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Primary prevention of essential hypertension

Report of a WHO
Scientific Group

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CONTENTS

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PRIMARY PREVENTION OF ESSENTIAL HYPERTENSION

Report of a WHO Scientific Group

INTRODUCTION

The meeting of a WHO Scientific Group on Primary Prevention of Essential Hypertension was opened by Dr I. Glasunov, Director, Division of Noncommunicable Diseases. He recalled that it had taken several decades to realize that arterial hypertension is a frequent and almost ubiquitous health disorder,[1] prevalent in both developed and developing countries. Prevalence in the latter, for example, in African populations, seemed to be similar to that in European or other technically developed societies. With prevalence ranging from 10% up to as much as 20%, and with the resulting cerebrovascular, cardiac and renal risks, arterial hypertension is clearly a major public health problem.

The World Health Organization has been concerned with hypertension since its early days. In 1958, the WHO Expert Committee on Cardiovascular Diseases and Hypertension (*1*) laid the foundations of international epidemiological research into hypertension by describing the criteria for hypertension and recommending standard methods of measurement. In 1961, another WHO Expert Committee (*2*) gave further specifications on terminology and classification, methodology of blood pressure determination, and stages of essential hypertension, and also considered some preventive and therapeutic measures. It concluded that, because of lack of knowledge, there were no effective measures to prevent the occurrence of essential hypertension and susceptible individuals could not be identified. Action was therefore limited to therapeutic remedies against the progressive effects of the disease. In 1978, a third WHO Expert

[1] Throughout this report, the term arterial hypertension indicates a chronically elevated systolic and/or diastolic arterial (blood) pressure. Hypertension in adults is arbitrarily defined as a systolic pressure equal to or greater than 160 mmHg (21.3 kPa) and/or a diastolic pressure (fifth phase) equal to or greater than 95 mmHg (12.7 kPa) (*3*).

Committee (*3*) enlarged on earlier methodological considerations, presented a clinical description of the disease and recommendations for therapy and made recommendations for the control of hypertension in populations. It also recommended continued research into the causes of essential hypertension, including the role of weight control and dietary, psychosocial and behavioural factors, in order to develop new approaches to prevention and therapy.

Since 1972, WHO has been carrying out an international multicentre project for the community control of hypertension, thereby gaining a considerable amount of experience and information. The Organization is also concerned with the problem of mild hypertension and, jointly with the International Society of Hypertension, has stimulated international cooperation in this field. The WHO Regional Office for Europe, Copenhagen, is concerned with hypertension research related to health care and is coordinating a European research programme in this specific field.

Current control of hypertension in populations is restricted mainly to long-term drug treatment of large numbers of individuals. However, although undoubtedly of great benefit, this should be regarded as only an interim solution. There are now a number of leads and possible openings in the domain of primary prevention[1] of arterial hypertension. The task of the Scientific Group was therefore:

(*a*) to review current knowledge on prevention;
(*b*) to identify avenues for future investigations;
(*c*) to define research priorities for the coming years; and
(*d*) to spell out preventive action that may be taken immediately.

The aims of the present report are to emphasize the need for primary prevention of essential arterial hypertension and to promote action related to it by endorsing the intentions of scientists who, through any of the relevant research disciplines, wish to investigate the possibilities of primary prevention, and by informing those concerned with health policy of the public health perspectives of primary prevention. An awareness among the health professions of

[1] Primary prevention has been defined as "all measures designed to reduce the incidence of disease in a population, by reducing the risk of onset" (*4*). This corresponds roughly to the traditional concept of prevention. Secondary prevention has been defined as "all measures designed to reduce the prevalence of disease in a population, by shortening its course and duration" (*4*). This takes in some aspects of treatment.

the state of the art and possible future developments is surely of considerable importance.

1. APPROACHES TO PRIMARY PREVENTION OF HYPERTENSION

Although it is obviously better to prevent than to cure a disease, interest has focused on primary prevention of high blood pressure only in very recent years. Hypertension is of importance mainly as a risk factor for heart and brain disease and, to date, efforts have been made to reduce high blood pressure levels rather than to prevent their development. Therapy of high blood pressure, whether by drugs or in other ways, is a primary preventive measure as regards cerebrovascular or coronary heart disease.

There are two approaches to the primary prevention of disease, and these are usually complementary: the high-risk approach or strategy and the mass approach or strategy.

The high-risk strategy may be especially appropriate in two situations: first, when there is still uncertainty as to whether the relationship between the risk factor and the corresponding disease is causal, and second, if the risk factor occurs with very low prevalence in the population. By contrast, the mass strategy is directed at the whole population, irrespective of individual risk levels. In the early history of risk-factor intervention in cardiovascular diseases, as recently as two to three decades ago, the total population approach was deliberately given a lower priority, because it was not considered defensible to subject every person in the community to preventive measures for which many had only a small need and for which benefit had not been established. The relative merits of the high-risk and mass strategies have been discussed by Rose (*5*) and a strong case for the mass strategy has been made in the report of a recent WHO Expert Committee (*6*).

With respect to blood pressure, the concept of the mass strategy is based on the fact that the risk of vascular complications and death rises continuously with increasing blood pressure, and a considerable number of events occur when blood pressure is moderately elevated. This conclusion is based upon several prospective epidemiological studies whose data can be viewed separately and collectively in the reports on the United States National Pooling Project and the Framingham Study (*7, 8*). In addition, the risk of cardiovascular complications is known to depend on a combination

of several risk factors, including moderately elevated blood pressure, lipid abnormalities, smoking and others. Thus it appears appropriate, at least theoretically, to try to reduce blood pressure, even in persons for whom antihypertensive drug treatment would not be recommended. It is not known whether blood pressure reduction in this group will also reduce the incidence of vascular events, but results from clinical drug trials using different regimens point toward such a possibility.

Detecting persons with elevated blood pressure in the population involves cost and effort; persuading them to change long-ingrained, unfavourable living habits is difficult; and compliance in taking medication is not easy to achieve. The mass strategy, if effective, would prevent blood pressure from rising to a point where treatment, with these and other difficulties, becomes necessary.

The aim of the primary prevention of hypertension may thus be expressed in both of the following ways, which are regarded as complementary: (*a*) in high-risk individuals, to prevent the attainment of levels of blood pressure at which the institution of management and treatment would be considered; (*b*) in the general population, to delay or arrest further progression of blood pressure levels beyond those attained upon reaching adulthood.

In summary, the need for primary prevention is clear. For it to have an adequate impact on the population, both the high-risk and mass strategies must be implemented. Questions requiring immediate answers are: (*a*) On the basis of existing knowledge, what can be done now? (*b*) What kinds of new study are required to provide a firmer scientific base for effective and efficient action?

The rationale and scientific basis for current recommendations concerning the primary prevention of hypertension are presented in the following sections, which address, in turn, natural history, genetic aspects, and environmental influences. On the basis of this information, recommendations are offered to promote both needed research and appropriate preventive action.

2. NATURAL HISTORY OF BLOOD PRESSURE ELEVATION

There is good evidence that in most populations average blood pressure increases with age. In such populations, the distribution curves (Gaussian) of blood pressure at the age of 20 years become progressively more skewed towards higher values for each successive

older age group (*9*). This skewed pattern is seen predominantly in societies in which clinical hypertension is common. In a few societies, there is little evidence of either increasing blood pressure with age, or skewed distribution curves at older ages (*10*).

Within a population, blood pressure does not rise with age to the same degree in every person. In many individuals, it may rise little, if at all, after adolescence, while in others, usually those with the highest blood pressures at the time of first observation, progressive increases occur which result in an average increase for the population as a whole. Blood pressure levels are evidently determined in part by genetic factors, but environmental influences operate as well; they are especially apparent when people from one society, previously free of hypertension, manifest it upon migration to a new environment (*11*). It follows that, if it were possible to identify and modify the environmental influences causing progressively increasing blood pressure, essential hypertension could be prevented.

2.1 Blood pressure in childhood and adolescence

The evidence concerning blood pressure changes from birth to school age (5 or 6 years) is more limited than that for changes at later ages but suggests that, in the USA, systolic readings increase some 20 mmHg (2.7 kPa) in the first two years of life, remain more or less unchanged until the age of 5 or 6 years, and increase a further 30 mmHg (4.0 kPa) for boys and 25 mmHg (3.3 kPa) for girls by the age of 18 years. For diastolic pressures, readings may increase by 4–5 mmHg (0.5–0.7 kPa) in the first two years, remain much the same until the age of 5 or 6 years, and increase a further 16–18 mmHg (2.1–2.4 kPa) for both boys and girls by the age of 18 years (*12, 13*). There are differences in absolute levels among populations, but the broad patterns of change with age may be relatively consistent; this is an important matter that requires confirmation in populations in different circumstances around the world. Even within a single country, such as the USA, the frequencies of blood pressures at given levels differ importantly from one population group to another (*14, 15*). The implications of this circumstance for the identification of high-risk groups and for monitoring the effects of preventive programmes are readily apparent.

