In 1956, when I began my graduate medical training, knowledge of the pathophysiology of the hypertensive diseases was fragmentary, at best, and existing treatment was difficult and hazardous. Doctor Irvine H. Page had offered his “Mosaic Theory” as a concept of the multifactorial nature of hypertension as a means for thinking of the myriad of mechanisms where by arterial pressure is controlled, and how the disease develops when these underlying mechanisms go awry. At present, we still think of hypertension along the same lines even though the mechanisms involved in arterial pressure regulation have become more complex. It now appears that as we learn more about the fundamental genetic, biological and other mechanisms, this mosaic of mechanisms will become all-the-more multifactorial.

With respect to antihypertensive therapy, there has been an equally amazing explosion in the management of the diseases. The rice fruit diet had already been shown to be effective in some patients by 1956. Ganglion blocking agents were being employed by some confident and bold clinicians; and malignant hypertension was becoming treatable. Clinical trials with hydralazine, veratrum alkaloids and reserpine were in progress. Nevertheless, hospital beds were filled with patients who were admitted with hypertensive emergencies, congestive heart failure resulting from hypertension, dissecting aneurysms, strokes, coronary heart disease, and myocardial infarction. Already, the promise of controlling and preventing glomerulonephritis by treatment of beta-hemolytic streptococcal infections was recently established.

How fortunate that in one’s own professional career, it has become possible to grasp a firm hold on a major clinical problem and to control it. Indeed, over these 40-plus years, deaths from stroke had been diminished by almost 70%; and, from coronary heart disease, by upwards of 50%; and intensive care units have far fewer patients with hypertensive emergencies. A new era of preventive cardiology has been established; and what remains to be achieved is the need for the primary care physicians to be constantly vigilant for detecting and treating patients with hypertension.

Over these years, it has been my privilege to edit several Medical Clinics of North America concerned with advances in hypertension. During this time, it has
been a most rewarding experience to work with a number of clinicians who have markedly effected exciting and satisfying changes in our understanding and treatment of the hypertensive diseases. This current article, which appears in two successive issues of the *Medical Clinics* presents an exciting update, the first of which is more pathophysiologically oriented and the second more therapeutic.

In the first article, Doctors Jiang He and Paul K. Whelton provide a current update concerning the potential to prevent hypertension by employing some of the very newest epidemiological and clinical research data. It was Doctor Whelton, Dean of the School of Public Health at Tulane University, who chaired the first “Prevention Working Group” of the National High Blood Pressure Education Program and published an encouraging review in 1993 on the potential for the primary prevention of essential hypertension.

The “genome project” is currently three years ahead of its plans to identify the entire human genome; and it is anticipated that there will be 100,000 genes identified, each one perhaps providing a potential underlying mechanism of disease. In the second article, Doctor Richard Re, Vice President of the Research Division of the Alton Ochsner Medical Foundation and Head of the Section of Hypertensive Diseases at the Ochsner Clinic, provides a stimulating review of the potential underlying genetic and molecular biological mechanisms of the hypertensive diseases. There is no doubt in my mind that by the time the next review on hypertension is published, there will have been an explosion of new information on this topic.

This chapter is followed by an update of my personal overview of the underlying pathophysiologic mechanisms of hypertensive disease. Entire textbooks have been published on the subject of the pathophysiology of hypertension; but, in this article, the focus is primarily on those cardiovascular and hemodynamic factors that have emerged concerning development and elaboration of the vascular, cardiac, and renal involvement in hypertension focusing primarily on essential hypertension. Among these areas of current clinical concern are endothelial dysfunction, one major factor relating to the clinical expression of hypertensive coronary vascular and glomerular involvement of hypertension. Another area of continuing concern is the risk associated with left ventricular hypertrophy, an issue which once again, is updated.

