The Goldblatt Memorial Lecture

Part II: The Role of the Kidney in Hypertension

NORMAN M. KAPLAN, M.D.

As one reviews the extensive writings of Dr. Harry Goldblatt, one theme remains constant: the kidney is responsible for hypertension. In searching for the role of the kidney in primary or essential hypertension, Dr. Goldblatt elucidated the role of the kidney in the major forms of secondary hypertension. Goldblatt's major findings were:

1. Partial clamping of renal artery induces permanent hypertension with preservation of renal function
2. Severe renal ischemia produces malignant hypertension
3. Relief of renal ischemia relieves hypertension
4. The hypertension of renal ischemia is induced by a humoral mechanism.

These findings led to the clinical recognition of renovascular hypertension, the application of surgery for its relief and the elucidation of the role of the renin-angiotensin system in the physiology of health and the pathogenesis of disease.

In the 45 years since Goldblatt's publication on the experimental induction of renovascular hypertension, overwhelming conclusive evidence has confirmed his view that renal ischemia is the cause of the hypertension and that this comes about by the release of increased amounts of renin from the ischemic kidney. Considerable confusion in the experimental and clinical literature resulted from the admixture of "one-kidney Goldblatt" and "two-kidney Goldblatt" models. As these two models have been correctly applied to clinical disease, the "one-kidney" model — one kidney clipped, the other removed — has been recognized to be a prototype for hypertension accompanying chronic renal disease with volume excess as the primary mechanism, while the "two-kidney" model — one kidney clipped, the other intact — is the counterpart for renovascular hypertension with renin excess as the driving force.

The evidence that renal ischemia evokes an excessive secretion of renin and thereby hypertension has been reviewed elsewhere along with the evidence that an inappropriately continued section of lower levels of renin likely contributes to the hypertension of chronic renal disease. In a word, the evidence, both experimental and clinical, overwhelmingly supports Dr. Goldblatt's views concerning hypertension from renal ischemia.

This paper will address the original question posed by Dr. Goldblatt: What is the role of the kidney in primary hypertension? The evidence to be presented will support Goldblatt's contention that the kidney is fundamentally involved but in a manner different from his concept. Whereas Goldblatt believed that structural damage, i.e., nephrosclerosis, was the initiating event, subsequent investigations by numerous people have placed functional derangements as the primary defect, leading in turn to structural damage.

Before proceeding, let us remember that no one single abnormality is likely to explain the entire hemodynamic disturbance. Cardiac output, body fluid volumes, peripheral resistance and all of the multiple factors that influence each of these must be involved. As succinctly put by an editorialist in Lancet, "Few factors which play a role in cardiovascular control are completely normal in hypertension: indeed, normality would require explanation since it would suggest a lack of responsiveness to increased pressure."

One more preliminary point should be made: the data to be presented have almost all been collected from patients thought to have early essential hypertension. Unfortunately the duration of elevated pressures in most patients cannot be ascertained and the critical determinants of hypertension may have already faded into another pattern by the time the blood pressure is definitely high. In the absence of long-time,
Intermittently increased sympathetic activity

Increased renin release

Constriction of renal efferent arterioles

Increased filtration fraction

Increased sodium reabsorption

Thickening of resistance vessels

Relative fluid volume excess

Increased peripheral resistance

Decreased renin release

Permanent hypertension

Nephrosclerosis

**Figure 1.** An overall hypothetical scheme for the pathogenesis of essential hypertension starting with an intermittently increased level of sympathetic activity.

Longitudinal studies from early life until the disease becomes established, data such as we now have will have to be used. But as more patients with early disease are studied, the data have become more uniform and compatible, providing the basis for the hypothesis that follows.

And lastly, only human studies are described. As fragmentary as they may be, the proper study of human hypertension must involve human subjects.

**Overall Scheme**

Presuming that the process must start somewhere, this hypothesis places the beginning at an intermittently increased sympathetic nervous activity, acting within a genetically predisposed subject (fig. 1). The stresses of modern life provide more than enough background for intermittently increased sympathetic nervous activity. Only those genetically predisposed or overwhelmingly stressed would proceed down the hemodynamic path to permanent hypertension.

**Evidence for Increased Sympathetic Activity**

A number of hemodynamic findings in early hypertension are most compatible with an increase in sympathetic activity. Evidence for an overactive sympathetic nervous system in early hypertension includes various hemodynamic consequences of increased sympathetic activity, such as fast pulse, increased stroke volume, increased cardiac output, redistribution of blood to central veins, elevated plasma catecholamines, high plasma renin levels (which are more prevalent in the young), and finally, increased renal vascular response to stress. Although the hyperkinetic circulatory state, first recognized in young hypertensive patients in 1957, may not invariably initiate the disease, there is a strong tendency for the cardiac output to be high at first and, with time, for peripheral resistance to go up as cardiac output falls.

