Heptinstall’s
Pathology
of the Kidney
SEVENTH EDITION
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Pathology of the Kidney

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To my loving wife, Yvonne, my wonderful daughters, Jennifer and Caroline, and my amazing granddaughters, Olivia and Augusta.

—J. Charles Jennette

In loving memory of my parents, Caroline and Arthur Olson.

—Jean L. Olson

To my lovely wife, Jean, and our wonderful daughter, Lindsay.

—Fred G. Silva

To my loving and supportive husband, Edward Imperatore, my sons, Edward and Paul, and my grandson, Edward James.

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This seventh edition of Heptinstall’s Pathology of the Kidney has the greatest increase in new knowledge and new insights into kidney diseases of any prior new edition. This comprehensive text maintains the excellence established by Robert H. Heptinstall, who edited and to a considerable degree authored the first four editions of this classic text first published in 1966. Since the publication of the sixth edition in 2007, there have been extraordinary advances in the understanding of the cellular, molecular, and genetic basis for kidney diseases; in the knowledge of pathologic and clinical manifestations of kidney diseases; and in the utilization of pathologic findings for directing new and more precise treatment of kidney diseases. This seventh edition has been thoroughly updated to include in-depth reviews of these important new advances that have clarified our understanding of kidney diseases, redirected research on the mechanisms of kidney diseases, modified the pathologic diagnostic evaluation of kidney diseases, and improved the treatment and prevention of kidney diseases.

The authors who contributed to the seventh edition are among the most capable and accomplished renal pathologists in the world. All of these authors have extensive hands-on experience with diagnostic renal pathology, teaching renal pathology at major medical centers, and advancing the field through clinical and translational research. They have contributed thousands of articles to the literature on renal pathology. In fact, many of the major advances in our current understanding of renal pathology have been made by authors of chapters in this book. The editors thank all of the authors of the seventh edition for their truly outstanding contributions.

We are saddened by the recent passing of two extraordinary real pathologists, Kendrick A. Porter and Gary S. Hill, who authored stellar chapters in earlier editions and were dear friends of Dr. Heptinstall. We are thankful for their many personal and professional contributions to our field of renal pathology. All of the editors and authors are honored by the opportunity and challenge afforded us by Dr. Heptinstall to sustain his preeminent book on renal pathology. We and all others who are interested in the study of kidney diseases are forever indebted to him for establishing this classic text. We are convinced that the seventh edition of Heptinstall’s Pathology of the Kidney is the most comprehensive, most authoritative, most thoroughly referenced, and best illustrated book on renal pathology ever produced.

J. Charles Jennette, MD
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he first edition of *Pathology of the Kidney* by Robert H. Heptinstall marked the watershed between autopsy- and biopsy-based studies of renal disease in human beings. Before the *Pathology of the Kidney*, renal pathology textbooks related the clinical evolution of “renal syndromes” and the associated autopsy findings. The percutaneous renal biopsy initially described by Iversen and Brun only 15 years prior to the publication of *Pathology of the Kidney* allowed a more dynamic view of kidney disease, and the text drew heavily on renal biopsy studies and immunofluorescence and electron microscopic findings in renal tissue. This new information had to be integrated with the autopsy-based renal literature for, as “Heppy” wrote in the preface to the first edition, “we are almost completely ignorant of the sequence of events that takes place during the evolution of a given disease, and … the nomenclature in use at the moment is most unsatisfactory. Most of our concepts and nomenclature of renal disease have been based on kidneys studied at autopsy, which except in rare instances represent the end stage of a process that has been going on for years. The renal biopsy has presented us with histological pictures that in the light of our present concepts are not only difficult to interpret but defy satisfactory labeling.” The enduring contribution of *Pathology of the Kidney* is that it brought order out of chaos and in doing so defined the central issues of modern renal pathology. Over the years, this classic textbook and its subsequent editions have provided guidance and insight not only to nephropathologists but also to nephrologists, renal physiologists, and the entire renal community.

The first edition of *Pathology of the Kidney* is also an outstanding example of medical authorship. The book was written with wit and style, and it is scholarly, authoritative, and comprehensive. This monumental achievement is even more remarkable when one considers that the first four editions were essentially monographs.

How Heppy accomplished his goals of presenting biopsy-based pathology, relating it to the existing classifications, and identifying a pathogenetic sequence deserves exposition. Much of the text is written in the first person because it was based on his extensive experience with renal pathology in biopsy and autopsy material. When writing on disputed topics, however, he was careful to quote “widely the opinions of others.” A complete and critical reading of the literature allowed him to correlate biopsy studies of acute and evolving renal diseases with the end-stage findings and nomenclature from autopsy studies. In the few areas where he did not have personal experience, he was exact in quoting published material, and whenever possible he reviewed the pathology material obtained by others. The superb illustrations complemented the text by demonstrating the pathologic lesions in all their phases allowing a pathogenetic connection between acute and end-stage lesions. Finally, his experience as an experimental pathologist aided him in critically evaluating and identifying relevant experimental studies.

Late Ramzi S. Cotran, no mean scholar himself, acknowledged the comprehensive and scholarly nature of the *Pathology of the Kidney* by insisting that it was the place to begin not only the workup of a difficult case but also an experimental study. Thus, Heppy has provided a fair template for those who would write chapters in pathology textbooks. In so far as we succeed, the credit is his, and if we fail, the responsibility is ours.
The task of presenting a comprehensible account of the pathology of the kidney is surprisingly difficult, as I have found to my cost over the past 3 years. The main difficulties are twofold: first, we are almost completely ignorant of the sequence of events that takes place during the evolution of a given disease and, second, the nomenclature in use at the moment is most unsatisfactory. Most of our concepts and nomenclature of renal disease have been based on kidneys studied at autopsy, which except in rare instances represent the end stage of a process that has been going on for years. The renal biopsy has presented us with histologic pictures that in light of our present concepts are not only difficult to interpret but defy satisfactory labeling. Many of these pictures are doubtless early stages of a process whose end stage we already recognize, but others very likely represent processes with which we are quite unfamiliar. Only by conducting intelligently planned studies with repeat biopsies over a long period of time can we hope to resolve these problems, and a greater degree of cooperation between the various groups of investigators will be required than has been the case up to now.

Accepting the imperfect state of our knowledge, I have attempted to present an account of the more common diseases that affect the kidney. The book is mainly for the pathologist and the internist specializing in renal problems, but it is hoped that it will be of use to others, such as the urologist and the obstetrician.

The pathology of the various diseases has been presented in the light of both autopsy and biopsy experience, and although many of the views expressed are my own, this being an author’s privilege, a balanced presentation has been attempted by quoting widely the opinions of others. The clinical sections are of necessity brief, for these aspects have been authoritatively dealt with on numerous occasions by people better qualified than I am. Experimental contributions have been quoted when appropriate, and in most chapters, the role of the newer techniques such as electron and fluorescence microscopy has been described. The traditional chapter on renal physiology has been omitted, and for this, I offer no apology. This is a highly complex subject that can hardly be compressed into one chapter; it is also one that I am not competent to discuss. Renal tumors are not discussed because they are adequately considered in existing texts on surgical pathology.

I have been fortunate in persuading Dr. J.M. Kissane to write chapters on the development and congenital defects of the kidney and Dr. Kendrick A. Porter to write on renal transplantation. These two former colleagues of mine are experts in their fields, and their respective chapters amply reflect their competence.

I am very grateful to all those who supplied us with illustrations and material from which illustrations were made. Professor Paul Beeson was asked to read the two chapters on pyelonephritis and promptly replied with four single-spaced pages of comments and suggestions; I was chastened but grateful. Dr. Abou Pollack has been a constant source of pearls of wisdom and exotic material; I am much indebted to this fine pathologist. Most of the photomicrographs for my own chapters were prepare by Mr. Chester Reather, and these, as always, were of matchless quality. The wearisome job of checking the references was bravely carried out by Miss Virginia Shriver, and her efforts, and those of the staff of the William H. Welch Medical Library at Johns Hopkins, are much appreciated. The most difficult job of all was done by Miss Mary Lakin, my secretary, who, starting out with scraps of paper adorned by nearly undecipherable handwriting, restored order out of chaos and produced the final manuscript. It is impossible to thank her enough.

Lastly, it is a great pleasure to acknowledge the help and stimulus over the years of Dr. A.M. Joekes. The biopsies we saw together provided a nucleus for many of the thoughts that have been expressed in this book, and to him belongs much of the credit (or blame) for the finished product.

Robert H. Heptinstall
Dr. Jennette thanks his wife, Yvonne, daughters, Jennifer and Caroline, and granddaughters, Olivia and Augusta, for forgiving the time spent away from them pursuing his passion for renal pathology. He thanks Dr. Fred Dalldorf for sparking his interest in renal pathology, Dr. Ron Falk for his decades of stimulating professional collaboration, and the many nephropathologists and nephrologists who have shared their insights on kidney disease with him. He especially thanks the nephropathology fellows and faculty who have been his associates at UNC over the years, including current faculty Volker Nickeleit, Sharan Singh, and Adil Gasim.

Dr. Olson thanks Drs. Manjeri Venkatachalam, Helmut Rennke, and Ramzi S. Cotran for their help during the formative part of her career. She also gives special thanks to Dr. Robert H. Heptinstall, her mentor and friend, for steering her toward renal pathology and for nurturing her early career.

Dr. Silva thanks all of the members of the Southwest Pediatric Nephrology Group (under the able direction of Dr. Ron Hogg) for the renal biopsy material used in the preparation of his chapters. He also thanks Dr. Conrad L. Pirani for all his years of mentoring.

Dr. D’Agati thanks above all her husband and children for the countless hours taken from them to pursue her career in renal pathology. She thanks Conrad L. Pirani for fellowship training, Jerry Appel and Jai Radhakrishnan for their valuable expertise and enthusiasm in clinical-pathologic studies, and the wonderful Columbia renal pathology team of Glen Markowitz, Barry Stokes, Leal Herlitz, Samih Nasr, and our many talented fellows for their support and stimulating collaborations. She respectfully acknowledges the thousands of patients with renal disease whose biopsies have provided a fascinating challenge and continuing education over the past three decades.
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ACUTE TUBULAR INJURY

Acute tubular injury (ATI) is a major cause of acute renal failure (ARF), a clinical syndrome characterized by rapid deterioration in renal function and glomerular filtration rate (GFR) over a relatively short period of time, ranging from hours to days. The result is a sudden inability to maintain normal fluid and electrolyte homeostasis. The acute reduction in renal function can be the result of the impairment of blood flow (so-called prerenal failure), obstruction of the urinary collecting system (so-called postrenal failure), or a variety of intrinsic renal diseases ranging from glomerulonephritis to interstitial nephritis to ATI (Fig. 26.1), which is the primary topic of discussion in this chapter. Based on the available literature, which uses somewhat variable definitions, ARF is commonly encountered in hospitalized patients, has a variety of risk factors and etiologies, and is associated with increased mortality (1). Its frequency ranges from 1% at admission to the hospital to as high as 31% in patients undergoing cardiopulmonary bypass or with other high-risk conditions. Clinical manifestations range from mild increase in serum creatinine (sCr) to anuric renal failure (2). A consensus panel of the American Society of Nephrology recommended that “acute renal failure” be replaced by the term acute kidney injury (AKI). The term AKI could be used to distinguish early from more advanced stages of kidney disease, in which there is more overt “failure” of clearance by the kidney. Use of the more general term AKI highlights the predictive value of acute or small changes in sCr and facilitates recognition of renal injury and dysfunction at earlier stages of disease, since even transient rise in creatinine is correlated with increased risk of death (3).

In 2004, a consensus definition was published, which included both GFR and urine output criteria (Table 26.1). The earliest phase, risk of renal dysfunction, was defined by an increase in sCr by 1.5 times, GFR decrease of more than 25%, or urine output below 0.5 mL/kg/h for 6 hours. Renal injury was defined by sCr increase by 2 times, GFR decrease of more than 50%, or urine output less than 0.5 mL/kg/h for 12 hours. Renal failure was defined as sCr increase by three times (or over 4 mg/dL), GFR decrease by 75%, urine output below 0.3 mL/kg/h for 24 hours, or anuria for 12 hours. Added to loss of function and end-stage renal disease, these comprise the “RIFLE” criteria (4). These criteria appear to be clinically relevant and have been widely used (5). They were modified in 2007 as the AKIN (acute kidney injury) criteria, eliminating the "loss-of-function and ESRD" categories (6). AKIN criteria defined AKI as “functional or structural abnormalities or markers of kidney damage including abnormalities in blood, urine or tissue tests or imaging studies present for less than 3 months.” However,
both classifications use diagnostic criteria of renal impairment (urine output, rise in sCr) that manifest at a late stage of injury and rely on knowledge of baseline creatinine (7). Inclusion of other more sensitive criteria, including biomarkers, may enhance definition criteria (8). There has also been lack of precision in the use of the term acute tubular injury/necrosis. The term should be reserved for the clinical pathologic entity of intrinsic renal failure that is the result of either an ischemic or toxic insult to the kidney, with evidence of tubular injury/dysfunction such as altered fractional excretion of sodium (8) and potentially other more specific biomarkers, when other causes have been excluded. As a result of the lack of uniformity in terminology, the percentage of cases of ARF that can be attributed to “acute tubular necrosis/injury” are difficult to accurately ascertain, but the condition is likely responsible for the majority of cases of ARF that require acute renal replacement therapy. The term acute tubular necrosis itself is a misnomer, since necrosis, while classically a feature of animal models, is only one morphologic manifestation of clinical ATI. It should also be noted that morphologic evidence of frank tubular necrosis is not a frequent feature in kidney biopsies obtained in the context of clinical ARF; however, morphologic changes of sublethal tubular injury are usually present. Just as in the clinical classifications, however, morphologic signs of injury appear in a later stage of injury; more sensitive markers are required to identify early tubular cell injury. The term acute tubular injury is more accurate and will be used throughout this chapter.

**Historical Background**

It was not until World War I that acute renal dysfunction was recognized as a distinctive clinical and pathologic entity. Hackradt (9) described what he called “vasomotor nephrosis” following crushing injuries. In a review of autopsy material, Minami (10) described the presence of pigment casts in medullary tubules associated with tubular changes and an interstitial infiltrate and suggested that myoglobinuria and subsequent precipitation in the tubules were factors involved in producing the observed anatomic and functional renal abnormalities. Shortly
of such kidneys frequently did not demonstrate significant necrosis of tubular cells associated with rupture of the adjacent tubular epithelium with denudation of the basement membrane, which remained intact. In the second type, which they termed the tubulorrhexic lesion, intratubular hemoglobin and myoglobin casts associated with focal necrosis of tubules, interstitial edema, and mild interstitial inflammation localized to specific portions of the nephron in the “crush syndrome or traumatic anuria.” This finding led to the hypothesis that tubular obstruction by necrotic debris and precipitated pigment was the prime cause of the observed oliguria.

Bywaters and Dible (13), however, believed that obstruction alone could not explain all the clinical findings or the abnormal character of the urine that was produced by such patients. Because patients with ARF had urine that was quite abnormal and resembled an unaltered glomerular filtrate, and because there was a marked discrepancy between the degree of anatomic change and the severity of the oliguria, they postulated that other factors must play a part. Lucke (15) emphasized that the discrepancy between structure and function could be related to the observed localization of histologic changes to the distal nephrons, and he coined the term lower nephron nephrosis.

Oliver et al. (16) used nephron dissections to study cases of ARF, and they were able to show two distinct types of renal tubular injury. In the first, as a result of the direct cytotoxic effect of a specific nephrotoxin, there was segmental necrosis of the proximal tubular epithelium with denudation of the basement membrane, which remained intact. In the second type, which they termed the tubulorrhexic lesion, there was focal necrosis of tubular cells associated with rupture of the adjacent basement membrane, allowing communication of the tubular lumen with the interstitial tissue, a lesion most commonly seen in the distal portions of the proximal tubule, most likely ischemic in origin. The focal and patchy nature of the necrosis, which was usually not associated with any interstitial reaction, was thought to be the reason that random histologic sections of such kidneys frequently did not demonstrate significant pathologic change. Oliver et al. suggested that these lesions could lead to the leakage of tubular fluid into the interstitial tissue, diminishing the amount of urine produced. Such leakage could cause a rise in intrarenal pressure, which could further potentiate oliguria by compression of capillaries, resulting in diminished glomerular filtration.

While these investigators were concentrating on the tubular changes, Goormaghtigh (17,18) called attention to the renal arteriolar changes in kidneys of patients with the crush syndrome. He observed considerable hypertrophy and an increase in granularity of the juxtaglomerular cells in the kidneys of patients with ARF and theorized that these cells produced a vasoactive or prevasoactive substance that could act on the renal vasculature. He suggested that the anuria observed in the crush syndrome was the result of vasoconstriction and postulated that glomerular hemodynamic changes would result in the diminution of glomerular filtration, emphasizing decreased glomerular function as a mechanism of oliguria.

