To delineate the role of nutrition in the regulation of blood pressure and the pathogenesis of hypertension, the National Heart, Lung, and Blood Institute in conjunction with the National Institute on Aging and the National Institutes of Health Nutrition Coordinating Committee, sponsored a Workshop on Nutrition and Hypertension in Bethesda, Maryland, on March 12 to 14, 1984. The purpose of the workshop was to identify the research needed to strengthen the understanding of the relationships between nutrition, blood pressure regulation, and hypertension. This research is important for two reasons: first, there is still an enormous amount of knowledge to be gained about the pathogenesis of hypertension, and any insights that can be derived about nutritional influences are highly desirable. Second, because the majority of patients with elevated blood pressure fall in the borderline and mild hypertensive categories, there is a need to support research on nonpharmacological strategies for management of these patients, in particular, nutritional interventions. The format of the workshop consisted of two major activities: position papers on selected dietary nutrients that may influence blood pressure and working group sessions devoted to the specification of research objectives. In addition to touching on an overview of hypertension and nutrition research methods, the position papers expounded on the roles of sodium and other electrolytes; caloric intake and obesity; dietary proteins, amino acids, carbohydrates, alcohol, and trace metals; and dietary fats and prostaglandins. Nutritional considerations of special populations, including the young and the elderly, also were addressed. The working groups charged with delineating short-term and long-term research objectives were organized along similar lines. The following is a synopsis of what transpired during the workshop.

**Electrolytes**

Is blood pressure responsiveness to dietary electrolytes related to age? Race? Interaction with other nutrients? Is there a dose-response relationship between dietary electrolyte consumption and blood pressure? Can subgroups of susceptible persons be identified? Approaches to these questions should include hemodynamic, neurobiological, and hormonal considerations with studies at the cellular and molecular levels. Electrolyte consumption studies in the young designed to determine the influence of such consumption on taste preference, as well as on the status of future physiological variables including blood pressure, need to be performed.

**Sodium Chloride**

In cross-cultural studies the prevalence of hypertension appears to be related to the magnitude of sodium chloride consumption. However, interpretation of these studies is limited by cultural differences other than sodium chloride intake and by questionable reliability of the estimates of dietary sodium chloride intake. A few studies with small numbers of hypertensive subjects suggest that elevated arterial pressure can be reduced by modest sodium chloride restriction. Populations and individuals vary in their sensitivity to short-term and long-term sodium chloride loading and deprivation. Susceptibility to sodium chloride may be determined by genetic and environmental factors. Sodium chloride sensitivity should be considered in quantitative rather than qualitative terms (i.e., it is not an all or none phenomenon).

Among the questions in need of further scientific investigation are the following: How can sodium chloride–sensitive persons be identified? What percentages of the normotensive and hypertensive populations are salt sensitive? Does modest sodium chloride
restriction prevent hypertension? In susceptible persons, is comparable sodium chloride restriction required for both prevention and treatment of hypertension? Is sodium chloride consumption at a young age predictive of blood pressure at a later age? Are there persons whose health would be threatened by modest sodium chloride restriction? Would altering the diet to achieve modest sodium chloride restriction cause a deficiency of other nutrients? In some hypertensive persons, does sodium chloride restriction result in paradoxical increases of blood pressure? What is the effect of modest sodium chloride restriction on doses of antihypertensive drugs required to achieve blood pressure control? Does sodium chloride affect blood pressure by way of the chloride ion? Is the effect of dietary sodium chloride on blood pressure mediated by calcium?

**Potassium**

Epidemiological evidence suggests that there is an association between high dietary potassium intake and lower blood pressures. A high potassium diet has been shown to lower blood pressure in animal models of hypertension and in human essential hypertension.

Among the questions in need of further scientific investigation are the following: Can the effects of dietary potassium be separated from sodium? Is it potassium or the dietary sodium/potassium ratio that is important? Can a subgroup of potassium-sensitive hypertensive persons be identified? What is the mechanism by which potassium influences blood pressure?

**Calcium**

There is suggestive evidence for an association between low dietary intake of calcium and high blood pressure in humans. Recent evidence also suggests a hypotensive effect of calcium loading on experimental hypertension and in some patients with essential hypertension. Recent evidence also suggests a hypotensive effect of magnesium on blood pressure.

