The CIBA Award for 1985
A Full Circle in Two Generations

HYPERTENSION has been recognized as a physiological abnormality since the discovery of the sphygmograph by Vierordt in 1854. The instrument was soon adopted by physicians with considerable enthusiasm, more probably because it offered one of the few quantitative pieces of clinical information that could be recorded at that time than because of any recognized value provided either in determining prognosis or in helping define a course of therapy. Until the advent of modern prospective clinical observation there was but a highly argued hypothesis that essential hypertension had an effect on longevity. The grave prognosis of malignant hypertension, the inexorable course of which could easily be plotted within the time span of a single year, was well recognized but somehow thought to be different from the more benign-appearing essential hypertension. George Perera, one of my medical school teachers and a distinguished clinical investigator, preached as late as 1955 that there was no reason to treat any form of hypertension except the malignant variety because he knew of no convincing evidence that treatment did any good. He spiced his medical school lectures with anecdotes of elderly women with blood pressures of 200/130 whose conditions he had followed for more than twenty years and who were at that time as healthy as when he had first met them.

The CIBA Award for Hypertension Research recognizes major turning points in our understanding of essential hypertension. In 1981 William B. Kannel was recognized for his monumental documentation of the effects of hypertension on the cardiovascular system during the Framingham Study. In the same year, Edward D. Freis was lauded for demonstrating that the treatment of hypertension was of value in altering prognosis. Many subsequent studies have now confirmed beyond doubt that prolonged and significant elevations of blood pressure are harmful and that normalization of pressure is beneficial.

It is remarkable, however, that one of the major risk factors for cardiovascular disease in the Western world is so poorly understood with respect to its underlying etiological mechanisms. As the readers of this journal well appreciate, we are still at the stage of dissection of control points in the regulation of cardiovascular homeostasis. Leading candidates for exploration are the central and autonomic nervous systems, renal fluid, and electrolyte excretion and the endocrine systems that control it. The renin-angiotensin-aldosterone system was the first of the endocrine systems to be explored and it is of interest to trace this thread among the CIBA Awards and the Stouffer Prizes that preceded them. In each instance, the advance recognized by the award was the result of early and successful application of contemporary science to the problem.

In the early 1930s, Harry Goldblatt (Stouffer Prize, 1966) revived the discredited concept of a renal hypertensive hormone (promulgated by Tigerstedt and Bergman at the end of the 19th century) and unequivocally showed its relevance by elegant physiological experiments that were on par with the best of his generation. He demonstrated that impairment of renal blood flow resulted in the secretion of a pressor substance by the kidney. Hypertension might initially be reversible through restoration of blood flow, but in certain models malignant hypertension could be created that soon
led to death. The importance of this discovery was that it established a defined physiological mechanism responsible for a form of hypertension that could be examined in detail. Irvine Page (Stouffer Prize, 1970) pursued this idea in the late 1930s while working at the forefront of the enzymological concepts of his day. He deduced that renin was an enzyme that acted on a substrate in plasma to release a third substance that was actually responsible for the hypertensive effect, which he named angiotonin. At about the same time, Braun-Menendez and his colleagues in Argentina identified the same mediator, which they named hypertensin. Later, the two names were combined in the hybrid name angiotensin that we recognize today.

Peptide isolation, sequencing, and synthesis were in their infancy. Yet these early methods, now considered cumbersome and laborious, were applied by Leonard Skeggs, Jr., to working out the precursor-effector relationship between angiotensinogen and angiotensin I and II; by W. Stanley Peart in the determination of angiotensin's amino acid sequence; and by F. Merlin Bumpus and Robert Schwyzer, who independently proved angiotensin's structure by synthesis. These workers jointly received the Stouffer Prize in 1968.

Almost contemporaneous with the rapid advances made in peptide and protein chemistry was the study of steroids as major metabolic regulators. Leaders in this broad area of investigation were James and Sylvia Tait (CIBA Award, 1977). Among their many contributions was the identification and structural analysis of aldosterone, the major salt-retaining steroid in humans. This was the compound that John Luetscher (CIBA Award, 1977) had implicated as playing a major role in heart failure, nephrosis, and sodium depletion; that Jerome Conn (Stouffer Prize, 1969) had involved in adrenal cortical hypertension; and that Jacques Genest, Franz Gross, and John Laragh (Stouffer Prize, 1969) and James Davis (CIBA Award, 1975) had linked to renin by demonstrating that its secretion was regulated by angiotensin II. Thus, angiotensin was shown not only to affect vasomotor tone directly, but also to regulate renal sodium excretion through aldosterone. Sergio Ferreira (CIBA Award, 1983) found snake venom peptides that inhibited an enzyme that was responsible for the degradation of bradykinin as well as the conversion of the prohormone angiotensin I to the active hormone angiotensin II, and then David Cushman and Miguel Ondetti (CIBA Award, 1983) converted this discovery into a practical drug, captopril, that has found widespread contemporary application in the treatment of hypertension. In the course of this orderly progression of research over a period of some 40 years, from the demonstration of the physiological role of renin to the clinical application of agents that block the renin-angiotensin system, very little was known of the structure and function of the central character of the drama, the enzyme renin itself. The solution had to await necessary progress in protein chemistry and molecular biology. Renin is a highly active enzyme and is present in the kidney in very low concentration. Though often attempted over the years, available methods of fractionation and purification were inadequate to obtain sufficient quantities of material for conventional amino acid sequence analysis. The CIBA Award for 1985 recognized two different solutions to the problem. Tadashi Inagami refined purification methods by the application of modern concepts of affinity chromatography and took advantage of the latest automated protein-sequencing methods to produce a complete structure of the renin molecule. Pierre Corvol and Joël Ménard avoided the protein altogether and inferred its structure from the RNA sequence, utilizing the modern technology of complementary DNA cloning. The two independent solutions agreed remarkably.

It would be tempting now to assume that a chapter in the hypertension story is complete, that the circle of discovery from Goldblatt to Corvol, Ménard and Inagami is closed. Yet for all the brilliant insights that are represented by these awards, we cannot yet define the precise role of renin in essential hypertension, even though renin blockade has become a major and surprising denouement.

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