CHAPTER 4

A BRIEF HISTORY OF
THE STUDY OF BLOOD PRESSURE CONTROL

Although the seriousness of high blood pressure in humans was appreciated in the 19th century, few studies were undertaken to help understand and correct the problem. Then in the 1900's the pace quickened with a rapid succession of advances. First one, then many, reliable experimental models came into general use. The renin-angiotensin system was discovered and characterized in considerable detail. The importance of sodium was investigated using dietary manipulation, epidemiological studies, animal models, and lessons from the management of patients with renal disease who were undergoing chronic hemodialysis. Most recently, the subtleties of neural dysfunction have been studied using sensitive assays for catecholamines.

THE SITUATION BEFORE 1900

Dr. Richard Bright (born 1789 - died 1858) of Guy's Hospital in London characterized a syndrome in 1827 that included albuminuria, atrophied kidneys, hypertrophied heart, vasoconstriction, and apoplexy (stroke). But, there were only minor additional advances in our understanding of hypertension over the next century or so. This was partly due to a lack of suitable experimental models. Wakerlin (967) has provided a concise history.

GOLDBLATT'S TECHNIQUE PRODUCED THE FIRST RELIABLE EXPERIMENTAL MODEL

In 1934, Dr. Harry Goldblatt of Western Reserve University in Cleveland described a hypertension that could be reliably produced in dogs using a clamp placed on the renal artery (353). Initially, in fact, bilateral clamps were used and Goldblatt thought that tightening the clamps produced a renal ischemia that somehow caused elevated arterial pressure.

Previous investigations had evaluated one form of renal
insult or another but with little success. For instance, Lundin and Mark in 1925 (609) showed that reduction of renal mass sometimes led to increased arterial pressure and Dominguez (240) attempted to produce hypertension by injecting uranium. Apfelbach and Jensen (26) injected particles of charcoal into the renal artery. These procedures usually produced severe uremia rather than hypertension.

Goldblatt's procedure produced the first truly reliable experimental model and it has been used most extensively ever since. A connection between the suspected renal ischemia and elevated pressure was provided by the subsequent characterization of the renin-angiotensin system. The following conclusion was a natural one: renal artery constriction leads to increased renin secretion by the kidney and the resultant increase in angiotensin production causes vasoconstriction and hypertension. Subsequent studies have indicated that the complete explanation will not be this simple in the majority of cases.

CHARACTERIZATION OF THE RENIN - ANGIOTENSIN SYSTEM

Although Tigerstedt and Bergman (622), (932) at the turn of the century demonstrated a pressor substance in the kidneys of rabbits, this observation was not utilized further in the years immediately following their report. Then in about 1940 both Page at Indianapolis (733) and Braun-Menendez and colleagues (105) in Argentina independently found a substance of renal origin that by itself was inactive. But, it was either activated by plasma or was involved in a reaction in the plasma that led to the formation of a vasopressor substance.

In the 1950's the vasoactive substance was shown by Skeggs and colleagues in Cleveland (876) and Elliot and Peart in London (256) to be a peptide, angiotensin II, that was formed from another peptide precursor, angiotensin I. The name "angiotensin" was a condensation of "angiotonin" suggested by Page and "hypertensin" suggested by Braun-Menendez (731).

The first chemical determinations of renin and angiotensin were indirect and most difficult. The involvement of the renin-angiotensin system in the genesis of hypertension was supported more by inference than by firm documentation. With accurate determinations of plasma