One of my colleagues in my earlier studies of the heart in hypertension and the role of extracellular (including plasma) fluid volume status in clinical hypertension was Doctor Robert C. Tarazi, of the Research Division of the Cleveland Clinic. After I left Cleveland for the University of Oklahoma School of Medicine, Doctor Tarazi continued with his research work on the role of plasma volume in hypertension and was joined in his studies by Doctor Fetnat M. Fouad-Tarazi, who continues this work at the Cleveland Clinic. Robert Tarazi was a vital link in the chain of our studies on the heart in hypertension and was a good friend whose personal and academic loss remains great. Doctor Fouad-Tarazi writes on this with a discussion of additional hemodynamic factors associated with hypertensive heart disease, including the entity of diastolic dysfunction. She elaborates upon her personal interest on the interactions of sodium and volume factors with the autonomic nervous system as determinants in the control of arterial pressure.

Still another associate at the University of Oklahoma and, later on the staff of the Ochsner Clinic, was Doctor Francis G. Dunn. His were the first echocardiographic studies reported on the heart in hypertension, providing the sequential changes associated with the pathophysiologic and electrocardiographic correlates associated with progression of left ventricular hypertrophy. While at Ochsner, Doctor Dunn Began his work on the inter-relationships that occur with
coronary arterial disease associated with hypertension; and he continued with this work at Stobhill Hospital, in Glasgow, Scotland. It is clear that occlusive atherosclerotic epicardial coronary artery disease is a frequent co-morbid pathophysiologic disease associated with hypertension, but the small vessel (i.e., arteriolar) hypertensive disease underlies this problem. In their chapter, Doctors Vinjamur S. Srikanthan and Dunn summarize their thoughts on the important interface that exists between hypertensive and coronary artery disease.

Doctor L. Gabriel Navar, Chairman of the Physiology Department at Tulane University School of Medicine, expands upon these pathophysiologic concepts by providing a comprehensive discussion about the underlying renal and other physiological mechanisms involved in hypertension. His article covers the newer concepts concerning the: renin-angiotensin system, prostaglandins and other arachidonic acid metabolites, kallikrein-kinin system, other peptides and factors including the nervous system and control of sodium balance that have direct bearing on renal function in hypertension.

Doctor Harriet P. Dustan, an esteemed associate (initially at the Cleveland Clinic) and close friend, has been a tireless worker in the multiple vineyards of hypertension research and treatment. I was particularly honored to have had the opportunity to work with her and Doctor Page for a number of years in Cleveland. These were, indeed, the "halcyon days" of our research together (as we fondly look back on those years). Doctor Dustan has been a major force in our society (through public, volunteer, and research activities) in placing hypertension in the proper perspective for the National Heart, Lung, and Blood Institute, the Institute of Medicine, American Heart Association, and the American College of Physicians. She and Doctor Jeffrey M. Rimmer, of the University of Vermont College of Medicine, next focus upon the subject of renal arterial disease. Dwelling upon Doctor Dustan's experience with the N.I.H. Cooperative Study on Renovascular Hypertension and her early work that led to the development of clinical-pathoradiologic correlations of fibrosing and atherosclerotic renal arterial lesions, they update our understanding of current techniques for the diagnosis and eventual treatment of renal arterial disease.

Doctor Robert S. Zimmerman, another associate and a member of the Section of Endocrinology at Ochsner Clinic, contributes the next article. Doctor Zimmerman's special area of interest has related to the role of peptide and other humoral factors in the control of arterial pressure. The number of these factors participating in the regulation of pressure and in the pathogenesis of essential hypertension continues to increase. Among the more common endocrine mechanisms that have been incriminated in the pathogenesis of hypertension are the varied steroidal hormones, growth hormone, thyroid hormone and parahormone. Other factors include the catecholamines, the kalirein-kinin system, atrial natriuretic factor, endothelin and insulin. Doctor Zimmerman brings these considerations into his chapter thereby adding considerable breadth to our consideration of pressor mechanisms participating in pheochromocytoma, adrenal steroideal tumors, insulin sensitivity and resistance, and the broader issue of factors that participate in essential hypertension.

