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CARDIOVASCULAR DISEASE RISK FACTORS: NEW AREAS FOR RESEARCH

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Members

Dr C. J. M. Lenfant, Director, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD, USA

Professor M. G. Marmot, Head, Department of Epidemiology and Public Health, University College and Middlesex School of Medicine, London, England (*Chairman*)

Dr J. A. Matenga, Department of Medicine, University of Zimbabwe, Harare, Zimbabwe

Professor P. J. Nestel, Clinical Professor in Medicine, Flinders University of South Australia, and Chief, Division of Human Nutrition, Commonwealth Scientific and Industrial Research Organisation (CSIRO), Adelaide, Australia (*Rapporteur*)

Professor A. Nordoy, Chairman, Department of Medicine, University of Tromsø, University Hospital, Tromsø, Norway

Professor M. Oliver, Director, Wynn Institute for Metabolic Research, London, England

Dr P. Rubba, Institute of Internal Medicine, Faculty of Medicine and Surgery II, University of Naples, Naples, Italy

Professor H. S. Wasir, Head, Department of Cardiology, Cardiothoracic Centre, All-India Institute of Medical Sciences, Ansari Nagar, New Delhi, India

Representatives of other organizations

International Council of Nurses

Ms C. Panchaud, Department of Nursing and Research, International Council of Nurses, Geneva, Switzerland

International Society and Federation of Cardiology

Professor W. Rutishauser, President, Geneva, Switzerland

World Hypertension League

Dr T. Strasser, Secretary-General, Geneva, Switzerland

Secretariat

Professor F. H. Epstein, Zurich, Switzerland (*Temporary Adviser*)

Dr I. Gyárfás, Chief, Cardiovascular Diseases, WHO, Geneva, Switzerland (*Secretary*)

Abbreviations

The following abbreviations are used in this report:

ADP	adenosine diphosphate
CHD	coronary heart disease
CVD	cardiovascular disease
HDL	high-density lipoprotein
HRT	hormone replacement therapy
IDL	intermediate-density lipoprotein
LDL	low-density lipoprotein
Lp(a)	lipoprotein (a)
PAI	plasminogen-activator inhibitor
PUFA	polyunsaturated fatty acids
SFA	saturated fatty acids
t-PA	tissue plasminogen activator
TRL	triglyceride-rich lipoprotein
VLDL	very-low-density lipoprotein

1. Introduction

A WHO Scientific Group on Cardiovascular Disease Risk Factors – New Areas for Research met in Geneva from 23 to 27 November 1992. Dr I. Gyárfás, Chief, Cardiovascular Diseases, opening the meeting on behalf of the Director-General, pointed out that the main emphasis in WHO's work in the context of cardiovascular diseases was on putting science into practice in programmes aimed at preventing and controlling these diseases in communities and nationwide. Thus WHO should strive to extend and improve its activities not only by supporting the implementation of prevention programmes but also by promoting research designed to develop more effective interventions.

The Scientific Group's report is concerned with risk factors other than those that can be considered as "classical" ones, with identifying areas where research is necessary, and with defining priorities. Certain areas are considered only briefly or not at all because they have been dealt with in recent publications (*1,2*).

The areas for research recommended by the Scientific Group and summarized at the end of each section are by no means exhaustive, but are intended to help scientists, research administrators and health workers to improve the allocation of human and material resources to research designed to improve human health.

1.1 Risk factors

The term "risk factor" in relation to cardiovascular disease (CVD), and specifically coronary heart disease (CHD), was used for the first time in 1961 in a paper on the Framingham Study (*3*). The risk factors themselves, in particular high levels of serum cholesterol, hypertension and smoking, have been measured in prospective epidemiological studies since their discovery in the late 1940s (*4-6*). Over the years, much has been learned about risk factors, in terms of both depth of understanding and the recognition of new predictors of risk. In the present report, no attempt is made to summarize current knowledge or to discuss to what extent a causal relationship between the many risk factors and the atherothrombotic vascular diseases already described has been established. Instead, the focus is the need for further research on established or suspected risk factors. Some of these are not new but need to be more precisely specified and more accurately measured, while others have emerged only recently.

Risk factors are used for two main purposes:
- detecting individuals and populations at elevated risk of CVD,
- determining the causes of CVD.

It is important to distinguish between these two purposes, since they have been confused by somewhat indiscriminate use of the term "risk factor". This usually refers to modifiable biological characteristics (serum lipids and their fractions, blood pressure, blood glucose and insulin, and

thrombogenic factors, among others) but can also be applied to a behaviour, such as smoking or physical inactivity. Other behaviours or lifestyles, in particular dietary habits, are also risk factors but are not commonly included under this heading. Social and psychosocial influences likewise carry risk but are not readily classified within this scheme. Biological traits (such as age and sex) may be called risk factors but cannot be modified. Some genetic risk factors are also not modifiable, but others interact with the environment.

For practical purposes, the term "risk factor" should be used pragmatically, i.e. when the factor concerned actually predicts risk. From the point of view of prevention, it is important to establish a cause-and-effect relationship between the various factors and CVD. Nevertheless, a risk factor may be useful as a predictor of risk without being causally linked to pathogenic mechanisms. Conversely, a risk factor that is not independently predictive could still be pathogenic.

1.2 Screening

There is a great need to increase the potential for CVD prevention in the entire population. The greater the number of risk factors found to be causally related to disease, the greater the power to reduce the disease burden in the community by reducing the levels of such pathogenic risk factors. In general, populations containing many high-risk individuals are characterized as high-risk populations (the issue of "sick individuals" versus "sick populations", as discussed by Rose (*7*)). Screening for the major risk factors – serum cholesterol, blood pressure and smoking – will leave undetected about half the individuals in the population who will develop disease, so that there is considerable scope for prevention through the control of other risk factors. It should be remembered, however, that the major risk factors also exert pathogenic effects at levels below those arbitrarily selected as indicators of high risk. In any assessment of the preventive potential of screening for and controlling risk factors, account must be taken of the fact that most of them are interrelated, the risk being increased if several of them are present at the same time.

Optimal screening for "high risk" requires methods that will detect the largest possible number of persons destined to develop CHD in the future among the smallest possible fraction of the total population. The limiting factor in a strategy that aims to detect and treat high-risk individuals is the imprecision with which individuals at risk can be detected. At present, the screening methods available and practically feasible permit the detection of approximately 50% of the future "victims" of disease among about 20% of the base population. If, say, 80% of future disease events could be concentrated among some 10% of the population, intervention could be targeted only on those at high risk. However, some calculations suggest that the 50% figure just mentioned cannot be increased to much more than 65-70%. While 50% and 65% are by no means low figures – and, indeed, are not even approached for any other chronic disease – it is highly

desirable to aim at maximal screening efficiency by including in the tests as many risk factors as are needed to ensure that the screening methods are of optimal sensitivity and specificity. To this end, "new" risk factors, more closely linked to pathogenic mechanisms, must be sought.

1.3 Causation

Epidemiological research on risk factors, taken together with clinical and laboratory research, is important in establishing causal pathways to disease. For example, plasma total cholesterol continues to serve a most useful function as a predictor of CHD, and provides at the same time a partial picture of the causal pathways involved. It is now clear, however, that we must at the very least distinguish low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol from other lipoproteins that contain cholesterol to have a clearer picture of the causal mechanisms. It turns out that the study of the different lipoproteins enables the disease to be predicted with greater precision. Yet this need not be the case. The power to predict depends not only on whether the appropriate causal factor has been identified but also on the precision with which it is measured.

The causal chain can be traced from genes and the environment through biochemical and other bodily changes to pathological alterations and clinical disease. Much of the research recommended in this report is aimed at finding such causal pathways.

It should be emphasized that the general orientation of the research recommended is the prevention and control of CVD. Basic biological research, although vital to the understanding of disease processes, was, in general, not considered by the Scientific Group.

In its report, the Group has tried to suggest new areas for research on CVD risk factors and to provide guidance on such research, confining its attention to the areas that appear to be of greatest promise. While this is only one aspect of research on the causes and prevention of CVD, it is one of key importance inasmuch as risk factors provide the link between the causes of these diseases and their prevention. It is recognized that some of the research needed is already in progress or will be undertaken irrespective of any recommendation by the Group. Nevertheless, current efforts are scattered and there has been no previous attempt to provide a reasonably comprehensive view of possible new directions for research. The present report is intended to fill this gap.

The main disease considered by the Group was CHD. Hypertension and cerebrovascular disease were touched on but not considered in depth, since this would have broadened the scope of the Group's terms of reference to an unmanageable degree. Other CVDs of worldwide importance – rheumatic heart disease, cardiomyopathies, venous pulmonary embolism – were not considered. Nevertheless, the research recommended by the Group is likely to be of worldwide public health

significance as CHD is the major cause of death in industrialized countries and is emerging as a significant cause of morbidity and mortality in developing ones.

2. Nutrition

2.1 Scientific background

Many studies have established that correlations exist between CHD and the amount of fat and saturated fat in food; there is impressive evidence that the same is also true for dietary cholesterol (*8, 9*). The evidence for an inverse relationship between CHD and the intake of vegetable oils is less convincing because of the variation in the fatty acid content of such oils (*10*).

However, dietary fatty acids are heterogeneous in their metabolic effects, only some benefiting plasma lipid levels, arterial thrombosis and cardiovascular risk in general. In this context, it is important to evaluate the effects on all relevant cardiovascular risks when assessing the benefits of an individual fatty acid.

There appears to be a hierarchy among the saturated fatty acids (SFA) in terms of their effect on plasma cholesterol, myristic acid (C14) raising LDL cholesterol most, followed by palmitic (C16) and lauric acids (C12) (*11*). Shorter-chain saturated fatty acids and stearic acid exert little effect. However, the effects on thrombogenesis are less well defined and constitute a priority area for research.

Our understanding of the role of mono-unsaturated fatty acids (effectively oleic acid, C18:1) in influencing LDL cholesterol has changed in recent years. Oleic acid is at least as effective as polyunsaturated fatty acid (linoleic acid) in lowering LDL when it replaces saturated fatty acids. Whether, in addition to this, mono-unsaturated and polyunsaturated fatty acids (PUFA) confer further cardiovascular protection (reduced thrombogenesis, antiarrhythmic effects) is an important subject for research.

PUFA (*9, 10*) form a group of families of fatty acids, and include the essential fatty acids linoleic (C18:2) and α-linolenic (C18:3) acids. Such acids may be classified as ω6 or $n-6$, mainly linoleic acid, and ω3 or $n-3$, mainly α-linolenic acid in plants and eicosapentaenoic acid (C20:5) and docosahexaenoic acid (C22:6) in fish. PUFA are unstable and are therefore more susceptible to oxidation than other fatty acids.

2.1.1 *Fatty acids*

Extensive evidence already published demonstrates that replacement of SFA in the diet by PUFA is associated with reduced coronary risk. The regular consumption of fish also appears to confer protection, although it

is not clear that the benefit is derived solely from the fish oil, since population studies suggest benefits from eating both white and fatty fish.

Populations with lower levels of linoleic acid in their adipose tissue and lower levels of eicosapentaenoic acid in platelets have high mortality from CHD (*12*). The mechanism underlying the protective effect of dietary linoleic acid is still not known. It is not clear whether there is any advantage in replacing saturated fatty acids in the diet by polyunsaturated or mono-unsaturated acids in terms not only of effects on lipoprotein metabolism but also of cardiovascular protection in general. A related issue is the question of the true biological effects of the isomeric (*trans*) fatty acids. Recent evidence indicates that these fatty acids resemble SFA in their effects on lipoprotein metabolism.

