Research Contributions Toward Prevention of Cardiovascular Disease

Research Related to the Underlying Mechanisms in Hypertension

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SUMMARY The pathogenesis and basic mechanisms of hypertension are not understood. Hypertension is now considered to reflect abnormality in one or more of the biologic systems that regulate flow and resistance. Its complications result from high intra-arterial pressure, and drug treatment substantially lessens these complications. The death rate from hypertension has dropped strikingly. Although current knowledge is not sufficient to develop predictably successful prevention programs, there is growing interest in applying available information. Epidemiologic studies have identified obesity as a major risk factor for hypertension; they have also been interpreted as showing that high dietary sodium intake causes hypertension in industrialized societies. Evidence on the role of obesity seems firm and can provide the basis for prevention programs. The role of sodium intake requires further study.

RESEARCH has provided a substantial understanding of hypertension, although fundamental knowledge concerning the pathogenesis of hypertension is lacking. To appreciate what has been accomplished, a review of what was known about hypertension 30 years ago is appropriate.

Then, hypertension was recognized as an illness that shortened life. A few causes were recognized — pheochromocytoma, renal parenchymal disease, acute porphyria and bulbar polypl — but most patients were considered to have essential hypertension. Although the renal pressor system had been described, attempts to implicate it pathogenetically had failed. Renal arterial stenosis had been suspected as a cause of hypertension, but it could not be diagnosed. The role of the autonomic nervous system in arterial pressure control was beginning to be studied, and the first ganglion-blocking drug, tetraethyl ammonium chloride, which had no therapeutic application, was used investigatively. Hemodynamic studies of hypertensive patients had revealed a normal cardiac output and elevated vascular resistance, so the heart was considered to be a passive bystander in hypertension, and in no way a participant. Some adrenal steroids were known, but none of them had great salt-retaining capacity. There were no simple treatments, and the hope of a physician for an asymptomatic patient was that the elevated pressure would not progress to malignant hypertension or to cardiac failure. When either occurred, therapy was usually supportive. Three treatments were available: rigid dietary salt restriction, sympathectomy and pyrogen therapy. These treatments were not simple and therefore, were not widely used. They probably had no impact on the national morbidity and mortality of hypertension.

At that time the prevention of hypertension was not even considered. Not enough was known about it even to allow development of effective therapy, and investigators were still looking for the cause of hypertension.

By 1951, the first orally active drugs with long-term effectiveness were available. The first thing learned by using these drugs was that malignant hypertension was not malignant, and that survival could be substantially prolonged. In 1967 the Veterans Administration study showed that treatment of moderately severe hypertension (i.e., diastolic pressure of 115-129 mm Hg) protected against development of cardiac failure, progressive renal arteriolar disease and stroke. Three years later, a similar beneficial effect of antihypertensive drug therapy was reported in patients with pretreatment arterial pressure averages of 105-114 mm Hg. Now there is a concerted effort to identify and treat all hypertensive patients. Public and professional education has been the emphasis of the American Heart Association and the National High Blood Pressure Education Program of the National Heart, Lung, and Blood Institute. The result has been a dramatic decrease in the death rate from hypertension.

This startling change did not develop in a vacuum but as part of a rapidly expanding body of information about hypertension. One of the most significant occurrences during this time was the acceptance of hypertension as being multifactorial in its pathophysiology. Arterial pressure is determined not only by vascular resistance but also by cardiac output, and the heart may well play a role in some hypertension; the stiffness of vascular walls is another determinant of pressure, and the degree of vascular filling is also important. It is also now recognized that many factors affect these primary determinants. The autonomic nervous system helps regulate both normal and elevated arterial pressure, and the controls are complex. Research in this area is just beginning.

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Salt and water, extracellular fluid volumes and sodium stores are very important. In susceptible subjects — human primates and animals — excessive salt and water cause vasoconstriction for reasons that have not been explained.9, 10 The renal pressor system has been extensively investigated.11 It plays an important role in some hypertensions because one of its components, angiotensin II, causes vasoconstriction, increases sympathetic vasomotor activity through central and peripheral mechanisms, is the prime controller of aldosterone production in man, affects salt and water excretion independent of an effect on aldosterone and evokes catecholamine release from the adrenal medulla. The adrenal steroid aldosterone plays a major role in salt and water homeostasis; other salt-active steroids become important occasionally, and there is still a search for others. Work is just beginning on the role of kinins and prostaglandins in arterial pressure regulation,12, 13 and they may be important local determinants of blood flow.

