analysed. Summary results for cholesterol and CHD from this study are illustrated in Figure 6. These data suggest that elevated mean blood cholesterol is clearly associated with higher rates of population CHD. The population with the highest median level of serum cholesterol (East Finland, 6.6 mmol/L) had a rate of CHD death 15 times that of the population with the lowest serum cholesterol, Ushibuka Japan (4.1 mmol/L).

Taking the aetiology one step further Keys (1980) goes on to demonstrate the close relationship between diets which are high in saturated fatty acids and the mean level of population blood cholesterol.

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Figure 8 **International relationship between CHD mortality and total blood cholesterol, 1986**
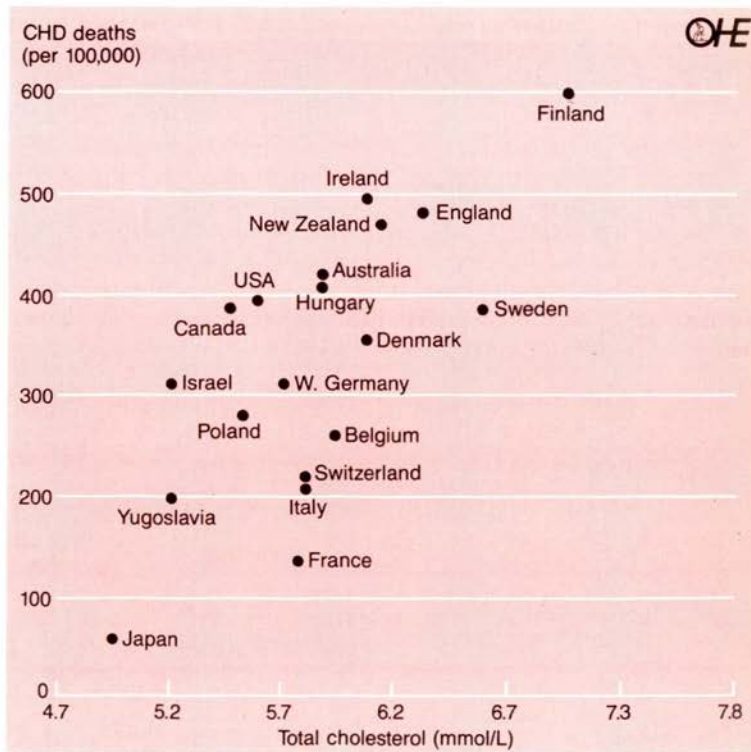
Source: Simons (1986)

Making an empirical link between diet and CHD via blood cholesterol the data in Figure 7 demonstrate how countries with a diet that has a low ratio of polyunsaturated to saturated fats experienced higher rates of CHD in the seven countries study. The so-called diet-heart hypothesis is discussed in Chapter 5.

A number of international comparative studies have found associations similar to those of Keys (1980). Data from Simons (1986) for 19 countries are presented in Figure 8 indicating the same relationship between blood cholesterol and CHD deaths. One of the puzzling aspects of such international data on CHD and risk factors is why countries such as Japan, with a high proportion of smokers and persons with hypertension (raised blood pressure), should have low levels of CHD. One possible explanation concerns the interaction of the three major risk factors. One argument is that smoking and hypertension serve to increase the pre-

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existing risk of CHD only in individuals who have elevated blood choles-
terol. Raised blood pressure and smoking are not risk factors for CHD in
individuals with low levels of blood cholesterol.

Prospective cohort studies

Broad international comparisons of CHD rates and hypothesised risk fac-
tors can lend general support to theories of CHD aetiology. But to quan-
tify the relationship between CHD and risk factors more precisely it is
necessary to design specific studies. A common study design for chronic
diseases is the prospective cohort where a population sample is iden-
tified, clinically assessed and then monitored for a number of years for
signs of the disease in question. If the sample is representative of the
population then such studies can be used to estimate changes in the inci-
dence and prevalence of the condition. Perhaps more importantly, by

**Figure 9 Relation between plasma cholesterol level and relative risk of
coronary heart disease (CHD) in three prospective studies:
Framingham Heart Study (solid circles), Pooling Project (triangles),
and Israeli prospective study (open circles)**
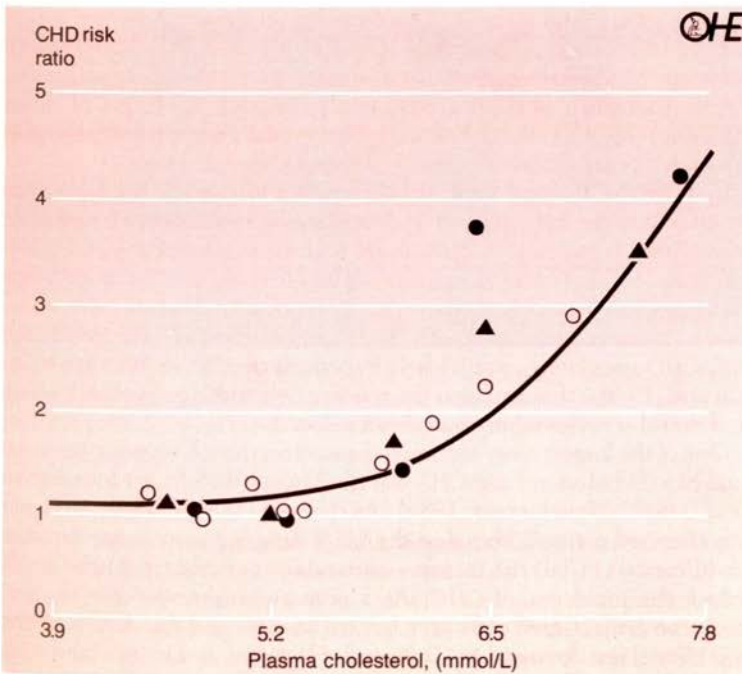
analysing the relationships between initial clinical assessments (e.g. blood pressure, blood cholesterol) for those who do develop CHD and those who do not, knowledge about risk factors can be improved and risk relationships quantified.

One of the earliest and best known cohort studies of CHD risk factors is the *Framingham Study* (Kannel *et al*, 1971). Although Framingham is only one small community in the USA, Shaper (1988) notes that it '. . . has become synonymous with the risk factor concept and is the source of much of our knowledge about the risk of CHD in individuals' (page 19). The study began in the 1940s and was designed to generate information that would help in the early detection and prevention of heart disease. Framingham is a small community 18 miles west of Boston in the USA and, starting with a small volunteer sample (N=740) in 1948, the study had grown into a major prospective survey. Some 5,000 men and women aged 30-59 were recruited into the study and examined at two-yearly intervals. Follow-up of these persons is still on-going in 1990 and data from the study have given investigators valuable knowledge about the relationships between various risk factors and CHD.

Data from cohort studies such as Framingham have indicated a clear relationship between elevated blood cholesterol and increased risk of CHD. Summary data from three cohort studies – Framingham (Kannel *et al*, 1971); the Pooling Project (Pooling Project Research Group, 1978) and the Israeli Prospective Study (Goldbourt *et al*, 1985) are presented in Figure 9. The results from these studies are remarkably similar and suggest that rates of CHD are relatively constant for levels of blood cholesterol up to around 5.2 mmol/L but beyond this threshold the CHD risk increases rapidly with rising cholesterol concentrations.

In 1969 the measurement of HDL cholesterol and triglycerides was introduced to the Framingham study and researchers observed an inverse relationship between HDL cholesterol and the incidence of CHD (Gordon *et al*, 1977). This association was also observed in other population studies around the world (Miller *et al*, 1977; Goldbourt *et al*, 1979; Keys, 1980). More recent data from Framingham serves to strengthen the HDL-CHD association, particularly in persons over 49 years of age (Castelli *et al*, 1986). (Evidence on the relative CHD risk attributable to HDL cholesterol is reviewed in more detail below.)

One of the largest cross-sectional datasets on the relationship between total blood cholesterol and CHD was the *Multiple Risk Factor Intervention Trial* (MRFIT; Stamler *et al*, 1986). As the name indicates this study was a randomised controlled trial in the USA designed to evaluate whether modification of CHD risk factors – particularly diet and smoking – could reduce the incidence of CHD. As a primary prevention intervention study the project met with very limited success and the details of the MRFIT trial are discussed in Chapter 5. However, to identify men with raised cholesterol to take part in the trial it was necessary to screen 361,662 men. Of these original screenees for MRFIT, 356,222 men aged

Figure 10 **Age-adjusted 6-year CHD and total mortality per 1,000 men screened for MRFIT according to serum cholesterol**
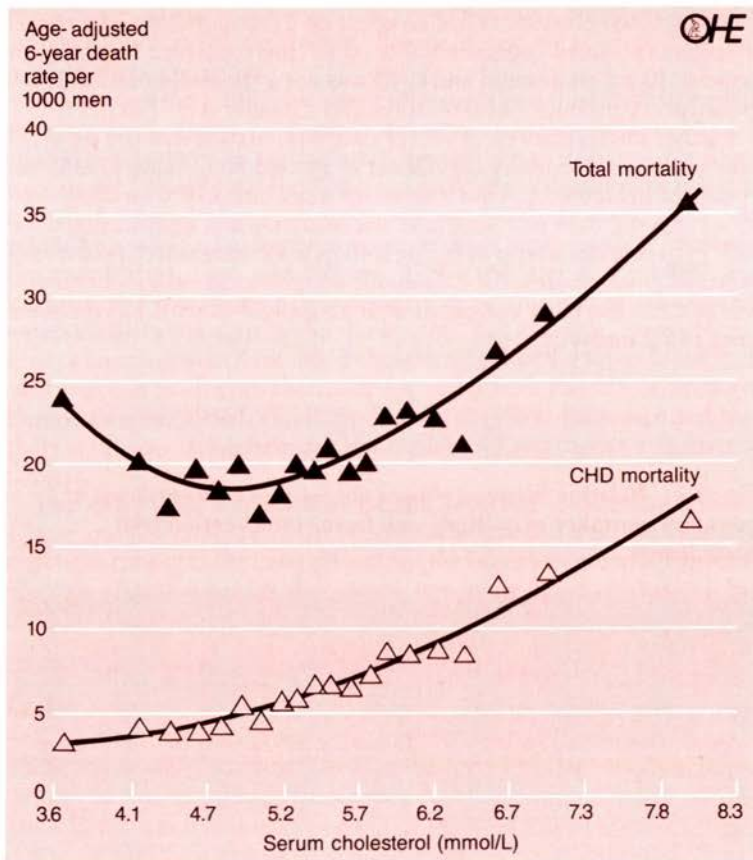
Note: Entire cohort of 361,662 men was divided into approximate twentieths, and each point represents the mortality (either CHD or total) and the mean cholesterol level in one of those twentieths. Hand-fitted lines are drawn through the points.

Source: Martin *et al* (1986)

35 to 57 years were followed-up after 6 years and the numbers of deaths caused by CHD and in total were recorded.

Six-year follow-up data from MRFIT screenees are presented in Figure 10 from the study by Martin *et al* (1986). These data demonstrate a clear positive association between blood cholesterol and deaths from CHD. Given the size of the sample from MRFIT screenees – seventy times larger than the Framingham study – this study offers the most compelling

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evidence of the blood cholesterol-CHD link. An advantage of this enormous sample size is that the MRFIT data could be used to address the important question of whether there exists a threshold below which reducing blood cholesterol has no effect on CHD mortality. The MRFIT invesigators stated unequivocably that the observed relationship between blood cholesterol and CHD was not a threshold one but it was graded and continuous with no threshold (Stamler *et al*, 1986).

Further interpretations of MRFIT data have argued that the CHD risk relationship is essentially curvilinear as plotted by Grundy (1986) and presented in Figure 11. Thus if we assign a risk ratio of 1.0 for cholesterol at 5.2 mmol/L then at 3.9 mmol/L the relative risk is significantly lower at 0.7. In contrast a level of 6.5 mmol/L is associated with a relative risk ratio of 2.0 and at a level of 7.8 mmol/L an individual faces four times the risk of CHD mortality compared with an individual with blood cholesterol of 5.2 mmol/L.

Figure 11 **Relation between plasma cholesterol concentration and coronary mortality in multiple risk factor intervention trial participants**
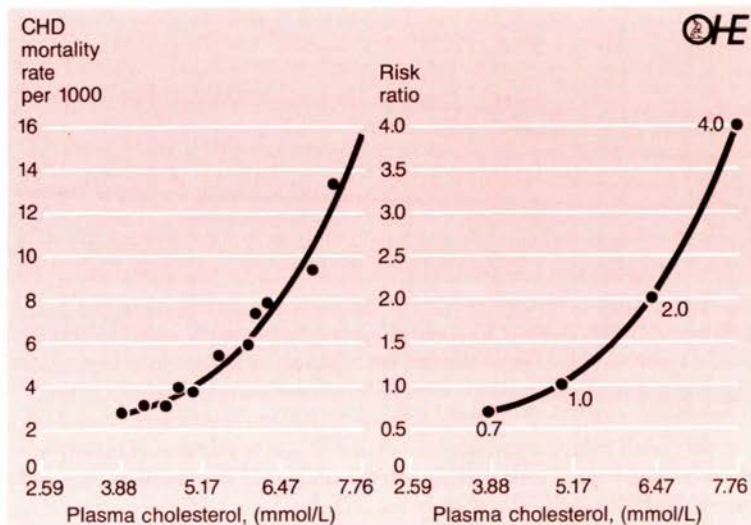
Left: Coronary mortality for all individuals who were normotensive at screening expressed as yearly rates per 1,000.
Right: Coronary mortality expressed by risk ratios.

24   *Source:* Grundy (1986)

Questions about low cholesterol

Taken to an extreme, the message from the MRFIT analysis is that given the apparent absence of a lower CHD risk threshold, the lower the level of blood cholesterol the better. But does low cholesterol have any adverse effect?

A feature of the MRFIT screenee follow-up data is that the relationship between total plasma cholesterol and total mortality appears to be J-shaped as illustrated by the higher of the two curves in Figure 10. Blood cholesterol falling below the 10th percentile of the distribution (approximately 4.1 mmol/L) appears to be associated with increased total mortality. This association has been found in other studies such as Hiatt and Fireman (1986), Rose and Shipley (1980) and Isles *et al*, (1989). But international comparative data do not support this inverse relationship especially between cancer and cholesterol. For example, nearly 90 per cent of Japanese men have blood cholesterol below 4.4 mmol/L but their cancer risk is no higher than that for males from the US or northern Europe (Katan, 1986). Similarly Peto *et al* (1989) have reported that there is no association between low cholesterol and cancer incidence in China.

The most likely explanation for the observed association between cancer and low cholesterol (in population studies) is that the causation runs from cancer to cholesterol, and not the other way around. Hiatt and Fireman (1986) conclude that cancer can lower blood cholesterol, but there is no evidence that lowering blood cholesterol can cause cancer.

Another concern about low cholesterol is the incidence of stroke. A recent follow-up of 350,977 MRFIT screenees examined whether the incidence of certain types of stroke (intracranial haemorrhage ICD-9; 431,432) was greater in persons with low blood cholesterol. Iso *et al* (1989) found that mortality from this type of stroke was three times higher in men with blood cholesterol lower than 4.14 mmol/L than in those above this level. But this risk needs to be placed in context. Iso *et al* (1989) point out that, relative to the cardiovascular risks (including those of thrombotic stroke) associated with high blood cholesterol concentrations, the relative risks of low blood cholesterol are small.

Further questions on the potential risks of cholesterol lowering are discussed in the context of data from clinical trials of cholesterol lowering drugs in Chapter 6.

Comparison and interaction with other lipid and non-lipid risk factors

The evidence from large datasets such as MRFIT is that the relationship between blood cholesterol and the relative risk of CHD is graded and continuous. But given that CHD is multifactorial in aetiology it is important to consider blood cholesterol in the context of other risk factors.

There are two questions to be addressed:

(i) What is the population attributable CHD risk of elevated total blood cholesterol? That is, allowing for other non-lipid risk factors such as smoking and blood pressure and other lipid factors such as HDL and triglycerides that might explain variance in CHD incidence within populations, how useful is total blood cholesterol as a predictor of CHD? Furthermore, to what extent are cholesterol subfractions such as HDL and triglycerides independent predictive factors in the incidence of CHD?

(ii) Since some persons will have multiple CHD risk factors, is it appropriate to assume that individual risk factors are additive or is there some interaction or synergism between factors which produces a multiplicative effect?

Evidence on both these questions is available from a large number of studies and a detailed review is beyond the scope of this monograph. However the main findings of such studies have been broadly consonant and the following sections are based on information from two large epidemiological data sources, the British Regional Heart Study (Shaper *et al*, 1985; Pocock *et al*, 1989) and the MRFIT study (Stamler *et al*, 1986).

The *British Regional Heart Study (BRHS)* (Shaper *et al*, 1981) is a prospective cohort study designed to relate variation in personal and environmental risk factors to variation in cardiovascular mortality. The sample consists of 7,735 men aged 40-59 years randomly selected from 24 towns in England, Wales and Scotland. A number of basic clinical measures relevant to cardiovascular risk were recorded at the initial contact with the sample. At regular intervals the men are assessed for cardiovascular morbidity and mortality.

Data from the prospective phase of BRHS were reported by Shaper *et al* in 1985. After a mean follow-up period of 4.2 years there had been 202 cases of major CHD (defined as myocardial infarction or sudden death). The BRHS investigators undertook two forms of analysis of variance – univariate and multivariate. The purpose of univariate analysis is to examine correlations between CHD events and each risk factors separately. The aim of multivariate techniques such as multiple logistic regression is to model the probability of CHD as a function of a number of factors simultaneously. This second approach can provide an indication of the marginal impact on CHD likelihood of a change in one factor (e.g. blood cholesterol) while allowing for effects from other risk factors. This form of analysis is relevant in trying to determine which factors have an independent influence on CHD and which factors are secondary, in that their mode of action is via influencing other risk factors.

Total cholesterol and non-lipid factors

Total blood (serum) cholesterol: BRHS data indicate a continuous and marked trend of increasing CHD risk with rising blood cholesterol. Men in the top fifth of the distribution have slightly more than three times the risk of CHD than men in the lowest fifth. After adjustment for other risk factors there is still evidence of blood cholesterol being an independent CHD risk factor.

Cigarette smoking: Men who have never smoked have a much lower risk of CHD than current or ex-smokers. BRHS data indicate no clear evidence of a dose-response relationship, with men smoking 1 or 20 cigarettes per day being about 3 times more at risk than non-smokers. This relative risk remains after adjustment for other risk factors.

Blood pressure: For diastolic blood pressure BRHS data indicate there is evidence of a threefold increase in CHD risk in the top fifth of the distribution (≥ 93 mmHg). After adjustment for other risk factors there is evidence that blood pressure is an independent CHD risk factor.

Body mass index: An indicator of obesity as a risk factor for CHD in a person's body mass index (BMI) which is the ratio of weight (kg) to height (m) squared (i.e. kg/m^2). The data suggest a doubling of risk for those in the top fifth of the distribution relative to the lowest fifth. However, after allowing for other risk factors there appears to be no independent effect of BMI on CHD risk.

Other lipid risk factors

A number of population studies, notably Framingham (Kannel, 1983), established a relationship between HDL cholesterol where increased levels of HDL appear to be a 'protective' factor against heart disease. This finding is consistent across a number of studies (Gordon *et al*, 1989), although the precise mechanism whereby HDL protects remains a mystery (Betteridge, 1989). The observation that HDL appears to be a protective CHD factor has lead to a popular dichotomy between 'good cholesterol' (HDL) and 'bad cholesterol' (LDL).