Among the questions linking dietary magnesium to blood pressure in need of further investigations are the following: Does dietary magnesium affect blood pressure? Is there any identifiable disorder of magnesium in hypertension? What is the relationship of dietary magnesium to other dietary constituents? What is the relationship of plasma and intracellular magnesium to calcium, sodium, plasma renin activity, and other biochemical parameters?

**Obesity**

Overweight or obesity refers to states of excess weight or adiposity relative to arbitrarily defined population norms for weight or adiposity. It is well established that adults who are overweight or obese incur an increased risk of becoming hypertensive.

In economically advanced countries, the incidences of hypertension and obesity increase in adults as they age. However, the incidence of hypertension does not increase or increases only slightly in developing countries whose adult populations do not show much fat accumulation between the age of 20 and 70.

Obesity/overweight is not a homogeneous disorder. Several types of obesity can be characterized by differences such as the pattern of fat distribution, adipose tissue morphology, body composition, age of onset, family history, and differences in hormonal and biochemical status.

Obese persons with borderline hypertension seem to be characterized hemodynamically by plasma volume expansion and increased cardiac output. The increase in cardiac output appears to be caused by the increased venous return (cardiopulmonary volume) to the heart. Normotensive, obese individuals tend to have dilatation of the left ventricle, perhaps related to an increased blood volume or venaconstriction or both.

Obesity is also associated with endocrine changes that may help to explain the predisposition of obese persons for becoming hypertensive. These changes include increased secretion of norepinephrine, renin, aldosterone, insulin, and triiodothyronine.

Current research efforts attempting to explain relationships between obesity, blood pressure control, and hypertension should be extended to more adequately clarify these relationships. To be meaningful, such studies should be designed to control for the many variables that could confound results. This requires taking into account several classes of variables including:

**Morphometric variables**

- Body build
- Body composition
- Pattern of body fat distribution
- Adipose tissue morphology
Hemodynamic variables  
   Plasma volume 
   Cardiac output 
   Cardiopulmonary blood volume 

Morphological variables  
   Heart size 
   Chamber volume 
   Ventricular wall thickness 

Endocrinological variables  
   Basal and stimulated plasma inulin concentrations 
   Plasma concentrations of norepinephrine, renin, aldosterone, thyroid hormones, corticosteroids, human growth hormone, and others 
   Growth hormone response to insulin-induced hypoglycemia 

Sociodemographic and clinical variables  
   Age 
   Sex 
   Race 
   Family history of obesity 
   Family history of hypertension 
   Smoking habits 
   Use of alcohol 
   Physical activity level 
   Personality type 
   Habitual diet 

Biochemical variables  
   Dietary intake and plasma levels of sodium, potassium, calcium, magnesium, and other elements 

Hypertensive disease-related variables  
   Type of hypertension 
   Severity of hypertension 
   Presence of hypertensive complications 
   Past and present use of antihypertensive medications 

These listed items are examples of factors that may represent important determinants linking obesity with hypertension or that may represent variables, which if not controlled, can confound results of otherwise carefully planned studies.

In view of the obvious difficulty of controlling for the many variables that could seriously flaw investigations of this problem in human subjects, special consideration should be given to the identification or development of suitable animal models for study of the obesity-hypertension problem. In this way, confounding variables can be minimized and investigators can systematically search for the factors associated with obesity/overweight that are principally (or solely) responsible for the obese person's predisposition to hypertension.

Proteins and Amino Acids

Studies in experimental animals, especially rats prone to hypertension, suggest that the amino acid tyrosine appears to influence blood pressure. Other amino acids that may alter blood pressure are tryptophan, methionine, and taurine. These amino acids probably act within the brain by affecting neurotransmitters; however, mechanisms for their effects are not well understood, and more investigation is needed.

In hypertensive rats that are prone to cerebrovascular lesions, the protein content of the diet appears to influence the likelihood for these lesions to occur. Low protein diets enhance the incidence of stroke, while an increase in dietary protein appears to reduce development of cerebrovascular lesions. One possibility is that the integrity of the cerebral vasculature depends on an adequate intake of protein. If so, low protein diets may predispose subjects to rupture of blood vessels.

