J Am Soc Nephrol 10: 2018–2028, 1999

How They Begin and How They End: Classic and New Theories for the Development and Deterioration of Congenital Anomalies of the Kidney and Urinary Tract, CAKUT

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CAKUT, a Family of Diseases with a Diverse Anatomical Spectrum

Congenital anomalies of the kidney and urinary tract (CAKUT) account for more than 50% of abdominal masses found in neonates and involve some 0.5% of all pregnancies (1,2). Despite recent advancements in prenatal diagnosis and early surgical intervention, these anomalies still remain the primary cause of kidney failure in infants. Notably, the therapeutic interventions that are available to adults and older children, such as kidney transplantation, are often not feasible in infants.

Ureteropelvic junction (UPJ) obstruction (*e.g.*, stenosis or atresia) is the most common cause of a palpable abdominal mass in the newborn (3). Other forms of CAKUT include multicystic dysplastic kidneys (MCDK); hypoplastic kidneys (HK); vesicoureteral reflux (VUR); nonobstructed, nonrefluxing primary megaureter (MU); and bladder outlet obstruction (*e.g.*, posterior urethral valves) (3,4). There are a number of well-recognized but puzzling features associated with CAKUT. For example, anomalies such as UPJ stenosis/atresia and MCDK are most often unilateral or highly asymmetrical. In the newborn, many of the abnormalities, such as UPJ stenosis/atresia, MCDK, prenatal hydronephrosis associated with VUR, and primary MU are overwhelmingly found in males (5–10). By contrast, in older children and adults there is a female preponderance of several of these entities (11). Some such anomalies are often concurrent (8–10,12). For instance, renal hypoplasia and dysplasia are often accompanied by VUR or UPJ stenosis/atresia involving the ipsilateral or contralateral kidney. The true incidence of this "dysmorphosis" is undoubtedly higher than that currently recognized since most involved kidneys are affected subclinically or escape detection by ultrasonography or other imaging modalities and do not usually receive a pathologic diagnosis (*i.e.*, biopsy or autopsy). It is also noteworthy that these abnormalities often take a familial pattern, showing incomplete and variable genetic penetrance (13). It is therefore believed that these *assorted anatomical anomalies* share a common genetic cause (14,15).

Genetic analyses on a number of families identified several different chromosomal loci that are associated with CAKUT. Indeed, a number of syndromes that involve multiple organ anomalies, including that of the kidney and urinary tract system, have been reported to take specific inheritance patterns, some autosomal dominant or recessive (16) and others X-linked dominant or recessive (17). Moreover, recent genetic analyses on several families identified several different chromosomal loci that are associated with CAKUT (18–20), although no specific gene involved has been identified from these studies. Most recently, the PAX2 gene was identified as the first specific gene whose mutation is associated with CAKUT (21). In view of the extremely high penetrance rate (autosomal dominant) of this anomaly within the same family and the uniform involvement of other organs, the PAX2 gene mutation appears to represent a special subgroup of CAKUT. Other forms of inherited VUR have also been reported in that 40 to 50% of siblings of affected children may also have demonstrable VUR early in life (22). Others have reported that VUR is possibly inherited in a dominant manner with a single familial gene acting with incomplete dominance (23). It is likely, however, that the remaining majority of VUR and other forms of CAKUT (which present with isolated involvement of the kidney and urinary tract and low penetrance within a given family) are examples of complex hereditary traits resulting from a minor mutation of multiple specific genes that are involved in normal embryogenesis.

Several theories have been proposed regarding the ontogeny of various forms of CAKUT. Many have been derived from human embryo dissection and others from animal experiments. In the absence of congenital animal models closely mimicking the human CAKUT, human CAKUT have often been equated with the structural changes that occur after surgical ligation of the ureter in young animals *ex utero*. Limited relevance of such animal models to humans has been noted for some time. For instance, human CAKUT are often identified *in utero* when nephronogenesis has not yet begun for many nephron units, whereas in postnatal animal ureteral ligation studies, nephronogenesis is already near completion. This discrepancy appears to underlie the numerous observations that histologic changes described in these animal studies vastly differ from those

Received November 10, 1998. Accepted February 6, 1999.
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1046-6673/1009-2018
Journal of the American Society of Nephrology

characteristically seen with CAKUT in human embryos or newborns.

Is the Obstructive Mechanism Intrinsic or Extrinsic to the Ureter?

Ruano-Gil and Tejedo-Mateu (24) studied normal human embryos of 5 to 55 mm. They found that the main ureteric duct (future ureter) undergoes a process of temporary obliteration followed by recanalization of the lumen as the embryos grow from the 14- to 22-mm stage. These processes begin in the middle zone of the ureters and progress proximally and distally until they cover its entire length. In embryos of approximately 17 mm in length the primitive ureter forms a solid cord, but in 23-mm embryos it is totally patent. The obliteration phase was found in conjunction with atrophy and loss of urine-producing function of the mesonephros, whereas that of recanalization follows generation of urine by the metanephros (the kidney precursor) and the intense longitudinal growth of the ureters. These observations in normal embryonic development are the basis of the theory that strictures of the ureteropelvic and ureterovesical junctions in CAKUT may arise from incomplete recanalization of the ureter at the most proximal and distal locations. This notion of "obliteration," however, has not been substantiated by other studies. This phenomenon is widely viewed, instead, to represent the status of a collapsed, although patent, lumen after mesonephric urine production has ceased but before the metanephros (*i.e.*, kidney precursor) has started producing urine, and hence this hypothetical intraluminal obstructive mechanism has not gained wide acceptance from the community.

