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Arterial hypertension

Report of a WHO Expert Committee

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Geneva, 13–21 March 1978

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ARTERIAL HYPERTENSION

Report of a WHO Expert Committee

A WHO Expert Committee on Hypertension met in Geneva from 13 to 21 March 1978. Dr T. Lambo, Deputy Director-General, opened the meeting on behalf of the Director-General.

1. INTRODUCTION

The Twenty-ninth World Health Assembly, in 1976, invited the Director-General of WHO to prepare a long-term programme in the field of cardiovascular diseases, with special emphasis on promoting research on prevention, etiology, early diagnosis, treatment, and rehabilitation.[1] It also stressed the need for the coordination of international activities in this field. The resolution was adopted because it is believed that cardiovascular diseases are now becoming prominent as a public health problem in developing countries as well as in industrialized ones, and, with progressive overall socioeconomic development, an increase in the toll of cardiovascular diseases is likely to follow.

Hypertension is the most common of the cardiovascular diseases and affects most of the populations in the world ; it was therefore considered to be a highly appropriate subject for discussion by the first WHO expert committee to be convened under the new long-term cardiovascular diseases programme.

Since the report of the WHO Expert Committee on Arterial Hypertension and Ischaemic Heart Disease [2] in 1962, there have been extensive advances in our understanding of hypertension, particularly with regard to its epidemiology, natural history, and treatment.[3]

2. CLASSIFICATION

The term arterial hypertension indicates a chronically elevated systolic and/or diastolic arterial (blood) pressure. The higher the

[1] WHO Official Records, No. 233, 1976, p. 31 (resolution WHA29.49).

[2] WHO Technical Report Series, No. 231, 1962.

[3] Comprehensive bibliographies of recent research on hypertension are given in the following two books : GENEST, J. ET AL., ed. *Hypertension*, New York, McGraw-Hill, 1977 ; GROSS, F., ed. *Antihypertensive agents*, Berlin, Springer-Verlag, 1977.

arterial pressure, systolic or diastolic, the greater the cardiovascular morbidity and mortality. This has been found true in all countries studied, in all age groups, and in both sexes.[1] Epidemiological surveys have demonstrated a continuous distribution of arterial pressure levels within the population, and any point separating " normal " from " elevated " pressure is therefore arbitrary. Absolute blood pressure levels vary with sex, age, race, and numerous other factors. Arterial pressure should be measured by standard methods, as used in epidemiological surveys and controlled therapeutic trials, which have quantified the associated risks and the effects of medical intervention.

The purpose of a classification of hypertension is to provide an easy and reliable method for the characterization of each patient. It allows assessment of severity of disease by reference to epidemiological data so that risk can be defined and appropriate treatment instituted.

Any definition of hypertension is based on the arbitrary choice of a threshold value from a continuous distribution of pressure readings. Similarly, classification by stages of development introduces an arbitrary element for assessing disease severity. The rate of progression of hypertension varies from one individual to another depending on the genetic and environmental background.

Arterial hypertension may be classified in three separate ways—by blood pressure level, by the extent of damage to organs, and by etiology.[2]

2.1 Classification by blood pressure level

It is emphasized that there is no clear demarcation between " normal " and " hypertensive " blood pressure levels. In epidemiological studies casual blood pressure measurements should be reported in the form of distribution curves and age-specific means. The predictive value of one casual blood pressure measurement has been demonstrated in a number of epidemiological studies, but it is recommended that for the clinical classification of hypertension at least three blood pressure readings be taken on at least two different occasions, under conditions to be described later, except in emergencies.

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[1] KANNEL, W. B. *Angiology*, **26** : 1 (1975).

[2] This classification differs from that adopted by the WHO Expert Committee on Arterial Hypertension and Ischaemic Heart Disease (WHO Technical Report Series, No. 231, 1962), which did not make a distinction between level of pressure and organ damage. In addition only one casual blood pressure reading of both systolic and diastolic pressure, $\geqslant$160/95 mmHg ($\geqslant$21.3/12.7 kPa), was required to define hypertension.

Normal adult blood pressure is arbitrarily defined as a systolic pressure equal to or below 140 mmHg (18.7 kPa), together with a diastolic (fifth Korotkoff phase) equal to or below 90 mmHg (12.0 kPa).

Hypertension in adults is arbitrarily defined as a systolic pressure equal to or greater than 160 mmHg (21.3 kPa) and/or diastolic (fifth phase) equal to or greater than 95 mmHg (12.7 kPa).

The term " borderline hypertension "[1] is used to denote blood pressure values between the normal and hypertensive ranges as described above.

The terms " mild ", " moderate ", and " severe " hypertension are used in this report in a descriptive sense only and are not defined precisely.

The blood pressure levels at which hypertension can be defined for children vary with age, but the precise levels are under review.[2] Clearly, values that would be regarded as hypertensive are lower in children than in adults.

2.2 Classification according to extent of organ damage : stages of hypertension

The rate of progression of hypertension varies from one individual to another depending on many influences, but the extent of organ involvement corresponds most closely to the level of pressure. Nevertheless, both blood pressure and organ impairment should be evaluated separately, since markedly high pressures, carrying a high risk, may be seen without organ damage and, conversely, organ damage may be present with only moderate elevation of blood pressure.

2.2.1 *Stage I*

No objective signs of organic changes are evident.

2.2.2 *Stage II*

At least one of the following signs of organ involvement is present :

— Left ventricular hypertrophy on physical examination, chest X-ray, electrocardiography, echocardiography, etc.

— Generalized and focal narrowing of the retinal arteries.

— Proteinuria and/or slight elevation of plasma creatinine concentration.

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[1] This term is also used by some clinicians to denote arterial pressure that is sometimes less than 140/90 mmHg (18.7/12.0 kPa) and sometimes greater.

[2] McLain, L. G. *American heart journal*, **92** : 634 (1976).

2.2.3 *Stage III*

Both symptoms and signs have appeared as a result of damage to various organs from hypertensive disease. These include :

— Heart : left ventricular failure.

— Brain : cerebral, cerebellar, or brain stem haemorrhage ; hypertensive encephalopathy.

— Optic fundi : retinal haemorrhages and exudates with or without papilloedema. These features are pathognomonic of the malignant (accelerated) phase (see section 8.2.5).

Other conditions frequently present in Stage III but less clearly a direct consequence of hypertension include :

— Heart : angina pectoris ; myocardial infarction.
— Brain : intracranial arterial thrombosis.
— Vessels : dissecting aneurysm ; arterial occlusive disease.
— Kidney : renal failure.

2.3 Classification by etiology

2.3.1 *Essential or primary hypertension*

This is defined as high blood pressure without evident organic cause.

2.3.2 *Secondary hypertension*

This is defined as hypertension with identifiable cause. The possible causes are classified below.

(1) Hypertension due to the administration of drugs.

— Hormonal contraceptives.
— Licorice and carbenoxolone.
— ACTH and corticosteroids.
— Others.

(2) Hypertensive disease of pregnancy.

(3) Organic disease.

— Coarctation of the aorta.
— Renal diseases (renal artery stenosis ; glomerulonephritis ; pyelonephritis ; radiation nephritis ; renal tuberculosis ; renal cysts ; hydronephrosis ; renal tumours, including renin-secreting tumours ; renal failure).

— Diseases of the adrenal cortex (primary hyperaldosteronism ; Cushing's syndrome ; tumours producing excess of other corticosteroids, e.g., corticosterone and desoxycortone ; inborn errors of corticosteroid biosynthesis).
— Diseases of the adrenal medulla (phaeochromocytoma).

3. TECHNIQUE OF BLOOD PRESSURE MEASUREMENT

3.1 Direct blood pressure measurement

Direct continuous recording of blood pressure by means of intra-arterial puncture has provided valuable information and has emphasized the lability of arterial pressure both in normal and in clearly hypertensive subjects throughout a 24-hour period.[1] Such blood pressure measurements are, however, not practicable for general clinical use.

3.2 Blood pressure measurement using a mercury sphygmomanometer

Blood pressure measurements with a mercury sphygmomanometer should be made by an observer who has been suitably instructed and shown to have normal hearing. The instrument should be kept in good working order. There must be no dust in the rubber tubes linking the inflation bulb with the mercury reservoir and no foreign matter in the space above the mercury column; the deflation valve must be in good working order; and the cuff itself must be in good condition. The standard cuff is 12.5 cm wide and sufficiently long to surround at least two-thirds of the upper arm. Cuffs of different widths are required for blood pressure measurement in children and in obese adults. The following widths have been recommended by the American Heart Association :

under 1 year	2.5 cm
1–4 years	5 or 6 cm
4–8 years	8 or 9 cm
average adults	12.5 cm
obese adults	14 cm

These measurements are a rough guide only ; the important point is that the inner bag must be wide enough to cover two-thirds of the length of the upper arm and long enough to cover at least two-thirds of

[1] BEVAN, A. T. ET AL. *Clinical science*, **36** : 329 (1969).

the circumference of the upper arm, while leaving the antecubital fossa free. For instance, when measuring the blood pressure of obese adults, cuffs 40 cm long are needed. If a choice must be made between a cuff which is too small and one which is too large, the larger one should be chosen. There have been reports that the use of the 2.5 cm cuff on infants produces spuriously high pressures.

The manometer itself should be placed on a horizontal surface. The subject will usually be in the sitting position and it is important that the arm should not be constricted in any way (for example, by clothing). The cuff is adjusted firmly, and the examiner locates the brachial pulse in the antecubital fossa and places a stethoscope over the artery. The cuff is then inflated rapidly to 20–30 mmHg (3–4 kPa) above the pressure at which the radial pulse disappears to palpation. The cuff is then gradually deflated at a constant rate of 2–3 mmHg per second (0.25–0.40 kPa per second). The mercury column is watched continuously and carefully. Systolic pressure is taken as the pressure at which the ear distinguishes the first arterial sound. The point at which the last arterial sound disappears (Korotkoff phase 5) is usually taken as the diastolic pressure.

Measurement of arterial pressure with the patient in the sitting position is most practicable for screening purposes. Measurement of arterial pressure with the patient in the lying position and again after he has been standing for 1–5 minutes gives useful information in the clinical examination of the hypertensive patient, particularly when under treatment.

It is valuable also to record the heart rate at the same time as the blood pressure measurement; this is particularly important during treatment with certain drugs (e.g., vasodilators, adrenergic inhibitors, and beta-adrenoceptor blockers).

In the presence of cardiac arrhythmias (e.g., atrial fibrillation), repeated measurements are needed in order to obtain a satisfactory approximation to the average systolic and diastolic pressures.

With children, it is important to obtain the confidence of the subject and to ensure that the circumstances of blood pressure measurement are quiet. The Korotkoff phase 4 sound gives the best indication of diastolic pressure in children, because the arterial sound may persist until the cuff pressure has fallen to zero. In pregnant women the Korotkoff phase 4 sound is also used for the indication of diastolic pressure.

For epidemiological studies, various devices are available that eliminate observer bias in recording blood pressure with a mercury sphygmomanometer.

3.3 " Casual " blood pressure measurement

Blood pressure recorded by the method recommended in the preceding paragraph is usually described as " casual ". Measurement should be made on the seated subject at a comfortable temperature. There should be no severe exertion, eating, smoking, or exposure to cold immediately preceding the measurement. Considerably lower values may be obtained if the subject is rested or sedated, or following several days in a hospital ward. Nevertheless, for practical clinical and epidemiological purposes, casual pressures have been shown to be reproducible, to give a good indication of the risk of complications, and to demonstrate the effectiveness of treatment. Casual blood pressures are therefore recommended for most clinical and epidemiological purposes.

