INTRODUCTION
The ability to define the pathological basis of kidney diseases has advanced substantially since the completion of the Human Genome Project. Moreover, advances in technology have been greater in the past decade than has ever been seen in modern medicine. These advances combine to open the door to a richer understanding of both normal and pathological processes involved in kidney function and consequent diseases.

Kidney disease is defined as either decreased ability to filter products of metabolism (such as creatinine) or the loss of protein in the urine (proteinuria). The ability of the kidney to filter metabolic substances into the urine is referred to as the glomerular filtration rate (GFR). With worsening proteinuria or deterioration in GFR, there is a greater risk of end-stage kidney disease (ESKD) requiring dialysis or transplantation, as well as increased risk of cardiovascular disease. The molecular pathogenesis of kidney diseases with Mendelian modes of inheritance are most well understood. Three such entities will be reviewed including focal segmental glomerulosclerosis (FSGS), Fabry disease, and polycystic kidney diseases. Additionally, Bartter’s and Gitelman’s diseases will be discussed as examples of renal tubular disorders, which can result in electrolyte and acid/base balance, as well as to the nephron’s ability to concentrate or dilute urine.

NORMAL KIDNEY FUNCTION
The kidney is composed of millions of nephrons, the individual functional units responsible for urine production. The glomerulus is the filtration component of the nephron that allows toxic substances accumulating in the body to pass from the blood to the tubules of the nephron from which they are excreted in the urine. The filtration barrier is comprised of fenestrated vascular endothelial cells, the glomerular basement membrane, and interdigitating epithelial cells (podocytes) connected by slit diaphragms (Figure 24.1). Water, ions, and small solutes are able to permeate the filtration barrier, but larger proteins, such as albumin, cannot pass through. This filtrate is collected in Bowman’s capsule and is then modified as it moves through subsequent tubules of the nephron. Tubular cells possess ion channels that are important to maintaining proper sodium, potassium, and acid/base balance, as well as to the nephron’s ability to concentrate or dilute urine.

FOCAL SEGMENTAL GLOMERULOSCLEROSIS
Focal segmental glomerulosclerosis (FSGS) is considered a disease, but in actuality is a histopathologic finding with numerous etiologies, each of which can vary dramatically in clinical course. FSGS is diagnosed with kidney biopsy. Light microscopy is characterized by scarring (sclerosis) of select portions (segments) of glomeruli. This should be differentiated from global sclerosis in which the entire glomerulus is scarred, and which can be a normal finding with age. Generally, not all glomeruli are involved, accounting for the focal portion of its name. FSGS leads to proteinuria, frequently resulting in decreased GFR and ESKD requiring dialysis or transplantation.

Clinical Presentation of Focal Segmental Glomerulosclerosis
The clinical presentation of FSGS is extremely variable. Onset can occur from the neonatal period to the seventh decade. The disease course can be self-limited, slowly progressive, or rapidly deteriorate to ESKD.
Patients present with proteinuria, which may be discovered on routine urinalysis, or they can be symptomatic with nephrotic syndrome. This is characterized by nephrotic range proteinuria (>3 grams/24 hours), edema, hypoalbuminemia, and hyperlipidemia. FSGS is the most common cause of acquired chronic kidney disease in children. The vast majority of FSGS is idiopathic. Idiopathic FSGS affects African Americans more than Caucasians, and is more likely to present in young adulthood. In the United States, idiopathic FSGS is responsible for approximately 4% of ESKD.

There are five histologic variants of FSGS, depending on the glomerular location and nature of the sclerotic lesion. The relevance of the histologic variant to etiology, clinical presentation, and response to treatment has been investigated. The collapsing variant has a predilection for African Americans, is resistant to treatment, and typically follows an aggressive course with a 3-year renal survival rate of 33%. This pathologic entity is found frequently in FSGS due to toxic exposures such as heroin or pamidronate. The tip variant is more common in Caucasians, is more likely to abate with immunosuppression, and has a better prognosis, with a 3-year renal survival rate of 76%. Perihilar FSGS most often is found in secondary forms of FSGS due to hyperfiltration states such as obesity and hypertension. The cellular variant is the rarest and is thought to possibly represent an earlier stage of FSGS. The final variant form of FSGS is termed FSGS not-otherwise-specified, and may represent a later stage of FSGS.

Familial FSGS is classified according to its Mendelian inheritance pattern and early (childhood) versus late (adult) onset. These forms of FSGS are more consistent in their clinical presentation and multiple genes have been discovered as the cause. Congenital nephrotic syndrome of the Finnish type (CNF) was first reported in Finland, explaining the derivation of its name. However, CNF since has been identified in multiple geographic populations. It is characterized by massive proteinuria, often 20–30 grams/24 hour in utero, and is inherited in an autosomal recessive pattern. Without bilateral nephrectomy and transplantation, complications from nephrotic syndrome result in an exceedingly high mortality rate within the first few months of life. It is caused by mutation of the gene for nephrin (NPHS1), a critical protein of the slit diaphragm component of the filtration barrier. A substantial portion of children who receive kidney transplants develop recurrence of disease, thought likely due to autoantibodies to nephrin or the glomerular basement membrane (GBM). Carriers of the mutation may have proteinuria, but typically do not develop chronic renal insufficiency.

