Developmental programming of a reduced nephron endowment: more than just a baby’s birth weight

Karen M. Moritz, Reetu R. Singh, Megan E. Probyn, and Kate M. Denton

1School of Biomedical Sciences, University of Queensland, St. Lucia, and 2Departments of Anatomy and Developmental Biology and Physiology, Monash University, Melbourne, Australia

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Almost half the deaths in Western society can be attributed, at least in part, to cardiovascular and renal disease (101a). Although a number of treatment options are available, the mortality associated with these diseases remains very high. Thus, understanding the underlying basis of these diseases is of great importance. It has long been recognized that genetic and lifestyle factors play an important role in these diseases. However, over the last 20 years, epidemiological studies have indicated that a suboptimal in utero environment may predispose or “program” an individual to be born with an increased risk of developing renal and cardiovascular disease (6, 9, 12). Many of the epidemiological research in this area has found links between a low birth weight, which has been used as a clinical marker of a poor intrauterine environment, and later adult disease (8, 10–12). Thus, much research has focused solely on low-birth-weight babies, with the assumption that a normal birth weight removes much of the disease risk. However, there is evidence that programming of cardiovascular disease can occur across a range of birth weights, including those considered normal (for review see Ref. 8). A number of recent reviews have examined the links between birth weight and adult blood pressure in the human and in experimental models (1, 59, 76, 108).

Over the last decade, an extensive range of animal models investigating underlying mechanisms of programming of adult disease has been developed (for reviews see Refs. 3 and 26). A common feature of many of these models is alteration of renal development, resulting in offspring with a reduced number of nephrons in the kidney (76). Given the role of the kidney in regulation of fluid homeostasis and blood pressure (46), it is not surprising that the kidney has been the focus of much study. As discussed below, a low nephron endowment has been strongly associated with the development of hypertension in the human and in a variety of animal models, although it is difficult to establish a direct cause-and-effect relationship. Although in many of the animal models the low nephron endowment and hypertension are associated with a reduced birth weight, there are a number of models of offspring with a low nephron number and hypertension, despite normal birth weight (see below). In this review, we consider the complex association between birth weight, nephron endowment, and development of adult disease. In particular, we give special consideration to animal models with a reduced nephron endowment and subsequent adult disease, despite normal-birth-weight offspring, inasmuch as such models provide an opportunity to explore underlying mechanisms of disease development without the confounding factor of a low birth weight.

Finally, in an assessment of the role of a low nephron endowment in the programming of hypertension, the methodology used to determine glomeruli (and, thus, nephron) number must be considered. The “gold standard” methodology for determination of total nephron number is unbiased stereology using the physical dissector/fractionator principle (14). This method enables determination of total nephron number and...
individual glomerular volume and does not make any assumptions about size, shape, or distribution of glomeruli within the kidney. However, other histological techniques that determine nephron density (rather than number) have been used (94). Acid maceration, which also determines total nephron number, has been used with success (66). The studies reviewed here have utilized unbiased stereology unless otherwise stated.

**DEVELOPMENTAL PROGRAMMING HYPOTHESIS**

Almost 20 years ago, an English epidemiologist, David Barker, reported that the highest rates of infant death in Britain in the early 1900s coincided geographically with areas with the highest incidence of death due to ischemic heart disease and coronary artery disease in adult life (11). This led Barker and colleagues to suggest that the high infant mortality may be due in part to poor growth in utero and, thus, that poor fetal growth may be linked to the development of cardiovascular disease in adulthood. This became known as the “fetal origins of disease” or the “Barker hypothesis” (7). It was proposed that exposure of the developing fetus to an insult in utero resulted in fetal adaptations to ensure immediate survival; however, the same adaptations increased the susceptibility to particular diseases in adulthood. Crucial to these observations was that low birth weight was used as the clinical marker of a “poor” or suboptimal intrauterine environment; babies whose birth weight was <5.5 pounds were almost twice as likely to die from coronary heart disease than those whose birth weight was between 8.5 and 9.5 pounds (89). Other adult-onset diseases, including metabolic disease, osteoporosis, some mental disorders, and renal disease, have also been linked to low birth weight (22, 47, 49, 52, 64, 100). A plethora of epidemiological studies from around the world show an association between low birth weight and development of many forms of cardiovascular disease (for recent reviews see Refs. 8 and 10), but a number of studies dispute this finding, showing no link between low birth weight and development of cardiovascular disease (38, 55, 56, 104). These apparent discrepancies may be due in part to the age at which blood pressure was measured in offspring and other confounders (43, 48).

