Current Challenges and Unresolved Problems in Hypertensive Disease

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EARLIER CHALLENGES FOR REFLECTION

Organizing this issue of the Clinics on hypertension every 5 years or so has been a truly satisfying, stimulating, and a tremendously rewarding experience for me personally. This educational exercise has permitted me to review the present “State of the Art” by outstanding authorities of a remarkable and unusual area of medicine. On first reflection, I was compelled to look back upon an area of clinical medicine, which was responsible for most of the hospital admissions at the time when I entered medicine. These patients included those with cardiac failure, myocardial infarction, severe angina, dissecting aortic aneurysm, end-stage renal disease, malignant hypertension, hypertensive encephalopathy, and many other problems, which we now lump into a heterogeneous category of “hypertensive emergencies.” In fact, many of these latter problems have not been included in the hypertension symposia of the Clinics for the past 20 years.

In its place, I believe a far more relevant sequence of discussions now appear in the current issue. They include risks related to hypertension by the person who coined the term “risk factors” and was the leader of the Framingham Heart Study; new concepts participating in the pathophysiology of hypertensive disease, involving its target organs from local hormonal and humeral systems to the role of oxidative metabolic stress; an enlightened discussion of the metabolic syndrome by the editor of the new journal dedicated to that problem; the role of aging and an important consideration of the significance of the large arteries in hypertensive disease; a current analysis of the problems associated with hypertensive heart disease (including ventricular hypertrophy, its underlying risks, and epiphenomena; systolic and diastolic failure, oxidative stress, the co-morbidity of atherosclerosis); end-stage renal and renovascular diseases, with current concepts of their treatment; obesity; and current major concerns about the continued intolerable problem of lack of adherence to therapy in hypertensive disease management. How different are these challenging aspects...
of the hypertensive disease today when compared with our treatment of this subject almost 30 years ago.

The reader’s brief reflections on these foregoing topics, I am certain, are equally as mind-boggling as mine. So, if the reader will bear with me for a moment more, consider the major contributions by the clinicians and dedicated investigators on the underlying mechanisms of hypertensive disease over these many years. Bear in mind that the first multicenter, placebo-controlled, therapeutic studies were first introduced to the broad field of cardiovascular therapeutics by Edward D. Freis’ landmark innovation of the Veterans Administration that demonstrated the feasibility, safety, and efficacy of hypertension treatment over four decades ago. Remember, please, the developments that ensued in the succeeding generation of cardiovascular therapeutics, including the introduction of vasodilators for heart failure, cardiovascular remodeling, and reversing and preventing ischemia, fibrosis, apoptosis, and inflammation of heart, vessels, and kidney. And, during these years, we have witnessed over 70% and 50% reductions in deaths from stroke and coronary heart disease, respectively.

Consider further the introduction of the discipline of clinical pharmacology to medicine by our early hypertension investigators. Furthermore, please also consider the impact of antihypertensive drugs on other areas of cardiovascular, renal, and endocrine diseases, and the remarkably not-yet conceived endocrine roles of the heart, vessels, kidney, brain, and adipose tissue by cardiovascular investigators of hypertension. Finally, consider the tremendous impact of these innovative approaches to hypertension and their consequences on the dramatic reduction of cardiovascular, renal, neurologic morbidity and mortality over these years. With these considerations now fresh in your mind, I am delighted to introduce this issue for your study and reflection, with some of our current challenges. I have no doubt that the material presented will provide many new practical concepts and insights for many medical clinics, not only in North America but certainly, worldwide.

CURRENT CONSIDERATIONS

From the foregoing introductory remarks, one might come to the conclusion that the problems related to hypertensive diseases have been resolved. But, now that we have achieved many therapeutic challenges, other major issues have emerged for greater pathophysiologic understanding and more specific means of treatment. Thus, once again, I am delighted to share with you several extremely exciting areas for elucidation and study. Therefore, although we now understand many of the underlying pathophysiologic processes associated with cardiac, vascular, and renal involvement of the disease, we must now look into others that have emerged, as well as new concerns and more specific means of unresolved problems.

