Long-Term Effects of In Utero Exposure to Cyclosporin A on Renal Function in the Rabbit

ANAÏS TENDRON-FRANZIN,* JEAN-BERNARD GOUYON,* JEAN-PIERRE GUIGNARD,† STÉPHANE DECramer,* EVE JUSTrABO,* THIERRY GILBERT,‡ and DENIS SALOMON SEMAMA*  
*Service de Pédiatrie 2, UPRES EA 563, Dijon, France; †Laboratoire de Néphrologie du développement, C.H.U.V., Lausanne, Suisse; ‡Inserm U574, Hôpital Necker-Enfants Malades, Paris, France

Abstract. The number of pregnant women who receive cyclosporin A (CsA) after transplantation or for autoimmune disease has increased. CsA and its metabolites can cross the placental barrier and thus interfere with fetal development. It was shown previously that rabbits that were exposed in utero to 10 mg/kg per d CsA from the 14th to the 18th day of gestation presented a 25% nephron reduction. Thus, this study was conducted to assess the long-term systemic and renal effects of a CsA-induced nephron reduction. Twenty-two pregnant New Zealand white rabbits were randomly divided into two groups: Twelve received 10 mg/kg per d CsA from day 14 to day 18 of gestation, and 10 were used as controls. Rabbits that were born to these animals were evaluated at 4, 11, 18, and 35 wk of life. Pups that were exposed antenatally to CsA presented first a permanent nephron deficit; second, glomerular, tubular, and intrarenal hemodynamics dysfunction; third, enlarged kidneys with numerous tubular and glomerular lesions; and, fourth, an endothelin-dependent systemic hypertension that worsened with age. In utero exposure to CsA induced a nephron reduction that led to systemic hypertension and progressive chronic renal insufficiency in adulthood. A long-term clinical survey is mandatory in infants who are born to mothers who were treated with cyclosporin during pregnancy.

Over the last few years, the number of pregnant women who have received cyclosporin A (CsA) after transplantation or for autoimmune disease has increased (1,2). CsA and its metabolites can cross the placental barrier and enter into the fetal circulation (3,4). These drugs have been associated with increased incidence of spontaneous abortion, prematurity, and intrauterine growth retardation (IUGR) (2). Most clinical studies report that children who are exposed in utero to CsA have a normal development and present a normal renal function during the neonatal period (5,6) and up to the age of 7 (7,8). However, some experimental studies showed that a prenatal exposure to CsA induced a vacuolation of proximal tubular cells in rats (9,10) and an impaired distal nephron development in mice (11). More recently, we showed that in utero exposure to 10 mg/kg per d CsA from the 14th to the 18th day of gestation (early nephrogenesis period) induced a 25% nephron deficit in newborn rabbits (12).

Nephron deficits, encountered in IUGR (13,14) or after in utero exposure to aminoglycoside (15,16), have been associated with increased incidence of systemic hypertension (17–19) and the development of glomerulosclerosis (15,20) in adulthood, but long-term outcome of renal function remains to be evaluated. The aim of the present study thus was to assess the long-term effects of CsA-induced nephron reduction on renal function in rabbit, an animal model that shows close similarities with human kidney function.

Materials and Methods

Animals

Twenty-two pregnant New Zealand white rabbits of known mating dates were used to generate newborn rabbits that were evaluated at 1 mo (renal maturity) and 11 (young rabbit), 18 (sexual maturity), and 35 (adulthood) wk of life. All pregnant rabbits were individually housed and had free access to food and tap water. The pregnant rabbits were randomly divided into two groups: A control group of 10 untreated pregnant rabbits and a CsA group of 12 pregnant rabbits that received a daily subcutaneous injection of 10 mg/kg per d Sandimmun (CsA, 50 mg/ml; Cremophor, 650 mg/ml; provided by Novartis, Rueil-Malmaison, France) from the 14th day to the 18th day of gestation. After the last injection, maternal blood CsA concentration was determined on day 19 of gestation, using the AxSYM cyclosporin test (Abbott Diagnostic, Saint-Remy sur Avre, France).

All pregnant rabbits delivered spontaneously at term. The newborn rabbits were weighted within 8 h after birth and were identified with indelible ink. After birth, each litter was left with the mother for 1 mo and allowed free access to food and water.