Although the early analysis of BRHS data by Pocock *et al* (1985) suggested that HDL cholesterol, when other factors were taken account of in a multivariate analysis, had no independent association with CHD incidence, a more recent analysis (by the same authors) with a larger follow-up experience now confirms that HDL appears to be an independent protective factor (Pocock *et al*, 1989).

Data from the recent analysis of BRHS data by Pocock *et al* (1989) are illustrated in Figure 12 where the annual risk of major CHD events per thousand males is analysed by total and HDL cholesterol and triglycerides. These plots are based on univariate and multivariate analyses of CHD incidence variance, corresponding to the unadjusted and

Figure 12 **Lipid risk factors from the British Regional Heart Study**
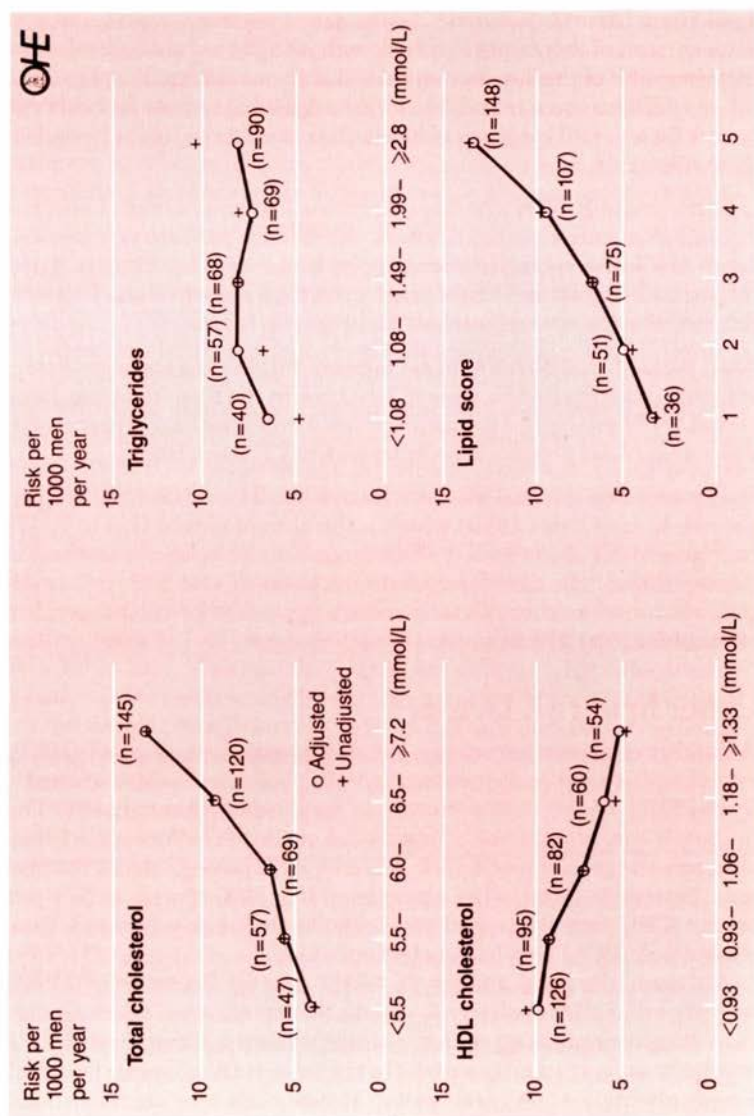
Note: Risk of major ischaemic heart disease events/1,000 men/year in each fifth of distribution of concentrations of serum total cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, and lipid score ((0.42 × times cholesterol concentration) – HDL cholesterol concentration). Numbers of cases of ischaemic heart disease in each fifth are shown in parentheses.

28   *Source:* Pocock and Shaper (1989)

adjusted (i.e. for other factors) plots respectively. Men in the highest fifth of the total cholesterol distribution (≥ 7.2 mmol/L) had 3.5 times the risk of CHD than men in the lowest fifth. For HDL cholesterol, men in the bottom fifth of the HDL distribution had twice the risk of CHD, after adjusting for other lipid and non-lipid factors. For triglycerides, although the unadjusted data suggest a positive CHD risk association, when adjustment for other risk factors is made there appears to be no independent association.

The main inference drawn by Pocock *et al* (1989) from their data is that, among the lipid predictors of CHD, the single lipid measurement with greatest predictive power is total blood cholesterol. Further knowledge of a person's HDL would increase the predictive power of a CHD risk model but by less than the marginal effect of knowing total cholesterol. The authors estimate that a combined 'lipid score' ($0.42 \times$ total cholesterol − HDL cholesterol) offers the best prediction of a persons CHD risk from lipid information.

Multiple factors and conditional risk

Although analysis of the marginal contribution to overall CHD risk by single factors is illuminating, how do different combinations of risk factors influence CHD risk? An important message from the 1985 analysis of the BRHS data is that the bulk of CHD incidence does not occur in those individuals who lie in the extreme tail of any single risk factor distribution, but rather in those individuals who have moderate elevations in a number of risk factors (e.g. mildly hypertensive smokers with moderately elevated blood cholesterol).

To illustrate the way in which CHD risk varies by multiple factors, data from the 356,222 MRFIT screenees have been plotted from Stamler *et al* (1986) to produce Figures 13(a) and 13(b). These figures indicate the 6-year CHD mortality rates for risk factor sub-groups according to blood cholesterol level, diastolic blood pressure (greater or less than 90 mmHg) and smoking status. It is noticeable that there is a marked difference between smokers and non-smokers; at all levels of blood cholesterol and for high and low blood pressure groups, smokers were at greater risk of CHD mortality. For example, smokers with cholesterol in the range 5.72-6.31 mmol/L and with diastolic blood pressure greater than 90 mmHg, when compared with the same group of non-smokers, were nearly three times more at risk of CHD mortality (16.6 per 1,000 versus 5.6 per 1,000).

The implication of these data is that the risk relationship between blood cholesterol and CHD is a conditional probability, i.e. the probability of developing CHD for a person with total blood cholesterol of 6.2 mmol/L given that they smoke, is higher than for a similar person who does not smoke. In other words a person for whom elevated blood cholesterol is the only CHD risk factor can have a higher level of blood

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Figure 13 (a) CHD mortality for non-smokers by plasma cholesterol and blood pressure: MRFIT
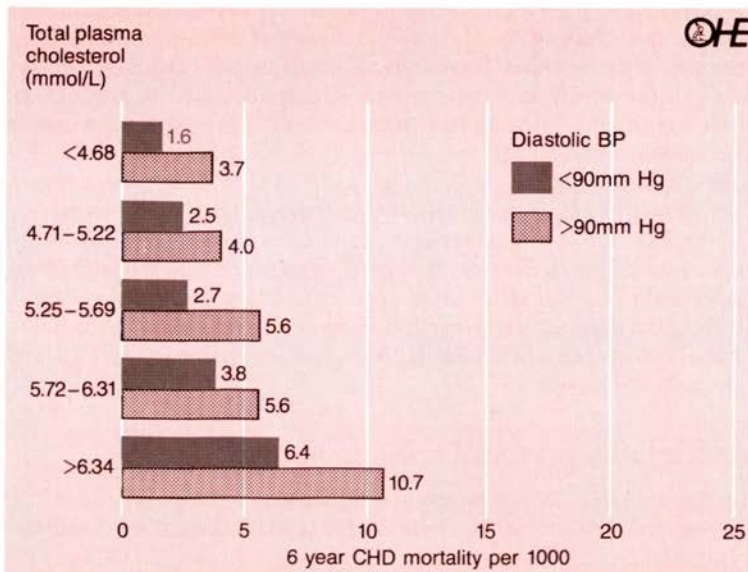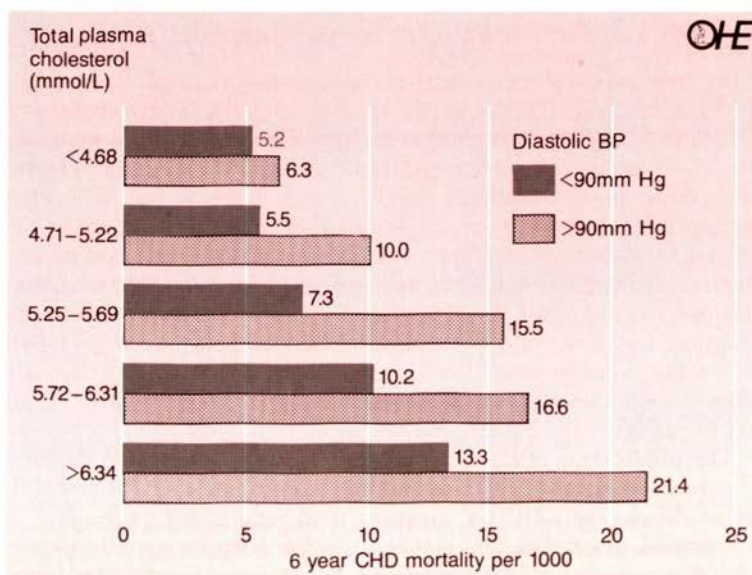

Figure 13 (b) CHD mortality for smokers by plasma cholesterol and blood pressure: MRFIT

Source: Stamler et al (1986)

cholesterol than a person who has two risk factors and still be at the same level of CHD risk.

As Grundy (1986) notes, the indication from multiple risk data is of a multiplicative (rather than simply additive) interaction between the three major risk factors. The extremes of the mortality distributions give a risk range from 1.6 deaths per 1,000 to 21.4 per 1,000 – comparing lowest levels (absence) of risk factors with highest levels (presence). These data illustrate the multifactorial nature of CHD and serve to underline the importance of assessing overall CHD risk rather than individual risk factors in isolation. In other words, there is not a single one-to-one relationship between high blood cholesterol and risk of CHD. For example, based on MRFIT data, a smoker with high blood pressure and blood cholesterol of 5.5 mmol/L would be at higher risk of death from CHD (15.5 deaths per 1,000) than a non-smoker with low blood pressure who had a blood cholesterol greater than 6.3 mmol/L (10.7 deaths per 1,000).

Lifetime CHD risk

A novel approach to illustrating the interaction of CHD risk factors was adopted by Grundy (1986) who considered how each risk factor accelerates the progress of atherosclerosis over a person's lifetime. He hypothesises that a critical point is reached when 60 per cent of the coronary surface is covered by atherosclerotic lesions and that in the absence of other risk factors a person with a total blood cholesterol of 5.2 mmol/L would reach this critical point at age 70 years. As illustrated in Figure 14, one way of thinking about additional risk factors such as smoking and hypertension is to see them as reducing the age at which this critical point of atherosclerosis is reached. Thus Grundy hypothesises that the addition of smoking to the baseline risk reduces the critical age to 60 years. The more risk factors that are added, the lower is the critical age and the life expectancy of the individual.

Grundy's representation of risk factors is also useful for demonstrating the importance of a person's age in the assessment of CHD risk from elevated blood cholesterol. Because the process of atherosclerosis is cumulative, with fatty deposits gradually building up in the arteries over time, a blood cholesterol concentration of, say, 6.5 mmol/L in a person aged 20 is a greater lifetime risk than in a person aged 55 years. For this reason the recommendations made by some authorities – such as the US National Institutes of Health – about desirable levels of population blood cholesterol are age-related.

Figure 14 **Relation of coronary atherosclerosis (percentage of surface of coronary arteries covered with raised lesions) vs age as modified by addition of risk factors**
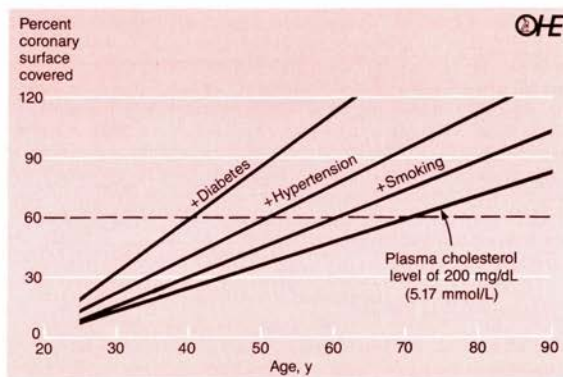
Note: In absence of other risk factors, patient with cholesterol level of (5.2 mmol/L) should reach critical stenosis at about age 70 years. Addition of smoking reduces age to 60 years, and addition of more risk factors (i.e. hypertension and diabetes mellitus) reduces age further.

Source: Grundy (1986)

Population susceptibility and risk factors

Shaper (1985) has summarised the CHD risk factor problem in a useful diagram which is reproduced as Figure 15. A distinction is made between indicators of susceptibility to CHD such as elevated blood cholesterol, existing atherosclerosis and the ratio of polyunsaturated to saturated fat (P/S ratio) in the diet, and risk factors which can either aggravate and worsen the situation (e.g. smoking, obesity, hypertension) or improve it (e.g. exercise and increased high density lipoprotein cholesterol). The initial susceptibility of a population to CHD, as determined by blood cholesterol and in turn diet (P/S ratio), is a key variable in determining the importance of other risk factors. As discussed above, in countries such as Japan smoking is not implicated as a CHD risk factor because the Japanese have a low susceptibility by virtue of low blood cholesterol and low dietary P/S ratio. However, in countries such as the UK where the diet is relatively high in saturated fats and mean blood cholesterol is about 5.9 mmol/L (Mann *et al*, 1988) the secondary risk factors such as smoking would seem to be of greater importance.

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Figure 15 **Community susceptibility and incidence of coronary heart disease**
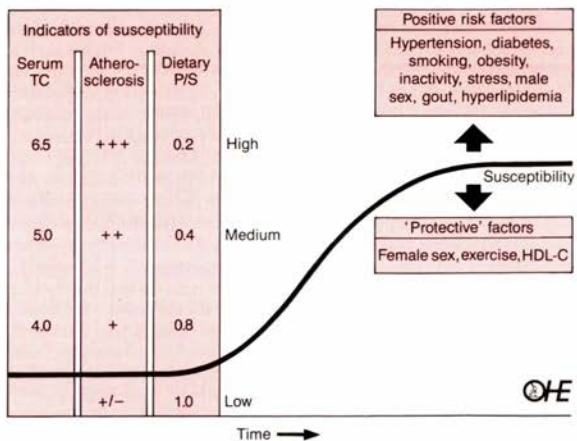
4. NORMAL VERSUS DESIRABLE BLOOD CHOLESTEROL LEVELS

Evidence about the causative relationship between elevated blood cholesterol and the incidence of CHD is overwhelming. Studies such as MRFIT have indicated that the relationship between CHD risk and blood cholesterol is graded and continuous – as the concentration in the blood increases so does the risk of CHD (Stamler *et al*, 1986). Many commentators have drawn a parallel between the nature of blood cholesterol and blood pressure as CHD risk variables (Standing Medical Advisory Committee, 1990). For purposes of classifying patients and populations into those who are hypertensive and those who are normotensive it is necessary to decide upon cutpoints in the distribution of (diastolic) blood pressure – conventions being mild hypertension 90-110 mmHg, moderate hypertension 110-130 mmHg and severe hypertension >130 mmHg. But as Beevers and Wilkins (1987) note there is no natural threshold in the distribution that defines when treatment should begin – the issue is one of balancing the risks of treatment against those of non-treatment. This is a difficult decision to make because often the person with raised blood pressure or cholesterol will have no symptoms – treatment will be prophylactic and aimed at preventing CHD events in the future.

What is the desirable level of blood cholesterol in the individual and in populations and how does this compare with levels normally observed? There has been considerable discussion about desirable blood cholesterol levels. A multidisciplinary workshop (Blackburn *et al*, 1979) proposed that the mean blood cholesterol of an adult population should not exceed 4.7 mmol/L. An expert committee convened by the World Health Organization (1982) set the desirable mean at less than 5.2 mmol/L. A US National Institutes of Health (1984) Consensus conference considered desirable levels to be age-related, with 5.2 mmol/L for those aged over 30 and 4.7 mmol/L for younger adults.

On what basis are such acceptable levels of cholesterol determined? There are two types of approach:

(i) abnormally high levels of any continuous variable such as blood pressure or blood cholesterol can be defined in relative terms, that is, by reference to the overall population distribution. For example, the US Consensus Conference on Cholesterol (National Institutes of Health, 1984), recommended that individuals with blood cholesterol above the 90th percentile of the US population distribution should be classified as high risk. Similarly, persons with blood cholesterol levels between the 75th and 90th percentiles were classified as being at moderate risk of CHD.

The problem with this type of approach is the inference that the average population level of blood cholesterol is desirable and increasing deviations upwards from this level are increasingly undesirable. Such

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definitions of elevated cholesterol as a diagnosis – hypercholesterolaemia – would tend to be country-specific, being a function of deviation from the country average. Furthermore, under such a relative definition 10 per cent of the population would always be defined as high risk even if the population mean fell substantially.

(ii) the second approach is to define specific concentrations of blood cholesterol which can be used in the definition and management of raised blood cholesterol as CHD risk factor. Given that the mean US blood cholesterol concentration was above 5.2 mmol/L the US Consensus Conference decided that defining risk groups only in terms of percentiles of the distribution would be inadequate. In consequence they defined (for men aged 40 and over) moderate risk as being greater than 6.2 mmol/L and high risk as greater than 6.7 mmol/L.

Cholesterol management algorithms

The United States was the first country to convene a Consensus Conference on the lowering of blood cholesterol to prevent heart disease and this was followed by a number of similar policy statements, including those of Britain, Europe and Canada. Some of the main points from these policy statements are summarised in Table 3. The general conclusions of these statements are broadly similar. Most authorities argue that dietary counselling for individual patients should begin when blood cholesterol is above 5.2 mmol/L and that if specific lipid-lowering diets are unsuccessful for those with blood cholesterol in the range 6.5-7.8 mmol/L then drug therapy should be considered.

The general treatment guidelines of the British Hyperlipidaemia Association (Shepherd et al, 1987) and the European Atherosclerosis Society (1988) are reproduced in summary in Table 4. It should be stressed that at all levels of blood cholesterol it is important that overall CHD risks are assessed because, as indicated earlier from MRFIT data, persons with raised cholesterol and other risk factors, such as smoking, are at greater overall risk of CHD. A key feature of this and other treatment guidance is that a lipid-lowering diet – reducing the amount of food energy from saturated fats – should be the first-line therapy. However, for especially high levels of blood cholesterol (>7.8 mmol/L) it is recommended that active treatment should be initiated with supervised dietary therapy and, commonly, drug therapy. (The treatment options – diets and drugs – are discussed with evidence on efficacy later).

In exploring the implications of such treatment guidelines it is necessary to distinguish between two approaches to the reduction of blood cholesterol in the prevention of CHD:

(i) the high-risk approach is a strategy where the value of such guidelines would be in determining the criteria for intervening to treat those at high risk. The strategy is selective not universal; the aim is to identify and

Table 3 **Consensus recommendations**[*]

Group	Level at which repeat testing done, mmol/L, and frequency of testing	Level at which dietary counselling started, mmol/L	Level at which drug therapy started, mmol/L
National Institutes of Health Consensus Conference (1985)	<5.2; every 5 years	6.2	6.7
National Cholesterol Education Program Expert Panel (1988)	<5.2; every 5 years	5.2	≥4.9 (low-density lipoprotein cholesterol)
Canadian Consensus Conference on Cholesterol (1988)		5.2	
British Hyperlipidaemia Association (1987)		5.2	6.5-7.8
European Atherosclerosis Society (1988)		5.2	6.5-7.8

[*] In men aged 40 to 60 years with no history of cardiovascular disease and no other risk factors. Values are total serum cholesterol levels except where stated otherwise.