Genetic Concepts

To my way of thinking, individual genes underlying hypertensive disease are not usually related to specific, causative biologic mechanisms of what we currently term “essential hypertensive disease.” It is true that there are some forms of hypertension for which specific genes have and probably will continue to be identified. But for the tremendous numbers of patients with essential hypertensive disease, for whom an even greater number of their parents and their forbears had hypertension, the likelihood of identifying the multiplicity of genes involved is far too great a challenge to envision at this time. Although this may eventually come to pass with improved sophistication of understanding the mechanisms of polygenetic diseases, this concept does not seem immediately probable. However, what seems more likely is
that clinical investigators working at the bedside and in the laboratory may identify specific underlying biologic processes and their respective participating genetic mechanisms that will eventually provide new areas not only for diagnosis, but also for more specific forms of treatment. Indeed, they will provide new thinking and insights into these processes, as they relate to the target organ involvements of hypertensive disease. Personally, I believe that these newer findings will also explain how certain environmental stimuli interact with specific biologic processes that will help elucidate new mechanisms as to how and why target organ involvement develops under the extrinsic influence. These possibilities shall be discussed below, using as an example how dietary salt excess may operate to exacerbate hypertensive disease in the target organs (e.g., heart, blood vessels, kidney, brain). Therefore, it is not necessary to concentrate our intellectual resources on a search for a specific genetic cause of what appears to be a polygenic disease at the present time. Rather, we should focus much of our efforts onto more enlightened searches for identifying biologic processes that have been closely identified with hypertensive disease (e.g., salt or alcohol excess, obesity, and other issues) that interact with the myriad of specific mechanisms accounting for the many metabolic and other biologic alterations associated with hypertensive disease. Currently, many investigators are focusing on racial, gender, and other issues that have emerged as major biologic factors in our ongoing search for the potential causes of hypertension and other diseases.

TARGET ORGAN CONCERNS

Heart

Almost four decades ago, investigators initiated a series of studies directed to identifying the clinical correlates of hypertensive heart disease and, thereby, the potential mechanisms underlying the intrinsic risk associated with left ventricular hypertrophy (LVH). At the time, earlier ECG indices associated with the progression of LVH were identified. It was shown that even before overt LVH could be recognized, evidence of left atrial enlargement could presage development of eventual cardiac dysrhythmias that are associated with LV structural and functional changes related to LVH. Subsequently, the first echocardiographic (echo) study relating structural and functional changes to the progression of hypertensive heart disease was reported. Thus, the ECG changes of atrial abnormality were associated with LV structural changes (i.e., increased wall thicknesses and mass) that indicated early LVH. It was further demonstrated that with obvious LVH, there were more specific structural and functional ventricular alterations. Soon, these observations were related to the increased risk of LVH identified earlier by the team of investigators from the Framingham Heart Study, and subsequently, it was reported that all antihypertensive agents and other therapeutic interventions that decreased arterial pressure reduced LV mass.

Many investigators have confirmed these findings and related the therapeutically promoted decrease in LVH (by ECG or echo) to the efficacy of certain classes of these agents to “reversing hypertrophy.” At this point, we only know clinically that this treatment reduced LV mass, although actual reversed hypertrophy of the cardiac myocytes was not demonstrated. It was also learned that associated with the therapeutically reduced LV mass, certain agents decreased ventricular collagen content, whereas other agents actually increased the collagen. Investigators soon became concerned that certain antihypertensive therapy might convert the LV into a fibrous chamber, thereby predisposing the patient to early cardiac failure when that therapy was withdrawn. Studies have demonstrated that most of the currently used agents were able to maintain LV function, and efforts were then directed to the underlying mechanisms associated
with the risk of LVH.\textsuperscript{9–17} Our studies, and those of others whose work is detailed elsewhere in this edition of the \textit{Clinics}, demonstrated that the risk of LVH was not a result of the hypertrophied myocytes, but of the associated epiphenomena of ischemia, fibrosis, apoptosis, and inflammatory changes related to the LVH.\textsuperscript{18} Our conclusion and present clinical and experimental efforts therefore, is not to demonstrate “reversed hypertrophy or mass” but to prevent or reverse those fundamental underlying mechanisms that promote the foregoing processes of ischemia, fibrosis, apoptosis, inflammation, and whatever other comorbid processes that occur in the heart with LVH.

