

## Preface



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*Guest Editor*

Organizing this issue on hypertension every five (or so) years has been a truly satisfying, stimulating, and tremendously rewarding experience for me. This educational exercise has permitted me to review the present state of the art about the pathophysiological and clinical aspects of a remarkable and unusual field of medicine. On first reflection, I was compelled to look back upon an area of clinical medicine that was responsible for most of the hospital admissions at the time when I entered into medicine. These patients included those with cardiac failure, myocardial infarction, severe angina pectoris, dissecting aortic aneurysm, end-stage renal disease, malignant hypertension, hypertensive encephalopathy, and many other problems that we lump into the heterogeneous category we now term as “hypertensive emergencies.” In fact, many of these latter problems have not been included in the hypertensive symposia of the *Medical Clinics of North America* for the past 20 years.

In its place, I believe a far more relevant sequence of discussions for this time now appears in our current overview. The discussions now include my personal reflections on some of the major clinical challenges concerning the pathophysiological aspects and clinical issues concerning the management of the hypertensive disease. One issue in particular concerns a subject that I had avoided in our pathophysiological studies until three or four decades ago; and that deals with the role of salt in hypertensive disease. (I was more concerned with the role of obesity in hypertension.) It was because of our experimental laboratory studies involving salt-loaded spontaneously hypertensive rats that I became convinced long-term salt-loading did much more than simply raising arterial pressure. We learned repeatedly in our studies that it also adversely affected the structure and function of the “target organs” of hypertensive diseases (ie, heart, kidneys, blood vessels). Through these experimental studies we have become convinced that conventional antihypertensive therapy can not only reverse but actually prevent these changes. This concept is particularly important at this juncture because one wonders why, despite the important (and frequently cited effects) of antihypertensive therapy to dramatically reduce cardiovascular morbidity and mortality, the important therapeutic trials and epidemiological reports failed to modify the adverse effects of hypertensive disease and its therapy on the increasing

rates of end-stage renal disease or of cardiac failure. My introductory discussion of this issue relates to this important subject and expands on this concept.

In the succeeding article, Dr. William B. Kannel, former director of the famous Framingham Heart Study, reflects on the risks inherent with untreated hypertension; and he also expands on some of his thoughts and prognostications. In this respect, it was Dr. Kannel who first coined the term “risk factors” in one of his earlier reports on identifying the first group of factors of risk responsible for the morbidity and mortality associated with coronary heart disease.

In recent years, much of our current thinking about the pathophysiological alterations associated with hypertension has been revitalized by new biological concepts that participate in the target organs of the disease. Perhaps much of this new information has been stimulated by a broadened concept of the role of the renin-angiotensin-aldosterone system (RAAS). We still consider the time-honored concept of this system in terms of its endocrine expression, thus, the enzyme renin is produced and released by the juxtaglomerular apparatus in the kidney and acts upon its substrate angiotensinogen produced in the liver. As a result of this action, the decapeptide angiotensin I is produced, which, in turn, is converted by the angiotensin-converting enzyme that cleaves off its terminal dipeptide to form angiotensin II. It is this octapeptide that acts upon vascular smooth muscle to promote vasoconstriction and on the adrenal cortex to release aldosterone, which is the most important steroid in regulating salt and water balance and metabolism. But, today, we have come to realize that there are local RAASs in heart, arteries, brain, adrenal, kidney, uterus, and additional organs that mediate other functions that are critically important in health and disease. Indeed, evidence is rapidly appearing that these local systems explain much of the mitogenic, inflammatory, oxidative stress, and other, heretofore unimagined actions that Irvine H. Page and Eduardo Braun-Menendez never conceived of when they and their colleagues first synthesized this octapeptide. These effects may be expressed through autocrine, paracrine, and, yes, even intracrine actions to explain many undreamed-of actions of this system. The concept of these local RAAS systems is cogently discussed by my colleague Dr. Richard N. Re of the Ochsner Clinic Foundation.

