

# The Developing Kidney and Environmental Toxins

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**ABSTRACT.** The effects of environmental chemicals, drugs, and physical agents on the developing kidney are influenced by the state of renal development and maturation. The development of the kidney, the major excretory organ after birth, consists of 3 stages: the pronephros, or cervical kidney; mesonephros, or thoracic kidney; and metanephros, or abdominal kidney, the definitive kidney. In humans, nephrogenesis and organogenesis occur from the 6th to the 36th weeks of gestational age. After 36 weeks, nephrogenesis is complete and each kidney has a full complement of nephrons. The extent of chemical-induced renal toxicity is related, in part, to the efficiency in which the particular compound is transported by renal tubules. Because renal tubular transport capacities vary with maturation, the degree of nephrotoxicity may also vary with maturation. The signs and symptoms of nephrotoxicity can appear acutely or insidiously. Unexplained acute renal failure, chronic mild proteinuria, or even hypertension can be a manifestation of nephrotoxic agents. Species differences occur, thus the need for studies in humans. *Pediatrics* 2004;113:1084–1091; kidney, toxins, development, angiotensin, prostanoids.

ABBREVIATIONS. RBF, renal blood flow; GFR, glomerular filtration rate; ACE, angiotensin-converting enzyme; OAT, organic anion transporter; OCT, organic cation transporter; OCTN, organic cation/carnitine transporters; PAH, p-aminohippuric acid.

The effects of environmental chemicals, drugs, and physical agents on the developing kidney are influenced by the state of renal development and maturation. The unique intrauterine conditions of mammals dictate that the placenta serve as the surrogate fetal kidney in the regulation of fluid, electrolyte homeostasis, acid-base balance, elimination of waste products of metabolism and toxins, and hormone production. An important function of the fetal kidney is to maintain a urine output sufficient to maintain amniotic fluid volume. Daily urine production is approximately 30% of fetal weight. The excreted urine does not serve real excretory or homeostatic function because the urine, via the amniotic fluid, is recycled back to the fetus by swallowing (25% of fetal weight). The most striking result of

impaired fetal renal function, therefore, is a significant reduction in amniotic fluid.

Human renal development involves 2 basic processes: morphologic formation and, ultimately, the acquisition of function. The anatomic formation of the human kidney occurs exclusively in utero. However, the acquisition of physiologic or functional capability begins with the earliest formation of the fetal nephron and accelerates after birth to reach adult levels. The anatomic and physiologic characteristics that distinguish the fetal and newborn kidney from the mature adult kidney present certain vulnerabilities to toxic injury. Thus, toxicity to the developing kidney may involve morphologic and functional changes that may be clinically relevant. Knowledge of the impact of toxins on the immature kidney is dependent on understanding the mechanisms of toxic injury and is useful to the practitioner.

Renal morphogenesis is a classic example of the principle that ontogeny recapitulates phylogeny. The development of the kidney, the major excretory organ after birth, has been well described and consists of 3 stages: the aglomerular pronephros, or cervical kidney; the mesonephros, or thoracic kidney, culminating in the initiation of the formation of the functional mammalian kidney; and the metanephros, or abdominal kidney. In the human, the pronephros appears at 3 weeks of gestational age and regresses by the fifth week. The pronephros is nonfunctional, but the pronephric duct becomes the mesonephric duct, which subsequently evolves into the ureteric bud. The ureteric bud is essential for nephron formation. The mesonephros, which is functional, develops caudal to the pronephros at the 3rd to 4th weeks of age and degenerates from the 5th to 12th weeks of gestational age. By the sixth week of life, the 2 essential components that trigger and sustain metanephric kidney formation are identified: the ureteric bud and the metanephric mesenchymal blastema. The definitive kidney, metanephros, develops from the interaction between the ureteric bud and the surrounding mesenchyme. Understanding the genes involved in the development of the metanephros has undergone remarkable progress.<sup>1</sup> The metanephric blastema forms the basic structures of the functioning nephron, the glomerulus and associated tubules. The processes involve ureteric bud induction, tubular formation, glomerulogenesis, and angiogenesis/vasculogenesis. Ultimately, the ureteric bud and its branches form the epithelial structures of the collecting ducts, intrarenal collecting system, ureter, and the trigone of the bladder.