These factors cause hypertension because they affect the balance between blood flow and vascular resistance. At present, abnormality of vascular resistance seems more important than abnormality of cardiac output. The causes of arteriolar vasoconstriction are becoming understood and the components of the contractile apparatus are being investigated.14 There is evidence for an abnormality or abnormalities of the cell membrane that causes the cell wall to leak, disturbing the normal sodium-potassium relationships; this disturbance could affect membrane potential or intracellular calcium stores.

Strains of hypertensive animals have been bred, but in only one, the salt-sensitive strain, has a genetically determined biochemical abnormality been identified. Other abnormalities in the other types are recognized, but their modes of inheritance have not been defined. Thus, in both the spontaneously hypertensive rat and the New Zealand strain, increased sympathetic activity seems to play a role in the genesis of hypertension. In the latter strain, diminished activity of prostaglandin 15-hydroxydehydrogenase has been described as well. Both the Milan and the Dahl strain seem to have a salt- and water-dependent hypertension, the former probably because of renal excretory insufficiency and the latter because of increased production of electrolyte-active steroids.

However, possible prevention of hypertension has only recently gained acceptance. Given the lack of information concerning the pathogenesis of hypertension, what is the likelihood for any reasonable prevention program? Clearly, much new knowledge is needed, but some already available seems good enough to be useful.

Obesity is a prime example of how current knowledge could be applied.15, 16 Arterial pressure is positively correlated with body weight, and the correlation is higher for systolic pressure than for diastolic pressure. The important variable seems to be body mass, not body fat. Obesity is found more frequently among hypertensive than among normotensive persons. The relationship of obesity to hypertension is greater for women than men; the relationship is also greater in persons with a family history of hypertension, and at ages less than 60 years. In one study, the correlation of arterial pressure with body weight was found to be highest between 30–40 years of age. Although several mechanisms for the hypertension of obesity have been proposed, we know that weight reduction strikingly reduces arterial pressure. The early suggestion that obesity hypertension results from increased salt intake along with increased calories16 has been questioned by a recent demonstration that weight reduction was antihypertensive even when salt intake was kept high.17

Despite these facts, there is no estimate of the proportion of hypertension in the United States that is attributable to obesity. In this country, arterial pressure rises with age, and so does body weight because of an inexorable increase in body fat. Also, little attention has been given to the possibility of abolishing a substantial proportion of U.S. hypertension by encouraging weight loss among obese persons, by preventing obesity through realistic caloric intakes and exercise programs for normotensive, normal weight people of all ages. There is enough evidence about the relationship of obesity to hypertension to plan obesity prevention and treatment programs while at the same time investigating the mechanism of the relationship.

Another case regarding the application of existing knowledge concerns dietary salt intake. It has been repeatedly implicated in the genesis of human hypertension, and because Americans eat a high-salt diet, the suggestion has been made that much, if not all, hypertension in this country could be either cured or prevented by a drastic decrease in dietary salt intake. The information on which this recommendation is made comes from several sources.9 The few primitive peoples who eat a low-sodium diet have an extremely low prevalence of hypertension and no rise of arterial pressure with age. Industrialized societies with high salt intake show a high prevalence of hypertension, and arterial pressure rises with age. Some animal models require excess salt intake for development of hypertension. And finally, rigid low-sodium diet therapy reduces arterial pressure in many hypertensive patients.

The data from epidemiologic studies have been interpreted as showing that a low salt intake prevents hypertension. However, in cultures with low-salt diets, weight does not rise with age, and this may explain the lack of increased arterial pressure. A recent comparison of some South American and North American communities showed that differences in arterial pressure are related to differences in body size.18 Weight reduction reduces arterial pressure in normotensives and hypertensives alike, whereas low-sodium diet therapy does not reduce normal pressure; nor does it reduce arterial pressure in every hypertensive patient.19

The obvious individual differences in response among hypertensive patients to a low salt intake and the lessons learned from the breeding of the salt-
sensitive and salt-resistant strains of rats indicate that a nationwide restriction of dietary sodium — even if it could be accomplished — could not be expected to render all hypertensive patients normotensive or to prevent development of all hypertension. Rather, much work needs to be done to develop palatable low-sodium diets for those patients known to be at risk of developing hypertension from high salt intake. These are the patients with most types of renal parenchymal disease, with decreasing renal function and with abnormalities of adrenal steroid production. In addition, attempts should be made to define precisely the mechanism or mechanisms of salt- and water-dependent hypertension and factors that increase the risk of its development.

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