This profile of blood pressure changes with age is based predominantly on cross-sectional studies. In assessment of longitudinal changes in blood pressure in the pre-adult years, the concept of

"tracking" has also been applied. The extent to which individuals do tend to remain in similar ranks in blood-pressure distributions over months or years has been studied in several ways in various groups of subjects, and over different age intervals. Tracking is more strongly evident in adolescents than in younger children and it becomes stronger still in older persons (*16*). The fact that blood pressures in children and adolescents are closely related to attained height (*17*) explains in part why tracking may appear weak over age intervals where growth rates are changing within individuals and vary between them. Attention to height as an adjusting factor and to greater numbers of measurements over time may be expected to increase the degree of tracking that is detectable. Despite the reservations cited, the essential observation is that blood pressure can be expected to increase progressively with increasing age for all children and adolescents and, under present circumstances, for a great many adults.

2.2 Blood pressure and aging

In both young and older adults the blood pressure increase with age is largely determined by the initial blood pressure levels. However, in connection with aging, isolated systolic hypertension deserves special consideration. It may be viewed as a concomitant of aging, being quite infrequent until the mid-fifties, rising further with advancing age and carrying an increase in the risk of cardiovascular disease (*18*).

2.3 Early manifestations of hypertension

A high initial blood-pressure level is the strongest, but still a weak, predictor of future hypertension. The frequency of established hypertension at the age of 40 years in persons whose blood pressure was in the "borderline" range at the age of 20 is about 20% (*19*). This figure is three times higher than the prevalence of later hypertension in the rest of the population. This borderline elevation of blood pressure in youth (blood pressure oscillating above and below 139/89 mmHg (18.6/11.9 kPa) or an average of multiple readings between 135–145/85–90 mmHg (18.0–19.4/11.3–12.0 kPa) (*19*) increases the risk of the development of hypertension. However, the majority of these patients with borderline elevation of blood pressure at 20 years of age do not develop hypertension by the age

of 40. Consequently additional methods to identify future hypertensive individuals have been sought. These are (*a*) provocative tests and (*b*) descriptive characteristics.

(*a*) *Provocative tests* are based on the notion that hyper-responsiveness of blood pressure to a pressor stimulus reflects an overall tendency to excessive blood-pressure fluctuation and that cumulatively such pressor episodes lead to sustained hypertension. Blood-pressure hyper-responsiveness during mental arithmetic tests and tilting has been described in persons with borderline hypertension, but the response to static exercise, dynamic exercise, volume expansion, and injection of pressor agents was found to be normal (*20*). The overall, naturally occurring variation in blood pressure in borderline hypertension is known to be normal (*21, 22*). The suggestion that repeated pressor episodes lead to established hypertension has not been adequately proved in experimental models.

(*b*) *Descriptive characteristics.* The following characteristics, in addition to raised blood pressure, are predictors of future hypertension: family history, racial background, overweight, and increased resting heart rate. Specific personality characteristics have been described in borderline hypertension, but their predictive value is doubtful.

It has been calculated from the literature that in a group of individuals having both borderline hypertension and all known risk factors at the age of 40 years the annual incidence rate of hypertension is up to 5.5% (*19*). Such individuals with all risk factors for hypertension are rare and in this multiple-risk factor prediction, the level of blood pressure still remained the strongest risk factor. The order of importance of the contributions of the other risk factors was family history, race, weight, and heart rate.

It is important to note that in many studies one or only a few baseline blood pressure readings have been used. It is clear that the predictive value of pressure measurements is increased if more readings are taken.

Haemodynamics of early hypertension

The so-called borderline hypertension, which may be a precursor of later hypertension, has been extensively investigated in selected populations. Most of the data have been obtained in white, middle-class males. In some patients, cardiac output is elevated, heart rate is very high, stroke volume and cardiopulmonary blood volume are

increased, and peripheral resistance is inappropriately high for the prevailing cardiac output (*20*). However, in the majority of subjects the haemodynamic pattern resembles that in established hypertension: normal cardiac output, decreased stroke volume, increased heart rate, and elevated vascular resistance (*23*). Plasma volume is decreased and plasma renin concentration may be normal or low. The increased total vascular resistance is detected in the forearm vessels; the resistance at maximal vasodilation is elevated, and the responsiveness to vasoconstrictors is increased—both indicative of structural changes in the arterioles (*24*).

These two different subsets of subjects with borderline hypertension raise the question whether there are two different conditions or two phases in the development of the same condition in which the hyperkinetic phase leads to a later normokinetic state. This issue cannot be resolved with the existing data.

2.4 Pathophysiology of early hypertension

A large number of pathophysiological abnormalities has been described in essential hypertension. In this section, only factors that could be influenced by primary prevention measures are discussed.

(1) *Possible role of psychosocial factors*

The evidence that psychological factors play a primary role in human essential hypertension is suggestive but inconclusive (*25*). For years, interest has been concentrated on the personality traits of hypertensive patients, who have often been described as lacking self-assertion or displaying scarcely suppressed hostility, aggression and anxiety. However, when bias is minimized by analysing personality in newly detected hypertensives there is little correlation between neuroticism and blood pressure (*26*). The claim that hypertension may be related to taxing living conditions has also raised interest. Some recent data suggest an increased frequency of hypertension in people with a low job satisfaction and a high role conflict at work and in people with more demanding occupations (*26*).

The often-quoted relationship between hypertension and anxiety should be viewed with the greatest caution. Anxiety may be the result rather than the cause of hypertension and anxiety can easily raise blood pressure at the time of measurement; recent data stress that the measurement of blood pressure by a physician often causes a

considerable rise in blood pressure through an alarm reaction (*27*). Whether this alarm reaction is in some way linked with, or is perhaps a marker of, the development of hypertension is unknown, but further research is needed to clarify to what extent this reaction interferes with current diagnosis of hypertension and assessment of hypertension prevalence.

Recent observations (*28, 29*) that the offspring of hypertensive parents show increased blood pressure or regional vascular responsiveness to mental stress deserve to be further studied, as they may indicate that some behavioural abnormalities are precursors of hypertension. The hyperkinetic state in borderline hypertension appears to be mediated by an abnormality in the autonomic control of the heart. Both increased sympathetic drive and decreased vagal inhibition of the heart have been described (*30*). The possible role of psychosomatic factors in the genesis of this autonomic abnormality has not been adequately substantiated, however.

(2) *Possible role of renal factors and sodium*

There is overwhelming clinical and experimental evidence that renal disease in man and a variety of experimental procedures in animals that affect renal function are associated with or induce hypertension.

It has been proposed that in the majority of instances of essential hypertension the kidney is intimately concerned in the triggering mechanism; this is postulated to be an inability to maintain adequate levels of sodium excretion except at raised levels of arterial pressure because of a rise in renal vascular resistance (*31*). In some instances the mechanism may arise within the kidney itself but in others it could be the consequence of mechanisms external to the kidney.

The question whether such a renal abnormality is the prime mover in essential hypertension or whether the increase in blood pressure is initiated by some extrarenal event, changes occurring in renal function only later, has still to be convincingly answered. It is most important to determine the sequence of such events in order to assess the value or otherwise of modifying dietary sodium intake. If, initially, the rise in arterial pressure were due to strictly extrarenal events, the kidney would be expected to respond by increasing natriuresis and there would be a tendency to sodium depletion. In these circumstances dietary sodium restriction might be of little or no value in reducing blood pressure. Only later, as hypertension-

induced alterations in renal function occurred, would there be a tendency to sodium retention, and thus possible benefit from sodium restriction. However, if the prime event were a renal inability to excrete sodium appropriately unless renal arterial pressure were raised, then dietary sodium restriction should be an effective initial measure.

Several lines of evidence, albeit indirect, suggest that the initial event lies outside the kidney. Mean values for exchangeable and total body sodium and potassium are normal in untreated essential hypertension. However, in contrast to findings in normotensive subjects (in whom there is no correlation between exchangeable sodium and blood pressure), in essential hypertension both exchangeable sodium and total body sodium are positively and significantly related to both systolic and diastolic pressure. Body sodium is subnormal in mild hypertension and increased in severe hypertension. Conversely, there is an inverse relationship between exchangeable potassium and total body potassium and blood pressure in essential hypertension (*32, 33*). While the positive relationship between blood pressure and body sodium is most marked with more severe hypertension and in older subjects, the inverse relationship with potassium is more evident in younger and milder hypertensives. These findings are tentatively interpreted as indicating that in early essential hypertension blood pressure is raised by a mechanism not involving sodium retention. Later, sodium retention may become important in pathogenesis, perhaps resulting from renal changes consequent upon the high blood pressure.

(3) *Possible role of obesity*

The mechanism by which the blood pressure–obesity correlation arises is unknown. Possible mechanisms include increased sodium intake, increased tubular reabsorption of sodium due to increased insulin levels, increased estrogen levels, disproportion between body mass and renal size, disproportion between increased blood volume and vascular capacity, and increased sympathetic nerve activity due to increased energy consumption. The view that obese persons retain more salt has recently gained support through the demonstration that the sodium pump is impaired in obesity (*34*). Moreover, obese persons may eat more salt than do others (*35*).

3. GENETIC ASPECTS

Blood pressure is affected by many genetic and environmental factors and their intricate interactions. The detailed mode and mechanism of heredity in hypertension has not yet been conclusively analysed. Several animal models of hypertension, established by selective breeding during the past three decades, have contributed to studies on genetics, gene–environment interaction or risk factors, primary pathogenetic mechanisms, and the detection of genetic disposition. They have also contributed to the understanding of essential hypertension (*36*).