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In humans, nephrogenesis, or the formation of individual nephrons, and organogenesis, or pattern formation, occur from the 6th to the 36th weeks of gestational age. After 36 weeks, nephrogenesis is complete and each kidney has a full complement of nephrons, approximately 1 000 000 nephrons per each kidney. Thus, the anatomic formation of the human kidney occurs exclusively in utero. Whether new nephrons can develop after birth in prematurely born infants remains to be determined. However, in many mammals, nephron formation continues after birth. Therefore, results of studies on renal function in rodents and other experimental models need to be interpreted carefully. Once the elemental structures are formed through differentiation, the initial process whereby primitive renal glomeruli and tubules attain their specific anatomic form, the assignment and increase of function, the process of maturation, ensues. This maturational process involves phenomenal growth as well as physiologic functional change.

A functional kidney has been observed at 6 weeks of gestational age.<sup>2</sup> Renal blood flow (RBF) and glomerular filtration rate (GFR) progressively increase during gestation and achieve full-term levels by the 32nd to 35th weeks of gestational age.<sup>3-6</sup> The values at term are less than those observed in adults even when corrected for body weight, kidney weight, or body surface area. For the human kidney, the period after birth is marked by striking growth and unique physiologic functional changes that facilitate not only the immediate demands for adaptation to extra-uterine life but also the progressive maturation to adult renal function. The most striking postnatal transition occurs in an increase in RBF resulting in a rise in GFR. In contrast, urinary sodium output drops so that retained sodium can participate in new tissue formation in this period of rapid somatic growth. Other tubular functions, such as urinary concentration and acid-base homeostasis, more progressively approach adult levels. Adult values (ml/min/1.73 m<sup>2</sup>) for RBF, GFR, urea clearance, maximum tubular excretory capacity for p-amino hippurate transport, and maximum renal concentrating capacity are achieved by 1 to 2 years of age. In contrast, an acid urine pH is achieved by 1 week of postnatal age in term infants, and maximum urinary acidification can be achieved as early as 1 to 2 months of postnatal age.<sup>3-7</sup> For preterm infants, renal functional maturation is influenced by conceptional age, not by postnatal age; adult values for RBF, GFR, albumin excretion, maximal concentrating ability, and kidney size are achieved sometime by 8 years of age.

Several risk factors for congenital renal disease have been identified, including in utero exposure to environmental toxins, drugs, and physical agents. Such agents may 1) stop, retard, or accelerate development; 2) promote abnormal development; and 3) interfere with orderly maturation after development. Although the developing/maturing kidney may be vulnerable to certain toxins, in other instances, the immaturity of the kidney may be "protective."

## ROLE OF HEMODYNAMICS AND RBF/GFR ON THE RENAL EFFECTS OF ENVIRONMENTAL TOXINS, DRUGS, OR STRESSES

In mammals, including humans, endotoxins produce glomerular visceral epithelial and endothelial cell swelling, polymorphonuclear leukocyte and platelet accumulation in the capillary lumina, tubular interstitial edema, and focal intertubular hemorrhage. In 10- and 28-day old rats, *S enteritidis* endotoxin required 1/350 the dose given to young adults to induce renal histopathologic changes. This suggests that the kidney in the young may be more vulnerable to hemodynamic changes than the adult. However, 10-day-old rats, which have lower renal blood flow than 28-day-old rats, had fewer glomerular changes than the older rats.<sup>8</sup> Thus, the low RBF and GFR in the neonate may offer protection that is lost with development. Because of a low GFR, substances that are eliminated mainly by the kidney may exert less nephrotoxicity in the young. The immature kidney has been shown to be more tolerant to the nephrotoxic effects of aminoglycosides because of the lower RBF as compared with adults.<sup>9</sup> Conversely, this possible "protective" effect of low GFR may render the developing kidney vulnerable to the consequences of abnormal decreases in RBF, resulting in renal ischemia. The sequence of neonatal multisystem organ failure is different in the neonate than in adults. Whereas in adults the lung is typically the first organ involved, in neonates this organ is involved later in the multiorgan sequence. Instead, the immature kidney of the neonate is the first organ affected in this pathophysiologic sequence.<sup>10</sup>

Several drugs could potentially interfere with the normal development of the kidney because their target genes/proteins have been shown to be important in the development of the kidney. Two systems have been shown to be important in the development of the kidney: prostanoids and the renin-angiotensin system.

