Hypertension Research Program at Ochsner: A Program in Translational Research

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For over 26 years, Ochsner has sponsored one of the world's most respected and productive hypertension basic and clinical investigative programs. This dedicated activity has developed a "cutting edge" clinical program that has been translated into national guidelines for the evaluation and treatment of hypertension. Indeed, we have been an official member of the Joint National Committee since 1970 — even before it was formally organized. The past 3 decades have encompassed an exciting era of clinical and basic science research progress in hypertension, during which the Ochsner program has contributed importantly to the field. We have hosted many national and international research activities, provided the editorial leadership for the American Heart Association's premier peer-reviewed scientific research journal ***Hypertension***, contributed to the leadership of a large number of national and world governmental organizational advisory panels and societal bodies, provided specialized training to many American and foreign physicians and scientists, and served on the faculties of the Tulane and Louisiana State University medical schools, as well as shared our knowledge and contributions at most schools of medicine in the United States and other academic institutions throughout the world. In return, we have received high honors and recognition by many academic centers and organizations bringing much respect and kudos to the Ochsner Clinic Foundation. This report summarizes some of these achievements for our staff and friends.

FUNDAMENTAL RESEARCH

Our research philosophy has been imbued with the excitement that can be engendered by developing an adept facility able to move easily from questions generated in the clinical setting to answers that can be provided in the experimental research laboratory, and, conversely, the necessity to develop questions in the laboratory that can be answered at the bedside and in the clinic. Over the past 35 years, we have developed techniques in our experimental laboratories that have permitted the assessment of hemodynamic changes over the natural history of hypertensive disease in the spontaneously hypertensive rat (SHR). This is an animal model of naturally developing, genetic hypertension that was originally bred in Japan's Kyoto University (by Drs. Okamoto and Aoki) and which was then provided to us by the National Heart, Lung and Blood Institute (NHLBI) of the National Institutes of Health (NIH). The SHR has been a useful experimental analogy for essential hypertension in patients. Early observations made in our laboratories have been confirmed in patients and, conversely, those which we have observed in our patients have been elucidated and elaborated on in this model. Over the years we have been honored by Japan's prestigious Okamoto Medal and will again have the honor of lecturing on this subject in Tokyo in 2003.

Our laboratory was the first to adapt to the small animal electromagnetic flowmetry for measuring cardiac output, radioactively labeled radiomicrospheres for determining cardiac output and blood flow and vascular resistance for every organ in the body, and a small catheter-tip balloon for assessing mean circulatory pressure. We adapted echocardiographic technology for long-term studies in the rat for assessing the development of left ventricular hypertrophy (LVH) and diastolic and systolic dysfunction. (Ours was the first clinical laboratory to adapt echocardiography for the hypertensive patient.) Our most recent experimental studies have confirmed in the rat all of the hemodynamic and structural changes that have been associated with LVH in human patients, and we have extended these findings to research applications that would not be possible in humans. Further, our laboratories were among the first to study the physiological and pathophysiological actions of the atrial natriuretic peptide, and we were the first to identify this hormone in the human heart. Over the years, our contributions have provided a

useful classification of hypertensive heart disease, knowledge of the ability of antihypertensive drugs to reverse structural and functional alterations associated with LVH, and the effects of these drugs on organ circulations (including the kidney). These findings have explained the very high risks associated with LVH and end-stage renal disease: ischemia and fibrosis. These disease outcomes are not only reversible with treatment, but we have recently demonstrated that there is great promise for their prevention.

More specifically, our findings on the renal effects of hypertensive vascular disease, using the highly sophisticated technique of micropuncture of the vascular and filtering elements within the kidney, have demonstrated that certain antihypertensive drugs will reverse the functional and structural alterations associated with kidney involvement, whereas other therapy will exacerbate the disease. These studies have added to the promise that, with existing antihypertensive therapy, it is possible to not only reverse the effects of the disease on its target organs, but also prevent the pathophysiological changes from occurring.

CLINICAL RESEARCH

Ochsner's hypertension clinical research program was established in 1976 when we brought to this institution a number of staff members who have and continue to provide tremendous support to our program and to the worldwide hypertension effort. Among those physicians who have worked in our program and continue to remain at our institution, providing new clinical research and health care contributions are Drs. Fred E. Husserl, Franz H. Messerli, Richard N. Re, and Hector O. Ventura. Others who have served on our staff and have contributed to our overall research program include Jose de Carvalho, MD; Francis E. Cole, PhD; Gerald Dreslinski, MD; Francis G. Dunn, MD; Merrill B. Kardon, PhD; Alan A. MacPhee, PhD; Barbara L. Pegram, PhD; Nicholos C. Trippodo, PhD; Ephrain Reisin, MD; and Gerald M. Walsh, PhD. In addition, there has been a large number of fellows-in-training who are now members of important medical school teaching faculties on five continents. Each of their contributions and achievements have provided a clearer insight into the fundamental pathophysiological mechanisms of the hypertensive diseases through their research efforts in experimental and clinical hypertension, and a deeper understanding of the underlying mechanisms of action of every class of antihypertensive drugs that has been introduced over these years.

Our hemodynamic research laboratory achievements have been reported in the major international peer reviewed journals concerned with the cardiovascular actions for each of the pharmacological classes of the antihypertensive drugs. These studies have elucidated the actions of these drugs on the systemic and the regional circulations and their respective effects on circulating neurohumoral substances in response to short- and long-term treatment. These studies, therefore, have provided important data on the mechanisms of the actions of diuretics; alpha-, beta-, and alpha- and beta-adrenergic receptor blocking agents; angiotensin converting enzyme inhibitors; angiotensin II receptor blockers; calcium antagonists; and dopamine receptor antagonists. Ours was the first laboratory to suggest the specificity of these various groups of antihypertensive agents on patients belonging to specific demographic groups (whether they are black or white, lean or obese, young or old, men or women).

