Pathogenesis of Vesicoureteric Reflux and Reflux Nephropathy

FIGURE 8-5
Experimental vesicoureteric reflux in pigs. This pathology specimen demonstrates surgically induced vesicoureteric reflux in a 2-week-old male piglet. Note that the submucosal canal of one of the ureters has been unroofed.

FIGURE 8-6
Experimental vesicoureteric reflux in pigs: cystourethrogram showing intrarenal reflux. Reflux of radiocontrast medium into the renal parenchyma is seen. The pressure required to produce intrarenal reflux is lower in young children than it is in older children or adults, which is consistent with the observation that reflux scars occur more commonly in younger children [10].

FIGURE 8-7
Experimental vesicoureteric reflux in pigs. The polar location of acute suppurative pyelonephritis and evolution of parenchymal scars. In urinary tract infections, reflux of urine from the renal pelvis into the papillary ducts of compound papillae predominantly

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FIGURE 8-7 (Continued)
Located in the poles (intrarenal reflux) provides bacteria access to the renal parenchyma, resulting in suppurative pyelonephritis and subsequent polar scarring [11,12]. Intact (A, C, E) and coronally sectioned (B, D, F) kidneys illustrating the three stages of reflux nephropathy: hemorrhagic with polymorphonuclear cell infiltrate (A, B); white, not retracted, with prominent mononuclear cell infiltrate (C, D), and retracted scan with prominent fibrosis (E, F).

FIGURE 8-8 (see Color Plate)
Experimental vesicoureteric reflux (VUR) in pigs: mesangiopathic lesions. Reflux of infected urine can result in glomerular lesions characterized by activation of mesangial cells, mesangial expansion, mesangial hypercellularity, and the presence of large granules. The granules test positive on periodic acid-Schiff reaction and are located inside cells with the appearance of macrophages. These glomerulopathic lesions occur by a process that does not require contiguity with the infected interstitium nor intrarenal reflux. These lesions are not related to reduction of renal mass. Similar glomerular lesions have been identified in piglets after intravenous administration of endotoxin. Whether similar glomerular lesions occur in infants or young children with VUR and reflux nephropathy is not known [13].

FIGURE 8-9 (see Color Plate)
Experimental vesicoureteric reflux (VUR) in pigs: 99mTc-Technetium-dimercaptosuccinic acid (DMSA) scan demonstrating reflux nephropathy. Radionuclide imaging using DMSA has been found to be safe and effective in investigating reflux nephropathy [14]. DMSA is localized to the proximal renal tubules of the renal cortex. Parenchymal scars appear as a defect in the kidney outline, with reduced uptake of DMSA or by contraction of the whole kidney. Currently, DMSA radionuclide renal scanning is the most sensitive modality used to detect renal scars relating to reflux. New areas of renal scarring can be seen earlier with DMSA than with intravenous pyelography [15].
Integrative View of Pathogenetic Mechanisms in Reflux Nephropathy

- Abnormal induction of metanephric mesoderm (ureteral bud)
- Defective mesonephric mesoderm
- High-voiding pressures
- VUR
- IRR
- Virulent bacterial strain
- Susceptible host
- Focal exudative reaction
- Pyelonephritic scar
- Glomerulosclerosis
- Reduced nephron population
- Hyperfiltration
- Progressive renal insufficiency

FIGURE 8-10
Integrative view of pathogenetic mechanisms in reflux nephropathy. Abnormalities of ureteral embryogenesis may result in a defective antireflux mechanism, permitting vesicoureteral reflux (VUR), incomplete bladder emptying, urinary stasis, and infection. Bacterial virulence factors modify the pathogenicity of different bacterial strains. Bacterial surface appendages such as fimbriae may interact with epithelial cell receptors of the urinary tract, enhancing bacterial adhesion to urothelium. Endotoxin is capable of inhibiting ureteral peristalsis, contributing to the extension of the infection into the upper urinary tract even in the absence of VUR. Inoculation of the renal parenchyma with bacteria produces an acute inflammatory response, resulting in the release of inflammatory mediators into the surrounding tissue. The acute inflammatory response elicited by the presence of infecting bacteria is responsible for the subsequent renal parenchymal injury. In addition, it is possible that immune complexes, bacterial fragments, and endotoxin resulting from infection may produce a glomerulopathy.

Even in the absence of urinary tract infection, VUR associated with elevated intravesical pressure is capable of producing renal parenchymal scars. The developing kidney appears to be particularly susceptible. Renal tubular distention resulting from high intrapelvic pressure may exert an injurious effect on renal tubular epithelium. Compression of the surrounding peri-tubular capillary network by distended renal tubules may produce ischemia. During micturition, elevated intravesical pressure is transmitted to the renal pelvis and renal tubule. This transient pressure elevation may produce tubular disruption. Extravasation of urine into the surrounding parenchyma results in an immune-mediated interstitial nephritis and further renal injury.

The reduction in functional renal mass produced by the interaction of the pathogenetic factors listed here induces compensatory hemodynamic changes in renal blood flow and the glomerular filtration rate. Over time, these compensatory changes may be maladaptive, may produce hyperfiltration and glomerulosclerosis, and may eventually in renal insufficiency. (From Kramer [16]; with permission.)

FIGURE 8-11
Vesicoureteral reflux and renal dysplasia. An abnormal ureteral bud resulting from defective ureteral embryogenesis may penetrate the metanephric blastema at a site other than that required for optimum renal development, potentially resulting in renal dysplasia or hypoplasia [17].