**ROLE OF POSTNATAL ENVIRONMENT IN PROGRAMMING OF DISEASE**

It is recognized that early postnatal growth and lifestyle factors can also influence the likelihood of disease development, giving rise to the broader concept known as the developmental origins of health and disease (36, 98). Poor growth in the 1st yr can lead to increased risk of coronary heart disease (41) and insulin resistance (37). Conversely, accelerated or “catch-up” growth in childhood may result in development of hypertension, obesity, and metabolic disease (36; see Ref. 102 for review). These findings suggest that factors affecting postnatal growth, during infancy and childhood, are important in determining later cardiovascular and metabolic health. As discussed below, lifestyle factors may act as a secondary insult to the kidney, further perpetuating disease.

**NEPHRON NUMBER, BIRTH WEIGHT, AND BLOOD PRESSURE IN HUMANS**

The concept of a link between a congenital nephron deficit and elevated blood pressure was proposed by Brenner and colleagues almost 20 years ago (17). They postulated that a congenital nephron deficit was likely to be associated with increased hydrostatic pressure in the glomerular capillaries and an increase in single-nephron glomerular filtration (glomerular hyperfiltration), resulting in compensatory glomerular hypertrophy to maintain overall normal glomerular filtration rate. However, this would ultimately cause glomerulosclerosis and nephron loss. Few studies have examined the relationship between nephron number and hypertension in humans, mainly because nephron number can be determined accurately only in kidneys obtained at autopsy. In a landmark study, Keller et al. (58) found that the kidneys of individuals with a history of hypertension contained only half as many nephrons as those with no history of hypertension. More recently, this has been demonstrated in a larger cohort of white Americans, but not in African Americans (54). A limitation of these studies is the uncertainty of whether low nephron endowment exists from birth or is secondary to hypertensive renal injury.

Only one human study has directly linked birth weight with nephron endowment: according to Hughson et al. (53), each kilogram increase in birth weight predicted an additional 250,000 nephrons. However, Hughson et al. studied adult kidneys and, therefore, could not take into account age-related loss in nephron endowment. A possibility that has yet to be investigated is whether the type of nephrons affected, cortical (short-loop) or juxtamedullary (long-loop) nephrons, is important in developmental programming of hypertension. This will be of considerable interest, given recent evidence that African Americans, a group with a greater incidence of renal and cardiovascular disease, have a greater renal concentrating ability than their white American counterparts and, thus, potentially more long-loop nephrons (5). These long-loop nephrons have been shown to be more vulnerable to hypertensive damage in an animal model (84).

**REDUCED NEPHRON ENDOWMENT: A COMMON MECHANISM IN PROGRAMMING OF ADULT DISEASE?**

Alterations in the development of various organs (including brain, heart, pancreas, and kidneys) have been implicated as important in disease development (44, 69, 90). The kidney appears especially vulnerable, since a wide range of insults result in reduced nephron endowment in a number of species (rat, sheep, and mouse). Many, but importantly not all, of these models also result in low-birth-weight offspring that develop hypertension or other disease outcomes in adulthood (see below; Table 1). This suggests a pivotal role for the kidney in cardiovascular disease and, in particular, nephron number in the programming of renal and cardiovascular disease. However, more recent evidence suggests that nephron number alone is unlikely to result in disease; thus other changes within the kidney (e.g., compensatory alterations) or in the postnatal environment (e.g., high-salt or high-fat diet after birth) are necessary for development of chronic disease (76, 113). It must be noted that rodents complete nephrogenesis ~1 wk after birth; therefore, in this species, postnatal influences can also affect nephron endowment (79).
Table 1. Birth weight and arterial pressure in animal models of reduced nephron endowment