To match the reduced litter size of the CsA-treated does, as already reported (12), each control litter was reduced to six pups. Each newborn rabbit was weighted every second day during the first month and weekly thereafter. Rabbit pups of both control and CsA groups were used as follows. At 1 mo, 11 wk, and 35 wk of age, functional and histologic renal evaluations were performed from 12 pups for
each group. At 18 wk of age, corresponding to sexual maturation in the rabbit, nine pups of each gender were used for renal function and histology evaluations. A total of 108 pups were analyzed in CsA and control groups. Animals’ care and experimental procedures were conducted according to the criteria outlined in The Guide for Care and Use of Laboratory Animals.

Surgical Procedures and Sample Collection

On the day of experimentation, the rabbits were anesthetized with sodium pentobarbital through the left marginal ear vein (loading dose, 30 mg/kg; maintenance dose, 10 mg/kg per h) and placed on a heated table to maintain body temperature in the range of physiologic rabbit values (39°C). The trachea was cannulated to allow mechanical ventilation (Babylóg 1, Polymed 201; Dräger, Antony, France). For 1-mo-old rabbits, respiratory rate was 40/min, airway pressure was 10 mbar, ventilator flow was 6 L/min, and fraction of inspired oxygen was 0.21. For 11-, 18-, and 35-wk-old rabbits, respiratory rate was 40/min, airway pressure was 20 mbar, ventilator flow was 12 L/min, and fraction of inspired oxygen was 0.21.

The left carotid artery was catheterized with a 20-G catheter for 1-mo-old rabbits and an 18-G catheter for 11-, 18-, and 35-wk-old rabbits (catheter Jelco 18 G and 20 G; Chatenay Malabry, Critikon, France) to allow blood sampling and continuous monitoring of arterial BP (Hewlett Packard Pressure Recorder, 78342A; Palo Alto, CA).

The right jugular vein was catheterized with a 22-G catheter for 1-mo-old rabbits and with an 18-G catheter for 11-, 18-, and 35-wk-old rabbits (catheter Jelco 18 G and 22 G; Critikon) to allow infusion of a sterile solution of Ringer-Mannitol at a rate of 17 ml/h for 1-mo-old rabbits and of 60 ml/h for 11-, 18-, and 35-wk-old rabbits. The infusate contained per liter 100 mmol of NaCl, 6 mmol of KCl, 100 mmol of NaHCO₃, and 50 g of mannitol.

After completion of surgery and to assess renal function, inulin and para-aminohippurate (PAH) clearances were measured. Priming doses of inulin (25 mg) and PAH (6.6 mg) were administered through the jugular vein, and their serum levels were maintained by a continuous intravenous infusion of a solution that contained 2.5% inulin and 0.66% PAH at a rate of 1.2 ml/h for 1-mo-old rabbits. For older rabbits, the priming doses were 125 mg of inulin and 33 mg of PAH, and serum levels were maintained by the same continuous infusion but at a rate of 6 ml/h. The bladder was catheterized for urine collection (Pediatric PTFE coated Foley catheter, 8Ch. Laboratoires Bard SA, France). Approximately 30 min was spent for animal preparation, and 60 min was then allowed for subsequent equilibration.

After the equilibration period, vesical voiding was obtained by applying gentle suprapubic pressure, and renal function and BP were assessed during three 30-min periods. Urine was collected for each period. Arterial blood sampling was collected at the midpoint of each period (3 ml of blood for 1-mo-old rabbits and 7 ml for 11-, 18-, and 35-wk-old rabbits). A total of 900 μl of blood was immediately used for blood gas and hematocrit determination; the remainder was centrifuged. The red blood cells were then reconstituted in macromolecules (Plasmion, Bellon, France) and immediately returned to the animal. At 35 wk of age, additional blood samples were collected and kept at −20°C to measure the plasma renin activity. Plasma and urine samples were kept at −20°C for subsequent analysis of inulin, PAH, sodium, and osmolality. At the end of the experiment, both kidneys were removed and weighed separately. The left kidney was prepared for nephron counting, and the right kidney was fixed with Duboscq-Brazil fluid for routine histology, as already described (12). All rabbits were then administered a lethal intravenous dose of sodium pentobarbital.