Detection of genetic markers in arterial hypertension is important for predicting the natural course of blood pressure and perhaps also for an understanding of the mechanisms. One aim of this approach is selective prevention, i.e., to detect subjects at higher risk and to suggest for those subjects a modification in their environment that may be effective in preventing or arresting the rise in blood pressure.

3.1 Evidence for genetic factors

A general consensus that human essential hypertension reflects a genetic trait (*37*) has developed as a result of population studies and genetic analyses of relatives, young and adult siblings, newborns, twins, and adopted children.

Familial resemblance of blood pressure levels among first-degree adult relatives has been noted to be statistically significant (*38*). Similarly, correlations of blood pressure between children over 2 years of age and their first-degree relatives have been observed in various studies. Such correlations may be detected between even younger children or the newborn and their mothers (*39*).

Twin studies (*40*) have confirmed the importance of genetic factors in hypertension as well as their interaction with environmental factors. The blood-pressure values of monozygotic twins are usually more strongly correlated than are those in dizygotic twins.

In contrast, no significant correlation has been noted between pairs of adopted children living together, or between adopted children and their adoptive parents or siblings (*41*).

3.2 Mode of inheritance

Most population studies have shown that blood-pressure values are distributed in a unimodal, continuous manner (*42*), suggesting that blood pressure is multifactorially determined. Although conclusions about the quantitative importance of genetic variations are still divergent, depending on different analytical methods and designs (*43*), most twin studies suggest that a substantial part of the variance in blood pressure can be ascribed to genetic factors (*44*).

In spite of strong evidence in favour of polygenic inheritance, the possibility cannot be excluded that a single pair of genes or a relatively small number of major genes is operative for determining blood-pressure levels (*45*). On the other hand, the "threshold" theory has been proposed as an alternative to the simple polygenic theory; this hypothesis assumes that hypertension develops with the cumulative action of many minor genes being above a certain threshold. Data analysed by Schull et al. (*46*) fitted best the threshold model, rather than dominant and recessive models.

Since evidence obtained in man is necessarily indirect, the mode of inheritance and the number of major genes involved in human hypertension have not yet been settled despite the extensive studies and theoretical discussions. However, experimental studies on different rat models of hypertension during this period have improved our understanding of the nature of heredity in hypertension (*36*). Since the mode of genetics so far analysed in these various models is not the same and since human essential hypertension may correspond not to one of these only but to a mixture of several models, it is essentially difficult to obtain a unanimous conclusion on the detailed nature of heredity in human hypertension, except for the consensus that differences in blood pressure may have a polygenic origin.

3.3 Genetic and familial predictors of hypertension

Evidence of genetic determination of blood pressure has led to a search for genetic markers for susceptibility to hypertension. Such markers may be either:

- a variable involved in the physiological control of blood pressure; or
- an associated characteristic that expresses genetic polymorphism but is unrelated to the actual blood-pressure level.

Several abnormalities have been described in normotensive subjects of hypertensive families, but most of these data require confirmation by more extensive studies.

(1) *Abnormalities in renal function*

Renal vascular reactivity has been reported to be abnormally high during neurogenic stimulation induced by mental calculation (*29*). In one study comparing monozygotic and dizygotic twins evidence was obtained for a genetic contribution to the renal handling of sodium as well as to plasma renin activity, aldosterone, and norepinephrine levels when environmental factors were carefully controlled (*47*). Lastly, the average renal resting blood flow was reported to be significantly higher in young normotensive subjects with hypertensive parents (*48*).

(2) *Abnormalities in the sympathetic nervous system*

An exaggerated increase in blood pressure has been found after mental stress in a group of normal adolescents with hypertensive parents (*49*). High levels of plasma norepinephrine or epinephrine were occasionally reported in subgroups of hypertensive subjects or in normotensives who were hyperreactive to certain stimuli (*50*). Abnormalities in norepinephrine storage have also been described in platelets of normotensive subjects belonging to families of hypertensives (*51*).

(3) *Abnormalities of transmembrane electrolyte transfer*

Several abnormalities in electrolyte transport and distribution across cell membranes have been described in hypertensives and their relatives (*52, 53*). These include a rise in the passive permeability to sodium and potassium of erythrocyte membranes (*54*), increased Na^+–Li^+ counter-transport (*55*), depressed Na^+–K^+ co-transport (*56*), a reduced efflux of $^{22}Na^+$ sensitive to ouabain (*57*), and increased activity of the sodium–potassium pump sensitive to ouabain (*58*). Alterations of intracellular calcium distribution have been found in erythrocytes and adipose cells of patients with essential hypertension (*59*). The consequences of abnormal cation transport and their intracellular distribution may be of pathogenetic importance in essential hypertension. However, divergent results have also been reported, and it is premature to suggest that any of these variations is a genetic marker.

(4) *Genetically-determined susceptibility to environmental factors*

In animal experiments, sensitivity to salt intake has been demonstrated as a genetic trait (*60*). In humans there have been reports of genetically-related sensitivity or insensitivity to salt intake. A genetic susceptibility to other environmental factors, such as stress, has also been observed in rats and in man.

(5) *Particular polymorphisms unrelated to pathophysiological mechanisms*

If an invariable characteristic of individuals is found to have a statistically significant association with a disease, that characteristic cannot be a consequence of the disease. In hypertension no such markers have yet been universally acknowledged, unlike, for instance, ankylosing spondylarthritis in which HLA B27 has been identified as a marker. No common HLA typing has emerged from several studies in various countries (*61*). However, C3 phenotypes may constitute a vascular-risk marker in hypertensives (*62, 63*).

In conclusion, it is desirable to continue and to extend research on genetic markers, and the comparability between studies should be improved by standardization of the methods and approaches as follows (*64*).

(*a*) *Selection and description of normotensive controls.* Characteristics of the control group to be studied should include: age, sex, sexual maturity (with respect to puberty and menopause), ethnic group (race), weight and height, blood pressure, pulse rate, smoking habits, 24-hour sodium/potassium excretion (may be replaced by sodium/creatinine ratio in morning urine), and, if feasible, dietary salt intake. Persons who take any kind of drug, including oral contraceptives, should be excluded from the control group.

(*b*) *Selection and description of study populations, in groups presumed to be genetically predisposed.* The study population should be described in the same way as the controls, and the same exclusions should be made. The actual blood pressure values of the patients or their relatives should be obtained according to the methods recommended by the WHO Expert Committee on Arterial Hypertension (*3*), since enquiry alone is inadequate to obtain precise and reliable information.

In addition to the validation of the laboratory test itself, improvements in the methods used in such studies could allow the early identification of hypertension-prone individuals. Long-term follow-

up of both marker and blood pressure should be performed to estimate the predictive value of the test (*64*).

4. ENVIRONMENTAL INFLUENCES

4.1 Body weight

(1) *Scientific evidence*

In a large number of cross-sectional observational studies, it appears that blood pressure and relative weight levels are highly correlated, not only in adults but also at younger ages (*65, 66*). In prospective observational studies, it is found that persons who gain weight show a greater rise in blood pressure over time than those who maintain their weight, while pressure falls with weight loss (*67–70*). Among such studies, the most persuasive data come from Evans County, Georgia, USA, indicating that those who are obese from the start and gain further weight are at 6 times higher risk of becoming hypertensive than thin people who stay thin (*71*). In several experimental population studies, it has likewise been observed that weight loss is accompanied by blood-pressure reduction (*72–74*). While, in some of these trials, dietary factors other than restriction of energy intake might also have been involved, there is at least one investigation in which it was shown that hypertension was reduced if only energy intake, but not salt, was restricted (*75*).

Until recently, explanations for the relationship between weight and blood pressure have been confined to the suggestion that obese people eat more salt (*35*). In the last few years, new evidence on mechanisms that may explain the relation between obesity and high blood pressure has been obtained and is summarized in section 2.

In evaluating cross-sectional data, the need to distinguish between overweight and obesity has to be kept in mind. In the studies reviewed by the Scientific Group, the weight indices used largely reflect body fat, though some contribution by body mass cannot always be excluded. It is also recognized that the application of insufficiently large sphygmomanometer cuffs to obese arms may lead to an overestimate of blood pressure readings, thus causing fictitiously high correlations between body weight and blood pressure; nevertheless, it is unlikely that this correlation results entirely from such artefacts because the problem has been recognized for some 20 years in epidemiological studies. Furthermore, weight reduction has

been shown to cause lowering of arterial pressure when the latter has been measured directly, using an intra-arterial catheter (*76*). However, in less-well-controlled situations and in clinical practice there remains a need to pay attention to the difficulties of making accurate blood pressure measurements.

(2) *Needs for further research*

A paramount need is to determine how much weight reduction is needed at various ages to lower blood pressure by a given amount and, even more important, to what degree avoidance of weight gain will prevent an undue rise in blood pressure with age. Furthermore, the mechanisms responsible for the association between obesity and blood pressure require more thorough investigation in order to provide plausible evidence for a causal relationship and more effective means of intervention.