### Prostanoids

Prostanoids produced by cyclo-oxygenases COX 1 and 2 regulate renal hemodynamics and tubular transport. In general, COX 1, found in the renal vasculature, glomeruli, and collecting ducts, is mainly involved in regulation of renal hemodynamics. In contrast, COX 2, found in the macula densa, thick cortical ascending limb of Henle's loop, medullary interstitial cells, and glomerular podocytes, is mainly involved in the regulation of renal sodium and water handling.<sup>11</sup> In general, patients with increased risk of COX inhibitor-induced renal toxicity include the elderly, patients with renal or hepatic disease, and those on diuretics or angiotensin-converting enzyme (ACE) inhibitors. Several therapeutic agents, such as nonsteroidal anti-inflammatory drugs, aspirin, and indomethacin, nonselectively inhibit both COX 1 and COX 2. Selective COX 2 inhibition leads to disruption of nephrogenesis in both mice and rats. Genetic ablation of COX 2 results in severe morphologic abnormalities, including impaired glomerulogenesis, cortical dysplasia, and dif-

fuse tubular cyst formation. Mice lacking COX 2 have reduced viability and develop renal dysplasia.<sup>12,13</sup> These studies confirm the potential teratogenic/developmental effects of prenatal use of non-steroidal anti-inflammatory drugs and selective COX 2 inhibitors leading to acute renal failure and renal dysgenesis, but adverse renal effects of COX inhibitors in fetuses, neonates, and children seem to be relatively rare.<sup>14</sup> However, the incidence of interstitial nephritis caused by COX inhibitors in children is not known.

### Renin-Angiotensin System

The activity of the renin-angiotensin system is increased in the perinatal period, and the vasoconstrictor activity of angiotensin II may contribute to the low RBF in the newborn.<sup>15</sup> Mice made deficient in angiotensinogen have a transient delay in maturation of renal glomeruli.<sup>16</sup> Adult mice lacking angiotensinogen and ACE develop renal vascular hypertrophy, focal tubular atrophy, and marked papillary atrophy and dilated calyces.<sup>17</sup> Mice have 2 renin genes, *Ren-1* and *Ren-2*, and individual disruptions of these genes do not result in renal anomalies, probably because of compensation by the remaining renin gene. There are 4 angiotensin (AT) receptors, and null mutants of AT<sub>1</sub> and AT<sub>2</sub> receptors have been generated. Null mutations of the AT<sub>1</sub> and AT<sub>2</sub> receptors also have abnormal renal morphogenesis. AT<sub>1</sub> receptor mutant mice initially have mild abnormalities in the inner medulla and papilla but subsequently develop obstructive uropathy because of poor development of the pelvis and defective ureteral peristalsis. AT<sub>2</sub> receptors have been suggested to play a role in ureteral budding and metanephric growth. Approximately 2% to 3% of AT<sub>2</sub> receptor mutant mice develop anomalies of the kidney and urinary tract, ranging from dysplastic kidneys to uretero-pelvic obstruction and duplicated ureters. Loss of function mutation of the AT<sub>2</sub> gene has been associated with these congenital anomalies in humans.<sup>15,18,19</sup> Suppression of the renin-angiotensin system in the perinatal period by protein restriction or high salt intake leads to a reduced number of glomeruli, glomerular enlargement, and hypertension in the adult rat.<sup>20,21</sup>

ACE inhibitor fetopathy, which develops when ACE inhibitors are given at approximately the 26th week of gestation, does not have a counterpart in animals.<sup>22-24</sup> ACE inhibition is associated with oligohydramnios, renal tubular dysgenesis, neonatal anuria, calvarial and pulmonary hypoplasia, mild to severe intrauterine growth retardation, persistent patent ductus arteriosus, and fetal or neonatal death. These developmental anomalies are thought to be attributable partly to a direct action of ACE inhibitors on the fetal renin-angiotensin system and partly to the ischemia resulting from maternal hypotension and decreases in fetal-placental blood flow and oxygen/nutrient delivery to the fetus. Use of ACE inhibitors in the first trimester has not been associated with fetal abnormalities. Angiotensin II receptor blockers that cross the placenta may produce the same defect.<sup>25,26</sup> The effects of decreased angiotensin

II levels or AT<sub>1</sub> receptor blockade probably occurs in the fetus after the first trimester because blood pressure and, thus, tissue perfusion (including the kidneys) are maintained by the renin-angiotensin system. In the immediate newborn period, angiotensin II maintains blood pressure and contributes to the low RBF. After the immediate newborn period, maintenance of blood pressure requires angiotensin II. However, basal RBF is no longer influenced by angiotensin II. Therefore, detrimental effects in the kidney caused by interruption of the renin-angiotensin system are not evident after the immediate neonatal period.