Table 4 **Intervention guidelines for primary hypercholesterolaemia recommended by the British Hyperlipidaemia Association and the European Atherosclerosis Society**

Total plasma cholesterol mmol/L	Actions	Treatment
5.2-6.5	Assess overall CHD risks	Dietary advice
6.5-7.8	Assess overall CHD risks	Specific lipid-lowering diet. Add drug therapy if cholesterol level remains high and other risk factors are present
>7.8	Assess overall CHD risks	Specific lipid-lowering diet and lipid-lowering drug together

Source: Shepherd et al (1987) and European Atherosclerosis Society (1988)

target those at the extreme of the blood cholesterol distribution who are most at increased risk of CHD;

(ii) the public health approach is a universal strategy where the aim is to prevent CHD by population programmes aimed at reducing the average level of blood cholesterol in the population. Researchers indicate that the majority of CHD mortality occurs in persons who are not in high risk groups according to blood cholesterol and hence reducing the level of blood cholesterol in the average person will have a small impact on a large number of persons rather than a large impact on a small number of people.

The two approaches to prevention are not alternatives but are complementary: by reducing the mean of the distribution the number in the extreme tail exceeding a given threshold will also be reduced. But the public health approach in isolation will provide no means of identifying and treating those persons at high risk.

Figure 16 **Mean blood (plasma) total cholesterol: Britain 1986**
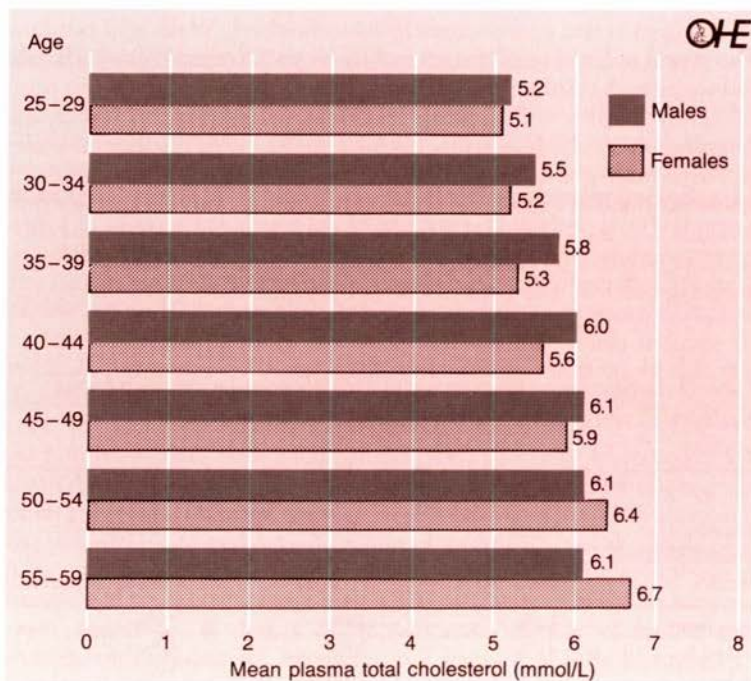
Sample N=12,092

Source: Mann et al (1988)

It is instructive to consider what impact adherence to these intervention and prevention guidelines would have in Britain. According to the various policy guidelines does the average Briton have a desirable level of blood cholesterol? Although data on population blood cholesterol are not routinely sampled, three recent studies have generated some valuable information.

In the first study Mann and colleagues (1988) surveyed 12,092 British men and women aged 25-59 years and assessed them for a variety of cardiovascular risk factors including blood (plasma) cholesterol – their results for the latter are presented by age and sex in Figure 16. The mean total plasma cholesterol concentrations were 5.9 (SD 1.2) mmol/L in men and 5.8 (SD 1.2) in women. As demonstrated in other surveys of blood cholesterol the concentration appears to increase gradually with age. However it is noticeable that differences between the sexes appear to vary over the life-cycle with concentrations in females being higher than males in the age range 50-59 years. Research has indicated that this age-related sex difference may be due to the effect of the female menopause (Matthews *et al*, 1989).

The results from Mann *et al* (1988) are very similar to those in a smaller (n=1,500) survey by the Office of Population Censuses and Surveys (1990) of men and women aged 18-64 in England, Wales and Scotland who found average total cholesterol levels of 5.8 mmol/L in both men and women. A third survey was recently undertaken as part of the Scottish Heart-Health and Scottish MONICA (Monitoring of trends and determinants in Cardiovascular disease) studies for WHO, they measured blood (serum) cholesterol in 10,450 representative men and women across Scotland in 1984-86. The results of all three surveys are presented in Table 5. It is clear from this table that in Britain only about one third of the population have blood cholesterol levels below 5.2 mmol/L, and only a quarter of the population in Scotland have levels below this

Table 5 **Estimates of percentage of British population with blood cholesterol above action thresholds of European Atherosclerosis Society**

Threshold for blood cholesterol mmol/L	Per cent of population:		
	Mann et al 1988	OPCS (1990) 1986-87	Tunstall-Pedoe et al (1984-86 Scotland)
Less than 5.2	34%	34%	25%
5.2 –	41%	39%	39%
6.5 –	21%	20%	25%
7.8 –	4%	7%	11%

Source: Standing Medical Advisory Committee (1990)

threshold which has been declared the 'optimal value' for the general population by the European Atherosclerosis Society (Shepherd *et al*, 1987).

Given this population distribution of blood cholesterol, what are the implications of intervention strategies? If the recommendations of the European Atherosclerosis Society (1988) were implemented in Britain for the 38 million adult population (aged 15-64) then using the Mann *et al* (1988) and OPCS survey data as a guide, the implications would be:

(i) approximately 5 per cent of adults (1.9 million) have blood cholesterol levels in excess of 7.8 mmol/L and require active treatment in the form of 'dietary treatment and, commonly, drug therapy needed with ongoing supervision to maximise response' (EAS, 1987: page 576).

(ii) approximately 25 per cent of adults (9.5 million) have levels greater than 6.5 mmol/L and if lipid-lowering diets are not successful then according to recommendations, drug therapy should be initiated;

(iii) approximately 66 per cent of adults (25.1 million) have levels greater than 5.2 mmol/L and should, according to recommendations, receive dietary advice.

Are cholesterol cutpoints constructive?

Epidemiologists such as Tunstall-Pedoe *et al* (1989) are critical of the way in which one-dimensional cholesterol management algorithms have been presented for adult populations irrespective of age and sex. Results from their survey in Scotland are presented graphically in Figures 17a and 17b, using what they term How-Often-This-High (HOTH) graphs which indicate, for each 10-year age band, the cumulative proportion of the sample with blood cholesterol values lying above specific thresholds of 5.2, 6.5 and 7.8 mmol/L.

The HOTH distributions in Figures 17a and 17b clearly indicate the marked differences in blood cholesterol distributions in Britain and Tunstall-Pedoe *et al* (1989) argue that '. . . there is no single value or range that can be applied indiscriminately to the adult population'. Although the data from Mann *et al* (1988) in Figure 16 indicate only small differences in average values by age and sex, the differences in the tails of these distributions are very large resulting in marked variation in the proportions of each age-sex group exceeding a given threshold (e.g. 6.5 mmol/L). Tunstall-Pedoe *et al* (1989) argue that a consequence of using fixed cholesterol cutpoints across all age-sex groups in management algorithms is that a disproportionate number of middle-aged women with cholesterol exceeding 6.5 mmol/L will be identified for intervention by diet or drug therapy.

Arguably the use of HOTH graphs by age and sex will help to inform and educate physicians about the nature of blood cholesterol distributions

Figure 17a **Decremental percentage frequency distribution of serum cholesterol in men by 10-year age-groups 25-64 (Scotland/Britain)**
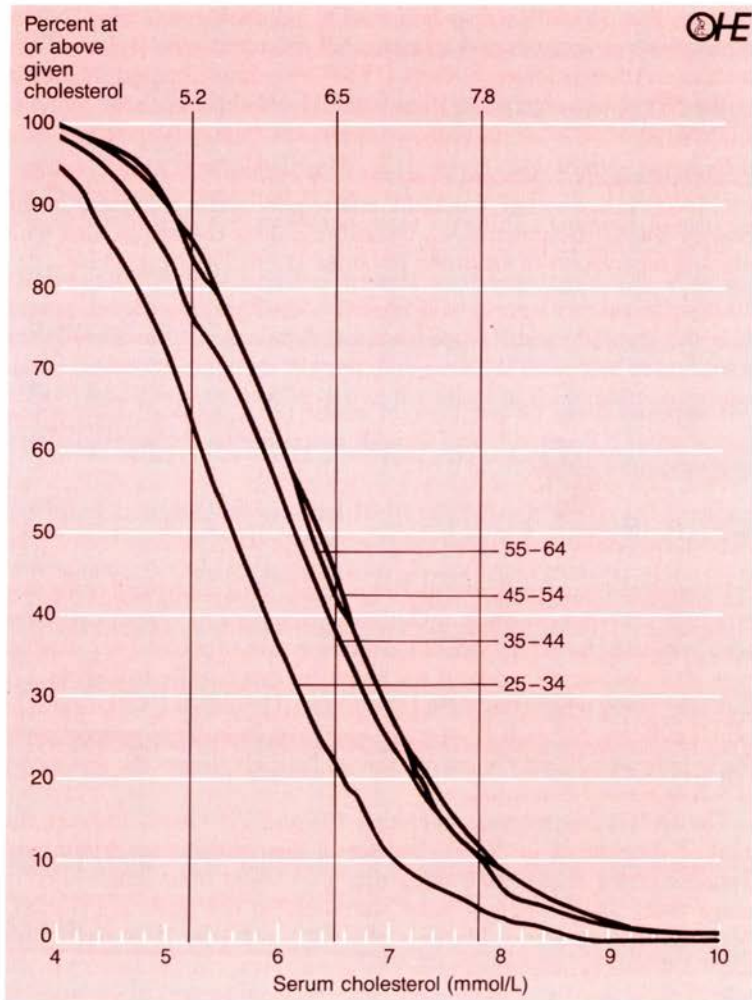
Source: Tunstall-Pedoe et al (1989)

Figure 17b **Decremental percentage frequency distribution of serum cholesterol in women by 10-year age-groups 25-64 (Scotland/Britain)**
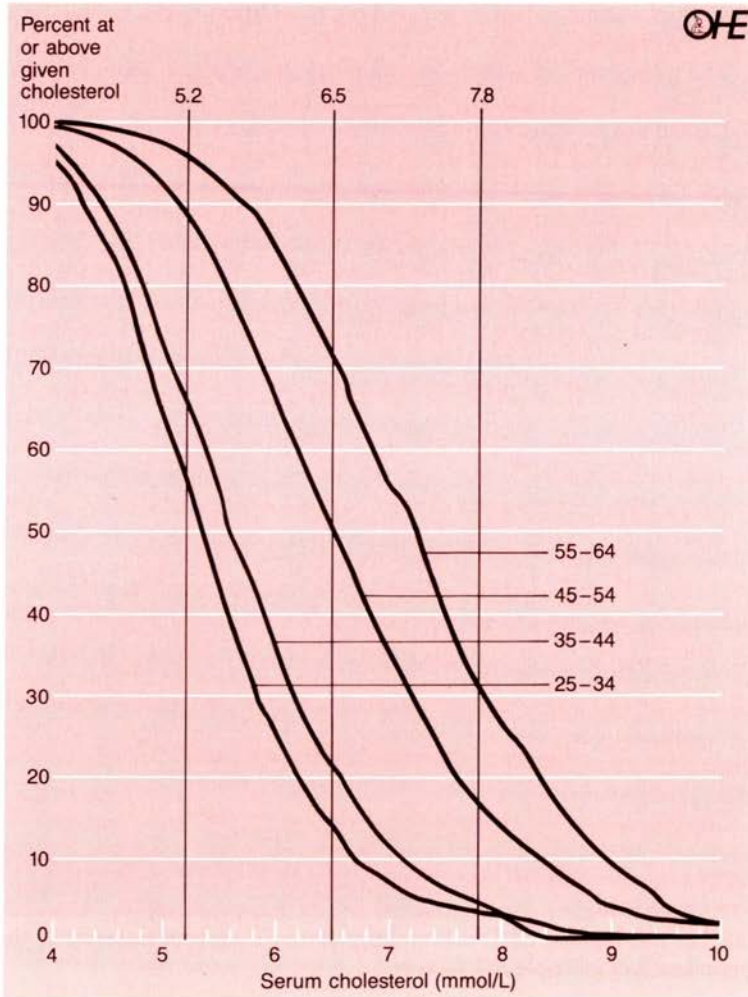
Source: Tunstall-Pedoe et al (1989)

and how individual patient measurements compare with age-sex norms for the population. An advantage of HOTH presentations is that they can help the medical practitioner assess cholesterol measurements in the context of normal values by age and sex in addition to the policy statements of desirable levels.

The second area of criticism concerning the one-dimensional cholesterol algorithms is the danger that undue emphasis might be placed on the single risk factor of blood cholesterol when assessing the risk of CHD in populations or individuals. Population assessment of CHD risk by blood cholesterol alone will generate different predictions to a multi-factor assessment. This point can be illustrated with interactional data from the on-going WHO programme for the *MONItoring of trends and determinants in CArdiovascular disease* (MONICA), WHO (1988). The MONICA programme is designed to generate international time-series data on CHD risk factor prevalence. Data on mean blood cholesterol concentrations are presented in Figure 18. Using the marker of 5.2 mmol/L suggested by many agencies as the risk threshold for desirable levels, it is clear from this figure that all countries represented other than China (4.1 mmol/L) have levels which are too high. Furthermore, given the population distribution of blood cholesterol is approximately normal (equating mean and median values, Tunstall-Pedoe *et al*, 1989) it is true to say that, for all the countries listed other than China, more than half the population has blood cholesterol exceeding 5.2 mmol/L.

If the risk of CHD was a single factor phenomenon then the rank-ordering of countries by blood cholesterol might serve as a satisfactory international CHD risk ordering. As indicated by the epidemiological studies reviewed in Chapter 3 there is a close association between blood cholesterol and CHD risk, but other factors such as smoking and hypertension contribute to the complete picture of CHD risk and data on these factors are also being collected by researchers in the MONICA study. In Figure 19 data are presented on the proportion of individuals in each country with zero, one, two or three risk factors. While the rank order of some countries such as China is the same for cholesterol and multiple risk factors the same is not true for countries such as Scotland which has the joint fourth highest concentration of blood cholesterol (6.2 mmol/L) but has the highest CHD risk ranking among countries in terms of the prevalence of multiple risk factors.

Figure 18 **WHO MONICA project: median total blood cholesterol (serum) levels males aged 35-64 years**

Country	mmol/L
China	4.1
USA	5.3
Poland	5.5
Italy	5.6
New Zealand	5.7
Hungary	5.7
Australia	5.7
West Germany	5.7
France	5.9
USSR	5.9
N. Ireland	5.9
Sweden	6.1
Iceland	6.1
Belgium	6.1
Scotland	6.2
Denmark	6.2
Switzerland	6.3
Finland	6.3
Czechoslovakia	6.3
Luxembourg	6.4

OHE

Source: WHO Monica (1988)

Figure 19 **WHO MONICA project: age-standardised proportions with zero to three CHD risk factors: males aged 35-64 years**
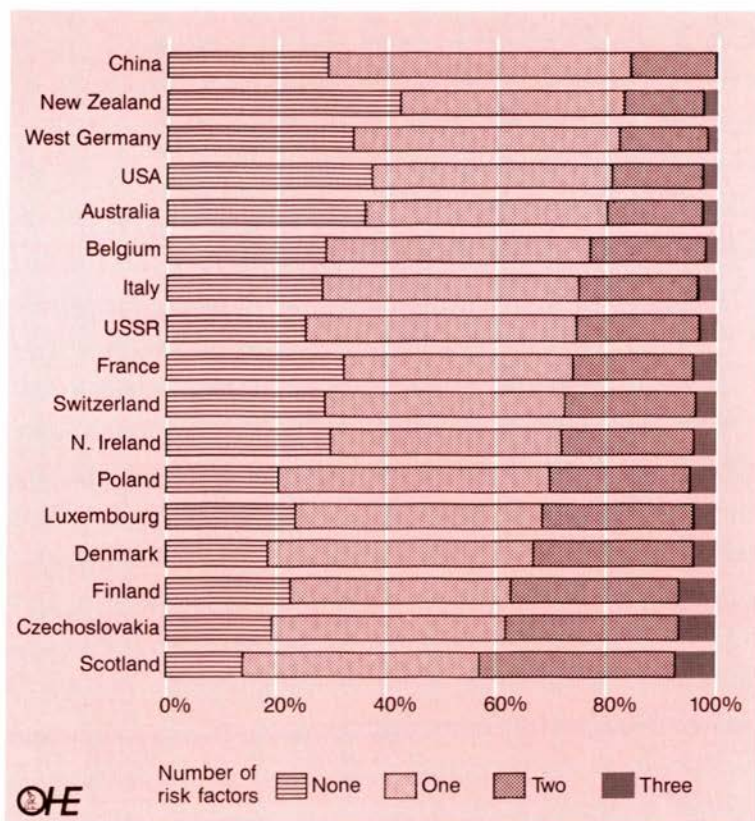
5. DIET AS CAUSE, DIET AS THERAPY

In 1984 an expert advisory panel to the government – the Committee on Medical Aspects of Food Policy (COMA) – were asked to review the evidence on the relationship between diet and cardiovascular disease and to make recommendations. This was the second time in ten years they had been asked to assess this issue (see COMA, 1974 on diet and heart disease.) After reviewing the scientific evidence they reported that:

'Nine of the ten members of the panel have concluded that there is sufficient consistency in this evidence to make it more likely than not that the incidence of coronary heart disease will be reduced, or its age of onset delayed, by decreasing dietary intake of saturated acids and total fat. We all agreed that the evidence falls short of proof' (paragraph 4.1.11, Committee on Medical Aspects of Food Policy, 1984).

The views of COMA are a cautiously worded endorsement of the so-called Diet-Heart Hypothesis. This simple chain of reasoning implicates diet – particularly consumption of saturated fats – as the major cause of elevated blood cholesterol and CHD, and diet as a potential solution. The logic of the diet-heart hypothesis is illustrated in Figure 20. Diets high in saturated fat (A) lead to an increase in population blood cholesterol (B) which leads to an increase in individual risk and population incidence of CHD (C). By implication there is a direct causative and preventive link between diet and CHD.

The causative chain of reasoning is endorsed by Marmot (1989) who argues that:

'Dietary fat clearly influences plasma cholesterol levels. Plasma

Figure 20 **The diet-heart hypothesis**

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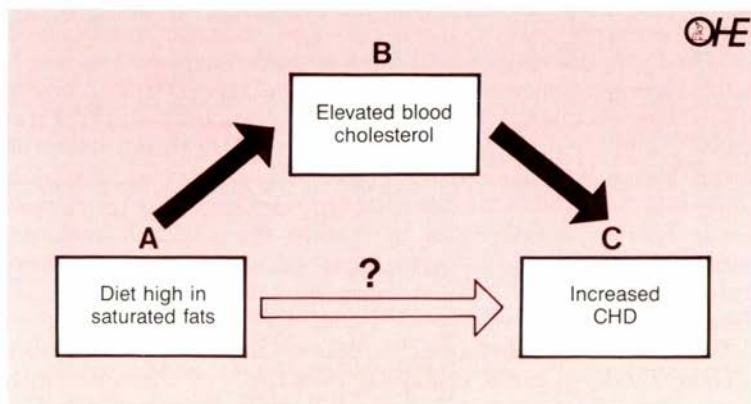
cholesterol levels are clearly related to CHD risk. It seems entirely reasonable to propose that dietary fat influences CHD risk. There is ample experimental, and pathological evidence to support this proposition'.