Many of us have been stimulated by new thinking about the multifactorial expressions of systemic hypertensive disease that we now term the “metabolic syndrome.” However, this syndrome is not really new. Clear thinking by W. W. Herick in 1923 (shortly after Banting and Best’s report of the production of insulin by the pancreas) was impressed by the frequency of the co-existence of hypertensive disease and hyperglycemia. Indeed, this astute clinician reported not only this observation in his published papers but also in a specific book detailing his large clinical experience at the Joslin Clinic in patients who have diabetes and hypertension. In that text, he was able to detail the prevalence of the co-existence of these two common diseases in over 50 percent of patients older than 50 years of age. Today, many recent reports express concern that the frequency of their co-existence is identical to that reported in 1923. And, in those early days, the definition of hypertension was usually greater than 160 mmHg systolic (not the 135 or 140 mmHg published in JNC-7)—particularly when co-existing with diabetes mellitus. What is new in the syndrome today is the close relationship between obesity and hyperlipidemia (the latter was not measurable in the 1920s); and the obvious association with aldosterone and insulin, the RAAs, and oxidative stress. These associations are discussed in detail by Dr. Camila Manrique and other associates of Dr. James R. Sowers at the University of Missouri in Columbia, Missouri, and the editor-in-chief of the new *Journal of Cardiometabolic Diseases*. No doubt these concepts will also be linked to the local RAASs and the

problem of endothelial dysfunction, which is so commonly discussed in today's cardiovascular literature.

In recent years, much information has appeared in the literature that relates to the co-existence of the aging process and hypertension (primarily systolic hypertension in the elderly). The earlier literature, while not stating that these two areas of major cardiovascular interest are interdependent, suggested that this relationship was explainable by the frequent appearance of the atherosclerotic process as part of the aging process in the elderly patient as a natural occurrence. It is true that atherosclerosis frequently appears in aging individuals, but the pathogenesis of isolated systolic hypertension in the elderly is not necessarily associated with atherosclerosis for several reasons. First, not all patients with atherosclerosis develop hypertension, and, secondly, not all elderly patients with isolated systolic hypertension have atherosclerotic vascular disease.

Much of our current thinking about these problems has been stimulated by the appearance of the results from recent multicenter, double-blinded, and placebo-controlled trials that firmly established the concept that cardiovascular morbidity and mortality could be safely reduced; and that this problem is eminently treatable with conventional antihypertensive therapy. But, additional concurrent research contributions (well-known and published prior to these trials) primarily by two groups of investigators who demonstrated that both biological processes, aging and development of systolic hypertension, were independent of atherosclerosis. One group was led by Dr. Edward G. Lakatta of the Laboratory of Cardiovascular Science of the National Institute of Aging of the National Institutes of Health in Baltimore. Their carefully conducted clinical and laboratory studies demonstrated fundamental biological changes associated with aging. These studies, conducted at the macroscopic and molecular levels, are carefully detailed in their discussion in this issue of *Medical Clinics of North America*. One lesson from their studies is that much of the microcirculatory findings reported from epidemiological studies in aging patients do not necessarily reflect changes associated with the development of atherosclerotic vascular disease. Thus, impaired forearm flow in these studies does not necessarily reflect atherosclerosis but the aging process itself. The second group of investigators has been led by Dr. Michel E. Safar of the Universite Paris Descartes and the Centre de Diagnostic et de Therapeutique in Paris. It was his team's work (as well as studies conducted by the many workers trained by Safar) and the early fundamental clinical studies reported by Dr. Michael O'Rourke in Australia. Their findings were painstakingly elucidated in their hemodynamic laboratories that demonstrated the changes that take place in the large arteries of aging individuals. For years they stressed that the changes occurring with age (impaired distensibility and loss of elasticity of the large arteries) had vast clinical implications on their function as well as the left ventricle and on the microcirculation. The bottom line of their findings is the importance of measurable hemodynamic indices on ascertaining the changes associated with aging and the development of systolic hypertension in the elderly. The current thinking of Lakatta and Safar are detailed in this issue of the *Clinics*.

The most common cause of hospitalization in Medicare patients in the United States is cardiac failure and, perhaps, the earliest involvement of the heart in hypertension is that of left ventricular hypertrophy (LVH). Indeed, discussion still abounds relating to the most sensitive clinical means of detecting LVH, which is by echocardiography, although, clearly, the most practical and cost-effective approach is by electrocardiography. Hence, the latter technique is employed most frequently for the initial clinical evaluation of the patient with hypertension. It is true that LVH is the earliest means of detecting clinical cardiac involvement; but surrounding this simple yet

