The growing prevalence of CKD across the world has intensified the search for factors responsible for progressive loss of kidney function over time. In the 1980s, Brenner et al. reported that reduced nephron number results in glomerular hyperfiltration and hypertrophy, leading to maladaptive further nephron injury. This was followed by Barker and Bagby’s observations linking low birth weight with adult cardiovascular disease, leading to the field now recognized as “developmental origins of health and disease.” More recently, a bridge was created between these lines of study in recognition of the wide variation in the number of nephrons in the general population. Using an unbiased but demanding stereologic approach called the disector technique, Bertram et al. demonstrated a 12-fold range in the number of nephrons per kidney in diverse populations. Accumulating evidence suggests that infants born with nephron number below the median are at increased risk for CKD and cardiovascular disease in adulthood. Although the majority of renal failure in adults results from diabetes and hypertension, recent reports demonstrate that renal failure as a result of congenital renal disorders is more likely to develop in adulthood than childhood.

In this issue of JASN, investigators from Rotterdam, The Netherlands, report two studies based on the Generation R Study, a population-based prospective cohort of healthy participants followed from fetal life through 5 to 8 years of age. In one study, fetal growth was measured by ultrasonography in the second and third trimesters, during which nephron number increases 50-fold. These data were correlated with renal growth and eGFR through 6 years of age in 6482 children. Notably, higher second-trimester fetal weight was associated with higher childhood GFR, and higher birth weight was associated with higher kidney volume and GFR. In the second study of 923 pregnant women and their children, fetal growth, kidney volume, and umbilical and cerebral artery blood flow were measured in the third trimester. These were followed by measurement of BP, kidney volume, and GFR in childhood. An increased fetal umbilical/cerebral blood flow ratio was associated with smaller childhood kidney volume and lower GFR. These physiologic and morphometric observations are the first to be performed sequentially from fetal through postnatal life in large numbers of healthy participants, and reveal the importance of the distribution of fetal blood flow as well as early fetal renal development in postnatal renal growth and function. Previous studies show that first-trimester fetal length smaller than expected for gestational age is associated with low birth weight and premature delivery. This finding, along with the association of reduced fetal growth with decreased GFR in childhood, suggests that early impairment of metanephric growth is a risk factor for reduced postnatal renal function.

In considering the changing epidemiology of CKD throughout the life cycle, it is useful to invoke the role of evolutionary principles in the biology of populations. Genetic variation (polymorphism) is an essential substrate for the action of natural selection. It should not be surprising that the number...
of nephrons is highly variable in the human population. The number of pancreatic islets also varies by 12-fold among individuals, and similar variation occurs for tissue enzyme activity and organic or inorganic constituents of blood.\textsuperscript{11} Importantly, human fetal mortality is very high in early pregnancy and decreases precipitously in early childhood, with a nadir at approximately 12 years of age.\textsuperscript{12} After the adolescent transition from childhood to the reproductive period, however, there is a nearly linear increase in mortality, which continues through postreproductive aging. This “U” mortality curve results from the intersection of two curves: (1) genetic variation is highest at conception, and natural selection accounts for most fetal and neonatal deaths, decreasing rapidly by adolescence; and (2) environmental factors (or “experience” of the individual) are proportionately low in the fetal milieu, but become progressively greater after adolescence.\textsuperscript{12}

Because natural selection is determined by reproductive fitness, selection pressures are overshadowed by environmental factors after the fourth decade of life. In fact, early life determinants, such as reduced nephron number, can increase risk of disease in later life (antagonistic pleiotropy).\textsuperscript{13}

Whereas genome-wide association studies are increasingly utilized to study disease epidemiology, environmental exposure is more difficult to quantitate. Rather than considering only external factors, a new paradigm was proposed to consider the body’s “internal environment” and “exposures” measured by physiologic responses to oxidative stress or inflammation (e.g., cytokines or the microbiome).\textsuperscript{14} The “exposome” therefore becomes the aggregate of environmental exposures throughout the life cycle.\textsuperscript{14} There is clearly a need for longitudinal studies of human renal growth and development through childhood and into adulthood. Although the National Survey of Health and Development is not focused on renal disease, the survey was begun by the Medical Research Council in the United Kingdom in 1946 and is the longest-running birth-cohort study in the world.\textsuperscript{15} By 2011, >5000 individuals had been followed from birth to their 65th birthday.\textsuperscript{15} It is hoped that some conclusions will be forthcoming regarding long-term renal health and its determinants. Although fetal kidney volume is not associated with microalbuminuria or BP at 6 years of age, it is likely (as noted by the authors of the study) that the latter would serve as predictors later in childhood or early adulthood.\textsuperscript{9} This is borne out by a study of children with solitary kidney followed through 9 years of age. Compared with children with solitary kidney who were followed <5 years, urinary microalbuminuria was significantly higher in those followed >5 years.\textsuperscript{16}