Analytical Procedures

Urine volume was calculated from change in weight of preweighed tubes without correction for specific gravity. Arterial blood for pH, PCO₂, and PO₂ measurements was collected anaerobically in heparinized tubes. Blood gas determination was performed with a pH/blood gas analyser (Blood gas system 168; Ciba-Corning Co, Melfield, MA). The automatic anthrome (21) and the Bratton and Marshall (22) methods were used for the determination of inulin and PAH concentrations, respectively (Autoanlyser II; Technicon Instrument Corporation, Tarrytown, NY). Plasma and urinary sodium and protein concentrations were performed using a Vitros 250/750 (Ortho Diagnostics, Raritan, NJ). Plasma and urinary osmolality (P_posm and U_posm) were determined using a freezing point measurement (13DR osmometer; Messtechnik, Roehling, Berlin, Germany). For 35-wk-old rabbits, analysis of plasma renin activity (PRA) and urinary endothelin (ET) was performed. At the end of the experimental study, a renal venous blood sample was collected in an EDTA tube and centrifuged at 3°C. After centrifugation, plasma was kept at −20°C to measure the PRA. The PRA determination involved an initial incubation of plasma to generate angiotensin I, followed by quantification of angiotensin I by RIA (GammaCoat Plasma Renin Activity 125I RIA Kit, Stillwater, MN). ET was determined on urine, using the ET 1-21–specific 125I Assay System (Amerlex-M Magnetic Separation, Amer sham Biosciences, Orsay, France).

Data Analysis

The renal clearances of inulin (C_in) and PAH (C_PAH) were calculated from standard equations and used as indices of GFR and renal plasma flow, respectively. A renal PAH extraction ratio (E_PAH) was used to calculate renal blood flow (RBF). The E_PAH was assessed by concomitantly collecting renal venous blood and arterial blood. The values of E_PAH were influenced by neither age nor treatment, so we used the mean calculated value of 0.86 ± 0.11 (n = 108) to determine RBF in all groups. RBF, renal vascular resistance (RVR), filtration fraction (FF), and fractional excretion of sodium (FENa) were calculated from the following equations: E_PAH = (a − v)/a, where a = arterial PAH concentration and v = PAH concentration in the renal vein; RBF (ml/kg per min) = C_PAH/E_PAH × (1 − Hct)!, where Hct = hematocrit; RVR (mmHg/ml per kg/min) = MBP/RBF, where MBP = mean BP; FF (%) = (GFR/RPF) × 100; and FENa (%) = (C_Na/GFR) × 100, where C_Na = renal clearance of sodium.

Statistical Analyses

All results are expressed as means ± SD. Comparisons between groups were performed using one-way ANOVA. The level of significance was set at P < 0.05.

Results

Postnatal Development after Antenatal Exposure to CsA

As already observed (12), the protocol of CsA exposure that we used (reaching maternal CsA residual blood values of 256 ± 44 ng/ml) did not interfere with intrauterine growth but led to a significant reduction of the litter size (9.1 ± 0.4 [n = 10 controls] versus 6.2 ± 0.5 [n = 12 CsA-treated does]). As shown in Table 1, no birth weight differences occurred among pups that were used at 1 mo, 11 wk, 18 wk, and 35 wk of life in both groups. At 1 mo of life, kidney weight was similar in both groups. At 11 wk of life, kidney weight was significantly greater in rabbits that were exposed in utero to CsA than in the control group. This renal hypertrophy increased with age, being 18% at 11 wk, 25% at 18 wk, and 30% at 35 wk of life.
The ratio of kidney mass to body weight, which was ~1% at 1 mo of life, decreased with age in both control and CsA groups. However, it was significantly higher in CsA subgroups from 11 wk onward. Concerning the number of nephrons per kidney, it was significantly lower in rabbits that were born to CsA-treated mothers than in age-matched controls, as expected (Table 1) (12). The degree of oligonephronia did not vary with the age.

**Short- and Long-Term Follow-up of Renal Function in Pups that Were Born to CsA-Treated Mothers**

At 1 mo of life, no significant difference was observed for renal function parameters (GFR, RBF, RVR, FF, V, FENa, proteinuria) between control and CsA groups. To the contrary, from 11 wk onward, renal function started to deteriorate in pups that were exposed antenatally to CsA. At 11 wk of life, rabbits that were exposed in utero to CsA showed a 44% increase in diuresis, a twofold increase in FENa, and a 30% augmentation in proteinuria as compared with controls. However, no significant difference was found for GFR, FF, RVR, and RBF between the CsA and control groups (Figure 1, Table 2). At 18 wk of life, rabbits reach their sexual maturity. Because no differences between female and male rabbits were noted in both control and CsA groups, functional data were gathered. At this age, diuresis and FENa did not significantly differ between the two groups. In the CsA group, GFR, FF, and RBF were decreased, respectively, by 37, 17, and 22% compared with the control group, whereas RVR was significantly increased by 55% (Figure 1). At this age, rabbits that were exposed in utero to CsA had a proteinuria significantly greater than control rabbits. At 35 wk of age, diuresis did not statistically differ between CsA and control groups, but FENa was significantly increased in the CsA group as compared with controls. GFR was reduced, but no difference was observed for FF and RBF between rabbits of control and CsA groups. RVR and proteinuria were increased, respectively, by 53 and 83% in the CsA group. Throughout the study, blood gases and pH were in the

