The frequent association of hypertension and intrinsic renal diseases has been universally recognized, and more recently a relationship has been demonstrated between hypertension and the concurrence of major renal artery disease and specific renal functional abnormalities. In searching for the etiology of essential hypertension, it seems logical, therefore, to consider the possibility that here also the kidney may play a causal role. In examining this thesis, we have found renal functional abnormalities which suggest that essential hypertension may arise from an alteration in perfusion of the kidney differing only in extent and site from that in renal artery stenosis. We are presenting here a brief summary of the evidence bearing on the guilt or innocence of the kidney in essential hypertension.

The high incidence of renal arteriolosclerosis in patients with established hypertensive disease has been cited to support the thesis that disease of the smaller renal vessels plays a primary role in the causation of hypertension. Moritz and Oldt re-examined this relationship in 100 patients with well-established hypertension of many years' duration and in a well-controlled study found renal arteriolosclerosis at necropsy in 97%. Absence of arteriolosclerosis, on the other hand, may just as reasonably be offered as evidence against a primary role of renal vascular changes in essential hypertension, and there is substantial evidence that structural change in the renal arterioles is not to be found in a significant number of instances. Bell in an autopsy study of 588 patients who died of essential hypertension noted the absence of renal arteriolosclerosis in 32%, and Castleman and Smithwick found either no or insignificant vascular disease in 28% of 100 open renal biopsies in patients with well-established essential hypertension. The presence of renal arteriolosclerosis in normotensive individuals can be used as an additional argument against the primary role of structural arteriolar disease in the causation of hypertension. Bell reported diffuse renal arteriolosclerosis in 16.3% of normotensive subjects over the age of 50 years with occasional hyaline deposits in an additional 22.1%; he also emphasized the frequency and severity with which this lesion occurs in normotensive patients with diabetes mellitus.

It seems unlikely that attempts to establish the presence or absence of renal vascular disease could settle the question as to whether alterations in the renal circulation play a primary role in the genesis of human hypertensive disease. When arteriolosclerosis is found, it is not possible to be certain whether it antedated the onset of hypertension; when arteriolosclerosis is not observed, the validity of this observation depends on how reliably it can be stated that this typically focal lesion is absent unless the entire renal vasculature is studied. The possibility remains, therefore, that disease of the renal vascular bed antedates the onset of hypertension but is not readily demonstrable by the techniques which

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have conventionally been used for the structural examination of the kidney. An inherent limitation of the anatomic approach derives from the circumstance that the appearance of the renal vessels may not characterize the functional status of the renal circulation. If an alteration in renal hemodynamics is responsible for a renal pressor mechanism in essential hypertension, the finding of arteriolosclerosis does not necessarily indicate that this specific alteration is present. Similarly, failure to find arteriolosclerosis does not ensure that the hemodynamic alteration capable of producing a pressor mechanism is not present. It would appear that physiological exploration of the renal circulation and specific renal functions might be more productive in an examination of the role of the kidney in the genesis of essential hypertension. Abnormalities in flow, pressure and resistance, as well as alterations in sodium, solute, and water excretion could be present in kidneys without demonstrable structural change and yet have pathogenetic significance.

Goldring and co-workers found a reduction in renal blood flow below the mean normal value and an increase in filtration fraction in essential hypertension. Further evidence that renal blood flow may in fact be reduced, even in those instances in which statistically its value falls within the normal range, was adduced by Baldwin and associates from the demonstration that one kidney had significant reduction in flow as compared to its mate in the majority of 50 patients early in the course of essential hypertension. Goldring and co-workers found that functional tubular mass (TmD) was also reduced but that the ratio of effective blood flow to functional tubular mass ranged downward from the mean normal value, indicating the presence of relative renal ischemia. Since this renal ischemia could be reversed by the administration of pyrogen, it was attributed to renal arteriolar constriction, representing the kidneys' participation in the generalized vasoconstriction present in essential hypertension. It was subsequently shown, however, that the degree of vasoconstriction in the kidney actually exceeds that in other vascular beds. Brod and associates have recently described exaggerated vasoconstrictor reactivity in the skin, kidney, and splanchnic bed during physical and intense mental effort in patients with essential hypertension; they attempted to explain the permanent elevation of blood pressure in essential hypertension as a manifestation of this altered reactivity. However, decreased renal blood flow and increased renal resistance may reflect neither the kidneys' participation in generalized vasoconstriction nor their specific response to stimuli in hypertensive patients but may represent, in fact, the critical alteration in hemodynamics which initiates a renal pressor mechanism in essential hypertension.

In examining the thesis that renal functional defects might be characteristic of the kidney in essential hypertension, it was thought that subtle abnormalities in sodium, water, and solute excretion not evident in studies of overall function might be revealed by simultaneous comparison of the separate kidneys. In order for renal functional impairment reasonably to be interpreted as primary, it was necessary to study patients judged to be early in the course of their disease and to this end we chose patients without retinopathy, cardiomegaly, or gross evidence of renal functional impairment. A disparity in sodium excretion and urinary volume between the two kidneys exceeding the limits established in normotensive subjects was observed in more than half of 50 hypertensive patients. By relating sodium excretion to glomerular filtration rate, two patterns of renal dysfunction were identified: one suggested total loss of function in some nephrons; the other, decreased sodium excretion due either to decreased filtered load or to excessive tubular reabsorption. These two distinct patterns of renal dysfunction have not been assigned separate pathogenetic significance; it may well be that they represent sequential manifestations of a common alteration in renal circulation.