A poorly understood area, but one of major public health importance, is that of interactions between specific dietary fatty acids that lead to a fatty acid mix which minimizes risk factors and avoids adverse clinical events. While oleic and linoleic acids are already major dietary unsaturated fatty acids in most populations, it is not clear whether the intake of $n-3$ PUFA (especially of marine origin) should be increased (*13*). Since the proportions of the $n-6$ and $n-3$ PUFA in the fatty acid mix influence the elongation and desaturation of both linoleic and α-linolenic acids, there is a need for more information about the optimal proportions of these acids.

SFA have been consistently associated with increased thrombotic tendency in a series of experimental and clinical studies (*14*). The relationship between individual SFA and haemostatic variables associated with CHD needs further evaluation. The relationship between PUFA of both the $n-6$ and the $n-3$ families and haemostatic variables indicates that, in particular, the very-long-chain fatty acids of both families play fundamental roles in thrombogenesis. Further studies on the effects of the individual PUFA and the interplay between them and the other dietary saturated and mono-unsaturated fatty acids in thrombogenesis are greatly needed. This is also true for the possible deleterious effects of the oxidation products of PUFA.

2.1.2 *Plant foods*

There is evidence for a protective effect of plant foods (*15*), since CHD rates are uniformly low in populations where the consumption of such foods is high. This applies both across countries and within them. Vegetarians, for instance, have on average lower aggregates of cardiovascular risk factors than do omnivores. Indices of plant food consumption in prospective studies have shown that the incidence of new CHD events is lowest among the highest consumers of plant foods.

Several of the beneficial factors have been identified, including the relative energy content, the fibre (non-starch polysaccharide) and complex carbohydrate contents, the degree of unsaturation of the predominant fatty acids and the antioxidant properties of vitamins (*10, 16*). Plant foods are

also low in sodium and high in potassium, which is beneficial for the control of hypertension.

Many other constituents of plant foods are candidates for CHD prevention, including compounds with potential antioxidant properties, e.g. flavonoids, plant sterols and other non-saponifiable lipids that lower plasma cholesterol.

Non-starch polysaccharides include a wide range of biological compounds that lower plasma cholesterol, improve carbohydrate utilization, and may have other benefits (*17*). Research on the chemistry and biology of plant constituents, from the point of view of reducing cardiovascular risk, is a high-priority area. In particular, the role of starch in general, the staple food of Asian and African populations, deserves greater scrutiny.

2.1.3 *Antioxidants*

PUFA are extremely susceptible to peroxidation, which may lead, under certain circumstances, to arterial damage and progression of atherosclerosis. One mechanism for this may be the oxidation of fatty acids in LDL in the arterial wall (*16, 18*). Most of the evidence comes from *in vitro* studies, while the data from *in vivo* models, even in experimental animals, are limited. High priority should be given to improving the methods used for assessing oxidation products in plasma and other tissues.

A relatively new issue in the area of dietary influences on CHD is the role of natural antioxidants of dietary origin, which may constitute a safe means of preventing peroxidation and antagonizing the atherosclerotic process (*16, 19*). An inverse relationship between vitamin E levels (standardized for cholesterol concentration) and CHD mortality has been demonstrated (*20, 21*). Data on other antioxidants (vitamin C, selenium, vitamin A and β-carotene) are less consistent.

The only prospective data available on antioxidants in relation to CHD are those provided by the Physicians Health Study in the USA. A subset of 333 individuals with chronic stable angina who received supplementation with β-carotene experienced a statistically significant reduction in combined end-points (myocardial infarction, revascularization, stroke or coronary death) in a 7-year follow-up (*16*). A case-control study of patients with angina performed in Scotland (*22*) has given further support to the hypothesis that levels of circulating antioxidants are inversely related to the risk of angina. Smokers have, in general, a poor antioxidant status, as reflected in lower levels of plasma antioxidants.

Preservation by antioxidants of endothelium-dependent regulation of blood flow in the coronary circulation is likely to be extremely important in conditions of acute ischaemia or disturbed blood flow, such as angina pectoris or myocardial infarction. *In vitro* incubation of isolated arterial segments with oxidized LDL has been found to produce marked impairment of endothelium-dependent relaxation (*23*). Better adaptability

to impaired perfusion might preserve myocardial tissue from irreversible necrotic changes or, in cases of severe ischaemia, reduce infarct size (*24, 25*).

More prospective data are needed before the effects of antioxidants on atherosclerosis can be definitely established. Furthermore, levels of antioxidants should be evaluated by means of multivariate analysis in the context of other well known risk factors. The possibility also exists that the size of tissue stores of iron is related to the promotion of oxidative processes. It is probable that, in future research, further potent antioxidants will be identified and characterized.

From the public health point of view, the key issues are how much and which antioxidants are required in relation to the type and amount of individual PUFA in the diet. Candidates for future intervention trials are vitamins E and C and β-carotene. The Group would welcome trials designed to resolve these questions.

2.1.4 *Nutrient–gene interactions*

Variability in the response to dietary factors, some of which is genetic in origin, is well recognized. Further research on the genetic basis of the responsiveness of individuals to nutrients that increase cardiovascular risk is urgently needed, and the continuation and extension of studies already under way should be encouraged.

2.2 Implications for prevention and control

For high-risk populations, the fundamental nutrient goal must be to reduce the intake of fat, and specifically of SFA that adversely affect CHD risk factors. As a partial replacement of SFA, the optimal mix of nutrients is likely to consist of starch and unsaturated fatty acids (*8, 26*). Oleic acid (the major dietary mono-unsaturated fatty acid) has recently been preferred to linoleic acid as the predominant substituting fatty acid. Furthermore, current recommendations favour increasing the consumption of $n-3$ fatty acids from plants and fish. National recommendations have been changing over the last three decades and are likely to be modified further in the light of new research.

The aim of altering eating habits in countries with high rates of CHD is to reduce its incidence, but this should not be considered in isolation. All-cause mortality must also be reduced. The relationship between plasma cholesterol concentration and all-cause mortality must be considered in the context of advice to reduce cholesterol levels (*27*). Current evidence suggests that the curve is J-shaped, the minimum being located to the left of the median and the left-hand limb of the curve possibly involving the lowest 5% of the cholesterol distribution (*27*). This relationship between low cholesterol and non-cardiovascular mortality should not prevent the taking of community-based measures to reduce atherogenic lipoprotein levels in populations and individuals at high risk.

The low incidence of CHD in some Asian and Mediterranean countries and most of the developing countries of Africa may be related to diets low in animal fats and high in non-starch polysaccharide (fibre). Changes in these traditional diets should be resisted, apart from those designed to ensure a correct balance of essential nutrients that will optimize growth and development. Public health policies should ensure that commercial interests do not disturb these dietary habits if CHD epidemics are to be avoided in these countries.

2.3 Research recommendations

1. The optimal mix of macronutrients (fat, carbohydrate, protein, types of fatty acid) to minimize the risk of CHD should be established.
2. Research should be undertaken to establish the biological effects and safety of the individual dietary fatty acids that make up the optimal mix for achieving a low prevalence of biological risk factors and of adverse clinical events (including the proportions and types of $n-3$, $n-6$ and isomeric (*trans*) fatty acids).
3. The biological effects of the major dietary SFA should be assessed so as to determine which do and which do not adversely affect CHD risk.
4. The constituents of plant foods that are protective against CHD (fatty acids, non-starch polysaccharides, antioxidant vitamins) should be identified.
5. The constituents of different types of fish that are protective against CHD (fatty acids, selenium, etc.) should be identified.
6. The type and amount of dietary antioxidants needed to prevent the oxidation of dietary PUFA should be determined.
7. Intervention trials of dietary antioxidants should be encouraged.

3. Lipids

3.1 Scientific background

3.1.1 *New lipoprotein phenotypes*

Lipoprotein interactions are a key feature of lipoprotein metabolism. Artificial compartmentalization of individual lipoproteins has obscured the atherogenicity of several lipoprotein species.

The significance of raised plasma cholesterol (and more specifically raised LDL cholesterol) and of reduced HDL cholesterol as major CHD risk factors is generally accepted. However, some patients develop premature CHD with apparently normal LDL cholesterol. The re-evaluation in recent years of the importance of dyslipidaemia (abnormal plasma lipids) in CHD has revealed a wide range of commonly occurring abnormal

lipoprotein phenotypes (or patterns) which are at least as important as hypercholesterolaemia. This has focused attention on the atherogenicity of new classes of lipoproteins besides LDL, as well as within the LDL group itself (*28*).

There is thus a need to identify the new lipid and lipoprotein factors clearly and precisely in order to determine the atherogenicity of lipoprotein particles more accurately. A better understanding of this issue is essential for both epidemiologists and clinicians.

3.1.2 *Triglycerides*

Of particular relevance is the question of the role of triglycerides in these new lipoprotein phenotypes and of the independence of plasma triglyceride as a risk factor. Raised triglycerides occur as a component of several common lipoprotein phenotypes found in patients with premature CHD and in about half the relatives of such patients (*29*), namely: (1) combined hyperlipoproteinaemia (raised LDL and very-low-density lipoprotein (VLDL)); (2) high triglyceride-low HDL cholesterol; (3) raised triglyceride, low HDL, polymorphic LDL (small, dense LDL), which commonly occur together with central obesity and insulin resistance; and (4) raised VLDL and hyperapobetalipoproteinaemia (raised plasma apoprotein B, the major protein of VLDL and LDL), in which the LDL concentration need not be raised but the number of LDL particles of the cholesterol-poor variety is increased; the presence of this phenotype is shown by the high plasma apoprotein B concentration.

Furthermore, triglyceride is carried in several lipoproteins that are remnants (or catabolic products) of chylomicrons or of VLDL, the particles in which dietary triglyceride and triglyceride made in the liver, respectively, are carried. These remnants are putative atherogenic particles.

It is now also evident from several large prospective and intervention trials that hypertriglyceridaemia (usually due to excess VLDL remnants) represents an independent risk for CHD when it is associated with low HDL and/or raised LDL (*30*).

The severity of atherosclerosis, as judged by coronary arteriography, has been shown in at least three studies to correlate independently with the concentration of intermediate-density lipoprotein (IDL), which is the smallest of the VLDL remnants and therefore regarded as part of the family of triglyceride-rich lipoproteins (TRLs). The relationship is stronger in women. In one large study, progression of coronary atherosclerosis was associated both with the IDL concentration and with low-molecular-weight LDL (*31*); this smaller, denser LDL leads to slow clearance of LDL as a whole. The smaller, denser particles also appear to be more susceptible to oxidation.

3.1.3 *Triglyceride–HDL relationship*

There is generally an inverse relationship between TRL and HDL metabolism. Since HDLs are partly derived from TRL catabolism, diminished TRL degradation, as in hypertriglyceridaemia, leads to reduced formation of HDL. The relationship between HDL and TRL is nowhere seen better than in the events following a fatty meal. Since such meals may give rise to TRL and therefore to an increase in atherogenic potential, it has been suggested that the postprandial triglyceride level may be a better index of CHD risk than the fasting value. That alimentary lipaemia may be present in CHD patients but not in normal subjects was reported some 40 years ago. Recent work has shown, *inter alia,* that: (1) the duration of alimentary lipaemia (or the accumulation of both chylomicron and VLDL remnants) is prolonged even in patients with CHD who have normal fasting triglyceride levels; (2) particles resembling remnants are present in the fasting state in CHD; and (3) HDL cholesterol levels are reduced because cholesteryl esters are transferred to the enlarged pool of TRL, enhancing atherogenicity (*32*). Whether prolonged clearance of remnants after eating fat is an independent risk factor, justifying a further measurement, has not been established. The situation will be clarified and simplified if a test can be developed for specific chylomicron remnants. Current methods are neither practical nor specific enough.