Based on direct observation of the kidney as well as angiographic and morphologic studies of intrarenal vascular patterns, Tueta et al. (19) proposed that the fundamental defect in the crush syndrome was a reduction of glomerular filtration as a result of the diversion of blood away from the outer cortical glomeruli through a juxtaglomerular shunt. Brian et al. (20,21) produced even more convincing evidence by measuring renal hemodynamics in vivo. Sheehan and Davis (22) and Sevitt (23) also believed that ischemia was important, but they suggested that the mechanisms of action were related to vascular damage following an initial period of ischemia, which prevented adequate reperfusion once blood flow had been established. Hollenberg et al. (24,25) studied patients with ARF following a variety of initiating injuries and noted that it was impossible to see the cortical arteries in such patients; they also documented disappearance of the cortical flow component of xenon washout from the kidney. Munck (26) verified that such a decrease in blood flow was sufficient to result in renal hypoxia. These early studies suggested several physiologic mechanisms of action for the resultant oligoanuria, including tubular obstruction, back leakage of tubular fluid, and changes in hemodynamics resulting in decreasing glomerular filtration.

The advent of micropuncture techniques led to the investigation of several animal models of ARF to identify the pathophysiologic mechanisms of action in greater detail. Oken et al. (27) studied experimental mercury- or glycerol-induced ARF, demonstrating that glomerular filtration progressively diminished as oliguria developed and suggesting that suppressed filtration was the key pathophysiologic factor. Early work in our own laboratory (M.K.) studied two different models of ARF (28), potassium dichromate–induced toxic cellular damage to the early (S1–2) part of the proximal tubule and administration of purified human globin, producing an intrarenal obstructive lesion of the distal nephron. Decrease in urine flow was accompanied by a diminution of the total and individual nephron GFR associated with a decrease in the tubular reabsorptive capacity, and there was evidence of mechanical tubular obstruction, reflected by an elevation of free-flow intratubular pressure. In addition, the glomerular filtration pressure appeared to be diminished, suggesting that the decreased glomerular blood flow and glomerular filtration were the result of preglomerular arteriolar constriction, mediated by activation of the local renin-angiotensin system. Studies of renal blood

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**TABLE 26.1** Clinical phases of AKI

1. Risk of renal dysfunction
   - Increase in sCr by 1.5 times OR
   - Decrease in GFR >25% for 6 h OR
   - Urine output <0.5 mL/kg/h for 6 h

2. Renal injury
   - Increase in sCr by 2 times OR
   - Decrease in GFR >50% for 12 h OR
   - Urine output <0.5 mL/kg/h for 12 h

3. Renal failure
   - Increase in sCr by 3 times or >4 mg/dL OR
   - Decrease in GFR by 75% or more for 24 h OR
   - Urine output <0.3 mL/kg/hr for 24 h OR
   - Anuria for 12 h

sCr, serum creatinine; GFR, glomerular filtration rate.
flow distribution demonstrated that a diminution of outer cortical flow correlated best with decreased glomerular filtration (29,30). These and other studies led to a proposal that tubular epithelial injury induced either by ischemia or by a toxin could be sublethal but had to be severe enough to result in decreased epithelial transport activity, which then would result in decreased tubular sodium reabsorption and local activation of the renin-angiotensin system. This, in turn, would alter glomerular hemodynamics and result in decreased glomerular filtration. Decreased tubular urine flow associated with the shedding of cellular debris and the presence of Tamm-Horsfall protein would result in tubular obstruction. When combined with focal areas of necrosis, as demonstrated by the microdissection studies of Oliver, this could lead to a back leakage of fluid, all of which contribute to the end result of oliguria. The term acute renal success was suggested by Thurau and Boylan (31), interpreting the pathophysiologic changes of decreased glomerular filtration as a defense against loss of intravascular volume caused by the inability of the damaged tubules to reabsorb the glomerular filtrate.

Although these studies primarily focused on pathophysiology and did not address the cellular pathologic characteristics associated with the oliguria of ARF, they did note the discrepancy between structure and function and emphasized the central role of alteration of renal tubular epithelial transport function by ischemic or toxic injury. Studies by Rosen and colleagues on renal pathology in experimental and human ATI have also emphasized the importance of sampling the nephron segments that are most vulnerable to a particular type of injury (32). This section of the chapter will focus on ATI caused by ischemia and/or nephrotoxins. Clinical features, pathology, and pathogenesis will be discussed for ischemia and toxic injury in general and for the major nephrotoxic agents.

**Clinical Presentation**

Patients with injury to the tubular epithelium have clinical and laboratory evidence of tubular dysfunction that is sometimes quite subtle. Loss of normal resorptive function may lead to polyuria, glucosuria, phosphaturia, or aminoaciduria; Fanconi syndrome has occasionally been reported. With more severe injury, intact and necrotic tubular cells appear in the urine sediment, individually or in cast form. Patients may become oliguric. In some cases, crystals, leukocyturia, and hematuria may also be detected on urinalysis.

Enzymuria is a useful marker for tubular cell injury; it is more sensitive than a rise in sCr and may be used to some extent to gauge the severity of cell injury. Elevated levels of β₂-microglobulin or enzymes may be detected in the urine and have been used in many clinical studies as markers of tubular toxicity. The presence in the urine of brush border enzymes, such as alkaline phosphatase and gamma-glutamyl transpeptidase, may reflect mild cellular injury. The appearance of lysosomal enzymes, such as N-acetyl glucosaminidase, and of cytoskeletal elements reflects more severe injury and cell loss from the tubular epithelium. Measurement of these factors has been used as a noninvasive marker of injury to the renal tubule in both ischemic and toxic tubular injury (33–35). New unbiased genomic and proteomic techniques are leading to the discovery of many potential biomarkers that may be useful in detecting early tubular injury. Biomarkers proposed for early detection of AKI include proteins present in urine (kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated ligand (NGAL), IL-18, cysteine-rich-61 (cyt61), Na(+)—H(+) antipporter isoform 3 (NHE3), lipocalin, actin), and, serum (cystin C, tumor necrosis factor-α (TNF-α) receptor, and NGAL) (33,34,36,37). Many of these markers can be found in prerenal azotemia as well as in renal injury, reflecting a continuum of ischemic injury. Differentiation of the two conditions relies on response of creatinine to expansion of circulating volume. Use of biomarkers for this purpose will likely require assay of a panel of candidate markers rather than a single marker.

ATI often results in reduction of GFR, with development of acute renal insufficiency and ARF. The acute reduction in renal function results in both biochemical and clinical abnormalities, related to the inability of the kidney to eliminate water, metabolic by-products, and acids and to regulate electrolyte balance. Oliguria is classically seen as an initial feature of many cases of ATI, but nonoliguric ARF is commonly recognized as well. While altered urine output is part of the definition of AKI, urine output can only be accurately measured in patients with a urinary catheter and is affected by blood volume status and diuretic use (8). Significant laboratory findings include elevations in blood urea nitrogen, sCr, and serum potassium; as noted above, rise in creatinine/fall in creatinine clearance (combined with urine output and other factors) defines AKI. Urinary sodium excretion is markedly amplified, with increased fractional excretion of sodium consistent with a decreased resorptive capacity of the damaged tubules.

Patients with toxic injury to the tubular epithelium also often show signs of renal failure. There is active research on biomarkers of nephrotoxic AKI (34). Hemoglobin and myoglobin are endogenous proteins that can function as nephrotoxins when they are present in large concentrations in the urine. ARF is associated with hemoglobinuria following acute hemolysis in patients with transfusion reactions and in patients with Plasmodium falciparum malaria. While the toxicity of hemoglobin may contribute to the pathogenesis of ARF in these instances, ischemia and microcirculatory disturbances probably play a greater role in its development. Myoglobinuria stemming from rhabdomyolysis as a result of trauma, viral infection, or heat stress produces a similar clinical picture. Rhabdomyolysis associated with cocaine abuse has also been demonstrated to result in ATI, as discussed in this chapter in the section on nephrotoxins. High concentrations of filtered light chains may also produce ATI, often with crystalline deposits in tubular cells (see Chapter 22).

A variety of exogenous agents can also cause ATI (Table 26.2). Between 15% and 30% of AKI is caused, at least in part, by exposure to drugs (1,38,39). The use of potentially nephrotoxic drugs such as aminoglycoside antibiotics or nonsteroidal anti-inflammatory drugs, which can accentuate renal ischemia, may predispose seriously ill patients to develop overt ARF. It must be noted that association of a particular drug or toxin with renal injury and dysfunction may be missed or may be difficult to establish as causative, especially in complex clinical settings. Repeated correlation of exposure and injury help to establish nephrotoxicity, and experimental models are often useful in defining the mechanism of injury.

Depending on the specific drug or toxin causing injury, renal dysfunction may occur soon after exposure or after a predictable interval, as is seen with aminoglycosides. Most patients experience a fall in GFR that is detectable on clearance
Antiviral agents
Nucleoside analogs
Antiretroviral agents
Antibiotics
Aminoglycosides
Amphotericin B
Cephalosporins
Colistin/polyoxymyxin B
Rifampicin
Sulfonamides
Vancomycin
Immunomodulatory agents
Calcineurin inhibitors
IVIG
Sirolimus
Antineoplastic agents
Cis-platinum
Other
Radiologic contrast media
Narcotics
Anesthetics
Herbal medications

*Discussed in Chapter 25.

Antiviral Agents. The nephrotoxicity of antiviral drugs has been reviewed (44–48). Acyclovir, an early nucleoside analog, was reported to be associated with renal dysfunction, and there is a significant incidence of renal dysfunction with newer agents as well. Tubular injury may lead to proximal tubulopathy and even Fanconi-like syndrome (cidofovir, tenofovir, foscarnet), distal tubular acidosis (foscarnet) and nephrogenic diabetes insipidus (foscarnet, tenofovir). The nucleoside reverse transcriptase inhibitors didanosine, stavudine, and lamivudine have rarely been associated with renal tubular dysfunction with acidosis and hypophosphatemia. Adefovir has been reported to produce proximal tubulopathy in up to 50% of patients at high doses (49). A variety of these agents have been associated with renal failure, including acyclovir (50,51), foscarnet (52), ganciclovir (53), cidofovir (54), indinavir (55,56), tenofovir (57,58), ritonavir (59), and adefovir (49). The widely used agent tenofovir has a rate of renal failure of less than 1% in those without preexisting disease (58), though renal failure is more frequent in those with preexisting disease. Risk factors for toxicity include baseline renal dysfunction, low CD4 counts, low body weight, and concomitant use of lopinavir or didanosine (47). Some agents are associated with crystalluria and/or nephrolithiasis (acyclovir, ganciclovir, indinavir, and much less commonly with the newer protease inhibitors atazanavir, saquinavir, nelfinavir, and lopinavir-ritonavir), and flank or abdominal pain may occur. Incidence may be up to 20% with antiretroviral regimens including indinavir, and more frequent when indinavir is pharmacologically boosted with ritonavir. Crystals are needle shaped and birefringent under polarized light and can be seen in voided urine. Proteinuria has also been described with cidofovir, more commonly than ARF.

Toxicity is dose dependent, and volume depletion may predispose to toxicity. For some agents such as tenofovir, toxicity depends on accumulation of drug in proximal tubular cells and may take weeks to months for injury to be detected (44). Renal failure often resolves rapidly when these drugs are discontinued, and the patient may be rechallenged with a lower dose of the drug without development of renal dysfunction. However, occasional cases of chronic renal failure have been reported in patients receiving cidofovir (60), indinavir (48), and tenofovir (57,61). Renal tubular functional defects may persist as well. Hydration to maintain diuresis may prevent renal toxicity, especially in those agents causing crystalluria. With acyclovir, toxicity has been described frequently with intravenous administration, but cases have been reported with oral administration as well. Combination with other nephrotoxic agents may enhance toxicity (57). Older age and preexisting renal failure are risk factors for ARF in patients receiving acyclovir. Preexisting renal impairment, common in the HIV population, is also a risk factor for ARF induced by tenofovir, cidofovir, foscarnet, indinavir, interferon, and ritonavir, and dosage adjustment is required. Because of renal toxicity, adefovir, cidofovir, and indinavir are not approved/recommended for primary antiretroviral therapy.

Antibiotics. Aminoglycoside antibiotics have long been recognized as nephrotoxic and ototoxic. They continue to be used, however, because of their efficacy in treating gram-negative infections. The incidence of ARF in patients treated with gentamicin is about 20% (62). The nephrotoxicity of the various aminoglycosides is greatest in those with the largest number of free amino groups (63). Streptomycin, the least toxic, has two amino groups; those with intermediate toxicity, such as gentamicin, tobramycin, and kanamycin, have four to five groups, and neomycin, which is the most toxic, has six free amino groups. Changes in dosing to once-daily administration have evolved to avoid nephrotoxicity. Once-daily dosing...
with monitoring of trough levels may enable avoidance of significant renal toxicity, even in elderly patients (64). However, with prolonged treatment, differences between once-daily and twice-daily dosing diminish (65). The toxicity of aminoglycosides may be potentiated by ischemia or other drugs, including thalidomide (66).

Gentamicin is a broad-spectrum antibiotic that has intermediate nephrotoxicity, and kanamycin also has an intermediate potential for nephrotoxicity. In humans, gentamicin alone may cause elevation of serum urea nitrogen (SUN) and sCr, although the incidence is difficult to assess because of a variety of concomitant clinical variables, including advanced age, presence of preexisting renal damage, or administration of other drugs that are potentially nephrotoxic. The frequency with which renal toxicity is reported varies from study to study, in part because of variable criteria for defining significant elevations in SUN and creatinine. Incidences ranging from 8% to 37% have been reported. Identified risk factors include advanced age, poor nutritional status, severe systemic illness, and administration of other drugs, including amphotericin B, vancomycin, methicillin, or cephalosporins, which are themselves potentially nephrotoxic.

Onset of a detectable rise in sCr is typically delayed for 8 to 10 days from initiation of therapy. Renal failure is usually mild, and most patients recover. Enzymuria may be detected in cases without elevations in sCr, suggesting the presence of subclinical injury in many patients. Occasional cases have been reported in which proximal tubular dysfunction is severe enough to produce Fanconi syndrome (67). Neomycin is the most nephrotoxic of the aminoglycoside antibiotics. Because it is poorly absorbed from the gastrointestinal tract, it is used primarily for parenteral use and has caused deafness and renal damage. ARF, usually of an oliguric type, has been reported; recovery has been reported in most patients (68,69). ARF occurs most commonly after intravenous or intramuscular administration of the drug, although it has been recorded after oral administration as well (69).

**Amphotericin B**

Nephrotoxicity is the side effect that most commonly limits the use of this important antifungal agent. Renal insufficiency is frequently observed, with a fall in the GFR and renal blood flow. In one large prospective series of patients being treated for cryptococcal meningitis, 26% had an increase in sCr level of more than 2 mg/dL (70). Such renal failure is usually reversible, but renal function may be permanently impaired in 40% of patients who receive more than 5 g of amphotericin (71). In addition, there is a defect in acid excretion by the tubules, resulting in renal tubular acidosis (72), which may precede a significant fall in the GFR and is generally reversible. A common side effect is an impaired ability to concentrate urine (73); this may be present without azotemia. Liposomal and lipid complex formulations may reduce nephrotoxicity (74). The different formulations are probably comparable (75).

**Cephalosporins**

While acute (proximal) tubular injury is rare with the penicillins and uncommon with the current generation of cephalosporins, it is a greater risk with the penicillins. The cephalosporin group of antibiotics comprises several “generations” of these useful agents, defined on the basis of antimicrobial activity. The first generation includes cefazolin, cephalexin, and cefadroxil. Cefamandole, cefonicid, cefuroxime, cefaclor, cefoxitin, and cefotetan are second generation, while the third generation includes ceftazidime, cefotaxime, and ceftriaxone. Cefepime is a fourth-generation cephalosporin that is more resistant to β-lactamase than the previous agents. Many of these drugs may be nephrotoxic (76). Cephalaridine and cephalexin are the most toxic of the group and are no longer used clinically in the United States but are used experimentally for toxicity studies. On the other hand, cefazidime and cefepime are not nephrotoxic.

The toxic cephalosporins are most likely to produce renal failure in patients with preexisting renal insufficiency, in those with drug overdose, and in those receiving other antibiotics or furosemide, probably related to the ability of furosemide to prolong the half-life of the cephalosporins. Many of the patients reported to have nephrotoxicity owing to cephalosporins are acutely ill with severe infections, and many are elderly. Cephalexin given alone or with gentamicin, tobramycin, or other agents can cause ARF in humans or can worsen preexisting renal insufficiency. The ARF is usually reversible. Cefalexin is less likely to cause nephrotoxicity, but acute renal dysfunction has been reported, with “acute tubular necrosis” (77,78). ARF with tubular proteinuria has been described with a combination of ceftriaxone and acyclovir (79) and cefotaxime and vancomycin (80).

