Kidney International, Vol. 68, Supplement 97 (2005), pp. S107–S111

Long-term consequences of low birth weight

LEONARDO REYES and REYNALDO MAÑALICH

Instituto de Nefrología, Habana, Cuba

Long-term consequences of low birth weight. There is accumulating evidence of the impact of low birth weight in adult age. Thus, the Barker theory and Brenner hypothesis gain more power. This article reviews and analyzes the evidence that supports the intrauterine origin of chronic noncommunicable diseases in adult age, particularly systemic arterial hypertension and chronic renal insufficiency. These are possibly related to lower nephron numbers, acquired in utero or later in life, which can increase susceptibility to kidney damage from diseases such as hypertension and diabetes mellitus, or cause arterial hypertension and secondary renal damage.

Resumen

Cada día es más evidente el impacto que tiene el bajo peso al nacer en la vida adulta. De aquí que la teoría de Barker y la hipótesis de Brenner cobren más fuerza. El presente reporte revisa y analiza la evidencia a favor del origen intrauterino de enfermedades crónicas no transmisibles del adulto, especialmente la hipertensión arterial sistémica y la insuficiencia renal crónica. Estas últimas se relacionan probablemente con un número bajo de nefronas, adquirido en la etapa intrauterina o en forma posterior, lo cual incrementa la susceptibilidad al daño renal en enfermedades como la hipertensión y la diabetes mellitus, o bien, el causar hipertensión arterial y daño renal secundario.

INTRODUCTION

Studies in the 1980s relating low birth weight (LBW) to chronic noncommunicable diseases in adult age allowed the formulation of Barker's hypothesis of the intrauterine origin of diseases suffered in adult age. Through time, this hypothesis has gained enough evidence that it is practically regarded as a theory today. This hypothesis has been enriched by others, such as Brenner's hypothesis [1], in more specific areas like systemic arterial hypertension (AHT) and chronic kidney disease (CKD), which has confirmed that LBW constitutes a risk factor for some diseases in adult age. The Brenner hypothesis also continues to gain increasing evidence and seems poised to become a theory in the near future.

Key words: low birth weight, oligonephronia, arterial hypertension, chronic kidney disease.

THE BARKER THEORY AND THE BRENNER HYPOTHESIS

These 2 concepts strongly complement one another. Barker's theory establishes a framework for the fetal origin of adult-age diseases. This theory is based on epidemiologic associations between fetal malnutrition due to different causes expressed by LBW in infancy and premature morbidity/mortality in adult age. The first association found was between LBW and AHT [2]. Other associations of LBW, such as ischemic cardiomyopathy [3] and stroke [4], were described later, followed by associations with glucose intolerance or type II diabetes mellitus (DM) [5], chronic obstructive respiratory disease [6], and syndrome X, which is essentially a combination of metabolic abnormalities, including type II DM, AHT [7], dyslipidemia, obesity, and high levels of corticosteroids [8–10]. But it was not until the studies from Brenner's group that Barker's theory was directly applied to AHT and renal diseases [11]. The reduced number of nephrons that accompany LBW can cause AHT or increase renal vulnerability to external agents predisposing subsequent AHT, thus facilitating the initiation and progression of CKD [12, 13].

In response to criticisms of the epidemiologic studies that support this hypothesis, this article will respond to some questions in reference to LBW and its relation to the development and evolution of noncommunicable CKD in adult age.

WHAT IS LBW?

Identifying, by their weight at birth, those newborns with restrictions in fetal growth is difficult, due to multiple factors that intervene in intrauterine growth. Nevertheless, a definition is necessary to unify statistics in the study of clinical epidemiology.

Mamelle et al studied the intrauterine growth potential in 72,000 births according to anthropometric measurements of the mother (age and height), calculated the lowest weight that should be considered a restriction in fetal growth, and identified a group of normal children (classified as constitutionally small) that could be wrongly classified on the basis of their gestational age [14]. Moreover, it is known that nephrogenesis ends at 36 weeks,

and Irving et al demonstrated that premature children, independent of birth weight, have risk factors for cardiovascular disease in adult age, thus making it very difficult to separate the effects of gestational age and birth weight [15]. However, the growth retardation for a given gestational age has greater relevance than the effect of prematurity on subsequent cardiovascular disease in adult age, as was demonstrated by Whincup et al [16]. Therefore, for a better interpretation of earlier studies and more recent ones, a limit of 2.5 kg is maintained to classify any given case as "restricted intrauterine growth" independent of gestational age (preterm or in term).

