

This Week in the Journal

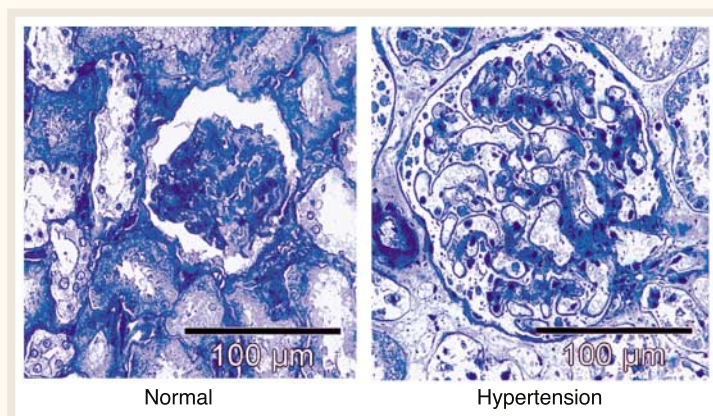
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ORIGINAL ARTICLES

Nephron Number in Patients with Primary Hypertension

The presence of a relatively low number of nephrons at birth, which may gradually damage the kidney as a result of the increased workload per nephron, has been proposed as a major contributor to the development of hypertension. The authors tested this hypothesis by comparing histologic findings and the number and volume of glomeruli in 10 middle-aged white patients with a history of primary hypertension or left ventricular hypertrophy (or both) with those in 10 normotensive controls; all the subjects had died in accidents. Patients with hypertension had fewer glomeruli, a larger glomerular volume, and more severe arteriosclerosis than did the controls.



The data support the hypothesis that the number of nephrons is reduced in some patients with primary hypertension.

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The Pattern of Alcohol Consumption and Coronary Heart Disease

It is widely accepted that moderate alcohol consumption protects against coronary heart disease. This large study in men adds new information by assessing the roles of the drinking pattern and the type of beverage consumed. Men who drank alcohol at least three to four times per week had a reduced risk of myocardial infarction. The association was strongest with beer and liquor, the predominant types of beverage consumed by this population.

The concept that a higher frequency of alcohol consumption (at least three to four days per week) provides enhanced protection against coronary disease is new, but it is tempered by an awareness of the known detrimental effects of alcohol consumption, such as hepatotoxicity and an increased risk of trauma.

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Treatment of Multidrug-Resistant Tuberculosis in Lima, Peru

This report describes a community-based outpatient treatment program for patients with chronic, multidrug-resistant tuberculosis. Probable cures were achieved in 55 of 66 patients who completed at least four months of individualized therapy. Predictors of a poor outcome were a low hematocrit and low body-mass index.

This program shows that effective outpatient treatment of multidrug-resistant tuberculosis is possible in an economically disadvantaged area. The results run counter to the conventional view that in low-income countries treatment of multidrug-resistant tuberculosis is too expensive and is not feasible outside referral centers.

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THIS WEEK IN THE JOURNAL

SPECIAL ARTICLE

Trends in Care by Nonphysician Clinicians in the United States

This study of data from national surveys of patients in 1987 and 1997 documents an increase in visits to nonphysician clinicians (e.g., nurse practitioners, physician assistants, and physical therapists) during this period. The increase was explained by a rise in the proportion of patients who received care from both physicians and nonphysician clinicians.

The increase in visits to nonphysician clinicians between 1987 and 1997 supplemented, rather than replaced, visits to physicians.

SEE PAGE 130; EDITORIAL, PAGE 164

MEDICAL PROGRESS

Pathophysiology and Treatment of Sepsis

Sepsis is the leading cause of death in critically ill patients in the United States. Yet the individual host response to septicemia is variable, depending on the patient's immune response, age, nutritional status, and coexisting conditions, as well as on the virulence of the organism and the size of the inoculum. This review examines evolving concepts of sepsis and discusses new and potential therapies. Recent clinical advances include therapy with activated protein C, stringent control of blood glucose, and early goal-directed therapy to treat cellular oxygen deficit. Future therapies may be focused on modulating the immune response in the light of the characteristics of the specific pathogen, the genetic profile of the patient, and the duration of the disease.