Allen (25) examined stenotic ureteral segments from patients undergoing surgery because of congenital ureteral strictures. These segments were microdissected and compared to normal urinary tracts. The obstructed segment of the ureter had a diminished ureteral caliber with reduced muscle bulk. In addition, it appeared that the obstruction had been aggravated by external compression from transient overlying vessels and by dilation of the urinary tract proximally with resultant kinking of the ureter. These observations appeared to indicate that the obstruction is fundamentally extrinsic in nature and not the result of a primary abnormality in neuromuscular development intrinsic to the urinary tract. Etiologically, the areas of obstruction appeared to represent areas of localized developmental arrest. Allen further explained that the three areas in the urinary tract where congenital strictures commonly develop—the UPJ, the mid-ureter at the level of the pelvic brim, and the ureterovesical junction (UVJ)—correspond to the three sites of major branches of the fetal arterial tree. He therefore postulated that the areas of ureteral stricture represent the sites of external compression by contiguous fetal vessels, resulting in incomplete muscularization of the ureter. Since most of the fetal vessels in this area become atrophied and vanish as a part of the normal ontogenic process, Allen speculated that this event of ureteral compression by vessels leaves the stricture behind as the sole evidence that the vessel ever existed. Of interest, Barnett and Stephens (26) described a common extrinsic form of UPJ obstruction caused by an anatomically normal lower pole hilar vessel that acutely angulated and held the upper ureter against the renal pelvis, thus providing supporting evidence that extrinsic vessels can indeed cause partial obstruction and hydronephrosis.

In addition to normal structural development of the ureter and pelvis, there needs to be normal peristalsis or propulsion of urine from the kidney downstream to the bladder. The normal flow of urine proceeds from the glomerulus through tubules to calyces and then into the pelvis, which is responsible for propelling urine down the ureter. Successful conduction of urine out of the renal pelvis requires both normal anatomic patency as well as intact and ordered transmission of peristaltic contractions down the ureter. Thus, an abnormality in not only the former but also the latter may result in a UPJ "obstruction." A narrowing or an amuscular segment of the UPJ are sometimes associated with pressure-dependent resistance to urinary outflow. Murnaghan (27) noted muscle bundles with abnormal configuration at the site of the UPJ "obstruction," while a decreased quantity of musculature was noted by Foote *et al.* (28). Electron microscopy has revealed disruption of the intercellular relationship between muscle bundles of the UPJ (29). These observations echo the notion that an intrinsic aperistaltic segment of the ureter may be found in association with the replacement of normal circular muscle by muscle having a predominant longitudinal orientation.

Is the Hypo- or Dysplastic Kidney a Fetal Form of Obstructive Nephropathy?

It has long been thought that renal dysgenesis, often seen in combination with other phenotypes of CAKUT, is caused by embryonic urinary tract obstruction. Although it is recognized that renal hypoplasia or dysplasia or both (hypodysplasia) present with a spectrum of severity, it is commonly accompanied by poor function in the involved kidney. The most severe form is the multicystic dysplastic kidney, which has no demonstrable function and is accompanied by complete obstruction in some part of the outflow tract.

Experimentally, complete unilateral ureteral obstruction in the fetal sheep can, but not always, result in dysplastic development of the ipsilateral kidney (14). Peters *et al.* created complete obstuction at various anatomic levels along the urinary tract of fetal sheep at 55 to 60 d gestation (comparable to 14 to 16 wk gestation in humans) and found a variety of responses by the renal parenchyma (14). Determinants of the response to obstruction included the anatomic level of obstruction (*i.e.*, where along the urinary tract) and the occurrence of spontaneous decompression of the collecting system (*i.e.*, forniceal rupture of the renal calyx secondary to the high intrapelvic pressures generated by the obstruction). They noted that the most remarkable consequence of fetal obstructive uropathy was its effect on the renal parenchymal growth. Specifically, with unilateral ureteral obstruction (UUO), kidneys were always smaller and more cystic/dysplastic than controls presumably because these kidneys had a small, poorly compliant collecting system, and thus had no capacity to dampen the

pressure increase resulting from obstruction. These observations led some investigators to believe that some degree of "obstruction" and the resultant abnormal dynamic forces generated in the upper urinary tract are the intermediary insult for the development of renal dysplasia.

Although surgically induced complete urinary obstruction in fetal sheep can produce dysplastic kidneys (14,30), other investigators question the role that "obstruction" plays in the development of renal parenchymal lesions associated with human CAKUT (31–41). Many have noted a lack of correlation in human specimens between the severity of renal parenchymal anomalies and the degree of obstruction (31). Moreover, studies have shown that an abnormality in the early embryonic process before nephron formation can bring about renal dysgenesis in several ways. Thus, experimental interference of the ureteric bud/metanephric blastema (*i.e.*, condensation of mesodermal cells) interaction, a key initial step for the formation of the kidney and ureter, can concurrently bring about both renal parenchymal dysgenesis as well as urinary tract stenosis/atresia. It may therefore be possible that the renal parenchymal changes are due to an abnormal ureteric bud/metanephric blastema interaction and that the "obstruction" is merely a epiphenomenon. Investigators have shown that manipulation of metanephric cells leads to dysplasia, even in the absence of obstruction (42), while abnormal morphogenesis also occurs when mesodermal cells are not allowed to condense against and make normal contact with the ureteric bud (43).

The ureteric bud invades the mesoderm and induces differentiation of mesodermal cells to epithelial cells, which ultimately develop into nephrons and possibly other cells. Not only is the physical interaction between the ureteric bud and metanephric blastema important, but the two components signal each other via various biologically active substances to promote nephrogenesis and development of the intrarenal collecting system. It has been shown that there are at least two distinct signals emanating from the ureteric bud cell which stimulate nephrogenesis: (*1*) secreted molecules that prevent the nephrogenic mesenchyme from undergoing apoptosis yet have no effect on epithelial differentiation; and (*2*) diffusion-limited molecules that trigger mesenchymal/epithelial differentiation upon direct contact with the mesoderm (44). It has been proposed that certain heparin-binding factors (*i.e.*, TIMP-2, or tissue inhibitor of matrix metalloproteinase-2) are the secreted molecules that allow the ureteric bud to "control" apoptosis of the metanephric mesodermal cells and thus to determine the number of available nephron units.