A less severe form of early-onset autosomal recessive FSGS is caused by mutation of the podocin gene (NPHS2). Age of onset ranges from a few months to 5 years. This form of FSGS is resistant to steroid treatment and progresses rapidly to ESKD. Posttransplant FSGS is relatively uncommon. NPHS2 mutations can also be found in sporadic FSGS, and have been identified mostly in children, but there are also reports in adults. Autosomal dominant (AD), adult-onset FSGS has been identified in families with mutations in either the alpha-actinin 4 (ACTN4) or transient receptor potential 6 (TRPC6) genes. Disease onset can range from adolescence to the fifth decade and there is variable progression to ESKD.

**Pathogenesis of Focal Segmental Glomerulosclerosis**

In the normal kidney, numerous branches emanate from the podocyte body, terminating on distinct capillary vessels where they are referred to as foot processes. Disruption, or effacement, of the podocyte foot processes occurs invariably in FSGS. The underlying mechanism of foot process effacement is not completely understood and may be due to multiple mechanisms. Alterations in the cell membrane, the structural integrity of the slit diaphragm, and/or actin cytoskeleton and signaling among these components can result in podocyte damage. The slit diaphragm is integral to maintaining cell polarity, regulation of the cell cycle, and intracellular signaling of external conditions. The intricate actin cytoskeleton of the podocyte maintains the normal architecture of the foot processes, and is capable of responding to a changing environmental milieu. Destabilization of the actin cytoskeleton leads to foot process detachment and effacement.

Podocyte damage initiates a vicious cycle of cytokine production, proteinuria, and hyperfiltration. Specifically, TGFβ, SMAD, VEGF, and angiotensin have been implicated in this process. These events lead to up-regulation of the inflammatory response with recruitment of T-cells and macrophages. Cell polarity and maintenance of the cell cycle is lost, resulting in apoptosis. As a terminally differentiated cell, the ability of the podocyte to regenerate is limited, resulting in
podocyte filamentation and exposure of the GBM. Collagen matrix deposition ensues, resulting in sclerosis and ultimately, obliteration of the capillary lumen.

FSGS is most often sporadic with no identifiable cause. However, many cases of FSGS are secondary to specific etiologic conditions. Environmental insults resulting in hyperfiltration can lead to FSGS, including hypertension, obesity, and unilateral renal agenesis. Viral infection with human immunodeficiency virus (HIV), parvovirus, and cytomegalovirus have been associated with some cases of FSGS. Other cases have been related to toxic exposures such as heroin, pamidronate, and interferon-2. FSGS can demonstrate familial aggregation with Mendelian inheritance patterns. This has led to the discovery of multiple genes which, when mutated, lead to disruption of the filtration barrier and subsequent proteinuria and sclerosis.

Some forms of FSGS may be the result of a circulating permeability factor, which damages the basement membrane and disrupts the adherence of the foot process. This is best exemplified in recurrent FSGS in those who have undergone kidney transplantation. Posttransplant FSGS can sometimes be treated successfully with plasmapheresis, which removes proteins, and presumably this circulating permeability factor, from the blood.

**Genetics of Focal Segmental Glomerulosclerosis**

Mutations in genes coding for important proteins in the slit diaphragm or the actin cytoskeleton can lead to monogenic forms of FSGS, and some predict responsiveness to treatment. To date, there are at least seven genes in which certain mutations can lead to FSGS. For illustrative purposes, this text will cover four such genes, including NPHS1, NPHS2, ACTN4, and TRPC6 (Figure 24.1).

Nephrin is a slit diaphragm protein, which not only forms one of the physical barriers to solute passage, but is also important to intracellular signaling and apoptosis. Certain mutations in nephrin result in CNF, the most severe clinical form of FSGS. Its mode of inheritance is autosomal recessive. Two mutations account for the vast majority of CNF, Fin major and Fin minor. Fin major is a frameshift mutation caused by deletion of nucleotides 121 and 122. Fin minor is a nonsense mutation resulting in a premature stop codon at amino acid 1109.

Podocin is a protein found at the base of the foot process that functions as both a structural protein in the slit diaphragm and also a signaling molecule. It acts with lipid rafts in the apical region of the cell membrane and recruits nephrin and CD2AP, another slit diaphragm-associated protein. Some podocin mutations result in autosomal recessive transmission of steroid-resistant nephrotic syndrome. Recently, several missense mutations have been associated with sporadic FSGS.

ACTN4 mutations can result in autosomal dominant adult-onset FSGS. ACTN4 anchors the actin cytoskeleton to the cell membrane, and certain mutants have been found to increase the affinity of binding. However, the podocyte’s ability to anchor to the GBM appears to be decreased with ACTN4 mutations, as demonstrated in animal models.

TRPC6 is a cation selective channel of the podocyte, localized near the slit diaphragm. It results in AD adult-onset FSGS with variable progression to ESKD depending on the specific mutation. TRPC6 regulates calcium entry into the cell, with certain mutations resulting in increased permeability, especially in the presence of angiotensin II. The effect of increased intracellular calcium is unknown. However, some investigators have suggested that the actin cytoskeleton may be pathologically altered.

**Treatment of Focal Segmental Glomerulosclerosis**

The mainstay of FSGS treatment is suppression of proteinuria with inhibitors of the renin-angiotensin system and immunosuppression with corticosteroids and cyclosporine. Genetic forms of FSGS typically do not respond to immunosuppressive treatment, especially in children. Sporadic FSGS is more likely to abate than familial FSGS. However, response is still quite poor. Ongoing efforts aim to identify pathogenetic mechanisms predicting response to immunosuppression. However, to date none has been consistently identified.