As techniques for measuring blood catecholamines have improved, high values have been found, with a positive correlation noted to the level of diastolic blood pressure. Some of the higher levels in hypertensive subjects may be attributable to the fact that their age is frequently older than the control populations, but, when suitably matched, those with hypertension have been shown to have higher plasma catecholamine levels which respond more to various stresses (fig. 2).
Increased Renin Levels

The highest plasma catecholamine levels have been found by some but not by others in those younger, early hypertensive patients with the highest plasma renin levels. Stimulation of the renal sympathetic nerves or exposure of the kidney to increased circulating β-adrenergic agonists will increase the release of renin, so the connection is a logical one.

Assuming that, as hypertension develops, the high systemic blood pressure is transmitted into the renal afferent arterioles thereby activating the baroreceptor mechanism within the juxtaglomerular apparatus, renin levels should be suppressed. Although no longitudinal studies of renin levels during the course of essential hypertension have been done, inappropriately high renin levels have been found in patients with apparently mild, uncomplicated hypertension. And, there is ample documentation of a progressive fall in average plasma renin levels with advancing age of the hypertensive population in cross-sectional studies. Thus, in early hypertension, renin levels tend to be inappropriately high and this may reflect increased sympathetic activation of renin release.

Renal Vasocostriction

The secondarily increased renin levels, in concert with the increased plasma catecholamines, would induce renal vasocostriction. As shown both functionally and by direct observation, this vasocostriction affects the efferent arterioles to a greater degree, resulting in a greater reduction in renal blood flow than in glomerular filtration, thereby producing an increase in the filtration fraction. With increasing mean arterial pressure, renal blood flow (RBF) tends to fall and filtration fraction to rise.

Radioxenon measurements of renal blood flow have provided strong evidence for a sympathetically mediated, reversible, intrarenal vasocostriction in early hypertension. These measurements were taken from 65 hypertensive patients, all under 35 years of age and most known to have hypertension for less than 2 years. When compared to the findings in 119 normotensive subjects of similar age, the renal blood flow averaged 20% below normal in about two-thirds of the hypertensives (fig. 3). In the remaining one-third, RBF was increased by an average of 20%, resulting in two Gaussian distribution curves.

This reduction in RBF in the majority of young, early hypertensive patients likely is mediated by increased sympathetic nervous activity since it usually could be reversed by the adrenergic blocker phenotolamine. The functional, active nature of the vasocostriction was further supported by the marked variability on sequential blood flow determinations, averaging more than twice the variability observed in normal subjects and patients with renovascular hypertension.

Thus, there is good evidence for a functional increase in renal vascular tone in early essential hypertension, which affects efferent arterioles more than afferent arterioles, resulting in an increase in filtration fraction.

Increased Sodium Reabsorption

The increase in filtration fraction results in an increase in sodium reabsorption. Though various intrarenal mechanisms may be involved, the most likely sequence is that the increase in glomerular filtration removes more water from the blood which circulates around the renal tubules, thereby increasing the peritubular oncotic pressure which acts as a stimulus for increased reabsorption of sodium from the tubular fluid (fig. 4).

This sequence involves a resetting of the normal pressure-natriuresis curve which Guyton and coworkers have postulated to be an essential pathogenetic mechanism for the development and persistence of hypertension. In the normal kidney, any rise in arterial pressure immediately leads to an increase in renal sodium and water excretion, shrinking effective blood volume enough to return the blood pressure to normal.

In the hypertensive kidney, where the pressure-natriuresis curve is reshifted presumably from the increased renal efferent arteriolar resistance, sodium excretion is not increased so that blood volume remains normal and the blood pressure remains high (fig. 5). With further rises in blood pressure beyond the reset point, the pressure-natriuresis mechanism comes back into action to modulate the rise in pressure.
**Fluid Volume Excess**

This sequence implies a relatively normal blood volume, inappropriately normal for the higher level of blood pressure but not expanded beyond the preexisting level. Such “inappropriately” normal blood volumes have been found in early hypertensives (fig. 5). The 106 hypertensives included in these data appear to have fairly early and mild hypertension with a mean age of 39 years and normal creatinine clearances.

