Hypertension and the Angiotensin System

Therapeutic Approaches

Editors
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Foreword

The ceaseless battle against disease is not confined to the boundaries of nations, nor is it likely that the outcome will be determined by the efforts of solitary genius. Medical science is cumulative, its revelations the end products of shared intellect and creative energy, which, when laced with serendipitous discovery, ultimately lead humankind nearer to solving the biological mysteries of life.

Throughout the world there have been ample rewards from this highly productive interaction as inquiring minds—acting on new information from every corner—have uncovered the root causes and pathological mechanisms of many elusive diseases and, in some cases, have developed new and dramatic medicines for their prevention or cure. Human beings, a bustling social species armed with the facility of language, cannot resist the expression of an idea; it is an idea codified in language and resilient to refutation that provokes and propels us onward.

But while the core of science is universal, medical practice and health needs vary greatly from country to country and from culture to culture. Thus, the Medical Advisory Council (MEDAC) was founded in 1973 as a forum for the discussion and evaluation of advances in medical science, changing trends in medical thinking, approaches to drug therapy, and the major issues confronting medicine throughout the world. The collective insights of MEDAC members, coupled with those of invited speakers, all chosen for their distinguished achievements in the fields of medicine and science, should provide a better understanding of the health needs of our times.

In these meetings we continue the exchange, "tossing into the center the products of our separate imaginations," to use the words of Dr. Lewis Thomas, Chancellor of Memorial Sloan-Kettering Cancer Center in New York. This is an ineluctable and satisfying process because it works. Dr. Thomas perhaps has said it best:

> It is in the abrupt, unaccountable aggregation of random notions, intuitions, known in science as good ideas, that the high points are made . . . an active field of science is like an immense anthill; the individual almost vanishes into the mass of minds tumbling over each other, carrying information from place to place, passing it around at the speed of light . . . (until) there suddenly emerges, with the purity of a slow phrase of music, a single new piece of truth about nature.

In this spirit, members of MEDAC convene annually, and in the exchange of facts, ideas, random notions, and intuitions, such as those that are presented in this volume, lies the exhilarating possibility that new truths about nature may emerge that in turn will help us as physicians prevent disease and improve the health and welfare of our patients.

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Introduction

The molecular biological and pharmaceutical revolution has brought forth powerful therapeutic agents effective in lowering blood pressure. Pickering was the first to declare his preference for a skewed Gaussian distribution over a proportionate Mendelian one. He declared that blood pressure was a mere metrical characteristic. But this has a fidgety personality that exasperates those who are more cc nfortable living with the illusion of precision than with the flux of flexible adaptive biology. The concept of homeostasis has been engraved on our minds since the time of Claude Bernard, but we now know that beneath that descriptive umbrella lurks a myriad of interacting components: there are structural organelles and cell membranes; proteins involving transport, secretion, contractility of blood vessels; multitudes of ill-characterized sensors responding to blood gases and blood volumes; receptors that bind proteins, peptides, hormones; and much else.

While to the medical student sequential biological cascades are little more than an intellectual joke, for pharmaceutical chemists and molecular biologists they provide opportunities to identify and dissect discrete therapeutic targets. It is not our task here to sort out the innumerable particulars but to focus on the one enzyme reaction that plays a key part in determining the rate at which angiotensin I is converted into angiotensin II. We know the structures of both and enough about the mechanism to devise inhibitors, the first of which, captopril, is already widely used.

The inhibitors have high promise for the treatment of hypertension, and we are here to explore the boundaries of this promise. For those of us who are physicians with responsibility for treating patients, this program may be too scientific; others may wince at the oversimplification of an exciting, rapidly developing topic. We cannot, however, discuss every facet of this large subject. We have chosen to focus primarily on the treatment of hypertension—this may be enlightened self-interest, as 30% of us may well develop hypertension requiring treatment.

