Despite the fact that essential hypertension was originally described as hypertension occurring in the absence of clinical renal disease,1 Dahl et al later showed by transplantation studies in experimental models of hypertension that the kidney is ultimately responsible for the elevation in blood pressure,2 a finding that was verified later in humans.3 Most authorities believe that the mechanism by which the kidney causes hypertension involves a physiological defect in sodium excretion as championed by Guyton et al.4 Support for this mechanism is extensive and includes both epidemiological5 and physiological6 studies.7

Several hypotheses have been proposed to explain the mechanism responsible for the defect in renal sodium handling. A favored hypothesis is that hypertension results from a polygenic defect in which there are alterations in the regulation or expression in tubular transport systems involved in sodium reabsorption and excretion.7,8 The recent discovery that many forms of genetic hypertension are associated with enhanced sodium reabsorption has provided support for this hypothesis.7,8 However, there are substantial arguments that mitigate this hypothesis as a major mechanism for the renal defect. First, most studies suggest that genetic mechanisms can only account for a minority of cases.9,10 For example, a study of 1003 identical twins found that when one twin was hypertensive, the other twin was hypertensive only 44% of the time.11 Even more convincing are epidemiological data that demonstrate a dramatic increase in the prevalence of hypertension over the last 100 years. Thus, studies in the early 1900s demonstrated a near absence of hypertension in Africa, Asia, Arabia, South America, Australia and New Zealand, and Oceania,12 but now hypertension is rapidly increasing in prevalence, along with the worldwide epidemic of obesity and diabetes.13 Similarly, hypertension was observed in only 10% of the populace in the United States in the early 1930s,14 yet it now affects >30% of the population.15 It is difficult to explain how a purely genetic mechanism could account for this rapid change in prevalence. Finally, a genetic defect in sodium excretion as a primary mechanism for essential hypertension does not easily account for studies that demonstrate that in early hypertension, blood volume and exchangeable sodium tend to be low,16–18 why early hypertension is frequently salt resistant (ie, is not altered by sodium intake),19 and why salt-sensitivity increases progressively with aging.19 Thus, although genetic factors clearly have an important role in the development of salt-sensitive hypertension, there must be other nongenetic mechanisms intricately involved in the pathogenesis.

A second favored hypothesis is that essential hypertension results from a congenital reduction in nephron number.20 The argument is based on a series of observations. First, there is evidence for a “maternal factor” in hypertension because hypertension travels more commonly via the mother than the father.21 Indeed, hypertension occurs more commonly if the mother has hypertension, preeclampsia, obesity, or malnutrition.22 In all of these conditions, the mother carries an increased risk for delivering a baby with low birth weight. In turn, low birth weight babies have fewer nephrons because of impaired development of the kidney during the third trimester.23 More importantly, low birth weight babies have an increased risk for hypertension as adults.22 Indeed, low birth weight is especially common among blacks,24 a race that carries the greatest risk for hypertension in the United States. Further support of this hypothesis is the observation that the experimental induction of malnutrition during pregnancy in rats results in pups that are born with low nephron number and later develop salt-sensitive hypertension.25 Autopsy studies of young hypertensive subjects dying from traffic accidents have also verified that the kidneys have significantly fewer nephrons than age-matched normotensive controls.26

Whereas the congenital nephron number hypothesis carries great appeal, it also is unlikely to account for the observed alterations in sodium handling. First, numerous studies in

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The observation that renal microvascular disease is present in the majority of subjects with hypertension led Goldblatt to postulate that the microvascular disease was primary and that it caused hypertension via a mechanism involving renal ischemia. However, his hypothesis was discarded because he had no mechanism to provide for how the microvascular disease would develop and because it appeared more likely that the microvascular disease was the consequence of hypertensive renal damage. However, recent interest in this pathway was rekindled when it was found that similar types of renal microvascular injury could be induced in animals by a variety of means (including transiently infusing angiotensin II or blocking NO synthesis), and that these animals subsequently develop salt-sensitive hypertension with similar histological, hemodynamic, and functional characteristics as those observed in essential hypertension in man. Furthermore, blocking the renal microvascular and interstitial injury with mycophenolate could prevent the cortical vasoconstriction and the development of salt sensitivity.

At first, one might postulate that renal afferent arteriolar injury or vasoconstriction should not cause salt sensitivity because Guyton et al provided strong evidence that a rise in preglomerular resistance should shift the pressure natriuresis curve to the right but in parallel, resulting in salt-resistant hypertension. Indeed, if the renal vasoconstriction or arteriolar disease is homogeneous (such as occurs when one places a clip to partially occlude a renal artery), then this is true. However, because the development of arteriolar disease varies in severity between nephrons, there will be variability in renal perfusion, resulting in some nephrons being underperfused and ischemic, whereas others may be overperfused. This would lead to heterogeneity in renin expression and a functional defect in which the renin-angiotensin system would fail to suppress for the degree of sodium intake, resulting in sodium sensitivity as proposed by Sealey et al. Furthermore, we reported that the cortical vasoconstriction with renal ischemia also results in the infiltration of mononuclear cells expressing oxidants and angiotensin II, which also contributes to the sodium retention and a rise in blood pressure.