**FABRY DISEASE**

Fabry Disease is an X-linked lysosomal storage disease that affects multiple organ systems, including the kidney. It is a rare disorder, with early-onset disease affecting approximately one in 40,000 males and late-onset disease affecting as many as one in 3,100 males. Fabry Disease results from deficiency of α-galactosidase (α-gal), a ubiquitous enzyme crucial to the metabolism of intrinsic cellular components, glycosphingolipids. These molecules accumulate intracellularly and result in disruption of normal physiology with irreversible damage. Clinical manifestations begin in childhood. The average life expectancy is approximately 55 years for men and 70 years for women.

**Clinical Manifestations of Fabry Disease**

The age of onset of classical Fabry Disease is in early childhood, typically by the age of 5 to 6 years in boys and 9 to 10 years in girls. The most common symptom during this period is acroparesthesias, tingling and burning in the hands and feet, which can become extremely disabling. Gastrointestinal symptoms are common and can include abdominal pain, nausea, vomiting, and diarrhea. Hypohydrosis, decreased sweating, is also typical and can result in exercise intolerance. During adolescence, approximately 40% of Fabry patients develop angiookeratomas (Figure 24.2a). These are painless,
nonpruritic red or purple nodules, typically over the central abdomen and groin region. Sensorineural hearing loss can occur at any age, but the prevalence increases with age. Corneal verticillata (Figure 24.2b), or corneal whorls, are linear opacities emanating from a single point in the cornea but do not interfere with visual acuity. These are seen in most male and many female patients and are diagnostic of Fabry disease.

Prior to the initiation of dialysis, the most common cause of death in males with Fabry Disease was ESKD. By early adulthood, many males and some females manifest with proteinuria and by age 50, most men will have decreased GFR. The mean time from decreased GFR to ESKD is 4 years (±3 years). There is a correlation between the age of onset of kidney disease and the residual α-gal enzyme activity, with those who have undetectable α-gal activity presenting with decreased GFR in their twenties versus forties for those with ≥1% α-gal activity. Some GLA mutations result in renal variant Fabry, whereby no symptoms manifest until adulthood when they present with kidney disease.

There are multiple cardiac and cerebrovascular manifestations of Fabry disease. The most common is left ventricular hypertrophy (LVH) and subsequent diastolic dysfunction, which can be severe. Premature atherosclerotic disease is a frequent cause of morbidity and mortality, with a first myocardial infarction or stroke occurring in men in their forties and women in their fifties. Conduction abnormalities are frequent, with shortened PR interval and resting bradycardia being the most common. Ventricular arrhythmias can sometimes be the first presenting sign of Fabry disease, and is the most common cause of cardiac death. Similar to renal variant Fabry, there are GLA mutations that result in cardiac variants of the disease in which the first clinical manifestation is cardiac disease.

Pathogenesis of Fabry Disease

Glycosphingolipids are constituent components of the plasma cell membrane. They typically undergo degradation after being endocytosed into the lysosome. With the absence of the intralysosomal degrading enzyme α-galactosidase A, these neutral glycosphingolipids, mostly globotriaosylceramide (GB3), progressively accumulate. Accumulation has been found to occur not only within the lysosomes, but also within the nucleus, cytoplasm, and cell membranes. Using immunohistochemical techniques, GB3 staining occurs most strongly in the kidney and heart. Virtually all cardiac tissue types stain positive, including endocardium, myocardium, endothelial cells of the coronary arteries and intracardiac nerves, and vasa nervorum. Staining within the kidney is more variable and mostly involves the glomerular and tubular epithelial cells. Accumulation of GB3 within the brain is almost entirely within the vasculature and in the skin typically is isolated to dermal blood vessels and epidermal fibroblasts.

The mechanism by which GB3 accumulation results in the clinical pathology of Fabry Disease is unknown. It does result in accelerated atherosclerotic disease, possibly due to the induction of reactive oxygen species, apoptosis, and interference with the fibrinolytic system. Glycosphingolipid accumulation may also interfere with intracellular trafficking between endosomal organelles and the endoplasmic reticulum. Signal transduction between cells, specifically via endothelial nitric oxide synthase (eNOS), may be disrupted by the accumulation of GB3 in the cell membrane.

Genetics of Fabry Disease

Fabry Disease results from mutation of the α-gal (GLA) gene located on the X chromosome. Since males possess only a single X chromosome, all those that carry a mutation in GLA manifest symptoms. In contrast, heterozygous females have a more variable course. The heterogeneity of Fabry Disease in females is due to X chromosome mosaicism. During embryonic development in the female, one X chromosome is randomly inactivated in each cell so that the transcriptional dosage of the X chromosome is the same in both genders. Different cell lines of the same cell type, within the same organ, may have a different...
activated X chromosome, and this is termed mosaicism. If there is a skewing of cell lines with the mutated X chromosome, a female can manifest with more severe Fabry Disease, similar to that of a male. The effect of skewed X-inactivation is best evidenced by monozygotic twins, wherein one twin is composed primarily of cells expressing the mutant gene and manifests with classic Fabry Disease versus the other twin who may remain completely asymptomatic.