ALEXANDER G. BEARN
June 1983

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Epidemiological Studies Bearing on Prevalence, Pathogenesis, and Mortality Trends in Hypertension

Edward D. Freis

With the exception of atherosclerosis, hypertension is the most common chronic cardiovascular disorder. The most recent national health survey in the United States estimates that there are about 60 million people with hypertension in the USA alone as defined by a systolic blood pressure of 140 mmHg or higher or a diastolic blood pressure of 90 mmHg or above, or both.[1]

The distribution of levels of blood pressure indicates that the great majority are in the borderline range of 90–94 mmHg diastolic or the mild range of 95–104 mmHg. Of the 38 million individuals estimated to have diastolic hypertension in the US survey,[1] only 5 million had moderate or severe levels of diastolic blood pressure.[2] The latter estimate may be somewhat low, however, because many of the patients with moderate and severe hypertension would have been treated or, if untreated, they may have died before the survey was taken.

Longitudinal studies indicate that the tendency toward hypertension manifests itself early in life. Most individuals maintain their position in the hierarchy of blood-pressure levels from youth to old age.[3,4] An individual whose blood pressure is in the upper quintile usually remains in that quintile as his blood pressure rises with age. Thus, at age 40 or 50 years, when his blood pressure rises above established norms, he is no longer called a "high normal" but is now considered to be hypertensive. While this gradual progression to hypertensive status is not universal, it is by far the most frequent route. In fact, the best predictor of future hypertension is the level of so called normal blood pressure during youth.

EMOTIONAL INFLUENCES ON BLOOD PRESSURE

The fact that blood pressure fluctuates considerably with emotional influences has not been given sufficient attention in epidemiological surveys. Yet it has been shown that blood pressure is often highest on the initial examination and tends to drift downward with repeated visits. In the Charlottesville screening program, for example, half of those screened who were originally classified as being hypertensive on the initial examination became normotensive on subse-

quent examination.[5] Follow-up of the placebo group in the Australian trial whose diastolic pressures on entry were 95 mmHg or higher indicated a steady downward drift in blood pressure over a period of months.[6] Diastolic pressure in nearly half of the patients fell below 95 mmHg without any treatment. The downward trend over time has been ascribed to deviation toward the mean. This does not seem to be the entire explanation, however, because the deviations from the initial visit show a systematic downward trend with the passage of time in most of the patients; only a minority of the patients showed an upward trend.

Twenty-four-hour monitoring of blood pressure in ambulatory subjects indicates that blood pressure fluctuates widely over time.[7] Pressure is lowest during sleep and rises abruptly on awakening. Peaks of pressure occur during periods of excitement. These peaks are due to central activation of the sympathetic nervous system and are part of the alerting response that is designed to prepare the organism for fight or flight. Because some apprehension may be associated with the initial examination, the alerting response will be activated to a varying degree in different individuals. Unless precautions are taken to guard against this response, misleading data may be collected on the total prevalence of hypertension in a given population and also on differences between various groups within the population. For example, unsophisticated rural Southern blacks were found to have a higher prevalence of hypertension than urban blacks in the north.[8] Single examination surveys also have shown an inverse correlation between level of education and the prevalence of hypertension.[9] The greatest incidence of hypertension was in the least educated. Might this reflect only a greater alerting response in unsophisticated individuals? We do not know, but it would be helpful if surveys could be done based on more than a single examination. It would be especially valuable to know if the risk is less in subjects whose blood pressure falls to normal on subsequent examinations.

AGE AND RACE

As already mentioned, since blood pressure rises with age, the prevalence of hypertension increases with age. In those aged 65 to 74 years, the prevalence of hypertension rises to 35%.[2] There is also a definite racial difference. The prevalence of hypertension in blacks is roughly twice that in whites in the United States.[2] The racial difference might be due to an increased inherited susceptibility in blacks or to environmental factors. With respect to inheritance American blacks take their origin from West Africans, and a representative survey of the blacks in the Ivory Coast showed the same prevalence of hypertension as in whites in the United States—that is, considerably lower than in United States blacks.[10] This leaves open the possibility that environmental factors may operate in blacks in the United States. With respect to salt ingestion, it is of interest that Ivory Coast blacks use salt in their diet in roughly the same amounts as American blacks.