The difficulty facing the COMA committee, and the reason for its cautious wording of advice, is not the causative role of diet in heart disease but whether there is sufficient evidence to support the claim that *interventions* to modify diet can *reduce* CHD rates. Considering the specific issue of dietary fat intake one member of the COMA committee, Professor Michael Oliver, commented that:

'The epidemiological evidence relating dietary saturated fat to CHD is impressive. But the evidence that reduction of dietary saturated fat will reduce the incidence of disease is not' (Oliver, 1987, page 10).

This chapter reviews evidence on the diet-heart hypothesis and examines whether change in what people eat or drink can reduce the risk of CHD. Given the vast literature on the topic, the review is selective but intended to be indicative of the major developments in principles, evidence and policy. Two general questions are addressed:

(i) What is the role of diet as a means of primary prevention of CHD in the general population?

(ii) What is the role of diet as therapy for individuals with high levels of blood cholesterol who are at increased risk of CHD?

International and historical variation

For a variety of climatic and cultural reasons there is wide international variation in diet. Of particular interest to the cardiovascular epidemiologist is the variation in the quantity and type of fats in national diets. There are three basic types of dietary fat – saturated, monounsaturated and polyunsaturated – and these are further explained in Box 2. Although expert committees such as the Committee on Medical Aspects of Food Policy (COMA, 1984) recommend that no more than 35 per cent of food energy should come from all fats combined, the major focus is on the proportion of all fat intake that comes from saturated fats. The major source of saturated fat in the diet is dairy produce such as butter and milk and animal fat in various meats. In countries where diet is high in saturated fatty acids there is a correspondingly high level of blood cholesterol and incidence of CHD which is consistent with the diet-heart hypothesis.

To illustrate the international diet-heart evidence, two countries such as Finland and Italy can be contrasted. From the Seven Countries Study data in Figure 7 it is evident that people in Finland have a diet high in

saturated fats and have a correspondingly low ratio of polyunsaturated to saturated fat (P/S ratio) compared with Italy (P/S ratio of approximately 0.05 versus 0.35). This difference in dietary fat intake is hypothesised to produce differences in mean population blood cholesterol levels as indicated by data from the WHO MONICA project in Figure 18 – the average Italian has a blood cholesterol concentration of 5.6 mmol/L compared with the Finnish average of 6.3 mmol/L. The final link in the diet-CHD chain is the differential incidence of CHD – as Figure 2 illustrates Italy has an annual CHD mortality rate per 100,000 men aged 35-74 of approximately 250 versus the rate for Finland of near 650.

The diet-heart inferences that can be drawn from cross-sectional data are similar to those from historical studies of mortality from heart disease during the years of World War II. Shaper (1988) notes that during the war there was a marked reduction in the consumption of meat, butter, eggs and other foodstuffs high in saturated fats and cholesterol. During the war years heart disease rates in the USA (where there was no rationing of food) continued to grow but rates in England and Wales – which had been rising steadily before the war – levelled off, only to rise again after the war.

Box 2 Types of fat found in foods

• Saturated fats
Elevated total blood cholesterol, and LDL cholesterol, is associated with diets high in saturated fatty acids. The main sources of saturated fat are meats such as beef, pork, lamb. Coconut oil, palm oil and palm kernel oil, hydrogenated or partially hydrogenated vegetable oil.

• Monounsaturated fats
Oleic acid is a monounsaturated fatty acid of vegetable and animal origin: olive and rape seed oils are rich sources. Substitution of monounsaturated fat for saturated fat in the diet reduces blood cholesterol but there remains controversy over the magnitude of the effect. Sources of monounsaturated fat include olives and olive oil, peanuts and peanut oil, avocados.

• Polyunsaturated fats
There are two main types of polyunsaturated fatty acids: *Omega-6 polyunsaturated fats* (e.g. linoleic acid) reduce the blood cholesterol when substituted for saturated fats, and are found in seed oils such as sunflower and corn oils. *Omega-3 polyunsaturated fats* are found chiefly in fatty fish and are beneficial in reducing triglyceride levels. Their effect on total and LDL cholesterol is uncertain.

UK government guidelines (COMA, 1984) on diet and cardiovascular disease recommend that the consumption of saturated fats should be decreased. No guidance is given on the intake of monounsaturated fats but it is recommended that the ratio of polyunsaturated (P) to saturated (S) fats (P/S ratio) should be increased. Overall it is recommended that only 35 per cent of food energy should come from fats in any kind.

Although such studies are generally consistent with the diet-heart hypothesis there are exceptions which do not fit with a simple diet model of CHD epidemiology. Oliver (1987) notes that although Sweden has undergone similar dietary change to the USA in recent years, their mortality from CHD has increased. Furthermore the Japanese have nearly doubled their consumption of saturated fat over the last 10 years and yet at the same time CHD mortality has decreased by 23 per cent. Such observations serve to re-emphasise the multifactorial origins of CHD.

Diet as primary prevention

The diet-heart hypothesis offers an explanation of how increased dietary intake of saturated fats can lead to increased risk of CHD. But the extension of this reasoning is that the risk of CHD can be reduced by reducing the intake of saturated fats. A conventional approach to testing this preventive hypothesis would be to conduct controlled experimental intervention studies – randomised controlled trials where half the sample maintained their usual diet while the other half followed a special diet designed to lower blood cholesterol. The primary outcome of such studies would be differences in the rate of fatal and/or non-fatal CHD events.

In the early 1970s the US medical establishment were keen to test the diet-heart hypothesis by randomised controlled trial, but a 1970 Task force on Atherosclerosis cautioned that a large scale clinical trial of diet alone to reduce CHD would not be feasible and would be excessive in terms of cost. Given that the effects of diet alone may be modest and require many years of follow-up the recommended strategy was to commission primary prevention trials which evaluated the effectiveness of multiple risk factor modification – including diet. Two of the largest and most widely discussed trials were the Oslo study (Hjermann et al, 1981) in Europe and the Multiple Risk Factor Intervention Study (MRFIT, 1982) in the USA.

The Oslo Study (Hjermann et al, 1981) was a randomised controlled trial of diet and smoking interventions to reduce CHD. From 16,202 Norwegian men (aged 40-49 years) who were screened for coronary risk factors, 1,232 healthy men with normal blood pressure but at high risk of heart disease were selected for a five-year randomised trial, to examine whether lowering their blood cholesterol and reducing their smoking could reduce the incidence of CHD.

At the initial evaluation the men had total cholesterol levels of 7.5-9.8 mmol/L and 80 per cent smoked cigarettes. The nature of the intervention was in the form of advice on diet and smoking. The men in the intervention group were advised to give up smoking and were given detailed advice on how to modify their diet to reduce their consumption of saturated fats and to increase slightly their consumption of polyunsaturated fats. After five years of follow-up total cholesterol levels were 13 per cent

lower and the number of cigarettes smoked each day 45 per cent lower in the intervention group than in the control group. There was a 47 per cent reduction in fatal and non-fatal CHD events in the intervention group relative to control.

A difficulty in the interpretation of such results is the extent to which the reduction in CHD events is attributable to reduced smoking or modification in diet, or both. To address this issue the authors analysed variance among outcomes using a form of multiple regression analysis and found that cholesterol lowering due to diet had a stronger association with reduced CHD events than reduced smoking. Overall the study provides evidence that, for middle-aged men with high initial levels of blood cholesterol (above the 95th percentile), interventions to reduce smoking and modify diet can reduce blood cholesterol and in turn reduce the incidence of CHD.

The Multiple Risk Factor Intervention Trial (MRFIT) was funded in the early 1970s by the US National Heart, Lung and Blood Institute. Moore (1989) describes how the trial was intended to be the flagship of coronary prevention by providing the definitive proof that primary prevention of CHD was possible with modification of the three principal CHD risk factors – blood cholesterol (via diet), smoking and blood pressure. MRFIT was one of the largest and most expensive trials ever mounted, recruiting patients from 25 institutions across the USA and costing around $115 million.

As with the Oslo study the design of MRFIT was in two stages: first a total of 361,662 men (aged 35-57 years) were screened for inclusion in the trial. From these men, 12,866 were selected for the trial on the basis of their CHD risk using a composite risk score devised from the Framingham population study. If men were in the upper 15 per cent of the risk score distribution they were included in the trial. Selected candidates were randomised to two groups.

(i) *Special Intervention:* This group (n=6,428) received advice and counselling to stop smoking, control blood pressure and alter diet to reduce blood cholesterol. They were seen at least every 4 months over the 7 year period of follow-up, to ensure adequate control of risk factors.

(ii) *Usual Care:* This group (n=6,438) received a medical examination by the trial investigators every year but no special advice about control of risk factors although all information from annual checks on risk factors was made known to usual care patients and their doctors.

Over an average period of 7 years follow-up, risk factor levels declined in both groups, but to a greater degree for special intervention men. Mortality from CHD was 17.9 deaths per 1,000 in special intervention men and 19.3 per 1,000 in the usual care group (a statistically non-significant difference of 7.1 per cent), while total mortality rates were 41.2 per 1,000 and 40.4 per 1,000 for special intervention and usual care respectively.

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Given the cost and effort of the trial the results of MRFIT were disappointing because a definitive answer could not be given to the initial hypothesis. There was only a small difference in CHD deaths and total mortality was actually higher in the intervention group relative to controls. With the benefit of hindsight it is easy to criticise the design of the trial and point to explanations for its shortcomings. There were three confounding elements that had not been anticipated by the trial investigators:

(i) the usual care group were aware they had been identified as being high risk and this may have influenced their behaviour towards CHD risk factors;

(ii) the regular physicians of the usual care group (as distinct from the trial physicians) were aware that their patients were in a high risk group; this knowledge may have altered the 'usual' pattern of care;

(iii) over the 7 years of MRFIT follow-up there was increasing public discussion and awareness of CHD risk factors – information that was available to both usual care and special intervention groups.

The overall problem with MRFIT was that the usual care group were not an adequate control group for special intervention men. Being aware (or their doctors being aware) that they were high risk brought about changes in their behaviour relating to diet, smoking and blood pressure. Some of the problems of designing cardiovascular primary prevention trials have recently been reviewed by Pocock and Thompson (1990).

Finally, an explanation put forward by the MRFIT investigators for the small margin between intervention and control CHD mortality was that those patients in the intervention group who received antihypertensive drug therapy may have had an effect on blood lipids and actually raised blood cholesterol and CHD risk. The evidence on the trade-off between treating hypertension and raising cholesterol is reviewed in Box 3.

UK policies for dietary primary prevention

The UK government has shown interest in the primary prevention of CHD by issuing public guidelines on the modification of diet. There have been two reports from the Committee on Medical Aspects of Food Policy (1974, 1984) on the relationship between diet and heart disease. The committee recommended that the consumption of saturated fatty acids in the UK should be decreased. Specifically they recommended an increase in the P/S ratio to 0.45 and that only 15 per cent of food energy should come from saturated fatty acids and in total only 35 per cent of food energy should come from fat. This latter recommendation falls short of that prescribed by the World Health Organisation (1982) which recommends that dietary energy from saturated fatty acids should be limited to 10 per cent and that from fat to 30 per cent of food energy. The COMA

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Box 3 Can lowering blood pressure raise blood cholesterol?

Grimm (1989) notes that the MRFIT study was one of the first to indicate that certain antihypertensive drugs have an effect on blood lipids. In men assigned to the special intervention group the degree of blood cholesterol reduction was lower in men taking thiazide diuretics – a common form of antihypertensive. A number of studies have since confirmed the adverse lipid effects of thiazides.

Grimm (1989) has reviewed the lipid effects of antihypertensives. In addition to thiazide diuretics, beta blockers may adversely affect lipids by increasing triglycerides and reducing HDL-cholesterol. However, new generation antihypertensives such as alpha antagonists (prazosin, terazosin, doxazosin) have been shown to lower blood total cholesterol, significantaly while drugs such as Angiotensin Converting Enzyme (ACE) inhibitors leave lipids largely unchanged.

These new agents are currently being assessed in a new US trial backed by the National Heart Lung and Blood Institute and various drug companies – the Trial on Diet and Drug Treatment of Mild Hypertension (TOHMS; Stamler *et al*, 1987). Phase 1 of the trial is dietary intervention for mild hypertension and began in 1986; Phase 2 began in 1990 and continues for 8 years comparing various drug treatments for mild hypertension.

Committee argued that the WHO recommendations were too stringent for the UK and would not prove a realistic dietary target for implementation.

Have the British public changed their diet in line with this dietary guidance? Using data from the National Food Survey it is possible to plot trends in the British diet over time. In Figure 21 it is clear that over the ten year period 1978-1988 the P/S ratio has been increasing towards the COMA recommendation of 0.45 – from 0.22 in 1978 to 0.37 in 1988. The evidence is of a gradual change in eating habits with respect to fat intake substituting foods high in polyunsaturated facts (e.g. vegetable oils) for those high in saturated fats (e.g. animal fats). An obvious example of this is the trend away from the use of butter towards margarines high in polyunsaturates such as sunflower oil. However, recent studies such as the *Health and Lifestyle Survey* (Cox *et al*, 1987) revealed that consumption of saturated fats varies within the population according to social class with those in lower socioeconomic groups being more likely to eat fried foods such as chips, for example.

The COMA committee gave no specific recommendation on dietary cholesterol. Studies such as that by Edlington *et al* (1987) suggest that dietary cholesterol – which is mainly in the form of eggs in the average diet – has only a very small effect on total blood cholesterol when individuals are already following a low fat diet. But this issue is controversial since some studies have shown an association between dietary cholesterol and the low density lipoprotein subfraction of blood cholesterol (Sacks *et al*, 1984). Overall population compliance with COMA gui-

Figure 21 **Fatty acids and ratio of polyunsaturated to saturated fats (P/S ratio) in the British diet**
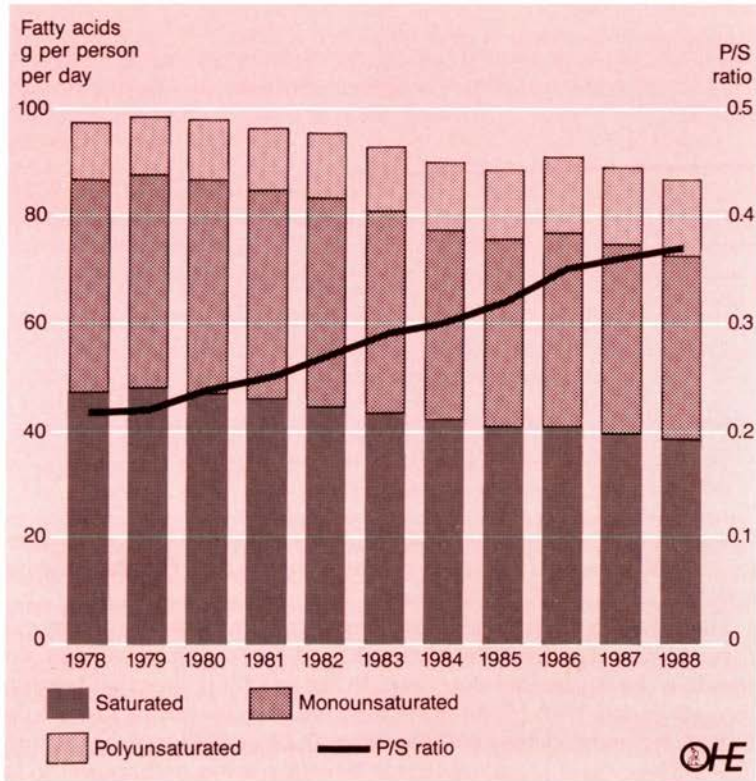
dance does not appear strong. A recent OPCS (1990) survey indicates that only 12 per cent of men and 15 per cent of women had fat intakes that met the COMA target of 35 per cent or less of food energy from fat.

There are two empirical questions which are prompted by such dietary policy guidelines: (i) if the population complies with the COMA dietary guidance, by how much will it reduce the population distribution of blood cholesterol? (ii) what will be the expected impact upon population rates of CHD by mass adoption of low-fat diets?

Lewis and colleagues (1986) have addressed the first question under various assumptions about population compliance with the dietary guidelines from WHO (1982) and COMA (1984). Using the mathematical model developed by Keys *et al* (1968) on the population distributions around mean blood cholesterol values, the results of their projections are

Table 6 **Percentage of UK population aged 25-59 with serum cholesterol exceeding selected limits**

	Assumed compliance	Assumed reduction in total blood cholesterol	Estimated percentage of population:		
			>6.5 mmol/L	>5.7 mmol/L	>5.2 mmol/L
Baseline (no diet):					
1984/85	–	–	23	45	63
WHO guidelines complete	16.5%	3.2	13	16	
COMA guidelines complete	12%	6	23	38	
COMA guidelines poor	7-9%	10-13	27-32	45-52	

Source: Lewis *et al* (1986)

summarised in Table 6. These data (based on a prevalence survey in 1984/85) suggest that 63 per cent of the population had blood cholesterol concentrations in excess of 5.2 mmol/L. Complete population compliance with WHO dietary guidelines could reduce this to 16 per cent of the population, but complete compliance with the less stringent COMA recommendations would only reduce this figure to 38 per cent of the population. Perhaps a more realistic assumption is that dietary compliance would be poor and only a 7-9 per cent reduction in mean blood cholesterol could be achieved by COMA recommendations resulting in 45-52 per cent of the population exceeding the 5.2 mmol/L cutpoint in the cholesterol distribution.

Even if population compliance with dietary guidelines was sufficient to reduce mean blood cholesterol, would this produce a reduction in the incidence of CHD? As indicated by the cautious wording of the COMA committee conclusions (see above quotation) reductions in CHD might be expected if dietary guidelines were followed but uncertainty surrounds the prediction for at least two reasons:

(i) much of the evidence from controlled clinical trials with diet and/or drugs relates to cholesterol lowering in people with initially high total plasma cholesterol (e.g. >7.8 mmol/L) and reductions observed in these samples may not be replicable in larger populations with lower concentrations of blood cholesterol. Furthermore the majority of studies have been in middle-aged men – there is comparatively little evidence about cholesterol lowering in women or children.

(ii) even in large randomised intervention studies of persons with raised cholesterol such as the Multiple Risk Factor Intervention Study (1982) and the Oslo study (Hjermann *et al*, 1981) where diet modification has been evaluated, there is not unequivocal evidence that lowering blood

cholesterol via diet alone reduces the incidence of CHD. The interpretation of such trials is made complex because more than one risk factor may have been modified in the intervention group.

Diet-cholesterol studies

Despite some uncertainties regarding the effectiveness of population dietary change the reduction in dietary saturated fat intake is the recommended first-line therapy for those identified as having elevated blood cholesterol (European Atherosclerosis Society, 1988). As indicated in Table 4, both the British Hyperlipidaemia Association (Shepherd *et al*, 1987) and the European Atherosclerosis Society (1988) recommend that persons with blood cholesterol in excess of 6.5 mmol/L should be placed on a specific lipid lowering diet.