3.4 Other devices for blood pressure measurement

Aneroid sphygmomanometers are subject to inaccuracies and should be regularly checked against mercury devices. A wide range of methods has been employed for simplifying the signal received, the Korotkoff sounds being variously transformed into visual signals or digital displays or transcribed from the recording device. Many such machines have been adapted for long-term semi-automatic recording of blood pressure at pre-set intervals over several hours. All these devices should be rigorously and repeatedly tested against the standard method.[1] In infants under 2 years of age, the "flush" technique[2] or one of the Doppler instruments is recommended.

3.5 Self-measurement of blood pressure

After suitable training, and with some modifications to the equipment normally used, a subject can measure his own blood pressure. It is notable that in these circumstances individuals often return lower arterial pressures than those obtained by an independent observer.

3.6 Units of blood pressure measurement

The attention of the Committee was drawn to resolution WHA30.39 adopted by the Thirtieth World Health Assembly, which recommended

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[1] STEGALL, H. F. ET AL. *Journal of applied physiology*, **25** : 793 (1968).

[2] VAUGHAN, V. C. & MCKAY, R. J., ed. *Nelson textbook of pediatrics*, 10th ed. Philadelphia, Saunders, 1975, p. 1003.

the adoption of the Système international d'Unités (SI), and thereby of the kilopascal (kPa). Since arterial pressures are universally recorded in terms of the millimetre of mercury (mmHg), the Committee is of the opinion that the kilopascal is not appropriate for clinical practice or epidemiological use and that the millimetre of mercury should therefore be retained for the time being.[1]

4. EPIDEMIOLOGY OF HYPERTENSION

The most extensive population surveys of blood pressure have been carried out in Australia, Japan, New Zealand, the USA and various European countries. Information from other areas is relatively sparse. A graph showing the distribution of blood pressure among different populations is presented in Fig. 1.

4.1 Prevalence

A large proportion of the adult population in many parts of the world has blood pressure ranges associated with an excess morbidity and mortality, regardless of what cut-off values are used in definition.[2–4] From 8 to 18% of adults have pressures above 160 mmHg (21.3 kPa) systolic and/or 95 mmHg (12.7 kPa) diastolic; however, recent information from China appears to indicate a lower prevalence in that country.

Only limited data are available on the prevalence of secondary hypertension in different communities and in different age groups. Several community surveys have indicated that the prevalence of secondary

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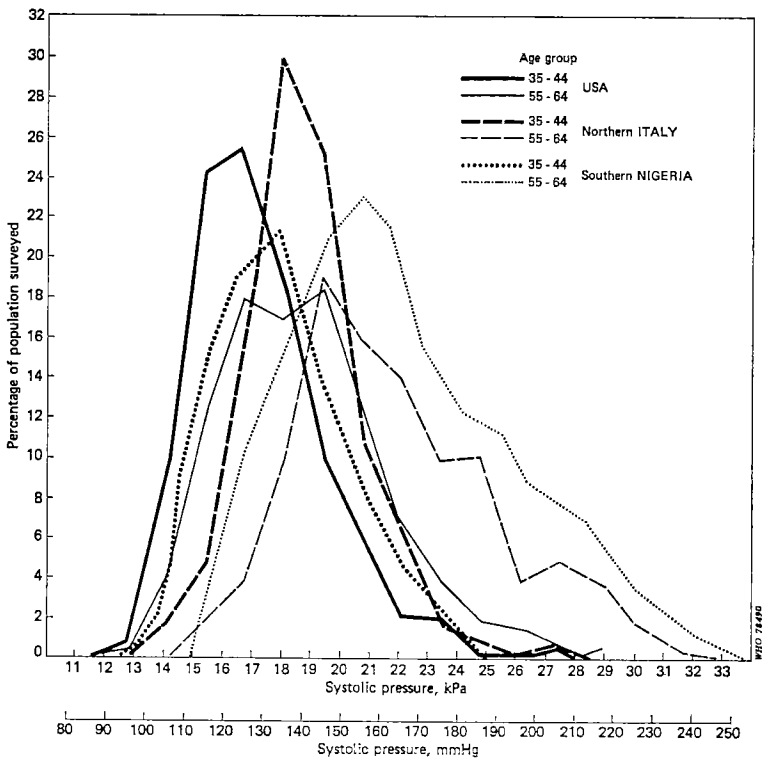
[1] In the discussions that led to the adoption of resolution WHA30.39, by which WHO policy in this matter is set, there was agreement among the delegates to the Thirtieth World Health Assembly that, while the Système international d'Unités should be adopted by the scientific community, the replacement of the millimetre of mercury by the SI unit, the kilopascal, would be premature; rather, both units should be used side by side for a period of time. In the resolution, the Health Assembly also recommended that " in addition to the scale in kilopascals, the millimetre (or centimetre) of mercury ... be retained for the time being on the scales of instruments for the measurement of the pressure of body fluids, pending wider adoption of the pascal in other fields ". Accordingly, all arterial blood pressures are expressed in both millimetres of mercury and kilopascals in this report. — ED.

[2] GORDON, T. & DEVINE, B. *Hypertension and hypertensive heart disease in adults : United States, 1960–62*. Washington, DC, US Public Health Service, 1966 (Series 11, No. 13).

[3] WILHELMSEN, L. ET AL. *Preventive medicine*, **2** : 57 (1973).

[4] HAWTHORNE, V. M. ET AL. *British medical journal*, **3** : 600 (1974).

Fig. 1. Distribution of systolic pressure in three populations



hypertension varies from 1% to 5% of the total hypertensive population.[1, 2] More extensive and accurate information is needed on secondary hypertension because it has important connotations regarding investigation and treatment.

4.2 Changing mortality

In some European countries and in the Americas there has been a slow decline in the mortality from hypertension and related diseases for

[1] GREMINGER, P. ET AL. *Schweizerische medizinische Wochenschrift*, **107**: 605 (1977).

[2] WILHELMSEN, L. & BERGLUND, G. *American heart journal*, **94**: 543 (1977).

over 30 years.[1] This trend preceded the modern era of pharmacological therapy although it may recently have been furthered by it.

4.3 Age and sex

Virtually all surveys, including those from Africa, Latin America, Oceania, and India, have shown a rise in blood pressure with age in both men and women, this phenomenon being more marked in women after the age of 50. The increase in systolic pressure appears to continue throughout life, whereas there is a tendency for diastolic pressure to level off around the age of 55 to 60.[2] Longitudinal studies have indicated that the increase of blood pressure with age is more marked the higher the blood pressure initially recorded at any age. In young adults in the USA the increase in pressure with age is greater in blacks than in whites ; hence, there is a significant excess prevalence of high blood pressure in the black population.

Several communities, usually isolated and primitive, have by contrast been observed in which there is little or no increase of systolic or diastolic blood pressure with age.[3, 4] These communities are situated in the highlands of Chile, Easter Island, Pukapuka, Tokelau, Papua New Guinea, and certain parts of Africa and Asia. They are usually small and isolated. There is typically a high level of physical activity, a low salt intake (4 g or less per day), a low overall energy-food intake, frequent periods when food is in short supply, and little or no involvement with a monetary economy.

4.4 Geographical aspects

People living in the mountainous regions of South America tend to have low blood pressure, but levels increase and show a normal rise with age when high-altitude residents migrate to less primitive lowland regions.[5] Interestingly, in Ethiopia, where highlanders have a higher socioeconomic status than lowlanders, they have higher average blood

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1 MORIYAMA, I. M. ET AL. *Cardiovascular diseases in the United States*. Cambridge, Harvard, 1971, pp. 157–171.

2 GORDON, T. *Blood pressure of adults by age and sex : United States, 1960–62*. Washington, DC, US Public Health Service, 1964 (Series 11, No. 4).

3 CRUZ-COKE, R. ET AL. *Lancet*, **1** : 697 (1964).

4 PRIOR, I. A. M. ET AL. *International journal of epidemiology*, **3** : 225 (1974).

5 CRUZ-COKE, R. ET AL. *Clinical science and molecular medicine*, **45**, Suppl. 1 : 55 (1973).

pressures. Tokelauans migrating to New Zealand also show subsequently a rise in blood pressure. Not all small communities have a tendency to low blood pressure; higher blood pressures have been observed in the Hebridean islands of Tiree and Todday than on the west of Scotland mainland.[1]

Many of these studies, although interesting, fail to disentangle the conflicting influences of genetics, geographical location, culture, socio-economic status, and diet.

Prevalence and incidence rates of coronary heart disease and hypertension demonstrate large national differences. However, the magnitudes of these rates are different for the two conditions; with hypertension there may be a twofold or threefold range by geographical distribution while with coronary heart disease there may be a fivefold or tenfold range. The distribution of other risk factors predisposing to coronary arterial disease may interact with hypertension and thus be subjected to substantial regional variations.

5. ETIOLOGY AND PATHOGENESIS OF ESSENTIAL (PRIMARY) HYPERTENSION

The evidence currently available indicates that the development of high blood pressure depends on the interaction of several genetic and environmental influences.

5.1 Genetic factors

Although the precise mode of inheritance of arterial hypertension has not yet been demonstrated in man it appears most likely to be polygenic.[2] The evidence supporting this contention is the following: (1) familial aggregation of blood pressure is significantly correlated among first-degree relatives (parents, siblings, children) at all ages; (2) the similarity between both systolic and diastolic blood pressures in monozygotic twins is significantly closer than those in dizygotic twins; (3) no significant correlation has been observed in the blood pressure of pairs of adopted children living together or between adopted children and their adoptive parents or siblings, although the available data are limited to a relatively short duration of adoption; (4) the tendency (when

[1] HAWTHORNE, V. M. ET AL. *British medical journal*, **4**: 651 (1969).

[2] CRUZ-COKE, R. & COVARRUBIAS, E. *Acta genetica et statistica medica*, **15**: 87 (1965).

values are adjusted for age and sex) for the relatives of hypertensive patients to resemble each other so far as their arterial pressures are concerned is the same at all levels of pressure and shows higher correlation among close relatives than among distant ones.

Although most workers now contend that polygenic inheritance is probable, the possibility is not excluded that a single pair of genes could contribute to the unimodal and continuous distribution of blood pressure seen in the population. The relatively low correlation coefficient clearly indicates that factors other than inheritance are important in determining the final blood pressure level.

5.2 Dietary influences

5.2.1 *Weight*

Virtually all epidemiological studies have shown a close relationship between blood pressure and weight. This applies to primitive as well as advanced cultures and in childhood and adulthood. Longitudinal studies have established that individuals who gain more weight show more increase in blood pressure.[1] Moreover, weight reduction has been seen to be accompanied by a fall in arterial pressure.[2] Much more needs to be learned of this phenomenon, which offers a potential approach to the primary prevention of hypertension. This is not exclusively a dietary consideration, since heredity and exercise are also factors.

5.2.2 *Sodium chloride intake*

Several communities whose daily intake of sodium chloride is 3 g (or less) have low average blood pressures and show little tendency for pressures to rise with age. When people migrate from such communities to areas where the daily salt intake is around 7–8 g, blood pressure increases proportionately, although there are several confounding factors such as social change and altered overall nutritional state. It remains unclear whether the change in salt intake is solely or partially responsible. Epidemiological studies among adult men and women in the USA, Europe, and New Zealand have failed to demonstrate a clear relationship between salt intake or excretion and blood pressure. It has been suggested that not only sodium but the proportions of sodium to potassium, sodium to calcium, and sodium to magnesium may be

[1] TOBIAN, L. *New England journal of medicine*, **298** : 46 (1978).