practical concept is our understanding of the development and implications of LVH. To be sure, in order for the heart to overcome the unrelenting increase in left ventricular afterload is the concurrent compensatory development of LVH. Moreover, for many years we have looked upon the presence of LVH as a major factor predisposing the patient with hypertension to increased risk of premature cardiovascular morbidity and mortality from coronary heart disease. Indeed, this was one of the first risk factors identified in their initial Framingham Heart Study on risk factors. But, if LVH is a normal adaptive phenomenon to the increased ventricular workload, what should be the underlying mechanism(s) predisposing the hypertensive patient to increased risk? In recent years, several pathophysiological epiphenomena have been identified that seem to explain that risk, and these include: ischemia of the ventricular muscle (either an absolute reduction in coronary blood flow or in coronary flow reserve, both of which are associated with increased coronary vascular resistance); fibrosis in the extracellular matrix as well as perivascular fibrosis within that wall; apoptosis of the ventricular myocyte, which reduces the number of contractile elements in the chamber, predisposing to cardiac failure; inflammatory changes within the ventricular chamber; and, most likely, other changes. It seems that these changes, in turn, are promoted, at least in part, through autocrine, paracrine, and intracrine mechanisms involving the local cardiac RAAS, and still others, no doubt, may account for production of these epiphenomena. This concept associated with specific approaches to treatment is discussed by Dr. Javier Díez, director of Cardiovascular Sciences and of the Centre for Applied Medical Research at the University of Navarra, Pamplona, Spain. His investigative group has contributed much exciting new information in recent years to our understanding of the development of a new paradigm related to hypertensive heart disease (HHD), also discussed herein.

Related to that subject is a series of discussions of the different aspects of cardiac failure and ischemia in this large group of patients. Perhaps the most common expression of cardiac failure in patients with HHD and, no doubt, the most frequent diagnosis is that of left ventricular diastolic dysfunction with preserved systolic function. This aspect of HHD is discussed by Drs. Anil Verma and Scott D. Solomon of the Ochsner Heart and Vascular Institute in New Orleans and the Brigham and Women's Hospital in Boston, respectively. Their vast experience in understanding the underlying clinical mechanisms associated with cardiac failure in patients with hypertension, as well as with occlusive ischemic cardiac disease in HHD, is widely perceived. Indeed, their personal experience concerning the well known contributions of the Brigham Group on the agents that inhibit the RAAS through controlled, double-blinded, multicenter trials. Their findings and those of others are detailed in their report that follows.

Cardiac failure is also manifest in other forms associated with hypertension. It may develop as a result of ischemic heart disease, following myocardial infarction complicated by other comorbid diseases (eg, diabetes mellitus, cardiac myopathy, etc.); and these common clinical experiences are detailed by Dr. Hector O. Ventura, director of the Cardiovascular Disease Training Program and section head of the Cardiomyopathy and Heart Transplant Program at the Ochsner Clinic Foundation in New Orleans. His and his colleagues' experiences with these patients are detailed in the following article.

The succeeding discussion on hypertension and myocardial ischemia in all its manifestations related to increased myocardial oxygen demand or by diminished myocardial oxygen supply is discussed by Dr. Francis G. Dunn and his colleagues of the Cardiac Department of the Stobhill Hospital, Glasgow, Scotland. Of great interest and importance is their discussion of the underlying mechanisms of ischemia—whether due to coronary atherosclerosis, microcirculatory dysfunction,

structural dysfunctional changes, or by endothelial dysfunction and neurogenic factors—which are reviewed clinically, diagnostically, and, of course, therapeutically.

Several other aspects of comorbid diseases associated with hypertension are discussed in the following articles. Perhaps the co-existence of diabetes mellitus and renal vascular dysfunction is of increasing importance because of our appreciation for the frequency of this complicating factor of diabetic vascular disease systemically and intrarenally in patients with hypertension is ever-increasing. Many nephrologists have pointed to the finding of proteinuria (or microalbuminuria) in the patient with diabetic renal disease that predisposes that patient to increased cardiovascular risk. However, we must appreciate that the existence of diabetic renal disease is the intrinsic renal vascular disease itself, which is part of the overall cardiovascular risk in these patients. This problem is discussed in clear detail by Dr. George L. Bakris, director of the Hypertension Center at The University of Chicago, and his colleagues. They discuss these and other aspects of the co-existence of the two diseases, including the current thinking about the approach to therapy and the various therapeutic trials that have served as the basis for our present-day recommendations for treatment.