**Polymyxin B and Colistin**

Polymyxin B and colistin (polymyxin E) are older antibiotics that are reemerging for treatment of multiple-drug–resistant gram-negative bacteria and are used for “salvage” therapy in critically ill patients. These antibiotics have well-recognized nephrotoxicity. At lower doses, proteinuria, casts, and hematuria may be seen, and at higher doses, renal failure occurs. Reduction in dosing, avoidance of coadministration of other nephrotoxic agents, and other supportive measures likely explain a lower incidence of nephrotoxicity in more recent clinical series compared to older reports (81,82). Incidence of nephrotoxicity in recent studies has been 10% to 24%, with comparable toxicity for colistin and polymyxin B regimens (83–86). When there is preexisting impaired renal function, smaller doses can produce renal symptoms. Renal failure may occur with oliguria. Recovery is usual after withdrawal of the drug.

**Vancomycin**

Vancomycin is a glycopeptide antibiotic that has been associated with nephrotoxicity and ARF since its introduction (87), limiting clinical use of the drug until the advent of methicillin-resistant *Staphylococcus aureus* (MRSA) and other drug-resistant organisms. Nephrotoxicity was initially reported at low rates of ≤5% with standard dosing (88), though higher rates were reported with use of concomitant nephrotoxic agents (89). With newer recommendations for use of higher doses for MRSA and hospital-acquired infections, increased rates of nephrotoxicity have been reported over the past decade (90–92). Risk factors include African American race, initial trough level, duration of treatment, and concomitant aminoglycoside use.

**Immunosuppressive/Immunomodulatory Agents**

**Cyclosporine**

Cyclosporine (CsA) is widely used in the prevention and treatment of transplant rejection and to treat autoimmune disease. The major side effect is nephrotoxicity, which is to some extent dose dependent. Both acute and chronic toxic effects have been described (93). With nephrotoxicity broadly
defined to include an asymptomatic mild decline in the GFR, it is likely that many patients treated with immunosuppressive doses of CsA experience nephrotoxicity. When more overt CsA-induced renal failure is superimposed on mild functional toxicity, it may manifest in the form of one or more clinical syndromes: acute reversible renal functional impairment, delayed renal allograft function, tubular cell effects, acute vasculopathy (thrombotic microangiopathy), and chronic nephropathy with interstitial fibrosis.

The occurrence of acute reversible renal failure, while not absolutely related to circulating drug levels, is generally seen with serum levels rising above 200 ng/mL and is common at drug levels above 400 ng/mL. Other features may include hyperuricemia, hyperkalemia, hypomagnesemia, sodium retention, and concentrating defects (94–96). These relatively high levels are seen more commonly in heart and liver allograft patients than in patients with renal allografts. ARF may be severe, with polyuria or oliguria (and even rarely anuria). In some cases, renal functional impairment can be rapidly reversed when CsA dosing is reduced (97). This rapid return of function is evidence that there is no direct tubular toxicity, as is the low fractional excretion of sodium, which indicates intact tubular reabsorption. In early phases, the underlying vasoconstriction can be reversed by dopamine (98). Cyclosporine can also produce significant injury to proximal tubule epithelium, potentially related to direct effects as well as to ischemic injury due to prolonged vasoconstriction. In this setting, renal dysfunction is not rapidly reversible on reducing dosage of the drug.

Cyclosporine also has a propensity for producing endothelial cell damage, which can lead to thrombotic microangiopathy. Glomerular thrombi and thromboembolic complications have been described in several series, and a hemorrhagic uremic type of syndrome (HUS) has been reported, initially in bone marrow transplant recipients and subsequently in other contexts as well (99,100). There may be ischemic tubulointerstitial changes downstream from involved vessels.

Myers et al. (101) were the first to show fibrosis with cyclosporine treatment, and many others have drawn attention to the fact that chronic nephropathy with striped interstitial fibrosis may occur following long-term CsA therapy, particularly in cardiac and other solid organ allograft recipients, as well as in patients receiving chronic CsA for autoimmune disease (102). Proposed risk factors include episodes of clinical toxicity, high CsA trough levels, concurrent administration of other nephrotoxic drugs, acute rejection episodes and therapy, and high variability in CsA levels (103,104). Myers et al. showed significant reductions in the GFR in cyclosporine-treated patients to approximately 50% of that in azathioprine-treated patients (101,105). Patients may also have severe hypertension, mild proteinuria, and evidence of tubular dysfunction. A similar long-term reduction in the GFR has also been reported in liver allograft recipients (106), and comparable changes have been reported in the kidneys of pancreas transplant recipients as well (107). Even low-dose CsA therapy for psoriasis may effect long-term changes (108,109). This type of chronic cyclosporine toxicity may not be reversible. Risk factors for the development of chronic cyclosporine nephrotoxicity include previous episodes of ARF, high-dose treatment, and (for heart transplant patients) increasing age (110,111).

Tacrolimus Tacrolimus (FK506) produces a spectrum of nephrotoxicity very similar to that of CsA (93,94) and is generally dose dependent; toxic reactions are common at or above 20 ng/mL (112) but can occur even when trough levels have been in a lower range (103). Reversible renal dysfunction has been reported with the use of FK506 for prevention of graft versus host disease in bone marrow transplantation and in renal and nonrenal solid organ allografts. Tacrolimus may have a lower nephrotoxic potential than cyclosporine in renal allografts, with less reduction in blood flow (113), and lower sCr and/or higher GFR at doses with comparable efficacy (114–116). Better graft survival has been reported in renal allografts (116,117), and less CRF may occur in other solid organ allografts with tacrolimus versus cyclosporine (118–120). In addition to induction of posttransplant diabetes, patients may develop hypertension (121). Higher incidences of urinary tract infection, of pyelonephritis, and of polyoma virus infection (122) have been reported as well, perhaps owing to the more potent immunosuppressive activity of the drug.

Intravenous Immunoglobulin Intravenous immunoglobulin (IVIG) may produce ARF (123,124). Addition of sugar excipients, and especially sucrose, to IVIG formulations has reduced side effects of pain, fever, chills, and fatigue but may increase the frequency of ARF. Renal failure may be attenuated by slowing the rate of infusion. Renal function generally returns to normal with discontinuation of the drug. Switching to a D-sorbitol–stabilized formulation may prevent toxicity (124). Avoidance of sucrose-stabilized formulations is recommended in patients receiving other nephrotoxins, in the elderly, in those with preexisting dysfunction, and in diabetics.

Sirolimus Nephrotoxic effects of sirolimus have been reported in transplant and native kidneys. Delayed graft function is more common in series of patients treated with sirolimus peritransplant (125,126); another study demonstrated that sirolimus-treated patients were half as likely to resolve delayed graft function (127). A few cases of acute oliguric renal allograft failure associated with combined use of FK506 and sirolimus have been described, apparently owing to ATI (128). In one study of high-risk renal allograft recipients, FK506-treated patients on reduced sirolimus (5 to 10 ng/mL) had a significantly higher incidence of biopsy-proven FK506 toxicity (129). Severe acute renal dysfunction with tubular injury with myoglobin casts has been reported in renal allograft recipients, with ATI, with myoglobin casts noted only in the cohort treated with rapamycin (130), some with elevated creatine phosphokinase and/or serum myoglobin levels. ARF/AKI has also been reported in series of patients treated with rapamycin for chronic glomerulopathy (131); renal biopsies were not performed, but most recovered function after discontinuation of the drug. Some cases of acute renal dysfunction caused by sirolimus have been associated with thrombotic microangiopathy (132).

Antineoplastic Agents Several antineoplastic agents produce toxic effects in the kidney. Immunotherapeutic agents, discussed earlier, are among them. In addition, antineoplastic agents that lead to rapid tumor lysis may cause hyperuricemia, with precipitation of uric acid in renal tubules; this syndrome may be largely avoided by hydration and careful monitoring of the patient. Specific agents that are toxic to the kidney are discussed here.
Cis-Platinum  Cis-platinum is a chemotherapeutic agent that frequently produces nephrotoxicity and is widely used in animal models of toxic tubular injury. Cis-platinum nephrotoxicity is dose related. In early studies, it was reported in 25% to 30% of patients on single-course therapy and 50% to 75% of patients on multiple courses (133,134) and remains high, affecting about one third of treated patients (135). Patients show gradual signs of elevations in SUN and sCr. Polyuria is a prominent early clinical feature, but even oliguric ARF may be seen. Other presenting symptoms include proteinuria, hyperuricemia, enzymbria, glycosuria, and electrolyte disturbances reflecting tubular dysfunction (136,137). Aggressive hydration, administration of diuretics, or coadministration of thiosulfate or thiophosphate reduces renal toxicity, and novel cytoprotective strategies based on understanding of pathophysiology are being tested in animal models (136–138). Delay of dosing is recommended if renal toxicity occurs. Recovery of renal function following cessation of therapy is the rule, but it may be delayed and incomplete, and subclinical dysfunction may persist (139). Chronic renal dysfunction is best predicted by the cumulative dose administered. Newer platinum derivatives, including carboplatin, spiroplatin, iriplatin, and oxaplatin, and liposome-entrapped platinum compounds appear to have limited nephrotoxicity. However, there is still a degree of nephrotoxicity with some of these formulations (138). Nephrotoxicity may be exacerbated by combination therapy with other agents such as Taxol (140).

Other Chemotherapeutic Agents  Nitrosoureas also produce nephrotoxicity. Streptozotocin, a nitrosourea compound, is toxic to pancreatic beta cells and is used to treat metastatic islet cell carcinoma, carcinoid tumors, and lymphoma. Up to 75% of patients experience some degree of nephrotoxicity with prolonged administration (141,142). The alkylating agent cyclophosphamide has only transient effects on water excretion, increasing urine osmolarity and decreasing plasma osmolality. However, its analog, ifosfamide, has significant renal toxicity. Renal proximal tubular dysfunction is the most common effect, and features of Fanconi syndrome and related electrolyte abnormalities, which may be severe, have been reported (137,138). Distal renal tubular acidosis occurs rarely. Mild decreases in the GFR are common, but severe ARF may occur as well, and irreversible chronic renal failure or continued deterioration after therapy has also been described (143,144). The major risk factor for toxicity is total dose of the drug (143). Other risk factors include age less than 5 years, previous exposure to cisplatin, underlying renal impairment, or tumor infiltrates in the kidney (145). Use of thiophosphates may reduce toxicity (146).

Other chemotherapeutic agents may also be nephrotoxic (137,138). High-dose therapy with mitomycin or methotrexate can result in renal failure, the latter via precipitation of methotrexate and 7-hydroxymethotrexate crystals in tubules. Azacitidine can produce renal symptoms and Fanconi syndrome or mild subclinical tubular dysfunction, which may necessitate bicarbonate and electrolyte supplementation. Imatinib and daziquone can also produce Fanconi syndrome and AKI. Zolendronate, a bisphosphonate used in conjunction with chemotherapeutic agents, has also been associated with ARF and should be avoided in patients with severe underlying renal disease.

Radiologic Contrast Media  Renal failure is an important complication of contrast media administration; the reported incidence of radiocast nephrotoxicity (RN) varies between 2% and 70%, averaging 5% to 10%. In the United States and Europe, RN has been reported to be the cause of 10% of hospital-acquired ARF (147). Differences in reported incidence are in part the result of issues with the definition of RN, optimally defined as “acute impairment in renal function following exposure to radiographic contrast materials.” This impairment is measured by a rise in sCr by most investigators. However, the degree of change in sCr that is considered to be diagnostic of RN shows great variation. Some prospective studies, which measured the sCr levels at regular intervals, diagnosed RN even after relatively small increases. Thus, some of these studies may overestimate the incidence of clinically significant RN. Urinary levels of tubular cell enzymes and markers of oxidative stress rise in the urine of patients with RN (148,149).

Certain underlying conditions predispose to the development of RN; the most important of them is preexisting renal insufficiency (150,151). Moore et al. (152) demonstrated that the incidence of RN in patients with baseline sCr levels between 1.5 and 1.9 mg/dL was 4.7%, the incidence for those with sCr levels between 2.0 and 2.4 mg/dL was 14.3%, and for levels between 2.5 and 2.9 mg/dL, it was 20%. Analogous findings were reported in a large study, with incidence of RN (rise in sCr of more than 0.5 mg/dL) ranging from 2.4% with sCr of 0.1 to 1 mg/dL to 30.6% for sCr above 3 mg/dL (150). A recent study in general ICU patients (153) using only iodinated nonionic low-osmolar or iso-osmolar contrast found an incidence of AKI of 16.4% using standard criteria (22.2% using KDIGO criteria); AKI was stage 3 (severe) in 25% of those who developed AKI. In contrast, with low-risk nonemergent CT, RN is uncommon among outpatients with mild baseline kidney disease (154). Dehydration is a risk factor for RN, which is not surprising because dehydration, and thus hypovolemia, may potentiate the development of renal failure owing to any insult. Effective prophylactic measures, such as rehydration, alleviate this problem. The efficacy of prophylactic hemodialysis and hemofiltration to reduce the incidence of RN in high-risk groups is controversial (151). A variety of protective measures have been proposed, including hydration and sodium bicarbonate, N-acetyl cysteine, combination therapy, and statin therapy (155).

Diabetes and multiple myeloma are also risk factors for RN. However, it appears that neither condition represents a higher risk if renal function is normal. Identified risk factors for contrast-induced nephropathy after coronary intervention studies include CHF, hypotension, intra-aortic balloon pump, age greater than 75 or 80 years, anemia, diabetes mellitus, contrast volume, and high preprocedural sCr (156). Whether dosage and route of administration are independent risk factors is a matter of debate. Some studies found a significant correlation between the volume of administered contrast media and the degree of nephrotoxicity, particularly in patients with underlying renal disease such as diabetes mellitus and in the setting of reduced renal function. Other studies did not confirm this relationship. These differences probably reflect biases in selection of patients. Dose may not be a significant risk factor in patients with normal renal function, but dosage as an independent risk factor has not been investigated in most published studies. An equation, to determine maximum acceptable
glomerular transcapillary hydraulic pressure, ACE inhibitors

Angiotensin II effect. There is ample evidence that by reducing efferent arteriolar vascular tone by antagonizing the Angiotensin-converting enzyme (ACE) inhibitors have become

Renal infarction is a rare complication; patients present with flank pain, fever, leukocytosis, pyruvic transaminase, and lactate dehydrogenase. Hypotension, associated with narcotic abuse are not different from myoglobinuric ARF associated with narcotic abuse are not different from myoglobinuric ARF of other origins.

Pathology of Acute Renal Failure/Acute Tubular Injury

Gross Pathology

At a gross level, as a result of extensive interstitial edema, the kidneys become enlarged and swollen. The combined weight of both kidneys is usually increased by about 25% to 30%. On cut section, the tissue bulges above the cut surface and has a flabby consistency. The cortex is widened and pale. The outer medulla may appear as a deep red band, in contrast to the more proximal tubular enzymuria has been described with aristocholate exposure (173–175). Cases caused by Takaout roumia (paraphenylenediamine) are often associated with rhabdomyolysis (176).
The lesions in both ischemic and toxic ATI primarily involve the tubules; the glomeruli are spared, as indicated by the nomenclature (178). Although no significant changes occur in the glomeruli, the parietal epithelium of the Bowman capsule is often prominent (Fig. 26.2), apparently reflecting reactive changes in the proximal tubule. Herniation of proximal tubular epithelium into the Bowman’s space is sometimes seen and may be the sole indicator of ATI when tubular epithelial changes are minimal. While these changes may be prominent, they are not specific. Glomeruli may show ischemic collapse, and the Bowman space may appear dilated.

Although “necrosis” has traditionally been included in the clinical term for ARF caused by tubular injury to distinguish this condition from other intrinsic causes of ARF (such as prerenal or postrenal failure or acute glomerular or interstitial nephritis), tubular epithelial cell death is often not evident by light microscopy (179). ATI is generally divided into two subcategories: postischemic ATI and nephrotoxic ATI. Morphologic changes of cellular injury are usually more subtle in the ischemic type, with more obvious cytopathologic changes in the toxic form. In addition, the sites of tubular damage along the nephron differ between the two forms (Fig. 26.3). In the ischemic form, tubular damage is patchy, affecting relatively short lengths of the straight segments of the proximal tubule and focal areas of the ascending limbs of the loop of Henle. In the toxic form, the tubular epithelial damage is more extensive along segments of the proximal tubule; the degree of involvement of the segments varies with the specific toxin. Although there is distal nephron damage, it is less extensive and more inconsistent in location than with ischemic ATI.