<table>
<thead>
<tr>
<th>Maternal Perturbation</th>
<th>Birth Wt/Late Gestation</th>
<th>Reduction in Nephron Endowment, %</th>
<th>Change in Arterial Pressure</th>
<th>Ref. No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-protein diet throughout pregnancy</td>
<td>↓</td>
<td>30–45</td>
<td>↑(10–15 mmHg)</td>
<td>111</td>
</tr>
<tr>
<td>Low-protein diet throughout pregnancy and postnatal life</td>
<td>↓</td>
<td>30</td>
<td>↓(8 mmHg)</td>
<td>51</td>
</tr>
<tr>
<td>Low-protein diet throughout pregnancy and up to postnatal day 10</td>
<td>↓</td>
<td>30</td>
<td>⇔</td>
<td>113</td>
</tr>
<tr>
<td>Uteroplacental insufficiency (day 18 of 22-day gestation)</td>
<td>↓</td>
<td>26</td>
<td>↑(16 mmHg)</td>
<td>106</td>
</tr>
<tr>
<td>Corticosterone (days 14 and 15 of 22-day gestation)</td>
<td>⇔</td>
<td>20</td>
<td>↑(8–10 mmHg)</td>
<td>96</td>
</tr>
<tr>
<td>Spiny mouse</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamethasone (days 20–23 of 39-day gestation)</td>
<td>⇔</td>
<td>13</td>
<td>⇔</td>
<td>29</td>
</tr>
<tr>
<td>Sheep</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamethasone (days 26–28 of 150-day gestation)</td>
<td>⇔</td>
<td>38</td>
<td>↑(7–12 mmHg)</td>
<td>30, 105</td>
</tr>
</tbody>
</table>

Although all the studies show a reduction in nephron endowment, low birth weight and hypertension are not common findings. All the studies used unbiased stereology to determine nephron endowment.

Models in Which a Low Nephron Number Is Associated With a Low Birth Weight

Placental insufficiency. In developed countries, placental insufficiency is the leading cause of intrauterine growth restriction and occurs in ~7–10% of pregnancies (42). Rat models of uteroplacental insufficiency have been developed through bilateral uterine vessel ligation in the later stages of pregnancy (~day 16–18 of a 22-day pregnancy). This results in significant fetal growth restriction due to lack of oxygen and nutrients (65, 107). In some cases, bilateral uterine vessel ligation also causes postnatal growth abnormalities due to effects on maternal mammary development (82). Low-birth-weight male offspring from this model have fewer nephrons than controls and develop hypertension as adults (106). Sheep studies of placental insufficiency, whereby microspheres are infused into the fetal circulation, also result in decreased placental perfusion and fetal growth restriction; starting this procedure at 110 days of gestation (full term = 150 days) reduces nephron endowment (114), whereas starting this procedure at 120 days does not (74). This contrast is most likely due to the fact that nephrogenesis is complete by day 125–130 in the sheep (79), and, therefore, the latter regimen affects only a very small period of nephrogenesis. Thus a crucial factor that links low birth weight and a nephron deficit may be the timing of the prenatal insult with respect to the stage of renal development.

Alterations in maternal nutrition. Manipulation of the maternal diet has been widely used to induce fetal growth restriction and investigate the mechanisms involved in adult disease development (for review see Ref. 3). In these studies, the mother is fed a diet that is low in calories or low in specific dietary components such as protein (66, 111, 112), vitamin A (68), or iron (21) throughout gestation or for specific parts of gestation. In almost all cases, the protein-deficient model results in a reduction in birth weight of offspring; however, adult disease outcomes, such as the development of hypertension, are highly variable. This is thought to be due in part to subtle differences in the composition of the diet (3). In many cases, a diet low in protein results in low-birth-weight offspring with a significant reduction in glomeruli number (66, 111). Interestingly, amino acid supplementation in combination with a low-protein diet has been shown to prevent the development of hypertension in the adult (57), although nephron endowment was not examined. The maternal low-protein model has particular relevance to developing countries, where protein intake during pregnancy may be very low and intrauterine growth restriction is exceedingly common (27). However, in more affluent societies, other prenatal insults/exposures are likely to be of greater importance.

A Model With a Low Nephron Number but No Change in Birth Weight

Exposure to maternal glucocorticoids. Exposure of pregnant animals to elevated glucocorticoids has been used to induce a suboptimal environment in a number of species (for review see Ref. 75). This model may be of increased relevance to women in Western society, where undernutrition is uncommon but increased cortisol levels due to stress may be more prevalent. Exposure to glucocorticoids over an extended period (>4 days in the rat) results in decreases in birth weight (85, 86, 110). In one study, the increase in glucocorticoids was associated with a decrease in maternal food intake, suggesting that glucocorticoids may cause effects through maternal calorie/protein restriction, rather than via a direct action (110). However, when glucocorticoids are administered over the short term (48–72 h), normal-birth-weight offspring are born (31, 32, 96). The results of this short-term glucocorticoid infusion are considered in detail in this review. A crucial aspect of this model is that the timing of exposure is of utmost importance, with only exposures at critical developmental periods resulting in adult disease (32, 88). Examination of a number of species has shown that glucocorticoid exposure very early in renal development appears to have the greatest effect on nephron endowment (see below).