[2] REISIN, E. ET AL. *New England journal of medicine*, **298** : 1 (1978).

important pathogenically.[1–3] In general, however, the entire question of salt intake and its implications for prevention remain unresolved. This is identified as one of the most important aspects requiring detailed and extensive research.

5.2.3 *Protein intake*

A high protein intake may be useful in attenuating the adverse effects of high salt intake on blood pressure. These observations are based on experiments in rats and on more limited human studies in Japan.[4] More data are needed to evaluate the wider relevance of these findings.

5.2.4 *Alcohol*

An association between hypertension and high alcohol intake has been indicated in Scotland,[5, 6] Sweden, and the USA,[7] but further studies are needed to confirm it.

5.2.5 *Soft water*

There is some evidence of an association between high blood pressure and the use of soft, demineralized water. Soft water may have a high content of sodium as well as of cadmium. Though controversial, there are suggestions that trace amounts of cadmium may exert a pressor effect in man.[8, 9]

5.3 Psychosocial factors

The role of psychosocial factors is the subject of considerable debate. In general, there is no evidence of any harm resulting from short-term

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[1] MENEELY, G. R. & BATTARBEE, H. D. *American journal of cardiology*, **38**: 768 (1976).

[2] FREIS, E. D. *Circulation*, **53**: 589 (1976).

[3] PRIOR, I. A. M. ET AL. *New England journal of medicine*, **275**: 515 (1968).

[4] YAMORI, Y. ET AL. *Clinical and experimental pharmacology and physiology*, Suppl. 3, p. 199 (1976).

[5] RAMSAY, L. E. *Lancet*, **2**: 111 (1977).

[6] BEEVERS, D. G. *Lancet*, **2**: 114 (1977).

[7] KLATSKY, A. L. ET AL. *New England journal of medicine*, **296**: 1194 (1977).

[8] UNITED STATES ENVIRONMENTAL PROTECTION AGENCY. Drinking water and health: recommendations of the National Academy of Sciences. *Federal register*, July 11, 1977, part III.

[9] GORDER, Z. A. Should municipalities soften water? In: *Water—its effects on life quality: proceedings of the seventh international water quality symposium, April 1974*. Norwalk, CT, David X. Manners Co., p. 107.

blood pressure elevations in response to acute psychological stimuli.[1] Long-term exposure to an adverse psychosocial environment might be important and might lead to permanent hypertension. Studies on migrant populations have lent some support to this hypothesis, although movement from a primitive culture to a more advanced one will obviously involve changes in dietary habits, nutrition, socioeconomic status, and other environmental factors. This entire area remains obscure and merits continued and extensive investigation.

6. PATHOPHYSIOLOGY OF ESSENTIAL (PRIMARY) HYPERTENSION

Hypertension of the essential (primary) type is a long-term and usually progressive disorder. There is increasing evidence that its existence may be recognized even in childhood, but not all potential hypertensive individuals recognized in youth necessarily develop distinct hypertension as adults. On the other hand, spontaneous remission of established hypertension in the adult is rare. Typically, hypertension has a long asymptomatic phase ; but the term " benign " for this type of hypertension is misleading and should be discarded because the presence of high blood pressure is clearly associated with a shorter life expectancy.

Elevated arterial pressure is associated with pathophysiological alterations involving the sympathetic (adrenergic) nervous system, the kidneys, the renin-angiotensin system, and various haemodynamic and humoral mechanisms. Much evidence comes from animal models of experimental hypertension, and further clinical support has been derived from the study of secondary forms of human hypertension. Research in this field should be encouraged because new knowledge may be extremely important in deciding the most appropriate measures for primary prevention or in selecting the most suitable antihypertensive drugs.

6.1 Haemodynamic changes

An increased heart rate is a fairly consistent feature of hypertension, and is observed with different levels of arterial pressure.[2, 3] Early in

[1] YAMORI, Y. ET AL. *Japanese circulation journal*, **33** : 399 (1961).
[2] FROHLICH, E. D. ET AL. *Circulation*, **44** : 446 (1971).
[3] LUND-JOHANSEN, P. *Acta medica Scandinavica*, Suppl. 603, p. 1 (1977).

the course of essential hypertension, cardiac output is elevated while total peripheral resistance may be within the normal range or only slightly raised. Together with mild arteriolar constriction in early hypertension there may be peripheral venoconstriction, which serves to redistribute the circulating blood from the periphery to the cardiopulmonary area. As constrictor influences on the capacitance and resistance vessels persist and progress, arterial pressure and vascular resistance increase further. Ultimately, the heart shows evidence of adaptive hyperfunction and left ventricular hypertrophy; and with advancing hypertension and further increase in total peripheral resistance the cardiac output, together with stroke volume, gradually falls until cardiac failure supervenes. With some exceptions, studies of regional haemodynamics have been limited in scope and need to be considerably expanded.

With progressive hypertension, there is a corresponding increase in vascular resistance in the kidneys and a fall in renal blood flow, although the glomerular filtration rate and overall renal function are initially well preserved. Eventually, however, as total peripheral resistance increases more steeply, there is a further rise in renal vascular resistance accompanied now by a fall in glomerular filtration rate and a deterioration in overall renal function.

The blood pressure limits between which cerebral flow is maintained have been described as being shifted upwards in established hypertension.[1] This is an important consideration in therapy, since if blood pressure is lowered too rapidly there is a danger that cerebral blood flow will fall and that cerebral ischaemia will be provoked. Studies in this area could be profitably extended.

Plasma volume tends to decline slowly with the progression of hypertension and as total peripheral resistance increases. Eventually, if renal function becomes impaired, intravascular volume may expand.

6.2 Neural changes

An increased cardiac output and heart rate in early essential hypertension may be manifestations of an exaggerated adrenergic influence on the cardiovascular system. The baroreceptors are reset in experimental and clinical forms of hypertension, as is evidenced by the general finding that the rise in blood pressure is not associated with bradycardia.[2]

[1] STRANDGAARD, S. ET AL. *British medical journal*, **1**: 507 (1973).

[2] ZANCHETTI, A., ed. *Neural factors and catecholamines in experimental hypertension*. Milan, Il Ponte, 1972.

Moreover, it has been shown that pressor and depressor reflex responses to carotid sinus manipulation are reset in experimental and clinical forms of hypertension. It is likely that neural influences on the kidney are important in moderating a tendency to natriuresis as the renal arterial pressure rises in essential hypertension.

Measurement of plasma catecholamine concentration has been employed to assess sympathetic nervous activity. There is conflicting evidence on whether circulating levels of catecholamines are increased in essential hypertension. Several authors have reported increased concentrations of noradrenaline in the plasma of patients with essential hypertension, although these results have not been confirmed by others with age-matched controls.[1] Such controls are needed because plasma noradrenaline concentration increases with age.

6.3 Humoral changes

The renin-angiotensin system has been extensively studied since the introduction of practicable assay methods for plasma renin and angiotensin II.[2–6] Patients with essential hypertension have been subdivided by some investigators into subgroups with low, normal, and high plasma renin on the grounds that the elevated pressure in these subgroups might have different mechanisms and in particular that those patients with low plasma renin might have excess mineralocorticoid activity. These theories are under intensive investigation but have not yet been substantiated. Plasma renin and angiotensin II values are continuously distributed in the hypertensive population, although they are spread over a wider range than in normal subjects. Further, peripheral levels of plasma renin and angiotensin II have been found to be related inversely to age in essential hypertension, and this has been taken as indicating suppressed renal renin release with progression of the disease.

Peripheral levels of antidiuretic hormone have been reported as being slightly suppressed in uncomplicated essential hypertension. More recent research has called attention to the possible implication of prostaglandins and the kallikrein/kinin system in hypertension.

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[1] AXELROD, J. *Clinical science and molecular medicine*, **51**, Suppl. 3 : 415 (1976).

[2] HOLLIFIELD, J. W. ET AL. *Mayo Clinic proceedings*, **52** : 329 (1977).

[3] PADFIELD, P. L. ET AL. *Lancet*, **1** : 548 (1975).

[4] BEEVERS, D. G. ET AL. *British medical journal*, **1** : 415 (1977).

[5] THOMAS, G. W. ET AL. *Australian and New Zealand journal of medicine*, **6**, Suppl. 3 : 44 (1976).

[6] BROWN, J. J. ET AL. *Cardiovascular clinics*, **9** : 55 (1978).

It is expected that all these issues will be greatly clarified with improved technology and assay methods.

7. HYPERTENSION WITH IDENTIFIABLE CAUSE (SECONDARY HYPERTENSION)

7.1 Hypertension due to drug administration

7.1.1 *Hormonal contraceptives*

Prospective controlled studies have shown that estrogen-progestogen oral contraceptives (containing 50 μg or more of estrogen) cause a distinct increase in systolic, and to a lesser extent diastolic, pressure in virtually all women.[1] In some individuals marked elevation of pressure can occur, and occasional patients have been seen in the malignant phase, but the mechanism of the rise in blood pressure is imperfectly understood. Almost invariably the pressure falls when the oral contraceptive is withdrawn. It is not known whether hormonal contraceptives with lower estrogen content or containing only progestogen cause a similar rise in blood pressure, and this needs urgent clarification.

7.1.2 *Licorice/carbenoxolone*

Licorice or carbenoxolone administration may elevate blood pressure. This is attributable to the mineralocorticoid activities of these medications and is initially mainly systolic ; hypokalaemia is usual. The hypertension usually resolves when the treatment is withdrawn.

7.1.3 *ACTH/corticosteroids*

An increase in blood pressure may follow administration of ACTH or corticosteroids. With ACTH it seems likely that this blood pressure rise is due mainly to adrenal release of ACTH-sensitive mineralocorticoids, although other classes of corticosteroids may be involved.[2] Therapeutic administration of corticosteroids with the intention of stimulating either mineralocorticoid or glucocorticoid activity may in some patients also produce a rise in blood pressure.

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[1] WEIR, R. J. ET AL. *British medical journal*, **1** : 533 (1974).
[2] BROWN, J. J. ET AL. *Cardiovascular clinics*, **9** : 55 (1978).

7.1.4 *Other drugs*

Other medications may on rare occasions produce a rise in arterial pressure. Examples are the abuse of nasal sympathomimetic vasoconstrictors, ephedrine, amphetamine, monoamine oxidase inhibitors, and tricyclic antidepressants.

7.2 Hypertension due to organic disease

7.2.1 *Coarctation of the aorta*

This congenital abnormality is a narrowing of the aorta, usually adjacent to the insertion of the ductus arteriosus. It gives rise to a characteristic form of hypertension in which the femoral pulses are diminished or absent and delayed in comparison with the radial pulses. An extensive collateral circulation around the thorax usually develops. The appropriate therapeutic approach is surgical correction of the lesion.

7.2.2 *Renal diseases*

The various changes in renal function that accompany the progression of essential hypertension have been outlined in section 6.1, and the renal complications of hypertension are described in section 8.2.3. In addition, a wide variety of renal diseases can cause or aggravate hypertension.

Renal artery lesions. The identification of unilateral or bilateral renal artery stenosis as a cause of hypertension has attracted much attention. The two principal lesions causing renal artery stenosis are atheroma and fibromuscular hyperplasia. Successful surgical correction of a renal artery stenosis may alleviate hypertension and thus avoid the indefinite use of antihypertensive agents. Nevertheless, enthusiasm for corrective renal artery surgery has moderated in recent years, and such an approach is now advised mainly in carefully selected younger patients, in patients who have not responded to antihypertensive drug therapy, or in cases where it is necessary to preserve renal parenchymal function.