**FIGURE 26.2** “Tubularization” of parietal epithelial cells lining the Bowman capsule (arrows). Reactive changes in the proximal tubule extend from the tubular takeoff to involve these epithelial cells, which have marked increase in cytoplasm compared to normal quiescent cells. (H&E; ×640.)

**FIGURE 26.3** Cartoon demonstrating the difference in the distribution of lesions between ischemic and classic nephrotoxic tubular injury. In addition to differences in localization along nephron segments, different degrees of damage are visible between cortical and juxtamedullary nephrons. In the ischemic form, the S3 segments are most severely affected, along with focal areas of the ascending limbs of the loop of Henle. The cortical nephrons show more extensive damage than the juxtamedullary nephrons. In the toxic form, tubular epithelial damage is more extensive. Whereas mercury shows some predilection for the S3 segment, other heavy metals and organic toxins often show more extensive involvement of all nephron segments, also with a greater predilection for cortical nephrons.
Ischemic Acute Tubular Injury

The histologic picture varies with the severity of renal failure and the evolution of the lesion. Early in the course, cellular changes can range from minimal alterations to severe cell swelling (Fig. 26.4) to individual cell necrosis with denudation of the basement membrane (Fig. 26.5). With injury, there may be shedding of both viable (Fig. 26.6) and necrotic epithelial cells (Fig. 26.7) into the tubular lumen. Exfoliated epithelial cells, some viable, can be demonstrated in the urine (Fig. 26.8) (180).

In sections stained with periodic acid-Schiff (PAS), the brush border of proximal tubules is often thinned or absent. Blebs of apical membrane and intact cells shed from their basement membrane anchor are present in the lumen of the tubules (Fig. 26.9). Focal lesions of individual cell necrosis with disruption of the basement membrane also occur in the ascending limb of the loop of Henle. Hyaline, granular, cellular, and/or pigmented casts are seen in the distal portions of the nephron and are often particularly prominent in the collecting ducts (Fig. 26.10). These casts consist of Tamm-Horsfall protein, which stains positively with PAS, mixed with cell debris (181). It is the relative prominence of these distal changes that gave rise to the term lower nephron nephrosis. In segments of the tubules that do not show significant necrosis, the tubules are often dilated and lined by flattened epithelial cells—so-called tubular simplification (Fig. 26.11). The denuded basement membrane sections are covered by proliferating adjacent viable epithelial cells. There may be evidence of transdifferentiation of tubular cells, which may express vimentin and other mesenchymal markers (Fig. 26.12). There is some evidence that transdifferentiated tubular cells may contribute to fibrogenesis in later stages (182).

As the lesion progresses after the initial injury, evidence of tubular regeneration can be seen. Histologic indicators of cellular proliferation, such as mitoses, hyperchromatic nuclei, and a high nuclear-cytoplasmic ratio, may be seen (Fig. 26.13). Recent studies using genetic fate-mapping techniques in mice after ischemia-reperfusion injury (IRI) showed that most of the injured tubule cells were replaced within 2 days through extensive proliferation by surviving neighboring cells (183). These results indicate that regeneration of injured tubule cells through proliferation of surviving tubule cells is the predominant mechanism of repair after ischemic injury (183). Proliferation can be demonstrated by staining for transcription factors (Fig. 26.14) and other markers.

The injured tubules are separated by sometimes markedly edematous interstitium. There may be a mild interstitial inflammatory infiltrate with small numbers of lymphocytes, macrophages, and neutrophils or, occasionally, eosinophils. The cellular infiltrate tends to be clustered around necrotic and ruptured segments of tubules or where Tamm-Horsfall protein has been extruded, forming small granulomas. It is in these late stages that distinctions have to be made between ischemic ATI and acute tubulointerstitial nephritis, but in general, the infiltrate is much less prominent in cases of ATI.
FIGURE 26.7  A: Detached necrotic tubular cells, several with pyknotic nuclei, in the lumen of proximal tubule. B: Granular casts with necrotic cell debris. Note flattened tubular epithelium in tubules containing necrotic debris. (H&E, ×640.)

FIGURE 26.8  Intact tubular cells in the urine from a patient with ischemic injury. (Papanicolaou; ×1,000.)

FIGURE 26.9  Apical blebbing from the surface of injured proximal tubular cells (arrowheads). Apical cytoplasmic blebs can be seen in tubular lumina. (H&E; ×640.)

FIGURE 26.10  Tubular cell casts in collecting ducts in papilla. Injured cells have detached from sites in proximal nephron and aggregate into casts, often around a protein core. (H&E; ×400.)

FIGURE 26.11  Dilated tubules with flattened epithelium in the regenerative phase after tubular injury. Marginating inflammatory cells can be seen in capillaries. (H&E; ×640.)
Tubular cell death during ischemia/reperfusion occurs via apoptosis as well as coagulative necrosis and has been documented both in animal models and in clinical renal disease (184–186). It is possible to detect the nuclear and cytoplasmic condensation of cells undergoing apoptosis by light microscopy. Apoptotic cells may appear triangular and may be extruded from the epithelium into the tubular lumen (Fig. 26.15). Apoptotic bodies, representing membrane-bound nuclear fragments, may also be detected in adjacent tubular cells, which have engulfed these cell remnants. However, the most reliable methods of detection are by nick end labeling (TUNEL) of the chromatin that has been cleaved in a characteristic “ladder” pattern by the endonucleases or by staining for apoptosis-associated markers, such as cytochrome c or apoptosis-inducing factor (AIF) (187). Coagulative necrosis is characterized by eosinophilic cytoplasm and pyknosis and eventual disappearance of nuclei (Fig. 26.16).

ATI in renal allografts can show changes similar to those found in native kidneys, but more frank necrosis of tubular cross sections may be seen, and calcium oxalate deposits may be numerous in renal tubules (188) (Fig. 26.17). The cellular lesions are most prominent in the $S_3$ segment of the proximal tubule and tend to be more uniform in character. Apical blebbing may be the only finding in milder forms, whereas the more severe cases also show focal necrosis with rupture of the tubular basement membrane. It is interesting to note that one study has shown a correlation of loss of Na$^+$,K$^+$-adenosine triphosphatase (ATPase) polarity with delayed graft function (189).

Electron microscopy has been helpful in evaluating the tubular epithelial changes in ATI (190–192). In ischemic ATI, scattered epithelial cell changes show a variety of different cytopathic alterations. These include loss of the apical brush border; blebbing of the apical membrane, with shedding of apical membrane blebs into the tubular lumina; high-amplitude swelling, with condensation of the cristae of the mitochondria; individual cell apoptosis, as demonstrated by cell shrinkage.
with nuclear fragmentation; and a variety of other cytopathic changes leading to necrosis (Fig. 26.18). Detachment of tubular epithelial cells may be seen (Fig. 26.19).

Interstitial inflammation is seen as a response to tubular injury. This inflammation is typically mononuclear and patchy. There is often associated interstitial edema, which may be severe (see Fig. 26.5). A particularly interesting and useful finding in cases of ARF is the accumulation of nucleated cells in the vasa recta of the outer medulla (193,194). This is a very common feature, and in many cases, it is the only histologic clue to the diagnosis of ATI (Fig. 26.20). The nature of the cells changes with progression of the ATI through its three different phases. Lymphocytes are predominant in the first 24 to 48 hours, followed later by immature cells of the myeloid series and eventually by nucleated red cells and red cell precursors. The accumulation of the larger nucleated cells in this location may be merely a reflection of the hemodynamic shifts that occur in ATI, with shifting of blood flow away from the superficial and midcortical glomeruli to the juxtamedullary glomeruli, resulting in a relative increase in blood flow to this nephron population, which gives rise to the vasa recta. The countercurrent nature of blood flow in the vasa recta would result in dilution of cellular elements as blood flows toward the hairpin turn, resulting in a concentration of cellular elements at the proximal end of the vasa recta vasculature in the outer medulla. There is also some evidence that up-regulation of adhesion molecules on ischemic endothelium leads to accumulation of leukocytes in the microvasculature, which may contribute to stasis and lack of reflow in ischemia-reperfusion injury (see section “The Inflammatory Response in Ischemic Injury”).

At the molecular level in AKI, in addition to transcription factors and markers of cell differentiation/transdifferentiation, there is altered expression of a range of proximal and distal gene products in kidney tissue sections, among which KIM-1 and NGAL are most prominently expressed (195–198). KIM-1 is primarily expressed at the luminal side of dedifferentiated proximal tubules (198). ER stress markers such as CHOP and GRP94 can also be identified in renal tissue in injured cells (199). Tissue (and urine) detection of fibrinogen
has been proposed as a sensitive early marker of AKI, with markedly increased expression (199,200). The L-1 cell adhesion molecule has been identified as a potential biomarker of distal tubular injury in AKI, with loss of normal polarized distribution in the collecting duct, and induction of expression in medullary thick ascending limb and distal tubule with injury (201). Apoptotic cell death, difficult to detect by histology, can be detected in tissue using techniques such as terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) (201). An increase in progenitor cells (e.g., CD133+ CD24+ CD106− cells) can be identified in tissue sections by immunostaining as a correlate of injury (202). Other potential injury markers in tissues are described below in the section on “Pathophysiology.”

**Nephrotoxic Acute Tubular Injury**

Tubules  Classically, toxic tubular injury may be associated with extensive epithelial necrosis, which tends to involve all nephrons more uniformly than in the ischemic form. However, a range of morphologic changes may be seen in the renal tubules as the result of toxic injury. The extent and severity of the changes will vary depending on the agent, the dose, and the timing of the morphologic assessment. Renal tubular cell changes detectable by light microscopy include the following:

- Alterations in the surface of the cells, including loss of brush border (detectable on PAS), loss of basolateral infoldings, and blebbing of apical cytoplasm
- Cytoplasmic swelling and vacuolation
- Intracellular inclusions
- Extensive tubular cell necrosis
- Loss of individual tubular cells, with gaps along the tubular basement membrane or tubular profiles with fewer and attenuated cells lining the tubule
- Intraluminal proteinaceous cellular debris, casts, or crystals
- Tubular dilation with flattening of tubular epithelium
- Tubular rupture with urinary extravasation
- Regenerative changes, including flattening of epithelial cells, cytoplasmic basophilia, heterogeneity in cell size and shape,

Swelling and vacuolation of proximal tubular cells may be seen; cells appear large and pale and may contain discrete vacuoles of varying size. Hypertonic solutions, including IVIG preparations (203), have been reported to produce severe swelling and vacuolation of renal tubular cells. Intracellular inclusions are occasionally seen in renal tubular cells exposed to drugs. Giant mitochondria, appearing as bright eosinophilic inclusions, have been described after the administration of relatively high doses of CsA to humans. In gold-induced nephropathy, gold can be demonstrated in tubular cells (204). Calcification of tubular cells has been described in cases of severe toxicity caused by amphotericin or bacitracin (205).

Extensive coagulative necrosis of tubular cells has been seen in cases of poisoning by heavy metals such as mercuric chloride, rarely seen today, or in cases of poisoning due to chemicals such as diethylene glycol (206). More often, changes are more subtle, with individual tubular cell necrosis or loss, though there may be more obvious and extensive necrosis than is seen in ischemic

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**FIGURE 26.19** An electron micrograph demonstrates an area of loss of an array of tubular epithelial cells. (×3,000.)

**FIGURE 26.20** Erythrocyte congestion and nucleated cells in dilated vasa recta in the outer medulla of a kidney with ischemic injury. (H&E; ×400.)
injury (207). It is clear that both necrosis and apoptosis occur in toxic nephropathies in experimental models as well as in clinical tubular injury (208,209). In vitro studies have documented apoptosis in cell culture on exposure to nephrotoxins. For example, LLC-PK1 cells exposed to sublethal doses of mercuric chloride in vitro undergo apoptosis (210), and apoptosis can be induced in Lewis lung cancer-porcine kidney-1 [LLC-PK1] cells by cisplatin as well via activation of caspases (211). Our understanding of the role of apoptosis in the pathogenesis of toxic renal injury has evolved over the past decade. AT1 due to cisplatin therapy depends also partially on Fas-mediated apoptosis driven by Fas ligand (FasL) expressed on tubular epithelial cells (212). Moreover, cisplatin down-regulates the expression of the tumor transporter gene TauT in LLC-PK1 cells (213). Taurine is one of the organic osmolytes, which have important antiapoptotic properties in the kidney (214). The antiapoptotic function of organic osmolytes in kidney cells is mediated through suppression of efflux of proapoptotic molecules, such as cytochrome c, from the mitochondria.

Tubular casts, which may include cells and cell debris, are frequently seen with toxic tubular injury. In addition, tubular crystalline deposits are found in cases of renal toxicity produced by nephrotoxins. Anesthetic agents, including methoxyflurane and halothane, and antiretroviral agents such as indinavir may produce tubular crystalline deposits. Mechanical obstruction may also result from deposition of intratubular crystals in cases treated with sulfonamides or acyclovir. In addition, radiocontrast agents are uricosuric and oxaluric, and casts and birefringent crystals have been identified following administration of these agents. Uric acid lithiasis with tubular obstruction has been reported with phenylbutazone (215). Finally, pigmented casts may result from hemolysis in rare cases of fulminant drug reactions and with the rhabdomyolysis caused by cocaine.

Vessels Vessels usually show no remarkable features unless there is intercurrent disease. However, newer studies in experimental models have refocused attention on injury to the microvasculature, which may have been underappreciated in clinical specimens. Certainly, vascular congestion in the outer medulla with margination has been noted.

Electron Microscopy Electron microscopy of injured tubules reveals loss of brush border microvilli and basolateral infoldings in the proximal tubules. Cells may show rarefaction of the cytoplasm, with intracellular vacuoles and swollen organelles. Degenerative changes in mitochondria, including swelling and loss of cristae, loss of endoplasmic reticulum, or alterations in lysosomes, are often visible. Within the cells, membrane-bound structures consisting of concentrically arranged whorls of membrane may form, especially with exposure to aminoglycosides; however, these so-called myeloid bodies do not necessarily indicate toxicity.

Pathology of Specific Nephrotoxins

As a preface to this discussion, it should be recognized that it is often difficult to establish a pathogenetic link between a pathologic lesion and a particular drug or toxin. Several factors contribute to this uncertainty, including concurrent factors that may produce renal injury, such as administration of other potentially nephrotoxic drugs, lack of or inadequacy of morphologic data in reported cases, and the fact that some drugs may have multiple effects. Moreover, experimental models of toxicity may not be relevant to a particular clinical context owing to interspecies variation and markedly different dosing of drug or toxin in these models. In general, we limit our discussion to those drugs for which toxicity has been well documented in humans by disappearance of toxic effects when the drug is withdrawn, recurrence of symptoms after readministration of the drug, or both.

A range of chemotherapeutic agents and other toxins may produce direct injury to the renal tubular epithelium. These agents are outlined in Table 26.2. The focus in this discussion is on primary toxic tubular injury, recognizing that secondary injury to the renal tubule may also occur with other types of toxic renal injury, including tubulo-interstitial nephritis, hemodynamic changes, and vascular disease.

Antibiotics

There have been many reports of renal damage associated with antibiotic therapy. Some drugs are more nephrotoxic and can promote acute renal injury even with brief exposure. One such example is the aminoglycosides (especially neomycin), which are classic nephrotoxins. However, in many cases, there is an association, but the causative role of the antibiotic in the etiology of tubular injury cannot be firmly established. There are several reasons for this. First, the infection for which the drug is being used may damage the kidney directly or indirectly. Second, infections are frequently treated with several agents, making it difficult to implicate a particular drug. Finally, the paucity of renal biopsy studies makes it difficult to define the pathologic changes produced by individual drugs and the pathogenetic mechanisms involved in producing renal injury.

Antiviral Agents In experimental animal models and in humans receiving acyclovir, indinavir, or ganciclovir, renal histologic examination often shows drug crystals in tubules, especially collecting ducts, with dilution of tubules reflecting obstruction (54,55,216,217) (Figs. 26.21 and 26.22). In other cases, there may be tubular dilation and tubular cell injury without detectable crystals in the urine or kidney (218); crystals, of course, might be missed if relatively few collecting ducts are sampled. Proximal tubular injury has been described.

FIGURE 26.21 Crystalline precipitates (arrows) in tubules in a patient treated with intravenous acyclovir. (H&E; ×640.)
especially with the nucleotide reverse transcriptase inhibitors adefovir and tenofovir, with degenerative changes, thinning and vacuolization of cytoplasm, loss of brush border, and even tubular cell necrosis, with nuclear changes reminiscent of viral inclusions (61,219–221). On electron microscopy, alterations in mitochondria have been observed, with swelling and dysmorphic changes. Changes include variable mitochondrial size, with some small and rounded and others swollen with irregular contours, clumping, loss and disorientation of cristae, and focal marked reduction of mitochondria (61). Giant mitochondria, in some cases, the size of nuclei, fuchsinophilic on trichrome stain but PAS- and silver-negative, may be seen in proximal tubular epithelial cells. Patchy interstitial inflammation has been described without crystals (222) and, occasionally, granulomas have been described. Renal tubular cell apoptosis has been detected in renal biopsies of a patient with irreversible cidofovir toxicity (223), and fibrosis and tubular atrophy have been described with tenofovir (61), with persistent renal dysfunction.