Sheep

Over the last decade, we have performed a large series of experiments utilizing an ovine model of short-term maternal glucocorticoid exposure. In the initial series of experiments, animals were treated for 48 h with a continuous infusion of dexamethasone (0.48 mg/h) at the end of the 1st mo of pregnancy (26–28 days gestation, full term = 150 days). This resulted in female offspring that, although of normal birth weight, developed hypertension by 6 mo of age (32). Interestingly, when the same treatment was performed later (~64–66 days) in gestation, the normal-birth-weight offspring did not develop elevations in blood pressure (32). Subsequent studies showed a reduced nephron endowment at 7 yr of age in the animals treated with dexamethasone early in gestation (105). We repeated these blood pressure studies in male offspring and found that they too develop hyper-
tension following early prenatal dexamethasone exposure (30). More recently, we administered the naturally occurring glucocorticoid cortisol (5 mg/h) to the pregnant ewe over the same early period of pregnancy and found that male and female offspring develop high blood pressure, despite a lack of discernible alteration in birth weight (31). Nephron number in the late-gestation fetus (after completion of nephrogenesis) was reduced by ~30–40% in male and female offspring from both prenatal glucocorticoid treatment groups (K. M. Moritz, unpublished observations).

Finally, in all these studies, kidney weight in fetal or adult life is unaltered by prenatal glucocorticoid exposure (77, 105). Other researchers used a clinical regimen (2 injections, 24 h apart) to administer betamethasone to sheep at approximately midgestation (80 days) and, using acid maceration techniques to determine glomerular number, found a decrease in nephron endowment (40). Similar to our studies, no growth restriction was found, but offspring did develop hypertension at 6 mo of age (40).

Rat

Maternal dexamethasone treatment in the rat has been reported to result in a nephron deficit and the development of hypertension in the offspring (87), although unbiased stereology was not utilized to determine nephron endowment. This outcome is highly dependent on the timing of the dexamethasone exposure and the sex of the fetus (88), with the greatest susceptibility during the early formation of the metanephric kidney. After our ovine naturally occurring glucocorticoid studies, we recently investigated the effect of prenatal corticosterone (Cort, the natural glucocorticoid in rodents) treatment (31). Nephron number in both male and female offspring (after completion of nephrogenesis) was reduced by ~30–40% in male and female offspring from both prenatal glucocorticoid treatment groups (K. M. Moritz, unpublished observations).

MECHANISMS LEADING TO FORMATION OF A LOW NEPHRON ENDOWMENT

It has been established that a low nephron endowment is common to a large number of developmental programming models and animal species; now, how is this low nephron number formed? A number of mechanisms, including delayed branching of the ureteric bud into the surrounding metanephric mesenchyme, decreased rates of branching morphogenesis, increased apoptosis, and early cessation of nephrogenesis, can be postulated. Although increased apoptosis in the kidney has been demonstrated after a maternal low-protein diet (103) and altered branching morphogenesis in vitro after glucocorticoids (97), most of these mechanisms have yet to be investigated in any model.

Inasmuch as branching of the ureteric tree is a critical regulator of nephron endowment, recently, we used metanephric organ culture techniques to investigate the mechanism through which glucocorticoids may affect branching morphogenesis during nephrogenesis. It was found that when dexamethasone was added to embryonic day 14.5 rat metanephroi, branching morphogenesis was significantly inhibited and glomerular number was reduced (97). Metanephroi cultured in dexamethasone for 2 days (embryonic days 14–15) also showed significant alterations in key genes regulating branching morphogenesis, including glial cell-derived neurotrophic factor, bone morphogenetic protein-4, and transforming growth factor-β1. Interestingly, similar gene expression changes were found in embryonic day 16 rat metanephroi in which the dam had been exposed to dexamethasone (0.2 mg·kg⁻¹·day⁻¹) for 2 days at embryonic days 14-15 in vivo (97). We recently repeated these metanephric culture studies using the natural rodent glucocorticoid corticosterone. Interestingly, as shown in Fig. 1, addition of corticosterone to metanephric cultures did not reduce the number of branch points or glomerular number. A report of a nephron deficit when corticosterone was administered in vivo to rats (96) suggests that either the mechanisms leading to a reduction in nephron endowment are different between the natural and synthetic glucocorticoids or the dose of corticosterone used in vitro was insufficient to reduce branching morphogenesis. There is emerging evidence in sheep that prenatal exposure to the different glucocorticoids (cortisol and dexamethasone) may produce different outcomes in adult offspring (33, 75). The reasons for this are unclear; however, different outcomes highlight the risk in extrapolating results from models using synthetic glucocorticoids to outcomes in women (or animals) with high levels of endogenous glucocorticoids. This is an area requiring further research.