Indeed, there is abundant and important recent laboratory and clinical evidence that clearly indicated that the therapeutic classes in current use accomplish much of these goals (see the article “Current thinking about hypertensive heart disease” by Diez, in this issue). Thus, to direct current costly efforts to simply demonstrate reduction in size of the LV without ascertaining whether the associated pathophysiologic alterations are also affected, only defers the need to consider a new paradigm for the understanding of LVH and its treatment (ie, to reduce the underlying mechanisms of risk). For current evidence of this effort, the reader is referred to the cited references in this and other articles in this issue. Furthermore, we also refer the reader to the articles concerning hypertensive heart disease, cardiac failure (systolic and diastolic), and to the associated comorbid disease of hypertensive heart disease coexisting with atherosclerotic epicardial cardiovascular disease, elsewhere in this issue (see articles by Solomon and Verma, Ventura and colleagues, and Dunn and colleagues).

\textbf{The Large Arteries}

As our knowledge concerning the pathophysiologic development of LVH was revealed, so did our concepts concerning the changes that occur in the aorta and other large arteries. Our diagnostic and instrumental sophistication concerning the assessment of the structure and function of the large arteries has improved greatly. Much of this information has been stimulated by the works of Michel Safar, in France, and Michael O’Rourke, in Australia.\textsuperscript{19} The reader is referred to the article “Hypertension, systolic blood pressure and large arteries,” by Safar in this issue of the \textit{Clinics} and to a remarkable series of symposia, published approximately every 3 or 4 years in \textit{Hypertension}, organized by Safar and his colleagues. Essentially, the thesis, which has been elaborated, demonstrated that with aging there is an impaired distensibility and loss of elasticity of the large vessels, which results in structural and functional changes as well as impairment of the recoil ability (ie, the “Windkessel” phenomenon) of the aorta. Much of these functional effects are translated into the increasing systolic pressure and pulse pressure that occurs with the aging process, and with the associated increasing prevalence of systolic hypertension in the elderly. A more detailed discussion of this important subject is presented in the related articles of this issue on hypertension, systolic pressure, and large arteries, and that of aging and hypertension. (See the article “Aging versus hypertension” by Lakata in this issue.) These discussions are of vital importance, as we face the need to approach this increasingly prevalent problem that has been shown to be eminently treatable and can reduce the associated cardiovascular morbidity and mortality.

\textbf{Kidney}

For many years, the problem of progressive decrease in renal structure and excretory function in hypertension had been only perfunctorily addressed in textbooks of hypertension and nephrology, and referred to as “benign nephrosclerosis.” We now are acutely aware of the fact that there is nothing benign about these problems. Indeed,
there was a notable absence of information until very recently, and what was published related to changes in renal function and microscopic studies of the kidney that severely affected the patients’ overall health and the increased problem of end-stage renal disease. Much of the information that was available concerned the consequences of aging and the effects of diabetes mellitus. However, soon after the development of those therapeutic agents that inhibited the renin-angiotensin system, much valuable information became available and was initially focused on diabetes. I became concerned, however, that much physiologic and pathophysiologic data were extrapolated from experimental models that were in no way identical with that which could be attributed to essential hypertension with developing end-stage renal disease or in patients with diabetes mellitus. Early efforts were by Gomez, who employed formulae to ascertain the progression of glomerular and arteriolar functional changes in patients with essential hypertension. These measurements were discounted by those who were focusing on the changes that could be ascertained experimentally by the technique of renal micropuncture. Of course, this latter methodology technique is not feasible for use in the patient with hypertension with structural and functional impairment.

Notwithstanding, the renal hemodynamic and glomerular dynamic effects of disease and their response to antihypertensive agents were studied, and there is general agreement on the renal involvement in patients with essential hypertension and nephrosclerosis, as well as in experimental models and treatment of hypertensive renal disease. We have devoted much time and effort to the spontaneously hypertensive rat (SHR), whose naturally developing hypertensive disease is exacerbated by the endothelial nitric oxide inhibitor L-NAME. In brief, as renal involvement progresses, renal blood flow and glomerular filtration rate and the filtration fraction decline, while renal vascular resistance increases. Furthermore, in our micropuncture laboratory, single nephron renal flow, glomerular filtration rate, filtration fraction decrease as afferent, and efferent glomerular arteriolar resistance, as well as the glomerular hydrostatic pressure, increase; these changes are associated with adverse glomerular and arteriolar injury scores. Furthermore, we showed that the angiotensin converting enzyme (ACE) inhibitors, angiotensin II (type I) receptor blockers (ARBs), and calcium antagonists (including those that bind with L-, N-, and T-type calcium channel receptors) will prevent, and to some extent, reverse these changes. The aldosterone receptor inhibiting agent eplerenone will prevent the inflammatory damage, but provides far less dramatic hemodynamic effects. These findings are in accordance with the renal hemodynamic and functional effects of these agents (although some controversy remains with the calcium antagonists) in patients with essential hypertension and diabetes mellitus. Thus, at the present time, there is strong advocacy for the use of the ACE inhibitors and ARBs in these patients.