There exists a large and expanding literature concerning the most effective diet for lowering blood cholesterol while maintaining adequate nutrition and a review of the many permutations is beyond the scope of the present discussion. However, the general principles can be illus-

Table 7 **The general lipid-lowering diet: principles and sources**

Principle	Sources
Decreased total fat intake and reduction of saturated fats	Butter, hard margarine, whole milk, cream, ice cream, hard cheese, cream cheese, visible meat fat, usual cuts of red meat and pork, duck, goose, usual sausage, pastry, usual coffee whiteners, coconut, coconut oil and palm oil-containing foods
Increased use of high protein, low saturated fat foods	Fish, chicken, turkey, game, veal
Increased complex carbohydrate and fruit, vegetable and cereal fibre, with some emphasis on legumes	All fresh and frozen vegetables, all fresh fruit, all unrefined cereal foods, lentils, dried beans, rice
Moderately increased use of polyunsaturated and monounsaturated fats	Sunflower oil, corn oil, soybean oil and products unless hardened (hydrogenated), olive oil
Decreased dietary cholesterol	Brain, sweetbreads, kidneys, tongue; eggs (limit to 1-2 yolks per week); liver (limit to twice per month)
Moderately decreased sodium intake	Salt, sodium glutamate, cheese, tinned vegetables and meats, salt-preserved foods (ham, bacon, kippers), high-salt mineral waters, many convenience foods

Source: European Atherosclerosis Society (1988)

trated with the lipid lowering dietary guidance issued by the European Atherosclerosis Society (1988) which is reproduced in Table 7. The general aim is to reduce consumption of fats in general but saturated fats in particular and to increase moderately consumption of polyunsaturated fats and complex carbohydrate. For example, substitute semi-skimmed milk for whole milk; soft margarine for butter; fish or chicken or turkey etc for red meat, pork or duck. Preference should be given to methods of cooking other than frying but if foods are to be fried then preference should be towards sunflower or corn oils rather than animal fat.

The effectiveness of different dietary regimens in reducing blood cholesterol can be evaluated by observational or interventional study. A good example of the former method is the Oxford Vegetarian Study – a prospective cohort study of 6,000 subjects who do not eat meat and 5,000 meat eating controls. Amongst those who do not eat meat are groups classified by their usual diet as being vegans, vegetarians or fish eaters (Thorogood, et al, 1990). Men who are meat eaters have a blood cholesterol near the UK average (5.9 mmol/L), with lower levels for fish eaters (5.6 mmol/L), vegetarians (5.3 mmol/L) and vegans (5.0 mmol/L).

The weakness of the uncontrolled study design is that the evidence can support a number of different hypotheses. For example, does an increase in fish consumption have any impact upon blood cholesterol *independent* from any reduction in meat consumption? In a 20 year dietary follow-up study in the Netherlands, and using multiple logistic regression to allow for other explanatory dietary factors, Krumhout et al, (1985) found a clear inverse relationship between fish consumption and death from CHD. Mortality from CHD was more than 50 per cent lower among those who consumed at least 30g of fish per day compared to those who did not eat fish. Such results are consistent with the hypothesis that diets high in fish oils (e.g. omega-3-polyunsaturated fatty acids) are protective against CHD. For example, Phillipson et al (1988) also found that such fish oils are potent in reducing blood triglyceride levels (see Box 2).

A good example of controlled study methods for investigating lipid lowering diets was published by Watts et al (1988). Three diets were identified for comparison: Diet A was the typical British diet as outlined in the COMA (1984) report with 42 per cent energy from fat (21 per cent saturated), Diet B conformed to the recommendations of COMA with 35 per cent energy from fat (14 per cent saturated) and Diet C with 27 per cent energy from fat (8 per cent saturated). A total of 15 hyperlipidaemic men were followed over a four week baseline period on Diet A followed by two four week experimental dietary periods in random sequence (i.e. BC or CB). Measuring change over baseline (Diet A), during consumption of Diet B total blood cholesterol fell by 8.6 per cent and for Diet C by 18.5 per cent.

In addition to the general programme of research into designing the optimum lipid lowering diet a number of studies are published each year with new hypotheses about specific dietary risk factors. An enduring

hypothesis for which there is growing evidence is that that blood cholesterol may be adversely affected by the consumption of coffee. Specifically, there is evidence from a randomised controlled trial that drinking boiled coffee (a method common in Scandinavia) can raise blood cholesterol whereas filter coffee is not associated with such an effect (Bak *et al*, 1989). The difficulty with studies such as Bak *et al* (1989) is that the authors do not forward any biological explanation of how boiled coffee raises blood cholesterol.

In addition to the types of food and drink consumed there is some evidence to suggest that the *way* we eat may influence blood cholesterol. A Canadian study by Jenkins *et al* (1989) compared the effects of two types of meal frequency – nibbling versus gorging – on subjects' blood cholesterol. The same daily food consumption was analysed as two diets: one diet consisted of 17 snacks a day (nibbling) while the other was 3 meals per day. Seven normal men were placed on each diet for two weeks using a randomised crossover design. Results indicated that, relative to the 3 meal diet, the nibbling diet was associated with a reduction in total blood cholesterol of 8.5 per cent.

One of the more topical and controversial dietary hypotheses is that the consumption of oat bran can reduce blood cholesterol.

The oat bran story

Robert Kowalski published a book in 1987 that sold over 2 million copies in hardback; its simple title was *'The 8 week cholesterol cure'*. The main argument in Kowalski's book is that blood cholesterol can be lowered by increasing the amount of oat bran in a persons diet, in addition to the conventional recommendations to reduce consumption of saturated fats.

Oat bran is a by-product in the production of oatmeal. The latter is made by treating the whole grain with steam and passing it through rollers to produce flakes. After grinding the oat flakes and sifting there are two fractions – flour and a coarse fraction known as oat bran. The difference between oat bran and wheat bran is that the former contains a large proportion of soluble fibre whereas wheat bran contains mainly insoluble fibre.

Conner (1990) reviews the clinical reasoning behind the hypothesis that diets supplemented with soluble fibre such as oat bran may help to lower blood cholesterol. It is thought that oat bran may act in a similar manner to the bile acid sequestrant drugs (e.g. cholestyramine) which are discussed in Chapter 6. Bile acids are used in the digestive process and are manufactured from cholesterol in the liver. If dietary fibre can bind with these acids and increase their excretion from the body then the body must make more bile acids in the liver and use up more cholesterol – thus reducing the overall level of blood cholesterol.

Researchers such as Anderson *et al* (1984) carried out early dietary experiments in hypercholesterolaemic persons and demonstrated that

the use of oat bran could reduce blood cholesterol. But the precise mechanism of such cholesterol reduction remained contentious. One recent hypothesis is that increasing the amount of fibre in the diet – soluble or insoluble – merely results in a beneficial dietary substitution effect; the more fibre a person eats the less fat they are able to eat.

Swain *et al* (1990) decided to test the hypothesis of the oat bran dietary substitution effect. Using a double-blind cross-over trial design they randomised persons with normal levels of blood cholesterol to two diets of the same total calorific value but one with 100g daily of oat bran and the other with 100g daily of a low-fibre wheat supplement. Results indicated that there was no difference between the diets in terms of their impact on blood cholesterol levels which fell by 7 to 8 per cent with either diet. Perhaps more important was the finding that on both diets the consumption of saturated fats had fallen during the study period, suggesting that the mechanism of cholesterol lowering was dietary substitution of fibre for fat. Although the methods and conclusions of Swain *et al* (1990) were fiercely criticised by correspondents to the *New England Journal of Medicine* (1990, volume 222, page 1746), they concluded that '. . . oat bran has little cholesterol lowering effect and that high-fibre and low-fibre dietary grain supplements reduce serum cholesterol levels about equally, probably because they replace dietary fats'.

The breakfast cereal manufacturers continue to benefit from the oat bran-cholesterol hypothesis with a range of products which cite the cholesterol lowering hypothesis in their advertisements. The claims are carefully worded to avoid the disputed issue of whether, independent of lowering dietary fat intake, increased consumption of oat bran can reduce blood cholesterol. Neatly summarising the issue with an example Conner (1990) notes, 'Clearly, people who eat large quantities of oat bran or other, similar cereals for breakfast have little room for bacon and eggs. . .'.

6. CHOLESTEROL-LOWERING DRUG THERAPY

For the majority of persons with elevated blood cholesterol, dietary measures alone can bring levels under control. But some individuals require treatment with prescription drugs. The aim of this chapter is to briefly review which drugs are prescribed to reduce cholesterol in the UK in the context of the available evidence on efficacy, effectiveness and safety from clinical trials of drug therapy for lowering blood cholesterol.

The various drugs available for lowering cholesterol have recently been reviewed by O'Connor *et al* (1990). Table 8 is reproduced from their survey and gives information on the effectiveness, tolerability and patient acceptability of these drugs.

Bile acid sequestrants

There are two bile acid sequestrants which are commonly prescribed to reduce blood cholesterol, they are cholestyramine and colestipol. Often referred to as the resin drugs, they have been on the market since the mid-1960s and are considered to be the first line drugs for treatment of

Table 8 **Lipid lowering drugs**

Generic (*proprietary*) names	Change in total cholesterol	Patient acceptability	Long term safety
Bile acid binding resins			
Cholestryramine (Questran)	Down 15-30%	} Poor – GI symptoms common 30% may not tolerate	Established
Colestipol (Colestid)	Down 15-30%		Established
Fibrates			
Clofibrate (Atromid-S)*	Down 5-15%	Good	Poor*
Bezafibrate (Bezalip)	Down 5-15%	Good	Established
Gemfibrozil (Lopid)	Down 5-15%	Good	Established
Nicotinic acid (Niacin)	Down 15-30%	Poor, causes flushing and pruritis	Uric acid and liver enzymes elevated
Statins			
Simvastatin (Zocor)	Down >30%	Good	Not established
Pravastatin (Lipostat)	Down >30%	Good	

*Evidence that clofibrate is lithogenic and may increase overall mortality (see text). The majority of prescriptions currently written for clofibrate are likely to be repeat prescriptions rather than new.

Source: adapted from O'Connor *et al* (1990) and Naylor *et al* (1990)

Fredrickson type IIa hyperlipidaemia (reference Table 1).

These drugs are not absorbed by the body but pass directly through the digestive system. In the intestine they bind on to the bile acids which are used in the digestive process and manufactured from cholesterol in the liver. The bound bile acids are then eliminated as part of the bowel movement. As bile acids are removed in this way the body must make more, thus using more cholesterol and reducing the amount circulating in the blood.

The bile acid sequestrants are marketed as powders that must be mixed with water or fruit juice or sprinkled on food (cholestyramine in 4g sachets, colestipol in 5g sachets). Recommended dosage is to begin with half a sachet twice a day and increase gradually to a maximum of 24g a day (cholestyramine) or 30g a day (colestipol).

The major clinical trial which demonstrated the effectiveness of cholestyramine in reducing blood cholesterol and CHD events was the Lipid Research Clinics (LRC) Coronary Primary Prevention Trial (1984). Some 480,000 US males aged 35-59 years were screened to identify 18,000 with total blood cholesterol levels of at least 6.85 mmol/L. These individuals were then placed on lipid lowering diets for four months which reduced cholesterol levels in 80 per cent of the remaining sample. Finally, the remaining 3,806 men who had been unresponsive to diet were entered into a randomised trial of cholestyramine resin (6 packets a day) against placebo, where trial endpoints were fatal and non-fatal cardiac events.

The results after seven years of follow-up are presented in Table 9. Total blood cholesterol levels were 9 per cent lower in the cholestyramine group relative to placebo and these patients experienced a 19 per cent lower incidence of fatal and non-fatal CHD events. Furthermore, in the treated group there were 20 per cent fewer cases of angina and 21 per cent fewer coronary bypass operations. Overall it was demonstrated that a 1 per cent reduction in cholesterol produced a 2 per

Table 9 **Lipid research clinics coronary primary prevention trial: follow-up for an average of 7.4 years**

End point	Placebo (n=1900)	Cholestyramine (n=1906)
Definite CHD deaths	38 (2%)	30 (1.6%)
Definite non-fatal MI	158 (8.3%)	130 (6.8%)
Definite CHD death and/or definite non-fatal MI	187* (9.8%)	155 (8.1%)

Note: MI = myocardial infarction

*A subject experiencing a myocardial infarction and CHD death is counted once in this category; hence the line is not the sum of the previous two lines. The difference between the two treatment groups is significant at the 5 per cent level (one-tail test)

Source: Lipid Research Clinics Program (1984)

cent fall in fatal and non-fatal myocardial infarctions. The findings of the LRC study were vigorously promoted and received wide publicity. Although the trial was concerned only with middle-aged men with diet-resistant hypercholesterolaemia the investigators argued that the results could be generalised:

'The trial's implications, however, could and should be extended to other age groups and women and, since cholesterol levels and CHD risk are continuous variables, to others with more modest ele-vations of cholesterol levels' (Lipid Research Clinics Program, 1984; page 360).

The extent to which the results of the LRC trial are replicable in a wider population will depend upon a number of factors, one of which is the assumed degree of patient compliance with cholestyramine. Although the drug does not enter the blood stream, so any side-effects are restricted to the gastrointestinal system, such effects include heartburn, feelings of being bloated, constipation or diarrhoea. More generally the prospect of drinking the medicine six times a day may lose its appeal over time.

The effectiveness of cholestyramine in reducing blood cholesterol depends upon compliance. The dose-response data from the LRC trial indicated that in patients taking the recommended 5-6 sachets per day blood cholesterol was lowered by 19 per cent and CHD risk by 39 per cent whereas those who averaged only 0-2 sachets per day lowered cholesterol by only 4 per cent and CHD risk by 11 per cent (Lipid Research Clinics Program, 1984). As summarised in Table 8 the bile acid sequestrants are effective agents which can lower total plasma cholesterol by 15-30 per cent and they are drugs which are not absorbed into the blood and in which many patient years of experience have generated confidence in their long term safety. The main drawback with these drugs is patient acceptability and compliance which is generally poor.

Fibrate drugs

The fibric acid derivatives are an effective group of drugs for regulating lipids. The parent compound – clofibrate – was studied in the first major trial of primary prevention where blood cholesterol levels were lowered by a drug (Committee of Principal Investigators, 1978). This multi-centre placebo-controlled trial indicated that at 5 years of follow-up there was an overall reduction of 9 per cent in blood cholesterol attribut-able to therapy and this was reflected in a significant reduction of 25 per cent in non-fatal myocardial infarctions, but no significant difference in CHD mortality.

A puzzling aspect to the WHO study, that resulted in a marked reduc-tion in the use of clofibrate, was that deaths from non-cardiac causes were significantly higher in the treatment group although no specific

illnesses or cancer were identified. This excess mortality was further discussed in a follow-up study (Committee of Principal Investigators, 1984) where it was shown that the difference in non-cardiac mortality between the treatment and control groups did not persist beyond the end of the trial. This suggests that the randomisation between the groups was not faulty but that some, still unexplained, factor associated with clofibrate increased non-cardiac deaths during the period of study.

Bezafibrate has been shown to be an effective lipid lowering drug, although the exact mechanism of action is not certain (Monk, 1987). One hypothesis is that LDL receptor activity is increased because of reduced hydroxymethylglutaryl coenzyme A (Hmg CoA) reductase activity, which reduces plasma LDL concentrations. Similar to other fibrate drugs, bezafibrate limits the production and promotes the catabolism of VLDL – the precursors of low density lipoproteins. As indicated in Table 8 this drug can lower total cholesterol by 5-15 per cent although its long term efficacy to reduce CHD events has not been established.

Gemfibrozil

Gemfibrozil is chemically related to clofibrate and works by lowering VLDLs and thus causing a decrease in LDL cholesterol. The drug also results in a small increase in HDL cholesterol which is a 'protective' CHD factor; and it also reduces triglycerides significantly.

The major trial of gemfibrozil was the Helsinki Heart Study (Frick *et al*, 1987). In this placebo-controlled trial 4,081 asymptomatic men aged 40-55 years with moderate hyperlipidaemia (LDL – plus VLDL – cholesterol >5.2 mmol/L) received a lipid-lowering diet and were randomised to gemfibrozil (600 mg twice daily) or placebo and followed for 5 years. Gemfibrozil was associated with a marked increase in HDL cholesterol and reductions in levels of LDL and non-HDL cholesterol and triglycerides. The incidence of CHD events at 5 years was 27.3 per 1,000 in the gemfibrozil group compared to 41.4 per 1,000 in the placebo group – a relative risk reduction of 34 per cent.

A second study from the Helsinki trial data provides more detail on the lipid changes and how these related to CHD incidence (Manninen *et al*, 1988). This study further demonstrates that the success of gemfribozil in reducing CHD events is related to its ability not only to reduce LDL cholesterol (as can drugs such as cholestyramine) but also to increase the level of HDL cholesterol (by 11 per cent over baseline) which is protective of CHD. Using multivariate methods of subgroup analysis the authors suggest that '. . . both elevating HDL and lowering LDL cholesterol levels are effective in the primary prevention of CHD'. Thus the evidence from this intervention study concerning the relationship between total and HDL cholesterol and CHD risk is consistent with the data from cohort studies such as Framingham and BRHS.

But one of the main concerns arising from the Helsinki Heart study

was that no difference in all-cause mortality was observed between treatment and control groups (Frick *et al*, 1987). This mirrors the all-cause mortality outcomes in the LRC trial of cholestyramine and the WHO clofibrate trial. Although the inability to show differences in all-cause mortality may be, in part, due to problems of insufficient sample size (or more precisely duration of follow-up), concern has focussed on the unexplained excess of deaths from accidents and violence which occurred in these trials (McCormick, 1988). It is not clear whether these association are due to chance (Frick *et al*, 1988) or whether, in some sense, such mortality constitutes a risk of cholesterol lowering.

Nicotinic acid (niacin)

The US National Cholesterol Education Program (1988) recommends that along with bile acid sequestrants, nicotinic acid (niacin) is a first line drug for treatment of type IIa hypercholesterolaemia. Niacin is a water-soluble B vitamin that lowers VLDL and LDL concentrations. Although the exact mechanism of action is unclear, it appears to reduce production of VLDL in the liver which in turn reduces the production of LDL. But high doses of this vitamin are required to reduce blood cholesterol: O'Connor *et al* (1990) report that patients generally require doses increasing gradually from 100mg three times a day to 3-6g a day – that is taking between 30 to 60 100mg tablets a day!

Canner *et al* (1986) report follow-up data from a large secondary prevention trial – the Coronary Drug Project – where men with previous myocardial infarction were randomised to therapy with either niacin or placebo. They report that at 15 years follow-up the incidence of non-fatal myocardial infarctions was significantly lower in the treatment group.

In 1987 there was great enthusiasm when a study demonstrated that the combined use of colestipol (a bile acid sequestrant) and niacin could actually reduce the progress of atherosclerosis. Blankenhorn *et al* (1987) randomised 162 non-smoking men aged 40-59 years with previous bypass surgery to treatment with combined colestipol hydrochloride and niacin therapy or placebo. During two years of treatment they observed a 26 per cent reduction in total plasma cholesterol, a 43 per cent reduction in LDL cholesterol and a 37 per cent increase in HDL cholesterol. By coronary angiography it was determined that there was a significant reduction in the average number of lesions per subject that had progressed and a lower rate of new atheroma formation. The success of this regimen prompted the authors to advocate that such therapy should be given to all patients after coronary artery bypass surgery.

Probucol

Probucol reduces LDL cholesterol by about 10 per cent but unfortunately it also causes a reduction of up to 25 per cent in HDL cholesterol (O'Connor *et al*, 1990). The exact mechanism of probucol is unclear. Unlike some of the other cholesterol lowering agents it has not been studied in large clinical trials with cardiac event endpoints and studies that demonstrate its long-term safety are not available.

HMG CoA reductase inhibitors (statins)

These drugs are a totally new class of agents for cholesterol lowering and are inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the rate limiting enzyme in the synthesis of cholesterol. The first of these, lovastatin was approved by the US Food and Drugs Administration in September 1987 and more recently simvastatin and pravastatin have been approved for use in the UK. The statins work by interfering with the normal production of cholesterol in the liver, where two thirds of the body's cholesterol is manufactured. The statins are potent inhibitors of HMG-CoA reductase which is an enzyme necessary for cholesterol production. A detailed review of the clinical pharmacology of HMG-CoA reductase inhibitors is provided by Grundy (1988).