**Aminoglycosides** Aminoglycosides are classic nephrotoxic agents. Accumulation of high concentrations within lysosomes and release to the cell cytoplasm promotes phospholipid membrane rupture, oxidative stress, and mitochondrial injury. As a consequence, proximal tubule cells develop apoptosis and necrosis. The pathologic lesion most often reported with gentamicin is ATI (224), although in some cases, this lesion has been attributed to concomitant volume depletion and hypotension. Tubulointerstitial inflammation with tubular necrosis also has been reported (225). Myeloid bodies can be seen by ultrastructural examination in the tubular epithelium of patients receiving gentamicin, which predominantly reflect exposure to the drug (224) (Fig. 26.23).

Zager (226) has shown experimentally that gentamicin in a dose that does not by itself cause renal failure will trigger severe renal failure when combined with 1 hour of moderate renal hypoperfusion, which also does not produce renal failure on its own. In those studies, there was tubular necrosis in the S3 proximal tubule segment, a pattern of injury characteristic of renal ischemia rather than gentamicin toxicity; this suggests that in some instances, gentamicin may worsen ischemic injury rather than causing injury to the S1 and S2 segments, which is more typical of toxic doses of gentamicin (226).

There are few descriptions of renal pathologic lesions in patients receiving kanamycin or tobramycin. In one patient with oliguria who received 21 g of kanamycin over a 2-week period (227), a renal biopsy was done 25 days after the onset of oliguria (21 days after diuresis) and was reported to show some flattening of tubular epithelial cells.

In cases of ARF resulting from a combination of gentamicin and cephalothin, the pathologic features are those of ATI with normal glomeruli and vessels. However, experimental studies in the rat have found no potentiating effect of cefalo- sporins on gentamicin nephrotoxicity (228).

**Amphotericin** In human autopsy or biopsy specimens from patients treated with amphotericin, extensive calcification in tubules, presumably developing in the context of severe tubular cell injury, has been reported (229) (Fig. 26.24A). There may be vacuolation of smooth muscle cells in small arteries and arterioles (230) (see Fig. 26.24B). This is a change that potentially reflects direct toxic effects on the arterial wall, some element of intrarenal vasospasm, or both, and it may be very striking.

**Cephalosporins** Renal biopsies have been obtained in relatively few cases of cephalosporin-induced renal injury, usually in those in which the older cephalosporins were given. In cases of cephaloridine-induced ARF, biopsies have shown a picture of interstitial edema with variable numbers of chronic inflammatory cells accompanied by tubular dilation or necrosis (231). The renal histologic features in these cases showed what is described as ATI, with interstitial fibrosis or edema and infiltration by lymphocytes and mononuclear cells. Pathologic changes in cases induced by cephalothin with or without other potential nephrotoxins consist of interstitial edema with variable numbers of lymphocytes and plasma cells; necrosis, swelling, and evidence of regeneration of tubular epithelium; and only trivial glomerular changes (232,233). Vacuolation of tubular cells has been evident on electron microscopy (232). A case of bilateral renal cortical necrosis (RCN) associated with cefuroxime has been reported (234). ATI has been described in patients treated with cephalaxin (77,78).
Polymyxin/Colistin On biopsy of patients treated with polymyxin, there is interstitial edema with eosinophils, plasma cells, lymphocytes, and, occasionally, neutrophils (235). The cellular reaction may have granulomatous characteristics. Tubules show swelling of the epithelium with intramuscular administration of colistin; the lesion described was ATI (236).

Vancomycin While ARF with vancomycin is associated with interstitial nephritis, acute tubulopathy has also been described. Acute tubular necrosis (ATN) with anuria has been described associated with vancomycin and one dose of aminoglycoside (237). Another case with biopsy-proven ATN has been described in a child (238). Another biopsied case in a
child with elevated vancomycin levels and ARF revealed focal tubular dilation with attenuation of brush border, hyaline casts, and one neutrophil cast without interstitial nephritis (239).

**Immunosuppressive/Immunomodulatory Agents**

**Cyclosporine** Functional CsA nephrotoxicity can occur without any morphologic changes. The most common morphologic change observed in the kidneys of patients treated with CsA is isometric vacuolation of the proximal tubular cells (Fig. 26.25); this change is characteristic but not specific. Other changes include tubular epithelial cell necrosis with or without calcification, inclusion bodies corresponding to giant mitochondria, and giant lysosomes (240). The megamitochondria and microcalcification in tubular cells of CsA-treated patients do not correlate with dysfunction (241). Strong staining for osteopontin protein and mRNA has been demonstrated in tubular epithelium in clinical CsA toxicity (242).

Vessels in CsA-induced acute renal dysfunction may show only vasospasm and vacuolation of smooth muscle cells, changes that often reflect vasoconstriction. The onset of hyaline arteriolar thickening, especially with nodular accumulation of hyaline in the periphery of the arteriolar wall, has been associated with CsA-induced renal dysfunction, although dysfunction can also exist without this change. The juxtaglomerular apparatus may be hyperplastic; this finding is significantly more prominent in renal transplant patients with CsA nephrotoxicity than in other posttransplant groups, probably indicating activation of the renin-angiotensin system (243). Thrombotic microangiopathy may be seen in particularly severe cases of toxicity.

Descriptions of the pathologic characteristics of both clinical and experimental long-term CsA toxicity have focused on interstitial fibrosis and tubular atrophy, which appears in a “striped” pattern reminiscent of ischemic injury, and hyaline arteriolar change, as described earlier. The fibrosis involves medulla and medullary rays in the cortex (244). Bertani et al. (245) have reported the renal biopsy changes observed in cardiac allograft recipients with renal failure after they had received cyclosporine for 31 to 48 months. Obliterative arteriopathy with ischemic glomerular changes was found. Serial reconstruction of the glomeruli showed the presence of populations of both abnormally small and abnormally large glomeruli. Sclerotic lesions were confined to the small glomeruli. Myers et al. (246) and Morozumi et al. (247) have also emphasized sclerosing glomerular changes with long-term CsA therapy. The pathologic findings and the differential diagnosis of CsA nephrotoxicity in renal transplant recipients are discussed in detail in Chapter 29.

**Tacrolimus** Pathologic changes owing to FK506 are very similar to those described for CsA. Changes include tubular cell vacuolization, calcification, myocyte vacuolization, necrotizing arteriolitis, thrombotic microangiopathy, arteriolar hyalnosis, and interstitial fibrosis. Morphologic changes with FK506 toxicity have been compared to those produced by CsA (248,249). Tubular cell vacuoles were small and focally confluent and involved proximal and distal tubules. Morozumi et al. (249) have suggested that FK506-related vacuoles are foamy and nonsmometric and present in straight and convoluted portions of the proximal tubules. We have noted involvement of tubules in outer medulla as well (unpublished).

Glomerular capillary and arteriolar thrombi have been seen in renal allograft recipients (250,251) and a few kidney/liver allograft recipients (250). In several of these cases, other factors, including prior CsA therapy in three cases and fungal sepsis in a fourth case, may have contributed to the endothelial injury underlying thrombosis. An HUS-like syndrome with thrombotic microangiopathy may be seen (Fig. 26.26); the estimated incidence is approximately 1% (251), and cases are frequently associated with high serum levels of drug. Hyaline arteriolar change and interstitial fibrosis have been reported with long-term therapy (240).

An increase in BUN and sCr has been documented in rats treated with FK506, with evidence of proximal tubular cell vacuolation and megamitochondria on histologic examination (249). Pathologic changes, including proximal tubular cell vacuolation and tubular regeneration similar to those reported with CsA therapy, also have been reported in canine allografts (252). Stillman et al. (253) developed a rat model of prolonged FK506 toxicity by combining FK506 with a low-salt diet for 6 weeks. In this model, sCr and plasma renin levels were elevated, and there was tubular atrophy and fibrosis in

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**FIGURE 26.25** “Isometric” vacuolization, with many small equal-sized vacuoles in tubular cell cytoplasm, in a patient with high serum levels of calcineurin inhibitor. (H&E; ×400.)

**FIGURE 26.26** Thrombotic microangiopathy in a patient on tacrolimus. Note the arteriole with very focal intramural fibrin (arrowhead), focal erythrocyte extravasation into the intima (long arrow), and focal erythrocyte fragmentation in the glomerulus (short arrows). (H&E; ×640.)
medullary rays and the inner stripe of the outer medulla. Tacrolimus alone produced increased juxtaglomerular apparatus granularity.

**Intravenous Immunoglobulin** Intravenous administration of immunoglobulins has been associated with severe swelling of tubular epithelial cells (254) (Fig. 26.27). Of note, the brush border of the cells is generally well preserved. Swelling may be severe enough to occlude the tubular lumen. In one series of transplant patients, isometric vacuolization appeared to precede the more severe cell swelling (255).

**Sirolimus** Rats given sirolimus (3 mg/kg orally) for 2 weeks on a low-salt diet developed magnesium wasting and structural renal lesions consisting of tubular collapse, vacuolization, and nephrocalcinosis (248). ATI has occasionally been described in patients (128). In one study of sirolimus-treated patients (also on FK506), there was a subset that developed striking intratubular cast formation, reminiscent of myeloma cast nephropathy (125). Vascular changes and glomerular disease have been reported with sirolimus. Some reports have appeared that sirolimus may delay recovery from tubular injury, exacerbate acute FK506 tubular cell toxicity (125,128), or exacerbate chronic calcineurin inhibitor toxicity.

**Chemotherapeutic Agents**

**Cis-Platinum** In the human kidney, focal necrosis of tubular cells is seen, primarily in the distal tubule and collecting ducts; cast formation and dilation of proximal tubules may be observed (250). In animals, tubular changes are found in the proximal nephron, with or without accompanying distal changes (257). Many patients show continuing damage and fail to regain pretherapy levels of renal function. Dobyan et al. (258) studied the effects of chronic administration in animals and found cyst formation, interstitial fibrosis, and tubular atrophy.

**Other** The pathologic picture produced by the alkylating agent ifosfamide is that of ATI or chronic tubulointerstitial changes (259). On pathologic examination of kidneys from patients with toxic injury caused by streptozotocin, there is ATI in the proximal tubules, with or without accompanying interstitial inflammation (142).

**Radiocontrast Agents**

Because renal biopsies are not indicated in patients with transient renal failure after contrast media administration, human studies are scant. Patients who undergo biopsy are those who do not recover from renal failure, and in most of these cases, the histologic picture reveals an underlying (and most likely preexisting) renal disease. The majority of publications describing renal morphologic changes are based on experimental studies. The induction of renal failure in experimental animal models usually requires administration of additional agents (e.g., indomethacin, gentamicin, glycerol), ischemia, water or salt depletion, or a combination of these factors (225,260–263).

The overwhelming majority of both experimental and clinical studies report variable, transient proximal tubular vacuolation, which appears as soon as 30 minutes following administration, disappears within a few days (264,265), and seems to be dose dependent (266). One study emphasizes the selective injury of the thick ascending limb of Henle in the outer medulla after coadministration of indomethacin and iohexol to unilaterally nephrectomized, salt-depleted rats (225). They describe mitochondrial swelling, pyknosis, cytoplasmic disruption, calcification, necrosis, and tubular collapse in the thick ascending limb of Henle in areas away from vascular bundles, suggesting hypoxic injury. They also report vacuolation of the proximal convoluted tubules.

Ultrasound examinations indicate that the vacuoles are membrane bound, probably representing lysosomes (225,264). The fine structure of the mitochondria and the endoplasmic reticulum remains intact. Tervahartiala et al. (264) believe that the vacuolation is caused by a nonspecific lysosomal injury and is not the consequence of osmotic diuresis. Autoradiographic and electron microscopic studies failed to demonstrate the presence of iodinated molecules within the vacuoles (225,267).

The most extensive studies in human beings come from the Necker Hospital in Paris, where radiocontrast examination of the kidney was routinely performed before renal biopsies in the 1970s (265,267). This group published the case studies of 211 patients who underwent biopsy within 10 days of urography or renal arteriography using ionic contrast media (267). Tubular vacuolation characteristic of “osmotic nephrosis” was found in 47 patients and was more severe in patients with preexisting renal failure; however, they did not find a correlation between the extent of tubular vacuolation and the degree of renal functional impairment. The same group later described osmotic nephrosis in 14 of 33 patients who received low-osmolality contrast media before renal biopsy (267). They reported the case of one patient who had evidence of ATI on initial biopsy and showed signs of advanced tubular atrophy and interstitial fibrosis on a second biopsy. Other patients in the Necker Hospital also had evidence of ATI in the renal biopsy, but it appears that these patients had ARF as a preexisting condition. They concluded that tubular vacuolation after radiocontrast administration probably does not represent true osmotic nephrosis and that it is not a reliable morphologic indicator of RN (267).

In 1970, two articles described hemorrhagic necrosis, primarily of the renal medulla, in six infants (268,269). Five of them underwent cardiac catheterization for heart problems, and one had excretory urography because of a flank mass. In these children, there were several confounding variables that might have contributed to the renal necrosis, such as seizures, cardiac developmental abnormalities, and sepsis. All six children died. Although
ATN has been reported only rarely in patients (265,267,270), recent studies have shown that radiocontrast agents induce apoptosis in proximal tubule cells (271). Increased ceramide synthesis, which stimulates apoptosis, is an important contributing factor to radiocontrast-mediated nephropathy (272).

**Narcotics and Myoglobinuric Acute Renal Failure**

The characteristic finding is the presence of pigmented casts, as in other forms of myoglobinuric ARF. Renal biopsy is rarely performed in affected patients, and for this reason, pathologic reports are uncommon (273,274). The characteristic casts show mild brown pigmentation and usually have a granular appearance with irregular globules. These casts are frequently bright red as seen by trichrome stain. Immunohistochemistry is helpful in identifying myoglobin casts (Fig. 26.28). Hyaline and granular casts not containing detectable myoglobin may be present. Other features of ATI, such as tubular epithelial damage with exfoliation of tubular epithelial cells, thinning of the tubular epithelium, and tubular calcification, are usually noted. Immunofluorescence is typically not helpful. On ultrastructural examination, the myoglobin casts frequently consist of very electron-dense, finely granular globules that may have a somewhat less electron-dense rim (Fig. 26.29). In addition, electron microscopic signs of ATI are readily visible.

**Anesthetics**

The renal lesion consists of interstitial edema with somewhat dilated tubules lined by flattened epithelium. In several cases, a striking degree of intratubular collection of oxalate crystals has been reported (275).

**Herbal Medications**

There are relatively few reports of biopsy findings in ARF caused by herbal medications. ATI has been described (reviewed by Isnard Bagnis et al. (169)). Pathology of the kidneys in patients with renal failure caused by *Aristolochia* species has shown hypocellular interstitial fibrosis and tubular loss, especially in the outer cortex, in lesions obtained later in the course of the injury (276).

**Etiology and Pathogenesis**

Although the number of disease entities that have been associated with ATI is large, the basic etiologic factors are very similar (Table 26.3; Fig. 26.30). Prolonged renal ischemia is the most common cause of ATI (277–279). In the hospital setting, it is frequently associated with major surgery, with extensive trauma such as crushing injuries and burns, or severe congestive heart failure and septic shock (280,281). The widespread use of nonsteroidal anti-inflammatory drugs (NSAIDs), which inhibit renal prostaglandins, is another potential mechanism through which renal ischemia can be initiated, and these drugs have been associated with the development of ARF, particularly in patients who are volume depleted or dehydrated.

The second major category of etiologic agents of AKI is exposure to nephrotoxic drugs. The kidney is uniquely susceptible to toxic injury, because it is the principal excretory organ of the body. Since metabolism and excretion of exogenously administered therapeutic and diagnostic agents are major functions of the kidney, the ingestion of drugs is significantly associated with kidney injury. A number of therapeutic agents have known nephrotoxic potential. Classic examples include antimicrobial agents, chemotherapeutic agents, analgesics, and immunosuppressive agents (44,65,282–286). A problem that has been observed in developing countries is the contamination of commonly used drugs by nephrotoxins during their preparation under less stringent conditions. Examples include the sudden occurrence of unexplained ARF in children in Pakistan and Haiti, where the cause was found to be contamination of the liquid vehicle of paracetamol with diethylene glycol (287,288). Interaction of herbal products with conventional drugs is also a potential source of toxicity. Examples of nephrotoxic herbal products include aristolochic acid, *Ephedra* species, and *Glycyrrhiza* species (169,289). Adulteration of food products may be another cause of kidney injury. One example is the addition of melamine to baby formula to increase the protein content, which caused AKI and nephrolithiasis in neonates (290). In many cases involving the use of diagnostic and therapeutic agents, the known risk of nephrotoxicity is outweighed by the clinical benefits of using the drug. While the range of injurious compounds is diverse, there are a limited number of patterns of injury produced in the kidney; the focus of this section will be on agents and specifically drugs that produce ATI.