WHAT ARE THE CAUSES OF LBW?

The supply of nutrients to the human fetus and its environment are the main influences that regulate fetal growth. Fetal growth depends on a series of long and vulnerable steps known as the fetal supply line, which includes the composition and height of the maternal body, its storage of nutrients, alimentary habits during pregnancy, transport of nutrients to and through the placenta, arrival of toxins to the placenta and the fetus, and other factors. The final consequence of the alteration of any of these steps is fetal-growth restriction.

In experimental models, the main causes of LBW are: protein malnutrition, vitamin A deficiency, antibiotics administration: aminoglycosides, beta-lactam, corticosteroid administration, insulin resistance, genetics.

In humans, the causes of LBW are multifactorial—sociodemographic factors: adolescent pregnancy, maternal weight below 50 kg, family dysfunction, malnutrition, especially during pregnancy; maternal gestational weight gain below 7 kg; chronic infections; AHT during pregnancy; LBW of the mother; glucose intolerance or DM during pregnancy; smoking; alcohol abuse; genetics; other.

WHAT ARE THE EFFECTS OF LBW AT THE RENAL LEVEL?

Animal studies

Studies of LBW in laboratory animals and the very few histomorphometric studies in humans provide conflicting answers to this question. Merlet-Benichou et al proposed a model of congenital oligonephropathy in rats provoking retardation in intrauterine growth by ligature of the uterine artery on day 17 of gestation. Weight at birth was significantly reduced, as well as the number of nephrons [17]. Schwedler et al found that intrauterine exposure to gentamycin in rats genetically predisposed to glomerular sclerosis produces a reduction in the number of nephrons and worsening of the glomerulosclerosis, as well as a reduction of birth weight, but this does not happen in animals not genetically predisposed to sclerosis [18]. Nathanson et al demonstrated that in vitro and in utero exposure to beta-lactam antibiotics in rats prevents nephrogenesis. They found a direct correlation between nephron reduction in exposed rats and their weight at birth [19]. Jones et al reported that animal models that produce a LBW use extreme situations such as a pronounced low-protein diet, administration of nephrotoxic agents, or ligature of a uterine artery, which produces models with a high fetal or neonatal mortality and limited applicability to clinical situations more frequently encountered in humans [20].

Vitamin A (retinol) and its main derivative, retinoic acid, are also involved in nephrogenesis, and rats exhibit a dose-dependent effect of vitamin A on nephron number. A mild vitamin A deficit during pregnancy could lead to a nephron deficit in the offspring that enhances the risk of kidney disease [21]. Human data on this relationship are not available.

In humans, nephrogenesis is completed before birth, at 36 weeks of pregnancy, but in rats it is completed 7 or 8 days after birth. Thus, postpartum nephrogenesis is very important to determine the final number of nephrons in the rat. If the protein restriction in rats is not very severe, a reduction in the number of nephrons is not observed in spite of LBW.

Human studies

Leroy et al examined the kidneys of children who died of nonrenal causes in neonatal intensive care units. Children with weight under the 10th percentile were compared with children with weight values above that figure of the same gestational age. In those with low weight for this classification, the kidneys weighed less and had fewer nephrons [22]. Hinchliffe et al found that children with retarded intrauterine growth had fewer nephrons but the same glomerular volume [23], and Mañalich et al found that children with a weight at birth below 2.5 kg had fewer nephrons and larger glomerular volume than children with higher birth weights. They observed a mean reduction of 20% of the nephrons in children with LBW [24].

More recently, other studies support these findings. Hughson et al have shown that weight at birth is a strong determinant of the number of nephrons and glomerular size, which confirms that LBW is accompanied by fewer large-volume nephrons than in individuals with normal birth weights [25]. Hoy et al, in a study of autopsies, demonstrated that corpuscular volume is inversely proportionate to the number of glomeruli [26]. In an indirect manner, by ultrasonographic renal measurements, this histologic birth-weight relation has been supported. Deutinger et al compared ultrasonographic quantitative measurements of renal growth with measurements of renal function and indicated the feasibility of an evaluation

of the functional limitations of the intrauterine urinary system [27]. Finally, Spencer et al demonstrated that the renal volume of individuals with LBW is lower than that of individuals with normal birth weight [28].

WHAT ARE THE CLINICAL CONSEQUENCES OF LBW?

The short-term consequences of LBW can be summarized as having up to 12 times higher perinatal mortality [29] and 3 times higher morbidity than that observed for a birth weight appropriate to gestational age [30]. A growing number of studies suggest that exposure to an abnormal intrauterine environment affects anthropometric, metabolic, and mental development, leading to increased risk of disease later in life.