Parenchymal renal lesions. In this broad group of diseases, which typically affect both kidneys, distinct impairment of renal function usually accompanies blood pressure elevation. Examples are : glomerulonephritis, acute or chronic ; radiation nephritis ; nephropathy due to abuse of analgesics (mainly phenacetin) ; polycystic disease ; and chronic pyelonephritis (although the value of prolonged antibiotic treatment in patients with asymptomatic urinary infections remains unclear). Drug

therapy is necessary to control hypertension, when present, in all these conditions, and the principles for such treatment are outlined in section 10.4.

Schistosomiasis of the urinary tract has previously been considered as a possible cause of hypertension, but recent epidemiological data have not supported this assertion.

In patients with advanced renal failure requiring regular haemodialysis, blood pressure is usually controlled by removal of salt and water in the process of dialysis and by restricting intake between dialyses. In a few instances the addition of antihypertensive drugs is needed. Occasionally patients develop refractory hypertension despite these measures; plasma levels of renin and angiotensin II are usually very high, and bilateral nephrectomy permits subsequent control of the blood pressure by dialysis alone.

Unilateral renal lesions. When such lesions are found in a hypertensive patient, removal of the affected kidney may sometimes reduce the blood pressure. Certain of these lesions require excision for reasons other than that of blood pressure control, but, if the latter is the only reason, careful evaluation is necessary before surgery is advised because a satisfactory reduction in blood pressure does not always occur and because the condition in such patients may be readily controlled with antihypertensive drugs. Examples of unilateral renal lesions are: hydronephrosis; single cyst; various benign and malignant tumours (including the rare renin-secreting tumour); and unilateral renal tuberculosis.

The initial detection of a unilateral renal lesion is usually made by intravenous pyelography (excretion urography). It should be emphasized, however, that in community surveys and general practice a significant renal abnormality leading to a change in the management of the patient will be discovered on intravenous pyelography probably only in about 1% of cases.[1] In these circumstances, therefore, intravenous pyelography is not recommended as a routine investigation. By contrast, with preselected patients this investigation is more rewarding.

Other more specialized investigative procedures that may be indicated, once the initial diagnosis of a renal abnormality has been made, include selective renal arteriography, ureteral catheter studies, renal biopsy, estimation of renin in samples collected simultaneously from the two renal veins, and assessment of the response to antagonists or inhibitors

[1] ATKINSON, A. B. & KELLETT, R. J. *Journal of the Royal College of Physicians of London*, **8**: 175 (1974).

of the renin-angiotensin system. For each patient the respective potential advantages and disadvantages of medical and surgical treatment of any renal abnormality must be carefully evaluated.

7.2.3 *Diseases of the adrenal cortex*

Primary hyperaldosteronism. This can be due to a single adrenocortical adenoma or to bilateral adrenocortical hyperplasia.[1] Aldosterone excess is associated with an increase in body sodium and a decrease in potassium. The plasma potassium level is typically low and plasma renin is suppressed. If the cause of the disease is a solitary adenoma, the hyperaldosteronism, and hence the hypertension, may be corrected by the surgical excision of the adenoma. Surgical treatment is not recommended in the non-adenomatous cases, for which long-term treatment with potassium-conserving diuretics is given.

Cushing's syndrome. About 80% of patients with Cushing's syndrome have hypertension, and this has been attributed to sodium retention and an excess of extracellular fluid due mainly to the mineralocorticoid effects of excess cortisol. Treatment must be directed to the cause of the disease, which may be excess secretion of ACTH or a primary abnormality of the adrenal cortex.

Inborn errors of corticosteroid biosynthesis. These may result in failure of cortisol secretion, leading to excessive production of ACTH. The consequent overproduction of ACTH-sensitive mineralocorticoids can be corrected following suppression of ACTH by dexamethasone.

7.2.4 *Phaeochromocytoma*

Overactive adrenal medullary tissue (within or outside the adrenal medulla itself) can produce sustained or paroxysmal hypertension. Phaeochromocytoma is characterized by excessive catecholamine secretion and the definitive treatment is excision of the tumour. In cases of widespread or metastasizing phaeochromocytoma, where surgical excision is not possible, concurrent treatment with both alpha- and beta-adrenoceptor blocking agents is called for.

7.3 Hypertensive disease of pregnancy [2]

The hypertensive disease of pregnancy (variously termed toxaemia of pregnancy, pre-eclampsia, eclampsia, and hypertension gestosis) is the

[1] FERRISS, J. B. ET AL. *American heart journal*, **95** : 375 (1978).

[2] For further details see : *Report of the meeting on hypertensive disorders of pregnancy, childbirth and the puerperium*, unpublished WHO document MCH/78.2.

major cause of premature birth and perinatal death and is also responsible for one-fifth to one-third of all maternal deaths. Infants of mothers who have hypertension with proteinuria in late pregnancy are small, more often stillborn, and have a high risk of death in the neonatal period. The reported incidence of this disease varies widely. Most information derives from hospital studies, which are not representative of the total population. More information is necessary from different parts of the world.

Diagnosis is traditionally based on the presence of two or more components of the triad: hypertension, proteinuria, and oedema. In view of the marked local variations in clinical practice, it is essential to define these signs and standardize the methods of measuring them.

The significance of absolute levels of blood pressure during pregnancy differs from that in the nonpregnant state, and it is invalid to extrapolate data from nonpregnant to pregnant women. Even slight elevations of arterial pressure are of pathogenic significance in pregnancy. A diastolic blood pressure recording of 85 mmHg (11.3 kPa) or more, irrespective of systolic blood pressure, should be considered abnormal, and if encountered in the third trimester indicates the urgent need for special medical attention. If prepregnancy recordings are available (or if sequential blood pressure recordings during pregnancy are available), a rise of 15 mmHg (2 kPa) or more in the diastolic reading should be considered abnormal.

Patients should rest in bed, avoid an excessive intake of salt, and be subjected to regular clinical monitoring. If these measures do not suffice, judicious use may be made of antihypertensive drugs. Diuretics, however, appear potentially harmful to both mother and fetus and should not be used except in very special circumstances.

8. COMPLICATIONS OF HYPERTENSION: CAUSES AND EFFECTS

8.1 Risk factors

Blood pressure is a graded characteristic, and no obvious distinction can be made between "hypertensive" and "normal". It is also a graded risk, the risk increasing in proportion to the level of pressure. Insurance and community data show an excess mortality from cardiovascular disease even when casual systolic and diastolic pressures have been below 140 and 90 mmHg respectively (18.7 and 12.0 kPa). The blood pressure level can in fact be regarded as directly responsible for

all complications. For example, despite earlier statements to the contrary, it has now been shown that patients with primary hyperaldosteronism are not immune to vascular complications.[1] Any relative immunity that a particular form of hypertension may carry is probably related to a milder elevation of pressure.

The relative risk of blood pressure elevation appears to hold for both sexes and all communities although the absolute risk varies widely, with distinct sexual and racial differences (see sections 4.3 and 4.4).

Prognosis is adversely affected by elevated total serum cholesterol, cigarette smoking, and diabetes mellitus.

8.2 Complications

Complications associated with blood pressure elevation fall into the following categories : cardiac, cerebral, ocular, vascular, and renal.

8.2.1 *Heart*

There are two main cardiac complications of hypertension—heart failure and ischaemic heart disease—and in many countries they constitute the most common cause of death. Left ventricular hypertrophy of varying degree may be solely the result of the increased total peripheral resistance and left ventricular work. Ultimately congestive heart failure may supervene and this condition may prove fatal. Ischaemic heart disease, the other major cardiac complication, is well known to be more common in hypertensive than in normotensive individuals. Angina pectoris, myocardial infarction, cardiac failure, and sudden death are all manifestations of this condition.

8.2.2 *Brain*

Stroke, which is a major complication of hypertension in most western nations, is even more prominent in Asia, including China, Japan, and the Republic of Korea. Cerebral, cerebellar, and brain stem haemorrhage is more closely associated with hypertension than is cerebral thrombosis, which is mainly caused by atherosclerotic lesions. Nevertheless, the unfavourable influence of hypertension in accelerating cerebral atherosclerosis has been indicated by extensive clinicopathological observations.

Transient cerebral ischaemic attacks are episodes of focal reversible neurological deficit of sudden onset and of less than 24 hours' duration. As these may be one of the earliest manifestations of cerebrovascular

[1] BEEVERS, D. G. ET AL. *Quarterly journal of medicine*, **45** : 401-(1976).

disease, early detection and treatment is important for the prevention of stroke.

Hypertensive encephalopathy is often associated with an extreme elevation of arterial pressure and is characterized by variable disturbance of consciousness ranging from transient confusion to coma, often with convulsions. Severe headache, nausea, and vomiting are common accompaniments. The syndrome may be promptly reversed by anti-hypertensive therapy.

8.2.3 *Kidney*

The renal complications of hypertension include premature or accelerated atherosclerosis of the renal arteries, nephrosclerosis, and, with the development of the malignant phase, necrotizing arteriolar fibrinoid changes. The first may also occur in the absence of hypertension, but is probably accelerated by an elevated pressure. The second produces slowly progressive renal impairment and only rarely renal failure. The third is diagnostic of the accelerated phase of hypertension, is rapidly progressive, and is associated with progressive uraemia and retinal haemorrhages, exudates, and papilloedema. In the accelerated phase the intense renal ischaemia may result in elevated circulating levels of renin and angiotensin II and hence secondary hyperaldosteronism.

8.2.4 *Blood vessels*

Dissecting aortic aneurysm—an uncommon but frequently fatal condition—is associated with degenerative disease in the aortic media. It is encountered more often in persons with hypertension. Peripheral arterial disease also is accentuated by high blood pressure.

8.2.5 *Accelerated (malignant) phase*

The essential pathological feature of this complication is fibrinoid arterial necrosis. Earlier reports have emphasized, as a diagnostic requirement, the presence of bilateral papilloedema as well as retinal haemorrhages and exudates. More recent studies, in which renal biopsies have been performed, have shown that renal fibrinoid arterial necroses are common in severe hypertension in association with retinal haemorrhages and exudates, but without papilloedema.[1] Since the

[1] BROWN, J. J. ET AL. *British medical journal*, **1**: 505 (1966).

accelerated phase demands prompt therapy, being uniformly and rapidly fatal if untreated, a more practical criterion for diagnosis appears to be retinal haemorrhages and exudates with or without papilloedema. With effective lowering of arterial pressure, these gross retinal lesions may resolve.

9. CLINICAL ASSESSMENT

9.1 Role of the physician

The role of the physician caring for a patient whose arterial pressure is abnormally high is :

— to make a firm diagnosis of arterial hypertension,
— to educate the patient,
— to make an assessment of overall cardiovascular risk,
— to seek, and if possible correct, etiological factors,
— to perform necessary supplementary examinations before instituting treatment, and
— to treat effectively.

9.1.1 *Diagnosis of arterial hypertension*

While the predictive value of single casual blood pressure measurements has been clearly demonstrated, it is unwise to perform a full diagnostic study or to institute treatment without at least three blood pressure measurements made on each of at least two separate occasions.

9.1.2 *Patient education*

The attention paid to the measurement of blood pressure must be properly explained to the patient at an early stage for two reasons—to avoid needless anxiety about what might be a minor anomaly and conversely to prevent the underestimation of a high-risk condition that might be reduced or eliminated by medical intervention. It is most important for the clinician to explain these matters to the patient at the outset and gain his full cooperation. It is also crucial to convey the idea of prophylactic treatment, since many patients are initially free from symptoms and will often experience some side-effects from therapy.

9.1.3 *Assessment of cardiovascular risk*

An immediate assessment may be provided by the magnitude of the blood pressure elevation. A more detailed clinical examination will

give firmer information on the extent and severity of disease as detailed in section 2.2.