(3) *Implications for prevention*

On the basis of present knowledge, it should be expected that avoidance of weight gain with age in adulthood and of undue weight gain in youth may prevent, diminish or postpone the rise of blood pressure with age in many populations, especially in hypertension-prone individuals. Moreover, weight control should result in a decreased prevalence of hypertension, and also in lower blood pressures in the non-hypertensive range. It can be calculated, on the basis of reasonable assumptions, that shifting the weight distribution in the population to the left could reduce the prevalence of hypertension by as much as 25% (*77*). This theoretical estimate gives an indication of the magnitude of the effect that might be expected.

4.2 Salt and other dietary factors

(1) *Scientific evidence*

(*a*) *Epidemiological studies.* It was postulated as early as 1904, by Ambard & Beaujard (*78*), that hypertension could be caused by an excess of sodium chloride in the diet. Further evidence of an association has come from studies in Japanese, American, and Eskimo populations (*35*). Several communities whose daily intake of sodium chloride has been 3 g or less have low average blood-pressure levels and show little tendency for blood pressure to rise with age. When people migrate from such communities, for example from Polynesia,

to areas where the daily salt intake is around 7–8 g, their blood pressure increases proportionately (*79*). Similar findings in Asia have also been published (*80*). There are, however, several confounding factors operating, such as social change and altered overall nutritional state. Thus, it remains uncertain to what extent salt intake is responsible for the blood-pressure differences (*81–83*).

Several epidemiological studies within adult populations in the USA, in Europe, and in New Zealand have failed to demonstrate a clear relationship between salt intake or excretion and blood pressure (*81*). However, positive relationships have been found within populations (*84, 85*), often with a relatively high sodium chloride intake (*86*). There are well known regional differences in the prevalence of hypertension (or stroke) in relation to salt intake in Japan (*87*). It has been suggested that the proportions of sodium to potassium, calcium, and magnesium may also be important pathogenetically (*88, 89*). The reasons for difficulties in showing associations within populations may, at least partly, be due to the large individual day-to-day variations in sodium and potassium excretion since, in some studies, it has been shown to be necessary to obtain six or more 24-hour samples for each subject to define their mean sodium intake. Wide variations in genetic susceptibility to sodium and the modulating effect of potassium, protein, and fat intake, as well as possibly other compounds further complicate the analysis.

Several reports suggest that potassium intake may be a major factor affecting the blood-pressure-raising effects of sodium. Walker et al. (*90*) found no relation between sodium excretion and blood pressure, but a significant negative association with potassium. Blood pressure was positively correlated with the urinary sodium/potassium ratio but not with sodium alone (*91*).

Recently, a claim has been made that blood pressure may be related to calcium intake (*92*). Further studies are needed in this field.

There has also been a belief for many years that certain kinds of animal protein raise blood pressure but these claims have never been substantiated. In contrast, inverse intercommunity and intracommunity correlations between dietary animal-protein intake (estimated by urinary-sulfate/urea-nitrogen ratios) and blood-pressure levels have been demonstrated in communities where the incidence of hypertensive complications is high (*93*). Recently, polyunsaturated fatty acids have been reported to lower blood

pressure, presumably mediated by prostaglandin derivatives (*94*); however, the effect is not marked. In another study, the blood pressure of young, normotensive persons was not influenced by the types of fat, protein, or dietary fibre.

(*b*) *Clinical and intervention studies.* The evidence from intervention studies is scanty. Since the earliest clinical observations were reported, studies under controlled conditions — for example by MacGregor et al. (*96*) — have shown a blood-pressure-reducing effect of sodium chloride restriction in most but not all subjects. Two recent reviews are provided by Freis (*89*) and by Page (*97*).

Blood-pressure rises in response to excess sodium intake have been found to be significantly higher in healthy, normotensive volunteers with a positive family history of hypertension than in those with a negative history (*98*). Familial abnormalities have also been described in urinary excretion of sodium and in blood pressure during changes in sodium and/or potassium intake (*47*).

(2) *Needs for further research*

(*a*) There is a definite need for further investigations in this field. For instance, the minimum collection periods of urinary samples should be defined, and the ways of verifying complete sampling by measurement of creatinine excretion should be specified by methodological studies.

(*b*) Further investigations of blood pressure in relation to sodium, potassium, calcium, magnesium, and probably other dietary ingredients are needed, especially in populations with very high and very low mean blood-pressure levels and hence variations in prevalence of hypertension.

A more sensitive way of detecting the effect of variations in the above-mentioned factors would be to conduct carefully designed intervention studies, preferably of double-blind design, of the effects of decreased or increased sodium intake when potassium, calcium, protein, and fat intakes, as well as body weight, are kept constant. The possibility of a threshold effect should be studied.

Similarly, studies on the effects of changes of potassium, calcium intakes and of polyunsaturated *versus* saturated fat intake, etc., are needed.

The necessity to conduct blind studies as far as possible is stressed (sodium chloride, oral placebo, etc., can be given in capsules, at least in short-term studies).

Intervention studies analysing hypothetical differences in sensitivity to various salt constituents in people with membrane cation transport defects are important, as well as studies on the effect of changes in intake of sodium, potassium, etc., in different age groups of males and females.

If such studies support the hypothesis that decreased sodium intake will decrease blood pressure, changes in dietary factors and/or other further studies are needed to evaluate the possibilities of:

— influencing diet at the population level;
— evaluating the effect on blood pressure distribution at the population level;
— investigating the usefulness of substitutes for ordinary salt (low-sodium, high-potassium salt);
— investigating the possible long-term effects of decreased salt intake which might be more extensive than those obtained in shorter-term experiments.

(3) *Implications for primary prevention*

Sodium intake, potassium intake, and other dietary factors may have important influences on blood pressure regulation in individuals with different genetic backgrounds. Thus, a decrease of sodium intake and/or an increase of potassium are potentially important primary preventive measures, but more scientific evidence on several aspects of the relationship between sodium, potassium, and other dietary factors and blood pressure are needed. Nevertheless, pending further information and firmer evidence, it now appears prudent to reduce the sodium content both of infant foods and of the usual diet towards 5 g of sodium chloride per day, especially in populations known to have a high salt intake or a high prevalence of elevated blood pressures.

A series of questions in relation to sodium and potassium intake requires critical study:

(*a*) Is a renal tendency to sodium retention an initiating mechanism in some or all instances of essential hypertension; or is the raised blood pressure triggered by some extrarenal occurrence, with hypertension-induced renal changes and a consequent tendency to sodium retention becoming important later?

(*b*) Are some persons particularly sensitive to the pressor effects of dietary sodium? If so, is such sensitivity determined by genetic or

other factors? (Overall renal impairment is one evident non-genetic factor).

(*c*) Is any pressor effect of dietary sodium continuous over the range of sodium intake encountered in life, or is there a pressor threshold that must be exceeded before blood pressure rises?

(*d*) Is any antihypertensive effect of sodium restriction apparent in all individuals or only in some?

(*e*) What is the dose–response relationship between sodium restriction and any resultant fall in blood pressure?

(*f*) Are any effects of changes in dietary potassium mediated through changes in sodium balance or internal distribution, or are some or all of them independent? (Potassium is natriuretic; hypokalaemia is also pressor).

(*g*) Are any hypotensive effects of increased potassium intake additive to any similar effects of sodium restriction?

(*h*) What are the circulatory effects of modifications of dietary sodium and potassium in subjects with hypertension of different severity, as well as in normal subjects? Formal trials are recommended; they should be double-blind, conducted for as long as is feasible, and should assess any adverse or beneficial symptomatic and biochemical effects.

4.3 Alcohol

(1) *Scientific evidence*

(*a*) *Epidemiology*. Many cross-sectional studies in different populations have shown a positive relationship between blood pressure and reported alcohol consumption or various indices of it (*99–104*). Studies of the dose–response relationship have given conflicting results; it appears that alcohol consumption raises systolic pressure more than diastolic. Adjustments for body weight had little effect on the associations.

(*b*) *Experimental studies*. Wallace et al. (*105*) have summarized studies on the acute effects of alcohol in humans, which may be a relative decrease, a relative increase, or no change in blood pressure. Alcohol cannot be given in a double-blind fashion in humans, which makes the pharmacological effect difficult to evaluate.

(*c*) *Intervention studies*. Henningsen et al. (*106*) reported a decrease in blood pressure following alcohol withdrawal which indicated that reduction or cessation of antihypertensive drug treatment might be

possible in alcoholic hypertensive patients if drinking stops. Saunders et al. (*107*) studied 132 alcoholic patients whose daily consumption exceeded 80 g. They found a significant correlation between blood pressure and mean daily alcohol intake, and also between the level of blood pressure and the severity of alcohol withdrawal symptoms. In most patients blood pressure fell to normal after abstinence, and remained so for at least a year in those who continued to abstain, but rose in those who started to drink again.

(*d*) *Possible mechanisms.* Several mechanisms may be involved: increased blood cortisol levels, increased catecholamine levels, and effects on the renin–angiotensin system or on antidiuretic hormone.

Alcohol withdrawal induces excess adrenergic discharge, which increases blood pressure transiently. Many studies of blood pressure have required some fasting and non-drinking prior to the examination so that many moderate to heavy drinkers may have been in a withdrawal state when examined.

