Renal Hypertension*

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The advances in our knowledge of renal hypertension over the last 75 years represents outstanding accomplishments in experimental and clinical medicine. A review of the highlights of this important investigation in hypertension should begin with Tigerstedt and Bergman's work in Scandinavia which demonstrated in 1898, that extracts of kidney possessed a hypertensive action. They gave the name "renin" to the impure substance which produced this effect. For the next 30 years much work was done on the vasoconstrictor action of extracts of the adrenal medulla, the nervous system and the kidney.

At the height of the depression, Harry Goldblatt, with a few hundred dollars, began his investigations on the production of hypertension. His classical report in 1934 gave investigators an easy method of producing permanent renal hypertension. He used a tiny adjustable silver clip on the renal artery of dogs to produce partial or incomplete ischemia of the kidney. His work was confirmed promptly by many others.

In 1938, Fasciolo, Houssay and Taquini in Argentina, by cross-venous techniques, demonstrated that the ischemic kidney produced a hypertensive substance, renin. In 1939, Braun Menendez and his group in Argentina extracted a substance which they called hypertensin, produced by the incubation of renin with plasma globulin or hypertensinogen. Page and Helmer, almost simultaneously in the United States, reached similar conclusions but used different terminology, renin plus renin activator produces angiotensin.

Over the next 15 years much work was done on these extracts and enzymes. Finally, a decapeptide substance was identified. In 1956, Skeggs showed that a converting enzyme made the substance an active vasopressor material by splitting off two amino acids.

A year later, Bumpus in the United States and Rittel in Switzerland synthesized angiotonin or hypertensin, depending on which group was involved. A year later, Page and Braun Menendez got together and came up with the bastard term—angiotensin. Levels of renin activity in patients were determined by the bioassay technique perfected by Gunnels until 1969, when Haber described a practical radioimmune assay for angiotensin which has gained wide acceptance by the medical profession.

On the clinical side, Butler in 1937, published the first report of nephrectomy for unilateral pyelonephritis with relief of hypertension. This began the era of nephrectomy for all sorts of diseases with the hope of relieving hypertension. In 1939, Blackman examined at time of autopsy renal arteries of 50 patients with so-called hypertension. A high percentage of arteries (87%) had arteriosclerotic plaques and 54% were found to have severe stenosis. This report was not accepted at the time by the profession. In 1944, Yuile classified renal artery obstruction occlusive disease into extrinsic and intrinsic types. Finally in 1948, after many years of indiscriminate renal sacrifice, Homer Smith laid down the criteria for cure of hypertension, 145/90, and this closed the era of imprecise diagnosis of renal hypertension.

In 1950, Parke Smith and Arthur Evans in Cincinnati published a large series of translumbar aortograms with a low incidence of complications, resulting in a wave of popularity for aortography by urologists and later vascular surgeons. Up to that time, it had not been widely accepted by the medical profession in the United States. In 1952, at the Cleveland Clinic, we began to apply aortography in hypertensive patients. In 1954, Freeman and his associates reported the first case of endarterectomy of the renal artery with relief of hypertension. In 1954, Howard and his colleagues at Johns Hopkins

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published their classical report of cure of hypertension by nephrectomy. They called attention to the importance of careful scrutiny of the intravenous pyelogram for renal atrophy and to the fact that urine from the affected kidney had a lower sodium concentration and lower urine volume.

In 1957, the first report on the use of homografts for correcting fibromuscular hyperplasia of the renal artery appeared. Since then many techniques have evolved for the correction of all kinds of renal artery disease.

Renin is a proteolytic enzyme with a molecular weight of about 40,000. Its only known activity is to break a specific leucine-leucine bond on renin substrate produced in the liver. Renin originates in the granular cells surrounding afferent arterioles adjacent to renal glomeruli. These juxtaglomerular cells, along with a few specialized distal tubular cells (macula densa) in the same region, form the juxtaglomerular apparatus. This structure may be considered a combination baroceptor and sodium sensor.

After renin acts on the substrate, angiotensin I is formed. As it passes through the circulation, it is acted on by the converting enzyme to form angiotensin II, the vasoconstrictor material causing arterial constriction and hypertension. Angiotensin II is also a major stimulus for aldosterone secretion by the adrenal gland, providing a feedback mechanism and completing the cycle initiated by renin release. Renin is inactivated in the liver, and angiotensin II is probably inactivated at its receptive sites. This is a dynamic, rapidly responding circuit. Renin is released within a few minutes after appropriate stimulation. Decline is equally rapid. Among recent discoveries, plasma and tissue enzymes have been found to exist which are capable of degrading angiotensin I and II to form a heptapeptide which exerts a powerful influence on the adrenal cortex to secrete aldosterone and preserve sodium.

We have used Haber's radio-immune assay technique for the last two and one-half years in Dr. Wan's biochemical laboratory at Norfolk General Hospital. This is a specific assay for angiotensin I generation rate, which in most situations provides a correct measurement of renin activity. Nearly 400 measurements of plasma renin activity were made between August 1970 and December 1971; over 900 determinations, which included 56 bilateral renal vein determinations, were done in 1972. Approximately 20 patients were selected for operation in 1972. In the first two months of 1973, we have operated on nine patients who have had this investigation recently at Norfolk General Hospital, reflecting in part the increased interest in renal hypertension since the use of renin assays on a wide scale.