The following points should be clarified:

- — personality of the patient;
- — family history of renal or cardiovascular diseases; death of father, mother, or siblings below the age of 65;
- — duration of hypertension; known blood pressure records; previous treatment;
- — history of known hyperlipidaemia in the subject and in his parents, grandparents, or siblings;
- — smoking habits—type, degree, and duration;
- — overweight condition—degree and duration;
- — existence of diabetes mellitus;
- — extent of physical exercise;
- — ingestion of oral contraceptives, glucocorticoids, etc.;
- — social circumstances.

9.1.4 *Search for possible etiology*

The potentially curable causes of arterial hypertension are uncommon. Nevertheless, a search should always be made for them, if possible before instituting therapy, and it should be more assiduous in children and young adults than in older patients because in these subjects the side-effects of any nonspecific drug therapy would have to be endured longest and also because secondary forms of hypertension may be more common in young people.

Relevant points in the history include the use of oral contraceptives; ingestion of licorice or carbenoxolone preparations or analgesics; evidence of past or present renal disease, including especially urinary tract infection, trauma, and haematuria; features suggesting a phaeochromocytoma, including neurofibromatosis, headache, anxiety, pallor, and attacks of sweating; and muscle weakness and tetany—symptoms suggesting hypokalaemia and alkalosis.

The clinical examination should take note of features of Cushing's syndrome and should include palpation of the femoral pulses, elicitation of abdominal or loin murmurs, palpation of the kidneys, and examination of the skin for evidence of neurofibromatosis.

9.1.5 *Additional examination*

The necessary minimum diagnostic examination in a hypertensive patient is a subject of debate. Investigations should progress from the

simplest towards the more complicated. It is always better to repeat a doubtful simple test rather than to perform a complex investigation at an early stage. The younger the patient, the higher the pressure, and the faster the development of hypertension, the more detailed the diagnostic examination should be.

When a diagnosis of arterial hypertension has been made, the consequences last for several decades. It is part of the education of the patient to get him to accept some simple examinations before drug treatment is instituted.

Any laboratory method should be standardized and submitted to regular validity checks, and results must be interpreted with caution. " Normal " limits recorded by laboratories must be viewed critically. When deciding on the extent of the laboratory examination, the reliability of the requested test should be taken into account. Indiscriminate use of laboratory facilities results in a very low yield of useful information.

The following diagnostic tests are commonly used.

Plasma creatinine concentration. A strongly recommended test. It gives information on renal sufficiency or insufficiency. It is not affected by water or protein intake and should therefore be given preference over the measurement of blood urea nitrogen.

Plasma potassium concentration. A strongly recommended test. Even though both primary and secondary hyperaldosteronism are uncommon, the resulting low blood potassium level may make it dangerous to use thiazide diuretics in treatment. Some caution is necessary ; forearm muscle contraction must not be used to aid venepuncture, because this can elevate plasma potassium level.

Serum cholesterol concentration. This is an important indicator of the cardiovascular risk associated with arterial hypertension.

Fasting (or 2-hour postprandial) blood glucose. Although this is an imperfect test for diabetes mellitus, its aim is to detect obvious additional cardiovascular and renal risks associated with hypertension. It also serves to identify the patient who might develop diabetes mellitus with diuretic therapy.

Plasma uric acid concentration. Even though elevation of the plasma uric acid level is not, as such, an important cardiovascular risk factor, it may affect the choice of therapy.

Haemoglobin. A strongly recommended test. It provides evidence of primary anaemia or of the anaemia of renal disease.

Haematocrit. This test indicates the presence of expanded or contracted plasma volume and confirms abnormalities of haemoglobin concentration.

Urinary analysis. A strongly recommended test. A dip-stick test for the presence of albumin, sugar, or blood in the urine should be done in all cases. If this is positive, verification is required, together with microscopic examination of urinary sediment. This latter test should always be performed in a patient with suspected renal parenchymal disease.

Electrocardiogram. A strongly recommended test. It is used to detect signs of cardiac involvement (left atrial hypertrophy, left ventricular hypertrophy), ischaemia and infarction (repolarization disorders, Q wave typical of necrosis), or disorders of atrioventricular conduction that might contraindicate certain forms of treatment. It is suggested that the Sokolow-Lyon voltage criterion (RV5 or RV6 + SV1 = 3.5 mV or more) for left ventricular hypertrophy be retained, although its limitations are recognized.[1]

9.2 Extended evaluation

Complications of hypertension may require special investigations. If a particular cardiovascular risk factor is found, complementary tests may be needed.

Various additional examinations may be performed in the search for a curable cause of hypertension, but, because of their cost, poor return, and, in some instances, risks and discomfort for the patient, they are carried out only as indicated by the results of the initial clinical and basic laboratory evaluation. Moreover, the need for an extended evaluation can always be reconsidered if a patient whose adherence to therapy is satisfactory remains hypertensive.

9.3 Hypertension in infancy and childhood

Reference has already been made to the precautions to be taken (including size of cuff) when measuring blood pressures in children. There is increasing recognition that children with higher pressures are more apt to develop hypertension in later life. Repeated periodic blood pressure measurements should be obtained in such children, and if the

[1] WHO Technical Report Series, No. 231, 1962, p. 8 ; SOKOLOW, M. & LYON, T. *American heart journal*, **37** : 161 (1949).

levels remain elevated investigations should be carried out as in any patient with arterial hypertension.

9.4 Hypertension in the elderly

Hitherto it has been considered normal for older people to have an elevated pressure. It is now known that systolic or diastolic pressure elevations, even in the elderly, are associated with a greater risk.

10. MANAGEMENT OF HYPERTENSION

In general, most patients with chronic arterial hypertension have no identifiable cause for the disease. Treatment usually involves drug therapy, and this commits the patient and the physician to a long-term association. Prior to the institution of an antihypertensive regimen, however, general therapeutic measures are necessary.

10.1 General measures

Attention to matters affecting the general health is always advisable with a chronic illness. These include weight reduction, cessation of smoking, and moderation in alcohol ingestion. Rigid salt restriction has been demonstrated to be effective in lowering blood pressure but is not practicable in everyday life. Several studies have shown blood pressure reduction in mild hypertension by modest dietary salt restriction to 4–6 g daily.[1, 2] Further evidence of the value of salt restriction in the treatment of hypertension is necessary (see section 12).

10.2 Withdrawal of a drug responsible for hypertension

The majority of patients respond to the withdrawal of drugs that cause hypertension (see section 7.1), but those patients whose blood pressure remains high require evaluation and antihypertensive treatment.

10.3 Surgical treatment

Lesions that may be responsible for high blood pressure and are amenable to surgery have been discussed in section 7.2. However, surgery may not always be indicated for a variety of reasons, and treat-

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1 PARIJS, J. ET AL. *American heart journal*, **85** : 22 (1973).

2 MORGAN, T. ET AL. *Lancet*, **1** : 227 (1978).

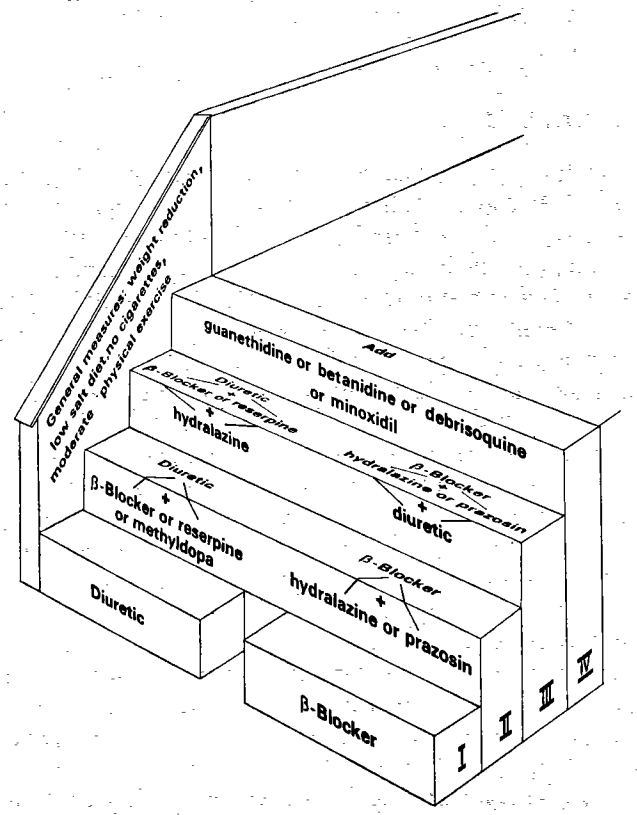
ment with antihypertensive drugs is then required. Moreover, only in some of those operated on will blood pressure subsequently fall to normal. Careful follow-up is necessary and institution of drug therapy may be required.

10.4 Drug treatment

Drug treatment is needed for the great majority of patients with essential hypertension and also for those in whom pressure does not fall to normal after correction of any identifiable cause. Effective treatment in adults can be regarded arbitrarily as maintained reduction of the casual blood pressure to 140/90 mmHg (18.7/12.0 kPa) or below, although treatment may be beneficial with less marked lowering of pressure. In most patients, it will not be necessary to reduce blood pressure rapidly. Indeed, a gradual lowering of blood pressure may be preferable, and a " stepped-care " programme (Fig. 2) may simplify therapy and reduce side-effects. It should be borne in mind that there are wide regional and national differences in the availability of drugs and in the kind of drugs most favoured. Economic considerations, especially the cost of drugs, are also important. The general principle of such a stepped-care programme is to begin treatment with an antihypertensive agent that may achieve only a modest reduction in pressure but which has relatively minor side-effects. The regimen progresses only to combinations of drugs if the simpler methods fail. The administration of two, three, or even more drugs with different mechanisms of action may be necessary to obtain control of blood pressure. The progressive addition of drugs in this scheme should be stepwise and systematic. In patients with severe hypertension, however, it may be advisable to start with a combined therapy, from which components may be withdrawn later when control of high blood pressure has been achieved.

The drugs most widely used for initial treatment are the thiazide and related diuretics or the beta-adrenoceptor blocking agents (β-blockers). In a second step, if necessary, these two agents may be prescribed in combination, or either of them may be combined with other antihypertensive drugs such as reserpine, methyldopa, hydralazine, or prazosin. In a third step, three of the above quoted drugs are given simultaneously, leading to combinations such as diuretic + β-blocker + hydralazine, or diuretic + β-blocker + prazosin, or diuretic + reserpine + hydralazine. In a fourth step still another potent drug such as guanethidine, betanidine, debrisoquine, or minoxidil may be added to any of the above

Fig. 2. Stepped-care therapeutic programmes



combinations. Drug treatment should always be accompanied by general measures such as weight reduction, low-salt diet, moderate physical exercise, and abstention from smoking.

When patients do not respond satisfactorily or become resistant to treatment, the physician should reassess the entire programme and pay particular attention to the patient's compliance with the prescribed drug regimen, the adequacy of the diuretic drugs, and the correct selection of drug combinations, the individual components being given at the maximum tolerable dose.

Particular care must be taken in lowering pressure in elderly patients. Such individuals are especially liable to postural hypotension and fluid and electrolyte imbalance. Depression and confusion frequently occur,

as does constipation or diarrhoea. A long-term study in elderly patients is in progress to evaluate critically the benefits to them of antihypertensive therapy.[1]

The reader is referred to Annex 1 on the pharmacology of antihypertensive drugs for a more detailed description of the compounds available.