Conversely, others have proposed that certain factors emanating from the metanephric blastema govern certain actions of the ureteric bud. Genetically engineered mice deficient in glial cell-derived neurotropic factor (GDNF) display complete renal agenesis owing to a lack of induction of the ureteric bud(45). High levels of GDNF expression have been noted in metanephric mesodermal cells but not in the ureteric bud. Thus, GDNF from these mesodermal cells may induce substances required for ureteric budding. Another strain of mutant mice lacking the gene of the specific receptor for GDNF have similar defects in kidney development (46). Thus, it appears that interruption of any of these ureteric bud and metanephric mesodermal cell signaling processes can lead to maldevelopment of the kidney and urinary tract. It remains to be demonstrated whether any defects in the specific biologic substances and their receptors described above underlie human CAKUT.

The Ureteral Bud Theory

A unique, but now popular, theory was derived from a different perspective via extensive studies of tissue specimens from human embryos and neonates. Renal dysmorphism (hypo- or dysplasia) is often accompanied by anomalies of the distal urinary tract. It was found that both severity of renal dysmorphism and lack of mature glomeruli (oligonephronia) correlate closely with the geographic location of the ureteral orifice within the bladder, specifically the degree of deviation from the normal site (40,41). The latter feature led Mackie and Stephens to propose the "bud theory" of kidney and urinary tract abnormalities (40).

The bud theory stems from two kinds of observed morphologic correlations: (*1*) between the location of the ureteral orifice *versus* the degree of kidney dys- or hypoplasia; and (*2*) between the location of the ureteral orifice *versus* the abnormalities of the ureter (*i.e.*, VUR, primary MU). The theory proposes that these abnormalities in both the kidney and the ureter are derived from a single common mechanism and are programmed at a very early stage of development, specifically at the first stage of ureteral budding from the Wolffian duct (Figure 1). Note that the ureteral orifice is transposed from its original budding site on the Wolffian duct into the bladder. This transposition is engendered by expansion of the terminal part of the duct with the budding ureter attached and its incorporation into the base of the bladder as the hemitrigone. If the bud arises more caudally on the duct, the orifice of the ureteral bud becomes incorporated onto an elongated cornu of the hemitrigone (lateral displacement). The ectopic situation of the orifice means that the length of the submucosal tunnel is abnormally short, the valve mechanism is defective, and vesicoureteral reflux ensues. Once the bud transposition is permanently located, bladder and ureter become clothed in muscle.

Another consequence of distal budding from the Wolffian duct is the effect on the developing metanephros (40). Alongside the distal end of the Wolffian duct lies the metanephros, which is heaped beside the normally located bud leading to development of the normal kidney. However, if the bud arises distal or proximal to the normal site, it projects into sparsely populated caudal or cranial nephrogenic mesoderm leading to oligonephronia and potentially dysplasia. Another consequence of bud ectopia is overexpansion of the distal end of the Wolffian duct and the ureteral bud leading to enlargement of the hemitrigone, enlargement of the ureteral orifice, shortening of the submucosal tunnel, and megamodeling of the ureter. In this context, two different clinical abnormalities (*i.e.*, VUR and renal dysplasia/hypoplasia) are derived from one abnormal embryologic event (*i.e.*, abnormal ureteral budding).