The finding that blood pressure returns to normal with abstinence suggests that alcohol-induced elevations are not fixed, and do not necessarily lead to a continuing rise of blood pressure over a long-term period. Longitudinal studies of factors associated with blood-pressure increases over a well defined follow-up period suggest that alcohol is not a major cause of the increases (*70*). However, this finding cannot be taken as an indication of fewer long-term sequelae in patients with alcohol-induced hypertension, since the age-specific death rate is high in heavy drinkers, and a direct relationship with the higher blood pressure in alcoholics has been reported in other studies (*109*).

(2) *Needs for further research*

Several methodological problems are involved in studies on alcohol and blood pressure. It is known that alcoholics tend not to participate in population studies, and are therefore not included to a sufficient degree in many blood-pressure studies. Answers to questions on alcohol consumption are not always reliable. Therefore the size of the problem in the community is not well known. The use of γ-glutamyltransferase or other enzymes as indicators of alcohol abuse should be further evaluated, concerning both its sensitivity/specificity and its acceptance by the public.

The pressure increase among heavy drinkers was estimated to be 10/6 mmHg (1.3/0.8 kPa) (systolic/diastolic) by Saunders et al. (*107*)

and these estimates require corroboration in further studies. Finally, whether constituents of alcoholic beverages are in part responsible for the effects attributed to alcohol requires further investigation.

(3) *Implications for prevention*

Recognition of heavy drinking in hypertensive patients is an essential aspect of management; presumably, it is important to take such behaviour into account prior to the appearance of hypertension as well. However, there is at present no scientific evidence that low-to-moderate consumption causes sustained blood-pressure elevation, and these consumption levels are probably of minor importance in the search for factors important for the prevention of blood-pressure increase in the majority of the general population.

4.4 Physical activity

(1) *Scientific evidence*

(*a*) *Epidemiology*. The relationship between physical activity and blood pressure has been little studied in large, well controlled population samples. In the Framingham Study no significant relationship was detected (*109*). In studies in Gothenburg relationships were not found between either leisure time or occupational activity and blood pressure and also there was no association between activity level and change of pressure with time (*70, 110–112*).

(*b*) *Intervention studies*. A more sensitive method of detecting a possible effect of physical activity on blood pressure would be to perform intervention studies. All the studies undertaken so far have been small and most of them have not used untrained, randomized control groups. In general, physical activity appears to have little or no effect on blood pressure in normotensive subjects but in the hypertensive groups some patients have shown a decrease in at least diastolic pressure. Effects on body weight and other variables have not been sufficiently reported (*113–115*).

Choquette & Ferguson (*116*) reported significant reductions in both systolic and diastolic blood pressures from a 6-months' training programme. Body weight remained unchanged. The differences in resting systolic and diastolic pressures were considerably more pronounced in hypertensives (16/8 mmHg, 2.1/1.1 kPa) than in normotensives (4/2 mmHg, 0.5/0.3 kPa), but it is not possible to

determine how much of the change was due to the phenomenon of regression to the mean.

Krotkiewski et al. (*117*) found that blood pressure decreased after training in 27 obese women and was not related to decrease in body fat.

A controlled clinical trial of physical training of post-infarction patients showed that pressures decreased significantly at rest in the training group, that the rise seen from 3 months to 1 year in the non-trained patients during submaximal exercise was not seen in the training group, and that there was no difference in body weight (*118*).

(*c*) *Possible mechanisms.* Both in the study of post-infarction patients and in that of obese women it was found that insulin levels decreased in those who trained effectively (*117, 119*); and in the latter there was a correlation between the decrease in plasma insulin on training and the decrease in blood pressure. It has been suggested by Horton (*120*) that this change in plasma insulin level may result in altered renal handling of sodium, which could explain at least part of the decrease in blood pressure. An additional blood-pressure-lowering effect of training might be decreased plasma concentrations or noradrenaline and adrenaline, probably with a decreased peripheral resistance (*121*).

(2) *Needs for further research*

More controlled studies corroborating the possible long-term pressure-reducing effect of physical activity are needed. Interesting associations between physical activity and hormonal factors have been demonstrated and seem to be implicated in blood pressure regulation. There is a need for a better understanding of the mechanisms of blood pressure regulation and of possible ways of preventing blood pressure increase by means of physical conditioning and specific modes of exercise.

(3) *Implications for prevention*

A metabolic disturbance—with obesity, impaired glucose tolerance, and higher fasting insulin levels compared with normals —is seen in some hypertensive patients (*122*) and may be one factor that could be influenced by physical training in efforts to prevent increased blood pressure.

4.5 Psychological and social influences

4.5.1 *Psychological influences*

Included under this heading are external and environmental influences that are understood or presumed to operate through mental processes, whether consciously or unconsciously, to produce physiological effects that may include blood-pressure elevation. Examples are the processes of migration, rapid modernization, and the experience of major life events. Such influences have been the subject of much research and continue to be entertained as possibly having an important bearing on the development of sustained elevation of blood pressure. Their relevance to primary prevention is reviewed briefly in the light of the scientific evidence available.

(1) *Scientific evidence*

(*a*) *Epidemiological findings.* Studies of populations under circumstances of environmental change have been undertaken in several areas of the world, for changes involving either migration to a new environment or rapid transition of local conditions for a stationary population. In such circumstances, many conditions may change within a given period; this requires careful assessment of all factors, such as dietary change, that may be plausibly related to any blood pressure changes that might be observed. Not the least difficulty lies in measurement of the presumed psychological influences themselves, whether this be through independent documentation of the broad social processes in themselves or through structured interview or questionnaire assessment of individual subjects. Thus the effects of confounding variables may be assessed and assurance given that conditions likely to constitute psychological influences are in fact present and perhaps impinging in different degrees on subgroups of individuals. Many of the studies in this area have been reviewed by Cassel (*123*), with the conclusion that the degree of adaptation to one's niche in society remains an important factor, alongside diet in general and salt intake in particular, in explaining differences in patterns of blood pressure among populations.

(*b*) *Clinical and laboratory evidence.* Acute emotional experiences certainly elevate blood pressure but the evidence that sustained, chronic stress, however defined, contributes to hypertension in man is controversial (*25*). In mice, however, the psychosocial stress of crowding causes sustained hypertension (*124*). Personality traits that

may be conducive to susceptibility to psychosocial stress have been described in hypertensives, but the matter is unclear (*26*). Although there is important potential for behavioural interventions to lower blood pressure, the degree and duration of their effect have so far been small (*125*).

This body of evidence, taken as a whole, stimulates continuing interest in psychological influences on blood pressure, leading both to recommendations for further research and to some comments on implications for primary prevention.

(2) *Needs for further research*

Several considerations bear on recommendations for further research in this area. For population studies there is a need to employ prospective designs whenever possible, to help distinguish between the psychological influences that are antecedents of blood pressure elevation and those that are possible maintaining factors or even the consequences of high blood pressure. It is desirable to choose situations with naturally-occurring population changes, wherein psychological influences may be studied independently of geographical relocation; a secondary choice would be situations in which subgroups experience different degrees of concomitant change in physical environment, diet, and other influences, so that psychological effects may be isolated analytically.

For clinical and laboratory research, emphasis should be concentrated on hypertension-prone normotensive subjects rather than on established hypertensives (in whom causative and maintaining factors are inextricably interwoven). Prospective studies of children of hypertensive parents can include investigation of personality traits, living conditions, cardiovascular reflexes, cardiovascular responsiveness, plasma catecholamines, etc., and should compare the measurements in offspring who develop and those who do not develop hypertension over the years. Help might also come from parallel measurement of some of the so-called membrane markers of essential hypertension, but it should be kept in mind that the meaningfulness of these markers is not yet fully elucidated. Finally, behavioural interventions require special training and substantial contact time; their widespread use cannot be recommended before their feasibility and efficacy have been reliably demonstrated. Nevertheless, given the pathophysiology of the early hypertension, it is eminently sensible to investigate whether reduction of stress,

modification of individual responses to stress, or measures to decrease central sympathetic outflow voluntarily may be useful in the primary prevention of hypertension.

(3) *Implications for primary prevention*

One conclusion to be drawn from the foregoing review is that it is quite possible that modification of psychological influences may be important as an approach to the primary prevention of essential hypertension. This approach is suitable for application now in carefully designed studies, although the further research suggested above may in time raise or lower its priority. Psychological influences may also require attention in four other respects: (1) Measurement of blood pressure and consequent decisions may be influenced by transient psychological factors; these should be controlled as far as possible in the measurement procedures employed. (2) Intervention to alter blood pressure levels may generate psychological influences as a side-effect; these can be avoided or diminished to a large extent; but in any case they warrant appropriate concern and should be monitored to the extent that circumstances permit. (3) If psychological influences, for some persons or groups, do in fact have a strong influence on blood-pressure levels, then overlooking this fact may lead to underestimation of the efficacy of other approaches, such as dietary change, to primary prevention. (4) Compliance by participants in any form of intervention programme depends upon development of a favourable psychological approach; without this an otherwise beneficial strategy may appear to be ineffective. This attention to psychological factors in compliance with intervention programmes is an essential component.

4.5.2 *Social influences*

Hypertension has been shown to be more prevalent in persons of lower social status, and in those with lower income and less education in many though not all studies. There are also differences according to whether residence is in an urban or a rural area.