A difference in potassium excretion in white and black Americans has been noted recently in one of the Veterans Administration cooperative studies[11] as well as by other investigators.[12] Twenty-four-hour urine collections were carried out in all patients in the Veterans Administration trial. Twenty-four-hour sodium excretions were nearly identical in both racial groups, but potassium excretion was considerably lower in blacks than in whites, reflecting a reduced potassium intake. This observation is interesting because there is other evidence that potassium may play a part in preventing hypertension.[11]

CARDIOVASCULAR MORTALITY ASSOCIATED WITH HYPERTENSION

It is well accepted that the risk of cardiovascular complications rises progressively with increasing levels of blood pressure, from the lowest levels to the highest. This basic concept is one of the principal arguments used for the treatment of the mildest forms of hypertension. In fact, some have proposed that patients with diastolic blood pressures in the high 80s should be given the benefit of treatment. Implementation of this proposal would require treating about half the adult population.

Recent analysis of the 18-year follow-up of the Framingham data, however, portrays a somewhat different picture.[13] Long-term follow-up indicates that the relationship between level of diastolic blood pressure and cardiovascular mortality is not a smooth curve. In the lower range, between 70 and 80 mmHg, the curve is flat or slightly inverted—that is, cardiovascular mortality is the same or slightly greater at 70 mmHg than at 90 mmHg. It is only in the ranges above 90 mmHg that the expected relationship between diastolic blood pressure and cardiovascular mortality becomes established. Therefore, there is no indication for treating patients with diastolic blood pressures in the high 80s and probably also no value in lowering raised blood pressure to the low 80s, as has been proposed by several investigators.

In contrast to this "dog leg" seen in the diastolic curve, the relationship between systolic blood pressure and mortality after 18 years shows a continuous increase in risk, beginning at 110 mmHg. Systolic blood pressure, while remaining a valid index of prognosis, is not as representative of hypertension, per se, since it also reflects arteriosclerotic changes in the large arteries. Furthermore, it is not yet known whether patients with borderline levels of systolic blood pressure between 140 and 160 mmHg will benefit from treatment.

With regard to specific causes of death in hypertension, the most frequent complication in Western countries is heart attack, especially in patients with mild hypertension. The death rate in hypertensive men due to this cause is about three times higher than in hypertensive women. Of cardiovascular deaths in hypertensive patients, 60% are due to coronary heart disease. Stroke accounts for about 20%, and hypertensive heart disease accounts for comparatively few deaths.

Other Risk Factors

At present, physicians are being encouraged to treat all patients with hypertension no matter how mild or uncomplicated. The prognosis in patients with borderline and mild hypertension, however, varies widely depending on the number of other risk factors present. Figure 1, taken from the Framingham data,[14,15] shows the risk of a coronary event in men aged 50 years at two different levels of systolic blood pressure—135 mmHg and 165 mmHg. The chart displays the effects of adding other risk factors such as hypercholesterolemia, cigarette smoking, diabetes, and electrocardiographic changes.

With no risk factors present other than raised blood pressure, the risk for the patient with mild hypertension is not much greater than that for the normotensive individual. With additional risk factors present, however, the risk in both groups increases drastically, as does the difference between normotensive and hypertensive individuals. Clearly, the widely accepted belief that the risk of a heart attack is doubled in the presence of hypertension is a generalization that is often not true for the individual patient. The risk may be more or less than the average risk depending on the number of additional risk factors present and the age of the individual, in addition to the level of blood pressure. These distinctions are important in making decisions on the treatment of individual patients.

