Preface

Innovative concepts of hypertension to understand and manage the disease

This issue of the Medical Clinics of North America is devoted once again to innovative concepts dealing with hypertensive disease. I say once again because this is the fourth time that we have organized an issue on this topic for this publication, and it has appeared approximately every 5 years. One could reasonably ask if enough new knowledge in this area mandates a new issue unless prior contents are reviewed. Indeed, our knowledge about the underlying mechanisms related to the pathophysiology of hypertension, new concepts about its prevention, and advances in patient management and therapy has drastically burgeoned, and the overall approach to this tremendously important clinical problem has remarkably matured and become far more sophisticated during the past 5 years. A cursory perusal of the content of this issue clearly attests to this assertion.

Pathophysiology

A recent sea change in advances in our pathophysiological understanding of the hypertensive diseases is demonstrated impressively throughout the first eight articles in this issue. Comprehension of the underlying genetic mechanisms of the hypertensive diseases is brilliantly explored by Dr. Friedrich C. Luft. We have long known from histories obtained from our patients that hypertension is a genetically predisposed disease because of exceptionally strong family histories of hypertension. However, to approach hypertension as a disease with a straightforward, single genetic causation is probably
expecting too much. In the vast number of patients with hypertension, there are some with monogenetic causes; however, by and far, most patients have multifactorial underlying polygenetic mechanisms. Thus Professor Luft presents an up-to-date discussion of the single Mendelian forms of hypertensive diseases, leaving a larger segment of his chapter to a more difficult area dealing with far more complex disease traits. His erudite discussion is particularly lucid and is supplemented by a very useful list of references for the interested reader.

In the succeeding discussion, Dr. Richard N. Re broadens our overall concept of the rennin–angiotensin–aldosterone system. At the outset of this series on innovations in hypertension, this system has been considered an important endocrine mechanism having positive and negative feedback controls. Its rate-limiting enzyme, renin, is released from the renal juxtaglomerular apparatus and acts on the hepatically synthesized protein substrate angiotensinogen to release angiotensin I from its protein attachment. Then, within a single circulation (through the lungs), this decapeptide is acted upon by the angiotensin converting enzyme (ACE) to form the potent octapeptide (angiotensin II) that constricts vascular smooth muscle, stimulates aldosterone release from the adrenal cortex, and stimulates thirst and other brain centers—just to mention a few of its very important (and growing) actions. However, in recent years this systemic endocrine concept system has expanded dramatically. Thus there is now a multiplicity of local rennin–angiotensin systems in such tissues as blood vessel, heart, liver, uterus, and brain, to mention those having benefitted from more extensive inquiry. These local systems have autocrine/paracrine as well as intracrine actions on their organ-specific tissues. For example, in the heart, angiotensin II has mitogenic, fibrosing, apoptotic, and other actions that help to explain its role in producing ventricular hypertrophy, extracellular fibrosis, apoptosis, and cardiac failure. Still more recent work has elucidated angiotensin’s role in endothelial dysfunction and in local aldosterone synthesis, opening the mind to additional pathophysiological explanations for disease and new modes of therapy. This and more is provided by Dr. Re, who has done much to open this area as well as our thinking about it.

The following article by Drs. Ernesto L. Schiffrin and Carmine Savoia continues to expand our thinking with a clear discussion of important new peptides produced by or acting on the cardiovascular system. The roles of the atrial natriuretic peptide, endotheilins, and adrenomedullin are explored. These agents received either no discussion or even ideation in previous issues. Whereas the atrial natriuretic peptide had been identified within the past two decades, its role in disease and in therapy have only recently been explored. Thus this peptide has been demonstrated to provide the logical negative physiological feedback for the overloaded circulation, and a similar peptide, produced by the brain (brain natriuretic peptide), has only recently been shown to be an index of occult (if not overt clinical) cardiac failure. The pharmaceutical industry has already taken advantage of this peptide
by combining its metabolic enzyme (decarboxylase) with ACE to provide a potentially sound and potent antihypertensive compound. Similarly, the endothelins have provided a broader insight into their vasoconstrictor and mitogenic cardiovascular effects, leading to newer therapeutic modalities that are currently under clinical investigation (some have already been introduced clinically). The role of adrenomedullin is still in its infancy and is currently being explored in many basic and clinical laboratories.