Dietary protein and amino acids could affect development of hypertension in other ways. For instance, different amino acids may have variable effects on the metabolism of electrolytes, namely, sodium, potassium, and calcium. Few if any studies have been carried out to examine these possible interrelationships.

More epidemiological studies are needed to examine the importance of proteins in the causation of hypertension. Some populations eat mainly vegetable proteins, while others ingest predominantly animal proteins. These populations should be compared. Also, some populations ingest low protein diets, and others eat high protein diets. Again, comparisons could be made. Differences in blood pressures should be sought, and a variety of other metabolic parameters should be studied, including plasma distribution of amino acids.

While the possible dangers of a low protein diet for predisposition to stroke are intriguing, there is a subset of persons in the hypertensive population for whom high protein diets could be dangerous. These are persons with progressive renal dysfunction. High protein diets may accelerate loss of renal function, and in these populations, low protein diets may retard the progression of renal disease. The National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases has already solicited proposals for a clinical trial to study this possibility. When this trial is executed, particular attention should be given to whether strokes are more common in subjects who are on the low protein diet.

Carbohydrates

There appears to be an interaction between carbohydrate metabolism and sodium metabolism. Through this interaction dietary carbohydrates might have an influence on blood pressure. For example, high carbohydrate loads have been shown to affect excretion of sodium. Studies on sodium excretion during fasting and with short-term carbohydrate loading might lead to the development of a provocative test to determine who has latent hypertension.

The long-term effects of a high carbohydrate diet on sodium metabolism and blood pressure regulation are unknown. An interesting possibility is that a high sodium, high carbohydrate diet may predispose to hypertension. This possibility is consistent with the experience in some parts of Japan where intakes of both salt...
and rice are very high. If high carbohydrate diets inhibit the excretion of sodium, they might accentuate sodium-induced hypertension.

Alcohol

There is a strong epidemiological link between alcohol intake and hypertension. The prevalence of hypertension among heavy drinkers is twice that of the general population. This correlation seems solid, but many unanswered questions need to be addressed about the relationship between alcohol and hypertension.

For example, it is important to know whether a certain intake of alcohol is required before a blood pressure response is seen. In other words, is there a threshold relation between alcohol ingestion and blood pressure response? It is not known whether systolic or diastolic pressure is more affected by alcohol, whether men are more prone to the effect than women, and whether whites are more affected than blacks. The influence of alcohol on blood pressure could be either direct or indirect. For instance, other confounding variables such as differences in dietary intake among drinkers or psychosocial stresses could also affect blood pressure in heavy drinkers. Another question is whether some persons are responders to alcohol while others are nonresponders. If so, the response to alcohol might uncover persons who are predisposed to hypertension. More studies are needed to determine whether there are long-term effects of alcohol on blood pressure that cannot be uncovered in short-term studies. Finally, it must be asked how alcohol affects other hypertension-related metabolic processes: 1) the renin-angiotensin system, 2) catecholamines, 3) cortisol-like hormones, 4) metabolic rate, 5) electrolyte metabolism, and 6) prostaglandin metabolism.

Several types of studies might prove useful in defining the relationship between alcohol intake and hypertension: 1) An animal model would be useful, and an effort should be made to develop such a model. 2) Carefully performed metabolic ward studies on the effects of alcohol on the numerous blood pressure-related metabolic processes listed above need to be carried out. 3) More epidemiological studies, possibly with the use of carefully kept diaries, are needed. 4) Particular attention should be given to the effects of alcohol on blood pressure in the elderly.

Dietary Fat and Prostaglandin Metabolism

The effects of dietary changes in polyunsaturated fatty acids, particularly linoleic and eicosapentaenoic acids, on the production of prostaglandins and thromboxanes (eicosanoids) in humans need to be evaluated. The addition of a range of doses of specified polyunsaturated fatty acids to the diet should be examined with respect to their effects on both arterial pressure and prostaglandins and thromboxanes. This measure should provide a rational basis for constructing long-term studies of either further dietary changes or supplementation with purified polyunsaturated fatty acids. Availability of the resultant dose-response curves would considerably increase the strength of the evidence.