(1) *Needs for further research*

It is not known how far these relationships are accounted for by differences in frequency of obesity, and in alcohol, sodium, and potassium intake or whether they may be partly due to psychosocial stresses of various kinds or other habits in low-income groups. There

is a great need to find the determinants of these relationships. It is also not known how social class and blood pressure are related in developing countries. Studies in these populations are required, especially at this time when marked social and cultural changes are in progress.

(2) *Implications for primary prevention*

In the long term, knowledge resulting from such studies could, in theory at least, permit protection of populations undergoing such changes from the development of hypertension. From a practical point of view, the need is to improve social conditions and, in the interim, make special efforts to reach and motivate people in unfavourable environments to take better care of their health.

4.6 Other influences

Several other environmental factors have been implicated in affecting blood-pressure levels but none of them, with the possible exception of noise and, conceivably, some constituents of air and water, has a bearing on the primary prevention of hypertension.

In the physical environment, water and temperature have been related to blood pressure. An inverse relationship between cardiovascular disease and water hardness, if confirmed, could be mediated in part by blood pressure, but, in the British Regional Heart Study, blood pressure and water quality were found to be unrelated (*126*). Cadmium in particular has been said to raise blood pressure but the evidence is controversial (*127*). Blood pressure varies inversely with the temperature in the examination setting (*128*) but it is not likely that this effect has a major influence on geographical differences in blood-pressure distributions. Similarly, it is difficult to separate the effects of altitude from other factors in explaining population differences in the average blood-pressure level among people living at different heights above sea-level. One such study has been reported from New Mexico (*129*) but it has been criticized because it failed to account adequately for social differences.

Latterly, it has been suggested that noise plays a role in contributing to elevated blood pressures in exposed population groups (*130*). This possible factor should be given further consideration.

5. SUMMARY AND RECOMMENDATIONS

(1) Primary prevention of hypertension is a desirable goal. There is considerable evidence implicating environmental influences, including excesses of dietary energy intake and dietary salt, as major factors in the pathogenesis of hypertension.

(2) It is not adequately established how much environmental change is needed to influence the level of blood pressure and to prevent a rise. Therefore, the time is now opportune for the initiation of research, on a large scale, into the effectiveness of measures designed to reduce blood pressure. These programmes need to be supported by governments, universities, and other institutions.

(3) Further research is required to define more precisely the factors causing sustained elevation of blood pressure. In particular, there is a need for new knowledge in the following areas:

(*a*) the processes causing hypertension;

(*b*) the effects of environmental factors, in particular dietary influences on blood pressure;

(*c*) early identification of hypertension-prone individuals;

(*d*) genetic markers of hypertension;

(*e*) the effects of measuring blood pressure and criteria to define elevated risk.

(4) Suitable studies will involve the application of preventive measures to discrete populations, with appropriately matched control populations. These studies need to be carefully designed to allow conclusions to be drawn as to their effectiveness in reducing blood pressure in the whole population studied. Such trials should be preceded by feasibility studies to ensure that the interventions suggested will be accepted by the study population.

(5) In order to develop methods of intervention in individuals and populations, studies need to be initiated to evaluate techniques for, and the effects of, alterations in:

(*a*) dietary sodium and other cations, total energy intake, dietary proteins and lipids, and alcohol intake;

(*b*) excess body weight;

(*c*) behaviour;

(*d*) physical exercise;

(*e*) exposure to noise.

(6) The reasons for the observed higher levels of blood pressure in the lower socioeconomic groups in industrialized societies require investigation. In particular, the influences of education and of income need to be defined, with a view to establishing programmes for the prevention of hypertension in these specific groups.

(7) In countries in which rapid and often large changes in lifestyle, type of employment, relative affluence, nutrition, and education are occurring, it is important to monitor any accompanying changes in blood pressure, for both research purposes and adaptation of the health care system to the changing needs.

(8) Detection of high-risk subjects should be encouraged by the optimal use of clinical methods now available. Precise measurements and documentation of blood pressure should be performed, particularly in the children and families of hypertensive patients. These individuals should be provided with information about hypertension and the risk factors that are already known.

(9) A firm recommendation concerning the primary prevention of hypertension should be extended to populations at large only if the suggested research programmes have provided a more definite scientific basis. However, in populations with high average salt intake, educational measures should be undertaken immediately to explain the potential importance of reducing excessive salt intake. Similarly, in populations in which overweight is prevalent, information on the links between overweight and blood-pressure elevation should be addressed to the general public. Individuals who are obese or accustomed to an excessively high salt intake should be adequately counselled.

(10) In order to help the population at large and hypertensive subjects in particular in their dietary choice, it is recommended that industrially processed foods should be labelled for their content of sodium (possibly also of potassium and other electrolytes). Research into methods of decreasing the use of sodium chloride as a food preservative should be stimulated.

REFERENCES

1. WHO Technical Report Series, No. 168, 1959 (*Hypertension and coronary heart disease: classification and criteria for epidemiological studies:* First report of the Expert Committee on Cardiovascular Diseases and Hypertension).
2. WHO Technical Report Series, No. 231, 1962 (*Arterial hypertension and ischaemic heart disease: preventive aspects:* Report of a WHO Expert Committee).
3. WHO Technical Report Series, No. 628, 1978 (*Arterial hypertension:* Report of a WHO Expert Committee).
4. HOGARTH, J. *Glossary of health care*. Copenhagen, WHO Regional Office for Europe, 1975, p. 302 (Public Health in Europe, No. 5).
5. ROSE, G. Strategy of prevention, lessons from cardiovascular disease. *British medical journal*, **1**: 1847–1851 (1981).
6. WHO Technical Report Series, No. 678, 1982 (*Prevention of coronary heart disease:* Report of a WHO Expert Committee).
7. POOLING PROJECT RESEARCH GROUP. *Relationship of blood pressure, serum cholesterol, smoking habit, relative weight and ECG abnormalities in incidence of major coronary events: final report of the Pooling Project*. Dallas, American Heart Association, 1978 (American Heart Association Monograph No. 60).
8. UNITED STATES DEPARTMENT OF HEALTH, EDUCATION AND WELFARE. *The Framingham Study: An epidemiological investigation of cardiovascular disease. Section 31. The results of the Framingham Study applied to four other U.S. based epidemiological studies of cardiovascular disease*. Washington, DC, 1976 (National Heart, Lung, and Blood Institute, Publication No. (NIH) 76–1083).
9. HAMILTON, M. ET AL. The aetiology of essential hypertension. 4. The role of inheritance. *Clinical science*, **13**: 273 (1954).
10. MADDOX, I. Blood pressures in Melanesians. *Medical journal of Australia*, **1**: 1123 (1967).
11. BEAGLEHOLE, R. ET AL. Blood pressure in Tokelauan children in two contrasting environments. *American journal of epidemiology*, **108**: 283–288 (1978).
12. EPSTEIN, F.H. & ECKOFF, R.D. The epidemiology of high blood pressure–geographic distributions and etiological factors. In: Stamler, J. et al., ed., *The epidemiology of hypertension*. New York, Grune & Stratton, 1967, pp. 155–166.
13. TYROLER, H.A. Hypertension. In: Last, J.M., ed., *Public health and preventive medicine*. New York, Appleton-Century-Crofts, 1980, pp. 1202–1227.
14. Why does blood pressure rise with age? *Lancet*, **2**: 289–290 (1981).
15. SKLO, M. Epidemiologic patterns of blood pressure in children. *Epidemiological reviews*, **1**: 143–169 (1979).
16. ROSNER, B. ET AL. Age-specific correlation analysis of longitudinal blood pressure data. *American journal of epidemiology*, **106**: 306–313 (1977).
17. KATZ, S.H. ET AL. Blood pressure, growth and maturation from childhood through adolescence. Mixed longitudinal analyses of the Philadelphia Blood Pressure Project. *Hypertension*, **2** (Suppl. I): I-55–I-69 (1980).
18. KANNEL, W.B. ET AL. Systolic blood pressure, arterial rigidity and risk of stroke. *Journal of the American Medical Association*, **245**: 1225–1229 (1981).
19. JULIUS, S. & SCHORK, M.A. Predictors in hypertension. In: Perry, H.M. & Smith, W.M., ed., *Mild hypertension: to treat or not to treat. Annals of the New York Academy of Sciences*, **304**: 38–52 (1978).