The relationship between hypertension and diabetes mellitus has been known for many years. With the introduction of the Benedict’s reagent as a test for blood glucose concentration as early as the 1920s, a number of clinical investigators have demonstrated the exceedingly high coexistence of these two diseases, a figure (in excess of 60%) that has not changed substantially over the ensuing generations. More recently, however, many investigators have explored further this classical relationship to describe in greater depth a metabolic syndrome involving the relationship of hypertension and diabetes with insulin, obesity, hyperlipidemia, and, of course, the potential linkages of these diseases with atherosclerosis. In the following article, Dr. James R. Sowers and I discuss this potential role and the phenomenon of insulin sensitivity and other clinical aspects of hypertensive disease. These concepts are of great value when one considers not only its obvious pathophysiological import but the potential role of newer and important therapeutic agents for diabetes, insulin sensitivity, and hypertension. For many years we have recognized that left ventricular hypertrophy (LVH) is a major risk factor underlying coronary heart disease. For too long, however, our studies have been directed to the potential importance of therapeutically diminishing the increased mass of the left ventricle to possibly reduce that risk. Our experimental and clinical investigative approach to this area in the 1970s was among the first of its kind; however, in more recent years, I questioned whether there was a sufficiently clear understanding of the underlying mechanisms that would satisfactorily explain the intrinsic risk associated with LVH. Our studies (and those of others) have pointed to a number of mechanisms explaining the risk associated with LVH, including ventricular ischemia, fibrosis, and apoptosis.

Among the more productive clinical investigators in this area has been Dr. Javier Diez and his team, including Dr. Arantxa Gonzalez. In their article, which explores the role of ventricular fibrosis in hypertension, they provide an excellent discussion of the implications of ventricular fibrosis in hypertension. We should conclude from this discussion that the laying down of fibrotic material in tissue should not be construed as the development of a permanent scarring of the cardiac wall that leads to impaired function, ischemia, failure, and death. First, they provide compelling evidence that the fibrosis is demonstrably reversible clinically and that it may be detectable—even quantitatively—by measuring the circulating proteolytic products of collagen in the circulation of patients. They are not alone in their experimental and clinical findings, and they have been confirmed and extended...
in other laboratories, including our own. Their work has also been expanded recently to demonstrate that angiotensin II is not only capable of producing ventricular fibrosis, but it also produces apoptosis of cardiac myocytes. This latter observation may lead to a keener insight into the repeated epidemiological finding that hypertension is the most common cause of cardiac failure. Indeed, Dr. Diez’s team’s most recent work has shown that therapy directed toward inhibition of angiotensin II not only diminishes ventricular fibrosis but also reverses the phenomenon of apoptosis. The references accompanying their discussion will be most valuable to the interested reader.

The phenomenon of ventricular fibrosis is not only important as an underlying mechanism explaining the high risk associated with LVH, it is also inextricably intertwined with another mechanism underlying the risk associated with LVH: ischemia. One of the early workers in this area has been Dr. Bodo-Eckehard Strauer and his team, including Dr. Malte Klem. Professor Strauer reported early on in his studies of ischemic heart disease that coronary heart disease is associated with hypertension—specifically, that coronary blood flow reserve may be markedly restricted in hypertensive LVH, even without co-existent occlusive atherosclerotic epicardial coronary artery disease. In these studies, they demonstrated that the impaired coronary blood flow reserve can be significantly improved with newer therapies, including ACE inhibitors. Professor Strauer’s group was the first to demonstrate, through septal biopsy studies, that coronary perivascular arteriolar and ventricular fibrosis were dramatically reversed with this therapy (as monotherapy). He and his colleagues describe these phenomena in their discussion, and they go far to instill in us the concept that coronary heart disease associated with hypertension is a distinct phenomenon and need not be present with coexisting atherosclerotic coronary arterial disease.

The innovative concept of remodeling and restructuring the ventricular wall experimentally and clinically must be credited to the work of Drs. Janice M. and Marc A. Pfeffer. They first demonstrated the heart’s ability to restructure itself using ACE inhibitory therapy in their studies of the spontaneously hypertensive rat with experimentally produced myocardial infarction; later, they demonstrated this in patients with myocardial infarction as well. Indeed, they coined this now-popular term. Their initial studies led to their landmark multicenter clinical trial known as the Survival and Ventricular Enlargement (SAVE) study, which demonstrated that ACE inhibition therapy was effective not only in preventing ventricular remodeling, but that prevention of this adverse consequence of myocardial infarction significantly reduced complicating congestive heart failure, repeated infarction, and death. Following this report, a number of other studies of similar concepts confirmed these findings.

Not to be minimized by the foregoing discussions of cardiac complications of hypertension are the effects of hypertensive disease on the kidney. Too often, in a discussion of the renal consequences of hypertension, there is extensive discussion of the adverse physiological consequences of hypertension on renal function and the unrelentingly increasing problem of
end-stage renal disease (ESRD) and its burdening costs to society in terms of disability, quality of life, death, and, most certainly, economics. In recent years, I have noted less discussion in reviews of hypertension dealing with clinical evaluation of renal function in patients with hypertension. Perhaps no individual in the area of experimental and clinical investigation of the renal complications of hypertension has been Dr. Norman K. Hollenberg. Doctor Hollenberg’s work (together with Dr. Gordon Williams) has been concerned with the relationships of renal involvement in hypertension with the rennin–angiotensin system, the clinical evaluation of hypertensive renal disease, and the evaluation of patients with ESRD and their kidney donors. With such extensive clinical experience, I thought it most appropriate to return to an earlier clinical discussion of evaluating the patient with renal functional impairment. I truly believe that this discussion is unique in this day and age, for it provides the important and vast clinical experience that Dr. Hollenberg brings to this important subject.