3.1.4 *LDL–receptor interactions*

LDL is the end-product of the VLDL–IDL–LDL cascade (*33*). The removal of LDL is largely a function of LDL receptors. LDLs are polymorphic, and the different LDL particles, which vary in both size and composition, have different affinities for the receptor besides differing in atherogenic potential. LDLs can also be modified in the circulation, e.g. by glycation in diabetics or by oxidation, which reduces their affinity for the normal LDL receptor and increases their potential atherogenicity.

LDL receptor activity influences the fates of VLDL remnants, IDL and LDL (*33*). High receptor activity reduces the precursors for LDL as well as increasing LDL removal. Conversely, LDL levels rise when LDL receptor activity is diminished. Dietary factors, such as cholesterol and possibly saturated fat, raise LDL levels by down-regulating receptors. LDL receptors are up-regulated by estrogens (hence the lower levels of cholesterol in premenopausal women) and may decline with aging, which accounts for some of the rise in plasma cholesterol with age.

3.1.5 *Role of HDL*

HDLs are central to the orderly catabolism of lipoproteins (*33*). They indirectly initiate triglyceride catabolism and remnant removal, and accept "redundant" surface lipid and apolipoprotein material from catabolized TRL (hence the inverse relationship between triglycerides and HDL). HDLs have a key function in cholesterol transport, as acceptors of free cholesterol from cells. It is important to establish which HDL particles are

antiatherogenic (best acceptors of cholesterol) and whether the HDLs in patients with CHD are functionally abnormal. Thus raised triglyceride–low HDL cholesterol occurs commonly in Asian and certain other populations, and may be related to their high carbohydrate diet, fat distribution or insulin resistance. It is important to determine whether this represents a risk factor or whether the lipoproteins differ from those seen in the similar phenotype associated with CHD in Western countries.

Apolipoprotein DNA polymorphism due to minor mutations of the genes concerned has been shown to account for a small percentage of CHD and of hypercholesterolaemia (*34*). Several minor mutations of genes that regulate lipid metabolism are associated with excess CHD or excess hyperlipidaemia, although the small numbers of subjects in the relevant studies has led to inconsistent results. The main importance of these genetic studies lies in the need to target those at highest risk. Whether this approach, when eventually simplified, has merit in public health terms is unclear.

3.1.6 *Lipoprotein (a)*

Raised lipoprotein (a) (Lp(a)) is clearly a major genetic risk factor for premature CHD (*35*). Lp(a) occurs as a complex between LDL and plasma apolipoprotein (a) and hence the association between raised Lp(a) and raised LDL may be important. Heterozygotes for familial hypercholesterolaemia show, on average, a 3-fold increase in Lp(a). The significance of this result lies in the finding that familial hypercholesterolaemia patients with CHD had high Lp(a) levels.

Biochemical and immunohistochemical studies have demonstrated the presence of apolipoprotein (a) in arterial atheroma. Its concentrations in artery correlate with those in plasma, suggesting a causal role for Lp(a) in atherosclerosis. Veins grafted into the coronary circulation become enriched in Lp(a) as they acquire atherosclerosis. The partial homology in the structures of Lp(a) and plasminogen has given rise to speculation about the effects on the fibrinolytic system, which are discussed later in section 6.

An interesting paradox is that the correlation between plasma Lp(a) and CHD incidence does not extend across all populations. It was not found, for instance, in Israel. More importantly, Africans have much higher Lp(a) concentrations than Caucasians, yet are relatively free of CHD (*35*).

Lp(a) concentrations are raised in chronic renal disease and in diabetics who have proteinuria; the reasons for this are not known, but the high Lp(a) levels may contribute to the high complication rate in the form of CHD.

3.1.7 *Oxidized lipoproteins*

There is increasing evidence that oxidative changes in some lipoproteins play an important role in atherogenesis and possibly in other areas of cardiovascular dysfunction (*18*). Most research has focused on LDL, but

oxidative modification of both VLDL and Lp(a) has recently been shown to increase the atherogenicity of these lipoproteins also (*35*). Many key cellular processes involved in atherogenesis have been shown experimentally to be enhanced by oxidized LDL.

The *in vivo* evidence is persuasive but not convincing. Atheromatous lesions contain a higher than normal content of LDL with the physicochemical and metabolic characteristics of oxidized LDL.

The significance of circulating oxidized LDL is highly contentious given the very small concentrations present and the possibility that the findings are artefactual; the existence of a large number of tests for peroxidation implies that no current test is sufficiently sensitive or specific to answer this key question.

3.2 Implications for prevention and control

New classes of lipoprotein phenotypes, including TRLs and Lp(a), have been found to exist in addition to the established lipid risk factors. For the prevention and control of CHD, therefore, improved and simplified technology is required to make it possible to determine the new atherogenic lipoprotein profiles at an early stage and thus improve clinical management and allow the prevalence of these phenotypes to be established at the population level. This has important implications not only for preventive strategies but also for assessing the value and safety of high-carbohydrate diets which raise triglycerides and lower HDL.

3.3 Research recommendations

1. New and simplified technologies should be developed for the identification of atherogenic lipoproteins, including chylomicron remnants, VLDL remnants, polymorphic small, dense LDL, and Lp(a), to facilitate preventive strategies.
2. Research is needed to test the hypothesis that the high triglyceride–low HDL cholesterol and insulin resistance found in some Asian and African communities in Western countries predispose to premature CHD, in order to establish the benefits of the pattern of food consumption of these communities.
3. The circumstances under which a high triglyceride concentration is an independent risk factor for CHD should be established.
4. The way in which HDL protects against atherosclerosis and the HDL measurement that provides the most precise antiatherogenic index should be established.
5. A simple LDL receptor assay for use in clinical and field trials should be developed.
6. An index of atherogenic lipoproteins, including the new risk factors, should be devised for use in intervention studies.

4. Insulin resistance

4.1 Scientific background

Evidence that there may be a distinct metabolic syndrome characterized, in particular, by insulin resistance and associated with increased CHD risk has been accumulating over the last 25 years (*36-38*). It may partly explain the high incidence of CHD in ethnically different communities and populations (*39*). The syndrome comprises insulin resistance and its associated hyperinsulinaemia, raised plasma triglycerides, low plasma HDL, raised blood pressure and reduced glucose tolerance as the central disturbances. The prevalence of the metabolic syndrome by age and sex is not yet known. Insulin resistance is present when the effectiveness of plasma insulin in reducing plasma glucose concentrations is diminished. A compensatory increase in pancreatic insulin secretion is then necessary to maintain normal glucose levels, leading to the hyperinsulinaemia characteristically seen in insulin resistance. Although there are rare, severe forms of insulin resistance, generally genetically determined, the metabolic syndrome is characteristically seen in milder forms associated with obesity or impaired glucose tolerance (*40*). In addition to the adverse lipid, lipoprotein and blood pressure profile associated with insulin resistance and hyperinsulinaemia, elevated insulin concentrations might also adversely affect CHD risk by promoting arterial lipid deposition and proliferation of smooth muscle cells (*41*).

Whether insulin resistance is a cause or a consequence of the metabolic disturbances associated with CHD is uncertain. Insulin resistance is characteristically seen in association with central obesity, and centrally located body fat has a relatively high rate of basal lipolysis, leading to elevated levels of free fatty acids, which may themselves cause insulin resistance (*42*). Obesity may also be associated with a reduction in insulin-stimulated blood flow, which could result in insulin resistance (*43*).

In comparison with men, premenopausal women have a preponderance of fat in the gluteofemoral region, and such peripheral adiposity is not associated with the insulin-resistance syndrome. At the menopause, however, rapidly dwindling estrogen concentrations are associated with a redistribution of fat into central stores, and with adverse changes in lipids and lipoproteins (*44*). Insulin resistance may also increase following the menopause, and there is evidence of reduced hepatic insulin uptake. These changes could all contribute to the increase in CHD seen in postmenopausal women, but detailed studies are lacking.

4.2 Implications for public health

A single prospective study of the development of the metabolic abnormalities of the insulin-resistance syndrome suggests that elevation of insulin concentrations may precede the development of lipid, lipoprotein and blood pressure abnormalities (*45*). An estimate of the prevalence of

this metabolic syndrome will have to await a more stringent specification of its characteristics.

The insulin-resistance syndrome might provide a unifying explanation for the high rates of non-insulin-dependent diabetes mellitus and CHD in south Asians (*46*). The use of glucose intolerance tests in communities differing in CHD incidence should provide further information concerning their metabolic similarity or dissimilarity. When there is insulin resistance, suppression of free fatty acids is reduced; when there is insulin sensitivity, the first-phase rise in insulin is greater. These responses are already helping to explain the incidence of CHD in ethnically different communities.

The relationship between the metabolic syndrome and non-insulin-dependent diabetes mellitus is not yet clear. In developing countries, particularly in southern Africa, the prevalence of this form of diabetes and hypertension in the urban black population is high and may be rising. The higher urban prevalence of these two conditions has never been adequately explained, apart from the observed high body-mass index of the urban population. Although both black diabetics and non-diabetics have a lower insulin response to oral glucose than whites, the obese blacks nevertheless have hyperinsulinaemia when compared with their non-obese counterparts.

Among south-east Asians, the high incidence of CHD cannot be entirely explained by the traditional risk factors.

4.3 Research issues

The development of both insulin resistance and central obesity may be hormonally determined. The influence of catecholamines, glucagon, gonadotropins, adrenocorticoids and perhaps prolactin on pancreatic beta-cell activity, insulin sensitivity and fat-cell responsiveness needs careful study.

Other issues to be resolved include the potential importance of factors other than insulin resistance that may contribute to variation in insulin concentrations. Progressive impairment of beta-cell function may be associated with increased proportions of the insulin propeptides, proinsulin and 32-33 split proinsulin (*47*). These propeptides have less than 10% of the biological activity of insulin but similar immunoreactivity in radioimmunoassay. It is therefore possible that much so-called "insulin resistance" is actually the result of beta-cell dysfunction, the increased proportions of insulin propeptides appearing as insulin in radioimmunoassay. The extent to which such beta-cell dysfunction is a feature of the insulin-resistance syndrome needs to be clarified. Reduced uptake of newly secreted insulin by the liver may contribute to increased insulin concentrations in the general circulation, and may be independently associated with adverse changes in lipoprotein concentrations (*48*).

The reasons for the redistribution of fat, either in association with or independently of insulin resistance, and the relationship between central obesity and CHD need investigation.

4.4 Research recommendations

1. The importance and relevance of the metabolic insulin-resistance syndrome in CHD should be studied in detail.
2. New prospective investigations should be conducted to determine the relative importance in CHD of the various characteristics of the syndrome.
3. Comprehensive population studies should also be carried out to establish the syndrome's true prevalence by age and sex.

5. Homocysteine

5.1 Scientific background

High levels of plasma homocysteine have been associated with the premature development of CVD and arterial thrombosis (*49-52*).

The normal values for total homocysteine in plasma vary between 7 and 14 mmol/l in fasting subjects. The dietary precursor of homocysteine is methionine, a sulfur-containing amino acid that is produced by the catabolism of dietary proteins. Methods for the determination of plasma homocysteine have recently been improved and standardized (*52*). The most frequent causes of hyperhomocysteinaemia are inherited deficiency of cystathionine β-synthase and nutritional deficiency of vitamin B_{12} or B_6 or of folate.

Cystathionine β-synthase deficiency is inherited as an autosomal recessive trait (*49*). The condition is characterized by severe hyperhomocysteinaemia with homocysteinuria, venous and arterial thrombosis, skeletal abnormalities, lens dislocation and mental retardation. Thrombophlebitis and pulmonary embolism are the most frequent vascular events; however, the latter is seldom a cause of death (*49*). In most instances, thrombosis of large and medium-sized arteries (carotid, renal, coronary arteries) is the terminating event.