<table>
<thead>
<tr>
<th>Table 1. Physiological parameters in control and CsA animals at 1 month and 11, 18, and 35 weeks of lifea</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group</strong></td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td>Birth weight (g)</td>
</tr>
<tr>
<td>Body weight (g)</td>
</tr>
<tr>
<td>Kidney weight (g)</td>
</tr>
<tr>
<td>Renal mass/body weight (%)</td>
</tr>
<tr>
<td>Nephrons/kidney</td>
</tr>
</tbody>
</table>

a CsA, cyclosporin A. b P < 0.05 significant difference when values are compared with age-matched controls.

Figure 1. Effects of antenatal exposure to cyclosporin A (CsA) on renal vascular resistance (RVR) in control and CsA animals at 1 mo and 11, 18, and 35 wk of life. *P < 0.05 significant difference when values are compared with age-matched controls.
Table 2. Renal effects of CsA at 1 month and 11, 18, and 35 weeks of age

<table>
<thead>
<tr>
<th>Group</th>
<th>1 Month</th>
<th>11 Weeks</th>
<th>18 Weeks</th>
<th>35 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CsA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GFR (ml/kg per min)</td>
<td>8.07 ± 1.82</td>
<td>6.40 ± 2.14</td>
<td>5.88 ± 1.58</td>
<td>5.60 ± 1.18</td>
</tr>
<tr>
<td>RBF (ml/kg per min)</td>
<td>4.27 ± 1.19</td>
<td>3.14 ± 1.66</td>
<td>3.09 ± 1.63</td>
<td>2.83 ± 1.56</td>
</tr>
<tr>
<td>FF (%)</td>
<td>0.34 ± 0.12</td>
<td>0.25 ± 0.118</td>
<td>0.26 ± 0.076</td>
<td>0.24 ± 0.069</td>
</tr>
<tr>
<td>V (mosm/kg H2O)</td>
<td>3.73 ± 2.48</td>
<td>2.71 ± 1.99</td>
<td>4.87 ± 2.89</td>
<td>4.80 ± 2.98</td>
</tr>
<tr>
<td>Uosm (mosm/kg H2O)</td>
<td>662 ± 32</td>
<td>567 ± 34</td>
<td>709 ± 27</td>
<td>616 ± 27</td>
</tr>
<tr>
<td>Proteinuria (g/L)</td>
<td>0.11 ± 0.02</td>
<td>0.01 ± 0.01</td>
<td>0.01 ± 0.01</td>
<td>0.01 ± 0.01</td>
</tr>
</tbody>
</table>

Discussion

Nephron Reduction and Glomerular Hypertrophy

We have previously demonstrated that in utero exposure to CsA during the onset of metanephros formation induced a nephron deficit (12). In the present study, rabbits that were normal range for all rabbits. Finally, although plasma osmolality did not statistically differ between age-matched animals, urinary osmolality was significantly reduced in pups that were born to CsA-treated mothers.

Renal Histology

Light microscopy examination of young and adult kidneys that have been exposed to CsA in the course of their development revealed multiple pathologic features. As previously shown, 1-mo-old animals displayed early signs of tubular and glomerular alterations. Although these lesions were patent, a minority of nephrons were apparently injured. As illustrated in Figure 2, aging of pups that belonged to the CsA group revealed a large panel of tubular lesions mostly encountered in the superficial renal cortex and outer stripe of the medulla, focal areas of inflammation, interstitial fibrosis, and severely damaged glomeruli. The renal cortex of rabbits that were exposed antenatally to CsA presented numerous tubules with micro- and macrovacuolation associated with cytoplasmic clarification (Figure 2B). Tubular dilation was also frequently observed (Figure 2, B, C, F, and I). Tubular microcalcification was present. In addition, numerous retracted glomerular tufts appeared from 18 wk onward (Figure 2, C and G). The size of the apparently unaltered glomeruli was considerably enlarged as evidenced in Figure 2, B and C, as compared with controls (Figure 2, A and D). At the age of 35 wk, renal injuries increased considerably. Tubular membrane thickening was frequently observed as well as tubular atrophy (Figure 2F). Prominent glomerular urinary chambers, tubular necrosis, interstitial inflammation, and cortical fibrosis were the main characteristics observed in adult kidney that was exposed antenatally to CsA (Figure 2, E, F, and G). Focus on the inner and outer stripes of the outer medulla is shown in Figure 2, H and I. Enlarged tubular lumen of Henle’s loops and collecting tubules were present (Figure 2I). A severe tubular vacuolation was also occasionally observed.