10.4.1 *Monitoring of drug treatment*

On initiating new treatment and while going through the " stepped-programme " until the desired reduction in blood pressure is achieved, the hypertensive patient should be seen at frequent intervals, according to the severity of the initial blood pressure levels, the promptness of the therapeutic response, the type of drug regimen chosen, and the nature of any side-effects. When the desired reduction is attained, the patient will be seen at more spaced intervals, e.g., every 2 months during the first 6 months of treatment, and then 2–3 times a year. The frequency of visits will naturally depend on the severity of the disease. Laboratory examinations should be repeated when the blood pressure is under control and subsequently once or twice a year. Electrocardiography and measurement of plasma creatinine concentration will be used to monitor the evolution of cardiac and renal damage. Plasma potassium, blood glucose, and plasma uric acid will also be measured if a diuretic is used.

10.4.2 *Treatment of a hypertensive crisis*

Even in the accelerated (malignant) phase of hypertension, although prompt reduction of blood pressure is needed, intravenous therapy is used only rarely—for example, if there is impending or established hypertensive encephalopathy and/or hypertensive heart failure.

Until recently, diazoxide by bolus injection has been the favoured form of intravenous therapy. The substance is made up in an alkaline solution, which can be irritant if extravasated. An alternative vasodilator is hydralazine, which also can be given intravenously. Since intravenous diazoxide and hydralazine stimulate the heart rate, they should not be given to patients with ischaemic heart disease or dissecting aneurysm unless the myocardium is protected with beta-adrenoceptor blocking drugs; nor should they be given to patients with cardiac failure. Intravenous labetalol, which does not cause tachycardia, can be given either by repeated incremental injection or by graded intravenous

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[1] AMERY, A. & DE SCHAEPDRIVER, A. *Clinical science and molecular medicine*, **45**, Suppl. 1 : 71 (1973).

infusion. Sodium nitroprusside, given by intravenous infusion, provides precise control of blood pressure ; however, pressure rapidly reverts to preinfusion levels when the infusion is stopped.

If there is associated heart failure it is advisable to include an intravenous injection of a diuretic acting on the loop of Henle, such as furosemide or etacrynic acid.

10.4.3 *Specific drug treatment for hypertension of identifiable origin*

Specific antihypertensive drug therapy can be given for phaeochromocytoma and for primary hyperaldosteronism. Such therapy may be definitive or it may precede surgery.

For phaeochromocytoma, both alpha- and beta-adrenoceptor blocking agents should be given. It is important that beta-adrenoceptor blockade is not established before effective alpha-adrenoceptor blockade has been achieved, otherwise more intense peripheral vasoconstriction will lead to dangerous increases in pressure.

Spironolactone, triamterene, and amiloride have been shown to be effective in treating primary hyperaldosteronism. Both the hypertension and the electrolyte imbalances are corrected.

11. BENEFITS OF TREATMENT

Before the advent of effective antihypertensive agents, the onset of the accelerated phase inevitably meant a rapidly fatal outcome. The accelerated (malignant) phase can now be reversed, with clearing of exudative retinopathy and papilloedema and healing of the arteriolar lesions. It is important that in the accelerated phase treatment should be instituted promptly. If renal function has been severely impaired because of hypertensive vascular damage to the kidney, long-term haemodialysis may be necessary.

Beneficial effects of lowering blood pressure have been demonstrated in controlled trials in the USA studying selected male patients whose diastolic pressures were 105 mmHg (14 kPa) and more.[1] In these studies there was a high prevalence of cardiovascular complications at entry to the trial and a high subsequent morbidity in the controls, indicating the existence of moderate to severe hypertensive disease. The significant benefits observed were a reduction in the incidence of stroke and dissecting aneurysm and the prevention of cardiac failure. Similar trials

[1] VETERANS ADMINISTRATION STUDY GROUP ON ANTIHYPERTENSIVE AGENTS. *Journal of the American Medical Association*, **202** : 1028 (1967) ; **213** : 1143 (1970) ; *Circulation*, **45** : 991 (1972).

on subjects with diastolic pressures of 90–104 mmHg (12.0–13.9 kPa) showed some, but less clear, benefits from drug treatment. A controlled trial in the United Kingdom of male and female patients with diastolic pressures of at least 110 mmHg (14.7 kPa) similarly demonstrated reduction of strokes in men and, less clearly, in women.[1]

None of these studies demonstrated a statistically significant reduction in the incidence of myocardial infarction. The introduction of beta-adrenoceptor blocking agents as treatment for hypertension has excited considerable interest in this connexion, since controlled trials have shown that in patients with myocardial infarction these drugs can prevent sudden death and reinfarction. Several uncontrolled studies[2,3] have suggested that the use of beta-adrenoceptor blocking agents in the treatment of hypertension can reduce the incidence of first myocardial infarction and sudden death. These results require confirmation in controlled trials. Any such benefits could well be due to an action of the beta-adrenoceptor blocking agents independent of their effect on blood pressure.

The problem of whether or not to treat mild hypertension is at present unresolved. Population surveys have indicated that of people in the age group 45–64 years, 40% or more may have casual diastolic pressures of 90 mmHg (12 kPa) and above. At the same time, even with drugs producing only mild side-effects, there is a point at which these side-effects may become more important than the therapeutic benefits. With the most mild degrees of blood pressure elevation, even though reduction can be achieved, treatment may not be economically and socially justifiable. One of the most crucial issues at present is to define more exactly in different communities and races and in both sexes the level of blood pressure below which the benefits of treatment are outweighed by the disadvantages. A number of controlled trials in mild hypertension are being conducted at present in various parts of the world with the aim of clarifying these issues.

12. PREVENTION

12.1 Prevention of essential hypertension

Since the cause or causes of essential hypertension remain unknown, any specific recommendations for prevention are purely conjectural.

[1] HAMILTON, M. ET AL. *Lancet*, **1**: 235 (1964).
[2] STEWART, I. *Clinical science and molecular medicine*, **51**, Suppl. 3 : 509 (1976).
[3] BERGLUND, G. ET AL. *Lancet*, **1**: 1 (1978).

A number of factors may influence the development of hypertension, but no intervention studies have yet been carried out to test their value. However, hopes of preventing essential hypertension and the increased pressure associated with aging have been strengthened by studies of populations with low blood pressure. These studies indicate that the factors to be considered in prophylaxis include reduction in weight and in the use of dietary salt, physical training, behavioural education, and if possible the elimination or moderation of adverse psychological and social influences.

12.1.1 *Weight control*

In both adults and children, body weight is directly related to the blood pressure level, while reduction in weight achieves proportionate lessening of arterial pressure. Therefore, long-term weight control may be an important preventive measure. It is strongly recommended that community-based experimental trials of primary prevention of high blood pressure by diet and weight control be initiated.

12.1.2 *Control of salt intake*

Population studies have shown that different communities may have highly significant differences in habitual salt intake and that those communities in which blood pressures are lower have notably lower salt intakes than those in which blood pressures are high. Increasing emphasis is now being placed on the desirability of salt intake being kept below 3–5 g per day. Nevertheless the role of salt intake in pathogenesis is not clear, and controlled trials are needed to evaluate the effect of salt restriction in the primary prevention of hypertension. A tentative case can perhaps be made for encouraging a more prudent use of salt in groups at high risk.

12.1.3 *Physical activity*

Physical exercise may have an indirect effect on blood pressure by reducing body weight. A few studies have also shown a significant reduction of blood pressure with physical training. However, the effect of exercise on established hypertension is unknown, and it is also not known what effect regular physical activity may have in the prevention of hypertension. Furthermore, there is no evidence that physical inactivity is a risk factor for hypertension. Controlled trials on the effect of physical exercise on various levels of increased blood pressure are recommended.

12.1.4 *Behavioural approaches*

There is no definite evidence that behavioural procedures such as biofeedback, relaxation, psychotherapy, yoga, and transcendental meditation can lead to sustained lowering of blood pressure. Such measures deserve further study.

12.1.5 *Psychological and social influences*

Prolonged adverse psychological and social factors have not been proved to contribute to blood pressure elevation, although both could well be relevant. This is a large and potentially profitable area for future research.

12.2 Prevention of secondary hypertension

A small, but important, contribution to the prevention of hypertension will be achieved by the more effective identification, surveillance, and management of subjects with these conditions. The uncertain role of chronic urinary tract infection in the pathogenesis of hypertension is emphasized, and further research in this area is recommended. Discouragement of abuse of analgesic drugs (especially phenacetin) is an important measure already adopted with success in several countries.

The rise in blood pressure with hormonal contraceptive therapy is not sufficiently widely recognized. It is recommended that women intending to take estrogen-progestogen pills should do so only after a blood pressure measurement. Moreover, the blood pressure should be checked every three or six months. It is not appropriate for anyone with established hypertension to receive estrogen-progestogen oral contraceptives. Research is recommended on the mechanism of the rise in blood pressure in women receiving oral contraceptive therapy and on the hypertensive effect of different oral contraceptives. It is not known whether the progestogen-only pill causes a similar rise in blood pressure. Answers to these questions are urgently needed.

13. CONTROL OF HYPERTENSION IN POPULATIONS

Hypertension is very common in most populations of the world and is responsible for much morbidity and mortality. Probably half the people with elevated blood pressure are not known to the medical profession and do not know of their own condition. However, hypertension can be identified and effectively treated, and a control programme

is justified provided that the resources are available. Control of hypertension among the population requires a wide range of public actions adapted to local (i.e., national, provincial, and regional) circumstances, resources, and constraints.

13.1 Definitions

The term " hypertension control " includes all measures for health protection and promotion related to high blood pressure. " Control programme " is the term applied to a set of widely ranging public health actions aimed at hypertension control.

13.2 Aims and scope

Hypertension control programmes may be established at international, national, regional, departmental, communal, or neighbourhood level. They may cover the general population of an area or defined occupational groups, such as workers in industrial plants. Bodies responsible for initiating and operating hypertension control programmes may be intergovernmental organizations, government health agencies, international or national scientific, lay, or mixed societies (such as heart associations or foundations and antihypertension leagues), and community health authorities.

Because of the particularly wide range of the health problems caused by hypertension, control programmes to be applied in populations should be specific (i.e., adequately focused on hypertension), but at the same time they should form part of a comprehensive programme covering many other important aspects of health. Thus in a developing country with insufficient numbers of health workers, a hypertension control programme should not drain the already scarce health manpower but should if possible employ medical assistants within the context of their usual activities. For example, where hormonal contraceptives are being dispensed in family planning clinics, a hypertension control programme should closely cooperate with those clinics and use them as a basis for detecting hypertension. In countries where ischaemic heart disease is common, hypertension control should be part of a comprehensive project for the control of cardiovascular or chronic diseases. The optimum choice of a specific and/or comprehensive approach depends on the varied epidemiological, health care, and socioeconomic circumstances of a given population.

13.3 Community control programmes

Considerable experience has been gained during the past decade with community programmes for the control of hypertension—" community " in this context meaning a group of people with common characteristics, living in a defined geographical area, or belonging to a certain occupational group, and comprising usually between tens of thousands and hundreds of thousands of people. This experience shows that programmes are most effective if integrated into existing health care systems in the community; the establishment of new units or organizations specifically for this purpose is not generally advisable. It therefore follows that a prerequisite for launching an effective programme is a careful assessment of existing health service resources. Detailed local epidemiological and socioeconomic data are a great asset, and the full cooperation of health personnel, public health authorities, and the public is essential.

Hypertension requires continued treatment, and screening should not be carried out unless resources are available to provide for the care and long-term follow-up of patients.

An adequate system for recording, storing, and retrieving data should be provided, using existing facilities as far as possible. This is essential for carrying out surveillance and evaluating the effects of the programme.

In some developing countries the control of hypertension may be considered in connexion with primary health care programmes. This naturally requires further study. There is a need for technology appropriate to community health workers who may be illiterate. The cost-effectiveness of various approaches must be evaluated.