### ROLE OF TUBULAR FUNCTION ON THE RENAL EFFECTS OF ENVIRONMENTAL TOXINS OR STRESSES

#### Response to Anoxia and Oxidative Stress

The immature kidney tolerates anoxia to a greater extent than the mature kidney, a characteristic that is also present in immature brain and heart.<sup>27</sup> Some antioxidant enzymes are not well expressed in the fetal kidney but are augmented after birth.<sup>28</sup> Renal superoxide anion but not hydrogen peroxide generation is low during the early postnatal development. The levels of antioxidant enzymes and sulfhydryl content in the developing kidney are low after birth but rise with increasing age.<sup>29</sup> The neonate may have a higher level of protection against peroxides but a lower capacity to detoxify superoxide anions.<sup>30,31</sup>

#### Role of Tubular Transport

The extent of chemical-induced renal toxicity can be related to the efficiency in which the particular compound is transported by renal tubules.<sup>32</sup> Increased tubular transport generally equates with increased tubular toxicity. Because renal tubular transport capacities vary with maturation, the degree of nephrotoxicity may also vary with maturation. There are species differences, however. Thus, in several instances in which renal toxicity has been observed in humans and other experimental animals, no age-related differences in nephrotoxicity have been seen in rabbits.<sup>33</sup>

### ORGANIC ANIONS AND CATIONS

Renal organic anion (OAT) and cation (OCT) transporters protect against endogenous and exogenous toxins by secreting these anionic substances into the urine.<sup>34,35</sup> Renal OATs (OAT1, OAT2, OAT3, and OAT4) belong to the amphiphilic solute facilitator family. Another superfamily includes the OCT families (OCT1, OCT2, and OCT3) and the organic cation/carnitine transporters (OCTN1 and OCTN2). By-products of many xenobiotics are organic cations and are excreted from the body by OCTs.<sup>35</sup> The nephrotoxicity of cephalosporins has been ascribed to effects on OCTs. Cephalosporins produce proximal tubular necrosis only after their transport into proximal tubule cells. Oxidative stress plays a major role in cephaloridine nephrotoxicity.<sup>36</sup> Cephaloridine depletes reduced glutathione, increases oxidized glutathione, and induces lipid peroxidation in renal cor-

tical tissue.<sup>33,36</sup> The toxicity of cephaloridine and ceftazolin is less in newborn than 2-week-old rabbits.<sup>33</sup> The decreased nephrotoxicity of cephalosporins in the young has been ascribed to decreased tubular transport. However, competition for transport of essential nutrients by cephalosporin, eg, cephaloridine, which is transported by OCTN2, can cause carnitine deficiency.<sup>37</sup> The excretion of both endogenous organic (aryl) acids, such as benzoic acid, and exogenous ones, such as p-aminohippuric acid (PAH), penicillin, and furosemide, is reduced in the human neonate and other immature animals. PAH is a good substrate for both OAT1 and OAT3. There is a decreased ability of the young kidney to extract PAH from the circulation.<sup>38–40</sup> The decreased secretion of these organic acids in the developing kidney is probably related to the developmentally regulated expressions of the OATs.<sup>41</sup> Penicillin can accelerate the maturation of organic acid transport (eg, PAH).<sup>42,43</sup>

### MYCOTOXINS

The most frequent dietary toxigenic fungi are *Aspergillus*, *Penicillium*, and *Fusarium* species. They produce aflatoxin B1 (transformed into aflatoxin M1 in milk), as well as ochratoxins and zearalenone, fumonisin B1, T-2 toxin, HT-2 toxin, and deoxynivalenol (vomitoxin), which are of increasing concern in human health. Some of their metabolites may be involved in human diseases. They can be found in many foodstuffs, particularly grains, and many times are not completely destroyed by normal processing or cooking, particularly because they are heat stable. They can produce a variety of toxic effects (liver, kidney, and hematopoietic toxicity; immune toxicity; reproductive toxicity; fetal toxicity and teratogenicity), which have been documented mainly in experimental models; the extrapolation to levels of exposure noted in humans is many times very uncertain.<sup>44,45</sup> Some mycotoxins can produce renal apoptosis, which subsequently may proceed to secondary necrosis. Little information is available on effects of these substances in developing kidneys.