Furthermore, we found that the diuretic agent, hydrochlorothiazide, will aggravate the renal hemodynamic and glomerular dynamic involvement, and these changes are associated with further glomerular and arteriolar damage. However, when the diuretic is combined with an ACE inhibitor or with an ARB (or both), these adverse effects of the diuretic when used alone were prevented.

CONCERNS ABOUT LIFESTYLES

Smoking and Obesity

Much concern has been and continues to be focused on three major lifestyles that impact adversely on the outcomes of hypertension and its morbidity and mortality: tobacco smoking, exogenous obesity, and dietary salt excess. Clearly, important
inroads have been made in recent years to minimize the effects of smoking but, unfortunately, much more must be done. These changes have been accomplished by changes in social, political, and economic behavior, and this discussion will not elaborate further on this issue except for three important points. First, we still must make an impact on the continued increase in the smoking rates of women and young people. Second, while restrictions on places to smoke have been instituted, the effects of secondary smoking (so-called “side-stream” smoking) still must be emphasized. And, third, while the cigarette sales have been reduced selectively by certain vendors, it makes no sense at all to permit cigarette sales to take place in stores whose products are devoted to promote health (eg, food stores and pharmacies).

The second lifestyle concern relates to the widespread and increasing problem of obesity; this problem is only beginning to be addressed socially and economically. Our early studies have been directed to the hemodynamic effects of obesity and subsequent weight reduction, but these changes are not uniformly observed by all patients with obesity and hypertension. It is important, at this juncture, to recognize the more recent efforts addressed by our colleagues, dealing more biologically with the major problem of obesity in children as well as adults. These studies are now focusing on the biologic role of the adipocyte and are discussed separately in this issue (see the article “Hypertension and the metabolic syndrome” by Sowers.) There is no doubt that much new and exciting information will soon appear with pertinence for this important and vital concern as it relates to hypertensive disease. There is much valuable information that will relate to hypertension, diabetes mellitus, the hyperlipidemias, and other metabolic problems; however, caution is urged for all of us to assimilate this information without exerting proper attention to making precipitous conclusions related to a single pathophysiologic entity. Let us remember that clear-thinking internists made the association of hypertension and diabetes over 80 years ago. Moreover, in reports documenting their experiences with large numbers of patients with both diseases, the prevalence of diabetes mellitus in elderly patients with hypertension was no greater at that time as it is today. Furthermore, their definition of hypertension began at much higher arterial pressure levels that we employ today. The lesson is clear: all answers to present concerns of disease are not presently available, especially with respect to an area of study that is experiencing vastly new concepts and exploding biologic information.

Salt

Perhaps one of the more perplexing problems that has confronted those of us in the area of hypertension has been the role of salt as a major concern. Until the last century, mankind had only been concerned with salt in economic, social, political, and other nonmedical areas. Then, astute clinicians became concerned with the role of salt in diseases. At first this interest was related to hypertension; more recently, there has been a major interest in its role in other cardiovascular, renal, and neurologic diseases. One existing problem is the lack of an adequate explanation for the remarkably high correlation of salt to the underlying mechanisms that explain the epidemiologic morbidity and mortality data related to salt excess. Perhaps this is because the term “salt sensitivity” eluded a more primary cause-effect relationship than simply the provocation of an elevation of arterial pressure with intravenous or other means of excessive salt challenges. This relationship remains a major enigma because, if there is such a highly significant correlation between the daily intake of salt in large populations and risk of hypertension, one should wonder why the prevalence of salt sensitivity clinically with salt challenge should be as low as approximately
30%, when salt loads are administered to individual patients with essential hypertension.43