Heterozygosity for cystathionine β-synthase deficiency is associated with a normal clinical appearance. It is estimated to be present in 1-2% of the general population (*52*).

Data from 18 studies (*52*) on basal plasma homocysteine (more than 1500 cases and 1400 controls) consistently demonstrated hyperhomocysteinaemia in a sizeable fraction of cardiovascular patients (20-40% of those with peripheral or cerebral vascular disease, 10-25% of those with coronary artery disease).

Dietary supplementation with vitamins B_{12} and B_6 and folate reduces plasma homocysteine levels (*50, 52*).

The interaction of hyperhomocysteinaemia with conventional cardiovascular risk factors is being investigated in a multicentre case-control study supported by the European Community (*53*).

5.2 Implications for prevention and control

Since hyperhomocysteinaemia is estimated to be present in 1-2% of the general population, screening for individuals at high risk of CVD because of this metabolic abnormality might become important on public health grounds in the near future.

5.3 Research recommendations

1. Screening tests for heterozygosity for cystathionine β-synthase deficiency should be improved and standardized.
2. The prevalence of hyperhomocysteinaemia in healthy populations and in people with CVD should be determined.
3. The benefits of dietary supplementation with vitamins B_{12} and B_6 and folate should be evaluated.
4. The extent to which dietary factors induce hyperhomocysteinaemia should be determined.

6. Haemostatic factors

6.1 Scientific background

The traditional risk factors for the development of CHD have mainly been abnormalities in lipid metabolism, high intake of saturated fats, smoking and hypertension. However, our ability to detect individuals who will eventually suffer acute coronary occlusions is incomplete. Recent angiographic and autopsy studies have clearly shown that occlusive thrombosis occurs in approximately 90% of patients dying from acute myocardial infarction. In addition, recent work on the relationship between platelet and endothelial cell metabolites and coronary spasm seems to suggest that, where myocardial infarction occurs but no thrombus has been observed, transient platelet-vessel wall interactions may also have triggered myocardial ischaemia. Recent studies in which a high incidence of thrombotic lesions during acute myocardial infarction has been found and the therapeutic success of treatment designed to modulate platelet function, coagulation and fibrinolysis have led to a search for risk factors more directly related to the thrombotic process. Thus prospective epidemiological studies in healthy individuals have established an association between disturbances of the haemostatic balance and the occurrence of coronary events (*54, 55*).

6.2 Thrombogenic/antithrombogenic factors

The following disturbances of the haemostatic mechanism may favour thrombosis since they are directly related to its occurrence:

- endothelial cell dysfunction,
- platelet hyper-reactivity,
- hypercoagulable state,
- diminished fibrinolytic activity.

These may be related to one or more of the individual factors leading to thrombus formation. Only a limited number of the potential factors have been extensively investigated in epidemiological and prospective studies.

6.2.1 *Endothelial cell dysfunction*

Very early studies suggested that damage to the vessel wall was one of the three main factors responsible for occlusive vascular disease. During the last 20 years a series of metabolites produced by the endothelial cells have been shown to be potential antithrombotic and prothrombotic substances. When the normal homoeostatic balance between them is disturbed, thrombosis may occur but, so far, the relationship between many of these factors and CHD remains hypothetical. The association between deficiency of proteins S and C and antithrombin III and risk for arterial thrombosis has still to be conclusively demonstrated. Low levels of tissue plasminogen activator (t-PA) have been associated with increased risk for CHD. Such increased risk has also been associated with high plasma levels of von Willebrand factor, and increased levels of plasminogen-activator inhibitor 1 (PAI-1) (*56, 57*).

An association between high levels of Lp(a), an established risk factor for CHD, and disturbances of the fibrinolytic system has been suggested. So far, no correlation has been established between plasminogen and Lp(a) concentrations in patients with CHD. However, experimental studies are suggestive of a similar association of other factors with increased risk. It may be predicted that during the coming years many of these substances (endothelium-derived relaxing factor, tissue factor pathway inhibitor, prostacyclin, etc.) will eventually find their place in the make-up of a risk profile. Furthermore, our knowledge of the relationships between endothelial cell damage *in vivo,* release of factors synthesized by endothelial cells and thrombogenicity is currently very limited. The potential for preventing CVD is exciting.

Many of the factors synthesized in endothelial cells are released when the cells are stimulated. Studies on the relationship between macrophages and endothelial cells should be given high priority. Activated mononuclear phagocytes mediate damage to endothelial cells and could play an important role in thrombogenesis.

6.2.2 *Platelet hyper-reactivity*

Platelets are major components of the final thrombus. They contribute to adhesion to the damaged vessel wall and aggregation with other platelets and help to accelerate the coagulation cascade. Other functions of platelets also contribute to the thrombotic process. Reduced antiheparin activity may accelerate antithrombotic activity, increased release of platelet-derived growth factor may stimulate proliferation of smooth muscle cells, and chemotactic activity may affect leukocytes. Thus, changes in one or more of the many significant platelet functions may stimulate thrombogenesis.

The relationship between changes in platelet function and CHD has been investigated in only a few prospective studies, two recent ones being of particular interest (*55, 58*). In a cardiovascular survey aimed at detecting previously unknown and unsuspected CHD, more than 2000 men aged 40–59 years were studied (*55*). At 13.5 years follow-up, subjects with the highest platelet number showed the highest CHD mortality. Those with the most rapid platelet aggregation response after ADP stimulation had increased CHD mortality. These associations could not be explained by differences in age, lipids, blood pressure or smoking habits (*55*). In the Caerphilly Collaborative Heart Disease Study, based on a cohort of 2398 men aged 49–66 years, a significant relationship was found between past myocardial infarctions and electrocardiographic evidence of ischaemia and ADP-induced platelet aggregation (both primary and secondary) (*58*). A similar trend in the results was reported in a study which showed that spontaneous platelet aggregation was a useful marker for predicting coronary events and mortality in a low-risk group of survivors of myocardial infarction (*59*).

In the 30 years since platelet aggregation studies were introduced into clinical medicine, a series of investigations have evaluated platelet aggregation *in vitro* and *in vivo,* platelet survival time, the release of substances from platelets (e.g. platelet factor 4, β-thromboglobulin, ADP and eicosanoids), platelet volume, platelet number and bleeding time, platelet lipid composition, platelet mobility, and other platelet function tests in patients with CHD. The results have not always been consistent. However, in most studies, increased platelet activity has been reported in patients with acute myocardial infarction or unstable angina pectoris. Other patients with CHD have also shown deviations from normal in platelet behaviour when exposed to various types of physical exercise. In most of these studies, however, the problem of cause and effect arises. Subjects with CHD usually already have serious atherosclerotic lesions, which can certainly induce secondary changes in platelet behaviour.

A high platelet number, large platelets, increased sensitivity of platelets to ADP, and changes in the fatty acid composition of platelet phospholipids (*60*) seem so far to be the main platelet characteristics associated with increased CHD incidence and mortality. Prospective studies of platelet function and biochemistry are needed.

6.2.3 *Hypercoagulability*

The interaction between the damaged vessel wall, cellular elements of the blood and the coagulation factors eventually leads to thrombus formation. In order to associate changes in the haemostatic system with an increased coronary risk in healthy subjects, thousands of probands are needed and they must be followed for many years. The Northwick Park Heart Study of Meade et al. (*54*) showed that a high fibrinogen level represented a haemostatic risk factor in subjects developing coronary occlusions years later. This has been confirmed in other prospective studies (*54, 61, 62*). In the Caerphilly and Speedwell collaborative study (*63*), viscosity and white blood cell count in addition to fibrinogen appeared jointly to represent important risk factors for CHD. In the Prospective Cardiovascular Munster Study (*64*), 55 patients with coronary events had a mean fibrinogen level of 286 mg/dl 4 years before the event, while the corresponding figure for the 2130 subjects without such an event was 262 mg/dl. High levels of factors VII and VIII have also been associated with increased cardiovascular risk in some studies. The association between high factor VII and CHD is particularly interesting, since it establishes a possible link between factor VII, triglycerides, overweight and probably also glucose intolerance and hypertension, all factors related to metabolic disturbances, increased insulin resistance, and risk for CHD. The risk associations of fibrinogen and factor VII have been shown to be independent when multiple regression analysis is used to correct for other known risk factors.

It should be stressed that, even if the differences between the levels of factors found in different groups are statistically highly significant, major differences in the levels are not found in individual subjects, so that such differences cannot be used for clinical purposes. So far, no significant prospective studies have been reported that relate the occurrence of activation peptides belonging to the coagulation system to coronary risk in healthy subjects. However, aging-associated changes indicating thrombin generation have been reported.

In a recent case-control cross-sectional study of patients presenting with angina pectoris, it was found that fibrinogen was the only significant coagulation factor associated with angina (*65*). European Concerted Action on Thrombosis and Disabilities has conducted a multicentre prospective study in 3033 patients showing clinical signs of angina pectoris and undergoing coronary angiography (*64*). At baseline, the haemostatic factors could be associated with the coronary status and with other known risk factors for CHD. The occurrence of more than 50% stenosis in one or more coronary branches showed a statistically significant association with increased fibrinogen, plasminogen, PAI antigen and activity, and t-PA. The diet and reinfarction trial, in which 1755 men recovering from an acute myocardial infarction were followed up, showed that plasma fibrinogen, plasma viscosity, white blood cell count and mean platelet volume were all significantly higher in the 92 men

who died within 18 months than in the survivors (*66*). Similar results were reported in the British studies (*63*). Very early studies indicated that factor VIII and fibrinogen were higher in patients with CHD than in a control group; there was also a highly significant correlation between factor VIII and fibrinogen levels. More recently (*56*), in a prospective study in Sweden, 123 patients under the age of 70 years with myocardial infarction were followed up with respect to outcome for a mean of 4.9 years. During the follow-up period, 36 patients had a reinfarction and 23 died. Significantly higher values of von Willebrand factor were seen both before and after venous occlusion in patients who died and in the reinfarction group. No significant differences between the groups were seen in the fibrinolytic variables (t-PA, PAI).

6.2.4 *Diminished fibrinolytic activity*

It has been suggested that several of the well established risk factors for myocardial infarction such as smoking, hyperlipoproteinaemia, diabetes and obesity are associated with decreased fibrinolytic activity. In the study by Hamsten et al. (*57*), 71 patients who had survived a myocardial infarction before the age of 44 were investigated. As compared with a control group, low t-PA activity after venous occlusion and high plasma levels of PAI-1 were observed; the latter were significantly correlated with the serum triglyceride concentrations. The same authors have also established that PAI-1 is an independent risk factor for recurrent myocardial infarction (*67*).

In a recent study (*68*), higher levels of t-PA antigen were observed in 46 patients with myocardial infarction and angina pectoris than in controls, but they showed a decreased fibrinolytic response after stimulus with venous occlusion. The results of this study may support Hamsten's suggestion that a slow, but continual release of t-PA from the vessel wall may take place, with subsequent low vascular deposits and decreased release by stimulation. It has been suggested that t-PA may represent a risk factor worth consideration.

6.3 Conclusions

The principal conclusion that can be drawn from the epidemiological studies is that fibrinogen, coagulation factor VII, platelet number and the two fibrinolytic modulators t-PA and PAI-1 are significant risk factors for the development of CHD. Other parameters reflecting endothelial cell and platelet function are under evaluation, and further studies should be encouraged. The dynamic response of the haemostatic system to physical exercise, dietary fatty acids and other environmental factors should be further investigated.