#### Ochratoxin A

Ochratoxin A is produced mainly by the *Aspergillus ochraceus* and *Penicillium verrucosum*. Contamination occurs in the field, during the storage of cereals, cereal products, and other plant-derived products. It is also found in meat.<sup>46</sup> The toxin has been classified a possible carcinogen but only after frank renal toxicity has occurred. OAT1 and OAT3 may be significantly related with the events in the development of ochratoxin-induced nephrotoxicity in the human kidney.<sup>47</sup> Dams and fetuses that are treated with ochratoxin have visceral and skeletal anomalies; the fetuses also have lower weights.<sup>48</sup> Age-related nephrotoxic effects of ochratoxin are not well documented.

#### Monocrotaline

Monocrotaline, a pyrrolizidine alkaloid, causes veno-occlusive disease of the liver, pulmonary arterial hypertension, and right ventricular hypertro-

phy.<sup>49–51</sup> It also has nephrotoxic effects similar to hemolytic uremic syndrome.<sup>50</sup>

#### Fumonisin

The only fungi that produce significant quantities of fumonisin are *Fusarium* species. These species cause *Fusarium* kernel rot of maize, an important disease in hot climates. Fumonisin are widely distributed geographically, occurring in maize in many areas of the world; considerable annual variations in contamination have been noted. Fumonisin B<sub>1</sub>, B<sub>2</sub>, B<sub>3</sub>, and B<sub>4</sub> are a group of structurally related compounds with B<sub>1</sub> being the form most commonly found in corn and for which most biological studies have been performed.

Fumonisin are poorly absorbed from the digestive tract but are rapidly distributed and eliminated. The liver and kidneys retain most of the absorbed material, and fumonisin B<sub>1</sub> persists longer in rat liver and kidney than in plasma. In pregnant rats and rabbits, very low concentrations of fumonisin B<sub>1</sub> are recovered in the uterus and placenta. No fumonisin B<sub>1</sub> was found in fetuses, indicating the absence of placental transfer. There is little evidence of significant transfer during lactation, and fumonisin do not seem to be metabolized in vitro or in vivo.<sup>52</sup>

Two cellular modes of action for fumonisin that are well supported by results obtained in vivo have been proposed. In both hypotheses, altered lipid metabolism is the initial biochemical mechanism. In one hypothesis, the initial biochemical lesion is presumed to be inhibition of ceramide synthase.<sup>53,54</sup> In the other, the biochemical lesion is attributed to disruption of the  $\delta 6$  desaturase and cyclooxygenase metabolic pathways.<sup>55</sup> In both hypotheses, it is assumed that other initial sites of action could contribute to the observed cellular responses. The 2 invoke similar cellular mechanisms, to the extent that fumonisin-induced imbalances in the rates of cell death and proliferation in target tissues are considered to contribute to cancer development.<sup>56</sup> Fumonisin also affect sites of cellular regulation that seem to be independent of the disruption of lipid metabolism, but cancer and the other toxic effects in animals seem to depend on disruption of various aspects of lipid metabolism, membrane structure, and signal transduction pathways mediated by lipid second messengers. The demonstrated cellular effects include altered cell proliferation, altered rates of apoptosis, altered cell-cell communication and cell adhesion, induction of oxidative stress, and modulation of gene expression. Because the proposed biochemical mechanisms of action involve alterations in de novo biosynthetic pathways, nutritional factors could play an important role in determining the potency of FB<sub>1</sub> and the observed toxicologic endpoints in rodents.

In many animal species, the kidney is a major target. Early renal effects include increases in free sphingoid bases, renal tubular cell apoptosis, and cell regeneration. In rodents, the toxicity of fumonisin is strain and sex dependent. For example, male BDIX rats are more sensitive to the hepatotoxic effects than male Fischer 344N, male Sprague Dawley, and male RIVM:WU rats, in which nephrotoxicity was ob-

served at lower doses than hepatotoxicity. In mice, the liver is more sensitive than the kidney to fumonisin-induced toxicity. Female mice seem to be more sensitive than male mice. Available studies clearly indicate that renal carcinogenesis must be preceded by renal toxicity; the potential for renal carcinogenesis is subsumed by the dose-response relationship for renal toxicity. Induction of renal tubule carcinomas in male rats may be partly attributable to the continuous compensatory regeneration of renal tubule epithelial cells in response to the induction of apoptosis by fumonisin B<sub>1</sub>.<sup>45</sup> Fumonisin B<sub>1</sub> induces not only hepatic toxicity but also pulmonary edema and hydrothorax in pigs. Both diseases seem to occur secondary to cardiovascular dysfunction. Cardiovascular effects have also been found in other species. Field outbreaks of equine leukoencephalomalacia and porcine pulmonary edema associated with consumption of fumonisin-contaminated maize have been reported in the United States and elsewhere.<sup>57</sup>