Data from existing and on-going clinical trials indicates that the statins are the most effective agents in reducing plasma cholesterol, with drugs such as simvastatin and pravastatin reducing total blood cholesterol by 30 per cent or more (O'Connor *et al*, 1990). Patient acceptability of statin

Table 10 **Drugs prescribed by UK general practitioners for diagnosis ICD 272, disorders of lipoid metabolism (includes ICD 272.0, hypercholesterolaemia): UK, 12 months to June 1990**

	Estimated number of items prescribed	*Per cent of all items prescribed for this diagnosis*
Bezafibrate	229,000	42.8
Cholestyramine	77,000	14.5
Simvastatin	73,000	13.8
Gemfibrozil	56,000	10.5
Clofibrate*	44,000	8.3
Eicosapentaenoic acid	23,000	4.3
Probucol	7,000	1.4
Colestipol	6,000	1.2
Acipimox	5,000	1.0

*Note: Given the poor safety record of clofibrate (see Table 8 and text), few new prescriptions are being written for this drug, items are mainly repeat prescriptions.

Source: UK Medical Data Index – Intercontinental Medical Statistics Limited
Copyright: Intercontinental Medical Statistics

drugs is good with few serious adverse effects reported to date (Bradford *et al*, 1990). Although their long term safety has still to be proved, data from Merck Sharp and Dohme (personal communication 1990) indicate that simvastatin has been prescribed to more than 700,000 people worldwide and that post-marketing experience is available on lovastatin for over 3 million patients.

UK prescribing

Using survey data from general practitioner prescribing for the diagnosis ICD 272 – disorders of lipoid metabolism – which includes hypercholesterolaemia (ICD 272.0) it is possible to examine the general prescribing pattern for lipid lowering drugs. Data supplied by Intercontinental Medical Statistics are presented in Table 10 and indicate that nearly 43 per cent of all items prescribed for ICD 272 were for bezafibrate followed by 15 per cent for cholestyramine, 14 per cent for simvastatin and 11 per cent for gemfibrozil. It should be noted that, given the questionable safety record of the drug, the 8.3 per cent of prescriptions for clofibrate are probably repeat prescriptions rather than new prescriptions.

These data indicate current prescribing patterns which are changing over time. For example, given their effectiveness the market share of the new statin drugs – simvastatin and pravastatin – is likely to increase markedly in the near future.

7. CHOLESTEROL TESTING: FOR AND AGAINST

The US National Cholesterol Education Program (NCEP) was founded on the recommendation of the Consensus Conference on Cholesterol held by the National Institutes of Health in 1984. The adult treatment panel of NCEP is a group of experts who have given detailed recommendations to American physicians and public on the management of elevated blood cholesterol. A central feature of this guidance is the recommendation that every adult over 20 years of age should have their blood cholesterol tested every five years. This is to be achieved either through large scale screening programmes – such as for breast cancer or cervical cancer – or through opportunistic case-finding where a physician would measure the blood cholesterol of patients as part of any medical examination.

But the measurement of total blood cholesterol is just the beginning of the US guidelines on testing. The risk classification of total blood cholesterol adopted by NCEP is that levels greater than 6.2 mmol/L are high risk and that persons should be referred for a more detailed lipoprotein analysis. The purpose of lipoprotein analysis is to assess a persons total blood cholesterol in terms of the subfractions – LDL cholesterol and HDL cholesterol. As noted earlier it is thought that high levels of LDL cholesterol are central in the process of atherosclerosis but that increased levels of HDL are protective of CHD. Once the results of lipoprotein analysis are known the NCEP guidelines suggest that treatment decisions on cholesterol lowering should focus primarily on the level of LDL cholesterol and the presence of CHD or other CHD risk factors (including low HDL cholesterol). Thus the LDL threshold for treatment initiation for a hypertensive smoker would be higher than for a person with no other risk factors.

'Know your number'

Catford (1989) has recently reviewed the impact that the NCEP programme has had in the USA. He notes that opportunistic screening by physicians has increased nine-fold since 1982 and that between 1987 and 1988 the number of medical visits for hypercholesterolaemia doubled with a similar marked increase in prescription of cholesterol lowering drugs.

Many supermarkets across America now offer finger-prick testing of blood cholesterol to the general public. The growth in public awareness about blood cholesterol is the result of an extensive promotional campaign by NCEP, exhorting the public to have their blood cholesterol measured and 'Know Your Number'. Population surveys show a marked increase in testing and public awareness. Strickland et al (1988) reported that by 1988 nearly 60 per cent of the American public have had their blood cholesterol measured and approximately one quarter of the popu-

Table 11 **Main recommendations of publications available easily to general practitioners on who should have their cholesterol concentration measured**

Source	Main recommendations
Working group on cardiovascular disease of the Faculty of Community Medicine, 1989 (Smith *et al*, 1989)	Screening of the population not recommended
Study group of the European Atherosclerosis Society, 1987	General screening to be carried out only if provisions have been made for treatment and follow up by medical practitioners; screening of specified high risk groups; screening of patients opportune during routine medical contact (examples given)
British Heart Foundation, 1987	Screening of people with a family history of coronary heart disease
Coronary Prevention Group, 1987	Screening of specified high risk groups
Royal College of General Practitioners, 1988 (Waine, 1988)	Ideally screening of all adults aged 20-70 or, if this is not possible, of specified high risk groups
Drugs and Therapeutics Bulletin, 1987	Ideally screening of all adults or, if this is not possible, of specified high risk groups
British Hyperlipidaemia Association, 1987 (Shepherd *et al*, 1987)	Screening of all adults, preferably before age 30
King's Fund Consensus Conference, 1989 (King's Fund Forum, 1989)	Opportunistic screening of persons with one or more other major risk factors
Standing Medical Advisory Committee (1990)	Opportunistic screening: priority given to those with greater number of CHD risk factors

Source: Leitch (1989) with King's Fund and SMAC added

lation know their number. The US target is for 90 per cent of the population to have had their blood cholesterol measured by the year 2000, and Catford (1989) has indicated considerable progress towards this level of awareness.

In the UK the question of who should have their blood cholesterol tested remains a controversial issue. In the summer of 1989 the King's Fund Forum (1989) convened a consensus development conference devoted to the question of blood cholesterol measurement. Two impor-

tant recommendations were:

'Mass measurement of blood cholesterol levels in the population is not justified';

'CHD risk assessment should be made on the basis of factors other than measured blood cholesterol levels. If one or more major risk factors is present we then recommend cholesterol testing' (page 9).

But while the King's Fund Conference was attempting to converge views into a consensus, a survey by Leitch (1989) in the British Medical Journal demonstrated the current confusion for UK general practitioners resulting from conflicting expert recommendations from professional bodies. The variations on expert guidance for blood cholesterol testing are reproduced as Table 11. Groups such as the British Hyperlipidaemia Association are in favour of screening all adults before age 30 – a view consistent with the US guidelines previously discussed. Similarly the Royal College of General Practitioners would 'ideally' implement policies to screen all adults ages 20 to 70. In contrast the British Heart Foundation only recommends testing of blood cholesterol for persons with a family history of CHD.

From his survey of expert guidance Leitch (1989) concludes that '. . . the results show that there is no consensus among British experts over who should have their cholesterol concentration measured'. This lack of clear guidance for primary care physicians came at a time when the technology for measuring blood cholesterol in the surgery was becoming widely available in the form of desk-top analysers (e.g. Reflotron) and when the government had placed renewed emphasis on prevention in primary care with financial incentives to GPs for doing preventive work.

The most recent contribution to the cholesterol testing debate was the consultative document issued by the Standing Medical Advisory Committee (SMAC) in May 1990. This report to the Secretary of State for Health had terms of reference to:

'consider whether opportunistic cholesterol testing can make a cost-effective contribution towards identifying and treating people at increased risk of coronary heart disease' (SMAC, 1990, page 1).

The main recommendations of SMAC are presented in Box 4. The main conclusion is a cautiously worded endorsement of opportunistic screening and treatment which is judged to have the 'potential' to make a cost-effective contribution. In the remainder of this chapter the proposed case for screening is evaluated as follows:

(i) Is the technology available for blood cholesterol measurement accurate and reliable? Moreover, to what extent does natural variation in levels within the same individual create problems of interpretation and diagnosis?

(ii) What is opportunistic screening and why is it preferable to systematic mass screening?

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(iii) On what basis should individuals be selected or prioritised for testing?

(iv) (In Chapter 8) is testing and treatment cost-effective?

Can blood cholesterol be accurately measured?

Before reviewing the arguments concerning whether blood cholesterol should be measured it is instructive to determine the extent to which it can be accurately measured. This question can be further divided. First there are questions of technical efficiency and measurement error, both in laboratory (ideal) circumstances and in actual use in doctor's surgeries. Second there is the question of natural variation in blood cholesterol levels which creates problems of interpretation and diagnosis.

The UK market leader in desk-top blood analysers is the Reflotron manufactured by Boehringer-Mannheim. The technical details of the Reflotron are detailed in Box 5. In summary the machine requires a simple finger-prick of blood and can produce a total blood cholesterol reading in 3 minutes. In a laboratory evaluation of the Reflotron for the NHS Procurement Directorate, Broughton *et al* (1989) found the machine was relatively inexpensive (c. £3,500 compared with the Abbott vision machine at £15,000), was compact in size and portable in weight. Tests took about 5 minutes to complete and they estimate that one operator could complete about 50 capillary blood specimens in one day. The machine is easy to use and could be operated by a practice nurse. It requires only about 2 minutes of maintenance a day.

Box 5 Measuring blood cholesterol in the GP's surgery

The feasibility of mass blood cholesterol testing has been facilitated by the development of compact measurement machines that can be operated with a minimum of skill within the general practitioner's surgery. A number of general practitioner surgeries are now using machines such as the Reflotron, manufactured by Boehringer-Mannheim, to test blood cholesterol.

The following summary of the Reflotron method is taken from a recent evaluation of the device for the NHS procurement directorate by Broughton *et al* (1989).

The Reflotron '. . . currently has a repertoire of 11 tests, each of which is done separately one at a time, and takes about 5 minutes. It uses a special dry reagent system which is impregnated on a narrow reagent carrier strip. After checking that the batch of strips has not passed its expiry date, the protective aluminimum foil is removed. For venous blood, plasma or serum, the sample is applied from a 32 μL pipette with a disposable plastic tip. Although this technique can be used for capillary blood, it is more convenient to collect this into a heparinised glass capillary up to the 32 μL mark, and then dispense it onto the strip. When using whole blood, the erythrocytes are retained by the top layer of the pad and plasma diffuses into the reaction area below.

Within 15 seconds of applying the sample, the strip is placed in the instrument and the flap closed. This brings the reagent and sample layers into contact, thereby initiating the reaction which is monitored by reflectance photometry. During the reaction period the instrument automatically displays the name of the test being performed, and shows a countdown of the time (in seconds) before the result will be displayed. Results can be given in either SI or non-SI units. The display also indicates if a result is outside the analytical range, or the kinetics of an enzyme assay are non-linear.

The instrument does not require calibration by the operator, but the manufacturer provides special strips to check the optical system, and lyophilised control sera (Precinorm) which, after reconstitution, are analysed regularly in the same way as patients specimens'.

The Reflotron weighs 5.5 kg, has dimensions 300 × 300 × 195 mm and costs £3,650 (plus VAT) in January 1989 prices.

The technical performance of analysers such as the Reflotron can be assessed in terms of accuracy and precision. Accuracy represents how far the measurement is from the 'true' value – the reference standard being set by conventional 'wet chemistry' methods of laboratory measurement. Precision represents the consistency of performance either for repeated measures by the same operator or inter-operator variation. Both criteria are important but a system with poor accuracy and good precision can be corrected to accurate values whereas those with poor precision cannot.

In the US the NCEP guidelines are that desk-top analysers should have a bias of no more than ±5 per cent for accuracy. Precision is expressed as a coefficient of variation (standard deviation/mean) and this should be less than 5 per cent with the long term goal of reducing CV to less than 3 per cent (Burke and Fischer, 1988). In the UK, Winder (1989) reports

that the Steering Committee on External Quality Assessment for General Clinical Chemistry is currently reviewing performance standards for blood cholesterol measurement.

A number of (mainly US) studies have compared the performance of desk-top analysers in controlled laboratory conditions and found them to be both reasonably accurate and precise (Burke and Fischer, 1988; Seftel et al, 1988). But a more recent study in the UK investigated the quality of blood cholesterol measurement in general practice settings and occupational health departments: Broughton et al (1989) found that the overall coefficient of variation from three surveys was 5.5 per cent. The meaning of this is that a GP would not be able to distinguish reliably between a cholesterol level of 5.2 mmol/L and 6.5 mmol/L – two of the action limits proposed in the cholesterol management algorithms (see Table 4).

Based on their findings Broughton et al (1989) stress the importance of external quality assurance for tests done in primary care. Most of the surveyed tests were performed by nurses with little or no experience of laboratory methods or the need for regular quality assurance. Common sources of error in measurement were poor technique and the use of outdated reagent strips. Independent from the reasons for measurement error, Winder (1989) discusses the important point that GPs should interpret measurements with an awareness of such error margins. Even with a low coefficient of variation of 2.5 per cent the 6.5 mmol/L action limit for management of raised cholesterol should be interpreted as a range from 6.2 mmol/L to 6.8 mmol/L. One way to reduce uncertainty from measurement error is to re-test the same individual 2 or 3 times to confirm a value. Tunstall-Pedoe (1989) claims that 'three or more readings are needed to establish an accurate baseline to monitor change'.

In addition to problems of measurement error there is known variation between and within patients due to various factors. Winder (1988) notes that, among other influences, blood cholesterol will be higher in pregnant women or women in the middle of their menstrual cycle and is generally higher for individuals in winter months (about 15 per cent higher, 1 mmol/L).

A recent study by Thompson and Pocock (1990) used data from the MRC Mild Hypertention Trial on repeat measurements of blood cholesterol for the same individuals in an attempt to quantify the problem of within-person variation in levels over time. For measurements 1 year apart they found a coefficient of variation of 7 per cent which is larger than the acceptable measurement of 5 per cent. Working through an example of the implications of such variation, the authors note that 28 per cent of middle-aged British men with a single cholesterol measurement above 6.9 mmol/L have a long-term average cholesterol below that value without intervention.

In summary, a clinician with the task of interpreting blood cholesterol measurements will face uncertainty of two different types: the natural

variation between and within individuals and measurement error. Recent studies suggest that natural variation is a greater problem than technical measurement error. Given such variation clinical decisions concerning initiation of diet or drug therapy for raised blood cholesterol, based on single figure action points (e.g. 6.5 mmol/L), should reflect the possible variation of the true value in a range.

As with any diagnostic technology the problem is one of balancing the two potential errors in diagnosis: a trade-off between sensitivity (true-positive rate) and specificity (true-negative rate) of the test. A false-positive test can result in a person initiating diet or drug therapy unnecessarily while a false-negative test will give a false re-assurance to a person that their blood cholesterol is in the desirable range and that no action need be taken. Given that measurement strategies will vary in these test characteristics the evaluation of alternative strategies will depend upon the weight attached (implicitly or explicitly) to the avoidance of the two different types of error.

Approaches to screening

The purpose of screening is to search for unsuspected disease or for factors which are thought to be causally associated with the development of the disease (risk factors). However, Catford (1989) argues that the terminology of 'screening' should not be used in relation to blood cholesterol since raised cholesterol is no more a disease than other CHD risk factors such as smoking and being overweight. For Catford (1989) the key term is 'measurement' of blood cholesterol because this may help to avoid some of the problems of labelling people as patients. (Having acknowledged this point the present discussion uses the well established terminology of methods for screening.)

The evidence reviewed in earlier chapters clearly supports the view that elevated blood cholesterol is a necessary, but not sufficient, condition of CHD development. The evidence that the development of CHD is multi-factorial is central to the debate on screening for raised blood cholesterol: identifying persons with elevated blood cholesterol is a proxy for those at high risk of CHD.

There are two basic approaches to screening:

(i) *Systematic population screening* is where asymptomatic persons are invited to attend a clinic where medical professionals test for some abnormality. Examples of systematic screening programmes are those for breast and cervical cancer. Thus in a systematic mass screening programme for elevated blood cholesterol all adults (for example) in the UK would be invited to attend for assessment at regular time intervals (e.g. every 5 years).

(ii) *Opportunistic screening* is by definition a non-systematic method of case finding which relies upon the testing of persons already presenting to the health care system for other reasons. The approach can be selective

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Table 12 **Basic criteria for an acceptable screening programme**

The disease should:
(1) be an important public health problem
(2) have a recognisable latent or early symptomatic stage
(3) have an adequately understood natural history
(4) have an accepted and effective treatment

The screening test should be:
(5) acceptable to the public and medical profession
(6) sensitive, specific and reliable
(7) cost-effective

Source: adapted from Friedwald (1987)

or non-selective. With non-selective case finding a GP or practice nurse would measure the blood cholesterol of all persons (or random samples of persons) presenting to the surgery (note that this will involve some degree of self-selection by virtue of GP attendance). In contrast, selective case finding would be a programme where particular groups of patients are targeted, such as those with one or more existing CHD risk factors.

Seven basic criteria for assessing whether a screening programme is desirable are adapted from Friedewald (1987) in Table 12. Because CHD is undoubtedly a major public health problem the first criterion is met. But there would still appear to be some debate (see earlier chapters) about the level of blood cholesterol which should be defined as abnormally high in relation to risk of CHD. The concept of strict action limits for interpreting screening test (e.g. 6.5 mmol/L, 7.8 mmol/L) may also be unwise given the problems of measurement error and natural variation. Furthermore there remain questions about the extent to which control of high blood cholesterol following identification by screening will lead to reduced risk of CHD.

Despite these problems the debate concerning the mass measurement of blood cholesterol has largely been focused on issues raised by the yield of the proposed screening test (i.e. high risk cases detected) versus the effort and cost.

The logistics of systematic mass screening

The average person in the UK has a blood cholesterol concentration above the WHO (1982) desired level of 5.2 mmol/L: estimates vary for the average male between 5.9 mmol/L (Mann *et al*, 1988) and 6.3 mmol/L (Shaper *et al*, 1985), although the demography of the two samples does differ. Supposing the management policy for blood cholesterol tests in excess of 6.2 mmol/L was that the person was referred to a specialist lipid clinic for lipoprotein analysis to determine the LDL and HDL subfractions

– the same practice as recommended by NCEP in the US Smith *et al* (1989) estimate that a mass screening programme coupled with such a patient management policy would result in at least half the population requiring lipoprotein analysis and nearly 80 per cent of those screened would require follow-up. The logistics and resource consequences of such mass screening are obviously enormous. Over half the population would become patients, most of them without any signs or symptoms of disease.

In addition to the large cost of running such a programme the yield would be uncertain due to problems of bias in attendance and compliance. Kinlay (1988) reviews evidence from systematic screening programmes for blood cholesterol where those who attended were more likely to be non-smokers with higher educational background – i.e. those likely to have lower CHD risk status overall. For reasons of logistics, cost and uncertain yield due to attendance bias, systematic mass screening for elevated blood cholesterol is not viewed as an atrractive option. For example, in their assessment of systematic mass screening Smith *et al* (1989) concluded:

> 'Screening programmes, in which doctors approach apparently healthy individuals to make them patients for a life time, ethically must ensure that treatment facilities are available, that treatment is of proven efficacy, and that it does more good than harm. Those requirements have not yet been satisfied by cholesterol screening. Individuals with positive results would be alarmed and the others – in whom most coronary events will happen – would become complacent. Moreover, screening would be extremely expensive.' (page 373).