Law et al reviewed 43 different studies since 1956, including 66,000 patients between 0 and 71 years of age and found a good correlation between birth weight and systolic and diastolic arterial pressure [31]. Nilsson et al analyzed blood pressure and LBW in 149,378 Swedish children and found a significant relation between birth weight and systolic arterial pressure. An increase of 1 kg of weight at birth was associated with a 0.8-mm Hg reduction in systolic pressure [32]. Likewise, Huxley et al reviewed the relation between systolic arterial pressure, birth weight, and postnatal growth. They analyzed 80 relevant articles published between March 1996 and March 2000, encompassing more than 440,000 individuals from 0 to 84 years of age of all races. Arterial pressure was noted to be approximately 2 mm Hg lower for each kg increase in weight at birth, and accelerated postnatal growth in LBW children was strongly associated with higher blood pressure levels [33].

New histomorphometric evidence in humans provided by Keller et al confirmed that fewer large-volume glomeruli are found in patients with primary AHT than in normotensive patients [34]. However, there are other clinical situations where nephron number is lower, yet AHT is either nonexistent or infrequent [35]. In total, more than 38 studies from different countries have demonstrated that people with LBW are likely to have higher arterial pressure in childhood and in adult age.

IMPACT OF LOW NEPHRON NUMBER

In the 1970s, the Laboratory of Kidney Electrolytes and Physiology, directed by Barry Brenner and the Department of Pathology of the Brigham and Women's Hospital, developed methods of renal micropuncture and mathematical models that allowed them to quantify the determinants of glomerular filtration. As a result, they showed that increased capillary pressure and glomerular flow were important contributors to glomerular damage, especially in models of kidney ablation [36–38]. Thus, the "glomerular hyperfiltration" theory emerged. The concept of glomerular hyperfiltration and hypertension in remnant nephrons as an adverse effect of the reduction in nephronal mass, and its association with systemic AHT, represents a critical stage in advancing the field of nephrology. Subsequent studies of intervention with protein restriction and inhibitors of the angiotensin-converting enzyme reinforced increased capillary pressure as the primary cause of glomerular damage [38, 39]. Lastly, the finding that renal damage was autoperpetuated in models of reduced nephron number was an important foundation for future studies of the progression of kidney disease [36].

INCREASE IN RENAL VULNERABILITY

There is evidence that the oligonephronia associated with LBW increases renal vulnerability or worsens the evolution of renal diseases in these individuals. Rossing et al reported a high risk of diabetic nephropathy among patients with type I DM and LBW [40], and later, Nelson et al reported the same risk among patients with type II DM [41]. Duncan et al indicated that LBW with reduced nephron number has an unfavorable influence in patients with membranous glomerulopathy [42]. Yudkin et al reported the presence of proteinuria and progressive renal disease in elderly patients without diabetes that had been of LBW [43]. Zidar et al indicated the unfavorable clinical course of nephrotic syndrome with minimal glomerular changes in children with LBW, as well as the more intense changes of glomerulosclerosis seen in the renal biopsies of children with glomerulopathy caused by immunoglobulin A and LBW [44, 45]. More recently, Sheu et al confirmed the unfavorable evolution and treatment response of nephrotic syndrome caused by minimal glomerular changes in children with LBW [46].

PROGRESSION OF RENAL INSUFFICIENCY

The partial ablation of renal mass, in combination with the congenital deficit of nephron number in individuals of LBW, may initiate a cycle of progressive glomerular damage accompanied by glomerular hypertrophy, intraglomerular hypertension, and systemic AHT. Response to decreased renal mass in humans varies according to age at loss, underlying condition, and extent of tissue loss. Several follow-up studies performed on renal donors, as well as patients nephrectomized secondary to trauma and unilateral diseases, suggest a relatively benign course after unilateral nephrectomy [47, 48]. By contrast, patients with nephrectomy for bilateral disease, more extensive loss of renal mass (bilateral tumors) [49], unilateral nephrectomy at a younger age [50], and unilateral renal agenesis [51] show a surprisingly high incidence of glomerular sclerosis, proteinuria, hypertension, and renal insufficiency.