6.4 Implications for prevention and control

A knowledge of the thrombogenic factors among the haemostatic variables will make it possible to take preventive measures both in

population groups and on an individual basis in high-risk subjects. Stimulation of the antithrombotic properties of endothelial cells (e.g. stimulation of fibrinolytic activity), modulation of platelet function (e.g. reduction of platelet aggregability) and reduction of hypercoagulable states are all examples of interventions directly related to the identification of a thrombogenic state. The consumption of diets low in saturated fats and supplemented with $n-3$ fatty acids may reduce the tendency to thrombosis. Similarly, regular physical activity may stimulate fibrinolytic activity and thus reduce thrombogenicity. A more rational use of antiplatelet and anticoagulant drugs in preventive medicine can be predicted.

6.5 Research recommendations

1. Candidate haemostatic and thrombogenic factors that predict future CHD should be validated.
2. Technologies (including standardized platelet function tests) should be developed which will allow ready measurement of key thrombogenic factors in population studies, and the effects of environmental factors (nutrition, exercise, etc.) to be studied.
3. The role of endothelial cell dysfunction in predisposing to atherothrombogenesis should be elucidated and relevant methodology established.
4. The conditions of heightened thrombogenicity in acute myocardial ischaemic syndromes should be studied.
5. A search should be made for haemostatic and thrombogenic factors amenable to modulation and suitable for incorporation into prevention programmes.

7. Alcohol

7.1 Scientific background

7.1.1 *Epidemiological evidence*

There is consistent and almost unanimous agreement that the curve for the relationship between alcohol consumption and total mortality rates is U-shaped (*69*). For CHD, the risk is greater for non-drinkers; for stroke, the reverse may be the case because of the adverse effect of alcohol on hypertension. The factors that determine the shape of this curve are less well understood and more controversial, since many of the key studies are flawed.

Among possible reasons for the existence of the left-hand limb of the U-curve, it has been suggested that:

- The category described as non-drinkers includes people who have given up drinking because they were unwell.

- Abstainers have a greater burden of ill-health than moderate drinkers, regardless of their previous drinking status.
- Lifelong non-drinkers are an unusual group in a society in which some alcohol is the norm.

While each of these factors may operate to determine the shape of the curve, they fail, both singly and in combination, to provide evidence that the increased coronary risk for non-drinkers is not real (*69-71*).

Confounding factors have received careful attention. However, the effects of cigarette smoking, social class, dietary factors and inaccuracies in taking down or giving information on drinking habits are not sufficient to invalidate the reality of the increased coronary risk among non-drinkers.

It can be concluded, therefore, that moderate drinking (10-30 g of ethanol daily, i.e. 1-3 drinks) provides a moderate protective effect against CVD, as compared with abstention and heavy drinking (*72*).

7.1.2 *Effect of wine*

It has been suggested that what has been called the French paradox for CHD (a high intake of saturated fat but low mortality from CHD) may be related to the high consumption of wine in France; support for this hypothesis has also come from some other Mediterranean countries (*73*). It has been argued that wine may be protective for reasons which are not clear but may include a favourable effect on haemostatic mechanisms, and that certain non-alcoholic constituents of wine may themselves be protective.

These arguments are not particularly convincing, although they may perhaps explain differences between countries and between populations; the U-shaped curve has been demonstrated sufficiently often in populations where wine does not account for the major part of the alcohol consumed.

7.1.3 *Biological mechanisms*

Possible reasons for the existence of the right-hand limb of the U-shaped curve include the following:

- Alcohol increases blood pressure and hence the risk of stroke.
- High intakes of alcohol are associated with cardiomyopathy.
- Excess alcohol intake is associated with a high incidence of cardiac arrhythmias.
- There is an increase in haemorrhagic stroke.

The protective effect of moderate alcohol consumption (as opposed to abstention) is related to the modulation of several well recognized pathogenic mechanisms leading to atheroma, including an increase in HDL (both HDL_2 and HDL_3), a reduction in plasma fibrinogen

concentrations and decreased platelet aggregation; in addition, moderate drinkers show less hypertriglyceridaemia than those consuming large amounts of alcohol.

Each of these mechanisms may be important, but the antithrombotic effects may possibly not have received sufficient attention. The protective effect against CHD seen in moderate drinkers is rapidly lost if they stop drinking; this is more likely to be mediated through a thrombotic rather than an atherosclerotic process. Similarly, the protective effect of alcohol appears to be greater for myocardial infarction and sudden cardiac death than for stable angina pectoris, which is more closely related to atherosclerotic lesions than to primary thrombosis.

7.2 Public health implications

A public health recommendation that emphasized the positive effects of alcohol might do more harm than good. Above three drinks a day (30 g of ethanol daily), there is evidence of both biological and social harm. An increase in alcohol consumption would increase the prevalence of heavy drinking.

7.3 Conclusions

It is probably better to conclude that moderate consumption of alcohol (up to 30 g of ethanol daily) does no harm to the cardiovascular system than to emphasize its protective effect because any public health encouragement to consume alcohol would often be misinterpreted and lead to excessive intakes with increased risk for total mortality.

7.4 Research recommendations

There is probably no further need for comprehensive epidemiological studies, since the nature of the relationship between alcohol and CVD has been established. However, it is recommended that additional studies should be conducted to: (1) assess the effects of different patterns of drinking, e.g. binge drinking as compared with regular consumption with meals; (2) determine the mechanisms whereby alcohol reduces the risk for CHD; and (3) investigate the possible protective effects of ingredients other than alcohol in alcoholic beverages.

8. Physical activity

8.1 Scientific background

Epidemiological studies published in the 1950s began to link physical activity to decreased incidence of myocardial infarction and sudden death. Physically active workers have been found to have fewer heart attacks than more sedentary fellow-workers (*74-76*). In more recent studies, in addition, exercise outside work has been examined and it has been shown that

physical inactivity, whether occupational or recreational, is associated with increased risk of CHD independently of other risk factors (*77-81*).

The mechanisms whereby exercise apparently protects against CHD may include its effects on blood pressure, serum lipoprotein profiles, obesity and insulin resistance.

The key issue is the frequency and intensity of the exercise needed to provide a protective effect. Regular physical activity intensive enough to improve and maintain cardiorespiratory fitness confers most benefits in the prevention of CHD, but light to moderate physical activity, when performed regularly, is also beneficial.

8.2 Implications for prevention and control

Increased physical activity in populations that have become sedentary in recent times is generally recommended as part of the strategy for CHD reduction. Although the evidence for its beneficial effect is compelling, it is not unequivocal. In particular, the amount of physical activity required either to lower CHD risk factors or to reduce the clinical manifestations is far from established. The implementation of physical activity programmes across whole populations is hindered by the uncertain psychosocial barriers that appear to prevent individuals from taking regular exercise and the lack of motivation to continue exercising.

8.3 Research recommendations

1. Observational studies of the characteristics of physical activity that lead to reduced CHD should be encouraged.
2. The nature, intensity and duration of exercise needed to reduce specific cardiovascular risks should be established.
3. The psychosocial factors underlying a preference for physical inactivity should be examined in order to develop strategies for successful population-wide exercise programmes.

9. Genetic influences

9.1 Scientific background

Genetic influences on CHD were considered at a conference in Moscow in December 1990 sponsored by WHO and the IPSEN Foundation (*Fondation IPSEN pour la Recherche thérapeutique*); the proceedings were published in 1991 (*2*). Because of its great importance, the topic is briefly dealt with here, although it was not specifically discussed by the Scientific Group.

It is well known that genetic factors play an important role in the etiology and pathogenesis of CVD and contribute to an individual's susceptibility or resistance to the disease. The application of modern genetic techniques

has led to the identification of the polymorphic markers involved in the normal regulation and function of a large number of cardiovascular risk factors, many of which may contribute to individual differences in the risk for CHD.

Progress in the development of DNA markers is likely to lead to better detection of persons with a genetic susceptibility to the disease, and may add a new individual- or family-oriented element to preventive medicine.

Current attempts to develop DNA markers focus on the "candidate gene" approach. For atherosclerosis and CHD there are several categories of candidates, such as genes whose protein products are involved in:

- lipoprotein structure, apolipoprotein metabolism or lipid metabolism;
- regulation of insulin, carbohydrate metabolism and obesity;
- thrombogenesis, thrombolysis or fibrinolysis;
- regulation of blood flow in coronary arteries;
- regulation of blood pressure;
- reverse cholesterol transport;
- regulation of the initiation of atherosclerotic lesions.

Evidence of "variability gene" effects is beginning to be produced by several laboratories interested in CHD risk, and this concept appears to be useful in the study of gene–environment interaction.

Sufficient knowledge is currently available for use to be made of genetically determined risk factors in cardiovascular prevention. Family history and the measurement of, for example, apolipoproteins, Lp(a) and homocysteine can be used to identify persons who have an increased genetic risk of contracting CHD. However, more precise genetic markers should be sought. If preventive efforts are started in early adult life, the chances of successful disease prevention will increase.

9.2 Research recommendations

1. Greater utilization of genetic risk markers in population studies should be encouraged.
2. Pedigree studies to establish inherited risks for CHD should be encouraged.
3. The usefulness of the "variability gene" concept in the study of gene–environment interactions should be assessed.
4. Genetic markers should be found that can be used to detect high-risk individuals at an early age so as to prevent or reduce future CHD.
5. The familial aggregation of high risk but low expression of CHD should be studied and the importance of new indices of "resistance" assessed.
6. The familial aggregation of high CHD incidence with minimal measurable conventional risk factors should be studied.

10. Women and non-contraceptive hormone use

During the last decade, several reports have been published on the morbidity and mortality of women from CVD, with particular emphasis on CHD. These reports have underscored the importance of these conditions in women and led to the realization that the public health problem posed by CVD is just as important in women as in men. The search for preventive and therapeutic interventions specific to women has therefore become a matter of considerable interest.

In this regard an important public health issue in the 1990s is the study of the relationships between non-contraceptive hormone use and morbidity and mortality from CVD.

10.1 Scientific background

Myocardial infarction is not the only clinical manifestation of heart disease in women, nor possibly the most important one. For example, in numerous studies, a high prevalence of angina in women has been reported, but there is no evidence that hormone replacement therapy (HRT) is, or could be, an appropriate intervention for this clinical manifestation. However, before the effectiveness of this therapy in reducing CHD risk is tested, a better understanding is necessary of the sex differences in the pathogenesis and pathology of specific clinical events. This will undoubtedly lead to better intervention in both men and women, as underscored by Khaw and Barrett-Connor: "Clues may come from comparing different populations where sex ratios vary, e.g. different ethnic or age groups (*82*), or from comparing conditions such as diabetes in which the sex difference for CHD is lessened or abolished" (*83*).

It is well recognized that CHD is commoner in men than in women. Although this difference is greater in the younger age groups, it persists into advancing age. The male CHD mortality rate may be 2–6 times that of women in some countries. It is noteworthy that, in others (e.g. the United States), the total number of CHD deaths is the same in men and in women as a consequence both of the greater number of women in the population and of their longevity.

Numerous reasons have been given to explain the difference in the prevalence of CHD in men and women (*83*). Are men exposed to greater risk factors than women, or are women naturally protected against such factors?

It is commonly believed that smoking and elevated blood pressure are more prevalent and of greater significance in men than in women. In general, premenopausal women also have a lower blood total cholesterol than men. Adjusting for these differences in risk factors does not, however, eliminate the sex difference in CHD prevalence. It is notable that serum lipid fractions are not equally distributed in men and women: indeed, the

level of HDL cholesterol is markedly higher in women than in men, which is significant since HDL is recognized as a protective factor against CHD.