In the 48 normotensives, total blood volume, measured under controlled conditions with an isotope-dilution technique using radiiodinated albumin, fell as diastolic blood pressure levels rose toward higher, but still normal, levels. In the hypertensives, blood volume was not usually lower as the level of blood pressure increased, so that 80% of the values fell above the 95% confidence levels of the normal curve. The authors use the difference between the normal relationship and that found in the hypertensives to calculate the degree of pressure-volume disturbance (ΔTBV). Whether or not such data can be used to quantitate the disturbance, they strongly support a

**PRESSURE NATRIURESIS**

- INCREASED ARTERIAL PRESSURE
- INCREASED PERITUBULAR HYDROSTATIC PRESSURE
- DECREASED Na+ REABSORPTION

**RESETTING IN PRESENCE OF HYPERTENSION**

- INCREASED RENAL VASCULAR RESISTANCE
- INCREASED FILTRATION FRACTION
- INCREASED PERITUBULAR ONCOTIC PRESSURE
- INCREASED Na+ REABSORPTION

**Figure 4.** The presumed mechanism for normal-pressure natriuresis (left) and for the resetting of this process in essential hypertension, (right). (Reproduced by permission from Brown JJ, Lever AF, Robertson JIS, Schalekamp MA: Renal abnormality of essential hypertension. Lancet 2: 320, 1974.)
relative fluid volume excess as a consequence of increased renal sodium reabsorption.

Other studies have found plasma volumes to vary inversely with both the blood pressure and peripheral resistance in patients with essential hypertension. Higher volumes were found in those with relatively mild hypertension and lesser elevations of peripheral resistance, in keeping with the concept that as hypertension is evolving, the plasma volume is relatively high; as the hypertension becomes fixed, with higher pressures and peripheral resistance, plasma volume could logically constrict.

Other derangements in body fluid volume may also be present. Among those supported by actual measurements are a decreased distensibility of capacitance vessels, mainly veins, which could result in a decrease in total effective compliance and a redistribution of blood into the central circulation and a shift of volume from the blood into the interstitial space. Although these and other derangements may be involved, the evidence in their support is uncertain and the presumed hemodynamic pattern of early hypertension does not require their contribution.

Thickening of Resistance Vessels

The small arterioles, where most vascular resistance may arise, become thicker as the blood pressure is raised, presumably as an adaptive hypertrophy of the medial smooth muscle. In animals, this structural thickening appears within weeks of a rise in pressure and, in man, considerable medial hypertrophy in smaller arteries and larger arterioles has been noted in uncomplicated essential hypertension. The thickening may also reflect an increase in sodium and water within the arterial wall which has been attributed to an increased passive permeability of vascular smooth muscle cells.

Increased Peripheral Resistance

Whatever the cause, thicker vessels increase peripheral resistance. There may also be an increased vascular reactivity to various pressor stimuli adding to the rise in resistance.

Now that peripheral resistance is high, particularly within the renal circulation, hypertension becomes persistent, remaining high even if the initiating stimulus is removed. Thus, the process changes from a functional, intermittent, reversible one to a structural, persistent, essentially irreversible disease.

Nephrosclerosis

Within the renal circulation, the high pressure accelerates the development of nephrosclerosis. The hyalinized and hyperplastic arterioles, considered by Goldblatt to be the probable initiating mechanism for essential hypertension, are almost certainly the consequence of the disease, already established through a process that may follow the sequence shown in figure 1.

The proliferative portion of the nephrosclerosis, invariably found in long-standing essential hypertension, may be at least partially reversed if the blood pressure falls. But the diffuse arteriolar thickening leads to a progressive fall in renal blood flow. Eventually, impairment of renal excretory function may be at least partially reversed if the blood pressure falls. But the diffuse arteriolar thickening leads to a progressive fall in renal blood flow. Eventually, impairment of renal excretory function may be at least partially reversed if the blood pressure falls.

Decreased Renin Release

Nephrosclerosis is likely involved in the progressive fall in renin levels observed with advancing age of the hypertensive population and accompanied by a progressive fall in renal blood flow. Multiple factors may lead to a decrease in renin secretion as hypertension persists which induces more nephrosclerosis.

1. Those vessels relatively unaffected would continue to be exposed to high perfusion pressures, diminishing the baroreceptor-mediated release of renin.
2. Those vessels partially hyalinized and thickened would likely have higher pressures within their
narrowed lumen, further inhibiting baroreceptor-mediated renin release.

3. As vessels become totally occluded, the J-G cells they nurture would drop out.

In addition, the relatively expanded circulating blood volume would suppress renin release.

Conclusion

The hypotheses contained within this scheme all have experimental support, but obviously other factors may be involved: renal sodium retention may be a primary event; renal production of vasodepressors such as prostaglandins may be deficient. An overactive sympathetic nervous system may not be the only key that opens the hemodynamic cascade of essential hypertension, but the evidence for a role of an increased adrenergic drive is becoming more and more persuasive.

Regardless, Dr. Harry Goldblatt was almost certainly correct in seeking the cause of essential hypertension within the kidney. The continued search for the exact mechanism will be our most fitting memorial to this extraordinary investigator and teacher.

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N M Kaplan

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