IS PROGRAMMING OF HYPERTENSION SIMPLY A REDUCTION IN NEPHRON NUMBER?

As outlined above, human and animal data strongly support an association between a reduced nephron endowment and adult hypertension. However, a reduced nephron endowment...
and hypertension may be simply coincident, and it is possible that compensatory changes in tubular function and/or renal hormonal systems must occur concomitantly for hypertension to develop (26). Furthermore, a reduced nephron number has been documented in the absence of hypertension (29, 51, 112) with or without changes in birth weight. Conversely, programmed hypertension has been demonstrated in the absence of changes in birth weight or decreased nephron number in a number of animal models, including maternal overfeeding, maternal hypertension, and maternal water restriction (16, 25, 70, 72), demonstrating that hypertension can also be programmed independently of a reduction in nephron number. Previously, we suggested potential mechanisms whereby this may occur, including alteration in the renin-angiotensin system, renal sympathetic innervation, and tubular transport mechanisms in the kidney (26).

COMPENSATORY RENAL CHANGES THAT MAY COMPOUND THE EFFECTS OF A REDUCED NEPHRON ENDOWMENT

Glomerular Hypertrophy

Renal function increases in a marked fashion in the newborn (79). Although no new nephrons form after birth in the human, renal maturation continues with significant tubular development of function (50). In large part, the ability of the kidney to cope with an increasing extracellular fluid volume, relative to body size, with age depends on associated glomerular hypertrophy (increased filtration surface area), increased arterial pressure (driving filtration), and the ability of the renal tubule to handle increased volumes of filtrate (67). The hyperfiltration theory of Brenner et al. (17) suggests that, in order to meet the metabolic requirements of the growing body, a reduced nephron endowment will result in compensatory glomerular growth, with a greater glomerular filtration rate per glomerulus, such that each nephron handles a greater volume of tubular filtrate. This compensatory process in the adult would seem to be an exaggeration of normal renal maturation of function at birth (19, 20). A previous study compared the impact of renal compensatory growth 4 wk after unilateral nephrectomy in young (~4 days of age) and adult (3 mo of age) rats on renal autoregulatory responses (19). It was demonstrated that the renal pressure–blood flow relationship changed significantly with normal renal postnatal maturation and that the impact of uninephrectomy on the autoregulation of renal blood flow differed in young and adult rats, with vascular resistance rising more sharply at low perfusion pressures in the young than in the adult rats (19). Thus the immature kidney compensates differently for a reduction in renal mass and, therefore, may be more susceptible to ischemic damage later in life. One mechanism suggested to underlie this differential response to uninephrectomy in young and adult animals is resetting of the TGF mechanism. TGF is a very powerful mechanism that maintains constancy of glomerular filtration rate and renal sodium reabsorption (93). TGF is not a static mechanism: the sensitivity and gain of this system can be reset by homeostatic challenge, resulting in appropriate salt and water conservation. However, under pathological conditions, this system can also be reset, with inappropriate salt and water retention leading to hypertension and cardiovascular disease. Perturbations in TGF are a primary factor in the development of renal dysfunction and hypertension (15, 24, 63, 83, 91). A preliminary report in lambs from dexamethasone-treated sheep demonstrates that TGF sensitivity is enhanced before arterial pressure increases and, thus, might contribute to the development of hypertension in this model (101).