Likewise, the number of viable nephrons of the donor kidney can determine the long-term prognosis of renal function of the graft. This is because renal ischemia, reperfusion, and acute rejection reduce the number of nephrons, and predispose the transplanted kidney to AHT and glomerulosclerosis, as has been shown in experimental studies [52, 53]. Chertow et al, in a study of survival in 31,515 kidney transplants performed in the United States between 1987 and 1991, demonstrated, with multiple regression analysis, that the risk of losing renal function increased when the donor kidney had fewer nephrons (as occurs in donors of advanced age, women, and African Americans) and when the recipient had a large body surface area [54]. These findings support the existence of antigen-independent factors that are associated with renal failure, and are consistent with the progression of renal damage that may occur in oligonephronia due to LBW.

CHRONIC KIDNEY DISEASE

There is a real epidemic of CKD among the Aborigines in Australia's Northern Territory, with an incidence between 1994 and 1996 of 2700 per million inhabitants that doubles every 4 years, being 20 times greater than in the non-Aboriginal population [12]. The association between LBW and CKD may be related to an impediment of nephrogenesis caused by intrauterine malnutrition and/or an adverse intrauterine environment, as has been shown in various studies [17, 22–24]. The frequency of LBW is more than double in the Aboriginal population, and the epidemic of CKD might be explained by the protein malnutrition and vitamin A deficit that provoked high mortality rates among children of LBW in recent decades [12]. However, other factors such as intrauterine stress or environmental exposures cannot be excluded [55, 56].

In recent years, a high incidence of CKD has been noted in the southeast United States. The incidence of terminal CKD is 345 per million inhabitants compared with 269 per million in the rest of the country. In South Carolina, the incidence of CKD doubled between 1987 and 1996, with AHT and DM as the main causes (71% of all patients). Additionally, a significant correlation was found between weight at birth and CKD in this study. LBW was more common in South Carolina than in other states and is more common among African Americans than Caucasians. The risk of CKD with AHT is 5 times greater in African Americans. There is a significant correlation of LBW and CKD among both African Americans and Caucasians, but LBW is twice as common among the former [13].

On the basis of this review, we conclude that LBW and associated prenatal AHT are important precursors to an increased vulnerability to renal disease in adult age.

FUTURE DIRECTIONS

Interventions through programs geared to adolescents, as well as prenatal attention, will contribute to improve the indicators of neonatal development, particularly gestational age, intrauterine growth rate, and birth weight. In high biologic, psychologic, and social risk groups, it is especially important to eliminate or attenuate deleterious intrauterine exposures/stresses and to monitor the mother's nutritional and health status before and during pregnancy. Such an approach will help promote normal fetal growth rates and birth weights, and reduce the incidence of premature births and subsequent exacerbation of increased incidence and severity of many diseases, including CKD, in adulthood.

Reprint requests to Leonardo Reyes, M.D., Instituto de Nefrologia, Ave. 26 y Boyeros, Plaza, Apdo. 6358, Habana 10600, Cuba.
E-mail: lreyes@infomed.sld.cu

REFERENCES

1. Brenner BM, Garcia DL, Anderson S: Glomeruli and blood pressure. Less of one, more of the other? *Am J Hypertens* 1:335–347, 1988
2. Wadsworth MEJ, Cripps HA, Midwinter RE, *et al*: Blood pressure in a national birth cohort at the age of 36 related to social and familial factors, smoking, and body mass. *BMJ* 291:1534–1538, 1985
3. Barker DJP, Osmond C: Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. *Lancet* 1:1077–1081, 1986
4. Barker DPJ, Osmond C: Deaths rates from stroke in England and Wales predicted from post-maternal mortality. *BMJ* 295:83–86, 1987
5. Hales CN, Barker DPJ, Clark PMS, *et al*: Fetal and infant growth and impaired glucose tolerance at age 64 years. *BMJ* 303:1019–1022, 1991
6. Barker DPJ, Godfrey KM, Fall C, *et al*: Relation of birth weight and childhood respiratory infection to adult lung function and death from chronic obstructive airway disease. *BMJ* 303:671–675, 1991
7. Barker DPJ, Hales CN, Fall CHD, *et al*: Type 2 (non–insulin-dependent) diabetes mellitus, hypertension and hyperlipidaemia (Syndrome X): Relation to reduced fetal growth. *Diabetologia* 36:62–67, 1993
8. Benediktsson R, Lindsay RC, Noble J, *et al*: Glucocorticoid exposure in utero: New model for adult hypertension. *Lancet* 341:339–341, 1993
9. Johannes CB, Stellato RK, Feldman HA, *et al*: Relation of dehydroepiandrosterone and dehydroepiandrosterone sulphate with cardiovascular disease risk factors in women: Longitudinal results from the Massachusetts Women's Health Study. *J Clin Epidemiol* 52:95–103, 1999
10. Phillips DI, Walker BL, Reynolds RM, *et al*: LBW predicts elevated plasma cortisol concentrations in adults from 3 populations. *Hypertension* 35:1301–1306, 2000
11. Brenner BM, Chertow GM: Congenital oligonephropathy and the etiology of adult hypertension and progressive renal injury. *Am J Kidney Dis* 23:171–175, 1994
12. Hoy WE, Rees M, Kile E, *et al*: A new dimension to the Barker hypothesis: Low birthweight and susceptibility to renal disease. *Kidney Int* 56:1072–1077, 1999
13. Lackland DT, Bendall HE, Osmond C, *et al*: LBWs contribute to high rates of early-onset chronic renal failure in the Southeastern United States. *Arch Intern Med* 160:1472–1476
14. Mamelle N, Cochet V, Claris O: Definition of fetal growth restriction according to constitutional growth potential. *Biol Neonate* 80:277–285, 2001
15. Irving RJ, Belton NR, Elton RA, *et al*: Adult cardiovascular risk factors in premature babies. *Lancet* 355:2135–2136, 2000