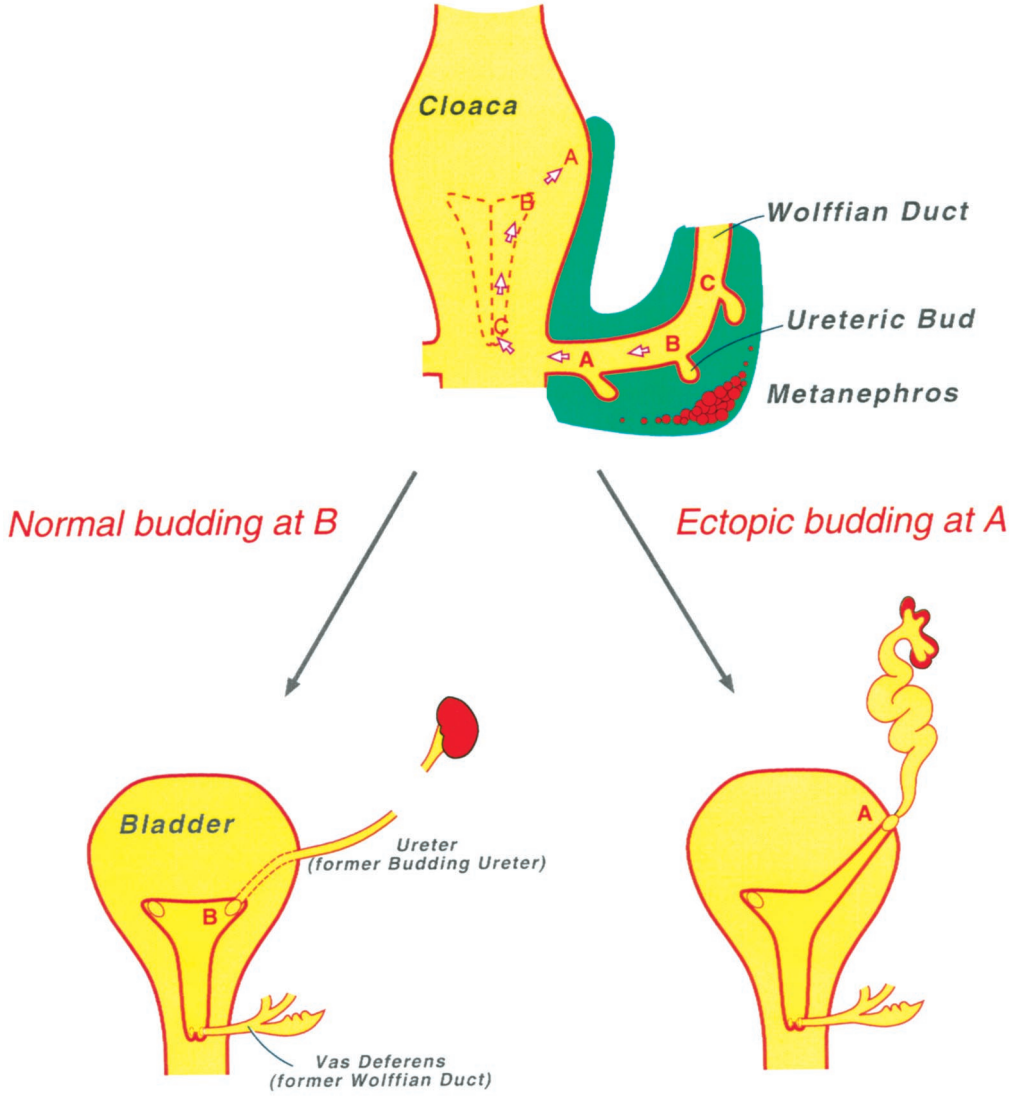

Figure 1. Dynamics of kidney and ureteral development and the ureteral bud theory. The orifice of the ureter in the bladder (vesicoureteral junction) and that of the vas deferens (ejaculatory duct) in normal mature animals are located at the lateral and caudal corners of the hemitrigone and in the prostatic urethra, respectively. These sites result from the migration and incorporation of the terminal segment of the Wolffian duct (ABC) into the urogenital sinus, ultimately forming the hemitrigone of the developing bladder. The migration places the normal ureteric bud orifice "B" on the lateral corner of the hemitrigone (left panel) and the ectopic bud orifice "A" on an extended corner "A" (right panel). The ureterovesical junction from the "A" ureteral bud is located in a lateral position that results in a short ureterovesical tunnel and vesicoureteral reflux. The metanephric mesoderm is well differentiated when interacting with a bud at the normal site "B" but sparse and poorly differentiated around bud "A" (and "C"). The interaction between bud and blastema is thus critical for the ontogeny of both ureter and metanephros, and abnormal interactions can result in various forms of congenital anomalies of the kidney and urinary tract (CAKUT) (reflux, hypodysplasia, obstruction, etc.)

A New Unified Theory

The lack of animal models has been a major stumbling block in understanding the evolution of CAKUT. In this regard, a mutant mouse strain recently generated by genetic engineering (47) has provided a unique opportunity to study this issue. The mutant mouse carries recombinant DNA in which the angiotensin type 2 (AT2) receptor gene (*Agtr2*) is selectively null-mutated by gene targeting. Importantly, this mutant strain carries phenotypes for virtually all key features characterizing common human CAKUT, including the diverse anatomical spectrum, high asymmetry, and a strong male preponderance. Data further suggest that an abnormality in the same gene is involved in CAKUT. Thus, a study on the human AT2 receptor gene (*Agtr2*) revealed that a minor population carries a functionally significant mutation within the so-called lariat branch point of intron 1, which results in a significant alteration in the quality and quantity of the mRNA due to abnormal mRNA splicing. Moreover, a pair of independent DNA studies on American and German populations of patients with CAKUT revealed a significant correlation between the incidence of CAKUT and this specific mutation in intron 1 (48). How might the dysfunction of the AT2 receptor bring about CAKUT?

Agtr2 is primarily an embryonic gene, and in humans and in rodents upregulation of AT2 transcriptional activity occurs in temporal and spatial association with the disappearance of the once densely populated undifferentiated mesenchymal cells (UMC) surrounding the embryonic urinary tract system. These are the mesenchymal cells that did not participate in the formation of the metanephric blastema or in the modeling of the distal urinary tract (*i.e.*, renal pelvis and ureter) (49,50) (Figure 2). *In vitro* studies have also shown that angiotensin II promotes apoptosis in certain types of cells via the type 2 receptor (51,52). Most recent *in vivo* and *in vitro* studies showed that activation of the AT2 receptor within these mesenchymal cells leads to enhanced apoptosis of UMC (53). It appears, therefore, that embryonic activation of the AT2 receptor promotes resolution of the UMC that did not participate in the formation of the ureter, metanephros, or nephrons by inducing apoptosis in these cells. It has also been shown that until the first ureteral budding occurs, the Wolffian duct is densely surrounded with UMC that intensely express AT2 receptors. In this regard, as discussed earlier, the ureteric bud induction requires biologic signals from the metanephros involving both ligand (*e.g.*, GDNF) (45,46,54) from the inducer (*i.e.*, metanephric blastema) and specific receptors to the ligand on the inducee (*i.e.*, Wolffian duct) (55–57). We therefore postulate that a failure in the timely apoptosis of these UMC will hinder the very first interaction between the ureteric bud and the condensed mesenchyme (metanephric blastema). This would result in ectopic (*e.g.*, caudal) budding of the ureter, which produces an abnormal location of the ureteral orifice, ultimately leading to VUR. The caudally sprouting bud, in turn, will make contact with portions of the metanephric blastema containing poorly differentiated, sparsely populated cells, resulting in a hypoplastic and/or dysplastic kidney. Of note, the growth-promoting signal from the ureteric buds to the metanephros is not diffusible, and hence must penetrate layers of UMC (45) where an abnormally persistent UMC layer is expected to mute the signals between the ureteric bud and the metanephros, thereby further interfering with the growth of both structures. Subsequent embryonic development of the kidney and urinary tract system involves several key biologic events, namely, opening of the ureteral lumen at the time of first urine formation, and enormously expansive growth of the ureter thereafter. These phenomena take place, again, in concert with the disappearance of UMC, which occupy the metanephros and densely surround the ureter and bladder. We further postulate that the delayed disappearance of undifferentiated cells around the urinary tract system could restrict the growth of the ureter and its supplying vessels (resulting in tissue ischemia), producing a tortuous or atretic/stenotic ureter.