Recent studies in spontaneously hypertensive rats (SHR) support the importance of the renal afferent arteriole in the pathogenesis of hypertension. Specifically, SHR are known to have a narrow afferent arteriolar lumen and to develop hypertension that has a salt-resistant and salt-sensitive component, in that the hypertension occurs even under low-salt conditions but is also exacerbated with increased sodium intake. Interestingly, SHR also have a reduced nephron number. To sort out which of these characteristics may be responsible for development of hypertension, studies were performed by crossing SHR with Wistar-Kyoto rats, which have a normal nephron number and normal afferent arterioles, and then examining whether hypertension tracked with nephron number or with the arteriolar abnormalities in the offspring. Interestingly, there was no association of hypertension with nephron number, whereas a narrowed arteriolar lumen was highly associated with development of hypertension. The importance of the arteriolar vasoconstriction and of the structural changes have led others to a similar
conclusion that it is arteriolar disease that is critical for development of hypertension.

A key question is what causes the renal microvascular and tubulointerstitial injury in essential hypertension. A possibility is that the renal microvascular injury may be initiated by transient rises in blood pressure induced by a hyperactive sympathetic nervous system (SNS). It is known, for example, that subjects at risk for developing hypertension frequently give a history of work stress, have type A personalities, or show enhanced cold pressor responses. White coat or episodic hypertension is also recognized as a major risk factor for development of hypertension, and \( \approx 40\% \) of early hypertension is associated with a hyperactive SNS and intermittent elevations in blood pressure. Indeed, infusion of catecholamines into rats also will induce renal microvascular and interstitial injury with the development of salt sensitivity that persists after stopping the catecholamine.

Another risk factor for hypertension is an elevated serum uric acid. An elevated serum uric acid not only predicts but is present in as many as 90% of new-onset primary hypertension in adolescents. Epidemiologically, the rise in the worldwide prevalence of hypertension and obesity correlates with a rise in the mean serum uric acid in the population. Experimental hyperuricemia in rats also results in hypertension and renal microvascular disease. Interestingly, the initial hypertension in hyperuricemic rats is mediated by systemic endothelial dysfunction and activation of the renin-angiotensin system and is salt resistant. However, over time, uric acid mediates renal microvascular disease, in part by a direct effect of uric acid on vascular smooth muscle cell (VSMC) proliferation.

Once the renal microvascular disease is substantial, the hypertension "switches" to a salt-sensitive form and is now independent of uric acid levels and driven by the kidney. In this case, lowering uric acid may be most effective as a preventative measure or in early forms of hypertension; indeed, preliminary studies suggest lowering uric acid may be effective at treating blood pressure in hypertensive adolescents.

A hyperactive SNS and hyperuricemia are thus likely initiators of renal microvascular injury and development of salt sensitivity. Interestingly, both would take the patient through an initial renal independent, salt-resistant mechanism, followed by development of renal microvascular injury and a volume-dependent, salt-sensitive pathway. This switch is likely the result of VSMC proliferation leading to a permanent state of decreased afferent flow equivalent to the vasoconstriction mediated by hyperuricemia. This is consistent with temporal studies in humans suggesting that hypertension in younger subjects is more frequently associated with salt resistance, low volume, high uric acid, and a hyperactive SNS, whereas hypertension in older subjects is more commonly associated with salt sensitivity, a reduced glomerular filtration rate, microalbuminuria, and more severe renal microvascular disease. These data are consistent with reports linking uric acid and a hyperactive SNS with elevated plasma renin activity, and with the proposal by Blumenfeld and Laragh that hypertension can be categorized primarily as either renin dependent or volume dependent.

Other mechanisms are also likely operative. Animal models indicate that the pathway can be engaged by angiotensin II, lead, cyclosporine, aging, chronic low-potassium diets, and even chronic hypoxia. There is accruing evidence that lead intoxication can induce renal arteriolar lesions and hypertension; lead can also raise serum uric acid. SHR suggest genetic mechanisms that may govern renal afferent arteriolar tone and structure. This potential plurality of triggers, working independently or in concert, is likely at the crux of the decades-long challenge of truly understanding essential hypertension.

In conclusion, acquired renal microvascular and tubulointerstitial injury becomes the most likely mechanism to account for the development of salt-sensitive hypertension. Uric acid, endothelial dysfunction, or a hyperactive SNS are likely key initiators of this process. Clearly, genetic and congenital mechanisms are contributory, but they are unlikely to account for the majority of hypertension. Interestingly, an elevated uric acid in the mother may also have a role in mediating a reduction in nephron number, and a reduced nephron number may predispose to development of preglomerular renal microvascular disease. Thus, the genetic and congenital nephron hypotheses are likely contributing cofactors involved in the hypertensive response. Finally, although this article reviews mechanisms that may result in the defect in sodium excretion as elegantly hypothesized by Guyton, we do not discuss how the renal defect leads to systemic vasoconstriction and development of hypertension. However, it is likely that transient retention of sodium results in the release of factors from the hypothalamus and adrenal, such as cardiotonic steroids, that may activate the Na\(^+\)/Ca\(^{2+}\) exchanger in VSMCs to cause systemic vascular vasoconstriction and a rise in blood pressure, as postulated by Blaustein and DeWardener, resulting in "autoregulation," as originally proposed by Guyton et al.

We have come a long way since the original debate 150 years ago between George "Kidney" Johnson and Gull and Sutton over whether hypertension is attributable to the kidney or to arteriosclerosis. The verdict may soon be in. Both are likely right.

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