16. Whincup PH, Cook DG, Papacosta O: Do maternal and intrauterine risk factors influence blood pressure in childhood? *Arch Dis Child* 67:1423–1429, 1992
17. Merlet-Benichou C, Gilbert T, Muffat-Joly M, *et al*: Intrauterine growth retardation leads to a permanent nephron deficit in the rat. *Pediatr Nephrol* 8:175–180, 1994
18. Schwedler SB, Gilbert T, Moreau E, *et al*: Nephrotoxin exposure in uterus reduces glomerular number in sclerosis-prone but not sclerosis-resistant mice. *Kidney Int* 56:1683–1690, 1999
19. Nathanson S, Moreau E, Merlet-Benichou C, *et al*: In utero and vitro exposure to beta-lactams impair kidney development in the rat. *J Am Soc Nephrol* 11:874–884, 2000
20. Jones SE, Nyengaard JR, Flyvbjerg A, *et al*: Birth weight has no influence on glomerular number and volume. *Pediatr Nephrol* 16:340–345, 2001
21. Merlet-Benichou C: Influence of fetal environment on kidney development. *Int J Dev Biol* 43:453–456, 1999
22. Leroy B, Josset P, Morgan G, *et al*: Intrauterine growth retardation (IUGR) and nephron deficit: Preliminary study in man. *Pediatr Nephrol* 6:C21, 1992
23. Hinchliffe SA, Lynch MR, Sargent PH, *et al*: The effect of intrauterine growth retardation on the development of renal nephrons. *BJOG* 99:296–301, 1992
24. Mañalich R, Reyes L, Herrera M, *et al*: Relationship between weight at birth and number and size of renal glomeruli in humans: A histomorphometric study. *Kidney Int* 58:770–773, 2000
25. Hughson M, Farris AB III, Douglas-Denton R, *et al*: Glomerular number and size in autopsy kidneys: The relationship to birth weight. *Kidney Int* 63:2113–2122, 2003
26. Hoy WE, Douglas-Denton RN, Hughson MD, *et al*: A stereological study of glomerular number and volume: Preliminary findings in a multiracial study of kidney at autopsy. *Kidney Int* 63(Suppl 83):S31–S37, 2003
27. Deutinger J, Bartl W, Pfersmann C, *et al*: Fetal kidney volume and urine production in case of growth retardation. *J Perinat Med* 15:307–315, 1987
28. Spencer J, Wang Z, Hoy WE, *et al*: LBW and reduced renal volume in Aboriginal children. *Am J Kidney Dis* 37:915–920, 2001
29. Davis JA, Dobbing J (editors): *Scientific Foundations of Paediatrics*, London, Heinemann, 1974, pp 69–80
30. Lin CC: Intrauterine growth retardation. *Obstet Gynecol Annu* 14:127–221, 1985
31. Law CM, Shiell AW: Is blood pressure inversely related to birth weight? The strength of evidence from a systematic review of the literature. *J Hypertens* 14:935–941, 1996
32. Nilsson PM, Ostergren PO, Nyberg P, *et al*: LBW is associated with elevated systolic blood pressure in adolescence: A prospective study of birth cohort of 149,378 Swedish boys. *J Hypertens* 15:1627–1631, 1997
33. Huxley RR, Shiell AW, Law CM: The role of size at birth and postnatal catch-up growth in determining systolic blood pressure: A systematic review of the literature. *J Hypertens* 18:815–831, 2000
34. Keller G, Zimmer G, Mall G, *et al*: Nephron number in patients with primary hypertension. *N Engl J Med* 348:101–108, 2003
35. Johnson RJ, Rodríguez-Iturbe B, Herrera-Acosta J, *et al*: Nephron number and primary hypertension. *N Engl J Med* 348:1717–1719, 2003
36. Olson JL, Hostetter TH, Rennke HG, *et al*: Altered glomerular permeselectivity and progressive sclerosis following extreme ablation of renal mass. *Kidney Int* 22:112–126, 1982