Finally, maturation of the renal parenchyma into normal adult form requires removal of the so-called septae, which are

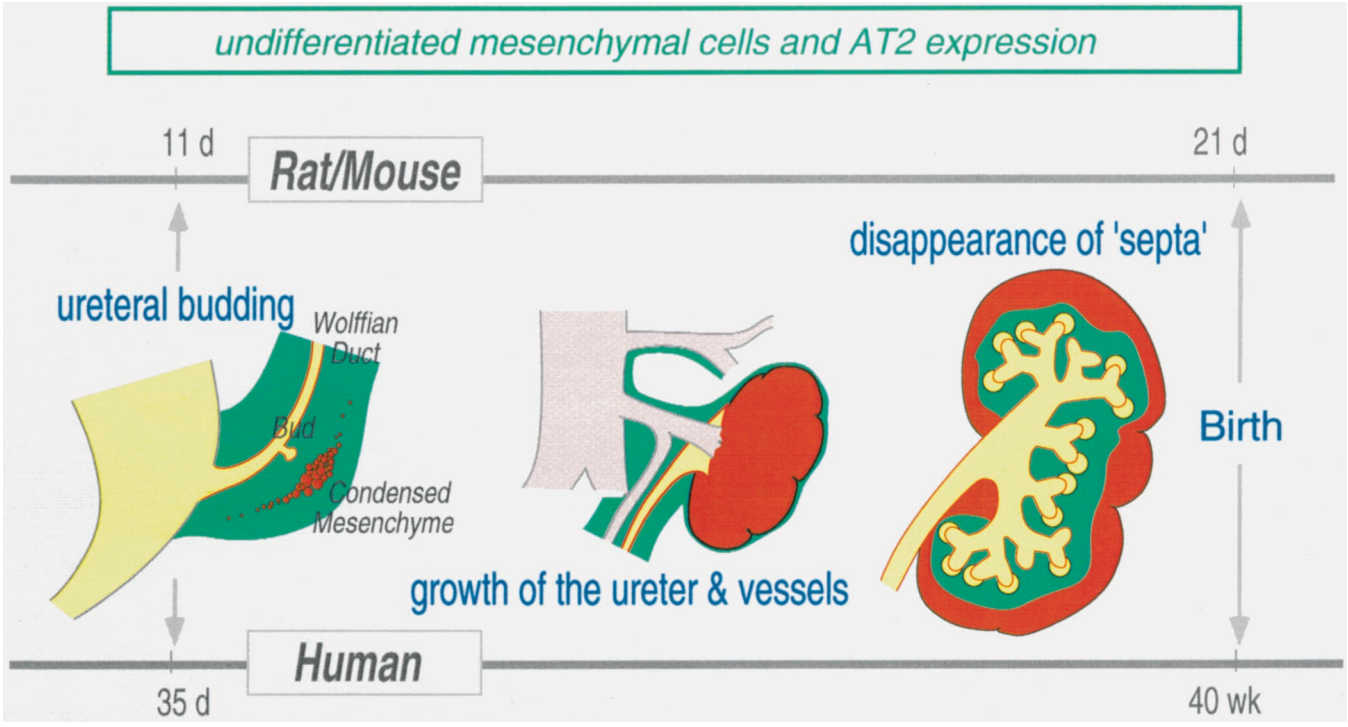

Figure 2. Ubiquitous undifferentiated mesenchymal cells (UMC) are present inside and outside the developing embryonic kidney and urinary tract. Undifferentiated mesenchymal cells are present in the vicinity of the metanephros and the ureter throughout the course of embryonic development. Early in development, the differentiating ureteral bud and metanephros are completely surrounded and interposed by UMC (green color, left). As the metanephros and its ureter ascend cranially while acquiring necessary blood supply from vessels that branch off, more cranial levels of the aorta, the ureter, vessels, and metanephros are densely surrounded by UMC (green color, middle). At the final stage of kidney maturation, the redundant septae between branched ureteral segments are resorbed to achieve the typical mature configuration. These septa are made of UMC (green color, right).

the spaces between Henle's loops, collecting tubules, and ducts. This is the interstitial space, which before its disappearance is filled with undifferentiated mesenchymal cells and strongly expresses AT2 receptors. It is expected, therefore, that a defect in the apoptosis of these cells occupying the interstitial space will bring about the typical histologic feature of dysplastic kidneys, which are characterized by abundance of undifferentiated interstitial cells that fill the interlobar and interlobular spaces.

These most recent hypothetical mechanisms for the ontogeny of CAKUT are in concert with similarly new emerging notions in broader biologic fields. First, ontogeny of a wide variety of organs is know recognized to involve massive cell apoptosis, or programmed cell death. This process is essential not only for eliminating injured cells or adjusting cell numbers, but also for deleting tissues that are unwanted for a particular gender determination, or needed only at earlier stages of ontogeny, as well as for sculpting organs into final fully functional units (58). Second, while angiotensin has long been known as a BP-raising agent, its involvement in kidney morphogenesis is now widely accepted based on a broad spectrum of data, although the majority of the latter are indirect in nature (59). Of note, a recent study on mutant mice selectively lacking angiotensin type 1 receptors (60) revealed that angiotensin, acting via this receptor, induces the smooth muscle development of the renal pelvis and ureter during the perinatal period. The latter is the period when urine output increases dramatically as the kidney takes over the hemodialyzing function of the placenta. An overview of the ontogenic mechanisms of CAKUT is shown in Figure 3 and reinforces the fact that the etiology of CAKUT, while possibly sharing a common genetic defect, clearly is multifactorial.