To accomplish an assessment of any changes in the biosynthesis of specific prostaglandins and thromboxanes, the synthesis of appropriate standards for the mass spectrometric analytical procedures will be required. The most powerful approach to quantifying eicosanoid production in humans in vivo is by measuring the excretion of their urinary metabolites by mass spectrometry. For this type of analysis, it is necessary to employ deuterium-labeled and tritium-labeled internal standards, although most of these standards are not yet available to investigators, which imposes severe limitations on the full realization of this research objective. This technical problem needs to be solved.

An evaluation of the changes in polyunsaturated fatty acid content of specific lipids in target organs with aging, as well as corresponding changes in eicosanoid biosynthesis with age, should provide important information that could shed light on the findings that blood pressure increases with age and that certain of the vectors regulating blood pressure (e.g., renin) change with age. Racial differences should also be explored.

Because prostaglandins and thromboxanes alter arterial pressure at multiple points of pressure regulation, such as renal sodium excretion, renin release, neurotransmission, and vascular tone, the mechanisms of action at these specific sites need clarification as does the determination of which site predominates in the blood pressure response to feeding linoleic or eicosapentaenoic acid.

At the human level, more epidemiological studies are needed on the relationship between dietary fat and blood pressure. Migration studies such as those used in the cholesterol field might be especially valuable. In human studies, investigations on metabolic wards would seem to be particularly important. However, these studies should be based on results obtained from 1) developments in the basic studies on prostaglandins, 2) studies in experimental animals on the relationship between dietary fatty acids and prostaglandin metabolism, and 3) the epidemiological studies alluded to previously. In any metabolic studies, the types of fatty acids fed should vary. The effects of saturated fatty acids and monounsaturated fatty acids should be examined as carefully as are those of polyunsaturated fatty acids. Also, some patients should be tested with high fat diets, while others should receive low fat diets. In these metabolic investigations, detailed studies should be made of prostaglandin excretion products, the renin-angiotensin system, catecholamines, and electrolytes.

Finally, on the basis of the metabolic ward investigations already outlined, intervention trials in free-living populations can be implemented. These trials should not be started prematurely before more basic information is obtained on the particular fatty acids and their effects on multiple metabolic processes related to blood pressure control.
In the pediatric age group body size is strongly correlated with blood pressure. Both large children and obese children have higher blood pressures than their average-sized and nonobese counterparts. In studies of children with elevated blood pressure, as in obese hypertensive adults, it is important to control the many variables that could be either major determinants of hypertension or serious confounders in the analysis of the results. Clearly, it is important to assess the relative contribution of adiposity versus that of lean body mass to obesity-related hypertension. Similarly, with borderline or overt hypertension, it is important to be able to determine by noninvasive means whether a compensated hemodynamic and/or metabolic disorder is present.

Since preventive medicine is most applicable in the pediatric age group, it is important to be able to identify children who are at special risk of becoming hypertensive as well as those who are most likely to become obese or hypertensive or both. This study involves the search for genetic markers of various kinds that might also be identifiable among the family members of the patient under study.

Elderly persons are especially vulnerable to the deleterious effects of hypertension; however, the elderly also may have problems in tolerating antihypertensive drugs. For these reasons, the value of a nutritional approach to the prevention and treatment of hypertension in older persons should be determined by means of clinical trials. Such trials could test the effect on blood pressure of sodium restriction. Other dietary measures such as potassium and calcium supplementation, reduction in intake of saturated fat, increase in intake of polyunsaturated fatty acids, and of course, weight reduction in the obese should also be considered for study.

Conclusions

There are numerous variables to consider in most dietary studies, especially ones conducted in humans. Epidemiological studies on the relationships between nutrient intake and hypertension are difficult to interpret. There is a need to evaluate the problems encountered in retrospective studies, including ascertainment of confounding variables and use of appropriate statistical methods. Because so many variables influence blood pressure, it is unlikely that dietary substances have direct effects on the blood pressure, but rather that they affect secondary factors, which in turn influence blood pressure. Therefore, while epidemiological and clinical nutrition studies can provide insights about the macrolevel relationships between dietary factors and hypertension, it is important to elucidate the various mechanisms that contribute to blood pressure regulation and then to determine how diet or dietary factors influence these mechanisms.

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