Clinical manifestations are also heterogeneous among males, depending on the genetic mutation and its effect on enzyme level and function. Over 300 mutations spanning all seven exons have been identified. More than 70% are point mutations, mostly missense or nonsense, and 25% represent small deletions. Mutations that result in a complete loss of enzyme function, such as nonsense mutations or rearrangements, traditionally yield phenotypes consistent with classic Fabry Disease. Male patients with these mutations will have no enzyme activity. Missense mutations, resulting in amino acid substitutions, may give rise to later onset Fabry symptoms such as the renal or cardiac variants. Specifically, conservative substitutions generally result in a later onset and milder disease course than those resulting in nonconservative substitutions. Moreover, the location of the mutation can also account for phenotypic variability of Fabry, depending on whether it is the active site of the enzyme that is affected or protein folding or enzyme stability.

Although Fabry Disease is a simple Mendelian disorder, the complexity of the disease process is revealed by the lack of genotype-phenotype correlation. Different families with the same genetic mutation, and even different family members within the same family, may manifest with different disease characteristics such as the age of onset, organ systems involved, and severity of disease. The basis for this lack of genotype-phenotype correlation is unknown, but it is likely that modifying genes and epigenetic factors play a large role.

**Diagnosis of Fabry Disease**

The nonspecific nature of symptoms in Fabry Disease often results in delayed diagnosis. The mean time from the onset of symptoms to correct diagnosis has been reported to be 15 to 20 years. The findings of angiokeratoma and corneal verticillata are virtually diagnostic. Once Fabry Disease is suspected, the diagnosis is fairly simple in men who can be diagnosed by measuring peripheral leukocyte or plasma α-gal activity. Levels less than 20% of normal are diagnostic and less than 35% of normal are suggestive of Fabry disease. However, enzyme activity levels in women are highly variable and rarely useful, as they can be within the normal range even in highly symptomatic women.

In women with suspected Fabry Disease, genetic testing for a known causative mutation should be performed. This is done by gene sequencing and will only be diagnostic if a known causative mutation is identified. Due to genetic heterogeneity, the occasion may arise that a previously unidentified mutation exists in a family. Hence, sequencing results from a questionably affected female would be difficult to interpret. If there are affected male relatives, a higher yield approach would be to sequence the male and then test for the specific mutation in the female. Prenatal diagnosis also occurs by sequencing for the known familial mutation.

**Treatment of Fabry Disease**

Intravenous enzyme replacement therapy (ERT) with α-galactosidase became available in the United States in 2003 and is the first specific therapy for Fabry Disease. The enzyme preparation utilized in ERT for Fabry Disease is called agalsidase. Antibody formation to agalsidase is common among treated patients, especially in males with <1% α-gal activity. The significance of these antibodies remains unknown, but *in vitro* studies suggest they may be inhibitory. ERT is generally well tolerated, although infusion-related reactions such as fever, chills, and rigors are frequently reported, especially during the first several treatments. There are no parameters to follow for assessing treatment efficacy. Levels of GB3 are variable and generally do not correlate with symptomatic improvement.

Agalsidase has been demonstrated to slow the progression of GFR decline and cardiac hypertrophy, decrease pain crises, and improve tissue clearance of GB3. Outcomes are best in those without significant kidney disease (GFR ≥55 mL/min/1.73 m²), although there are a few reports of decreased kidney and cardiovascular events even in advanced Fabry Disease. In addition, improvement in hearing, sweating, and gastrointestinal symptoms have been reported in patients treated with therapy. Treatment is recommended for all adolescent boys or older. Treatment recommendations for children and women are less well defined, but those who are symptomatic should likely receive therapy. Clearly, early diagnosis and treatment are important to assessing the maximal beneficial effects of ERT in Fabry Disease.

**POLYCYSTIC KIDNEY DISEASE**

Though there are multiple diseases of the kidney that may present with the pathological finding of cyst formation, classically, this terminology is used to refer to two specific disorders that in most cases have a genetic basis for the pathology: (1) autosomal dominant polycystic kidney disease and (2) autosomal recessive polycystic kidney disease. Differences in the patterns of inheritance, clinical presentation, and appearance of the kidneys reflect the differences in the underlying pathogenesis of these disorders.

**Autosomal Dominant Polycystic Kidney Disease**

Autosomal dominant polycystic kidney disease (ADPKD) is the most commonly inherited renal disease, with a prevalence of one in 400 to one in 1000 individuals. There are estimated to be 600,000 cases in the United States.
States and over 12 million cases worldwide. Although cyst formation begins in utero, disease onset has a bimodal pattern, with most patients presenting in the third to fifth decades of life and a clinically significant subset of patients presenting in infancy and childhood. Progression to renal failure occurs in nearly 50% of patients with ADPKD by age 60. ADPKD accounts for approximately 2.5–3.0% of cases of ESRD in the United States.

**Clinical Presentation and Diagnosis of Autosomal Dominant Polycystic Kidney Disease**

ADPKD cyst formation begins in utero, but signs of the disease may not be detected for several decades. Over time, multiple renal cysts that arise from distal nephron segments result in renal enlargement and progressive loss of kidney function. Although bilateral renal involvement is reported most frequently, approximately 15% of cases have asymmetric renal involvement—a finding that is more common in children. The typical adult presentation includes decreased renal concentrating ability (polyuria), hematuria, and flank pain resulting from cyst expansion. Hypertension is noted in 70–80% of affected individuals, and typically predates the development of renal insufficiency. Hypertension likely results from activation of the renin-angiotensin-aldosterone system (RAAS). When this occurs, cyst compression of the surrounding parenchyma causes local ischemia.