Management and therapy

Over the years of coverage of innovative concepts in the Medical Clinics of North America, there have been dramatic introductions of new concepts developed about primary as well as secondary prevention of hypertension, as well as new classes of pharmacological agents introduced for its treatment. As part of the National High Blood Pressure Education Program, established by the National Heart Lung and Blood Institute in 1972, periodic guidelines have been promulgated by its Joint Coordinating Committee (JCC) to provide current updates on the detection, evaluation, treatment, and prevention of hypertension. Over the years, seven reports have been published; the most recent, JNC-7, was published in May 2003. These reports have provided new scientific information concerning hypertension, results of the periodic National Health and Nutrition Surveys that detail important demographic and other data as they relate to hypertension, results of outcomes of multicenter therapeutic trials conducted throughout the world, and the consensus of individuals currently representing the major related health organizations in this country.

Several new concepts were presented in JNC-7. First, the number of individuals who are aware that they have hypertension and are currently receiving antihypertensive therapy, and whose pressures are under control, represent only 34% of all hypertensives. Although this number is greater than that reported in JNC-6, it is a far cry from a number that health care providers can be proud of. Clearly, we all have a better job to do in this respect.

Second, the term prehypertension was introduced to cover all adults whose systolic pressures are between 120 and 139 mmHg and whose diastolic pressures are between 80 and 89 mmHg. These pressures were
formerly designated as *high normal* pressures, a term that had been used ever since JNC-3 was published. To my way of thinking, the latter term still is more appropriate because there is no assuredness that individuals with prehypertension will be inappropriately rated for health insurances, especially because this term is to receive a diagnostic code. In choosing this new term, the JCC hoped that more people who were at subsequent risk of developing stage 1 hypertension (140–159 mmHg systolic and 90–99 mmHg diastolic) would receive primary prevention measures of lifestyle modification. Let us hope that these noble desires do not jeopardize the insurability of these people and the economics of health care delivery.

A third issue in JNC-7 that continues to provoke controversy is the recommendation that antihypertensive therapy be initiated with a thiazide diuretic for all individuals with uncomplicated hypertension (having no other compelling conditions). Although this recommendation is not that different from prior reports, it has already been construed by many as a call for the initial treatment of all patients with a thiazide diuretic. This just isn’t so: the guidelines carefully point out that any of the other classes of agents may be employed to control pressure as determined by the responsible health care provider.

My fourth concern is the recommendation to initiate therapy with two agents simultaneously in patients with stage 2 hypertension. Again, to my way of thinking, unless the situation is truly emergent, the simultaneous prescription of two agents is unwarranted. Should a side effect of treatment occur, the agent responsible would not be known. If pressure is not promptly controlled, then a second agent can be introduced. The report was published rapidly in a so-called “express” format, and a longer explanatory report is anticipated in the near future.

In the very first discussion concerning management of hypertension in this issue of the *Clinics*, Dr. Norman M. Kaplan presents his overview of the subject. In it he ventures into what internists and primary care physicians, who most often see patients with hypertension, might expect from the new JNC-7 guidelines. A thoughtful leader in the field of hypertension for years, Dr. Kaplan’s discussion provides an excellent overview of the current status of his (and most key leaders’) work in the field. As stated above, the JNC reports have consistently recommended that therapy should be initiated with a thiazide diuretic. This report is no different, especially since its promulgation immediately followed the release of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). This large multicenter study demonstrated once again the value of diuretics and their equivalence in endpoints with other agents (ie, the calcium antagonists and the ACE inhibitors). Dr. Kaplan’s discussion of this concept is timely, clear, and especially important for the practitioner.

The importance that multicenter clinical trials have assumed over the years in identifying endpoints and meaningful clinical outcomes for any therapeutic modality, be it in the area of hypertension or any other disease,
cannot be minimized. This value should be of prime importance to the pharmaceutica industry, regulatory bodies, the practicing physician, and third-party providers. It becomes a major source of news (and controversy) in the lay media when the results of any new trial is published. This publicly announced information immediately whets the appetites and concerns of the public, who apply the reported findings to each individual’s health concerns. Thus, on the morning after a report is made public by the media, practicing physicians find stacks of notes reflecting the number of telephone messages from patients. For this reason, we have invited Drs. George L. Bakris and Kevin C. Abbott to review what we have learned and what we can take away from the recent and current trials of antihypertensive agents. Dr. Bakris speaks with great authority as an active participant in many multicenter clinical trials, in addition to being a highly sought-after consultant to industry and government. In this review, Drs. Bakris and Abbott speak to each of the major recent drug trials and provide valid points of view from their unbiased and enlightened authority.