Although there are numerous hypotheses regarding the etiology of CAKUT, no single one answers all the questions. CAKUT is not a single disease entity, but a term meant to include all congenital anomalies occurring in the kidney and/or urinary tract. As a result, one single defect is unlikely to be responsible for all of the various forms of CAKUT. It would be interesting to find, however, a common defect (albeit due to a variety of causes) that would account for the abnormal development.

While the studies described earlier identified a specific gene (*i.e.*, *Agtr2)* and a specific biologic event (*i.e.*, defective apoptosis) that were involved in a presumably large population of CAKUT, the studies also revealed likely involvement of other genes and environs since the *Agtr2* genotype–phenotype relationship is not uniform in humans, and the penetrance (or transmission) of abnormal phenotypes in *Agtr2* null mutant mice was imperfect. Thus, it is likely that minor mutations in other genes are concurrently involved in the majority of CAKUT in humans. Indeed, the timely disappearance of UMC around the developing urinary tract must be under the control of a number of proliferative/antiproliferative and apoptotic/antiapoptotic genes, mutations of which may collectively contribute to the appearance of CAKUT.

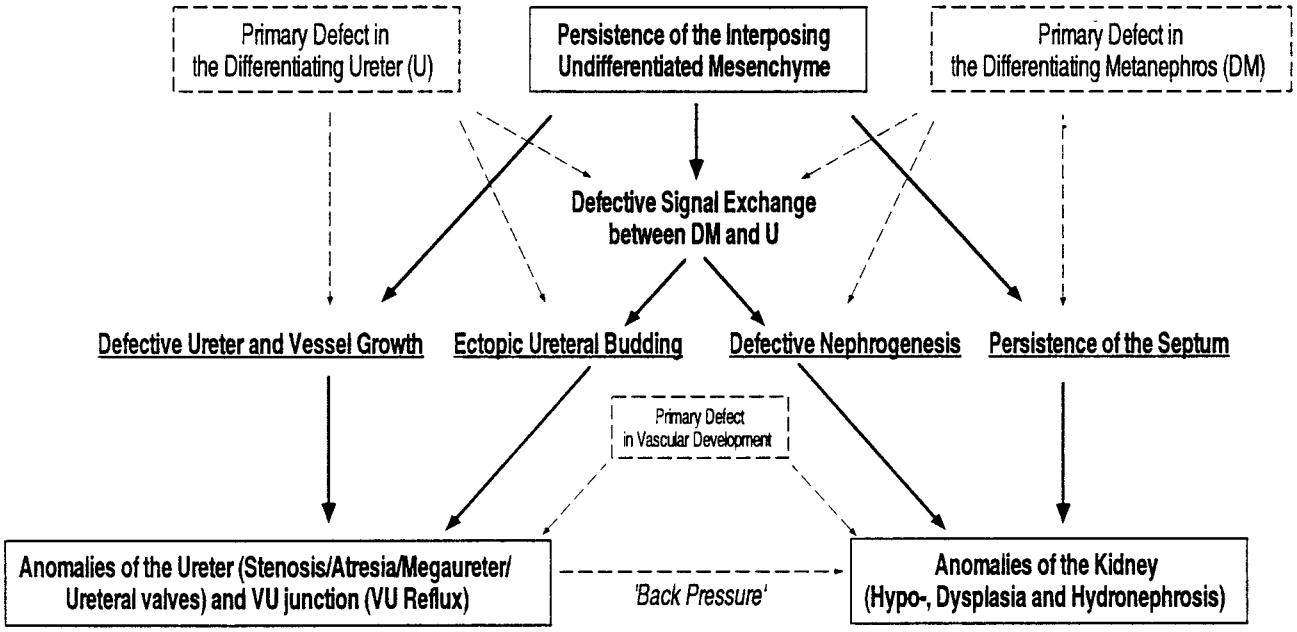

Figure 3. Ontogenic mechanisms involved in the formation of CAKUT. A primary defect in either the growing ureter or the differentiating metanephric blastema can cause both ureter and kidney. Also, since regulatory signals from both ureter and metanephros control their subsequent differentiation, an abnormality in one can cause anomalies of the other. Obstruction and the resulting high back pressure imposed on the parenchyma may promote development of hydronephrotic or dysplastic kidneys. A primary defect in vascular development can also lead to renal dysplasia. Persistence of UMC, due to attenuated apoptosis of these cells, is believed to trigger the key event documented in the ureteral budding theory (*i.e.*, ectopic ureteric budding). Persistent UMC are thought to disturb other events subsequently, including opening and expansive growth of the ureter, nephronogenesis, and disappearance of the "septae" from the metanephros.

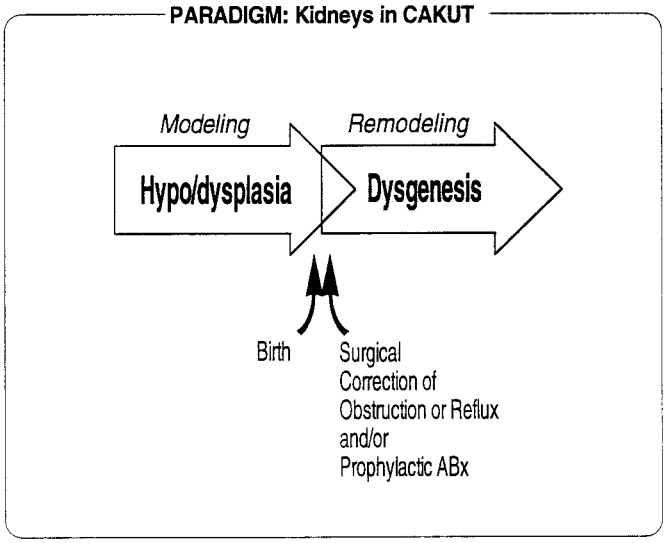

Figure 4. Paradigm of kidneys carrying CAKUT. During nephrogenesis *in utero*, CAKUT develop in a vast spectrum of distinctive structural abnormalities. CAKUT appears in the kidney in the form of hypo/dysplasia or hydroureteronephrosis. CAKUT with severe bilateral kidney involvement may result in spontaneous abortion or death shortly after birth. Often, those that survive the first few weeks suffer later from progressive deterioration of renal function despite successful surgical correction of obstruction.