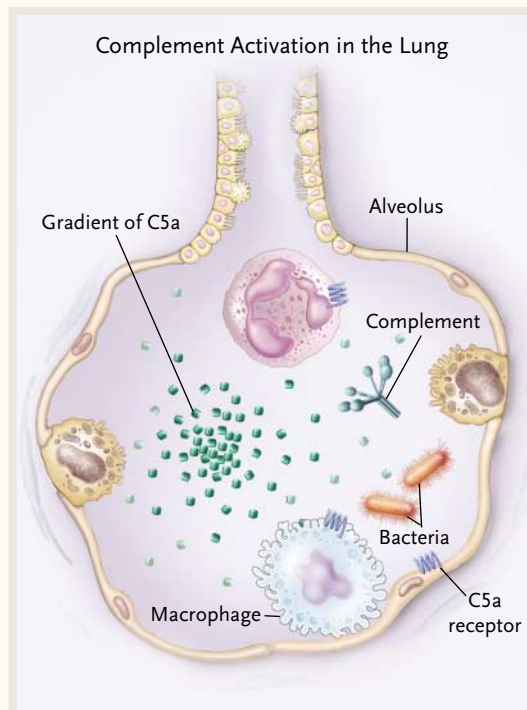
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CLINICAL IMPLICATIONS OF BASIC RESEARCH

Complement C5a in the Sepsis Syndrome

In sepsis, activation of the complement system introduces large amounts of C5a into the circulation. The excess of this peptide paralyzes neutrophils and increases susceptibility to infection. In tissues, by contrast, C5a has effects on neutrophils that protect against infection. Neutralization of circulating C5a by an antibody protects against the lethal effects of sepsis in an animal model.

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Is Microanatomy Destiny?

Julie R. Ingelfinger, M.D.

Dissecting the pathogenesis of primary, or “essential,” hypertension has proved elusive. In recent years, the hypothesis that having relatively fewer nephrons renders an otherwise healthy person more susceptible to renal disease, hypertension, or both has been supported by a substantive body of experimental data. However, data in humans have been largely circumstantial and indirect.

In this issue of the *Journal*, Keller et al. (pages 101–108) present carefully derived evidence that bolsters this hypothesis. Kidneys from 10 persons who had died in accidents and who had had hypertension were compared with kidneys from 10 age-matched persons with normal blood pressure who had also died in accidents. Such a study is straightforward yet technically demanding: the investigators counted glomeruli using a technique that permitted three-dimensional stereologic analysis of both glomerular number and volume. They also evaluated the morphology of glomeruli and tubules. On the basis of data obtained over the past century or so, the widely quoted figure for glomerular number in humans has been 1 million nephrons per kidney, although the estimates have varied from about 300,000 to 2 million per kidney, most likely because of different measurement techniques. Keller et al. found that the kidneys from persons with hypertension had significantly fewer glomeruli — a median of 702,379, as compared with 1,429,200 in the matched controls. At the same time, the glomeru-

lar volume was greater in the hypertensive kidneys, suggesting that the glomeruli in the persons with hypertension were overworking, or hyperfiltering. The authors sought but did not find obsolescent glomeruli in the hypertensive kidneys (finding a high number of such glomeruli would have implied ongoing nephron loss). Thus, the persons with hypertension most likely had not lost glomeruli over time, but rather had a small number at birth. Such observations provide support, if post hoc, for the concept that having too few nephrons may in itself be associated with primary hypertension.

What determines nephron number? The embryonic human kidney develops in three consecutive structures: the pronephros, the mesonephros, and the metanephros. The pronephros largely disintegrates and is incorporated into various ligaments and pelvic structures. The latter two embryonic structures become intimately linked, as the vestiges of the mesonephros form the ureteric bud that induces development of the kidney from the metanephric cap. The subsequent induction of nephron branching culminates in the final complement of nephrons. If this process is insufficient, there will not be enough nephrons. Nephrogenesis is complete 4 to 6 weeks before a full-term baby is born at 40 weeks of gestation. The kidneys subsequently grow substantially, but primarily because of tubular and interstitial growth and not because new glomeruli develop. All studies to date, however, show that there is a varia-

Table 1. Genes and Aberrant Nephrogenesis.*

Renal Abnormality	Involved Gene or Product	Associated Disorder in Humans
Renal aplasia	PAX2 (a transcription factor)	Renal hypoplasia; vesicoureteral reflux; colobomas of the optic nerve
Renal neoplasia	WT-1 (Wilms' tumor 1, a zinc-finger nuclear factor)	Wilms' tumor; Wilms' tumor, aniridia, genitourinary malformation, and mental retardation; Denys-Drash syndrome
Reduced nephron mass: hypoplasia or dysplasia	EYA-1 (eyes absent 1) Lmx-1b	Branchio-oto-renal syndrome Nail-patella syndrome
Cysts	Peroxisomal assembly factor 1	Zellweger's syndrome
Obstructive syndromes	Angiotensin II type 2 receptor	Syndrome of congenital anomalies of the kidney and urinary tract (CAKUT)

* Many additional genes and proteins are involved in nephrogenesis: transcription factors, secreted factors and secreted factor inhibitors, receptors, cell adhesion molecules, and matrix receptors.