37. Hostetter TH, Olson JL, Rennke HG, *et al*: Hyperfiltration in remnant nephrons: A potentially adverse response to renal ablation. *J Am Soc Nephrol* 12:1315–1325, 2001
38. Anderson S, Meyer TW, Rennke HG, *et al*: Control of glomerular hypertension limits glomerular injury in rats with reduced renal mass. *J Clin Invest* 76:612–619, 1985
39. Meyer TW, Anderson S, Rennke HG, *et al*: Reversing glomerular hypertension stabilizes established glomerular injury. *Kidney Int* 31:752–759, 1987
40. Rossing P, Tarnow L, Nielsen FS, *et al*: LBW: A risk factor for development of diabetic nephropathy? *Diabetes* 44:1405–1407, 1995
41. Nelson RG, Morgenstern H, Bennett PH, *et al*: Birth weight and renal disease in Pima Indians with type 2 diabetes mellitus. *Am J Epidemiol* 148:650–656, 1998
42. Duncan RC, Bass PS, Garrett PJ, *et al*: Weight at birth and other factors influencing progression of idiopathic membrenous nephropathy. *Nephrol Dial Transplant* 9:875, 1994
43. Yudkin JS, Phillips DI, Stanner S. Proteinuria and progressive renal disease: Birth weight and microalbuminuria. *Nephrol Dial Transplant* 12(Suppl 2):S10–S13, 1997
44. Zidar N, Cavic MA, Kenda RB, *et al*: Unfavorable course of minimal change nephrotic syndrome in children with intrauterine growth retardation. *Kidney Int* 54:1320–1323, 1998
45. Zidar N, Cavic MA, Kenda RB, *et al*: Effect of intrauterine growth retardation on the clinical course and prognosis of IgA glomerulonephritis in children. *Nephron* 79:28–32, 1998
46. Sheu JN, Chen JH: Minimal change nephrotic syndrome in children with intrauterine growth retardation. *Am J Kidney Dis* 37:909–914, 2001
47. Fogo A, Ichikawa I: Glomerular growth promoter: The common channel to glomerular sclerosis. *Semin Nephrol* 4:213–225, 1990
48. Fotino S: The solitary kidney: A model of chronic hyperfiltration in humans. *Am J Kidney Dis* 13:88–98, 1989
49. Novick AC, Gephardt G, Guz B, *et al*: Long-term follow-up after partial removal of a solitary kidney. *N Engl J Med* 325:1058–1062, 1991
50. Di Tullio MT, Casale F, Indolfi P, *et al*: Compensatory hypertrophy and progressive renal damage in children nephrectomized for Wilms' Tumor. *Med Pediatr Oncol* 26:325–328, 1996
51. Argueso L, Ritchey ML, Boyle ET, *et al*: Prognosis of patients with unilateral renal agenesis. *Pediatr Nephrol* 6:412–416, 1992
52. Heemann VW, Azuma H, Tullius SG, *et al*: The contribution of reduced functioning mass to chronic kidney allograft dysfunction in rats. *Transplantation* 58:1317–1322, 1994
53. Mackenzie HS, Tullius SG, Heemann VW, *et al*: Nephron supply is a major determinant of long-term renal allograft outcome in rats. *J Clin Invest* 94:2148–2152, 1994
54. Chertow GM, Milford EL, Mackenzie HS, *et al*: Antigen-independent determinants of cadaveric kidney transplant failure. *JAMA* 276:1732–1736, 1996
55. Igosheva N, Klimova O, Anishchenko T, *et al*: Prenatal stress alters cardiovascular responses in adult rats. *J Physiol* 557:273–285, 2004
56. Mone SM, Gillman MW, Miller TL, *et al*: Effects of environmental exposures on the cardiovascular system: Prenatal period through adolescence. *Pediatrics* 113(Suppl 4):1058–1069, 2004