OKAMOTO INTERNATIONAL AWARD LECTURE

Edward D. Frohlich, M.D., Alton Ochsner Medical Foundation, New Orleans, LA

First, I want to thank each of you for this very high honor and warm recognition that represents our mutual quest over these many years. We are all interested in a clearer understanding of hypertensive disease; and this award, named in honor of Professor Kozo Okamoto, represents for me 25 years of inquiry into the underlying mechanisms of essential hypertension in man as well as in an experimental model that continues to remain the best laboratory counterpart presently available for study of this world-wide ubiquitous disease, the spontaneously hypertensive rat. This honor is deeply appreciated, and I genuinely and sincerely express to you my heartfelt appreciation.

An award such as this cannot be accepted in my name only. I want to express my tremendous gratitude to the many fellows from Japan and from elsewhere around the world who came to my laboratories in Oklahoma and Ochsner over these years. I also wish to express my appreciation to my many colleagues at Oklahoma and Ochsner who collaborated with me in our studies. Each of these people labored long hours in the laboratory and at home with data analysis and manuscript writing to share out results with you and our fellow workers around the world. What a satisfying experience this has been! And what lasting memories!

Surely, such an honor cannot be received without expressing my unbounding appreciation to my wife Sherry and my children who have afforded me the many hours from their company, stimulation and love at home so that I could pursue these studies and share these experiences with our fellow scientists.

I also wish to express my appreciation to my institution and colleagues of the Alton Ochsner Medical Foundation and the Ochsner Clinic for the ambiance and resources so that we could continue this deep-seated commitment to understand hypertension better. To all, I express my deep gratitude for the professional career that has been a continuing source of satisfaction.

Over 30 years have flown by since Professor Kozo Okamoto and his hard-working team from Kyoto University introduced their genetic breed of spontaneously hypertensive rats, the SHR. Over these years, the SHR was made available for the broad use of investigators throughout the world to become the primary genetic experimental model for essential hypertension. AS you all know, Professor Okamoto deeply believed that the study of disease could be served importantly and provides a more comprehensive understanding by experimental models. To this date the SHR remains an invaluable means for elucidating the underlying disease mechanisms of hypertension as well as for the evaluation of mechanisms of action of innovative antihypertensive therapy. This picture from the American Heart Association's journal HYPERTENSION, presents Professor Okamoto along with Professors Yukio Yamori and Kuzo Aoki on the occasion of their selection to receive the esteemed CIBA AWARD in 1982 for their outstanding contribution to hypertension research.

It was about at that time, in the Fall of 1982, that I was deeply honored by many of you when I was invited by the Japanese Society of Hypertension to present the annual visiting lectureship. At this time, my wife and I were so very pleased to spend some time with Professor Okamoto along with his close friend and colleague Professor Yamori. We visited Nara together one most delightful morning, and then we enjoyed a most pleasant luncheon in nearby Kyoto. Those were most pleasant

days and I reflect warmly at the wonderful opportunity to visit personally with this remarkable foresighted scientist and physician whom we honor today.

Shortly after Professor Okamoto's first publication introducing his SHR strain, I discussed with Doctor Aoki on several occasions their new and exciting model of genetic hypertension. These conversations occurred while he was working with Doctors George Masson and Irvine Page at the Research Division of the Cleveland Clinic. At that time I was on the staff of the Research Division and was very interested in comparing the systemic and local hemodynamic characteristics of this new model of experimental hypertension with those of our patients with essential hypertension. However, before I could arrange to extend our studies to the SHR I left Cleveland to establish a new clinical and experimental hypertension program at the University of Oklahoma. Fortunately, soon after my arrival there, while attending a meeting at the National Institutes of Health in Bethesda, I met with Professor Yamori while he was at the National Heart Institute working with Doctors Lovenberg, Sjordsma, Spector and Udenfriend. One Saturday morning I came to Dr. Yamori's laboratory at five or six o'clock to bring the first of our SHR "breeders" to our Oklahoma laboratories. It was this unforgettable meeting that launched our team into our "SHR Odyssey" and into a warm personal contact with Drs. Yamori and Okamoto.

This slide presents to you my two close colleagues and dear friends, Doctors Janice and Marc Pfeffer. At the time that this picture was taken, Marc had just received his PhD degree prior to beginning his postdoctoral fellowship and his entrance into the School of Medicine of the University and before Janice began her doctoral work in physiology in my laboratory. At the time she was our most valuable research associate. The Pfeffers, with the help of my son Bruce (during his summers and weekends), carefully bred our rats in three different buildings on our campus so that, were an infection or any other disaster to occur, all would not be lost.