The significant association of fetal kidney volume with childhood kidney volume and eGFR in the study by Bakker \textit{et al.}\textsuperscript{7} underscores the importance of renal mass as a determinant of renal function. Renal length increases at a rate of 3 mm per month at birth, decreases to 2 mm per month at 6 months, and then slows markedly to 0.25 mm per month thereafter.\textsuperscript{17} Most maturational (as well as compensatory) renal growth is primarily dependent on proximal tubular growth. Because of the centrifugal pattern of nephron maturation (the most mature glomeruli are juxtamedullary, whereas the least mature glomeruli are subcapsular), variability in proximal tubular length is greatest at birth, with a >10-fold difference between the shortest and longest.\textsuperscript{18} By 1 month of age, the ratio of the shortest to longest proximal tubules is 1:3.5, and decreases further to 1:1.5 in adults.\textsuperscript{18} Of particular interest, renal length increases more rapidly from 20 to 40 weeks of gestation in fetuses with unilateral renal agenesis or unilateral multicystic dysplastic kidney compared with normal fetuses.\textsuperscript{19} This suggests that nephron growth adapts to a reduction in total nephron number before the completion of nephrogenesis, and before excretory function is shifted from the placenta to the neonatal kidney.

Is the “renal reserve” a function of the number of nephrons, subject to the limits of glomerular and tubular growth? By comparing the assembly of nephrons in mammalian species of varying size, Sperber posits that the length of renal tubules is limited by Poiseuille’s law.\textsuperscript{20} Thus, small animals such as rodents have a unipapillary kidney, and whales have “multirenunculate” kidneys (nephrons packaged as clusters of “small kidneys” arranged as grapes on a vine).\textsuperscript{21} It appears that maladaptive ineffective repair mechanisms are invoked when the physical limits of adaptive nephron growth are reached, leading to tubular and podocyte loss and finally to interstitial deposition of collagen and glomerulosclerosis. It is likely that there is a continuum between the range of normal participants included in the study by Bakker \textit{et al.}\textsuperscript{7} and infants born with nephron numbers in the bottom decile. The latter include those with congenital anomalies, intrauterine growth restriction, or prematurity. Smaller kidneys represent a risk factor throughout life, which will be compounded by hypertension, obesity, infection, or trauma.

The study by Kooijman \textit{et al.}\textsuperscript{9} reveals that fetal hemodynamics affect renal growth, thereby implicating placental function and maternal health. Similar to normal fetuses with smaller kidneys, fetuses with intrauterine growth restriction have elevated umbilical/cerebral blood flow.\textsuperscript{22} Whereas the population of mothers in the study of Kooijman \textit{et al.} was relatively low risk with 66% secondary or higher education, the study of Bakker \textit{et al.} included participants with a broader range of education.\textsuperscript{7,9} There was a greater fraction of mothers with higher education consenting to blood sampling, and children in this group had greater combined kidney volume.\textsuperscript{9} Disadvantaged children in the Carolina Abecedarian Project included 57 children assigned to a stimulating early childhood environment and 54 assigned to a control group; all were followed through 30 years of age.\textsuperscript{23} Children assigned to the treatment group had a lower prevalence of risk factors for cardiovascular and metabolic diseases, which was particularly notable in boys.\textsuperscript{23} The investigators conclude that early life interventions can prevent disease and promote health.

To understand the interaction of multiple genetic and environmental factors in the progression of CKD, it is time to expand population studies of renal health through the entire life cycle. This is the conclusion of the Kidney Research
DISCLOSURES
None.

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The Seen and the Unseen: Clinical Guidelines and Cost-Effective Care
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In the department of economy, an act, a habit, an institution, a law, gives birth not only to an effect, but to a series of effects. Of these effects, the first only is immediate; it manifests itself simultaneously with its cause—it is seen. The others unfold in succession—they are not seen: It is well for us, if they are foreseen.

Frédéric Bastiat (1850)1

Clinical guidelines advise physicians on treatment choices in order to optimize outcomes and avoid costly or ineffective interventions.2 One aim is to reduce the waste that occurs because of the lack of adoption of proven best practices.