Another aspect of the kidney and hypertension relates to the one underlying diagnostic cause of hypertension and its associated renal disease; and this relates to the diagnosis of renal vascular hypertension. One of our major authorities in this area is Dr. Stephen Textor, vice chair, Division of Nephrology and Hypertension at the Mayo Clinic in Rochester, Minnesota. His great experience with the diagnosis and the still-present controversies concerning its approach to therapy (eg, medically, surgically, and by endovascular stenting) is frequently sought out personally and at many national and international meetings. Each of these aspects of renovascular hypertension is highlighted in his review.

Still another co-existing problem associated with hypertension is that of exogenous obesity. An authority who has contributed much to this area over many years is Dr. Efrain Reisin, chief of the Section of Nephrology and Hypertension at Louisiana State University School of Medicine, New Orleans. He and his associate, Dr. Avanelle V. Jack, discuss many of the aspects related to the co-existence of these two very increasingly common problems. In their discussion, they cover the underlying pathophysiological mechanisms, the rationale for the nondrug as well as pharmacological approaches to each of the various classes of antihypertensive drugs, and the rationale for their use.

We conclude this issue with one of the major unresolved clinical problems with respect to the treatment of hypertension. This problem relates to the appalling number of patients who are known to have hypertension although they remain untreated optimally. This problem was initially termed as a “lack of compliance” in years past, suggesting that the fault explaining its existence resides with the patient’s refusal to be subservient to the managing physician. In response to this untenable argument, Dr. Harriet P. Dustan and myself suggested another term to the National High Blood Pressure Education Program years ago, one that relates to the lack of adherence, suggesting that both therapeutic partners are at fault. This term remains unsatisfactory, although many efforts toward its containment continue to frustrate. At the very best, these approaches remain incomplete. One committed and long-standing worker in this area is Dr. Marie Krousel-Wood, director of the Center for Health Research at the Ochsner Clinic Foundation and assistant provost, at Tulane University School of Medicine, New Orleans. Her epidemiological investigations on medication adherence (the Cohort Study of Medication Adherence among Older Adults) has been concerned with a number of heretofore unexplored mechanisms underlying the lack of

compliance or adherence to medication in patients with hypertension immediately following Hurricanes Katrina and Rita in New Orleans. One of the issues (in addition to the usual explanations for non-adherence) is the frequency of depression among these patients. While the ready explanation may be attributed to the many problems that can easily be associated with these tragic disasters, it may also be explained by the compounding of problems of a chronic illness, such as hypertension, or yet other mechanisms. To my way of thinking, her study is providing a fresh approach to this important clinical problem.

Perhaps one of the most recent of the many pathophysiological mechanisms underlying hypertension is the development of oxidative stress in hypertension. I have indicated above that in past issues we focused in great depth on the existence of many fundamental mechanisms participating in the mosaic of hypertension (in terms of the overall pathophysiology of the disease), but this relatively new mechanism has been shown to inter-relate with many other less appreciated mechanisms, including the role of the immune system and the expression of reactive oxygen species in the target organs of the disease. There is no doubt at this point that angiotensin II and its receptors are important actors in the process of oxidative stress in the response of the target organs of hypertension, most likely, in part, through the NADPH oxidases. Furthermore, at the rate that new biological mechanisms appear in the clinical literature, there is no doubt that this subject is an imminent and important topic for the clinician. To this point, Dr. David G. Harrison and his colleague, Maria Carolina Gongora, of the Division of Cardiology in the Department of Medicine at Emory University in Atlanta provide a most exciting discussion for us.

Thus, once again, I am excited and honored to have been invited to organize this symposium or issue of the *Medical Clinics of North America*. Presented herein is a current approach by clinical investigators with a lifetime commitment to our understanding of one of the most common multifactorial diseases. The overall material is thoughtfully presented and details new and current thinking of an important disease having major health implications.

Before I close my expression of many personal thoughts about hypertension and its understanding and clinical management, there is one more thought I wish to share with you, our readers. Today, there is a dearth of clinically oriented physicians committed to a systematic study of the underlying pathophysiological and clinical aspects of hypertension. On behalf of the various contributors to this issue of the *Clinics*, we hope that some of you who are also interested in this subject—particularly those still in your training years or early in your medical careers—have become stimulated in a field that has enjoyed many years of leading contributors. Please, therefore, accept our joint invitation to join us in this field. There are many investigators with exciting preclinical credentials, but we are in desperate need for new and fresh clinical blood.

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