As a result, in an exciting sequence of studies, the three of us first adapted the new technology of quantitative electromagnetic flowmetry to the small animal. Until that time this had not been possible for the rat. We thereupon demonstrated remarkable similarity of the systemic and regional hemodynamic findings between the SHR and patients with essential hypertension. We demonstrated the role of cardiac output in the development and elaboration of hypertension in the SHR; similar stages of hypertensive heart disease with stable hypertrophy and left ventricular pumping ability until "old age" (of 90 weeks); similar ventricular geometric changes, in both forms of hypertensive LVH; and similar increased sodium sensitivity of resistance vessels. In addition, we were also able to obtain an excellent assessment of the hemodynamic effects of a wide spectrum of pharmacologic agents. In addition, we developed: a balloon-tipped catheter for measurement of mean circulatory filling pressure in the unrestrained conscious SHR; the first adaptation of radionuclide-tagged microspheres for quantifying organ blood flows and vascular resistances in conscious SHR; the description of a reproducible protocol for three-week treatment of male WKY and SHR to evaluate the local and systemic hemodynamic effects of various forms of antihypertensive therapy. These latter studies permitted the demonstration of a dissociation of the various hemodynamic and nonhemodynamic components responsible for the development and reversal of left ventricular hypertrophy.

The foregoing studies, from ours and others laboratories throughout the world continue to reaffirm Professor Okamoto's thesis that the SHR remains the best experimental model that is presently available that mimics the characteristics of essential hypertension in man. Both are subserved by polygenetic mechanisms that may relate to sodium sensitivity, various components of the renin-angiotensin system and, perhaps, neural mechanisms. Both are hemodynamically manifested by an increased total peripheral resistance that is more-or-less uniformly distributed throughout each of the organ circulations. In both forms of hypertension, left ventricular hypertrophy represents a structural adaptation to pressure overload, although we have also advanced the thesis that nonhemodynamic components may be dissociated in a series of studies related to both the development as well as the reversal of hypertrophy. Moreover, studies have also demonstrated pathophysiologically important participation of neural, renopressor, and intravascular volume components. For the most part, these findings have been supported by the similarity in the responses of both the SHR and patient with essential hypertension to the various antihypertensive agents.

More recently we have reported the biochemical responses of the heart to the various forms of antihypertensive therapy and the molecular biological support to the concept that reversal of left ventricular hypertrophy is, in part, an active process. We are also investigating the systemic hemodynamic and coronary flow and flow reserve responses to maximal treadmill exercise in the WKY and SHR. Other studies are exploring the various intrarenal hemodynamic characteristics of the untreated and treated SHR. The following segment of this lecture briefly summarizes some of these recent and ongoing investigations.

With respect to our studies concerning left ventricular hypertrophy, we have indicated that just as the mechanisms involved with development and elaboration of essential hypertension are multifactorial, so are those responsible for the development and reversal of left ventricular hypertrophy. In presenting this concept in 1988 at the Kyoto meeting of the International Society of Hypertension, I emphasized various aspects of this mosaic including those relating to the stage of disease, demography, the role of collagen and, or course, the evidence supporting local growth, humoral and hormonal factors.

Of concern therapeutically was the concept that, LVH is associated with its own intrinsic cardiovascular risk, independent of the height of systolic or diastolic arterial pressure; and we do not know whether pharmacological reversal of the hypertrophy would reverse that risk. Thus, hypertrophy develops in response to the increasing pressure overload over a prolonged time. However, with pharmacological therapy, the hypertrophy becomes diminished within as short a time as three weeks. This was first demonstrated in the SHR and, later, clinically. We were initially concerned whether the heart would be able to perform as well following reversal, particularly if therapy were suddenly withdrawn. Our studies demonstrated that not all therapy produced the same structural and functional responses. The prototypic drug that reversed hypertrophy, methyldopa, was associated with impaired pumping ability; and it not only reduced the mass of the hypertrophied left ventricle but also the nonhypertrophied right ventricle. Moreover, not all angiotensin converting enzyme inhibitors had the same structural effects on each of the cardiac chambers or on the pumping ability of the left ventricle. Furthermore, we demonstrated in the SHR, as well as clinically, that whereas both the ACE inhibitors and calcium