The decrease in the male–female difference in CHD prevalence with age occurs at the time of the menopause and is accompanied by an increase in LDL levels and a decrease in HDL levels in women. This has led to the hypothesis that premenopausal endogenous estrogen production protects against CHD by raising the HDL level. Although this hypothesis is attractive because of its implications for the prevention of the rise in CHD risk in postmenopausal women, it should be noted that in premenopausal women the use of oral contraceptives is associated with an increase in CHD and other CVD.

Irrespective of the relationship between sex hormones and serum lipid profile, it is known that several other biological mechanisms are sex-related (e.g. clotting, insulin regulation). Knowledge of these mechanisms is continuously increasing, and it is therefore likely that the complexity of the explanations for the sex difference in CHD risk will also continue to increase.

Since the 1980s, numerous observational studies have consistently documented reduced cardiovascular mortality in postmenopausal users of non-contraceptive hormones (*84*). More recently, several investigators have also published results from observational studies showing that the use of these agents substantially reduces the risk of subsequent cardiovascular events in women with angiographically confirmed disease.

10.2 Implications for prevention and control

Because of the consistency of the findings from these observational studies, and because of the strength of the apparent association between HRT and the reduction in the CHD risk, HRT is commonly recommended for indications other than the primary one of controlling menopausal symptomatology. As the age distributions of the populations of the industrialized countries shift towards the older age groups, the public health implications of the consequences of CVD for women will become of greater importance and will thus increase the pressure for generalizing the use of HRT. In addition, the evidence that the use of non-contraceptive hormones reduces the risk of osteoporosis, and therefore of osteoporotic fractures, is a further incentive for the prescription of HRT.

However, the effects of postmenopausal hormone use are complex, and understanding of the various relationships is limited, partly because of incomplete information about the risks and benefits of estrogen and of the progestational agents used in non-contraceptive hormonal therapies. This difficulty is, in part, a consequence of the wide variety of agents available. Additional complications result from the numerous dose schedules by which estrogen can be administered, as well as from the possible addition of a progestational agent. The route of administration of non-

contraceptive agents also varies, leading to variations in their metabolic effects.

Furthermore, most of the data on the benefits of hormonal therapy in reducing mortality from CVD are derived from American research in which one agent, a conjugated equine estrogen (Premarin), was mainly used. In the USA, the form most commonly used was unopposed in women both with, and without, a uterus. This distinction is important, as European physicians rarely prescribe unopposed estrogen to women with a uterus.

Virtually no data are currently available from which estimates can be made of the risks associated with long-term exposures to either estrogen or progestational agents, as would be required for the effective prevention of CHD.

Assessment of the cancer risks associated with long-term exposure to non-contraceptive hormones is of particular importance. The potential cardiovascular benefit of non-contraceptive estrogen (as well as the risks and benefits of progestational agents) must be assessed in the light of possible changes in the risk for endometrial and breast cancers (*85, 86*).

As already pointed out, myocardial infarction may not be the most important component of heart disease in women. It is necessary, therefore, to assess whether other highly prevalent conditions would benefit from HRT.

10.3 Research needs

Research needs in this area of public health are both important and urgent.

Although the evidence indicating the benefits of non-contraceptive estrogen use as a protection against cardiovascular events is, in many respects, compelling, a cause-and-effect relationship has yet to be clearly established. Except for one small trial conducted in the late 1970s, all the data showing that postmenopausal estrogen users are protected from cardiovascular events are derived exclusively from observational studies. Research is needed, therefore, in several major areas, which are discussed below, together with their rationale.

10.3.1 *Mechanisms of action of estrogens and progesterone on risk factors*

That estrogens can potentially confer cardiovascular benefit is biologically plausible. Although their actions are both incompletely understood and complex, the effects of estrogens are numerous and include alterations in several body systems, including lipid, carbohydrate and bone metabolism. Estrogen replacement reduces the levels of the atherogenic components of cholesterol (LDL and apolipoprotein B), but increases the levels of VLDL, the precursor of LDL. However, it is hypothesized that the primary effect on LDL is on the rate of clearance (catabolism). Thus, the enhanced production of VLDL caused by estrogen administration does not result in increased production of LDL, as would otherwise be expected.

Total triglyceride levels are also elevated following estrogen exposure. However, the triglyceride-rich VLDLs may not carry an increased risk, especially since LDL levels are lowered and those of HDL increased. Estrogen also increases HDL cholesterol. The subfraction most affected, HDL_2, is believed to convey most of the cardiovascular protection provided by HDL.

The addition of progestogen to non-contraceptive estrogen to prevent endometrial cancer may negate many of the beneficial lipid-related effects. Whether the potential loss of cardiovascular protection resulting from the addition of these agents is justified (i.e. whether postmenopausal women would be better off using unopposed estrogen) has been the subject of some debate. As previously noted, European clinicians and researchers generally do not use unopposed estrogens in women who have a uterus.

There is even greater debate as to the minimum dose of progestogen necessary to protect the endometrium, as well as considerable discussion as to the possibility of achieving a pharmacological compromise, i.e. a dose regimen of progestogen that will adequately protect the endometrium, while avoiding any reduction in the beneficial lipid effects produced by estrogen (Table 1).

The effects on lipids, however, constitute only one aspect of the potential for biologically plausible beneficial effects associated with estrogen administration. Estrogen also has the potential to affect other risk factors for CVD. It is believed to reduce blood pressure, as well as blood glucose and insulin resistance, and has also been shown to have antioxidant effects. More recently, estrogen receptor sites in the arterial wall and myocardium have been identified, suggesting that estrogen may have direct effects on arterial tone and metabolism, although this has not yet been proved. It has also been postulated that estrogen administration increases levels of prostacyclin (which is produced by the endothelium of blood vessels), leading to vasodilation, which in turn leads to reduced platelet adhesiveness; the latter is believed to be important in atherosclerotic plaque formation. At the same time, estrogen may decrease levels of

Table 1
Non-contraceptive hormone effects on lipids/lipoproteins

Lipid/lipoprotein	Estrogens	Progestogens
LDL cholesterol	↓	↑
Apoprotein B	↓	↑
VLDL cholesterol	↑	↓
Total triglyceride	↑	↓
HDL cholesterol	↑	↓
HDL_2	↑	↓
Apoprotein A-1	↑	↓

thromboxane; produced by platelets, this is a vasoconstrictor and increases platelet adhesiveness.

Estrogen may exert its effects on prostacyclin and thromboxane levels via the enhancement of prostacyclin-stabilizing factor, which is believed to be closely related to HDL cholesterol. Estrogen may thus strongly influence the microcirculation (Table 2).

Although estrogen replacement therapy looks promising from the point of view of protection against CVD, its cancer-causing potential requires careful consideration and attention, as discussed below.

10.3.2 *Endometrial cancer*

Unopposed non-contraceptive estrogen use can lead to endometrial cancer. Approximately 40 000 incident cases of this type of cancer occur annually in the USA; mortality is around 3500 per year. The incidence of endometrial cancer increases with age, being highest during the postmenopausal years. Risk factors for endometrial cancer suggest that unopposed estrogen carries approximately the same increased risk as obesity.

The cancer risk has increased the complexity of the discussion on non-contraceptive hormone use, which has made it difficult to evaluate critically the potential cancer risks *vis-à-vis* the potential cardiovascular benefits. Part of this difficulty is associated with the issue of endometrial hyperplasia resulting from unopposed estrogen use. It has been conventionally assumed that hyperplasia should be avoided. Since unopposed estrogen frequently results in hyperplastic changes in the endometrium, its use has been discouraged by some clinicians. Within the lay public (and to some extent the medical community), hyperplasia is often interpreted as synonymous with a diagnosis of cancer. However, hyperplasia covers a spectrum of histological changes, ranging from simple exaggeration of the normal proliferative state to extreme changes which are precursors of endometrial cancer. Most studies indicate that the risk of endometrial cancer is concentrated in the hyperplasia categories with cytological atypia, which is thus the single most important indicator of the subsequent development of carcinoma (*87*).

Table 2
Non-contraceptive estrogen effects

↓	Blood pressure
↓	Blood glucose
↓	Plasma insulin
↑	Prostacyclin
↓	Thromboxane
↑	Arterial tone and metabolism
↑	Effects on microcirculation

10.3.3 *Breast cancer*

Reports that non-contraceptive estrogen increases the risk of breast cancer have been appearing since the mid-1970s. More recently, results have been published suggesting that combinations of non-contraceptive estrogen and progestogen may also be associated with an increased risk of breast cancer (*88*), which is the second most commonly occurring cancer in American women. If, in fact, non-contraceptive estrogen (or estrogen plus progestogen therapy) significantly increases the incidence of breast cancer, and long-term (i.e. decades of) use of non-contraceptive estrogens becomes the standard, an epidemic of breast cancer cases could emerge in the next 20-40 years.

Several reviewers have attempted to analyse the published data on the association between non-contraceptive estrogen use and the risk of breast cancer. Meta-analysis of the studies published over the past 15 years indicates that non-contraceptive estrogen use was associated with an increase in the risk of breast cancer by a factor of 1.07 (*89*). However, the large variation in the estimated risks between studies indicates either possible differential use/types of replacement therapies among studies or that factors other than replacement therapy influenced breast cancer risk. From the results of this meta-analysis, it can be concluded that low doses of conjugated estrogens (0.625 mg per day or less) were not associated with an increased risk of breast cancer. However, this preliminary conclusion must be confirmed by a randomized prospective study.

10.4 Research recommendations and priorities

The evidence that the use of non-contraceptive estrogen reduces cardiovascular as well as all-cause mortality needs strengthening. The preventive potential inherent in such protection must be evaluated. It could be considerable, especially in view of the worldwide trend towards an increase in the size of the older age groups in the population.

The assessment of the long-term health effects of non-contraceptive estrogen treatment should be broadened to include morbidity, in addition to mortality, as an end-point. The benefits in terms of fatal and non-fatal cardiovascular events must be balanced against any possible risks related to fatal and non-fatal non-cardiovascular disorders, especially endometrial, breast and other types of cancer. Cardiovascular benefits may appear long before the cancer risks.

Rigorous evaluation and further research are needed to determine the effects of duration, dose and recency of estrogen use and of the addition of progestational agents.

The assessment of the public health implications of non-contraceptive hormone therapy is still in the data-collection phase. Its use cannot therefore be generalized at present, but must be limited to women with specific indications and carefully monitored.

effect on mortality of material circumstances. In the United Kingdom, a measure of social deprivation, including the proportion of households that had access to cars, the percentage unemployed, the percentage of owner-occupiers, and the extent of overcrowding, was strongly related to mortality – the greater the deprivation the greater the mortality (*96-98*).

Besides providing a guide to the socioeconomic status of individual residents, these area-based studies may be important for other reasons. The Human Population Laboratory in Alameda County, California, showed that people living in a poverty area experienced a higher mortality rate than those living in non-poverty areas, independently of a wide range of personal characteristics including income and health behaviours (*99*).

11.1.2 *International variations in mortality*

Trends in mortality and life expectancy vary significantly in the industrialized countries (Table 3). In the countries of Western and Southern Europe, for example, improvements in life expectancy of 4-5 years for men and 6 years for women were the rule between 1965 and 1989. This contrasts with the countries of Central and Eastern Europe where, during the same period, life expectancy for men in Czechoslovakia and Poland improved by one year, and not at all in Hungary. The decline in infant mortality was balanced by the rise in mortality from chronic diseases, mainly CVD in middle age.