Although there is evidence that fumonisins are embryotoxic *in vitro*, currently no published data exist to support the conclusion that fumonisins are developmental or reproductive toxicants in farm animals or humans. Except in 1 study in hamsters, embryotoxicity occurred in laboratory animals (rats, mice, and rabbits) secondary to maternal toxicity. A specific role for fumonisins in the development of neural tube defects has been proposed. The hypothesis includes a critical role of fumonisin in disruption of folate membrane transport, but no specific studies have been designed or performed to confirm this proposed mechanism.<sup>57</sup>

#### ELEMENTAL CONTAMINANTS

Infants and young children can be at an increased risk of toxicity to elemental contaminants, such as lead, because of a higher intake and a greater intestinal absorption relative to body size.<sup>58</sup> Because renal tubular transport is decreased in the young, acute renal toxicity may be less in younger than in older individuals.<sup>59</sup> Kidney concentrations of copper and selenium did increase with fetal age but markedly increased during the postnatal period.<sup>60</sup> However, there were greater accumulations of mercury, cadmium, and lead in the kidney than in brain during fetal and postnatal development.<sup>61</sup> Toxicity is influenced not only by tissue concentrations but also by deleterious cellular activities. Decreased elimination of these elements may result in greater mortality as a result of toxic effects in organs other than the kidney. Moreover, the impact on effector proteins may be less in the kidney than in other organs. Nevertheless, it has been proposed that kidney weight may be a better discriminative index of excess lead exposure than simple neurobehavioral indices.<sup>62</sup>

#### Lead and Cadmium

Lead is a commonly encountered nephrotoxic metal. Chronic exposure to lead at levels found in industrial exposure has been associated with the development of renal insufficiency, renal cancer, and hypertension.<sup>59,63</sup> Rats that are exposed to lead at a younger age accumulate more lead in several organs,

including the kidney, than those that are exposed at an older age that may have been related to increased gastrointestinal absorption in younger rats.<sup>58</sup> Cadmium and arsenic are also transported in the proximal tubule, where their toxic effects are expressed. In juvenile rats, cadmium does not produce any significant alteration in renal PAH excretion, caused, likely, by the immaturity of renal tubular transport processes.<sup>64</sup> Chronic toxicity may be expressed differently from acute toxicity. Thus, asymptomatic proteinuria as a result of interstitial fibrosis rather than proximal tubular dysfunction may be seen in chronic lead toxicity. Examples of the age-related effect of elemental contaminants on the kidney are discussed below.

#### Uranium

Naturally occurring uranium in drinking water is a significant health concern in several areas of North America.<sup>65</sup> Uranyl nitrate decreased GFR and urine flow, increased fractional sodium excretion, and produced proximal tubular morphologic changes to a greater extent in older than in younger puppies. In contrast, RBF was reduced to a greater extent in younger than older puppies.<sup>66</sup> Similarly, proteinuria, glycosuria, and hematuria were more frequent and severe in younger than in older rats. Urinary enzymes may not be reflective of tubular damage in the young.<sup>67</sup> In rats, lactate dehydrogenase, leucine aminopeptidase, and alkaline phosphatase are reliable indicators of nephrotoxicity in the adult, but only alkaline phosphatase seems to be an indicator of nephrotoxicity in 15- to 20-day-old rats.

#### Mercury

The nephrotoxic effects of inorganic mercury are modified by age, gender, and concomitant exposure to other agents such as dieldrin and phenobarbital.<sup>68-70</sup> Inorganic mercury is also transported by the proximal tubule; thus, its toxicity is expected to be less in the young. However, the dose of inorganic mercury that induced mortality in rat pups at 1 day of age was much less than that noted at 15 days of age.<sup>71</sup> After 2 weeks of age, the decrease in blood urea nitrogen was similar to 8-week-old rats, but mortality was still greater in the youngest rats.<sup>72,73</sup> These studies suggest that extrarenal effects of toxins may be more prominent in the young because of decreased tubular transport and, therefore, the excretion rate.