One of the problems with finding an explanation is in arriving at a testable definition of just what is meant by the term “salt sensitivity.” This term has been used clinically over many years to refer to the response of arterial pressure to salt-loading in either short-term clinical studies or in epidemiologic investigations; it has not been used generally for application by the clinician. Thus, it seems inappropriate to relate this term simply to the response of arterial pressure to salt overload. Rather, it seems wiser to demonstrate the response of salt-loading not only to the response of arterial pressure, but also the structural and functional responses of the target organs of hypertensive disease (ie, heart, aorta, vessels, kidney, and brain). This can be related to measurable sodium intake (ie, by 24-hour urinary sodium collections). I have arrived at this concept because the traditional relationship between arterial pressure and salt-loading has been highly correlated statistically in epidemiologic studies, a less frequent relationship tested epidemiologically rather than clinically with individual patients. Thus, over the past three decades our experimental studies have related chronic salt-loading in the SHR, a genetic form of hypertension,44 to the responses of not only arterial pressure, but to the structural and functional responses of the target organs of hypertensive disease. It has been most satisfying to see recent clinical studies concerned with target organ involvement by hypertensive disease (vide infra).

Our initial studies involved chronic dietary salt excess to increased cardiac mass even before arterial pressure and total peripheral resistance increased.44,45 In contrast, their normotensive control Wistar-Kyoto rats did not increase arterial pressure, but they responded by an increased cardiac output,44 suggesting that salt-loading exerts nonhemodynamic actions independent upon the response of arterial pressure. Our subsequent studies in the SHR demonstrated development of increased left and right ventricular mass associated with diminished coronary blood flow and flow reserve, increased fibrosis of the ventricular extracellular matrix and perivascularly, as well as impaired ventricular diastolic function, all important responses of the heart to aging.45–48 With respect to the age factor, all older adult SHRs and 75% of the younger adult SHRs demonstrated diastolic dysfunction with preserved systolic function, very similar to cardiac failure in adult patients with essential hypertension without conclusive atherosclerotic coronary disease. The remaining 25% of the younger adult SHRs demonstrated impaired systolic function with overt cardiac failure.47,48 Thus, with respect to the experimental laboratory cardiac responses to salt overload, there was a small but significant increase in arterial pressure; in addition, there was a more profound increase in ventricular fibrosis, bilateral ventricular ischemia, and impaired diastolic function.

More recently, clinical studies have confirmed our findings, providing credence to the highly common occurrence of cardiac failure (even without atherosclerotic coronary arterial disease).33,49 Subsequently, we extended these findings by treating older adult SHRs with an angiotensin II (type 1) receptor blocking agent (ARB) and prevented the development of ventricular fibrosis and ventricular diastolic dysfunction, which was remarkably unassociated with any reduction in arterial pressure.50 Additionally, in these studies we demonstrated that the cardiac alterations observed with salt overload was accompanied by impaired aortic distensibility, massive proteinuria, and severe renal dysfunction, which were also prevented by the ARB.50–52

These foregoing findings supported our conviction that prolonged dietary salt-loading promoted structural and function derangements of the target organs of hypertensive disease independent of its pressor action. We continued with our experimental studies on the kidney, using either 4%, 6%, or 8% chronic dietary salt loads.
group developed severe proteinuria (and microalbuminuria), even before arterial pressure increased slightly (but significantly), within 2 weeks before arterial pressure increased further over the entire 8 weeks of study, the same time employed without cardiac studies. Although it was not possible to perform renal micropuncture studies in those SHRs receiving the 8% salt overload, we did demonstrate diminished renal blood flow, glomerular filtration rate, and renal filtration fraction in these rats, as well as severe glomerular and arteriolar damage. However, in those SHRs receiving either the 4% or 6% salt overload, their renal micropuncture data demonstrated decreased single-nephron renal plasma flow and glomerular filtration rate, with increased filtration fraction, afferent and efferent glomerular arteriolar resistance, and glomerular hydrostatic pressure in proportion to the extent of the salt overload. In addition, microscopically, their kidneys demonstrated progressively more involved renal glomerular and arteriolar injury in proportion to the magnitude of the dietary sodium intake. More recently, using one of two different ARBs (including the agent used in our earlier cardiac study), the renal function and structural derangements were reversed without any pressure reduction.

These data have continued to support our initial hypothesis that the role of salt excess in hypertensive disease is far more complex than that which had been concluded from earlier epidemiologic studies (ie, that salt or sodium excess simply raises arterial pressure). We are therefore convinced that chronic salt excess produces and exacerbates the adverse structural and functional derangements in the target organs of hypertensive disease, and that this may be totally independent of its pressure-elevating action.