In addition to kidney cysts, patients with ADPKD may develop cystic lesions of the liver, pancreas, and occasionally the lung. Berry aneurysms within the brain usually involve the circle of Willis and have been reported in 10–15% of cases with a tendency to cluster in families. Coronary artery aneurysms, cardiac valve anomalies, ovarian cysts, inguinal or ventral hernias, colonic diverticula, and subcutaneous cysts also have been reported. Intracranial aneurysms are a severe presentation and may result in headache or even stroke. On the other end of the spectrum, nearly 50% of individuals with ADPKD will remain undiagnosed based on the silent nature of cyst formation. ADPKD can present as an incidental finding or as surveillance of apparently unaffected family members of known cases. ADPKD may be discovered as a result of a workup for abdominal mass or hypertension.

In patients with a positive family history, the diagnosis of ADPKD is established by radiologic evidence of bilateral, fluid-filled renal cysts. Because of cost and safety, ultrasonography is most commonly used as the imaging modality. Typical findings include large kidneys and extensive cysts scattered throughout both kidneys. The Ravine ultrasonographic criteria use patient age and family history to suggest the diagnosis of ADPKD (Table 24.1). Important issues related to the diagnosis of ADPKD include the presence or absence of a family history of the disease, the numbers and types of renal cysts, and the age of the patient. The presence of liver or pancreatic cysts confirms a diagnosis of ADPKD.

**Table 24.1** Ravine Ultrasonographic Criteria for Diagnosing Autosomal Dominant Polycystic Kidney Disease

<table>
<thead>
<tr>
<th>Age</th>
<th>Positive Family History</th>
<th>Negative Family History</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30 years</td>
<td>2 cysts bilaterally</td>
<td>5 cysts bilaterally</td>
</tr>
<tr>
<td>30–60 years</td>
<td>4 cysts bilaterally</td>
<td>5 cysts bilaterally</td>
</tr>
<tr>
<td>&gt;60 years</td>
<td>8 cysts bilaterally</td>
<td>8 cysts bilaterally</td>
</tr>
</tbody>
</table>


Genetic testing is available for both *PKD1* and *PKD2*. Current genotype testing identifies approximately 70% of the known pathogenic mutations, and hence diagnosis is more often made on radiologic grounds.

**Genetics and Pathogenesis of Autosomal Dominant Polycystic Kidney Disease**

As the name indicates, ADPKD typically is inherited in an autosomal dominant fashion and results from the inheritance of mutations in one of two genes: *PKD1* or *PKD2*. Eighty-five percent of families with ADPKD have a mutation in the *PKD1* gene and another 15% in *PKD2*. Family history is absent in nearly 10% of cases, suggesting that there are also a significant number of sporadic mutations leading to ADPKD.

*PKD1* is located on the short arm of chromosome 16 (16p13.3 region) and its gene product is Polycystin-1 (PC1). Polycystin-1 is expressed predominantly in the distal convoluted tubule and collecting ducts of the kidney. PC1 is a primary cilium transmembrane glycoprotein that plays a role in regulating tubular and vascular development in the kidney as well as other organs (liver, brain, heart, and pancreas). These cilia detect environmental signals and increase the flow of calcium through a cation channel formed in the plasma membrane by Polycystin-2 (PC2), the gene product of *PKD2*. Normal calcium flux results in inhibition of cell proliferation. When calcium entry is impaired by a mutation in one of these proteins, proliferative cell pathways predominate, leading to renal cyst formation. From this standpoint, the cysts of ADPKD are a benign renal tubular neoplasm that expands by increasing the mass of proliferating epithelial cells that surround a cavity filled with fluid.

The pathogenesis of ADPKD is attributed primarily to a two-hit mechanism, in which an inherited germ-line mutation is compounded by a second somatic mutation. In a cell that has one allele carrying the genetic mutation, a second hit to the remaining normal
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allele triggers a sequence of events that leads to the proliferation of the tubule cell as described earlier. Once a cyst reaches 2 mm in diameter, it separates from the parent nephron and will function as an autonomous fluid-filled sac/tumor. Cysts expand and destroy normally functioning renal tissue, and this provokes the complications of polycystic kidney disease.

PC2 is a member of the transient receptor potential channel (TRPC) superfamily of nonselective cation channels. As described earlier, PC1 and PC2 function as a regulated ion channel complex. Though mutations in PKD1 are associated with earlier disease onset and a more severe disease course than mutations in PKD2, a mutation of either polycystin protein can disrupt this normal function of the cilium and result in a similar pathology. PC2 also functions as a Ca\(^{2+}\) release channel in the endoplasmic reticulum and has been localized to the apical primary cilia of epithelial cells, where the PC1–PC2 complex is thought to participate in flow-induced mechanosensation.

**Treatment of Autosomal Dominant Polycystic Kidney Disease**

There are currently no treatments that have been shown in randomized trials to slow the formation of cysts or slow disease progression in patients with ADPKD. Therefore, basic treatment measures aimed at ameliorating the effects of associated findings (such as hypertension) take a primary role. Blood pressure should be controlled to less than 130/80 in adults and to the normal range for sex- and age-matched children. A retrospective analysis has shown that an Angiotensin-converting-enzyme inhibitor (ACEI) or an Angiotensin II receptor blocker (ARB) is associated with preservation of renal function in patients with ADPKD. Salt restriction plays a role in hypertension control (as well as experimentally in lowering vasopressin as a potential growth factor for cysts).