Our pathophysiologically oriented clinical studies have demonstrated the importance of the hyperdynamic beta-adrenergic circulatory state (which we initially described), and we have focused attention on the effects of hypertensive vascular disease on its target organs (particularly the heart and kidney). Our studies were the first to emphasize the importance and significance of LVH in hypertension by providing the first clinical classification of hypertensive heart disease and an exposition of the underlying mechanisms that explain the high risk of LVH on cardiovascular morbidity and mortality. We have recently demonstrated that this risk is not due to the enlarged cardiac muscle cells, ***per se***, but to the associated ischemia and fibrosis of the pressure-overloaded left ventricle. Our studies have continuously emphasized the need to identify the very earliest clinically identifiable indices associated with cardiac (left atrial abnormality) and renal (elevated serum uric acid concentration) involvement in hypertension and their respective prognostic significance.

SCIENTIFIC MEETINGS

Soon after I arrived at Ochsner, while serving on the Scientific Advisory Board of the International Society of Hypertension (ISH), our invitation was accepted to bring and host that Society's first meeting in the United States. In 1980, about 1500 ISH members came to New Orleans to learn of the advances in hypertension research and to hear of Ochsner's contriubtion to this area. This highly successful meeting was followed by other important national and international meetings. Ochsner hosted research study sections (the groups that recommend approval of research grant applications) of the American Heart Association (AHA), NIH, Veterans Administration (VA), and the United States Phamacopoeia. Additionally, a large number of research leaders came to our institution to visit and lecture from all over the world. We have conducted several international workshops that dealt with new concepts in cardiovascular medicine including molecular biology, the atrial natriuretic peptides, and the local cardiac renin-angiotensin-aldosterone system. The latter workshop was recently conducted at Ochsner and its proceedings are to be published in the ***Journal of Molecular and Cellular Cardiology***. A follow-up to this meeting will be held at Ochsner next year.

LEADERSHIP OF SCIENTIFIC ORGANIZATIONS

In addition to the ISH, we have served in important roles of other major organizations: President of the American Society of Clinical Pharmacology, Chairman (President) of the AHA's Council for High Blood Pressure Research, American representative to the Cardiovascular/Hypertension Committee of the World Health Organization, and representative of the American College of Cardiology (ACC) to the Joint National Committee of the National High Blood Pressure Education Program since 1971. We have also served on several advisory panels and scientific study sections (review panels for research grants-in-aid) for the AHA, VA, and the NHLBI, including Chairmanship of one NIH study section for 5 years and three Specialized Centers of Research in Hypertension review panels. We will chair another important NIH Study Section on Obesity later this year and another for the European Community. As an especially high honor, we served as Editor-in-Chief of ***Hypertension***, one of the five AHA scientific journals. Tenure of this editorship is for 5 years, but the author was invited to remain for an additional 3 years and a succeeding 1-year period until a succeeding editorial team could assume its leadership. Over these years, the journal increased its manuscript submissions twofold, its scientific impact factor, and its competitiveness and quality reputation. Other leadership roles have included Governor and member of the Board of Trustees of ACC, Chair of many ACC and AHA committees, and various committees of the American College of Physicians (of which the honor of Master was conferred), and the American College of Chest Physicians. We selected this latter organization for the annual presentation by Ochsner of its annual Alton Ochsner Award Relating Smoking and Health, which has been presented annually at its convocation for the past 16 years. [*see page 255, Ed.*]

TRAINING AND HONORS

During these years, over 130 physicians and scientists have come to Ochsner from five continents for research training in hypertension. All of our fellowship positions have been funded extramurally over the past 26 years. Many of these men and women came from Argentina, Brazil, and Japan; others were from China, Colombia, Great Britain, France, Germany, Israel, Poland, Spain, and Yugoslovia. These scholars returned to their home medical schools to continue their research and teaching, where they have assumed academic leadership roles. As a most flattering honor, we have been honored by memberships and awards from several of their national societies, and academic degrees, ***honoris causa***.

CONCLUDING REMARKS

It has truly been a pleasure and a most rewarding privilege to spend the majority of my career in hypertension research at Ochsner. Over these years I have been richly rewarded by the stimulation and satisfaction that I received from providing health care to my patients. It was their stimulation and clinical problems that have continued to provide me with ongoing questions about the disease that has been the preoccupation of my professional life. I am truly delighted that I remain in their service and continue with our research work. Many challenges remain in our understanding and treatment of problems associated with hypertensive diseases, but one personal observation preoccupies my professional thoughts. When I entered into medicine in 1956, treatment of hypertension was practically nonexistent. Those therapies that were available were either ineffective or were associated with severe side effects. Most hospitalizations at that time were related to complications of the hypertensive diseases: myocardial infarction, cardiac failure, hypertensive emergencies, strokes, and end-stage renal disease, among others. Today, patients with hypertension are managed year in and year out on an outpatient or clinic basis. Those requiring hospitalization today are usually for comorbid diseases or in specialized hospital units (e.g., coronary care, hemodialysis), and most of the latter patients are treated effectively and discharged. This is a thrilling observation for all of us to share. Finally, I have many thanks for my colleagues, fellows, associates, and our institution for allowing these experiences I have just shared to be possible.

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