#### Halogenated Hydrocarbons

Maternal exposure to halogenated hydrocarbons can decrease kidney growth in the offspring.<sup>74</sup> The diverse group of hydrocarbons that induce a specific spectrum of nephropathies include decalin, an alicyclic hydrocarbon; JP5 jet fuel, a mixture of C12-15 straight and branched-chain hydrocarbons; C10-11 isoparaffinic hydrocarbons; Stoddard solvent, a mixture of straight and branched-chain paraffins, naphthenes, and alkyl aromatic hydrocarbons; 2,2,4-trimethylpentane, a branched-chain hydrocarbon; and d-limonene, an aromatic hydrocarbon. The toxicity of halogenated hydrocarbons, like other toxins, is

influenced by gender and species. Male rats but not other mammals develop nephrotoxicity on exposure to decalin. Decalin apparently produces nephrotoxicity in male rats because of the accumulation of  $\alpha_2$  microglobulin, a protein that is seen in proximal tubules of mature male but not female rats. This is another example of animal studies that may not be applicable in humans.<sup>75</sup>

### Diethylene Glycol

Idiopathic acute renal failure has been traced to contamination by diethylene glycol of glycerin, used in the formulation of medicinal syrups.<sup>76</sup> This has occurred in many countries, including the United States.

### MANIFESTATIONS OF TOXIC NEPHROPATHY

The renal manifestations of exposure to toxic agents are similar in children and in adults. However, the extent of renal involvement and the severity of the manifestations of the direct and indirect effects of nephrotoxins are modified by the stage of renal development. For example, serum creatinine level is the best endogenous indicator of GFR. However, serum creatinine level is affected by muscle mass, to a greater extent, and to ingested sources, to a lesser extent. Immediately after birth, the neonatal serum creatinine is a reflection of maternal creatinine. Depending on the conceptual age, sometime after birth, serum creatinine levels decrease to reflect endogenous creatinine production and renal function. Because muscle mass is less in the young compared with adults, serum creatinine levels are lowest in infants and increase with age reaching adult values with accretion of muscle mass.

The effects of intrauterine or neonatal renal toxic injury may result in an impairment of glomerular filtration, tubular function, and hormonal production or catabolism. These could present as renal failure with retention of waste products of metabolism (increased blood urea and creatinine), proteinuria, aminoaciduria, glycosuria; inability to dilute and concentrate the urine, eliminate metabolically produced or ingested acids and alkali (metabolic alkalosis or acidosis), or regulate electrolyte balance; and low or high blood pressure. An early clue of renal tubular injury may be proteinuria (albuminuria, globulinuria,  $\alpha_1$  or  $\beta_2$ -microglobulinuria) or the presence of abnormal urinary sediment (increased urinary levels of red blood cells, pyuria, casts, or renal tubular epithelial cells).  $\alpha_1$ -Microglobulinuria has been suggested to be a marker of cadmium exposure.<sup>77</sup> Urinary enzymes may also reflect tubular injury. Noonan et al<sup>78</sup> reported that in individuals 18 years and older but not in children 6 to 17 years of age, N-acetyl- $\beta$ -D-glucosamide and alanine aminopeptidase adjusted for creatinine and other potential confounders were positively associated with urinary cadmium. The utility of different biomarkers to detect nephrotoxicity has not been proved.<sup>79</sup> The signs and symptoms of renal dysfunction may manifest acutely or insidiously. An outbreak of idiopathic acute renal failure could be caused by exposure to

nephrotoxic agents. In general, however, toxic nephropathy is not a common cause of acute renal failure, the most common causes being hemolytic uremic syndrome, glomerulonephritis, sepsis, hematologic/oncologic complications, and postcardiac surgery.<sup>80</sup>

### CONCLUSION

The manifestations of renal toxicity are strongly influenced by renal development. Toxic effects of xenobiotic compounds, including drugs and environmental chemicals, may be seen at a particular gestational age but not at other ages, depending on the stage of renal development. The low RBF and decreased tubular transport may serve to protect the kidneys from the effects of toxins. However, decreased tubular transport and, therefore, excretion result in accumulation of toxins and can lead to deleterious systemic, nonrenal effects that are greater than that seen in adults, whose renal function is more developed. However, many of the studies have been performed in experimental animals. There are many gaps in the characterization and understanding of the effects of drugs and environmental toxins in the developing human kidney in prenatal and postnatal life.

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