The role of the RAAS system in ADPKD progression is the focus of the ongoing HALT Progression of Polycystic Kidney Disease (HALT PKD) study. This randomized, double-blind, placebo-controlled study is assessing whether pharmacologic interruption of the RAAS affects disease progression or the rate of decline in renal function in ADPKD.

Although there is currently no therapy that would replace the function of the abnormal protein, there are experimental therapies being considered based on a best science approach. For instance, it is known that cyclic AMP (cAMP) increases the proliferation of epithelial cells in cist walls and increases the rate of fluid secretion into cysts. Therefore stimuli that result in increased cAMP production should be avoided on a theoretical basis. This includes caffeine and theophylline, as well as beta-adrenergic agonists.

Arginine vasopressin (AVP) is a potent activator of renal adenyl cyclase, another protein that plays a role in epithelial cell proliferation. From a nonpharmacologic standpoint, suppression of arginine vasopressin release by high water intake appears to limit cyst formation. The arginine vasopressin V2 receptor antagonists such as tolvaptan have been shown to inhibit the development of polycystic kidney disease in animal models. Additionally, the results of phase 2 and phase 2–3 clinical trials suggest that tolvaptan is safe and well tolerated in ADPKD. A phase 3, placebo-controlled, double-blind study will determine whether tolvaptan is effective in slowing down the progression of cystic kidney disease. Although data from randomized controlled trials are lacking, on theoretical grounds it may be reasonable to encourage generous water intake to ensure that endogenous AVP is suppressed and while we await the results of the V2 receptor antagonist trials, when a therapy such as this is considered, the risk of hyponatremia must always be considered.

The mammalian target of rapamycin (mTOR) is a protein kinase and a central regulator of cell growth and proliferation. Building on the observations that ADPKD is associated with dysregulated cell proliferation, animal studies have tested sirolimus, an mTOR inhibitor, and have noted reduced cyst formation. Human trials are now being considered.

**Autosomal Recessive Polycystic Kidney Disease**

Autosomal Recessive Polycystic Kidney Disease (ARPKD) is a severe form of cystic disease that affects primarily the kidneys and biliary tract. ARPKD occurs in approximately one in 20,000 live births and can involve a wide spectrum of phenotypes, depending on the type of mutation and age of presentation. In affected fetuses the principal pathological findings are enlarged, ectopic cystic kidneys. Oligohydramnios occurs due to insufficient fetal urine production. Nearly half of affected neonates die shortly after birth, as a result of the pulmonary hypoplasia that results when urine production is decreased. Among neonatal survivors, morbidity and mortality results from severe systemic hypertension, renal insufficiency, and portal hypertension due to portal-tract hyperplasia and fibrosis.

**Clinical Presentation and Diagnosis of Autosomal Recessive Polycystic Kidney Disease**

Clinical manifestations of ARPKD are quite variable but usually include a significant impairment in renal function. In severe prenatal cases, involvement of the kidneys leads to massively enlarged echogenic kidneys, oligohydramnios, and pulmonary hypoplasia. Approximately 30% of these neonates die as a result of pulmonary hypoplasia from the oligohydramnios sequence. Respiratory distress and pneumothorax often worsen the clinical picture. In the severe perinatal form of ARPKD, the kidneys are markedly enlarged because of the cumulative effect of dilatation of all the collecting ducts. Most infants with ARPKD have an elevated serum creatinine, oliguria, and hyponatremia during the first days of life. Infants and children typically develop systemic hypertension, and approximately 60% of cases progress to ESRD by 20 years of age.
Although most infants presenting in the perinatal period ultimately require renal transplantation, the age at transplantation is very variable and occasionally can be delayed until adulthood.

Some children present with liver-predominant symptoms, but all will develop variable degrees of congenital hepatic fibrosis and subsequent portal hypertension. Patients may manifest with hepatic cysts and biliary dilatation often complicated by acute bacterial cholangitis. Portal hypertension and its associated complications tend to become progressively more severe with age but also can occur as the predominant clinical feature initially. The rates of progression of hepatic and renal disease can vary, even among patients carrying the same \( \text{PKHD1} \) mutation, and are independent of each other.

**Pathogenesis of Autosomal Recessive Polycystic Kidney Disease**

To date, all typical cases of ARPKD are linked to a single locus on chromosome 6p12, \( \text{PKHD1} \). \( \text{PKHD1} \) is a large gene containing 66 coding exons, which encode several alternatively spliced isoforms. The gene codes for the protein fibrocystin, a hepatocyte growth factor receptor-like protein that functions on the primary cilia of the renal collecting duct and biliary epithelial cells. The most severe form of ARPKD involves two protein-truncating mutations, whereas milder forms of the disease typically have one or more missense mutations. Dysfunction of fibrocystin leads to abnormal ciliary signaling, which is normally required for regulation of proliferation and differentiation of renal and biliary epithelial cells. The exact function of the numerous isoforms has not been defined. The widely varying clinical spectrum of ARPKD may depend, in part, on the nature and number of splice variants that are disrupted by specific \( \text{PKHD1} \) mutations.