20. JULIUS, S. & SCHORK, M.A. Borderline hypertension – A critical review. *Journal of chronic diseases,* **23**: 723–754 (1971).
21. WATSON, R.D.S. ET AL. Factors determining direct arterial pressure and its variability in hypertensive man. *Hypertension.* **2**: 333 (1980).
22. MANCIA, G. ET AL. Blood pressure variability in man: its relation to high blood pressure, age and baroreflex sensitivity. *Clinical science,* **59**: 401s–404s (1980).
23. LUND-JOHANSEN, P. Hemodynamics in early essential hypertension. *Acta medica scandinavica,* **482** (Suppl.): 1–105 (1967).
24. SIVERTSON, R. ET AL. Evidence for peripheral vascular involvement in mild elevation of blood pressure in man. *Clinical science,* **51**: 65s (1976).
25. ZANCHETTI, A. & BARTORELLI, C. Central nervous mechanisms in arterial hypertension: experimental and clinical evidence. In: Genest, J. et al., ed., *Hypertension.* New York, McGraw-Hill, 1977, pp. 59–76.
26. STEPTOE, A. *Psychological factors in cardiovascular disorders.* London, Academic Press, 1981.
27. MANCIA, G. ET AL. Haemodynamic alterations triggered by blood pressure assessments by the doctor. *Clinical science,* **63** (Suppl. 8): 387s–389s (1982).
28. FALKNER, B. ET AL. Cardiovascular characteristics in adolescents who develop essential hypertension. *Hypertension,* **3**: 521–527 (1981).
29. HOLLENBERG, N.K. ET AL. Essential hypertension: abnormal renal vascular and endocrine responses to a mild psychological stimulus. *Hypertension,* **3**: 11–17 (1981).
30. JULIUS, S. Abnormalities of autonomic nervous control in borderline hypertension. *Schweizerische medizinische Wochenschrift,* **106**: 1698–1705 (1976).
31. GUYTON, A.C. ET AL. Arterial pressure regulation: over-riding dominance of the kidneys in long-term regulation and in hypertension. *American journal of medicine,* **52**: 584 (1972).
32. BERETTA-PICCOLI, C. ET AL. The relation of arterial pressure with body sodium, body potassium and plasma potassium in essential hypertension. *Clinical science,* **63** (Suppl. 8): 89s–92s (1982).
33. LEVER, A.F. ET AL. Sodium and potassium in essential hypertension. *British medical journal,* **283**: 463–469 (1981).
34. DE LUISE, M. ET AL. Reduced activity of the red-cell sodium-potassium pump in human obesity. *New England journal of medicine,* **303**: 1017–1022 (1980).
35. DAHL, L.K. Salt and hypertension. *American journal of clinical nutrition,* **25**: 231–244 (1972).
36. YAMORI, Y. Experimental models of hypertension as a tool for the control and prevention of clinical hypertension. In: Gross, F.H. & Robertson, J.I.S., ed., *Arterial hypertension.* Tunbridge Wells, Pitman Medical, 1979, p. 209.
37. BAUR, J. Genetics of essential hypertension. *Acta genetica et statistica medica,* **18**: 577 (1968).
38. HAVLIK, R.J. ET AL. Blood pressure aggregation in families. *American journal of epidemiology,* **110**: 304–312 (1979).
39. LEE, Y-H. ET AL. Familial aggregation of blood pressures of newborn infants and their mothers. *Pediatrics,* **58**: 722 (1976).
40. MCILHANY, M.L. ET AL. The heritability of blood pressure: An investigation of 200 twin pairs using the cold pressor test. *Johns Hopkins Hospital medical journal,* **136**: 57 (1975).
41. BIRON, P. ET AL. Familial aggregation of blood pressure in adopted and natural

children. In: Paul, O., ed., *Epidemiology and control of hypertension,* 397. New York, Symposia Specialists Medical Books, 1975.
42. PICKERING, G. *The nature of essential hypertension.* London, Churchill, 1961.
43. MIALL, W.E. & OLDHAM, P.D. The hereditary factor in arterial blood pressure. *British medical journal,* **1**: 75 (1963).
44. FEINLEIB, M. ET AL. Studies of hypertension in twins. In: Paul, O., ed., *Epidemiology and control of hypertension,* 3. New York, Symposia Specialists Medical Books, 1975.
45. CAVALLI-SFORZA, L.L. & BODMER, W.F. *The genetics of human populations.* San Francisco, Freeman, 1971.
46. SCHULL, W.J. ET AL. Heredity, stress and blood pressure, a family set method: epilogue. *Journal of chronic diseases,* **30**: 71 (1977).
47. GRIM, L.E. ET AL. Effects of sodium loading and depletion on normotensive first-degree relatives of essential hypertensives. *Journal of laboratory and clinical medicine,* **94**: 764–771 (1979).
48. BIANCHI, G. ET AL. A renal abnormality as a possible cause of essential hypertension. *Lancet,* **1**: 173–177 (1979).
49. FALKNER, B. ET AL. Cardiovascular response to mental stress in normal adolescents with hypertensive parents. *Hypertension,* **1**: 23–30 (1979).
50. KOPIN, I.J. ET AL. The sympathetic nervous system and hypertension. In: Laragh, J. et al., ed., *Frontiers in hypertension research.* New York, Springer-Verlag, 1981, pp. 283–289.
51. MATTIASSON, I. & HOOD, B. Net efflux rate of norepinephrine from platelets in normotensive individual belonging to families with a heavy accumulation of essential hypertension. *Clinical and experimental hypertension,* **3**: 727–736 (1981).
52. GARAY, R. & MEYER, P., ed., Proceedings of the Symposium Genetic Markers in Essential Hypertension. *Clinical and experimental hypertension,* **3**: 569–895 (1981).
53. ZUMKLEY, H. & LOSSE, H., ed., International Symposium on Intracellular Electrolytes and Arterial Hypertension. Stuttgart, Georg Thieme, 1980, pp. 1–286.
54. POSTNOV, Y.V. ET AL. Altered sodium permeability, calcium binding and Na-K-ATPase activity in the red blood cell membrane in essential hypertension. *Pflügers Archiv,* **371**: 263–269 (1977).
55. CANESSA, M. ET AL. Increased sodium-lithium countertransport in red cells of patients with essential hypertension. *New England journal of medicine,* **302**: 772–776 (1980).
56. GARAY, R.P. & MEYER, P. A new test showing abnormal net Na^+ and K^+ fluxes in erythrocytes of essential hypertensive patients. *Lancet,* **1**: 349–353 (1979).
57. WALTER, U. & DISTLER, A. Abnormal sodium efflux in erythrocytes of patients with essential hypertension. *Hypertension,* **4**: 205–210 (1982).
58. WOODS, K.L. ET AL. Familial abnormality of erythrocyte cation transport in essential hypertension. *British medical journal,* **284**: 1186–1188 (1981).
59. POSTNOV, Y.V. ET AL. Alteration of intracellular calcium distribution in the adipose tissue of human patients with essential hypertension. *Pflügers Archiv,* **388**: 89 (1980).
60. DAHL, L.K. ET AL. Role of genetic factors in susceptibility to experimental hypertension due to chronic excess salt ingestion. *Nature,* **194**: 480 (1962).
61. Immunogenetics and essential hypertension, *Lancet,* **2**: 409–414 (1978).

62. KRISTENSEN, B.O. Immunogenetic markers in essential hypertension. *Clinical and experimental hypertension,* **3**: 763–774 (1981).
63. SHAADT, O. ET AL. Association between the $C3^F$ gene and essential hypertension. *Clinical science,* **61** (Suppl. 7): 363s–365s (1981).
64. Cationic markers of hypertension. *Bulletin of the World Health Organization,* **60**: 711–713 (1982).
65. CHIANG, B.N. ET AL. Overweight and hypertension – a review. *Circulation,* **34**: 403–421 (1969).
66. KOTCHEN T. & HAVLIK, R., ed., High blood pressure in the young. *Hypertension,* **2** (Suppl. I): (1980).
67. MIALL, W.E. ET AL. Relation between change in blood pressure and weight. *British journal of preventive and social medicine,* **22**: 73–80 (1968).
68. KANNEL, W.B. ET AL. The relation of adiposity to blood pressure and development of hypertension. The Framingham Study. *Annals of internal medicine,* **67**: 48–59 (1967).
69. PAFFENBARGER, R.S. ET AL. Chronic disease in former college students, VIII. Characteristics in youth predisposing to hypertension in later years. *American journal of epidemiology,* **88**: 25–32 (1968).
70. SVÄRDSUDD, K. ET AL. Factors associated with the initial blood pressure level and with the subsequent blood pressure increase in a longitudinal population study. The study of men born in 1913. *European heart journal,* **1**: 345–354 (1980).
71. TYROLER, H.A. ET AL. Weight and hypertension: Evans County Studies of Blacks and Whites. In: Paul, O., ed., *Epidemiology and control of hypertension.* New York, Stratton, 1975, pp. 177–206.
72. HEYDEN, S. ET AL. Diet treatment of obese hypertensives. *Clinical science,* **45**: 209s–212s (1973).
73. CAGGIULA, A.W. ET AL. The Multiple Risk Factor Intervention Trial (MRFIT): IV. Intervention on blood lipids. *Preventive medicine,* **10**: 476–500 (1981).
74. STAMLER, J. ET AL. Prevention and control of hypertension by nutritional-hygienic means. Long-term experiments of the Chicago Coronary Prevention Evaluation Programme. *Journal of the American Medical Association,* **243**: 1819–1823 (1980).
75. REISIN, E. ET AL. Effects of weight loss without salt restriction on the reduction of blood pressure in overweight hypertensive patients. *New England journal of medicine,* **298**: 1–6 (1978).
76. REISEN, E. ET AL. Hemodynamics of weight reduction in obesity hypertension. Proceedings of the Ninth Scientific Meeting of the International Society of Hypertension, Mexico City, Mexico, 21–24 February 1982. *Clinical science,* (in press).
77. EPSTEIN, F.H. Estimating the effect of preventing obesity on total mortality and hypertension. *International journal of obesity,* **3**: 163–166 (1979).
78. AMBARD, L. & BEAUJARD, E. Causes de l'hypertension artérielle. *Archives of internal medicine,* **1**: 520 (1904).
79. PRIOR, I.A.M. ET AL. Sodium intake and blood pressure in two Polynesian populations. *New England journal of medicine,* **279**: 515–520 (1968).
80. PAGE, L.B. ET AL. Blood pressure of Quash'Qai pastoral nomads in Iran in relation to culture, diet and body form. In: Kesteloot, H. & Joossens J.V., ed., *Epidemiology of arterial blood pressure,* The Hague, Martinus Nijhoff, 1980, pp. 401–420.