Recently, the Trial of Hypertension Prevention studies (TOPH I and II), involving 2,382 prehypertensive participants, reported that dietary sodium restriction (which had been previously shown to lower blood pressure) demonstrated highly significant cardiovascular risk reduction (by 25%–35%) than those individuals not receiving such a diet. The highly significant primary outcomes (ie, composite of stroke, myocardial infarction, coronary artery bypass graft, percutaneous transluminal angioplasty, cardiovascular death—even when those patients who had bypass grafts and angioplasty—were excluded) were demonstrated in the large group of prehypertensive subjects whose diet was not restricted in sodium intake. Thus, these findings provided further support for those earlier more controversial epidemiologic reports in which a single determination of urinary sodium excretion was used to demonstrate diminished risk of stroke and coronary heart disease. In addition, a number of clinical studies have been reported that demonstrated the structural and functional alterations associated with salt-loading and, taken together with the foregoing observation, strongly suggest that salt excess over a prolonged time produced not only an elevated arterial pressure in patients, but many of the long-term clinical derangements seen in patients, including progressive chronic diastolic cardiac failure with and without systolic dysfunction, increased prevalence of end-stage renal disease, and isolated systolic as well as systolic-diastolic hypertension. Furthermore, our experimental findings suggest that angiotensin II receptor blockade may prevent (or, at least, ameliorate) these severe target organ findings.

We have therefore postulated that the pathophysiologic changes that we have demonstrated experimentally may be mediated through local cardiac, vascular, and renal mechanisms that involve local renin-angiotensin and, perhaps also, aldosterone-(RAAS) mediated actions. In recent, years much evidence has accumulated supporting the existence of local RAAS systems in the heart, vessels, kidney, and in other organs. Thus, despite the abundant evidence that renin release from the juxtaglomerular apparatus is suppressed with sodium overload, while renal and cardiac
fibrosis occurs, we have documented that the use of small or large doses of ARBs produces impressive reversal of the structural and functional changes induced by sodium excess. Thus, a vast body of clinical information has accumulated over the years that have demonstrated the importance of inhibition of the RAAS in preventing cardiac, vascular, and renal endpoints of the disease. We therefore propose that dietary salt excess does not simply raise arterial pressure, but that it also promotes severe structural and functional alterations that promote cardiac and renal failure. We further postulate that dietary sodium restriction will prevent cardiovascular and renal outcomes through structural and functional pathophysiologic changes induced by sodium that are independent of the RAAS, and will further diminish that risk by reversing those structural and functional derangements. In further support of this concept, we must be aware that cardiac failure is the most common cause of hospitalization in Medicare patients in this country in hypertensive and normotensive patients, and end-stage renal disease continues to increase in these patients at an alarming rate.\(^{33}\)

**CONCERNS REQUIRING FURTHER THOUGHT**

**Prolonged Diuretic Use Without Cardiovascular-Renal Protection**

Over the years, successive national and international guidelines dealing with the evaluation, diagnosis, and treatment of hypertension have documented the increasing prevalence of cardiac failure and end-stage renal disease, despite the continued decrease in the morbidity and mortality resulting from stroke and coronary heart disease.\(^{33,34}\) Why this enigmatic occurrence takes place, despite the continued use of antihypertensive therapy, remains to be explained. Perhaps some of our thinking about this major concern may be offered from our experiences with salt excess experimentally and in clinical studies.

In many patients with hypertension, long-term use of diuretics promotes increased plasma renin activity. It is believed that this is promoted through local and systemic RAAS in heart, vessels, and kidney.\(^{40}\) These changes, in turn, may produce effects similar to the alterations that have been observed with prolonged dietary overloading with sodium excess. Furthermore, findings from experimental studies with prolonged treatment with hydrochlorothiazide that were produced by stimulation of the RAAS have been reported.\(^{35}\) Moreover, these data suggested that local RAAS stimulation may be prevented with cotreatment with either an ACE or an ARB agent.\(^{36}\) Others have also speculated on this occurrence and recent experience with salt excess and its effects on the target organs of hypertension.