It is of particular interest to consider the role of aging in the pathogenesis of hypertension. As the hypertensive process progresses in severity and arterial pressure rises, total peripheral resistance increases and cardiac output declines. Moreover, organ blood flows including that to the kidney and the splanchnic organs also fall and, with it, so do organ functions. Each of these alterations mirror the changes that occur with aging suggesting that hypertension is a disease that could be characterized as one associated by a more rapid "ticking" of the biologic clock. Doctor Dinko Susic, a physiologist on the staff of the Research Division of the Alton Ochsner Medical Foundation, takes into these
considerations as well as other changes that are associated with atherosclerosis. In his article that follows, he suggests that one common mechanism which is shared by hypertension, aging, hyperlipidemias and atherosclerosis, is a dysregulation of endothelial function. Thus, with impaired generation of nitric oxide by the endothelium in the foregoing states (as well as even associated with cigarette smoking), local vasodilation is impaired and, with it, are changes that impair organ function that tend to increase the morbidity and mortality of the patient.

Two outstanding graduate students in physiology at the University of Oklahoma were Doctors Janice M. and Marc A. Pfeffer. Their work in expanding our understanding of the development of left ventricular hypertrophy and the hypertensive heart disease of the spontaneously hypertensive rat (SHR) was an exciting, stimulating and most rewarding experience for us all. Following Doctor Marc Pfeffer’s graduation from the medical school in Oklahoma, they continued their work at Brigham and Women’s Hospital, Harvard University. Their studies on the remodeling of the left ventricle following myocardial infarction have since become classic cardiovascular work in our understanding of the morphology of the ventricular chamber following myocardial infarction. Doctors Gary F. Mitchell and Janice and Marc Pfeffer discuss the heart and conduit vessels in the responses to pressure overload in the development of ventricular and vascular hypertrophy, with decompensation, as well as in response to treatment.

One important area of clinical investigation related to the kidney that has escaped major emphasis has been the role of the endothelium in naturally developing nephrosclerosis. Nephrosclerosis may develop naturally in the aging normotensive individual; but, for yet to be determined reasons, some patients with essential hypertension may demonstrate a progression of the nephrosclerotic process into endstage renal disease (ESRD). Over the past several years I was rewarded with my association with Doctors Hidehiko and Yuko Ono of Dokkyo University in Japan. In their work in my laboratory with the SHR, they demonstrated that these factors that may occur naturally; and they then developed a model for ESRD by administering to young SHRs an inhibitor of endothelial nitric oxide synthesis. Their article on nephrosclerosis and hypertension provides an exciting summary of this most important problem in today’s medicine. This is particularly important since ESRD in hypertension continues to increase progressively even though deaths from stroke and coronary heart disease is declining.

The remaining articles in these issues on hypertension relate to treatment. Ever since publication of the Joint National Committee’s Third Report on the Detection, Evaluation and Treatment of Hypertension, the role of nonpharmacological modalities (now termed “lifestyle modifications”) have been considered of major importance. Acceptance of these measures by the general public and, in particular, those individuals who may be at increased risk for later development of essential hypertension, has been of major importance. As a result of their broad acceptance, the numbers of patients in the United States with hypertension has significantly decreased from 59 to 43 million adults; and, with this reduction has been the very strong suggestion that there is a great potential for the primary prevention of essential hypertension. Doctor Efrain Reisin, of the Louisiana State University School of Medicine (New Orleans) and a long-standing clinical investigator in this area (particularly related to obesity hypertension), contributes the following article on the varying non-drug approaches to antihypertensive therapy.

Doctor Edward D. Freis was the first person to conceive of and to establish a multicenter, placebo-controlled drug trial that clearly demonstrated the safety and efficacy of antihypertensive therapy not only in controlling arterial pressure
but in reducing overall and cardiovascular morbidity and mortality. Under his leadership, his series of landmark Veterans Administration Cooperative Study reports have become a classical feature in the history of medicine. For this major work, Doctor Freis has been recognized for organizing and insuring the scientific conduct of these major findings that continue even until today. It is to the credit of the outstanding design of these studies and to their findings, that the Joint National Committee's Fifth (and forthcoming Sixth) Report(s) refer to the preference of the diuretics and beta-adrenergic blocking drugs for the initial treatment of hypertension. It is my honor and privilege to have begun my initial research work in hypertension under the aegis of Doctor Freis who has contributed the chapter on the current status of the diuretics, beta-blockers, alpha-blockers, and alpha-beta blockers in the treatment of hypertension.