The Standing Medical Advisory Committee (SMAC, 1990) also concluded that 'inviting members of defined target populations to attend for blood cholesterol testing is unlikely to make a cost-effective contribution in situations where a programme of opportunistic testing is already established' (paragraph 7.3.6). The emerging consensus view appears to be in favour of opportunistic screening rather than systematic screening. The issue then is whether such testing should be random or selective, and if the latter, how individuals should be identified for testing.

Selective versus non-selective opportunistic screening

Discussing strategies for CHD screening Epstein (1987) comments that 'the prerequisite of effective screening is a powerful predictive test'. In the case of blood cholesterol screening two types of predictive power might be distinguished. The first is the accuracy of the measurement procedure as defined by sensitivity and specificity: this is, can the measurement accurately predict a person's blood cholesterol? The second is the central issue of the extent to which the factor being screened for is an

accurate predictor of future CHD events. Taken in isolation, although blood cholesterol is correlated with CHD incidence it is a weak predictor of total future CHD events. A much quoted characteristic of the relationship between blood cholesterol and CHD mortality is that the majority of CHD deaths occur in persons with blood cholesterol levels below the action limit of 6.5 mmol/L (Kannel *et al*, 1971).

Such an observation prompts two arguments:

(i) a population strategy (e.g. health education on diet) to move the whole cholesterol distribution is desirable, in addition to any policy for high risk screening and intervention.

(ii) the method of high risk screening might have greater predictive (of CHD) power if based upon multiple risk factor.

The case in favour of selectively screening the blood cholesterol of those persons who already have one or more other CHD risk factors, such as hypertension or cigarette smoking, is supported by logistic regression analysis of CHD events from both the Framingham study and the British Regional Heart Study (BRHS) which indicated that the predictive power of multiple risk factor models is superior to single factor models (Shaper *et al*, 1987). Figure 22 illustrates the logic of selective screening based on the 3 basic risk factors. Borrowing the method of the Venn diagram it is useful to think of persons presenting to a GP as distinct groups or CHD 'risk sets'. Of those who have some CHD risk, set C have only one

Figure 22 **Venn diagram of CHD risk sets based on 3 risk factors**

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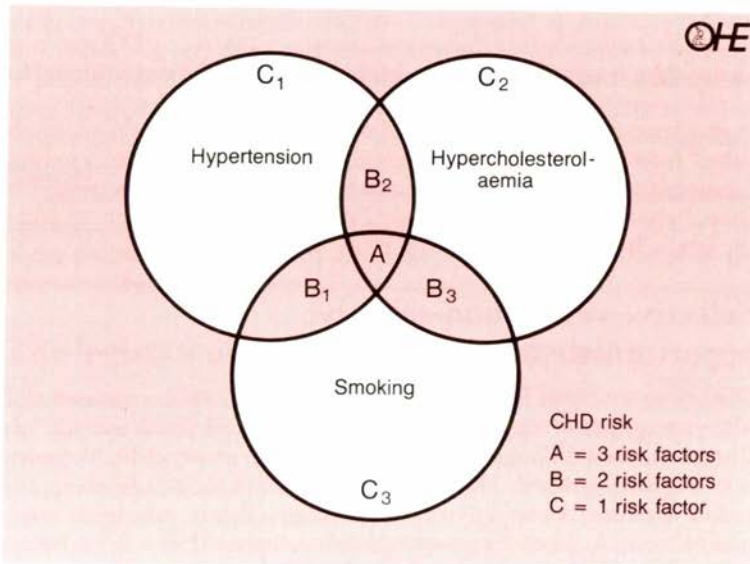
Table 13 **Three systems for scoring the risk of a heart attack. The two electrocardiographic criteria are mutually exclusive**

Risk factors	Full	Intermediate	Basic (GP)
Age (years)	× 4.0	–	–
Smoking (years)	× 3.5	× 5.0	× 7.5
Systolic BP (mmHg)	× 2.5	× 3.0	× 4.5
Cholesterol (mmol/L)	× 38	× 51	–
ECG-definite MI	+110	–	–
ECG-ischaemia	+ 45	–	–
Diagnosis of IHD	+100	+170	+265
Current angina (Q)	+ 75	+100	+150
Diagnosis of diabetes	+ 75	+ 95	+150
Parental death from 'heart trouble'	+ 40	+ 50	+ 80
% IHD 'cases' in top fifth of score	59	58	54

Note: A score greater than 1,000 indicates that the patient is in the top fifth of the CHD risk distribution. Thus the Full Scheme was able to accurately assign 59 per cent of the BRHS patients to the top fifth.

Source: Shaper *et al* (1987)

risk factor, set B have two factors and set A have all three factors. Thus in terms of CHD risk, the sets can be rank-ordered: A > B > C. Extending this reasoning, the yield per screen in terms of future CHD events avoided and life-years gained would also be ranked in the same way.

The recommendation of the King's Fund Forum (1989) was that blood cholesterol should only be measured in those persons who present with evidence of one or more other risk factors – i.e. selective opportunistic screening. The Standing Medical Advisory Committee (1990) gave similar advice but did not restrict screening to those with one or more existing risk factors, rather their existence was viewed as grounds for giving priority for testing. Using the simple 3-factor model outlined above, a person might present who smokes and who is initially in CHD risk set C_3, to determine whether they are in CHD risk set B_3 (higher risk) a blood cholesterol measurement would be done. Based on relative risk a greater priority would be to measure the blood cholesterol in patients who present in CHD risk set B (hypertensive cigarette smokers) to identify those individuals who are in CHD risk set A.

Scoring systems

The SMAC recommendations (see Box 4) set an individuals priority for cholesterol testing in terms of the number of CHD risk factors present. But this ignores the observation that some CHD risk factors and combinations of factors have greater CHD predictive power than others.

Using data from the British Regional Heart Study, Shaper *et al* (1987) have devised three risk scoring schemes for CHD screening in middle

aged men based upon multiple risk factors. They have quantified the marginal contribution of a given risk factor to a person's overall risk of CHD and various additive or multiplicative weights are assigned to the various factors in Table 13. The full scheme requires the taking of basic demographic details such as age, family history, number of smoking years and clinical measures such as blood cholesterol, systolic blood pressure and an electrocardiogram. If a man scores over 1,000 then he is predicted to be in the top 20 per cent of the CHD risk distribution. Based on analysis of BRHS data the full scoring scheme would accurately categorise 59 per cent of persons who will ultimately experience a CHD event into the top 20 per cent of the risk distribution.

In contrast to the full score the basic (general practitioner) score does not involve clinical measures but can be done by a practice nurse as a questionnaire prior to consultation. The predictive power of the system is 54 per cent and Shaper *et al* (1987) recommend that the basic score should be calculated for all men aged 40-60 years who attend the GP practice for whatever reason. Thus if (CHD) predictive power is a criterion for judging the need for cholesterol screening there may only be small marginal gains in knowledge of CHD risk from such measurement. Overall however, the basic GP score could be used as a criterion to judge whether it is worthwhile to measure blood cholesterol in the individual patient. Although it may be simpler and less time consuming to add up the number of risk factors (SMAC recommendations) the use of scoring systems may provide a more accurate prediction for stratifying patients.

Is effective follow-up available?

Although predictive power is important it is not the sole criterion for the acceptability of screening. In an editorial on cholesterol testing Tunstall-Pedoe (1989) comments that 'Increasing the accuracy of predicting coronary disease by cholesterol testing is not an end in itself. What matters is the follow through'.

One of the important aspects of follow-up from a positive screening test is the ability of the GP or primary health care team to give appropriate dietary advice to the patient. Francis *et al* (1989) studied whether such workers were able to give appropriate dietary advice and they found some significant gaps in knowledge. They found that only 71 per cent understood that dietary intake of polyunsaturated fats as a proportion of total fat intake should be increased as part of a lipid lowering diet. Advice that would have led to the patient losing weight (rather than specifically lowering lipids) was given by 27 per cent of primary care workers surveyed. This study suggests that prior to widespread blood cholesterol measurement there should be increased effort in training primary health care workers in dietary counselling of those who test positive.

Another aspect to the follow-up of those who have been screened and tested negative is that they may be discouraged from following the dietary

guidelines of population strategies. Kinlay and Heller (1990) found evidence in Australia that high risk strategies that require everyone to be tested for high blood cholesterol may interfere with population strategies designed to reduce everyone's dietary intake of fat.

In some situations there may be little or no medical back-up to counsel individuals who test positive. The measurement of blood cholesterol in non-medical settings (e.g. supermarkets) is considered by the Standing Medical Committee (1990) who advise that all testing should be done under medical supervision.

Value of information to the patient

Almond *et al* (1989) report the use of the Reflotron desk top analyser to measure blood cholesterol in a general practice has been accepted well by patients and that measurement is in demand. This raises the interesting question of the value of the information about blood cholesterol to the person themselves. An argument considered by the King's Fund Forum (1989) consensus conference was that the measurement of blood cholesterol may have a motivational value to patients by encouraging them to modify their diet.

The King's Fund Forum (1989) found no evidence to support this concept and recommended further research. The Standing Medical Advisory Committee (1990) were more positive about the role of information and concluded that 'it is likely that providing individuals with information about their blood cholesterol levels will lead to changes in public attitudes and behaviour, in this way influencing food manufacture and labelling' (paragraph 7.2.2). The idea that blood cholesterol measurement has some value to the public, independent from clinical diagnosis and management, is also supported by the observation that some people are willing to pay (about £7) for such tests in high street shops. But whether such persons are willing to pay out of curiosity or a desire to motivate themselves towards dietary change remains unclear.

In summary, if the recommendations of the Standing Medical Advisory Committee (1990) are accepted by the government and the medical profession then programmes of opportunistic blood cholesterol testing will become part of the workload of the general practitioner. No mention is made in the SMAC report about whether GPs should be offered any special financial incentive for such preventive work and this may be due, in part, to the overall uncertainty about the cost, in time and other resources, of such screening and treatment programmes. The conclusion of SMAC was that opportunistic testing and treatment had the 'potential' to be cost-effective; the various aspects of this potential are reviewed in the next chapter.

8. QUESTIONS OF COST-EFFECTIVENESS

The recent development of potent new medicines for the treatment of elevated blood cholesterol, such as the HMG-CoA reductase inhibitors, and the advent of relatively inexpensive desk top analysers for blood cholesterol testing, have produced growing interest in the economics of cholesterol testing and treatment. In a number of countries, health policy makers are confronted with a variety of difficult choices. Is cholesterol testing an efficient use of limited health care resources? Is treatment with drugs more cost-effective than diet? How do the various cholesterol lowering drugs compare in terms of benefits and costs? The aim of this chapter is to assess the main economic questions raised by cholesterol testing and treatment programmes and to review the available evidence from the few studies that have been completed.

Economic evaluation

Health economics concerns itself with the basic fact of life that the number of potential projects and programmes for improving a nation's health far exceed the available resources. This situation is exacerbated by the rapid growth in (often expensive) medical technology coupled with an ageing population with greater demands and expectations about the level and quality of health care provision.

Scarcity of resources necessitates the need to make choices and this gives rise to the economist's definition of opportunity cost where the cost of using resources to test and/or treat (e.g.) raised blood cholesterol is measured in terms of the health benefits foregone from other treatment programmes such as arthritis or AIDS. In making such difficult choices a guiding principle of economics is that programmes should be evaluated and compared in terms of their efficiency: the aim being to select those programmes that maximise the surplus of benefits over costs. Hence economic evaluation typically requires the measurement of the costs and benefits (effects) of interventions using common units that permit the calculation of ratios such as cost per life-year gained which can be used to compare the relative efficiency of various programmes.

The methods available for economic evaluation are well documented in general (Drummond et al, 1987) and for pharmaceuticals in particular (Drummond et al, 1988; Luce and Elixhauser, 1990). It is generally recognised that there are four distinct techniques of analysis, each differing in the extent or type of benefit measurement (O'Brien and Rushby, 1990). The various techniques of analysis are summarised in Box 6.

The appropriate form of economic analysis will depend upon the alternatives being compared and the perspective taken. Blood cholesterol programmes can be grouped into those which are targeted on high risk persons, such as screening and drug therapy and the more general public health policies targeted at reducing blood cholesterol in whole popula-

Box 6 Methods of economic evaluation

● **Cost-minimisation analysis** is where two therapies are compared only in terms of cost, with the least costly intervention being preferred. For such cost comparisons to be a useful indicator of efficiency there should be reasonable evidence that the interventions are equivalent in terms of effectiveness.

● **Cost-effectiveness analysis** results in the computation of a ratio of costs to effects where the latter are in the natural units of outcome from the therapy. Thus hypertension programmes might be compared in terms of the cost per unit (in millimetres of mercury) blood pressure reduction or more generally the cost per life-year gained.

● **Cost-benefit analysis** requires the health benefits of interventions to be valued in monetary terms to permit the computation of the net benefit of a treatment (i.e. the extent to which benefits exceed the costs). Programmes with the greatest net benefit are most preferred. Methods for monetary valuation of health benefits include the indirect valuation of production gains or losses (human capital method) or the direct method of assessing willingness-to-pay for a given health benefit.

● **Cost-utility analysis** is an extension of cost-effectiveness where the benefit measure is a generic health metric encompassing changes in survival and health-related quality of life (e.g. days of well-being or quality-adjusted life-years). The method requires utility scores to be attached to health states such that a health index ranging from (e.g.) death to perfect health can be constructed.

tions. In many ways the high risk and public health approaches are complementary and not alternatives: raising public awareness about issues of diet and CHD is not a substitute for intervening to treat hypercholesterolaemia in individual patients.

Reliable data for evaluation are more difficult to obtain from public health programmes on diet for at least two reasons:

(i) Such programmes are likely to have multiple health effects not confined to CHD. A diet which is low in fat and high in fibre is likely to reduce diseases such as cancer of the colon as well as impacting upon CHD. Public health programmes designed to change the nation's diet will also have a multitude of effects on the food industry and food prices.

(ii) Although data on the expenditure into programmes such as 'Look After Your Heart' by the Health Education Authority is available (£5 million in 1987-88: National Audit Office, 1989), the measurement and attribution of improved health outcomes to such programmes is difficult. Typically such programmes are evaluated using intermediate outcomes of changes in public awareness and knowledge.

The majority of research in the economics of cholesterol has mainly been studies comparing alternative programmes for the management of

high risk patients. There are at least three important areas of enquiry:

(i) Selective versus non-selective opportunistic screening and treatment. Is it more cost-effective to target interventions on those who will (potentially) benefit most?

(ii) Among the various forms of intervention for lowering blood cholesterol in high CHD risk individuals, is drug therapy more or less cost-effective than diet?

(iii) Given that some hyperlipidemias will be resistant to diet it is also useful to compare one drug (e.g. simvastatin) against another (e.g. cholestyramine) in terms of cost-effectiveness.

All three of these questions have been investigated using cost-effectiveness and cost-utility methods. A common feature of such studies is that the primary measure of patient benefit is gains in life expectancy which are predicted to be associated with reductions in blood cholesterol. Before reviewing the individual studies and their conclusions an assessment is made of methods for effectiveness and cost measurement.

Effectiveness: cholesterol elasticities

Starting from the principle that the main, but not the only, benefit of interest from blood cholesterol lowering therapies is the reduction in mortality due to CHD, perhaps the ideal situation would be that every economic analysis is built upon the firm foundation of a randomised controlled trial where the endpoint was mortality. But such trials require large sample sizes and many years of patient follow-up. In most circumstances mortality outcome data are not available from a trial and a pragmatic 'second best' is to conduct short-term trials with surrogate endpoints of blood cholesterol change and use change in short-term cholesterol to predict change in long-term mortality. As Ellenberg (1990) notes, the use of surrogate endpoints in clinical trials is valid provided there is a clear statistical relationship with the true endpoint. The epidemiological evidence previously cited confirms the high correlation between elevated blood cholesterol and CHD mortality.

The most common method of forecasting mortality change from cholesterol changes is to utilise retrospective data from a longitudinal study which relates multiple CHD risk factors, including blood cholesterol, to the incidence of CHD mortality. Variants of this method have been used in the economic analyses of the Standing Medical Advisory Committee (1990), Oster and Epstein (1987), and Martens et al (1989). The general method is to forecast CHD mortality using logistic regression techniques on data from longitudinal studies such as Framingham where a binary dependent variable (0/1 alive or died from CHD at time t) is regressed against a number of demographic and clinical measures. The resultant coefficients from the statistical model give a measure of the

association of one factor (e.g. blood cholesterol) with the incidence of CHD mortality, while allowing for variation in the other factors (e.g. age, sex etc). Such models have been built to simulate the future incidence of CHD in the USA (Weinstein, 1987) and appear to have good short-term predictive value.

A comprehensive account of estimating cholesterol effects in this way can be found in the report of the Standing Medical Advisory Committee (1990). This study calculates cholesterol 'elasticity' values by age and sex, where elasticities are unit-free measures of responsiveness (i.e. proportional rates of change between cholesterol and CHD). The SMAC analysis is based upon an overview of cholesterol lowering clinical trials by Richard Peto which indicates that a 10 per cent reduction in blood cholesterol is associated with a 30 per cent reduction in CHD incidence.

Using similar methods Taylor *et al* (1987) quantified the gains in life-expectancy from reductions in blood cholesterol. The context of their model was a simple personal policy decision: what gains in life expectancy would an individual get by undertaking a dietary programme that reduced their blood cholesterol? Their model considered asymptomatic adults with total blood cholesterol levels between 4.7 mmol/L and 7.8 mmol/L. CHD risk status was defined on the basis of blood pressure, blood cholesterol (high density lipoprotein), and smoking status. Their base-case estimate of the effect of diet was taken from the MRFIT study where dietary intervention was associated with a 6.7 per cent fall in blood cholesterol.

Summary results from the model by Taylor *et al* (1987) are presented in Table 14. These data suggest that for a 40 year-old man at high risk of CHD (see table for definition) a 6.7 per cent reduction in blood cholesterol would only add 7 months to his life expectancy and a reduction of 20 per cent only 18 months. The gain in life expectancy is lower for older persons but generally higher for women than men. The authors also compare other interventions for reducing CHD and increasing survival. The gains in life expectancy associated with reducing or stopping smoking or reducing blood pressure (systolic assumed down 14.3 per cent) are generally higher than the benefits of base-case cholesterol reduction. For example, if a 40 year-old high risk man quits smoking his life expectancy increases by 63 months; if he reduces his systolic blood pressure by 14.3 per cent he increases his life expectancy by 34 months.

The estimates of increased longevity by Taylor *et al* (1987) are not without criticism – the construction of such predictive population models is a science based on a number of assumptions that may not be shared by others. For a contrasting view the study by Stamler and Shekelle (1988) based on follow-up data from the Chicago Western Electric Study (Shekelle *et al*, 1981) predicts that dietary cholesterol modification can increase life expectancy by 3-4 years.

Although such CHD mortality suggests that the gains in survival are, on average, quite modest, it must be remembered that reducing blood

Table 14 **Months added to life expectancy from selected changes in risk factors for persons at high risk** *

Age	Cholesterol reduction†			Smoking reduction††		Blood pressure reduction†††
	3%	6.7%	20%	Program	Quit	
Years	◄——————————————— Months ———————————————►					
Women						
20	2	4	12	17	37	19
40	4	9	24	17	37	26
60	5	11	29	11	23	22
Men						
20	2	4	11	32	70	24
40	3	7	18	29	63	34
60	1	2	5	15	32	24

* High risk is defined as systolic blood pressure, cigarette smoking habit, and total serum cholesterol level each at the 90th percentile of the age- and sex-specific population distribution and high-density-lipoprotein cholesterol level at the 10th percentile of the age- and sex-specific population distribution.