Why Do Many CAKUT Lead to Renal Failure?

The dilemma faced by clinicians is often not the anatomic problems associated with CAKUT, but rather the associated incidence of progressive renal deterioration and azotemia that are resistant to treatment (Figure 4). This progressive loss of renal function is not merely a lack of kidney growth corresponding to somatic growth as widely believed, but also appears related to some form of intrinsic developmental impairment of the kidney, which is progressive over time. Several studies have been performed that examine the efficacy of surgical management of various forms of CAKUT. It had been assumed that surgical correction would ameliorate further renal damage and stop the progression of the disease. Unfortunately, several large prospective studies have shown that this is not always the case. The Birmingham Reflux Study Group demonstrated that patients treated with surgical correction of their reflux showed no advantage with regard to renal excretory function, renal growth, progression of renal scars, or the development of new scars (61). These findings in a relatively small patient population suggested that a certain group of patients was at risk of renal failure despite surgical intervention. In 1992, the International Reflux Study in Children also found that a small group of patients have progressive renal functional deterioration despite surgical correction (62), again suggesting that there is a subset of patients in whom there is relentless progression of injury to the renal parenchyma due to underlying, preprogrammed abnormalities within the urinary tract. In the case of congenital urinary tract obstruction, it has also been shown that surgical correction often does not prevent deterioration of renal function, again pointing to the existence of patients in whom renal failure is inevitable and this course is likely to be preprogrammed in the embryo.

For example, until recently, it had been thought that "sterile" reflux posed little risk for subsequent nephropathy. In patients with normal bladder function and no infections (*i.e.*, pyelonephritis), renal damage was thought to be quite rare. However, ultrasonic and nuclear medicine studies have commonly shown demonstrated areas of dysmorphism loosely called "scars" that occur even in the absence of infection. Anderson and Rickwood found that 60% of reflux kidneys in infants were abnormal by renography (63). Scott also demonstrated that 45% of kidneys in newborns with reflux had radiographically defined dysmorphism. Moreover, 80% of children with grade II and 47% with grade III reflux had abnormal kidneys, indicating that even in low grades of reflux, parenchymal defects were quite common(64).

Wallin and Bajc reported three major types of abnormal states seen on dimercaptosuccinic acid radionuclide scan in children with VUR: dysplasia, medial defects, and polar defects. All patients (both those with and without a history of pyelonephritis) showed a similar distribution with regard to these types of renographic defects (normal in 31 and 28%, dysplasia in 23 and 24%, medial defect in 25 and 21%, and polar defects in 175 and 24%, respectively). These studies suggest that renographic dysmorphism cannot be fully explained by the severity of the reflux or the occurrence of pyelonephritis. Instead, the findings point to additional intrinsic intrarenal predispositions (*i.e.*, developmental) that promote subsequent progressive deterioration (65).

The natural history of UPJ obstruction and its role in renal parenchymal morphology continue to be debated as well. Clearly, in some individuals, there is significant and profound parenchymal injury that is often progressive. Unfortunately, there is little information available concerning the precise number of patients with such progressive disease. This is due mainly to the fact that the degree of each UPJ obstruction is highly variable and the lesion is usually unilateral with the contralateral kidney compensating functionally for the affected kidney. Some studies, however, showed improvement in function in children whose obstruction was corrected surgically in the first month of life (66–71). Urologic pressure flow studies, although not ideal, are currently the hallmark for defining ureteral obstruction. These studies involve antegrade infusion of saline through a percutaneous nephrostomy tube, and the pressure differential between the renal pelvis and the bladder is then used to estimate the degree of ureteral obstruction. These studies, however, have not been directed toward establishing the relationship between defective parenchymal morphogenesis and the back pressure effects of obstruction (72). In fact, some kidneys do well despite proven obstruction while others do poorly despite lack of or removal of obstruction. The implications are that aside from the offending effects of UPJ obstruction, the kidney may be oligonephronic or already carry preprogrammed intrinsic characteristics that bring about its future demise.

The presence of such preexisting intrinsic abnormalities can be appreciated in studies on normal animals in which complete

ureteral obstruction is created experimentally immediately after birth. Changes similar to adult-type obstructive nephropathy developed in the renal parenchyma, including contraction of glomerular volume, glomerular sclerosis, tubular atrophy, and a marked increase in renal vascular resistance (73). These changes, however, were reversible upon early removal of the obstruction. This contrasts with many CAKUT, as surgical correction of the anatomic abnormality often fails to interrupt progression of renal injury.

CAKUT May Be Programmed in a Manner Similar to Other Deteriorating Chronic Kidney Diseases

A number of studies (74–77) have shown that in experimental animals, a critical reduction in renal mass (*i.e.*, congenital renal hypodysplasia, surgical removal of renal tissue mass, acquired renal disease) leads to progressive structural and functional deterioration of the remnant nephrons. In humans as well, severe oligonephronia is linked to the development of renal failure. An example of this situation is oligomeganephronia, a condition characterized by a marked congenital/developmental paucity of nephrons that is accompanied initially by a marked compensatory hypertrophy of the remaining individual nephrons and later by progressive glomerular sclerosis.