Both the polycystins and fibrocystin are essential for maintenance of the differentiated, polarized, predominantly reabsorptive tubular epithelial phenotype, and for the normal maintenance of low rates of proliferation. Functional disruption of one of these proteins produces many cellular biochemical abnormalities with excessive cell proliferation and excessive fluid secretion predominating.

To date, greater than 300 different \( \text{PKHD1} \) mutations are known. Of these, 60% are missense mutations and 40% are predicted to truncate the protein. Approximately one third of \( \text{PKHD1} \) mutations are unique to a single family. Some ancestral mutations are common in particular populations. In fact, the T36M mutation of northern European origin accounts for approximately 17% of mutant alleles. The average reported mutation detection rate is approximately 80%.

**Treatment of Autosomal Recessive Polycystic Kidney Disease**

Similar to the treatment of ADPKD, blood pressure control with ACEI and ARBs is likely to be quite useful in the treatment of ARPKD. As this renal disease occurs much more frequently in childhood, nutritional issues are likely to require more precise management. Finally, as with ADPKD, there are no proven therapies that will reduce cyst size or stop cyst formation and in general therapies should be considered experimental at this time. Studies in the \( \text{PKHD1} \)-deficient rat demonstrate that V2R antagonists retard renal cystic disease progression, making V2 receptor antagonists an interesting therapeutic option. In addition, small studies have shown that pharmacologic targeting of the EGF receptor pathway rescues the renal and biliary lesions in animal models of ARPKD. These observations suggest that pharmacologic interruption of cAMP-related pathways and EGF receptor-related axis may provide promising therapeutic strategies for patients with ARPKD.

A significant issue for the pharmacological management of ARPKD is the age of the affected patient and the lack of either controlled or adequate kinetic data to support the use of the experimental drugs being tried in ADPKD in this patient population. Nonetheless, each of the drugs with theoretical promise in ADPKD may be considered in this patient population in the future.

**DISORDERS OF RENAL TUBULAR FUNCTION**

There are many disorders that affect the individual tubular segments of the nephron. The following two examples, although not common, are classic in their presentation and involve the handling of sodium chloride by the kidney—one of the most important functions of the kidney. Bartter’s and Gitelman’s Syndromes are a group of autosomal recessive disorders characterized by an abnormality in one of the transporters involved in sodium chloride reabsorption in the nephron. Since the main determinant of intravascular volume (and water reabsorption) is salt reabsorption, the resultant renal salt wasting leads to hypotension and a host of other signs and symptoms for affected patients. There is considerable overlap in the presentations of these similar diseases.

**Bartter’s Syndrome**

The estimated prevalence of Bartter’s Syndrome is one per million people. Classic Bartter’s Syndrome involves an abnormality that limits the ability of the nephron to reabsorb sodium chloride in the Loop of Henle—an important segment of the nephron. The Loop of Henle is the point of the nephron where pharmacological salt wasting is intentionally encouraged by the use of the so-called loop diuretics (i.e., furosemide) in order to cause a diuresis in individuals who have edema and require the loss of water. The key associated biochemical findings in Bartter’s Syndrome include hypokalemia and metabolic alkalosis. Additionally, salt wasting and hypotension can trigger hyperreninemia and hyperaldosteronemia in this patient population.
Clinical Presentation and Diagnosis of Bartter’s Syndrome

Classic Bartter’s Syndrome presents in early life. The initial presentation can be in the perinatal period with polyhydramnios (the in utero equivalent of polyuria) and preterm delivery or in the first few years of life with polyuria, polydipsia, failure to thrive, and frequent episodes of dehydration. The diagnosis of Bartter’s Syndrome is by exclusion. Surreptitious vomiting and diuretic use are the two other major causes of unexplained hypokalemia and metabolic alkalosis in a normotensive or hypotensive patient. Vomiting can be ruled out by detecting a low urine chloride. The use of diuretics is either obvious from the history or can be detected chemically by a urine assay for diuretics.

Distinguishing Bartter’s Syndrome patients from Gitelman’s Syndrome patients is difficult given the marked variability of clinical phenotypes and the overlapping ages at presentation. The genetic diagnosis of this disorder is possible. However, genetic diagnosis is not widely used clinically, primarily because of its availability in only a few research labs, the heterogeneity of the mutations encountered, and the high cost of mutational testing.

Pathogenesis of Bartter’s Syndrome

Bartter’s Syndrome involves defects in key transport proteins in the thick ascending limb of the Loop of Henle. On the apical membrane, the Na-2Cl-K co-transporter (NKCC2), encoded by \( SLC12A1 \), transports sodium and potassium down an electrochemical gradient. For enhancement of the efficiency of this transporter, potassium is recirculated across the apical membrane through the renal outer medullary potassium (ROMK) channel. The apical recycling of potassium establishes a transepithelial voltage gradient that drives the paracellular reabsorption of calcium and magnesium. On the basolateral membrane, sodium is actively transported from the cell via the Na-K-ATPase, whereas chloride exits through at least two chloride channels, predominantly CIC-Kb (encoded by \( CLCNKB \)), and to a lesser degree, CIC-Ka (encoded by \( CLCNKA \)). The subunit protein, barttin (encoded by \( BSDN \)), regulates the function of these chloride channels. Mutations in \( SLC12A1, ROMK1, CLCNKB \), and \( BSDN \) cause Bartter syndrome types I, II, III, and IV, respectively (Figure 24.3a). Within the various causes of Bartter’s Syndrome, there appears to be no direct correlation between the clinical phenotype and the underlying genotypic abnormality.