Similar information in relation to women aged 50 years[14,15] is shown in figure 2. The risk is much lower than in men and does not rise as much with increasing numbers of risk factors as it does in men. Also, the difference between normoten-

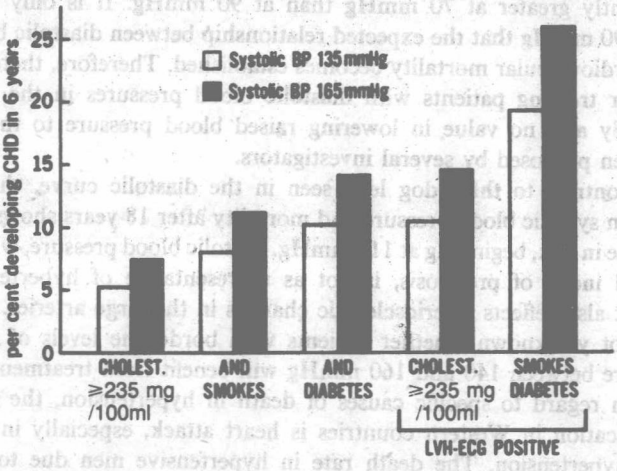

FIG 1—Probability of developing coronary heart disease (CHD) over a 6-year period in men aged 50 years with systolic blood pressures of 165 mmHg (black columns) and men of the same age with normal systolic pressures of 135 mmHg (white columns). Risk of CHD varies widely in both groups according to the number of other risk factors present. (Taken from tabular data in Insull.[6])

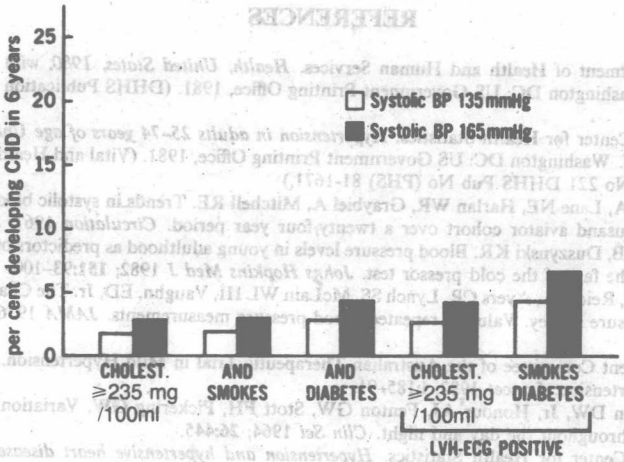

FIG 2—Probability of developing CHD over a 6-year period in women aged 50 years with systolic blood pressure of 165 mmHg (black columns) and women of the same age with normal systolic blood pressure of 135 mmHg (white columns). Other notations as in figure 1.

sive and mildly hypertensive women is not as great as in men. If we assume that treatment neutralizes the increased risk of fatal heart attack, which may or may not be true, it is evident that without other risk factors the therapeutic benefit, particularly in women, may not justify exposing the patient to the potential risks, discomforts, and expense of lifelong drug treatment.

Decline in Mortality

There has been a striking decline in death rates due to cardiovascular disease from 1968 to 1978.[1] Deaths secondary to cerebrovascular disease have shown the greatest reduction, of about 40%, although there also has been a highly significant downward trend in mortality associated with ischemic heart disease, averaging about 25%. While there has been a downward trend in cardiovascular mortality for many years, the pace of the decline has accelerated since 1968. In fact, the reduction in the 7 years from 1970 to 1977 was as great as that observed in the 20 years from 1950 to 1970. The decline has been greater in blacks than in whites during 1968 to 1978. As previously mentioned, before 1968 blacks showed a cardiovascular mortality twice as high as that in whites. The reasons for the greater decline in mortality in blacks may be associated with improvement in their medical care, more widespread screening for hypertension, and the provision of more facilities for treatment. Although the reason for the reduction in the number of coronary deaths is uncertain, the dramatic decline in the number of deaths due to stroke seems most likely to be due to the more effective control of hypertension in recent years.