Another very close friend from my Cleveland Clinic days is Doctor Ray W. Gifford, Jr. Doctor Gifford is the "clinician's clinician" in the area of hypertension, and is as "au courante" of the fundamental developments in the many areas of hypertension research as he is in the sphere of clinical practice. He served as the chairman of the Fifth Joint National Committee Report and continues to provide his expertise in the most practical areas of medicine, nephrology, and hypertension to the American Medical Association and the National High Blood Pressure Education Program. Doctor Gifford lends us his expertise in contributing to the next article on antihypertensive therapy as it relates to the angiotensin converting enzyme inhibitors, calcium antagonists, and angiotensin II receptor antagonists.

Over 20 years ago, Doctor Franz H. Messerli joined the hypertension group that we were developing at the Ochsner Clinic following his experience at Bern University in Switzerland and the Cardiovascular Research Institute in Montreal. Doctor Messerli focused his attention on the pathophysiologic characteristics of patients with hypertension and the hemodynamic and other mechanisms of action of the increasing number of antihypertensive agents that continued to emerge. As a result, a number of reports were forthcoming on the physiologic characteristics of essential hypertensive patients who were lean or obese, young or elderly, black or caucasian, male or female, and with or without target organ involvement. The series of reports that emanated from our hemodynamic laboratory pointed to a potential preselection of patients for antihypertensive patients based upon their demographic and physiologic characteristics. The concepts which ensued are included in Doctor Messerli's chapter which follows on hypertension in special populations of patients.

Hypertension has been the major cause of congestive heart failure ever since the Framingham Heart Study's earliest of reports in the 1960s and 1970s. More recently, its reports continue to indicate that hypertension continues to be a major cause of cardiac failure. The timeliness of this problem is only emphasized by the fact that heart failure is the most common cause of hospitalization in the United States today. Not only is hypertension a major underlying cause of cardiac failure today, but its treatment with cardiac transplantation and pharmacotherapy with the varied immunosuppressive agents is associated with further development of hypertension. This issue is discussed by Doctor Hector O. Ventura and his associates of the Advanced Heart Failure and Cardiac Transplantation Team (Doctors Mandeep R. Mehra, Dwight D. Stapleton and Frank W. Smart) of the Ochsner Clinic in their chapter on cyclosporine-induced hypertension in cardiac transplantation.

The final article of this two-part Medical Clinics is written by Doctors Isaac Kobrin, Vincent Charlon, and Michael Bursztyn. Doctors Kobrin and Charlon are in the Clinical Development Department of Hoffmann-LaRoche Laboratories and Doctor Bursztyn, of the Hypertension Unit of Hadassah University, Mount...
Scopus, in Jerusalem. It was Doctor Kobrin who joined our laboratory for a number of years to engage in some fundamental and clinical pharmacological studies concerned with hypertension and antihypertensive agents. Drawing from his experience, Doctor Kobrin and his associates discuss for us in the concluding article newer developments in antihypertensive drug therapy. Included in their discussion are the newer agents that antagonize vasopressin, endothelin, angiotensin, renin, and the calcium ion selective T-type channel receptors as well as inhibitors of renina and natriuretic peptide clearance.

I am truly grateful to the authors, friends, and colleagues for their continuing interest and support in this work of our mutual academic love. To these individuals, and a much larger number of colleagues and fellows, I am indebted for their past contributions, my continuing educational experience, and our joint efforts in the excitement of clinical and laboratory investigation. It goes without saying, however, that without the ongoing stimulation from my patients the search for “new knowledge” and experience would not have been possible.

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