Early Development of Hypertension in Pups that Were Born to CsA-Treated Mothers

As shown in Figure 3, rabbits that were exposed antenatally to CsA developed an arterial hypertension that worsened with age. Although the MBP was not significantly different between control and CsA groups at 1 mo of age, CsA rabbits showed a 15% increase in MBP at 11 wk, a 17% increase at 18 wk, and a 35% increase at 35 wk of age. To determine whether this hypertension was renin dependent or endothelin dependent, we measured PRA and urinary ET in 35-wk-old rabbits. PRA was decreased by 65% in rabbits of the CsA group as compared with rabbits of control group (3.94 ± 0.78 versus 11.36 ± 3.15 ng/ml per h; P < 0.05). The excreted amount of ET in the urine of CsA rabbits was significantly higher as compared with control group (5.13 ± 0.38 versus 3.38 ± 0.69 pg/ml; P < 0.05).

Discussion

Nephron Reduction and Glomerular Hypertrophy

We have previously demonstrated that in utero exposure to CsA during the onset of metanephros formation induced a nephron deficit (12). In the present study, rabbits that were...
exposed in utero to CsA presented the same magnitude of nephron reduction (ranging from 23 to 33%). The birth weight of CsA animals was similar to that of rabbits that were born to control mothers, suggesting that this nephron reduction was not the consequence of an IUGR, a well-known condition associated with nephron deficit (20,23). These overall data strongly suggest a direct toxicity of CsA on fetal renal growth.

At 1 mo of life, kidney weight was not different between CsA and control groups. Thereafter, the increase in kidney weight was more important in CsA groups as confirmed by a 25% increase in the ratio of kidney mass to body weight in CsA animals as compared with controls from 11 to 35 wk of life. This phenomenon has been attributed to renal tissue compensation to the loss of renal mass (24,25). This renal hypertrophy was associated with a glomerular hypertrophy, as previously reported (12,24,26). The glomerular hypertrophy that was initially observed in the deep cortex extended to the superficial cortex at 1 mo (12). The mechanism of this glomerular hypertrophy has already been described (27). Nephron reduction decreases glomerular surface area with subsequent decrease in glomerular filtration. To maintain glomerular filtration and glomerular blood flow, glomeruli undergo a compensatory hypertrophy regarded as a structural adaptation. To increase the filtering surface area, glomerular capillary segments elongated and/or new capillary developed (28). Unfortunately, contrary to the endothelial cells, podocytes displayed a low mitotic index and therefore must be stretched to cover the enlarged capillary area (29). This phenomenon increases epithelial cell detachment from the peripheral capillary wall (30). This structural alteration contributes to the proteinuria observed from 11 wk onward in CsA rabbits. This proteinuria associated with the existence of hyperfiltration in a single nephron may lead, in the long term, to a tubulointerstitial fibrosis (31).

**Nephron Reduction and Hypertension**

Previous clinical and experimental studies reported that nephron reduction was associated with the development of systemic hypertension (17,19,32–34) and impaired renal function (35,36) in adulthood. However, despite a marked nephron deficit, rabbits that were exposed in utero to CsA had initially, at 1 mo of life, a normal arterial BP as compared with control animals. Then, at 11 wk, they developed a marked systemic hypertension that worsened with age. This hypertension can increase glomerular capillary hydraulic pressure, which may induce progressive glomerular sclerosis and decrease renal function, which jointly may in turn worsen arterial pressure and glomerular injuries (36,37).