ARF in the newborn may have a prenatal onset associated with maternal hypotension or occur in the setting of congenital diseases, such as renal dysplasia or polycystic kidney disease (279).
In the postnatal period, hypoxic/ischemic injury and toxins are the most common etiologies. Toxic ARF is most commonly associated with administration of aminoglycoside antibiotics and NSAIDs given to close a patent ductus arteriosus. Decreased renal function can be documented in about 40% of premature infants receiving indomethacin; the decrease is usually reversible. 

In hospitalized patients, ATI/ARF often occurs in the setting of both ischemic and toxic insults. Multiorgan failure, with or without sepsis, is a common scenario. Incidence of ARF increases with enhanced severity from moderate sepsis to septic shock with positive blood cultures (291,292). Clinical course and outcomes will be determined by multiple clinical factors and “cross-talk” between and among affected organs (293) (see Section Acute Renal Failure in Sepsis). ARF occurring in the critically ill has a significant impact on morbidity and mortality (294).

Much of our understanding of ATI and ARF has derived from experimental models, and extrapolation to human ARF may be problematic (295,296). This likely underlies the failure of various therapeutic agents defined in animal models to have clinical efficacy (297). Although they are imperfect, experimental models have provided important insights. New techniques, including imaging studies, may enable more precise definition of mechanisms of ARF in vivo (298). The rarity of renal biopsies in this setting has contributed to the difficulty of defining the pathobiology in humans (177). However, new techniques will likely make it possible to more precisely define mechanisms in clinical ARF in the future. Micro–magnetic resonance imaging techniques may ultimately be useful in assessing tubular cell function. Detection of renal inflammation may also be possible using these techniques (299). Imaging of subcellular processes, including apoptosis, enzyme markers, and cell pH and calcium, may ultimately be widely applicable in vivo (41–43,298).

**Ischemia**

**Mechanisms of Injury and Cell Death**

Alterations in cellular metabolism underlying ischemic cell injury in the kidney are analogous to those in ischemic injury in other organs and have been directly related to the severity of changes in renal cell structure and function regardless of the cause of ATI. Ischemia and reduced oxygen delivery to highly metabolically active tubular epithelial cells reduce oxidative metabolism and cell stores of high-energy phosphate...
TABLE 26.3 Causes of acute renal failure

<table>
<thead>
<tr>
<th>Causes</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prerenal azotemia (renal hypoperfusion)</td>
<td>Cardiogenic shock, hemorrhage, gastrointestinal loss</td>
</tr>
<tr>
<td>Decreased cardiac output</td>
<td></td>
</tr>
<tr>
<td>Diminished intravascular volume</td>
<td></td>
</tr>
<tr>
<td>Postrenal azotemia (obstructive uropathy)</td>
<td>Stone, clot</td>
</tr>
<tr>
<td>Intrarenal obstruction</td>
<td>Tumor, fibrosis</td>
</tr>
<tr>
<td>Lower urinary tract obstruction</td>
<td>Urethral occlusion, prostatic disease</td>
</tr>
<tr>
<td>Renal causes of ARF</td>
<td></td>
</tr>
<tr>
<td>Glomerular/vascular disease</td>
<td>Glomerulonephritis, malignant hypertension, scleroderma, thrombotic thrombocytopenic purpura, emboli, arterial/venous occlusion</td>
</tr>
<tr>
<td>Interstitial disease</td>
<td>Drug induced, hypercalcemia, hypokalemia, pyelonephritis, papillary necrosis</td>
</tr>
<tr>
<td>Intrarenal tubular occlusion</td>
<td>Crystal (uric acid, oxalic acid), protein (myeloma) deposition</td>
</tr>
<tr>
<td>ATI</td>
<td></td>
</tr>
<tr>
<td>Ischemic injury</td>
<td>Severe trauma, aortic cross-clamping, hemorrhage</td>
</tr>
<tr>
<td>Nephrotoxic injury</td>
<td>Aminoglycosides, contrast material, heavy metals</td>
</tr>
<tr>
<td>Pigment associated</td>
<td>Myoglobinuria, hemoglobinuria</td>
</tr>
</tbody>
</table>

The apical microvillar surface of proximal tubule cells is especially sensitive to ischemic insults. After as little as 5 minutes of ATP depletion, there is loss of polarity, degeneration of the microvillar F-actin core with internalization, and blebbing of the apical brush border membranes (305). Renal ischemia in vivo results in increased solubility of Na⁺,K⁺-ATPase in rat renal proximal tubule cells, indicating disassembly from the cortical cytoskeleton. Shortly thereafter, basal lateral Na⁺,K⁺-ATPase migrates from the basolateral to the apical membrane. The alterations in cytoskeleton and Na⁺,K⁺-ATPase redistribution stemming from ATP depletion result in loss of Na⁺,K⁺-ATPase activity and the normal sodium and potassium gradients across the cell. The influx of sodium in conjunction with cytoskeletal disruption results in cell swelling, which has been proposed to also contribute to renal dysfunction (308). Moreover, the mislocation of the Na⁺,K⁺-ATPase leads to increased Na delivery to the distal nephron, which further decreases GFR through the tubuloglomerular feedback mechanism.

The actin-binding protein family of ADF/cofilin proteins plays a critical role in the breakdown of the apical microvilli in response to ischemia (309,310). Ischemia induces rapid activation and relocation of ADF/cofilin from the cytoplasm to the apical cell membrane and membrane-bound vesicles in proximal tubule cells (310). These vesicles shed into the tubular lumen where they aggregate and cause obstruction, leading to increased intratubular pressure and subsequent decrease in GFR.

Reactive oxygen species (ROS) have been implicated as important effectors of cell injury in a variety of systems, including the kidney. Following ischemic injury, ROS generated by the injured tubular epithelium can induce perturbations in cytoskeletal structure and function that largely stem from reduction in ATP levels. ROS contribute to impaired ATP synthesis through several mechanisms. The activation of DNA repair enzyme poly(ADP-ribose) synthetase depletes cellular NAD (311). ROS also compromise mitochondrial respiration and function by impairing the ATP-synthetase complex and other components of the oxidative phosphorylation pathway (312). Moreover, ROS have been shown to act as signal transduction molecules in the regulation of gene transcription and in the activation of transcription factors such as nuclear factor-κB (NF-κB) and activator protein-1 (AP-1), which may lead to cell and tissue pathology (313,314). ROS are also generated by infiltrating leukocytes (315). There is further evidence of ROS-dependent injury up to 72 hours after reperfusion, compounds. Reperfusion with return of oxygen delivery enhances generation of oxygen free radicals, with resultant damage to cell components. An increase in intracellular calcium ion related to membrane injury enhances activation of injurious enzymes such as proteases and phospholipases. To some extent, these changes are reversible, but if severe or prolonged, they result in cell death. Definition of molecular mechanisms is a very active area of investigation; some major findings are outlined in the following sections (see Fig. 26.30).
demonstrating long-term complications of reperfusion in addition to the immediate damage by ROS generation (316).

Nitric oxide (NO) plays an important role in the pathogenesis of ATI, but its effects are complex. NO is generated by three separate nitric oxide synthase (NOS) enzyme systems, and its effects depend on site of production, duration of effect, and concomitant levels of other ROS. Endothelial NOS (eNOS) results in transient high-level NO release, activating potentially protective heme-containing enzymes such as guanylate cyclase, mediating vasorelaxation, and triggering an antiapoptotic phenotype. Treatment of mice with L-NAME, which is a non-specific NOS inhibitor, has been reported to worsen ischemic renal injury (317). In contrast, generation of NO by inducible NOS (iNOS) results in sustained NO levels that may lead to lipid peroxidation, DNA damage, and apoptosis. In vitro, NOS inhibition prevents hypoxic damage in fresh proximal tubular preparations (318), and transfection of iNOS antisense oligodeoxynucleotide (AS-ODN) prevented nitrite accumulation and lethal cell injury in cultured green monkey kidney (BSC-1) cells (319). Proximal tubules isolated from mice with targeted deletion of iNOS were resistant to hypoxia (320). Imbalance between eNOS and iNOS activities is therefore important in the pathophysiology of ARF (321,322). In vivo, oligodeoxynucleotide administration protected renal function and prevented tubular necrosis and decreased loss of brush border and cast formation (323). Effects of superoxide and NO may occur via formation of metabolites such as peroxynitrite and nitrotyrosine that cause tubular damage during ischemia (324,325). α-Melanocyte–stimulating hormone protects against experimental ischemia/reperfusion injury via blockade of both iNOS induction and leukocyte infiltration (326).

**Mechanisms of Apoptosis and Necrosis in Ischemic Injury**

Lethal injury to renal epithelial cells follows the same pathways and mechanisms that result in ischemic cell death in other cell types. Lethal injury can result in coagulative necrosis and/or apoptosis, depending on the nature of the agent and

**FIGURE 26.30** Graph depicting several important mechanisms of acute tubular cell injury, which are shown in separate parts of the cartoon labeled 1–6: (1) Ischemic injury due to prolonged vasoconstriction, which is mediated through cytokines such as endothelin-1. (2) Tubular cell injury due to cytokines, which are secreted by inflammatory cells, such as macrophages and plasma cells. (3) Lysosomal injury due to enhanced protein uptake by the brush border megalin receptor. (4) ROS-induced mitochondrial injury that may lead to the induction of mitochondrial proapoptotic pathways. (5) Cell death due to mitochondrial injury and subsequent loss of ATP production. (6) Cell injury due to enhanced lipid peroxidation leading to loss of Na+,K+-ATPase function with subsequent swelling and rupture of proximal tubular cells.
duration and severity of the insult. There is evidence that these two pathways may be parallel, may be activated by some of the same stimuli, and share common elements, including endonuclease activation, role of mitochondria, and activation of caspases (327). Apoptotic cells are rapidly removed from the environment, modulating the inflammatory responses to injury. Apoptosis may also be important in the tissue remodeling that occurs after tubular epithelial injury. Studies have also focused on the pathways that regulate cell death as potential targets for modulating recovery from acute renal injury (184).

One of the first studies to document apoptosis in ischemic ARF was conducted by Schumer et al. (328). A number of additional studies have described DNA laddering and morphologic changes consistent with apoptosis, which in vivo occurs predominantly during the reperfusion period (329–333). A large body of literature has addressed the signaling pathways that initiate or modulate apoptosis. The best characterized surface death receptors are members of the tumor necrosis factor superfamily, including Fas (CD95) and TNFRI (CD120a) (334,335). Mitochondria participate in inducing apoptosis after ischemia and reperfusion injury through multiple pathways, including generation of ROS, release of calcium, altered membrane permeability transition, and release of proapoptotic factors such as cytochrome c and AIF. These molecules activate downstream effector caspases that initiate the nuclear changes of chromatin condensation, fragmentation, and marginalization of chromatin. Caspases are cysteine proteinases (336), which can functionally be divided into initiator and effector caspases. The expression and activity levels of caspases are altered after ischemia-reperfusion injury (337). Caspases also affect proapoptotic oncogenes that mediate additional steps in the proapoptotic signaling process. Intracellular proapoptotic oncogenes (p53, c-myc, c-fos, Bax, Bad) and antiapoptotic oncogenes (Bcl-2 and Bcl-Xl) keep a delicate balance, which determines cell death or cell survival following ischemic injury. Activation of caspase-3 is mediated by Bax translocation from the cytoplasm to mitochondria and subsequent cytochrome c release through modification of the mitochondrial permeability transition pore (338,339). Several in vivo studies showed up-regulation of p53, c-myc, c-fos, and c-jun in renal tubule cells of ischemic kidneys during reperfusion (329,333,340,341). Bcl-2 mRNA and Bcl-2 protein have been shown in regenerating proximal tubule cells of the outer medullary region, indicating that the expression of antiapoptotic protooncogenes correlates well with the regeneration process following ischemic injury (341). Moreover, the proapoptotic oncogene Bax showed increased mRNA and protein expression within 1 to 7 days following ischemic injury in cortical collecting duct and medullary thick ascending limb of the loop of Henle (341). These data show that the regulation of antiapoptotic and proapoptotic oncogenes may vary within different cell types in the kidney, both during the acute phase of kidney injury and during the regeneration process in the recovery phase of the disease.

Actin disassembly and altered adherence of cells to the tubular basement membranes may trigger apoptosis (342,343). Caspases have also been shown to be able to use the cytoskeletal proteins fodrin and actin as substrates. It is interesting to note that their cleavage appears to have its peak at the same time as the peak of apoptosis during reperfusion after acute ischemia in experimental models, further suggesting the contribution of loss of polar distribution of Na\(^+\), K\(^+\)-ATPase (and therefore disruption of its function) not only in the development of necrosis but also in apoptosis.

Other cysteine proteases, such as calpain, have been shown to be activated in experimental ischemic/hypoxic injury to tubules in vitro (344,345). Inhibition of calpain attenuated hypoxic injury, decreasing lactate dehydrogenase release (346). Calpastatin, an endogenous cellular inhibitor of calpain activation, is down-regulated by caspases during hypoxia (345). Calcium activation of phospholipase A has also been shown to contribute to ischemic renal injury (347). Other mediators of apoptotic cell death include intracellular pH, calcium, free radicals, ceramide, and ATP depletion. Guanosine triphosphate depletion is an independent trigger of apoptosis via p53 (348). Guanosine triphosphate salvage with guanosine or pifithrin-α inhibits apoptosis with a protective effect on experimental ischemic injury (349).

Necrosis has long been thought of as a passive process as a consequence of ATP depletion, subsequently leading to cell swelling, membrane blebbing, and cell rupture. However, recent studies have shown evidence of active signaling steps in the generation of cell necrosis (350,351). A type of programmed necrotic cell death (necroptosis) requires the activity of receptor-interacting protein kinase 1 (RIP1 kinase) (352). Similarly, a programmed necrosis pathway independent of cell death receptor activation can be initiated by the assembly of a protein scaffold in the cytoplasm, termed “ripoptosome” (353). The protein complexes found in these pathways contain RIP1 and require its kinase activity but can result in either apoptosis or necrosis. The decision to engage in the necrosis pathway is dependent on the kinase activity of another enzyme, RIP3. RIP1 kinase activity however also contributes to the tubular epithelial damage in a mouse model of ischemia-reperfusion injury (354).

The ROS-mediated volume increase and calcium influx in necrosis are thought to be initiated by binding of free radicals to ion channels including nonselective Ca\(^{2+}\) channels, resulting in high intracellular calcium levels. Increased cytoplasmic calcium activates endonucleases to degrade DNA and to activate cellular proteases, such as calpain to degrade structural and signaling proteins, leading to cell collapse (355). Overactivation of poly(ADP-ribose) polymerase (PARP), one of the molecules involved in necrotic cell death, has been demonstrated in renal ischemia (356). This leads to cellular depletion of substrate NAD\(^+\) and ATP, inducing cell injury. Expression of proinflammatory factors and adhesion molecules is also increased in ischemic kidney with PARP activation. Inhibitors of PARP-1 or gene ablation have been shown to reduce energy depletion and inflammation and improve renal function in ischemic kidney (357). There is evidence that the mitogen-activated protein kinase (MAPK) pathway also plays a role in oxidant injury to the kidney. Up-regulation of extracellular signal-regulated kinase (ERK) by previous ischemic pretreatment has been shown to provide protection against ischemia/reperfusion functional injury and c-jun N-terminal kinase (JNK), p38, and MAPK activation (358). In an in vitro mouse proximal tubule preparation, inhibition of JNK activation of ERK ameliorated oxidant-induced necrosis (359), an effect mediated by cyclic adenosine monophosphate (AMP) response element–binding protein (360).

**The Inflammatory Response in Ischemic Injury**

The inflammatory response to ischemia has been invoked as an amplifier of ischemic injury during the reperfusion period in a variety of organ systems and has been the focus of recent investigation in ARF (361–363). Both innate and adaptive immune responses
play a role in the pathology of ischemic injury. While the innate response involves activation of neutrophils, monocytes/macrophages, and NK cells and usually occurs early after ischemic injury, the adaptive response is initiated within hours and may last over the course of several days after injury. The adaptive response includes dendritic cell maturation and antigen presentation, T-lymphocyte proliferation and activation, and T- to B-cell interaction. The tubular epithelial cell plays an active part in the inflammatory response following ischemic injury by generating proinflammatory and chemotactic cytokines, such as TNF-α, monocyte chemoattractant protein-1 (MCP-1), transforming growth factor-β (TGF-β), and several cytokines (361). Moreover, tubular epithelial cells express Toll-like receptors (TLRs), complement receptors, and other costimulatory molecules that regulate T-lymphocyte activity. TLRs are transmembrane receptors that can bind to either exogenous microbial proteins or endogenous ligands that are released following injury (364,365). Following ischemic injury tubular epithelial cells express increased amounts of TLR2 and TLR4, which modulate a proinflammatory response marked by release of cytokines (366).