13.4 Detection and follow-up

It is emphasized that unless the existing health care system is able to cope with the identified hypertensive patients a programme of detection and follow-up should not be initiated. In some countries evidence has shown that around 80% of the population consult a doctor within a period of three years. Therefore, if blood pressures were measured at such physician visits (incidental screening), a major portion of the hypertensive subjects in the community would be detected every few years. Efforts to increase the interest of all physicians and their assistants in recording blood pressures in the office, clinic, or hospital and in taking suitable action concerning evaluation, referral, and long-term treatment are now being adopted in many countries and should be encouraged in

others. Dentists and public health personnel could also play a part in blood pressure screening of this type.

Screening covering entire communities and combined with other health programmes has alternatively been shown to be feasible as a relatively inexpensive method of identifying hypertensive subjects. However, such programmes can be recommended only if there are resources for referral of the hypertensive subject to the medical care system for evaluation and management. In China and Cuba, large-scale programmes are now being conducted in which screening and the follow-up of hypertensive patients are carried out by physicians, health assistants, and medical students.

A central problem is the ability of the patient to adhere faithfully to the prescriber's instructions (" compliance "). Experience in the USA has shown that only about 60% of individuals with hypertension at initial screening will be adequately followed and even fewer will be effectively treated. In other countries, especially where a close collaboration between screening and follow-up has been achieved, the success rate is higher. This aspect requires a specific analysis and approach in each local community.

13.5 Investigation and treatment

The clinical examination of patients with hypertension is set out in section 9. Therapy may follow a standard approach, but with treatment adjusted appropriately for each individual and community.

13.6 Education

13.6.1 *Education of health personnel*

Health personnel at all levels should be advised about the programme before it begins. Their support should be sought early and they should be involved in the planning, implementation, and evaluation of the programme. Basic instruction should include : the principles and methods of health education ; simple physiological facts about the circulation ; blood pressure regulation under normal circumstances and in the presence of hypertension ; the causes and consequences of hypertension and the methods of detecting and treating it ; and advice concerning the education of the patient.

13.6.2 *Patient education*

Clear basic information is needed to motivate the patient to accept long-term treatment. In presenting this information, the physician or

health worker should take account of each patient's educational level. The aim is to gain his cooperation and to ensure that he understands his illness, his medication, and other aspects of treatment such as weight reduction. Information on the various resources available to him should also be given. Some patients can be trained to measure their own blood pressure. Education of this kind can be conducted in the physician's office, the health clinic, the hospital, the home, or the workplace. The methods used will vary and could include individual and group education using audiovisual materials.

13.6.3 *Public education*

The aim of public education is to engender a sense of responsibility towards the control programme. This can be carried out by all health workers who engage in patient education but particularly by those in the preventive health services. The press, radio, and television are powerful media for health education, and in some countries volunteer organizations, heart foundations, leagues against hypertension, and other bodies perform valuable educational functions. School health education, including the instruction of teachers, can also be useful in hypertension control. As with all health education it is important not to create a demand that cannot be met.

13.7 Evaluation

The impact of the programme should be assessed by methods generally used in the evaluation of health programmes. The assessment should include the effect of the programme on public awareness of the problem, on blood pressure distributions, and in the long term on morbidity and mortality. Randomizing communities into intervention and nonintervention groups can provide an important means of evaluation.

14. CONCLUSIONS AND RECOMMENDATIONS

Hypertension is a massive health problem affecting at least 8% of the adult population in most countries. Because it causes high morbidity, invalidism, and death and because it can be identified easily and treated effectively, the Expert Committee strongly recommends that the public health authorities of each country give prompt attention to this disease.

The present report provides an outline of the existing state of knowledge of the hypertension problem and of the means of assessing and treating patients. It makes suggestions for a community approach to prevention and control in countries having varied health care systems, and, most important, recommends research for closing major existing gaps in knowledge.

1. Arterial blood pressure should be measured in every individual, using standardized methods described herein, to identify those who may require observation and treatment.

2. The use of the proposed classification of hypertension is recommended to facilitate comparison of patients and population groups and to evaluate risks of complications and benefits of therapy.

3. It is recommended that for purposes of classification people with arterial pressures equal to or above 160 mmHg (21.3 kPa) systolic and/or 95 mmHg (12.7 kPa) diastolic (average of three readings taken on at least two occasions) be arbitrarily considered as having hypertension.

4. The etiology is unknown in over 95% of cases of elevated blood pressure. Few data are available from community-based studies on the prevalence of the various types of hypertension that do have an identifiable cause. The Committee therefore strongly recommends further research into the etiology and pathogenesis of essential hypertension as well as into the identification of etiological factors in the various forms of secondary hypertension. Prevention and more specific treatment will depend on the results of such research.

5. It is important to detect and study a predisposition to, as well as the actual presence of, hypertension in infants and young children, both to learn more about the earliest stages of elevated arterial pressure and to apply preventive and therapeutic measures at the most favourable time.

6. Preventive and general therapeutic measures may be forthcoming by ascertaining more precisely the role of weight control, dietary factors (e.g., salt, proteins, trace metals), alcohol consumption, and psychosocial and behavioural factors. Controlled intervention trials in these fields are recommended.

7. The benefits of antihypertensive drug therapy have been demonstrated most clearly for patients suffering from moderate to severe hypertension. Since these trials were predominantly concerned with male patients, it is recommended that further studies include females. Con-

tinuing prospective trials should provide further information on mild hypertension, as well as on hypertension in elderly individuals of both sexes. It is suggested that critical quantitative evaluation be made of the benefits of reducing blood pressure to various levels by drug treatment and other methods.

8. Although hormonal contraceptives are widely used, it is not sufficiently appreciated that they may elevate blood pressure and may account for a substantial proportion of secondary hypertension in women. Therefore, it is urgently recommended that the role of each component of hormonal contraceptives in elevating pressure and the mechanism of the pressure elevation be determined. Until these factors are known and modified, women using oral contraceptives should be warned of the risk of hypertension. Research programmes relating to family planning and hypertension should be pursued with high priority.

9. Once an individual with hypertension is identified, evaluated clinically, and treated, the control of the problem and the compliance of the patient will be ensured only by a clear understanding by the patient of his disease and by the continuing interest of the physician and allied health personnel in the patient and his condition. It is recommended that studies be initiated to facilitate better understanding of the problems of compliance.

10. Successful control of hypertension in a population is based on an effective community control programme. This requires an assessment of existing health service resources, which, whenever possible, should be utilized in preference to the creation of new ones. There is need for the full cooperation of all individuals involved—health personnel, patients, volunteer helpers, and the general public—if the health resources are to be used with greatest efficiency.

11. The problem of hypertension exists in countries whose economic resources are only now being developed. To this end, the report deals with simple means of detection, diagnosis, and treatment. Nevertheless, the Committee strongly urges the development of new and still simpler techniques in these areas.

12. When hypertension programmes are established in communities —whether in more industrialized or in developing countries—they should be fully adapted to local circumstances and subjected to continuous evaluation.

13. Despite important achievements in understanding the mechanisms underlying hypertension, in synthesizing chemical compounds

for its treatment, and in significantly reducing morbidity and mortality from hypertensive cardiovascular disease, it is necessary to obtain further knowledge of the control of arterial pressure, to elucidate the cause or causes of essential hypertension, and to develop new approaches to prevention and therapy. The Committee therefore strongly recommends continued research in these areas.

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Annex 1

ANTIHYPERTENSIVE AGENTS

Hypertension is today one of the few chronic diseases that can be controlled by drugs—a result of continuous research and development over the past 20 years. The various drugs or classes of drugs differ in their pharmacodynamic properties and modes of action, which makes it possible to influence different mechanisms involved in the regulation of blood pressure. Hence, the combined use of two or even three types of antihypertensive agent may result in an additive or synergistic effect. Antihypertensive drugs fall into four major categories :

(1) agents that interfere with the activity of the sympathetic system,
(2) vasodilators that relax vascular smooth muscle,
(3) diuretics, and
(4) drugs that interfere with the renin-angiotensin system.

Drugs acting on the sympathetic nervous system

These drugs affect the central sympathetic areas in the brainstem where alpha-adrenoceptors are located. Some of them may deplete the central stores of catecholamines.

Methyldopa enters the brain, where it is decarboxylated to alpha-methyldopamine and then, by beta-hydroxylation, transformed into alpha-methylnoradrenaline. The latter is a peripheral vasoconstrictor, but when it acts centrally on alpha-adrenoceptors it lowers arterial pressure. Alpha-methylnoradrenaline is found in peripheral adrenergic nerve endings where it acts as a " false " transmitter.

Clonidine, also a peripheral vasoconstrictor, passes the blood-brain barrier and acts on central alpha-adrenoceptors, reducing the central sympathetic outflow to reduce arterial pressure. When clonidine is withdrawn suddenly, catecholamine output increases and may remain at a high level for several days, accompanied by dangerous rebound hypertension and arrhythmias. The drug should therefore be used with great caution.

The antihypertensive effects of methyldopa and clonidine may be partly due to the stimulation of presynaptic alpha-receptors, which inhibits neurotransmitter release from peripheral sympathetic neurones.

Reserpine also acts centrally, depleting hypothalamic and other central stores of noradrenaline, dopamine, and serotonin. It acts similarly in the periphery, where it interferes with noradrenaline reuptake at the adrenergic neuroeffector junction and with the granular storage of noradrenaline in the nerve endings. A major part of its antihypertensive effect appears to be due to this peripheral action.

All three of these centrally acting drugs cause sedation or may induce or unmask depression. Dry mouth and nasal stuffiness are other side-effects. Fever and hypersensitivity hepatitis have been reported with methyldopa, though rarely. Reduced sexual potency and libido have also been described.

Ganglionic blocking drugs are competitive antagonists to acetylcholine at the ganglionic synapses. They cause a marked, mainly orthostatic, hypotension. Because parasympathetic as well as sympathetic transmission is interrupted, these agents induce a variety of unwanted side-reactions, including blurred vision, dry mouth, constipation, and impotence. In the chronic treatment of hypertension they are now of only historic interest.

Guanethidine, *betanidine*, and *debrisoquine* interfere with the storage and release of noradrenaline at adrenergic nerve endings. They enter these nerve endings and partially replace noradrenaline at its storage sites; they also inhibit the reuptake of noradrenaline. The resulting "chemical sympathectomy" produces a marked antihypertensive effect with a distinct orthostatic component. These drugs are generally reserved for severely hypertensive patients whose condition is not readily controlled by other means. Diarrhoea and, in the male, retrograde ejaculation may occur. Tricyclic antidepressants interfere with the action of the drugs on the reuptake of noradrenaline.

Beta-adrenoceptor blocking agents, while representing the most important contribution to antihypertensive therapy during the past decade, have a mode of action that is as yet imperfectly understood. Numerous products are available differing in their relative cardioselectivity, intrinsic sympathomimetic (agonist) activity, metabolism, and duration of action. Despite these variations all appear to have a similar antihypertensive effect. The immediate reduction in heart rate and cardiac output that they induce does not seem to be responsible for their later antihypertensive effect. Suppression of the renin-angiotensin system, although it may be a component in some patients with high levels of renin, cannot be responsible for the lowering of blood pressure induced in most patients with uncomplicated essential hypertension.

Plasma renin activity estimation has not proved reliable as a guide to whether or not a beta-adrenoceptor blocking agent will be effective in any given case. Although a central site of action cannot be excluded at present, there is no clear understanding of how this may occur. The hypotensive effect of these agents is only moderate, but it is achieved in both standing and recumbent positions with no orthostatic reactions. These features alone make them acceptable. However, these agents should not (unless accompanied by digitalis and/or diuretics) be used in patients with congestive heart failure, marked bradycardia, atrioventricular block, obstructive lung disease (e.g., asthma), or peripheral arterial insufficiency (e.g., intermittent claudication or Raynaud's phenomenon).