Table 3
Percentage change in age-standardized death rates from all causes (age 30–69) and life expectancy at birth in 1965 and 1989[a]

	% change in death rate				Life expectancy at birth			
	M		F		M		F	
Country[b]	1952–1967	1970–1985	1952–1967	1970–1985	1965	1989	1965	1989
North America								
Canada	- 4.7	- 24.2	- 23.0	- 23.1	69	74	75	81
USA	- 3.8	- 27.3	- 16.3	- 23.3	67	72	74	79
Asia								
Israel	—	- 23.5	—	- 32.5	71	74	74	78
Japan	- 27.1	- 36.2	- 41.5	- 44.5	68	76	73	82
Eastern Europe								
Bulgaria	—	21.0	—	- 6.6	66	70	73	75
Czechoslovakia	- 5.3	2.1	- 25.5	- 9.6	67	68	73	75
German Democratic Republic	—	- 3.1	—	- 10.9	—	—	—	—
Hungary	1.4	33.8	- 22.3	9.5	67	67	72	74
Poland	—	18.6	—	0.4	66	67	72	75
Romania	—	13.5	—	- 4.4	66	68	70	73

Country[b]	% change in death rate M 1952–1967	% change in death rate M 1970–1985	% change in death rate F 1952–1967	% change in death rate F 1970–1985	Life expectancy at birth M 1965	Life expectancy at birth M 1989	Life expectancy at birth F 1965	Life expectancy at birth F 1989
Northern Europe								
Denmark	9.5	0.5	-15.3	-4.1	70	72	75	78
Finland	-4.7	-25.0	-25.6	-32.4	66	72	73	79
Iceland	—	-28.9	—	-37.7	—	—	—	—
Ireland	-6.8	-15.4	-22.5	-25.2	69	71	73	77
Norway	13.6	-11.9	-17.3	-15.2	71	74	76	81
Sweden	-2.9	-8.3	-28.2	-19.4	72	75	76	80
United Kingdom:								
- England and Wales	-8.1	-21.4	-16.5	-14.4				
- Northern Ireland	-7.0	-13.8	-26.1	-19.8	68	73	74	79
- Scotland	-6.8	-17.5	-21.7	-13.0				
Southern Europe								
Greece	—	-7.7	—	-19.1	69	74	72	80
Italy	-0.7	-17.9	-24.1	-29.0	68	73	73	80
Malta	—	-16.9	—	-30.2	—	—	—	—
Portugal	-5.7	-23.3	-18.0	-31.2	62	72	68	78
Spain	-17.6	-18.9	-31.1	-34.5	69	74	74	80
Yugoslavia	—	1.4	—	-13.1	64	69	68	75
Western Europe								
Austria	0.6	-22.8	-17.1	-27.7	66	72	73	79
Belgium	1.8	-21.8	-17.2	-26.7	68	73	74	80
France	-7.4	-17.1	-27.5	-28.2	68	73	75	81
Germany, Federal Republic	5.5	-24.1	-18.7	-30.7	67	72	73	79
Luxembourg	—	-30.3	—	-25.1	—	—	—	—
Netherlands	16.5	-17.2	-22.8	-21.0	71	74	76	81
Switzerland	-8.8	-22.4	-29.7	-28.5	69	74	75	81
Oceania								
Australia	-3.9	-33.8	-16.3	-34.8	68	73	74	80
New Zealand	4.1	-21.9	-14.8	-17.9	68	72	74	78

[a] Sources: Refs *100* & *101*.
[b] Country names are those valid at the time of data collection.

Japan provides a contrast of a different type. Life expectancy has increased by 8 years for men and 9 years for women, and the country now has the longest life expectancy in the world: 76 for men and 82 for women.

One conclusion from these data is that inequalities in mortality are increasing internationally just as they are within countries. CVD plays an important role. The differences in trends in life expectancy are closely mirrored by trends in cardiovascular mortality.

In Japan, the trends cannot easily be related to trends in diet or smoking. It

has been suggested that socioeconomic factors may play an important role in accounting for these international differences (*102*).

It is notable that favourable trends in CHD mortality are now appearing among the more affluent countries. Within these countries, however, it is the least affluent who have the higher rates of CHD. This is in marked contrast to the situation that prevailed at an earlier period. As CHD rates rose worldwide, the epidemic was seen first in the more affluent countries; within these countries, it was most prominent among men of higher status. Over time, that situation has changed, CHD rates rising more quickly among those of lower status. As CHD rates have started to decline, it is the higher-status groups that have been the first to benefit (*103*).

In the less affluent countries, there are indications that CHD is commoner in those of higher status. This is similar to the situation, described above, that prevailed at an earlier period in the industrialized countries.

11.1.3 *Socioeconomic differences in morbidity*

In general, because of a relative lack of data, social class differences in morbidity have not been studied as extensively as those in mortality. Existing data have been well reviewed by Blaxter (*104*), who discusses the various problems with self-reported ill-health and shows that, in national surveys in Britain, there is a consistent inverse association between social class and reported morbidity.

11.1.4 *Ethnic variations within countries*

Substantial ethnic variations exist within countries in the rate of occurrence of CVD, which may to some extent be related to socioeconomic status. There are, however, clear ethnic variations that cannot be explained in this way. In the USA, for example, blacks have traditionally had a higher prevalence of hypertension and a lower rate of CHD than whites. These relative differences have changed in magnitude, and black women now have higher rates of CHD than white women, while the rates for black men are similar in magnitude to those for white men. Marked ethnic differences exist in the United Kingdom: migrants from the Indian subcontinent have a high rate of CHD; Afro-Caribbeans have high rates of hypertension and stroke (*105*).

Other factors must be involved, and these may be grouped under the headings of culture and biology. The fact that disease rates change when people migrate suggests that there will not be a simple genetic explanation for ethnic differences in CVD. For example, CHD rates in Japan are among the lowest in the industrialized world. People of Japanese ancestry living in the USA have rates of CHD intermediate between the low rates in Japan and the high rates in the USA (*106*).

The potential behavioural and biological pathways whereby differences in

culture translate into different rates of CVD will include those discussed in other sections of this report.

11.1.5 *Psychosocial factors*

The role of the psyche in the genesis or aggravation of CHD has long been known. Population surveys indicate that stress looms large in the perception of the public as a cause of heart disease (*107*). Despite the substantial body of evidence derived from the research of cardiologists, psychologists, sociologists and epidemiologists, the concept of stress has been seen by some as non-scientific and has therefore not been universally accepted. Stress remains difficult to define and measure, and continues to excite disagreement as well as to stimulate much interesting research.

There has, however, been substantial progress in the measurement of psychosocial factors, partly because attention has turned from the more general problem of defining stress to the more specific issues of defining particular psychological features and aspects of the social environment that relate both to neuroendocrine pathways and to CVD. Although the underlying paradigm is one of "stress", more specific and more precise measurement have together resulted in scientific progress. From this large body of research, it is worth singling out four areas that appear promising.

Behaviour and personality

The concept of the Type A behaviour pattern has emerged from the large body of work on personality and CVD (*108*). This behaviour pattern is characterized by aggression, competitiveness, a chronic feeling of being in a hurry, impatience, suppressed anger and hostility. A number of studies showed that Type A behaviour was related to CHD independently of other risk factors (*109*), but some subsequent studies have failed to provide unequivocal support for these initial findings. The hypothesis has emerged from this new body of research that it is not the whole behaviour pattern that is related to CHD but specifically hostility. This has been shown to be a predictor for coronary events and mortality (*110*).

Stressful life events

Two different lines of research have been pursued here (*111*), of which the first has been concerned with the effect on cardiovascular risk of specific life crises, e.g. bereavement, migration and retirement. In the second, life changes in general, as expressed in a summary measure of such changes, have been studied. While this latter approach has been used extensively in the study of mental health, it has been applied less often in the field of CVD. There is suggestive evidence, however, that stressful life changes may be related to both the incidence of, and the prognosis after, myocardial infarction (*112*).

Social networks, social support and social isolation

The use of a variety of measures has shown that low levels of social support and of participation in social networks are related to increased risk of

CHD. This has led to two hypotheses: either social isolation is in itself a stress that increases the risk of disease, or social supports act as a buffer that helps people to cope with other stressful circumstances.

Psychosocial work environment

Approaches to studying occupational stress were transformed by the studies of Karasek & Theorell (*113*). Rather than assume that busy people in high-status jobs are under stress, they proposed a model that involved two factors: demand and control. A large body of research supports the hypothesis that people in jobs characterized by high levels of demand and low levels of control are at increased risk of CVD. In general, these jobs are of lower status, so that this may be one of the factors linking low status to higher cardiovascular risk in industrialized countries.

The generalizability of these findings internationally is a prime area of research.

11.2 Implications for prevention and control

These inequalities in health within and between countries are of profound public health and hence social importance. It is important to understand them both because they may help in the understanding of disease etiology and because improving the health of populations requires that these inequalities be addressed.

In all societies, some are better off than others. Wherever data exist, these differences appear to have consequences for health. The magnitude of these social differences in health varies from country to country and, within a particular country, over time. It is important, therefore, to take them into account when debating public policy.

There are at least four ways in which research on social, cultural and psychological factors has implications for the prevention and control of CVD.

Firstly, research on the pathways linking social status and ethnic group membership to CVD is likely to prove important in understanding disease causation in general. For example, the study of dietary, psychological or metabolic differences between socioeconomic or ethnic groups will help to elucidate the causes of such diseases.

Secondly, the public health aim should be to trace the pathways linking health to the socioeconomic status of individuals, social groups and countries so that appropriate action can be taken. For example, the evidence strongly suggests that social class difference in smoking rates is one of many reasons for higher CVD rates in lower-status groups, and intervention should take this into account. A smoking-control policy that relies on health education alone is likely to have greater impact among higher-status groups. Policies aimed at increasing the price of tobacco will affect lower-income groups to a greater extent. Similarly, the recognition

of ethnic differences related to culture and biology should lead to interventions that take these into account.

It should be noted that the study of migrants is to some extent the study of ethnic differences in disease, but also the study of the stresses, socioeconomic factors and lifestyle changes associated with the act of migration and the consequences of being a migrant. This is, worldwide, a problem of great magnitude. The study of CVD in migrants will contribute to the understanding of the health problems of this large and diverse group of people.

Thirdly, the economic and social policies of both governments and employers are likely to have a major impact on the social environment, education and employment, which in turn will affect disease rates. The implications for public health are profound.

Finally, if it is true that interventions aimed at reducing the stress to which cardiac patients are exposed lead to a decreased incidence of recurrent cardiac events, this has important clinical implications. Although there is currently no established methodology for assessing human stress, there are valid and reliable methods of assessing stress behaviours that are clinically relevant to the investigation of stress as related to coronary events. Modification of such behaviour patterns could change the natural course and outcome of CHD.

11.3 Research needs

Four types of research are needed in this area, as follows:

1. Measurement of the extent of socioeconomic and ethnic differences in the prevalence of CVD and monitoring of changes over time.
2. A search for explanations for the social and ethnic differences in CVD with a view to finding potentially modifiable factors.
3. A study of the biological pathways whereby these factors operate.
4. Evaluation of the strategies that are intended explicitly or implicitly to deal with the social and ethnic variations in health status.

The first of these requires precision in measurement. As indicated above, there is good evidence that, within a range of industrialized countries, the same measures of socioeconomic status predict mortality. There is a further need to refine these measures for use in: (a) the countries of Central and Eastern Europe that have recently undergone profound political change; and (b) developing countries, where CVDs are emerging as major health problems.

The major research need is in the area of explanations. Previous research suggests that potential explanations for socioeconomic differences in health can be grouped as shown below.

11.3.1 *Medical care*

Although the evidence suggests that socioeconomic differences in mortality are greater than can be accounted for solely by differences in medical care, the situation may vary among countries and should be investigated.

One way of examining this issue would be to examine mortality from causes judged to be amenable to medical care, and compare it with mortality from other causes (*95*).