Renal Transporters

During the postnatal period, renal transporter number, transporter isoform, intracellular mechanisms regulating the transporters, and cellular permeability are set (13). There has been little study of these parameters in models of programmed hypertension. However, if nephron number is reduced at birth and hyperfiltration occurs, the nephrons will need to process a greater filtered load; this may alter the number or function of the ion transporters and/or the permeability of the tubules, thereby contributing to the programming of hypertension (92). Changes in sodium, calcium, and water handling have been documented in several models of programmed hypertension (4, 23, 60, 71), but such mechanisms require further study. It is possible that, in programming models with a reduced nephron number that are not associated with adult hypertension under basal conditions (112, 113), a secondary insult may unmask a reduction in renal functional reserve (113). If so, compensatory increases in renal function due to changes in sodium in the diet, obesity, or diabetes may be limited, resulting in vascular fluid accumulation, thereby increasing arterial pressure and the risk of cardiovascular disease.
As assessing the importance of a reduced nephron endowment

In all models in which the mother is exposed to an insult during pregnancy, a number of organs and systems in the fetus are likely to be affected. Thus assessment of the relative importance of a reduced nephron endowment per se in the onset of adult disease is extremely difficult. In human patients with unilateral renal agenesis, in whom nephron endowment is reduced from birth, the incidence of renal insufficiency and proteinuria is common (2, 61), and, in many cases, infants with one kidney also have contralateral renal abnormalities (18, 35, 62), the most common of which may further contribute to renal problems. Children with unilateral renal agenesis often develop elevated arterial pressure (73, 95), although it is difficult to know whether this is directly due to a reduced nephron endowment.

An argument often used against the hypothesis that nephron number may influence blood pressure is that kidney donors, in whom nephron number is dramatically reduced in the adult, have reported normal maintenance of long-term arterial pressure (39, 45). Taken together, these studies suggest that it may be a decrease in nephron number during nephrogenesis, rather than a decrease in nephron number after completion of nephrogenesis, that predisposes the adult to renal and cardiovascular disease.

Evidence demonstrating the importance of a low nephron endowment from early in life: models of fetal unilateral nephrectomy

The relative importance of a low nephron number from early in life without confounding effects on other systems or a low birth weight has been investigated using a model of unilateral nephrectomy in two different species, the rat and the sheep. In the neonatal rat, removal of a kidney on postnatal day 1 (when nephrogenesis is continuing) resulted in adult rats that developed hypertension and impaired renal function (109). Of greater relevance to the human, fetal unilateral nephrectomy in the sheep (a species that, similar to the human, completes nephrogenesis before birth) at 110 days of gestation leads to normal-birth-weight male and female offspring that grow normally after birth but develop hypertension by 6 mo of age (80) (Fig. 2); this hypertension is maintained over a number of years (78). This model supports the concept that a reduced nephron endowment from birth results in hypertension, most likely involving a number of compensatory changes after birth. Although fetal uninephrectomy represents a quite severe model of low nephron endowment and is associated with increased blood pressure relatively early in postnatal life, it is also associated with only mild renal insufficiency. The total glomerular filtration rate in this model is reduced by only ~30%, meaning the remaining kidney has dramatically increased filtration to compensate for the loss of one kidney (80). The degree of renal compensation is great, with no difference in renal mass in the adult. In our ovine model, we have evidence of increased nephrogenesis, inasmuch as the single kidney of nephrectomized fetuses has more nephrons than the kidney of control fetuses (34). However, the tubular hypertrophy is considerable. Investigation of tubular function in this model, as well as the kidney’s ability to cope in the face of physiological challenges, will be of considerable interest in future studies.

Conclusions

Impaired renal development, particularly a reduced nephron endowment, is likely to play a major role in the etiology of some adult-onset diseases, including hypertension. Although a low birth weight may be one indication of a reduced nephron endowment, a normal birth weight does not necessarily indicate a normal nephron number. Similarly, a low nephron endowment, although a risk factor, is not essential for the development of hypertension and is probably only one of a number of mechanisms contributing to hypertensive disease onset and progression. An important question is whether there is a critical level of nephron endowment at which hypertension develops (i.e., a threshold effect). This has yet to be addressed in a single model.

Future studies are needed to devise methods for the determination of nephron endowment in living individuals; this would allow the early identification of individuals who have a nephron deficit and who would therefore require careful monitoring. Although therapeutic interventions to increase nephron endowment are unlikely, at least in the near future, identification of individuals at risk of hypertension would allow the postnatal lifestyle to be optimized to minimize future disease risk. We also need to look beyond nephron endowment and examine other aspects of renal development, including tubular development and compensatory adaptations after the initial insult.
REFERENCES


REduced nephron endowment and birth weight