81. SIMPSON, F.O. Salt and hypertension: a sceptical review of the evidence. *Clinical science,* **57**: 463 (1979).
82. WILHELMSEN, L. Salt and hypertension. *Clinical science,* **57**: 455 (1979).
83. SWALES, J.D. Dietary salt and hypertension. *Lancet,* **1**: 1177 (1980).
84. ELLISON, R.C. ET AL. Obesity, sodium intake and blood pressure in adolescents. *Hypertension,* **2** (Suppl. I): I-78–I-83 (1980).
85. WATSON, R.I. ET AL. Urinary electrolytes, body weight and blood pressure. Pooled cross-sectional results among four groups of adolescent females. *Hypertension,* **2** (Suppl. I): I-93–I-98 (1980).
86. YAMORI, Y. ET AL. Hypertension and diet: multiple regression analysis in a Japanese farming community. *Lancet,* **1**: 1204–1205 (1981).
87. SASAKI, N. High blood pressure and the salt intake of the Japanese. *Japanese heart journal,* **3**: 313 (1962).
88. MENEELY, G.R. & BATTARBEE, H.D. High sodium-low potassium environment and hypertension. *American journal of cardiology,* **38**: 768–785 (1976).
89. FREIS, E.D. Salt, volume and the prevention of hypertension. *Circulation,* **53**: 589 (1976).
90. WALKER, W.G. ET AL. Relation between blood pressure, and renin, renin substrate, angiotensin II, aldosterone and urinary sodium and potassium in ambulatory subjects. *Hypertension,* **1**: 187–91 (1979).
91. LANGFORD, H.G. & WATSON, R.L. Electrolytes and hypertension. In: Paul, O., ed., *Epidemiology and control of hypertension.* New York, Stratton, 1975, pp. 119–30.
92. KESTELOOT, H. & GEBOERGS, J. Calcium and blood pressure. *Lancet,* **1**: 813–815 (1982).
93. YAMORI, Y. ET AL. Nutritional improvement for stroke prevention. In: Yamori, Y. et al., ed., *Prophylactic approach to hypertensive diseases,* New York, Raven Press, 1979, pp. 587–593.
94. IACONO, J.M. ET AL. Reduction in blood pressure associated with high polyunsaturated fat diets that reduce blood cholesterol in man. *Preventive medicine,* **4**: 426–443 (1975).
95. BRUSSARD, J.H. ET AL. Blood pressure and diet in normotensive volunteers: absence of an effect of dietary fibre, protein or fat. *American journal of clinical nutrition,* **34**: 2023–2029 (1981).
96. MACGREGOR, G.A. ET AL. Double-blind randomized trial of moderate sodium restriction in essential hypertension. *Lancet,* **1**: 351–4 (1982).
97. PAGE, L.B. Can hypertension be prevented? *Journal of cardiovascular medicine,* **7**: 753–761 (1982).
98. NARA, Y. ET AL. Sodium-accelerated platelet aggregation in men predisposed to essential hypertension. *Clinical science,* **63** (Suppl. No. 8): 391s–393s (1982).
99. CLARK, V.A. ET AL. Effects of various factors on systolic and diastolic blood pressure in the Los Angeles Heart Study. *Journal of chronic diseases,* **20**: 571 (1967).
100. PINCHERLE, G. & ROBINSON, D. Mean blood pressure and its relation to other factors determined at a routine executive health examination. *Journal of chronic diseases,* **27**: 245 (1974).
101. MYRHED, M. Alcohol consumption in relation to factors associated with ischemic heart disease. *Acta medica scandinavica,* Suppl. 567 (1974).
102. GYNTELBERG, F. & MEYER, J. Relationship between blood pressure and physical

fitness, smoking and alcohol consumption on Copenhagen males aged 40–59. *Acta medica scandinavica,* **195**: 375 (1974).
103. KLATSKY, A.L. ET AL. Alcohol consumption and blood pressure. *New England journal of medicine,* **296**: 1194 (1977).
104. DYER, A.R. ET AL. Alcohol consumption, cardiovascular risk factors, and mortality in two Chicago epidemiologic studies. *Circulation,* **56**: 1067 (1977).
105. WALLACE, R.B. ET AL. Alcohol and hypertension: Epidemiologic and experimental considerations. The Lipid Research Clinics Program. *Circulation,* **64** (Suppl. 3): III-41–III-47 (1981).
106. HENNINGSEN, N.C. ET AL. Hypertension, levels of serum gamma glutamyl transpeptidase and degree of blood pressure control in middle-aged males. *Acta medica scandinavica,* **207**: 245 (1980).
107. SAUNDERS, J.B. ET AL. Alcohol-induced hypertension. *Lancet,* **2**: 653 (1981).
108. KOZAREVIC, D. ET AL. Frequency of alcohol consumption and morbidity and mortality. The Yugoslavia cardiovascular disease study. *Lancet,* **1**: 613 (1980).
109. DAWBER, T.R. ET AL. Environmental factors in hypertension. In: Stamler, J. et al., ed., *The epidemiology of hypertension;* Proceedings of an International Symposium New York, Grune & Stratton, 1967.
110. WILHELMSEN, L. ET AL. Physical activity, physical fitness and risk of myocardial infarction. *Advances in cardiology,* **18**: 217 (1976).
111. BERGLUND, G. & WILHELMSEN, L. Factors related to blood pressure in a general population sample of Swedish men. *Acta medica scandinavica,* **198**: 291 (1975).
112. SVÄRDSUDD, K. & WILHELMSEN, L. Change of blood pressure in relation to other variables and to development of hypertensive disease indices in a longitudinal population study. The study of men born in 1913. *European heart journal,* **1**: 355 (1980).
113. EKBLOM, B. ET AL. Effect of training on circulatory response to exercise. *Journal of applied physiology,* **24**: 518 (1968).
114. HANSON, J.S. ET AL. Long-term physical training and cardiovascular dynamics in middle-aged men. *Circulation,* **38**: 783 (1968).
115. BOYER, J.L. & KASCH, F.W. Exercise therapy in hypertensive men. *Journal of the American Medical Association,* **211**: 1668 (1970).
116. CHOQUETTE, G. & FERGUSON, R.J. Blood pressure reduction in "borderline" hypertensives following physical training. *Canadian Medical Association journal,* **108**: 699 (1973).
117. KROTKIEWSKI, M. ET AL. Effects of long-term physical training on body fat, metabolism, and blood pressure in obesity. *Metabolism,* **28**: 650 (1979).
118. WILHELMSEN, L. ET AL. A controlled trial of physical training after myocardial infarction. *Preventive medicine,* **4**: 491 (1975).
119. BJÖRNTORP, P. ET AL. Effects of physical training on glucose tolerance, plasma insulin and lipids and on body composition in men after myocardial infarction. *Acta medica scandinavica,* **192**: 439 (1972).
120. HORTON, E.S. The role of exercise in the treatment of hypertension in obesity. *International journal of obesity,* **5** (Suppl. 1): 165 (1981).
121. TRAP-JENSEN, J. ET AL. Arterial noradrenaline and circulatory adjustment to strenuous exercise with trained and non-trained muscle groups. In: *Physical fitness.* Proceedings of a Satellite Symposium of the XXV International Congress of Physiological Sciences. Prague, University of Karlova Press, 1973, p. 414.

122. BERGLUND, G. ET AL. Body composition and glucose metabolism in hypertensive middle-aged males. *Acta medica scandinavica,* **200**: 163 (1976).
123. CASSEL, J. Studies of hypertension in migrants. In: Paul, O., ed., *Epidemiology and control of hypertension,* New York, Stratton, 1975, pp. 41–58.
124. HENRY, J.P. & STEPHENS, P.N. Stress, health and the social environment: A sociobiologic approach to medicine. New York, Springer-Verlag, 1977.
125. SHAPIRO, A.P. ET AL. Non-pharmacologic treatment of hypertension. *Annals of the New York Academy of Sciences,* **304**: 222–235 (1978).
126. SHAPER, A.G. ET AL. The British Regional Heart Study: cardiovascular mortality and water quality. *Journal of environmental pathology and toxicology,* **4**: 89–111 (1980).
127. SHARRETT, A.R. & FEINLEIB, M. Water constituents and trace elements in relation to cardiovascular diseases. *Preventive medicine,* **4**: 20–36 (1975).
128. HELLER, R.F. ET AL. Blood pressure measurement in the United Kingdom Heart Disease Prevention Project. *Journal of epidemiology and community health,* **32**: 235–239 (1978).
129. MORTIMER, E.A. ET AL. Reduction in mortality from coronary heart disease in men residing at high altitude. *New England journal of medicine,* **296**: 581–585 (1977).
130. ANDRIEN, L. Cardiovascular effects of noise. *Acta medica scandinavica,* Suppl. 657 (1982).