11.3.2 *Health-related behaviours*

Health-related behaviours may be important in generating social and ethnic differences in health. Numerous studies have shown social class differences in smoking, diet, alcohol intake, physical activity and obesity. These need to be studied wherever socioeconomic and ethnic differences in CVD occur.

To the extent that differences in behaviours do account for social gradients in health, this raises a new set of questions, one step further back in the causal chain: what causes the social gradient in behaviour? An analysis of the health risks of smoking will be flawed if it fails to take into account the association between smoking and low social status, which, in turn, is associated with ill-health for reasons other than smoking.

11.3.3 *Factors operating at different stages of life*

What is known as "health selection" is based on the argument that health may determine social status rather than vice versa. There are several periods during life when selection might operate, and also several potential mechanisms, varying in plausibility and in the amount of evidence in support of them. Although health selection does not appear to be the prime explanation of socioeconomic differences in CVD among adults, it should not be ignored in future research.

Another version of the selection hypothesis suggests that, while social selection based on health status is not a crucial contributor to health differentials, common background factors determine both social status and health in adulthood. People bring with them into adulthood the results of influences in their earlier life: genetic factors, the biological consequences of early experiences, educational, cultural, psychological and social factors. It has been argued that unbalanced nutrition *in utero* and immediately after birth may have a major influence on subsequent health and cardiovascular risk. It is possible that both social status and health in adulthood are determined by common early life influences.

The focus on the childhood origins of adult disease has been criticized because influences in early life shape the lives people lead and the social environments in which they live and work. It may be the conditions of adult life that are related to ill-health, and the effect of childhood conditions may

therefore be indirect. It is clearly not easy to separate the direct effects on health of early and later life experiences. Nevertheless, it is important to attempt to distinguish between these two sets of influences since their relative importance is crucial to determining the appropriate locus for interventions which may both improve overall adult health and reduce socioeconomic differentials. This is a vital area for further research.

11.3.4 *Material conditions*

The Black report in the United Kingdom (*114*) emphasized the importance of material conditions as an explanation for social inequalities in health. In fact, Black referred to materialist or structural explanations, emphasizing hazards to which some people have no choice but to be exposed, given the present distribution of income and opportunity. These can be interpreted as broader than simply material conditions, and as including psychosocial influences inherent in position in society.

The study of material conditions calls both for household measures of prosperity and for social environmental measures of deprivation.

The difficulty in understanding material explanations is to know how they operate. Where poor living conditions mean polluted water, overcrowded and insanitary housing with high rates of cross-infection, and bad working conditions, it is not difficult to see how these could be responsible for poorer health among the socially deprived. This would be in addition to the effects of inadequate diet, which also forms part of the material conditions of life. As conditions have improved in the industrialized countries, the mortality of all social groups has decreased, but the social gradients in mortality persist. This is an important area for further research.

When wealthy countries are compared, differences in life expectancy are predicted not by differences in wealth, but by differences in the inequality of income distribution.

Relative position in society may have an influence on health that acts independently of the other potential explanations discussed. What is important may not be absolute but relative deprivation. This would account for a social gradient in ill-health, because each group, while not necessarily suffering from greater effects of bad housing, etc., has "less" than the group above it. It would also account for the widespread finding of social inequalities in health in societies with very different levels of health. The social gradient in ill-health will vary in magnitude depending on the magnitude of the relative differences in "deprivation".

In a society that has met the subsistence needs of its members, "relative deprivation" may be psychosocial in origin (see below).

11.3.5 *Psychosocial factors*

Psychosocial factors are important not only in themselves but also in relation to socioeconomic and cultural differences in health; several of the

major potential psychosocial explanations for the occurrence of CVD – hostility, adverse psychosocial work environment, lack of social supports – may differ according to socioeconomic status. There may, in addition, be a "personal control" factor intimately related to social status. This is a fertile area for research.

Psychosocial factors may also be involved in the international differences in health. If the economy fails to deliver an improved standard of living in line with people's expectations, this may lead to widespread feelings of lack of control. Once the basic material subsistence needs are met, what people regard as a reasonable standard of living changes. The difficulty that large sections of the population have in achieving this may lead to widespread feelings of lack of control which may be translated into behaviours not conducive to health such as smoking or into obesity, or may affect health through more direct stress pathways.

11.3.6 *Biological mechanisms*

Process-oriented research is required to highlight the biopsychosocial or psychophysiological mechanisms that mediate the stress behaviour-CHD pathways. The pathways that may mediate the therapeutic effects of behaviour modification or drug interventions also need to be clarified.

Research on the factors responsible for socioeconomic and ethnic differences in disease is also important; this is covered to some extent elsewhere in section 11.3, but research in this area should also include metabolic, haemostatic and other biological mechanisms.

11.4 Recommendations

Research on the factors underlying social and cultural variations in CVD should have high priority. Such variations are now a major feature of the epidemiological picture of CVD worldwide, and effective prevention and public health policies need to take them into account. The only way to do this in an informed way is to understand the factors linking social and ethnic group membership to disease. These will include psychosocial factors but also many of the others featured in this report. The specific areas in which research is needed have been outlined above.

12. Conclusions and recommendations

12.1 Conclusions

1. There is a great need to increase the potential for CVD prevention in the entire population. The greater the number of risk factors known to be causally related to the disease, the greater the power to reduce the disease burden in the community by reducing the levels of such pathogenic risk factors.

2. Dietary fatty acids are heterogeneous in their metabolic effects, only some of them benefiting plasma lipid levels, arterial thrombosis and cardiovascular risk in general. Lauric (C12), myristic (C14) and palmitic (C16) acids raise plasma cholesterol most. Although oleic (18:1) and linoleic (18:2) acids are equally effective in lowering plasma cholesterol, they may have different effects on other cardiovascular risks. The $n-3$ ($\omega 3$ fatty acids), especially those in fish oils, are more effective in reducing cardiovascular risk, and their intake from plants and fish may be suboptimal in Western societies.
3. There is evidence for a protective effect of plant food, thanks to the fibre (non-starch polysaccharide), PUFA ($n-3$ and $n-6$), antioxidant vitamins, plant sterols and other putatively beneficial constituents that it contains.
4. Natural antioxidants of dietary origin may provide a safe method of preventing the peroxidation of lipoprotein fatty acids and of opposing other atherogenic processes.
5. A substantial part of the variability in the response to dietary factors is genetic in origin, and the final outcome of dietary change reflects the interaction of environmental factors and the polygenic nature of lipid regulation.
6. Lipoprotein interactions constitute a key feature of lipoprotein metabolism, resulting in a close interdependence of the metabolism of triglyceride-rich and cholesterol-rich lipoproteins (VLDL, LDL, HDL). Statistically derived prioritization of the risks attributable to individual lipoproteins may underestimate their true biological significance.
7. Raised plasma LDL cholesterol and reduced HDL cholesterol are generally accepted as major CHD risk factors, but there is a spectrum of lipoproteins of varying degrees of atherogenicity and anti-atherogenicity in each of them.
8. Raised triglycerides occur as part of several lipoprotein phenotypes particularly common in patients with premature CHD; these include raised triglyceride-rich lipoproteins plus low HDL, and raised triglyceride-rich lipoproteins plus raised LDL. Because only some triglyceride-rich lipoproteins appear to be atherogenic, and then probably only when present within atherogenic lipoprotein phenotypes, the true risk associated with plasma total triglyceride is uncertain.
9. Raised Lp(a) is clearly a major genetic risk factor for premature CHD, but the mechanism underlying its atherogenicity is not clear.
10. Oxidative changes in some lipoproteins play an important role in atherogenesis and possibly in other CVDs.

11. The "metabolic syndrome" may be related to the high incidence of CHD in several communities and populations. It comprises hyperinsulinaemia and insulin resistance, central obesity, raised plasma triglycerides, low plasma HDL and raised blood pressure.
12. High levels of plasma homocysteine are associated with the premature development of CVD and arterial thrombosis.
13. Endothelial cell dysfunction, platelet hyper-reactivity, hypercoagulability and diminished fibrinolytic activity may be reflected in haemostatic parameters directly related to an increased arterial thrombotic tendency. These parameters may represent independent cardiovascular risk factors and may also be related to the mechanisms whereby other established risk factors exert their effects.
14. The relationship between alcohol consumption and total mortality rates takes the form of a U-shaped curve. For CHD, the mortality rate is greater for non-drinkers; for stroke, the reverse may be true because of the adverse effect of alcohol on hypertension.
15. Physical activity, whether occupational or recreational, is associated with a decreased risk of CHD.
16. Genetic factors play an important role in the etiology and pathogenesis of CVD and contribute to an individual's susceptibility or resistance to the disease.
17. Much less attention has been paid to CVD in women than in men. It has been known for many years that the prevalence of CHD in premenopausal women is low and that it increases rapidly around and after the menopause. The exact mechanisms whereby ovarian function protects against CHD and its withdrawal increases risk are not fully understood, although it is known that an adverse serum lipoprotein pattern develops after the menopause. The protective effects of estrogens and the actions of progestogens on lipid and insulin metabolism, the endothelium and thrombogenesis need intensive study, particularly in view of the apparent benefits of HRT in CHD.
18. Social, cultural and psychological variations are now a major feature of the epidemiological pattern of CVD worldwide.

12.2 Recommendations and research needs

1. Several areas of research have been found to be of immediate interest in relation to the development of new projects with relevant public health implications. In the area of nutrition and CVD, major emphasis should be given to research on dietary fatty acids (biological effects and interactions), antioxidants and plant foods: the results are expected to influence health policies in all countries (see section 2).

2. Despite the large body of knowledge on lipid metabolism, there is a continuing need for further research designed to characterize and measure atherogenic and antiatherogenic lipoproteins, to determine their prevalence in healthy populations and in those with atherogenic disease states, and to investigate their regulation and precise role in atherosclerosis and CHD (see section 3).

3. The metabolic syndrome of insulin resistance, central obesity, associated lipoprotein abnormalities and hypertension requires further population studies to determine its importance as a risk factor for CHD in Caucasian, Asian and African communities. Studies are needed to elucidate the origin of the metabolic syndrome and the interaction between its various features, including hormonal influences. A future preventive strategy might be the control of insulin resistance (see section 4).

4. Further research is needed in the area of the metabolism of sulfur-containing amino acids: if moderate hyperhomocysteinaemia turns out to be an independent and modifiable risk factor for CHD, there is a great need for data on the prevalence of this metabolic disturbance in the general population, as determined by accurate and well standardized methodologies and tests (see section 5).

5. A key research issue is the identification of haemostatic variables representing risk factors for arterial thrombosis. An enormous body of knowledge has accumulated in recent years pointing to thrombosis as a fundamental event in most cases of CHD. Studies relating thrombogenesis to risk for CHD should be given highest priority (see section 6).

6. Further studies are needed on drinking patterns and CVD (see section 7).

7. Studies on the dose-response characteristics of, and motivations for, physical activity are needed (see section 8).

8. Although not specifically considered by the Scientific Group, the use of DNA technologies to identify and target those at high risk for CHD has enormous potential, and research in this area should be encouraged (see section 9).

9. The problem of CHD in women is of increasing concern in affluent societies. Background knowledge of the natural history of the disease before, during and after the menopause is deficient and more research is needed on menopause-related pathobiological and metabolic changes. HRT appears to reduce the incidence of CHD, but there is a need for further research to determine the extent to which there may also be an increase in certain cancers (see section 10).

10. Psychological influences in relation to CHD can now be evaluated in a more standardized way, taking advantage of the development of

increasingly precise models for the interpretation of health gradients in different socioeconomic groups. The availability of quantitative estimates of psychosocial influences offers researchers the possibility of relating their findings to other biological mechanisms responsible for cardiovascular damage. New hypotheses of pathogenesis should be tested in this way (see section 11).

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