**ISSUES THAT YET REQUIRE CLEARER UNDERSTANDING**

**Meta-Analyses**

Do studies involving meta-analysis have the full credibility of undeniable truths? One issue of concern is the acceptance of a metaanalytic report without some intellectual question. For example, a number of reports have been published in recent years that suggest that when one lumps all statistically acceptable articles into a statistically meaningful conclusion, that concludes that a specific approach to treatment is or is not acceptable. This has been raised in the area of at least two classes of antihypertensive agents in recent years: the calcium antagonists and the beta-adrenergic receptor-inhibiting drugs. The concerns about former agents have dissipated, for the most part. But excitement and controversy about the latter agents are more recent, and they threaten the well being of those individuals who have been the undeniable beneficiaries of their value. First, there are patients with hypertension who have
been taking beta-blockers for control of arterial pressure and cardiovascular symptoms, as well as for the secondary prevention of a recurrent myocardial infarction. These patients have been frightened by reports in the lay media of the lack of value of the beta-blockers (if not injury), just as other patients were concerned earlier about the calcium antagonists. As a result, they have pressured their physicians to discontinue the beta-blocker drug. Second, there are some patients with hypertension (for example, the younger patient with a hyperdynamic circulation) who have had excellent control of their blood pressure, with remission of their cardiovascular symptoms. Although these individuals may be less in number than other patients receiving this treatment, their consideration has been ignored in the sweeping conclusion of the almighty meta-analysis. Trialists supporting these reports have disregarded these relatively fewer patients in the sweeping conclusion made in their “evidence-based” reports. These remarks do not invalidate the concept of evidence-based medicine. Rather, one should remember the caution once made in jocularity at the height of the calcium antagonist controversy: “analysis is to meta-analysis as physics is to metaphysics.” Let us remember not to throw out the entire concept and rationale for the use of one form of therapy with the therapeutic bathwaters!

The Quest of the Holy Grail in Terms of “Biomarkers”

In recent years we have been captivated by the general acceptance of specific (or nonspecific) biomarkers. One such cardiovascular biomarker has been the C-reactive protein. There is much merit for using this index of pathophysiologic changes relating to the generation of specific inflammation or immunologic entities that suggest great diagnostic and therapeutic significance underlying an impending cardiovascular event. This biomarker is currently under intense study and has prompted the inquiry for introduction of other biomarkers of pathologic changes in other organs and diseases. Let us permit the scrutiny of the myriad of agents under study. Let us also remember the present day value of the erythrocyte sedimentation rate. It still is of value under certain circumstances, but should this measurement be done in all patients on hospital admissions, as has done until relatively recently? In this respect, we have recently witnessed the withdrawal of measurement of certain phase reactants for the patient with acute coronary syndrome following the abrupt decision by one respected institution. And what will be the ultimate fate of the brain natriuretic peptide measurement? Biomarkers are vitally important and have value, but should we rely on their value as an absolute index without great study and scrutiny?

What about Other Diagnostic and Therapeutic Issues?

At the present time we are awaiting judgment about the value for carotid and renal arterial stenting. At present there are several multicenter studies funded by the National Heart, Lung, and Blood Institute to provide recommendations from well-controlled studies. Let us not make premature decisions until the answers from these trials provide the appropriate rationale. And, in this relative lull in the introduction of new therapeutic classes for the treatment, let us once again await the recommendations from appropriate trials without precipitously initiating new forms of diagnosis or therapy without valid studies.

CONCLUDING THOUGHTS

Over the past four or five decades hypertension and cardiovascular medicine has experienced dramatic and innovative changes that have significantly reduced morbidity and mortality. A vast array of new antihypertensive compounds have
been developed that are able to affect the outcomes of many pathophysiologic mechanisms in patients with hypertension. The result has become a remarkably bright outcome for our patients with hypertensive disease. Many of these therapeutic breakthroughs have been the result of active participation of clinical scientists, with tremendous and remarkable knowledge of and experience with the fundamental mechanisms of disease. In more recent years, much new information has appeared concerning the basis genetic and biologic mechanisms involved in cardiovascular and renal diseases. New information, both fundamental and clinical, has appeared, and these advances have provided new means to develop and conduct new approaches to evaluate disease mechanisms and therapeutic actions. No doubt, much more will appear and enthrall us. In addition, innovative approaches to drug evaluation will become elucidated through individual studies into disease and drug mechanisms. These advances have been accompanied by mind-boggling multicenter controlled trials involving thousands of patient volunteers. Still more amazing is the realization and pride that many of these remarkable changes have emanated from the hypertension academic community. What remains of utmost importance is for members of the academic community with a wide spectrum of experience and points of view to continue to work intimately with industry. These associations are mutually beneficial and should include academicians with a wide spectrum of experience and points of view whose relationships must never be tainted, and who must always be open and known to practicing physicians, medical scientists, and to the general public.

REFERENCES