antagonists reduced the mass of the hypertrophied left ventricle, only the calcium antagonists simultaneously increased right ventricular mass while, for the most part preserving pumping ability. Recently, we demonstrated the biochemical correlates to these findings. Thus, whereas both the ACE inhibitors and calcium antagonists reduced left ventricular DNA was not reduced although RNA and collagen content were significantly diminished; and co-treatment with both agents had no additive effect on the left ventricle. However, whereas the right ventricle was unaffected by the ACE inhibitor, collagen content was increased by the calcium antagonist and this was prevented by co-treatment with the ACE inhibitor. Thus, the increased right ventricular weight produced by calcium antagonists was not produced by increased muscle mass but, by collagen deposition that could be prevented by inhibition of another biological system and co-treatment with an ACE inhibitor. Very recently, we continued to support our hypotheses that structural responses to antihypertensive therapy are actively mediated through non-hemodynamic biological mechanisms that may involve more than one molecular system. On this slide, responses to two different ACE inhibitors are presented. One agent induced expression of the *c-fos* proto-oncogene within three hours yet another ACE inhibitor produced this effect in six hours, and this response was far much weaker at three hours. This was also shown with *c-myc* and *c-jun*; and a protein stimulated by this early gene expression has also been elucidated. These molecular biological studies are under active investigation at present and underscore the possibility that reversal of left ventricular hypertrophy in the SHR with drug therapy is not simply a passive response to reduced pressure overload work but is a very active process.

Let us shift for a moment to the intrarenal circulation of the SHR. Using classical renal micropuncture techniques, we have demonstrated that the alpha-1 adrenergic receptor agonist phenylephrine produces an increased responsiveness of these receptors in the SHR efferent glomerular arteriole but not in the WKY. Moreover, inhibition of the alpha-1 adrenergic receptor prevented this increased responsiveness and decreased efferent arteriolar resistance in the SHR, but not the WKY. These studies were conducted acutely with intravenous administration of these agents. Indeed, most renal micropuncture studies in the SHR have been conducted have been conducted in this manner; they have not involved prolonged treatment with antihypertensive agents. We therefore elected to treat several groups of WKY and SHR in the same manner that we studied antihypertensive agents on the heart for three weeks using the usually prescribed antihypertensive agents: hydrochlorothiazide, hydralazine, the combination of both of these agents, the ACE inhibitor quinapril, the alpha-1 receptor antagonist terazosin, both of these agents, or simply their respective vehicles as controls. In these studies only two of these agents, hydralazine and quinapril, actually reduced efferent arteriolar resistance and glomerular hydrostatic pressure. Co-treatment of hydralazine with the thiazide attenuated the beneficial intrarenal hemodynamic response of hydralazine, and co-treatment with terazosin similarly attenuated these same beneficial responses of the ACE inhibitor quinapril. These findings provide, to our way of thinking, some very early inkling as to why the earlier antihypertensive therapeutic trials were not at all associated with reduction of the renal effects associated with hypertension.

Thus, over the past 25 years of study in our laboratory, each of our findings have continued to support Professor Okamoto's thesis, and that the SHR continues to remain a superb experimental model for patients with essential hypertension.

Moreover, these studies have afforded us the unique opportunity to move back and forth from the clinical setting to the experimental laboratory, investigating in the more controlled laboratory situation mechanisms and questions that could not have been approached clinically. This means to study disease is precisely what Professor Okamoto had in mind when he developed the SHR. There is no doubt that Professor Okamoto has provided the world with major fundamental laboratory models of disease. He has, therefore, importantly permitted a more comprehensive understanding and improved management of hypertensive diseases and stroke. Thus, through his SHR, Professor Okamoto continues to provide us his guidance, stimulation, support and friendship.

In closing, may I again say how honored and pleased I am to have been selected to receive this esteemed Okamoto International Award. In developing his strain of spontaneously hypertensive rats he has provided a continuing gift to science and his fellow man. Over these past 25 years this has permitted me and my colleagues and, of course, all of our research associated with the unusual opportunity to investigate more systematically the one enigmatic problem that continues to capture our professional intellect - hypertensive cardiovascular disease.

In behalf of my fellow workers, past and present, I am truly grateful to you for this wonderful honor and privilege. I am certain that you share with me the thought that there is nothing more valued to any of us professionally than the esteem of one's peers. In this spirit, I am particularly deeply grateful to Professor Okamoto for his lasting gift. Thank you so very much for your very warm, tangible and, personally, a very meaningful and memorable recognition of our research team's contributions.