Several studies have implicated T cells and B cells in the etiology of ischemic ARF. Marked depletion of T cells using anti-T-cell antibodies in thymectomized mice conferred protection of renal function and structure after ischemia/reperfusion (367). B-cell–deficient mice were also partially protected, with ischemic phenotype restored by serum transfer but not B-cell transfers (368). However, T- and B-cell–deficient mice (RAG-1 deficient) were not protected from ischemia/reperfusion injury, and adoptive transfer of B cells or T cells into these mice afforded partial protection, indicating complex interactions between T cells and B cells in this setting (369). The proximal tubular epithelium expresses MHCII and can present antigens to T cells and express costimulatory molecules (370). T-cell ligands, such as CD40, induce activation of cell surface receptors in proximal tubule cells (371). CD40 can induce production of the chemotactic cytokine CCL5/RANTES in human tubular epithelial cells, resulting in the recruitment of leukocytes to the place of injury (372).

In addition to T cells, neutrophils, macrophages, and dendritic cells are important contributors to ischemic injury. Neutrophils attach to the endothelium of the peritubular capillaries of the outer medulla within 30 minutes after ischemia/reperfusion (373). Neutrophils enhance the local production of proteases and ROS, which leads to increased endothelial permeability (374). Certain monocyte subsets migrate into the kidney and differentiate into macrophages or dendritic cells, depending on the underlying pathologic condition. Monocyte infiltration is mediated by the CCR2 and CX3CR1 signaling pathways (375,376). Monocytes can differentiate locally into M1 type (“inflammatory”) or into M2 type (“repair”) macrophages. M1 macrophages produce ROS, nitrogen intermediates, and inflammatory cytokines that enhance the Th1 immune response, while M2 macrophages enhance the Th2 response. Tubular injury can lead to activation of dendritic cells, which then present antigens that activate T cells, thus linking the innate with the adaptive immune response. In both the early and late phase of ischemia-induced AKI, both T lymphocytes and macrophages/dendritic cells can facilitate not only injury but also repair (377). Regulatory T cells are anti-inflammatory lymphocytes that facilitate repair in the ischemia-reperfusion mouse model (378).

Following ischemia-reperfusion injury to the kidney, activation of the complement system is predominantly mediated through the alternative pathway (379). CXC chemokine production by tubular epithelial cells is dependent on the activation of the alternative complement pathway (380). Complement C3 stimulates the expression of adhesion molecules on endothelial cells and leads to maturation of dendritic cells, which leads to activation of the T-cell response (381,382). Inhibition of the alternative pathway protects the kidney against ischemia-reperfusion injury (383,384).

**Renal Vasculature in Ischemic Injury**

Endothelial injury and dysfunction clearly play a role in initiation and especially the maintenance/extension phase of ischemic tubular injury (385). Endothelial cells are crucial in the regulation of vascular tone, leukocyte function, and smooth muscle responsiveness (386). Following ischemic injury, the small arterioles respond strongly to the effects of vasoconstrictive mediators such as endothelin 1, thromboxane A2, angiotensin II, and sympathetic nerve stimulation (387, 388). Studies have further documented the role of decreased levels of vasodilators, such as acetylcholine and NO in altering blood flow in response to ischemic injury (389,390). Imbalance in iNOS and eNOS, oxidative stress, and generation of peroxynitrite have roles in the pathophysiology (322). The resulting vasoconstrictive effect is further amplified by vasoactive cytokines such as IL-6, IL-12, IL-15, IL-18, IL-32, and endothelin, which are generated as a result of enhanced leukocyte-endothelial adhesion and leukocyte activation that are characteristic of ischemic kidney injury (361). Indeed, administration of a monoclonal antibody to intercellular adhesion molecule type 1 (ICAM1) protected the kidney from perfusion injury both functionally and histologically when administered at the time of bilateral renal ischemia. Furthermore, anti-ICAM1 protected the kidney when administered 0.5 to 2 hours after restoration of blood flow but not after 8 hours. The protection corresponded with the degree of neutrophilic infiltration and suggested that leukocyte-endothelial adhesion and migration do contribute to reperfusion injury in the kidney, as they do in other organs (391). In a complementary study, inhibition of leukocyte adhesion using antibodies to the leukocyte adhesion molecules CD11/CD18 also resulted in a significant protective response (392).

Alteration of regional blood flow is another important factor in the pathogenesis of ischemic kidney injury. Blood flow to the outer medulla is decreased disproportionally to total kidney perfusion in animal models of AKI and in humans following ischemic injury (393). Outer medullary congestion is a vascular hallmark of acute renal ischemia, and it has been proposed that this may worsen hypoxic injury to the S3 segments and medullary thick ascending limbs, which traverse this area of the kidney (393). This congestion and stasis could be the result of altered hemodynamics, increased viscosity, compression by interstitial edema and/or swollen tubular cells, and up-regulation of cell adhesion molecules with stasis of leukocytes. Some toxic agents, including ACE inhibitors, angiotensin 2 receptor blockers, and NSAIDs, exert toxic effects on the kidney via reduction of renal blood flow.

The endothelium further contributes to the pathogenesis of ischemic kidney injury through additional mechanisms. Endothelial cell damage leads to loss of glyocalyx; disruption
of the actin cytoskeleton, which leads to alteration of endothelial cell attachment to adjacent cells and basement membrane; and breakdown of the perivascular matrix leading to increased microvascular permeability and loss of fluid to the interstitium (394, 395).

Another detrimental effect of ischemic injury on the renal microvasculature is the decline of peritubular capillary numbers, especially in the outer medulla. This leads to decrease in VEGF synthesis and enhanced production of inhibitors of angiogenesis (394, 396). Loss in total number of peritubular capillaries leads to chronic hypoxia, which perpetuates tubular injury and leads to progression of interstitial fibrosis (394, 397). Moreover, there are functional consequences of vascular dropout in the kidney medulla, including the development of salt-sensitive hypertension and altered concentration ability (394).

**Regeneration following Tubular Injury**

Reestablishment of normal cell organization comes about during recovery from renal ischemia at a rate dependent on the severity and duration of the insult; it is preceded by restoration of cellular ATP. Restoration of basal lateral Na⁺,K⁺-ATPase localization and of the brush border is a necessary prerequisite for restoration of tubular function (306, 307, 398). Restored localization of basolateral Na⁺,K⁺-ATPase is not caused by new synthesis of Na⁺,K⁺-ATPase subunits, rather than increased biosynthesis, is the way in which renal tubule cells repolarize after an ischemic insult. Similar recycling of apical membrane proteins occurs in the restoration of the brush border. The role of heat shock proteins can be invoked in this process, because they can serve as chaperones to protect the misfolded or misplaced proteins from degradation until ATP levels are restored and reorganization can take place (400).

Proper organization of the fodrin cytoskeleton is necessary to maintain Na⁺,K⁺-ATPase in its basolateral location. Fodrin is able to self-associate and bind actin (401), a process modulated by a unique regulatory cascade. Studies have demonstrated that this regulatory cascade appears to be involved in the disruption of the Na⁺,K⁺-ATPase ankyrin-fodrin complex following ischemia in hippocampal neurons as well as in the kidney (300). After 45 minutes of renal ischemia, the presence of fodrin cleavage products can be detected. Cleavage products increase during reperfusion, peaking at 6 hours; afterward, there is a gradual return to a normal pattern, which corresponds to the repolarization of Na⁺,K⁺-ATPase to the basolateral membrane. This temporal pattern suggests that fodrin has a role in the loss and return of Na⁺,K⁺-ATPase polarity after ischemia and during recovery. Cleavage of the cytoskeleton and initiation of the stress response can also result from activation of the enzymes involved in the programmed cell death pathway that leads to apoptosis (342, 343, 402).

The response of ankyrin to renal ischemia is similar to that of Na⁺,K⁺-ATPase. After ischemia, there is a loss of the normal distribution of ankyrin, and ankyrin is immunodetected in the apical domain and in subapical vacuoles. During recovery, ankyrin codistributes once again with Na⁺,K⁺-ATPase to the basolateral membrane. Examination of ankyrin turnover after renal ischemia has yielded interesting results that may help in analyzing its role in recovery. Kidney tissue that has been rendered completely ischemic displays a major time-dependent loss of ankyrin that is essentially complete after 2 hours of ischemia (403). This profound loss is not accompanied by the appearance of proteolytic degradation products and was not observed in the ischemic brain or heart. These observations suggest that ischemia causes significant tissue-specific inhibition of ankyrin mRNA transcription, stability, or translation.

Studies of the biosynthetic response of ankyrin during recovery from renal ischemia have revealed that shortly after reperfusion, there is a significant loss of immunodetectable ankyrin associated with a concomitant loss of Na⁺,K⁺-ATPase polarization. However, after 6 hours of reflow, the amount of ankyrin increases to levels close to those of control kidney at a time when restitution of Na⁺,K⁺-ATPase polarity has commenced. After 24 hours of reperfusion, immunodetectable ankyrin levels exceed control levels concomitant with the restitution of Na⁺,K⁺-ATPase polarity. These studies also suggest the potential role of the stress response (or the heat shock response) in ankyrin processing. This could occur by protecting the transcriptional apparatus for ankyrin so that its rapid synthesis can take place at a time when other protein synthesis is restricted. A second possibility is that the loss of ankyrin immunoreactivity is the result of interaction with heat shock protein 70, resulting in a pool of ankyrin available for recycling (399).

Disruption of the cytoskeleton is associated not only with loss of cell polarity of transport proteins but also with relocation of basal integrins, tethered via the cytoskeleton and associated binding proteins in the basolateral domain. For example, nonlethal oxidative stress in cultured mouse tubular cells disrupts focal adhesion sites and is associated with redistribution of integrins to the apical domain (404). This results in disruption of the interaction of the cell with the underlying matrix, with loss of attachment of the epithelial cells from the basement membrane. Both cell-matrix and cell-cell adhesion may be disrupted with ATP depletion (405). Inhibition of cell-matrix adhesion in vitro by hydrogen peroxide has been shown to be reversible; recovery was associated with increased alpha-6 integrin expression (406). Inhibition of integrins during recovery can in turn lead to increase in cell apoptosis (407). Exfoliation of the epithelium into the tubular lumen can occur while the cells are still viable (180). Exfoliated cells and cell debris may interact with other epithelial cells, potentially with Tamm-Horsfall protein as a matrix. Aggregation of the exfoliated cells and adhesion to basally oriented cells may result in tubular obstruction. These exfoliated cells may interact with other cells via surface integrins (408). Arginyl-glycyl-aspartic acid (RGD) peptides, which block these interactions, have been shown to ameliorate ARF in vivo (409). Gaps in the tubular epithelial barrier via cell loss or altered tight junctions could also be sites of back leak of glomerular filtrate.

**Heat Shock Protein and Other Chaperones in Acute Tubular Injury**

Heat shock proteins (hsp) are molecular chaperones that play a key role in the adaptive response of cells to stress conditions. Both the gene expression levels and protein abundance of hsp70 and hsp27 increase in response to ischemia (410). The message for inducible hsp70 is found within minutes of an ischemic
insult (410). Hsp70 is a molecular chaperone that is involved in protein folding (411). Since hsp 70 prevents aggregation and refolding of denatured proteins, up-regulation of hsp 70 has been found to be cytoprotective in kidney cells (412). The inducible protein appears shortly after the message and accumulates over several days after the injury. The protein is found in membrane fractions as well as in cytosol, suggesting that it may be complexed with a variety of proteins that have been disassembled or denatured as a result of the ischemic insult (412). Hsp25, the murine homolog of hsp 27, can be detected in vivo in renal epithelium, especially in proximal tubular cells.

The induction of hsp70 under stressful conditions has been found to occur rapidly through activation of the heat shock factor (hsf). Hsf is a constitutively active transcription factor that is inhibited by hsp70 under normal conditions. However, increased levels of denatured proteins compete for binding of hsp70 and thereby initiate activation of hsf, resulting in increased transcription of hsp genes (413). While a variety of injurious agents result in protein degradation and hsp activation, the initial mechanisms of induction may differ. Adenosine triphosphate depletion, increases in intracellular calcium, decreases in intracellular pH, activation of phospholipases, and release of arachidonic acid metabolites have been shown to either initiate or modulate the heat shock response in a variety of cell systems.

There is evidence of the importance of hsp during recovery from ischemia (414,415). Following renal ischemia and hsp70 induction, disrupted proteins such as Na,K-ATPase are restored within the cytoskeleton, which correlates with recovery of proximal tubule cells from ischemia (416,417). In ATP-depleted LLC-PK1 cells, inducible up-regulation of hsp70 protects against apoptosis (418). In vivo, up-regulation of hsp70 improves recovery from ischemia/reperfusion, associated with protection from apoptosis (419). The protection of cells from apoptosis by heat shock proteins depends on the subunit involved in refolding of damaged proteins and is apparently upstream from the mitochondrial-dependent activation of apoptosis. Heat shock protein 70 also affects signaling pathways for onset of apoptosis. This heat shock factor interacts with protein complexes such as apoptosis signal–regulating kinase 1 (ASK1) and binds to the caspase activator recruitment domain of apoptosis protein–activating factor, preventing activation of caspases and apoptosis.

Other protective mechanisms are also being defined. Caveolae are plasma membrane structures containing proteins. The caveolins are potential participants in protection and repair in both ischemic and toxic renal injury (420). Altered caveolin-1 expression and localization may affect renal cell survival following oxidative stress. Up-regulation of caveolin-1 has been demonstrated in ATI (421,422). More studies are required to determine whether this up-regulation contributes to cell survival or is an epiphenomenon. Lipoxins are lipoygenase-derived lipid mediators with anti-inflammatory and prorepair properties. There is some experimental evidence that these compounds have therapeutic potential in ARF. Bioactivity of lipoxins is mediated through receptor cross-talk (423). KIM-1 appears in the urine early during AKI and is potentially a reliable and early biomarker of renal damage. The protein contains a novel immunoglobulin–like domain and a mucin domain and is up-regulated in renal injury in dedifferentiated cells undergoing replication (196,424). It is proposed that shedding of this molecule allows the tubular epithelial cells to move and reconstitute the tubular epithelial barrier (425).

Improved understanding of the interesting interrelationships among alterations of cellular metabolic processes, the integrity of cellular structure and function, and those systems that may serve to protect or repair the injured epithelium will doubtless provide insights into the type of fundamental biologic processes that may be modified therapeutically to modulate the severity of injury and enhance recovery.

**STEM CELLS AND GROWTH FACTORS IN TUBULAR EPITHELIAL INJURY AND RECOVERY**

While cells that have suffered anoxia-induced sublethal injury can recover, those cells that are lethally injured must be replaced. Renal epithelial cells are stable cells that do not normally divide but must be stimulated by growth factors to undergo mitosis. A number of growth factors have been shown to play an important role during renal development and also in reparative processes following ischemic injury: They include epidermal growth factor (EGF)-like peptide, insulin-like growth factor type 1 (IGF-1), and hepatocyte growth factor (HGF). EGF is a ubiquitous polypeptide growth factor capable of stimulating proliferation of many different epithelial cells. Administration of EGF to animals with ischemic ATN shortens the recovery time (426). This is likely due to activation of downstream cell survival pathways. In addition to EGF, a number of growth factors are activated in sublethally injured cells following anoxia; they include IGF-1 and HGF. IGF-1 has stimulatory effect on cell growth and regeneration, and its receptor is abundantly expressed in the proximal tubule. Following ischemic injury, expression of IGF-1 is up-regulated in surviving proximal tubule cells (427,428). Although several different mechanisms of action have been proposed, including changes in the GFR, the effect of IGF-1 on enhanced DNA synthesis and its action as an anabolic agent seem most likely to be important in the beneficial effects that are achieved (429). Similar results have been obtained with HGF administration, but whereas IGF-1 has a definite anabolic effect, HGF appears to exert its effects primarily by enhancing DNA synthesis. In animal models of ischemic tubular injury, HGF therapy markedly accelerates renal recovery (430). HGF also promotes adhesion of tubular cells to the basement membrane, decreasing cellular loss and preventing obstruction (431). Moreover, HGF helps to maintain cell polarity through preserved E-cadherin expression (432). It seems likely, therefore, that each of these growth factors contributes in different ways to the recovery process and that they act synergistically to achieve resolution of the injury (429).