Disparity in sodium excretion between the two kidneys in patients with essential hyper-
tension raised the possibility that an abnormality in the handling of sodium might be typical of the kidney in this disease. Since the renal capacity to form solute free water \( (C_{H_2O}) \) depends on sodium reabsorption in specific segments of the nephron, a study of the diluting capacity was undertaken in an effort further to characterize the excessive sodium reabsorption. Free water formation was examined during osmotic loading to permit comparison at the same levels of solute excretion and was found to be equal in normotensive and hypertensive subjects. However, by comparing the separate kidneys it was possible to demonstrate impairment of free water formation in the majority of hypertensive patients as evidenced by significant disparity between the two kidneys. Once again, two patterns of dysfunction were identified: in one, free water and sodium excretion were decreased in one kidney in proportion to a decrease in its filtration rate, suggesting total loss of function in some nephrons; in the other, free water and sodium excretion were decreased out of proportion to decrease in filtration rate. In this latter group \( C_{H_2O} \) in the antinatriuretic kidney was normal for the level of solute excretion or could be increased to normal during mannitol diuresis, suggesting that the decrease in \( C_{H_2O} \) resulted from reduced delivery of sodium to the diluting segment secondary to excessive reabsorption of sodium in more proximal segments of the nephron.

In order to explore further the possibility that excessive reabsorption of sodium occurs in the proximal portions of the tubule early in the course of essential hypertension, examination of urinary concentrating capacity was then undertaken. It was found that urinary osmolality was decreased in hypertensive patients at all levels of solute excretion. However, when compared to the normal at the same solute load per nephron (per 100 ml of glomerular filtration), osmolality was decreased at low but not at high solute loads. This impairment of the urinary concentrating mechanism at low solute loads was attributed to excessive reabsorption of sodium proximally, since normal osmolality resulted when sodium delivery to more distal segments of the nephron was experimentally enhanced. We have interpreted this impairment as additional evidence of an abnormality in sodium reabsorption characteristic of early essential hypertension.

Renal ischemia in essential hypertension, which has been adduced from reduction in the ratio of renal blood flow to functional tubular mass, may be due either to uniform decrease in blood flow throughout the vascular bed or to focal decreases resulting from an abnormality in the intrarenal distribution of flow. Since conventional clearance can only provide information concerning total renal blood flow, a method of determining the intrarenal distribution of blood flow utilizing indicator-dilution curves recorded across the renal vascular bed was developed. Utilizing a series of integral transformations, a continuous distribution curve was derived which expresses the relative frequency of theoretical units having different specific blood flows (blood flow per unit volume). The mean specific blood flow was lower in hypertensives as compared to normotensives, but the shape of the frequency distribution curve was unaltered in hypertensives, indicating that the specific blood flow is reduced uniformly throughout the vascular bed. These results suggest that hemodynamic changes are uniform throughout the kidney. However, the dye-dilution method may not be capable of detecting small but significant variations from the normal. Furthermore, focal changes in arteriolar resistance and flow due to structural disease may be present but masked either by general arteriolar constriction or by alterations in hemodynamics of the postglomerular capillary bed. In any event, the demonstration of uniform reduction in specific blood flow does not necessarily absolve the kidney since general rather than focal ischemia may well be the pathogenetic hemodynamic alteration in essential hypertension.

Even if the kidney were indicted as culprit by identification of a characteristic pattern of hemodynamic and functional abnormality in essential hypertension, the exact mechanism
by which the elevation in blood pressure is produced would still remain unknown. In this regard, investigative programs concerned with the renin-angiotensin system and the relationship between it and aldosterone production may provide evidence which bears on this question. Morris and associates\(^\text{13}\) did not find an increase in concentration of angiotensin II in the arterial blood of patients with essential hypertension,\(^\text{13}\) and Kahn and co-workers\(^\text{14}\) reported such small increases that they were unable to conclude "as to its effectiveness in producing vasoconstriction." It has been suggested that increased secretion of aldosterone, through its relationship to the renin-angiotensin system, may be of importance in essential hypertension, but Laragh and associates\(^\text{15}\) have demonstrated that aldosterone metabolism is normal in hypertensive disease. It appears that a humoral pressor agent arising directly or indirectly from the kidney is yet to be demonstrated in essential hypertension.

It is apparent from this review that the structural and functional abnormalities thus far demonstrated have not established the pathogenetic role of the kidney in essential hypertension. Aside from its inability to characterize the dynamics of the renal circulation, the anatomic approach does not permit one to choose between the primary or secondary nature of the vascular changes. On the other hand, the renal hemodynamic and functional alterations (relative renal ischemia, increased filtration fraction, decreased maximal tubular excretory capacity, reduced sodium excretion relative to filtration, decreased formation of free water, and impaired elaboration of an osmotically concentrated urine) are demonstrable early in essential hypertension and favor a primary renal mechanism. Continued exploration of the kidneys' hemodynamics and functions early in essential hypertension has resulted in the disclosure of an increasing number of abnormalities. We believe that further study may well establish its role as culprit.

### References

The Kidney in Essential Hypertension Victim or Culprit
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