On the basis of these observations, it is now believed that a common mechanism exists for the progression of many common renal diseases. Although specific theories centering on this common mechanism vary in detail, they share the following theoretical features. Initial pathogenic insults, congenital or acquired in nature, cause a lack of functioning nephrons through disease-specific processes. The latter leads to dysfunction of the kidney as an excretory organ, which subsequently leads to abnormal accumulation of biologically active substances in the circulation. The pathophysiologic importance of such systemic circulatory substances, although yet to be defined, has been verified in the rat model of subtotal nephrectomy. Thus, subtotal nephrectomy leads to progressive deterioration of initially normal remnant nephrons, whereas prolonged treatment of rats with peritoneal dialysis or administration of oral charcoal adsorbent markedly attenuates the progressive deterioration (76). The results indicate the existence of circulating substances that are removable by dialysis or adsorbent, and play an active role in the progressive deterioration of renal parenchyma. Under the influence of such circulating substances, alterations in metabolism harm the remnant leading to fewer functioning nephrons. There are a number of possible substances that may be involved in these changes of nephron function and metabolism, including altered local hemodynamic forces (77) and cytokines, most notably transforming growth factor-β. The ultimate outcome of this vicious cycle is the end-stage kidney (Figure 5).

CAKUT are other prime examples of disease states in which there may be a significant congenital deficiency in nephron mass resulting from the intrinsic abnormal development of the kidney. It has been documented that CAKUT are often accompanied by oligonephronia on the contralateral kidney, particularly when accompanied by VUR (78). The nephrons in ipsilateral and contralateral kidneys are typically characterized by compensatory hypertrophy, which in turn makes radiologic quantification of oligonephronia and initial renal mass virtually impossible (our unpublished data). Furthermore, the progressive deterioration of CAKUT carries other important features of chronic renal diseases. For example, a recent study indicates that, as in diabetic nephropathy (79–85) and IgA nephropathy (86–91), the risk of progression to renal failure in CAKUT is affected by a specific ACE genotype (92,93). These are all in concert with the evidence provided by Stephens *et al.* more than two decades ago showing that the thin renal parenchyma in VUR is secondary to abnormal development of the kidney tissue *per se*, instead of hydrodynamic back pressure effects imposed on the normal kidney.

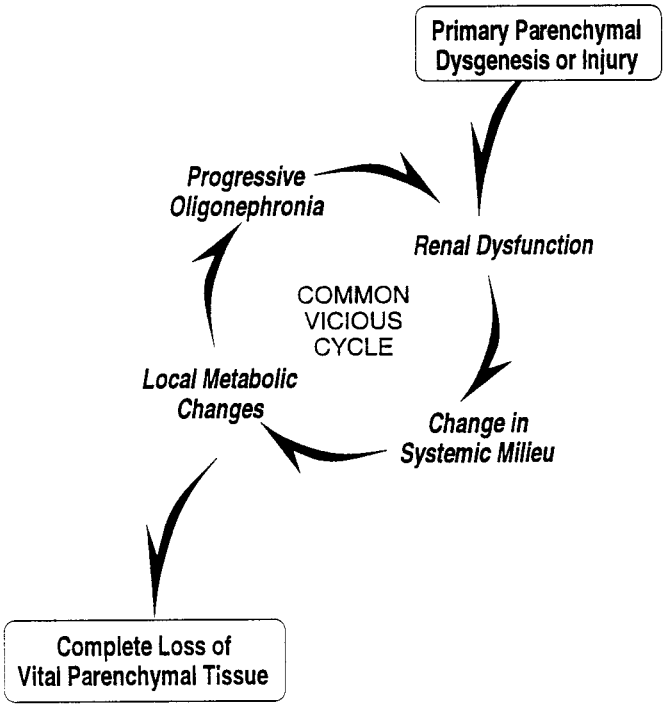

Figure 5. Vicious cycle of progressive functional and structural deterioration shared by many chronic renal diseases. Initial pathogenic causes, either congenital or acquired, lead to oligonephronia or loss of functioning nephrons, respectively (right top). The latter alters the systemic milieu due to reduced excretory function of the kidney and presumably alters the local tissue metabolism (*e.g.*, induction of cytokines and growth factors), causing further damage to relatively well-preserved portions of the renal tissue. The collective consequence of this vicious cycle is complete scarring of the renal parenchyma, which characterizes chronically failing kidneys.

Summary

CAKUT are problems that often require surgical intervention or, in the worst case, lead to renal failure and the need for dialysis and/or renal transplantation. It is believed that these anomalies share a common genetic cause and to date there has been no good animal model with which to study these abnormalities. Although the abnormal interaction between the ure-

teral bud and metanephric blastema leads to renal hypodysplasia, vesicoureteral reflux, and ectopic ureters to name a few, the genetic and biochemical modulation of urinary tract development is not understood. Studies using the mouse strain mutant for angiotensin type 2 (AT2) receptors have given new insight into this mystery. The animals show defective apoptosis of undifferentiated mesenchymal cells in the area surrounding the developing kidney and urinary tract. This abnormal apoptosis may well interfere with the normal interaction between the ureteral bud and metanephric blastema resulting in CAKUT. This abnormal interaction would theoretically lead to preexisting intrinsic abnormalities of the kidney, which are programmed and take effect early in embryonic development. In the worst cases, the renal abnormalities would lead to progressive deterioration of renal function. Undoubtedly, there are more genes and biochemical modulators involved in this process other than the RAS and AT2 receptors. Our current animal model gives new and unique possibilities with which to study development of the kidney and urinary tract and ultimately seek ways of preventing an often debilitating disease process.

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