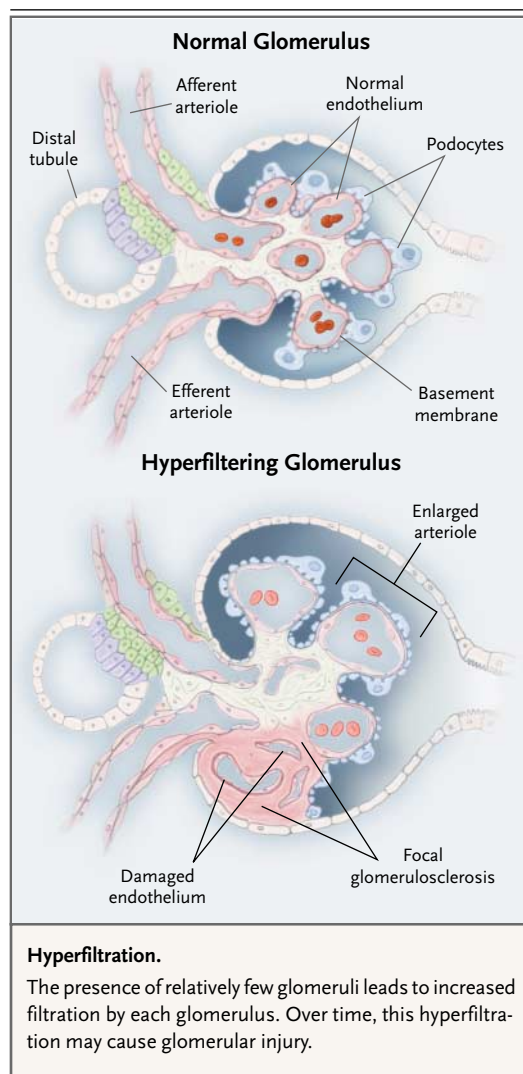
tion among phenotypically normal persons, with some having more nephrons than others.

Mutations in genes key to renal development, such as PAX genes, WNT genes, genes of the renin-angiotensin system, and others, are associated with substantial renal maldevelopment (see Table). Toxic exposures during gestation also influence the expression of genes important to renal development, affecting the microarchitecture of the kidney. For example, a fetus exposed through the placenta to medications that inhibit the renin-angiotensin system, such as angiotensin-converting-enzyme inhibitors, will have abnormal kidneys. But what about more subtle influences, such as diet?

“Perinatal programming,” the term coined to describe the observation that events during gestation can have far-reaching effects into adulthood, may be particularly relevant. This concept was first discussed by Barker et al.,¹ who observed an inverse relation between birth weight and cardiovascular disease in a cohort of middle-aged British men. A large body of clinical and experimental data amassed since that observation suggest that alterations in intrauterine nutrition, especially protein-calorie restriction, may “program” the fetus for later susceptibility to hypertension, cardiovascular disease, and stroke. Furthermore, studies in experimental models show directly that relatively minor insults, such as protein restriction, can result in fewer nephrons. Although most would agree that essential hypertension is a complex phenotype, with contributions from both polygenic and nongenetic factors, there is growing evidence that intrauterine events may have far-reaching consequences.

An additional concept, eloquently enunciated by Brenner et al.,² is that persons with fewer nephrons are likely to have a relatively high glomerular filtration rate in each available nephron and that this hyperfiltration has consequences, which may include renal injury or hypertension (see Figure). The concepts of perinatal programming and hyperfiltration fit together like pieces in a puzzle: persons who undergo intrauterine stress, even fairly subtle, may not develop a full complement of nephrons. Over time, the compensatory efforts of the kidney go awry, leading to increased filtration by each nephron, then subtle dysfunction and scarring and, ultimately, hypertension.

Does renal microanatomy forecast cardiorenal destiny? The data from the study by Keller et al. are provocative but not definitive. The number of subjects involved was small, and all were from similar



ethnic and racial backgrounds. In addition, it is hard to prove that the difference in glomerular number was congenital. The roots of hypertension are multiple, and it would be an oversimplification to state that nephron number alone is the key to primary hypertension. Yet the concept of decreased nephron endowment is useful, because it points to at least one possible preventive action: improved nutrition for pregnant women, a strategy that might decrease the frequency of hypertension in susceptible offspring during their adult lives.

REFERENCES

1. Barker DJ, Osmond C, Golding J, Kuh D, Wadsworth ME. Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. *BMJ* 1989;298:564-7.
2. Brenner BM, Garcia DL, Anderson S. Glomeruli and blood pressure: less of one, more the other? *Am J Hypertens* 1988;1:335-47.