Treatment of Bartter’s Syndrome

The mainstay of treatment for Bartter’s Syndrome is replacement of fluid, sodium chloride, and potassium chloride. Chronic hypokalemia can be addressed further with either amiloride or aldosterone antagonists. Circulating prostaglandins, which often are elevated in Bartter syndromes I and II, and which are integral to maintaining the electrolyte abnormalities in this syndrome, can exacerbate the polyuria and cause fever as well as gastrointestinal side effects. The cyclooxygenase inhibitors indomethacin, ibuprofen, and COX-2 inhibitors may be effective therapeutic additions in this setting. Some patients, particularly those with Bartter III, have hypomagnesemia that necessitates oral magnesium replacement therapy.

Gitelman’s Syndrome

The estimated prevalence of Gitelman’s Syndrome is one per 400,000 individuals. Gitelman’s Syndrome is also an autosomal recessive disorder of renal tubular function that limits the ability of the nephron to...
reabsorb sodium chloride. However, in this particular disorder it is an abnormality of the distal tubule. Gitelman’s Syndrome tends to be a more benign condition compared to Bartter’s Syndrome, and often is not diagnosed until late in childhood or even into adulthood.

**Clinical Presentation and Diagnosis of Gitelman’s Syndrome**

Gitelman’s Syndrome is diagnosed in childhood or adulthood often because of weakness, tetany, or joint pain. It is not uncommon for the diagnosis in asymptomatic patients to be prompted by an incidental finding of hypokalemia on routine laboratory studies. Patients with Gitelman’s Syndrome have milder renal salt wasting and often have normal or only slightly low blood pressures. Hypokalemia and metabolic alkalosis are important to the diagnosis and as mentioned earlier, hypomagnesemia and hypocalciuria are relatively common.

Similar to Bartter’s Syndrome, diagnosis of Gitelman’s Syndrome is by exclusion. Surreptitious vomiting and diuretic use are again in the differential and they can be ruled out by history, urine chloride, and a urine assay for diuretics. As mentioned previously, distinguishing Bartter’s Syndrome patients from Gitelman’s Syndrome patients is difficult and there may be little clinical utility in doing so. When this cannot be done, the designation of salt wasting nephropathy may be preferred. The genetic diagnosis of this disorder is possible. However, genetic diagnosis is not used clinically because of its limited availability, the heterogeneity of the mutations, and the high cost of mutational testing.

**Pathogenesis of Gitelman’s Syndrome**

The vast majority of patients with Gitelman’s Syndrome have heterogeneous defects in SLC12A3, the gene that encodes the sodium chloride cotransporter NCCT located in the distal tubule (Figure 24.3b). The distal tubule is the point of the nephron where pharmacological salt wasting is intentionally encouraged by the use of the thiazide diuretics (i.e., hydrochlorothiazide) in order to cause a diuresis in individuals who have edema and require the loss of water. There are a small number of patients with the Gitelman phenotype who have been shown to have mutations in CLCNKB, a chloride channel that is also thought to play a role in Bartter’s Syndrome. Hypocalciuria and hypomagnesuria are classical features of Gitelman Syndrome, but the pathogenic mechanisms for this finding are not known.

**Treatment of Gitelman’s Syndrome**

As with Bartter’s Syndrome, the mainstay of treatment is the replacement of fluids, sodium chloride, and potassium chloride. These patients are also more likely to require magnesium replacement. Chronic hypokalemia can be addressed further with either amiloride or aldosterone antagonists. Circulating prostaglandins are not elevated in Gitelman’s Syndrome and therefore inhibitors are of little benefit in Gitelman’s Syndrome.

**KEY CONCEPTS**

- The pathogenesis of focal segmental glomerulosclerosis involves effacement of podocyte foot processes. This can be due to derangements in structural components and intracellular signaling of the slit diaphragm, podocyte cell membrane, or actin cytoskeleton. Genes important to both familial and sporadic FSGS include nephrin (*NPHS1*), podocin (*NPHS2*), ACTN4, and TRPC6. Treatment response to FSGS is not favorable, and a substantial proportion of patients progress to ESKD.
- Fabry Disease is an X-linked lysosomal storage disease due to mutation in the gene for the α-galactosidase enzyme that is responsible for catabolism of glycosphingolipids, important components of cell membranes. The classical form of Fabry Disease begins in early childhood with acroparesthesias and angiookeratomas, and progresses to early-onset kidney and cardiovascular disease in adulthood. X-inactivation and mosaicism in women and severity of genetic mutation, modifying genes, and epigenetics in all patients account for the wide variability in disease manifestations.
- Renal cysts of tubular epithelial cell origin are a hallmark of autosomal dominant polycystic kidney disease (ADPKD) and autosomal recessive polycystic kidney disease (ARPKD). Causative genetic loci are PKD1 and PKD2, which code for the polycystins, and PKHD1, which codes for fibrocystin in ADPKD and ARPKD, respectively. Due to the size and complexity of these genes, diagnosis is still made predominantly using radiologic findings and family history.
- Bartter’s and Gitelman’s Syndromes are salt wasting diseases of the kidney that lead to acid-base and electrolyte disturbances. They can be caused by mutation in a number of genes that encode proteins of the thick ascending limb in Bartter’s Syndrome or in the distal tubule in Gitelman’s Syndrome.

**SUGGESTED READINGS**