The renin-angiotensin system (RAS) and ET, an endogenous vasoconstrictor, seem to be involved in the hemodynamic changes associated with renal mass reduction (38,39). We measured PRA and urinary ET levels to analyze the underlying mechanism of the hypertension observed in our model. Our results suggest that
systemic hypertension was, at least in part, ET dependent, whereas decreased renin activity suggests an adaptive response of RAS (34). Noteworthy is that ET also presents renal effects, it can (1) induce a marked elevation of glomerular capillary hydraulic pressure; (2) decrease glomerular capillary ultrafiltration coefficient (40); and (3) induce a slow-developing and long-lasting vasoconstriction of both afferent and efferent renal arterioles, with preferential efferent arteriolar vasoconstriction, that leads to a dramatic decrease in renal blood flow and GFR (41,42). Recent studies also reported that an overload in filtered protein induces an augmentation in proximal tubular cell activity with subsequent increased secretion of ET (43–45).

Nephron Reduction and Renal Function

Despite a 23 to 33% nephron deficit, renal function was not affected in 1-mo-old CsA rabbits. These results are in agreement with clinical studies reporting that children who are exposed in utero to CsA present a normal renal function during childhood (5–8). This phenomenon could be explained by the adaptive glomerular hypertrophy (12) with subsequent glomerular hyperfiltration in single-nephron units (24).

However, at 11 wk of life, urine flow rate and sodium excretion were significantly increased in the presence of a normal GFR and RBF for age in CsA group. These results associated with a decreased U/P insulin ratio suggest a tubular (decreased water and sodium tubular reabsorption) rather than a glomerular mechanism. These increased diuresis and FENa could be pressure related (46) and/or ET dependent. It has been reported that acute hypertension may lower Na+/K+ ATPase activity and thus reduce sodium reabsorption in proximal tubule (47). Similarly, ET is able to induce an inhibition of renal tubular sodium and water reabsorption (48) by suppression of Na+/K+ ATPase activity (49). Noteworthy is that rabbits that were exposed in utero to CsA presented a lower renal concentration capacity as compared with control animals, a phenomenon already reported in adult patients who receive CsA for hepatic transplantation (50). These results are strengthened by our histologic observations showing tubular injuries: tubular micro- and macrovacuolation and tubular atrophy.

At 18 wk of age, in addition to worsened tubular injuries (Figure 2), GFR decreased, as evidenced by histologic and functional findings. First, glomerular sclerosis observed in CsA animals induced a decrease in the number of functional nephrons. In addition, the increase in RVR induced a decrease in RBF and GFR, suggesting also a vasomotor origin to the impaired glomerular function. The decrease in FF suggests a predominant afferent vasoconstriction.

At 35 wk of age, CsA rabbits still had an impaired GFR. However, despite elevated RVR, RBF of CsA animals was not different from that of control animals. This phenomenon could be explained by the increasing MBP that could have maintained RBF through the vasoconstricted vessels. Such an observation has been made in aortic snare studies confirming the dependence of RBF on systemic perfusion pressure (40). Conversely, an age-dependent decrease in renal hemodynamics (41% decrease in RBF in the control group between 1 mo and 35 wk of life) could conceal the long-term renal hemodynamic effects of CsA.

In conclusion, rabbits that were exposed in utero to CsA, during the early period of nephrogenesis, have a nephron reduction that leads to (1) morphologic renal alteration (hypertrophy), (2) systemic hypertension, and (3) progressive chronic renal insufficiency at long term. These data strongly suggest that follow-up of infants who are born to mothers who are treated with CsA during pregnancy should be maintained in adulthood.

Acknowledgments

Part of this work was presented at the annual meeting of the Pediatric Academic Societies, May 3–6, 2003, Seattle, WA.

We thank Novartis (Rueil Malmaison, France) for kindly providing CsA. We acknowledge Dr. Artur (Laboratoire de Pharmacologie, C.H.U., Dijon, France) for help in CsA concentration determination. We thank Mme Demangeat (Institut de Physique Biologique de Strasbourg, France) for analysis of PRA, Mme Coumaros (Institut de Chimie Biologique de Strasbourg, France) for urinary ET analysis, and Mme Mosig (Laboratoire de Néphrologie du développement, Lausanne Suisse) for technical assistance.

References

45. Vlachojannis JG, Tsakas S, Petropoulou C, Gounenos DS, Al-}
47. Zhang Y, Magyar CE, Norian JM, Holstein-Rathlou NH, Michieff AK, McDonough AA: Reversible effects of acute hyper-}
51. Access to UpToDate on-line is available for additional clinical information at http://www.jasn.org/