Alpha-adrenoceptor blocking agents such as phentolamine, phenoxybenzamine, and the hydrogenated ergot alkoloids, have no useful hypotensive effect, except in phaeochromocytoma. However, a new development is the combination of alpha- and beta-adrenoceptor blocking activity in the same compound. One such drug, labetalol, has been introduced and may be used orally in the treatment of both essential hypertension and phaeochromocytoma. In the latter circumstance, the ability to block both alpha- and beta-adrenergic receptors has the advantage of lowering both blood pressure and the incidence of cardiac arrhythmias. Initial studies with intravenous labetalol for hypertensive emergencies have also been promising, because the drug does not induce tachycardia as pressure is reduced. Contraindications to labetalol are similar to those for the beta-adrenoceptor blocking drugs.

Prazosin is a new type of alpha-adrenoceptor blocking agent, differing from others in having its main effect on postsynaptic alpha-adrenergic receptors. Nevertheless, the drug does not produce marked tachycardia. It is not known whether this different mechanism of action is of significance in its antihypertensive effect or whether an additional vasodilating component is also present. Caution is advised at the initial dose since orthostatic hypotension may occur.

Vasodilators

Hydralazine and *dihydralazine* both produce a fall in pressure and a reflex increase in heart rate through a peripheral action on vascular smooth muscle. The mechanism has not yet been elucidated. Because the hypotensive effect is partly associated with an increased heart rate, the drugs may with advantage be given together with a beta-adrenoceptor blocking agent. This combination will prevent tachycardia (and hence

the danger of angina pectoris) and headaches. A syndrome resembling that of systemic lupus erythematosus may occur with prolonged treatment when daily doses above 200 mg are used.

Diazoxide, chemically related to the thiazide diuretics but causing sodium retention, produces marked peripheral vasodilation. It must always be given with a diuretic agent. The hypotension is accompanied by tachycardia, which can be counteracted, at least in part, by beta-adrenoceptor blocking agents. An undesirable side-effect is inhibition of insulin release and subsequent diabetes mellitus. Use of the drug should therefore be restricted to the treatment of hypertensive emergencies, and the physician is warned about reports of myocardial ischaemia or infarction following its intravenous administration.

Minoxidil is one of the most effective drugs available for the control of hypertension. Its hypotensive effect induces a marked reflex tachycardia and fluid retention, and it must therefore be given in combination with a diuretic and a beta-adrenoceptor blocking agent (" triple therapy "). One unpleasant side-effect that limits its use is hypertrichosis.

Nitroprusside should be used only in hypertensive emergencies. Since it is rapidly metabolized, it must be given intravenously, its hypotensive effect being limited to the infusion period. Nitroprusside not only reduces arteriolar resistance but also acts on the capacitance vessels to reduce venous return to the heart. When given for prolonged periods cyanide poisoning may occur, but this can be prevented by thiosulfate. Sodium nitroprusside must be restricted to hospital use.

Diuretics

The mechanism by which diuretic drugs lower the blood pressure is complex. Given intravenously, they may have a prompt and sometimes powerful pressure-reducing effect. Given orally, thiazides have a mild antihypertensive effect that is associated initially with reduced plasma volume and cardiac output. With prolonged treatment there is a reduction in total peripheral resistance, associated with a maintained contraction of plasma and extracellular fluid volume. It seems likely that part of the mode of action results from a mechanism comparable to that achieved by low dietary sodium intake, but too few data are available to confirm this view.

Thiazides. Drugs of this group produce a slight but distinct lowering of arterial pressure, and for many years they have been the basic therapy

for mild hypertension. Because they enhance the excretion not only of sodium but also of potassium, hypokalaemia may develop, sometimes requiring the addition of potassium supplements or, preferably, potassium-conserving diuretics. The thiazides can cause an increase in blood sugar, uric acid, and circulating lipids.

Potassium-conserving diuretics. Drugs in this group, which include spironolactone, amiloride, and triamterene, have a weak natriuretic effect and produce a small reduction of blood pressure. They are nevertheless valuable in maintaining normokalaemia when given together with the thiazides. More specifically, spironolactone and amiloride may be employed in the preoperative or definitive therapy of primary hyperaldosteronism. Amiloride and triamterene produce their effect mainly on sodium and potassium exchange in the distal renal tubules. Spironolactone is a more specific aldosterone antagonist. Caution is advised with these agents in patients with renal insufficiency and in prescribing potassium supplements at the same time. Spironolactone often induces gynaecomastia and menstrual irregularities.

Loop diuretics. These powerful diuretics (furosemide, etacrynic acid, and bumetanide) produce a rapid natriuresis and an immediate vasodilation when given intravenously. They are valuable in the treatment of severe hypertension, particularly when there is accompanying cardiac failure, fluid retention, or renal insufficiency. None is recommended for the long-term treatment of hypertension except in cases of renal failure. Since they also produce hypokalaemia they should be used with great caution in patients receiving digitalis. In elderly male patients with prostatic enlargement the rapid diuresis may produce acute urinary retention.

Drugs selectively interfering with the renin-angiotensin system

In cases of renin-dependent hypertension, pressure may be lowered by administering antagonists or inhibitors of the action of the renin-angiotensin system. Two main types of agent are being investigated: (1) synthetic analogues and competitive antagonists of angiotensin II and (2) inhibitors of the enzyme responsible for converting the inactive angiotensin I into the active peptide angiotensin II. Enzyme inhibitors may also cause an accumulation of circulating bradykinin, which may contribute to their antihypertensive effect.

Annex 2

RESEARCH ON HIGH BLOOD PRESSURE

Research on the pathogenesis of hypertension has greatly improved our understanding of the mechanisms underlying the chronic elevation of blood pressure. In animals as in man hypertension may be the primary manifestation of a genetic disorder or the consequence of some other pathological event. Hence, both in man and in animals, we can distinguish between essential and secondary hypertension, the latter being subdivided into renal, endocrine, neurogenic, and dietary forms.

Hypertension is one of the human diseases that can be reproduced in experimental research. Various forms of experimental hypertension have been regarded as corresponding closely with some types of clinical hypertension, but it has to be kept in mind that the analogy between the experimental models and the human disease is often imperfect (see table).

Comparable forms of experimental and clinical hypertension

Experimental	Clinical
Spontaneous hypertension of rats	Essential hypertension (?)
Renal artery stenosis (rat, rabbit, dog)	Renovascular hypertension
Renal infarction (rat, rabbit)	Renal infarction
Perinephritis (wrapping, figure-of-8 ligature) (rat, dog)	Perinephric haematoma
Overdose of glucocorticoids (rat)	Cushing's syndrome
Overdose of mineralocorticoids (rat, pig)	Primary aldosteronism (adenoma, hyperplasia) ; overproduction of desoxycortone or corticosterone ; overdose of licorice
Overdose of salt (rat)	Chronic high salt intake
Subtotal nephrectomy (rat)	Various forms of renal damage ; loss of nephrons

Nevertheless, each experimental model of hypertension has been useful in facilitating understanding of pressor mechanisms as well as of modes of action of antihypertensive drugs. Experimental research has

given substantial insight into the role of the renin-angiotensin system in the maintenance of homoeostasis and in the chronic elevation of blood pressure in renal artery stenosis and related disorders. Evidence has also been provided that the stimulation of the renin system by sodium depletion may contribute to the maintenance of normal blood pressure. This research has been of importance for providing insight not only into the pathogenesis of renal hypertension in human beings but also into the role of the renin-angiotensin system in the regulation of blood pressure in normal circumstances. Further, the development of sensitive methods for the measurement of catecholamines has provided new information on the contribution of the sympathetic nervous system in mineralocorticoid hypertension as well as in hereditary hypertension in rats.

Various rat strains with genetic hypertension have been bred independently in several laboratories. These animals may develop moderate to severe hypertension and also complications typical of the human disease, including myocardial haemorrhages and infarctions, cardiac hypertrophy, cardiac failure, and lesions in various vascular beds. Thus it has been possible to investigate the mechanisms responsible for these various complications as well as the factors that may influence their localization. Haemodynamic studies on some strains of spontaneously hypertensive rats have revealed that even at an early stage in the development of hypertension, the response to vasoconstrictor agents may be greater than normal, indicating that a primary vascular factor may be responsible for the increase in peripheral resistance. These and other haemodynamic investigations have greatly extended our understanding of hypertensive heart disease in man.

The study of spontaneous hypertension in rats has produced much knowledge applicable to man but it has also defined numerous problems that can be settled only by investigations in man. Hypertensive patients show changes not seen or not easily reproducible in experimental animals, such as borderline hypertension or hyperkinetic increase in blood pressure. Hence, although studies in experimental animals can be of help in the analysis of haemodynamic factors in human hypertension, they can never replace investigations in humans.

As indicated, experimental models of hypertension are useful tools for research on new antihypertensive agents. Although most drugs used in the treatment of high blood pressure in humans also reduce pressure in normal animals, their administration in animals with different types of hypertension not only helps in the understanding of their mode of action but indicates in which type of hypertension they might best be

used. It has also been demonstrated that by antihypertensive drug treatment, as well as by dietary measures such as reduced sodium intake, the incidence and severity of complications can be reduced. Although care has to be taken not to extrapolate from these observations in animals to human disease, the findings are of great value and should stimulate further research.

Annex 3

TERMS USED IN THE REPORT

In the course of its deliberations the Expert Committee considered certain terms that are widely used in the field of hypertension and assigned the following meanings to them.

accelerated (malignant phase) hypertension : rapidly progressing arterial hypertension characterized pathologically by necrotizing arteritis with fibrinoid degeneration and clinically by high arterial pressure, retinal haemorrhages and exudates, and often, but not necessarily, papilloedema.

arterial hypertension : a clinically elevated systolic arterial pressure ($\geqslant$ 160 mmHg or 21.3 kPa) and/or diastolic arterial pressure ($\geqslant$ 95 mmHg or 12.7 kPa).

average blood pressure : the arithmetic mean of several pressure measurements made on one subject and relating to systolic pressure, or to diastolic pressure, or to mean arterial pressure.

borderline hypertension : arterial pressure levels of 140–160 mmHg (18.7–21.3 kPa) systolic and/or 90–95 mmHg (12.0–12.7 kPa) diastolic. This term is also used to refer to arterial pressure characteristics in patients whose pressures at times are less than 140/90 mmHg (18.7/12.0 kPa) but at other times are greater than this level. " Labile hypertension ", the term formerly used to describe this second condition, is deprecated because all pressures are labile.

casual blood pressure : an arterial pressure reading obtained without any major preparation of the subject (see section 3 of the report for more precise methodology).

compliance : strict adherence by the patient to the prescriber's instructions.

diastolic hypertension : diastolic arterial pressure equal to or greater than 95 mmHg (12.7 kPa).

essential hypertension : hypertension of undetermined cause ; primary hypertension.

high blood pressure : see arterial hypertension.

labile hypertension : deprecated ; see borderline hypertension.

malignant hypertension : see accelerated hypertension.

mean arterial pressure : an integrated mean arterial pressure usually obtained from a single arterial pressure pulse curve (although it may be taken as the sum of the diastolic pressure plus one-third of the arterial pulse pressure).

primary hypertension : see essential hypertension.

risk factor : a factor that is significantly associated with the development of a disease.

secondary hypertension : hypertension attributable to an identifiable cause.

systolic hypertension : systolic arterial pressure equal to or greater than 160 mmHg (21.3 kPa).