We then present a series of discussions concerning the specific classes of antihypertensive agents, beginning with an article on the diuretics and β-adrenergic receptor blocking agents by Drs. Marvin Moser and John F. Setaro. Dr. Moser has been a member of the JCC and has spoken to the value of the thiazide diuretics for these many years. In their article, he and Dr. Setaro provide an up-to-date review of the efficacy and safety of diuretics and β-adrenergic receptor blocking agents and the rationale for keeping these agents at the forefront of initial treatment of hypertension. One aspect of their discussion should be placed into perspective; they reiterate the point made above that although the use of diuretics for initial therapy is clear, JNC-7 does not state unequivocally that all patients must be started with that initial therapy. All classes of antihypertensive agents are included in the recommendation for initial therapy, and there are specific compelling indications for the use of other classes of antihypertensive therapy.

The following discussion is by Drs. Murray Epstein and Vito M. Campese. Both authors are pre-eminent in the field of hypertension, have been members of the JCC for several years, and are eminently qualified to write on the evolving role of the calcium antagonists in the management of hypertension. They both have considerable experimental and clinical background on the subject and, in their discussion, they discuss many controversial points concerning this class of drugs. What was not said in their support of the use of these agents is that there are many patients with hypertension whose pressures may not respond to the diuretic or, for that matter, to ACE inhibitors or the angiotensin receptor blocking (ARB) agents. Moreover, they might not be able to take the β-adrenergic receptor blocker because of significant bradycardia. In these patients, the calcium antagonists become the major group of agents for consideration. Furthermore, there are those patients who may have bilateral occlusive renal arterial disease or, for other conditions (eg, pregnancy) and preclude the use of ACE inhibitors or the ARB agents.
These additional clinical points provide additional need for a clear understanding of the calcium antagonists. As with the other discussions, the references included in their paper provide important reference for the interested clinician.

In the light of the foregoing discussion concerning renal functional impairment in hypertensive disease, I have prepared the following discussion dealing with our experimental experiences in the laboratory with the spontaneously hypertensive rat of naturally occurring hypertension, as well as recent clinical studies dealing with ACE inhibitors and ARB agents. Thus, it is now possible to study an experimental model of hypertension that is a close counterpart of essential hypertension in man without the necessity to produce ESRD and hypertension by experimental extirpation of most of the animal’s renal tissue, administration of high dose steroids and salt, or even the administration of lethal or severe nephrotoxins. Thus, we must understand systemic and renal hemodynamics, glomerular dynamics, renal function, and the clinical consequences pathophysiologically without taking drastic measures. In our studies, we have also demonstrated that it is possible to reproduce the natural renal consequences associated with aging and hypertension by administering a specific agent that interferes with local endothelial production of nitric oxide, which naturally regulates local blood flow and renal function. In our studies, we demonstrated that the newer antihypertensive agents (ie, ACE inhibitors, angiotensin II type 1 receptor antagonists, and certain calcium antagonists) not only reversed naturally occurring ESRD but also prevented the development of this drastic consequence of hypertension. Therefore, we not only demonstrated reversibility of the renal consequence of hypertension, but we also demonstrated similar effects on the heart. Furthermore, we provide the necessary confirmatory support of our experimental findings with new clinical data that have been reproduced in many recent multicenter clinical studies. Hence, I believe that we are at the cusp of a new era in which there is a potential promise of the reversal of the cardiac and renal consequences of hypertension.

In the final report of this issue, Dr. Marie Antoinette Krousel-Wood and her colleagues discuss the very reasonable expectation for the prevention of essential hypertension. This concept has been championed by the National High Blood Pressure Education Program and Dr. Krousel-Wood’s colleague Dr. Paul Whelton ever since his initial report of the working group of that program demonstrated feasibility of primary prevention of hypertension. The very real concept that essential hypertension can be prevented primarily by lifestyle modifications is rigorously supported and detailed in their report.

Thus, we present a variety of innovative concepts on the pathophysiology of hypertensive diseases and the fundamental information that has permitted the demonstration of continued reduction of morbidity and mortality associated with essential hypertension and its involvement of the target organs of the disease. Hopefully, in our next pentannual report, we will
provide additional new and exciting information concerning the pathogenesis and pathophysiologic underlying mechanisms of arterial pressure elevation and the therapeutic interventions that will continue to stimulate your interest and excitement about hypertension and its complications.

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