† Reduction of total serum cholesterol level by 6.7 per cent is the 'base-case' assumption: reductions by 3 per cent and 20 per cent are the low and high amounts of cholesterol reduction considered in the sensitivity analyses (lag period for the achievement of full benefit = 3 years; discount rate = 0 per cent).

†† Program for smoking reduction is defined as a 46 per cent reduction in cigarette smoking; quit is defined as a complete discontinuance of cigarette smoking (lag period for the achievement of full benefit = 3 years; discount rate = 0 per cent).

††† Reduction of systolic blood pressure by 14.3 per cent (lag period for the achievement of full benefit = 3 years; discount rate = 0 per cent).

Source: Taylor et al (1987)

cholesterol will also reduce non-fatal CHD events, the avoidance of which will improve an individual's quality of life. None of the published economic studies of cholesterol management measure changes in quality of life although some make arbitrary assumptions. For example, the Standing Medical Advisory Committee (1990) assume that a non-fatal heart attack reduces quality of life by 10 per cent over the remaining lifetime and they use this assumption to convert estimates of compara- tive survival into quality-adjusted survival. But their calculations do not take account of any (potential) adverse effects from drug therapy nor of the unpleasantness of taking medicines such as cholestyramine. In con- trast Drummond and McGuire (1990) argue that the quality-of-life effects of non-fatal infarcts and drug side-effects might effectively cancel each other out. (A neat assumption which precludes the need to measure either effect!) Clearly the whole question of quality-of-life associated with cholesterol lowering interventions is in need of further study.

Costs

Costs of blood cholesterol testing need to be assessed in relation to the actions that would be taken by a doctor if levels were considered too high. Merely to compare screening strategies in terms of cost per 'case' detected is not helpful because identification of a case (i.e. hypercholesterolaemia) implies that some action will be taken that will generate further costs and effects. (A prior ethical condition for screening for a 'disease' is that some effective therapy exists). This was the general philosophy of the economic assessment of opportunistic testing and treatment undertaken by the Standing Medical Advisory Committee (1990). A pivotal assumption of their analysis is what proportion of cases detected would ultimately be placed on drug therapy.

In estimating the costs of alternative drug treatment regimens for cholesterol lowering an obvious starting point is the relative costs of the drugs themselves. In Table 15 five of the most commonly prescribed agents are listed along with recommended adult dose ranges and annual treatment costs have been computed. There is a marked variation in annual drug costs for these maintenance therapies: a year on a typical dose of cholestyramine (16g taken as four 4g sachets a day) would be £608 compared to £116 on bezafibrate, or £476 on 20mg per day of simvastatin.

In addition to drug costs there are other health care costs which are attributable to therapy, such as costs of monitoring therapy by GPs or lipid clinic specialists; costs of treating any side-effects from drug therapy; cost savings due to CHD events, such as myocardial infarction, which are avoided as a result of taking drug X or drug Y. In addition to these costs, analysts such as Oster and Epstein (1987) also include cost estimates for additional routine health care for non-cardiovascular diseases which a person would consume as a consequence of living longer.

Table 15 **Costs of maintenance therapy with selected lipid lowering drugs**

	Recommended adult dosage per day	Annual cost
Cholestyramine (Questran)	12-24 g	£456-£912
Bezafibrate (Bezalip)	600 mg	£116
Gemfibrozil (Lopid)	1,200 mg	£350
Probucol (Lurselle)	1,000 mg	£163
Simvastatin (Zocor)	10-40 mg	£238-£952

Source: Dosages and prices taken from MIMS (January 1990)

Cost-effectiveness

(i) *Opportunistic testing and treatment*

The Standing Medical Advisory Committee (1990) consultative document investigates a variety of testing and treatment options. Their analysis calculates the cost per quality-adjusted life-year (QALY) gained for each option, although (as noted above) the quality-adjustment is by assumption rather than empirically determined. The basic results of the SMAC analysis are presented in Tables 16 and 17. (Note that these analyses should be regarded as provisional because, at this time, the SMAC document is circulated for consultation.)

The baseline SMAC testing and treatment programme is one of opportunistic screening for adults aged 40-69 years. They estimate that the annual cost of such a programme would be £271m, this being £19m on blood lipid testing, £8m on dietary counselling and £241m on drug therapy. Overall they estimate that this combined programme would calculate to £3,128 per life-year or £2,979 per QALY gained over no screening or intervention.

It is particularly important to consider the incremental cost-effectiveness of drug therapy over and above diet. SMAC calculate that diet therapy alone generates one QALY at a cost of £176 but that each incremental QALY gained from drug therapy is at a cost of £19,000. This observation prompts the committee to stress that results are sensitive to assumptions made about the proportion of cases which are treated with drug therapy as this is the major cost component of the programmes evaluated. However, the committee also calculates that drug treatment with more potent agents which are more effective at lowering cholesterol such as the new HMG-CoA reductase inhibitor drugs will have a better incremental performance at £13,500 per QALY compared to the baseline assumption of drug therapy with cholestyramine. The second mediating factor on drug therapy is that the committee predicts that the prescribing rate for cholesterol lowering drugs will be lower in general practice than their baseline assumption which is based on the rate in a typical lipid clinic.

The incremental analysis in Table 17 demonstrates the importance of selectivity in the testing and treatment of raised blood cholesterol. The table gives cost per QALY calculations for CHD risk sub-groups, i.e. by sex, hypertension, smoking status. Consistent with the previous discussion on the multiplicative nature of CHD risk factors there is marked variation between the groups. It is much cheaper to generate one QALY by screening and treating men (£1,957) than it is for women (£6,521) given that men are already more predisposed to CHD. Furthermore among men it costs only £712 for each QALY gained if hypertensive smokers are identified and treated in contrast to £4,076 per QALY for normotensive non-smokers.

A strength of the SMAC study is the way it presents data in an incremental way which emphasises that cost-effectiveness is a relative and conditional concept; it should always be presented relative to an alterna-

Table 16 Cost-effectiveness of blood cholesterol testing and treatment: incremental estimates for different treatment assumptions

	Cost per QALY (1988/89 prices)
Baseline programme: Adults aged 40-69 years, diet and drug therapy	£2,979
– diet therapy alone	£176
– incremental impact (i.e. in addition to diet) of basic drug therapy	£19,000
– incremental impact of more powerful drug therapy*	£13,500

*i.e. treatment with HMG-CoA reductase inhibitors
QALY = quality-adjusted life-year

Source: Standing Medical Advisory Committee (1990)

Table 17 Cost-effectiveness of blood cholesterol testing and treatment: incremental estimates for different CHD risk groups

	Cost per QALY (1988/89 prices)
Baseline programme: Adults aged 40-69 years, diet and drug therapy	£2,979
– Men aged 40-69 years	£1,957
– Women aged 40-69 years	£6,521
Men aged 40-69 years who are:	
Smokers	£1,176
Non-smokers	£2,849
Hypertensives*	£1,133
Normotensives	£2,500
Hypertensive smokers	£712
Normotensive non-smokers	£4,076

*Diastolic BP >91 mmHg

Source: Standing Medical Advisory Committee (1990)

tive and it is conditional upon the pre-existing CHD risk factors of those screened and treated, and the treatment initiated. The SMAC report essentially offers a menu of options to health authorities to help them judge what resources they wish to direct into blood cholesterol testing and treatment. In turn this will require decision makers to compare – implicitly or explicitly – the performance of other health care programmes in terms of costs and benefits with that of blood cholesterol testing and treatment.

The main weakness of the SMAC study are (i) no data on quality of life were incorporated nor was the sensitivity of the 10 per cent assumption

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for non-fatal infarcts examined; (ii) no attempt is made to estimate the treatment costs of future non-fatal CHD events avoided or incurred by virtue of the cholesterol lowering intervention, whereas this had been done in other studies such as Oster and Epstein (1987); (iii) because cholestyramine is soon to come off patent the committee assumes a lower than current market price in its calculations and does not give details of the sensitivity of estimates to this assumption.

(ii) *Cholestyramine versus no intervention*
Oster and Epstein (1987) assumed that cholestyramine therapy reduces total blood cholesterol by 8.8 per cent in adults and they compared this regimen with no intervention for high risk patients who have already been identified as being at high risk (i.e. no screening costs are included). They calculated the cost per life-year gained by life-long cholestyramine treatment. For an adult male aged 40-44 with a pre-treatment level of blood cholesterol of 7.49 mmol/L the cost per life-year gained from drug therapy was US$76,500 in 1987 prices. Their analysis clearly demonstrates that it is less costly to produce life years in younger patients and those with higher levels of pre-treatment blood cholesterol. Depending upon such parameters values range from $56,100 per life-year gained to in excess of $1 million per life year.

Although the absolute numbers vary due to alternative model specifications and drug price assumptions, the Oster and Epstein (1987) results are broadly consistent with the incremental analysis of SMAC (1990). Both studies found that the incremental cost-effectiveness of treatment is a function of pre-existing CHD risk and that it is less costly to generate life-years in persons with greater numbers of CHD risk factors.

(iii) *Cholestyramine versus colestipol versus Oat Bran*
Kinosian and Eisenberg (1988) analysed the cost-effectiveness of treatment for persons with blood cholesterol in excess of 6.85 mmol/L with either cholestyramine, colestipol (another bile acid sequestrant) or oat bran. They used 7-year mortality data from the Coronary Primary Prevention Trial of the Lipid Research Clinics Program (1984) to compute the cost per life-year gained for each intervention which ranged from $117,400 (cholestyramine) to $70,900 (colestipol) and $17,800 (oat bran).

Kinosian and Eisenberg's (1988) analysis suggests that if a decision is made to treat with a bile acid sequestrant then colestipol offers greater benefit at lower cost than cholestyramine. Overall the authors conclude that their results on oat bran suggest that a public health programme aimed at dietary modification/supplementation may be the most cost-effective strategy. (But note the earlier questions and debate on the effectiveness of oat bran as an independent protective factor for CHD.)

(iv) *Cholestyramine versus simvastatin*
The results of the Martens *et al* (1989) study for cholestyramine and simvastatin, one of the new HMG-CoA reductase inhibitors, confirm the

inverse relationship between pre-treatment cholesterol level and cost-effectiveness and the latter's relationship with age at start of therapy. Martens *et al* calculate, using different assumptions to Oster and Epstein (1987), but the same Framingham projection model to predict CHD mortality, that the cost per life-year gained for cholestyramine ranges from 220,000 to 510,000 Dutch guilders (approximately £65,000 to £150,000) and for simvastatin from 50,000 to 100,000 Dutch guilders (£15,000 to £32,000). These results are also consistent with the relative difference in incremental cost-effectiveness between standard and more potent drug therapy in the SMAC (1990) analysis.

The results of Martens *et al* are comparable with the preliminary findings of a UK cost-effectiveness study of simvastatin which is forthcoming and cited by Drummond and McGuire (1990). These preliminary results give cost per life-year figures for simvastatin in the range £9,000 to £25,000 (1988-89 prices) and £40,000 to £104,000 for cholestyramine. Thus on the basis of present evidence simvastatin is clearly superior to cholestyramine in terms of cost-effectiveness.

In summary, although precise estimates vary between studies because each is built upon a foundation of predictions and assumptions, there appears to be a broad consensus emerging on some of the relevant parameters of the cost-effectiveness of blood cholesterol testing and treatment. It is clear that cost-effectiveness – in screening and treatment – is a function of a person's overall CHD risk and that it is a more efficient use of resources to identify and treat those persons who are at greater risk of CHD. But policy makers may wish to trade-off efficiency for other distributive or equity objectives; the implication of the SMAC (1990) analysis is that positive sex discrimination in favour of men receiving blood cholesterol testing and treatment would be an efficient use of resources, but it may not be a politically popular policy.

The results of cost-effectiveness studies and the attendant policy prescriptions that follow should be viewed with caution and with an eye for the validity of the many assumptions (often implicit) that such analyses contain. For example, policy makers should not presume that the *efficacy* of cholesterol lowering drug therapy observed in clinical trials will be commensurate with the *effectiveness* of such therapy in every day clinical practice, where problems such as patient non-compliance will serve to dilute the effect. Cost-effectiveness studies should focus on realistic expectations of benefit rather than projections from ideal experimental settings.

Concerning costs, if the perspective of policy making is societal then the economic equation should not only include costs to the health service but should include costs to individuals; this is particularly important when evaluating dietary modification policies which may have low NHS costs but high individual costs.

9. CONCLUSIONS

Given that the debate about the measurement and management of blood cholesterol and the risk of coronary heart disease is on-going, the conclusions from this brief review can only offer markers of the story so far. At the outset it was noted that CHD is a major public health problem in the UK and developed world, but that it is a largely preventable disease of adverse lifestyle and diet. That elevated blood cholesterol is a major risk factor for the development of CHD is largely undisputed by the experts.

Controversy began when millions of dollars were put into clinical trials of diet and drug therapy which provided some evidence that reducing blood cholesterol could reduce CHD mortality. The consensus panel of the US National Institutes of Health endorsed the findings of studies such as the Coronary Primary Prevention Trial (Lipid Research Clinics Program, 1984) and proposed that they could be immediately translated into prevention policies for the US population. As Kolata (1985) records, a number of eminent physicians, epidemiologists and biostatisticians believed that the limited available data had been over-interpreted to support an aggressive national programme of dietary change.

The cholesterol debate gathered momentum in the USA with the establishment of the National Cholesterol Education Programme (NCEP, 1988) who issued detailed guidelines on the management of elevated blood cholesterol and recommended that all adults should have their blood cholesterol measured every 5 years. Americans have been urged to 'know your number' and Catford (1989) reports that by 1989 about two-thirds of the US population are thought to know their blood cholesterol level.

As indicated by Figure 3, the USA leads the international league table in CHD prevention having reduced mortality rates by about 50 per cent in the period 1970-85. It is not yet clear what contribution programmes such as NCEP will make to this downward CHD trend which reflects long-term changes in US public and physician behaviour towards other CHD risk factors such as blood pressure and smoking. However, the existence of a national system for monitoring trends in CHD risk factor, including total blood cholesterol, means that the impact of (e.g.) dietary policies can be monitored over time. Such systems also exist in Australia who are second in the CHD prevention league table (Figure 3).

In the UK the policy debate on blood cholesterol has been fuelled by concerns about adopting the US approach as a role model – with aggressive management policies for hypercholesterolaemia dictating the need for costly measurement programmes. An assessment of the UK debate is best conducted in the component parts of the population strategy and the high risk strategy.

'Population' strategy

The major element of the UK population strategy is the issuance of dietary guidelines by expert committees such as COMA (1984) which are promoted by programmes such as 'Look After Your Heart' (LAYH), in England under auspices of The Health Education Authority. Consistent with the diet-heart hypothesis discussed in Chapter 5, the expectation is that population rates of CHD can be reduced via reductions in the intake of saturated fat and consequent expected reductions in blood cholesterol.

But it is difficult to judge whether greater or lesser resources should be put into such programmes because their effectiveness is largely unknown. Surveys to monitor public awareness of programmes such as LAYH (Chambers, 1989) are of limited value; a person can be aware of the need for dietary change but not comply with the advice. Some indirect evidence of change in diet can be elicited from National Food Survey data; as indicated in Figure 21 there is a desirable upward trend in the ratio of polyunsaturated to saturated fat in the British diet. Ultimately however, it would be valuable to have some national scheme of CHD risk factor monitoring which included the monitoring of blood cholesterol.

Such data would also be useful in determining the need for, and likely cost-effectiveness of, screening programmes for high risk persons. In evidence to the Committee on Public Accounts (1989) the National Forum for Coronary Heart Disease Prevention recommended that:

'The Government should establish a comprehensive system for monitoring national and local data on mortality, morbidity and trends in risk factors, to enable the effectiveness of prevention measures taken by the health departments to the quantified' (page 27).

In the light of this evidence and the report from the National Audit Office (1989) the Committee on Public Accounts (1989) recommended that:

'We note that in England the Department of Health have been slow to introduce comprehensive monitoring for the risk factors, and stress the need for them to pursue this urgently in the light of advice from the Standing Medical Advisory Committee' (paragraph 25).

A further criticism of population CHD prevention policies in the UK is that they have been fragmentary. The consensus statement of the King's Fund Forum (1989) called for a national strategy towards the prevention of CHD which would incorporate health objectives into national food policy and such a nationally co-ordinated effort is also supported by the Standing Medical Advisory Committee (1990). Such proposals recognise the fact that attempts to improve the national diet will only be

successful if they are co-ordinated policies which are pursued by relevant government ministries in addition to the Department of Health. Fiscal policy can be used to target health objectives and reduce CHD risk: recent experience has shown that tax changes in favour of lead-free petrol can significantly change consumer demand and increases in tobacco duty can help to reduce the incidence of cigarette smoking.

'High risk' strategy

Rapid development in the technology for measuring blood cholesterol has accelerated the debate in the UK about appropriate clinical policy with regard to patients at high risk of CHD. The first problem is the definition of high risk. A fundamental aspect of CHD risk is that it is multifactorial; a rank-ordering of persons by total blood cholesterol concentration is not equivalent to a rank-ordering by CHD risk. If stratification of the population into CHD risk groups is to be valid and reliable then those interpreting blood cholesterol measurements should do so with reference to pre-existing risk factors and with an awareness of the potential synergism between factors.

Definition of the factors which place a person at greater or lesser risk of CHD is a knowledge base which is evolving over time and controversies will arise as new potential risk factors are discovered. Although cholesterol subfractions such as HDL cholesterol have been demonstrated to be independent (protective) factors, the incremental predictive value for overall CHD risk gained from HDL is modest relative to the measurement of total cholesterol (Pocock et al, 1989). Furthermore, the measurement of HDL requires more detailed lipoprotein analysis than that for total cholesterol so the ratio of yield to effort will be lower.

Opportunistic screening for elevated total blood cholesterol is already being undertaken in some general practices (Almond et al, 1989) using desk top analysers such as the Reflotron. The Standing Medical Advisory Committee (1990) consultative document has indicated that selective opportunistic testing and treatment based on CHD risk factors has the 'potential' to make a cost-effective contribution. The caution of the committee reflects uncertainty about the likely costs and consequences of programmes in the future.

The SMAC analysis believes that general practitioners will not be keen to place patients on cholesterol lowering drugs and that costs will be contained and cost-effectiveness maintained. But prophets of doom can also be found – Vines (1989) comments that 'the worry is that overworked GPs have neither the time nor the expertise to give patients detailed advice about diet and exercise'. Vines (1989) goes on to speculate that 'most doctors concerned about their patients' cholesterol levels will probably adopt the time-honoured solution of prescribing drugs'.

Professional groups such as the British Hyperlipidaemia Association (Shepherd et al, 1987) recommend that drug therapy should only com-

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mence once diet has failed. For those persons with elevated blood cholesterol who fail to respond to therapy with a lipid lowering diet there are a variety of prescription drugs to choose from. Historically, the recommended first line therapy is one of the bile acid sequestrant drugs such as cholestyramine. However, the new generation of HMG-CoA reductase inhibitors such as simvastatin may be the drugs of first choice in the future because early evidence suggests they are more effective in reducing blood cholesterol (O'Conner et al, 1990) and early studies suggest they may be more cost-effective than bile acid sequestrants (Martens et al, 1989).

Given the medical, commercial and public interest it is clear that blood cholesterol testing and treatment programmes will develop in the UK through the 1990s. But the costs and effects of such programmes remain uncertain. In the UK the Standing Medical Advisory Committee (1990) has made a first attempt to predict the likely outcomes from different programmes of case-finding and treatment but as new cholesterol lowering therapies are developed the debate on cholesterol and CHD risk is far from over.

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