Restoration of structure and function following ATI is dependent on the replacement of necrotic or exfoliated tubular epithelial cells by viable epithelium. Several possible mechanisms have been suggested to participate in the regeneration of tubular epithelial cells. Wound healing may occur by extension of adjacent viable epithelial cells to close gaps along the basement membrane through proliferation of existing tubular epithelial cells stimulated by paracrine growth factors. There is evidence from studies of ischemic injury in chimeric mice that restoration of epithelial integrity resulted from intrinsic tubular cell proliferation and not from circulating bone marrow–derived cells (433). Using a genetic tag to label mesenchyme–derived renal epithelial cells, a recent study found that 95% of regenerated
tubular epithelial cells in a model of ischemia-reperfusion carried the genetic tag and that no dilution of cell fate marker was observed (183). These findings indicate that tubular repair is predominantly a function of cell proliferation. However, studies of transplanted kidneys of male patients who received an allograft from a female donor have demonstrated a potential role for recipient-derived cells in reconstituting epithelial damage (134). Other studies have suggested that circulating recipient cells (presumably circulating pluripotent cells) play a role in renal remodeling after injury (435–437). Moreover, experimental studies from several different groups have demonstrated that hematopoietic stem cells are capable of protecting the kidney from ischemic injury and assisting in repair and recovery from ischemia/reperfusion and toxin-induced injury (437–440). In one study, mobilization of bone marrow cells by granulocyte colony-stimulating factor rescued mice from cisplatin-induced renal failure, an effect enhanced by macrophage colony-stimulating factor (M-CSF) (441). While all groups concluded that the majority of tubular repair occurred via proliferation of endogenous renal cells, the exact mechanism by which renal trophic stem cells participate in this repair was unclear.

Several studies have demonstrated that administration of in vitro expanded stem cells may protect against and/or enhance recovery from ATI (435,436,442–444). Necrotic lesions in the proximal and distal nephron may mediate migration of mesenchymal stem cells (MSC) to the kidney. MSC may have a stimulatory effect on the proliferation rate of residual tubular epithelial cells (443). Moreover, one study found that MSCs injected after ischemia-reperfusion injury had a beneficial effect, but only if conditions favored differentiation of MSCs to endothelial cells (433). These findings indicate that stem cells might have an important role in the regeneration process of tubular epithelial cells through unknown factors, which might act in a paracrine fashion upon injured epithelial cells.

**Drug Toxicity and Acute Kidney Injury**

In vivo and in vitro experimental models have been used to identify the underlying pathogenic mechanisms of renal tubular injury produced by the various types of drugs. Aminoglycoside antibiotics and cis-platinum have been the most widely studied nephrotoxic drugs; pathogenesis of injury owing to these and other agents is discussed in detail later in this chapter. Some drugs and toxins are injurious in their native form. In other cases, metabolic by-products are the actual injurious agents. Drug catabolism may take place in the liver, at other systemic sites, or in the renal epithelium. In the case of many drugs and toxins, injury to the nephron may be zonal, depending on the site of uptake or catabolism. A few agents specifically injure segments of the proximal tubule (e.g., aminoglycosides), whereas others produce effects distally (e.g., lithium).

Polymorphisms of genes encoding proteins involved in the metabolism and renal elimination of drugs have been described and correlate with various levels of drug sensitivity. Loss of function mutations in apical secretory transporters and mutations in kinases that regulate drug carrier proteins can impair drug elimination and promote toxicity by elevating intracellular toxin concentrations (445). Cells of the loop of Henle exist in a relatively hypoxic environment due to the high metabolic rate required to actively transport solutes via the Na⁺,K⁺-ATPase–driven transport. This excess cellular workload and hypoxic environment promote increased sensitivity to injury when exposure to nephrotoxic substances occurs (446). Elevated tissue concentrations of toxic compounds in the medulla promote toxic injury through direct cell toxicity or by ischemic damage as a result of decreased levels of vasodilatory prostaglandins.

Toxic agents may interfere with normal mitochondrial function and oxidative metabolism, leading to depletion of high-energy phosphate compounds, which causes impairment of ATP-dependent enzymes and cell transport mechanisms. Some alter lysosome function and integrity, causing leakage of digestive enzymes leading to cell membrane injury or disrupted protein synthesis. ROS compounds may be produced by systemic or local metabolism of a drug, by impaired mitochondrial function, or by drug effects on cell metabolism. Free radicals can interact with lipids to produce membrane damage and with proteins to alter cellular enzyme activity. Membrane damage results in loss of critical cell compartmentation, leading to loss of the normal cellular distribution of ions and the breakdown of gradients that drive critical cell processes. Increased concentrations of intracellular ionic calcium result in impaired cell enzyme function and breakdown of cytoskeletal elements, causing loss of the normal cell substructure.

While apoptotic mechanisms play an obvious and important role in ischemia–reperfusion injury, their contribution to toxic nephropathies may be even more complex. Toxins may initiate apoptosis not only through the mitochondrial pathways discussed above but also by directly initiating the signaling pathway for tumor necrosis factor signaling pathway or through p53 via genotoxic stress. Paracetamol toxicity has been linked to the direct activation of Bcl-xL in mouse proximal tubular cells in culture (447). The antiviral drug cidofovir has been shown to induce apoptotic epithelial injury in renal biopsy and human renal tubular cells in culture, via direct effects on epithelial cell membranes (223). Exposure of proximal tubule cells in vitro to cisplatin induced phosphorylation of the proapoptotic protein Bad (211).

Some nephrotoxic agents interfere with renal function by altering renal hemodynamics. In some cases, the effects are prerenal, but tubular epithelial cell injury may ensue if vasoconstriction/hypoperfusion persists. In addition, inflammatory cells may play a role in some forms of toxic injury. Finally, mechanisms of recovery are likely analogous to those described for ischemic injury. Removal of the offending agent or significant reduction in dose may be necessary to allow recovery.

There is currently a focus on prediction of nephrotoxic action by identification of toxicity-related biomarkers (448,449). Profiling of gene expression microarray in rats exposed to a range of nephrotoxins revealed clustering based on similarities in severity and type of pathology. A set of potential biomarkers showing time- and dose-response related to progression of proximal tubular toxicity included several transporters: KIM-1, IGF bp-1, osteopontin, α-fibronectin, and glutathione transferase (Gst-α). Other potential biomarkers include c-myc, multidrug resistance gene (MDR-1), clusterin, vimentin, and hepatitis A virus cell receptor (HAVcr-1) (450). Similar studies in cynomolgus monkeys using gentamicin and everninomicin as nephrotoxins confirmed modulation of genes identified in rodent models, including uaf-1, matrix metalloproteinase-9, and vimentin. Three early gene biomarkers predictive of drug-induced nephrotoxicity included clusterin, osteopontin, and HAV cr-1 (451).
Mechanisms and Treatment of Drug-Induced Renal Injury

Antiviral Agents

Tubular cell necrosis is a common consequence of toxic injury due to antiviral drugs (i.e., foscarnet, acyclovir, and cidofovir). However, certain antiviral agents may cause more subtle injury without cell necrosis or apoptosis, resulting in isolated tubular defects such as Fanconi syndrome (cidofovir, tenofovir), distal tubular acidosis (foscarnet), and nephrogenic diabetes insipidus (foscarnet) (284,452).

Accumulation of high intracellular concentrations of antiviral drugs is a major mechanism of injury (207). Moreover, intrarenal obstruction occurs due to crystalline deposits that form in the renal tubules in response to acyclovir, ganciclovir, and indinavir therapy (207). Deposition of crystals in the kidney is seen with a variety of these agents, including acyclovir and indinavir (453,454).

Several of these agents have relatively low solubility in urine; rapid infusion, volume depletion, and underlying renal insufficiency are important risk factors for crystal formation.

There is experimental evidence that acyclovir has additional direct effects on tubular function. A recent study showed that acyclovir is the substrate for the human breast cancer resistance protein (BCRP) (455). BCRP plays a role in acyclovir transport in human kidney cells and may also play a role in acyclovir-dependent nephrotoxicity. Moreover, increased influx of drug via organic ion transporters, or decreased efflux via the multidrug resistance protein (MRP), may enhance acyclovir cytotoxicity (456,457). Genetic defects in transporters, such as organic anion transporters (OATs) and organic cation transporters (OCTs), or in MRP may induce renal insufficiency. Nucleoside analogs, such as cidofovir, enter the cell by the hOAT or hOCT system (456,458). Increased uptake through this transport mechanism induces proximal tubular injury. Moreover, drug interactions may increase the nephrotoxic potential of certain antiviral drugs. Tubular secretion of lamivudine is significantly impaired by trimethoprim in the isolated perfused rat kidney and in humans, suggesting that the two drugs share a common organic cation transport (459). This leads to increased accumulation of intracellular toxic levels of lamivudine.

Programmed cell death and effects on mitochondrial function have been invoked as potential mechanisms of renal toxicity of antiviral agents (44). Stimulated by tubular cell apoptosis in a renal biopsy of a patient with irreversible ARF caused by cidofovir, Ortiz et al. (223) studied induction of apoptosis in primary cultures and a cell line (HK2) of human proximal tubular cells with time and dose parallel to clinical toxicity. Apoptosis was prevented by probenecid and by an inhibitor of caspase-3. IGF-1 and HGF were protective as well. Additional proapoptotic pathways may be induced when antiviral drugs damage mitochondria. The human equilibrative nucleoside transporter 1 and the apical human concentrative nucleoside transporter 1 in mitochondrial membranes (460,461) are transporters important in mediating the transport of nucleoside and nucleotide (i.e., antiviral and anticancer) drugs across membranes (462). Didanosine, zalcitabine, stavudine, and zidovudine are substrates of human nucleoside transporter, which likely plays a role in intracellular accumulation of these drugs.

Some antiviral agents, such as foscarnet, induce nephrogenic diabetes insipidus by down-regulation of the water channel aquaporin-2 or inhibition of vasopressin responsiveness. The proteinuria seen in patients treated with cidofovir is likely caused by tubular injury and failure of normal resorption.

Aminoglycosides

Molecular mechanisms in aminoglycoside toxicity have been reviewed (463,464). Aminoglycosides are freely filtered by the glomerulus and are not metabolized in the body. About 10% of intravenously administered drugs accumulate in the kidney, with little uptake in other tissues. A key aspect of aminoglycoside nephrotoxicity is the tubular toxicity. Treatment of experimental animals results in both apoptosis and necrosis of tubular epithelial cells. Gentamicin toxicity occurs in the epithelial cells of the cortex, especially in the proximal tubule but also in the distal tubule and collecting duct (465). At the brush border of proximal tubular cells, polyatomic inositol phospholipids serve as the binding site. Megalin and cubulin form a giant endocytic receptor complex, which is expressed at the apical membrane of the proximal tubule. This complex plays a major role in binding and transporting these drugs by endocytosis (463). Aminoglycosides then traffic through the endosomal compartment and accumulate in the lysosomes, Golgi apparatus, and endoplasmic reticulum (466). Studies in megalin knockout mice demonstrated almost no renal accumulation of H₄-gentamicin, compared to 10.6% of the total dose accumulated in the kidney in control animals (466). Other megalin ligands also have been shown to reduce gentamicin accumulation and nephrotoxicity (467). There is some evidence that gentamicin is trafficked retrogradely through the secretory pathway and is released into the cytosol via the endoplasmic reticulum (468).

Clinical pathologic findings and experimental studies support the direct toxic effects of aminoglycosides on renal tubules. These drugs induce formation of myeloid bodies containing phospholipids and proteins, apparently related to proximate cationic side chains and an apolar ring structure, resulting in a high affinity for the phospholipid components, and especially the acidic phospholipids, of cell membranes. Via binding, aminoglycosides also inhibit lysosomal phospholipases, leading to accumulation of phospholipid myelin figures in the lysosomes. The interaction of the drugs and the membranes leads to lamellar aggregates and lysosomal drug accumulation (469). Membrane aggregation correlates with the toxic potential of aminoglycosides and may contribute to its toxicity (470).

Aminoglycosides have been shown to traffic rapidly to the Golgi complex in cell culture. Cells previously depleted of nucleotides accumulated significantly more gentamicin within a dispersed Golgi complex (471). Destabilization of lysosomal membranes allows escape of enzymes, which cause further cell injury. The lysosome bears the highly active proteases cathepsins, which mediate cell death by directly cleaving execution caspases and inducing the proteolytic activation of the proapoptotic factor Bid (472,473). In addition, aminoglycoside in the cell cytoplasm interacts with mitochondrial membranes and microsomes. There has been evidence for some time that gentamicin inhibits mitochondrial respiration and cellular protein synthesis (474). Aminoglycosides affect protein synthesis as well as protein-protein interactions involving protein disulfide isomerase (PDI). Gentamicin and ribostamycin have been shown to bind to PDI, an enzyme that stabilizes some proteins and participates in mechanisms degrading misfolded proteins in the cell, inhibiting its chaperone activity (475–477). Gentamicin binds to a number of kidney microsomal proteins, including calreticulin, a chaperone protein, and has selective effects on chaperone activity of this molecule in vitro (477).
Gentamicin also enhances the generation of reactive oxygen metabolites in renal cortical mitochondria, and many studies suggest that oxygen and hydroxyl radicals have an important role in gentamicin-induced ARF (478). Chelators and antioxidants depress aminoglycoside-induced oxidant stress (479,480). Gentamicin-induced ROS are inhibited by N-nitro-L-arginine methyl ester (L-NAME), consistent with a role for endothelin receptor–β/NO pathway in toxicity (481). Aminoglycosides stimulate endothelin 1 and subsequently NO in proximal tubules (482), which can be blocked by L-NAME. Aminoglycosides also increase intracellular calcium levels and ERK activity in proximal tubular cell lines, correlating with cell injury (483). The effects of different aminoglycosides followed the pattern of known in vivo toxicity. These changes, and lethal cell injury, presumably result from the mechanisms of action described earlier.

The N-methyl-D-aspartate (NMDA) receptor plays a major role in gentamicin-induced ototoxicity, and expression of NMDA receptor has been shown to be increased in gentamicin-induced renal toxicity in rats. Endothelin B receptor expression and urinary nitrite concentration were also significantly increased, with increases in blood pressure, urine pH, and creatinine; an NMDA receptor antagonist ameliorated these effects (484). Calpain isoforms were unaltered by the short-term regimen used.

Mechanisms of fibrosis and progression following gentamicin exposure have been explored. In one study, rats treated with gentamicin were sacrificed at 5 and 30 days after drug injections. Fibronectin, α-smooth muscle actin (myofibroblast marker), ED-1 (monocyte marker), endothelin, angiotensin II, and TGF-β were all increased in renal cortex compared with controls. At 30 days, treated rats also had fibrosis and increased TGF-β content in cortex, despite normalization of creatinine (485).

Amphotericin B has been shown to bind to sterol-containing membranes, causing changes in their permeability via formation of intramembranous pores (486,487). This property, which underlies its antifungal efficacy, may also cause the vascular or tubular toxicity produced by the drug. Studies in rats have shown potentiation of tubular toxicity, as measured by fractional excretion of sodium, with potassium depletion (488). Amphotericin also affects water and urea transport in the inner medullary collecting duct. While amphotericin B causes hypokalemia, which may itself produce a concentrating defect, the defect may be seen with normal serum potassium as well (489). It may also come about in part as the result of the fall in the GFR that can develop in these patients.

In dogs and rats, vasoconstriction has been documented after infusion of amphotericin into the renal artery (490). Experimental studies in the rat have suggested that the vasoconstriction brought about by amphotericin B is in part thromboxane mediated (491) and involves activation of the tubuloglomerular feedback response (492). It appears, however, that the vasoconstriction brought about by amphotericin may also be the result of a direct effect on renal vessels.

Cephalosporins appear to be capable of producing direct toxic injury to tubular cells. Tune and Hsu (493) have shown that cephalosporins interfere with mitochondrial function in the renal tubule via inhibition of substrate transport across the mitochondrial inner membrane. Cephaloridine has structural homology to carnitine, and it has toxic effects on carnitine transport and fatty acid metabolism in rabbit renal cortical mitochondria in vivo; in vitro effects on pyruvate metabolism were seen, although only at very high concentrations (493). Cephaloridine also produces lipid peroxidation and acylation and inactivation of some tubular cell proteins. Other cephalosporins that lack cephaloridine’s side group constituents largely affect tubular cell proteins and especially mitochondrial anionicsubstrate transporters. In vitro, proximal tubular cells show evidence of cytotoxicity on exposure to cephaloridine (greatest injury), cephalaxin, and cephalothin, while distal tubules do not; these studies provide evidence of the role of oxidative stress, cytochrome P450 activation, and mitochondrial dysfunction in tubular cell toxicity (494). Cytochrome C oxidase has been shown to be a target in LLC-PK1 cells (495).

Cephalexin, ceftazidime, and cefotaxime have also been shown to produce dose-dependent disruption of LLC-PK1 monolayers in vitro, as measured by transethelial potentials, morphologic changes, and enzyme release (496). Cephaloridine was the most toxic and cefotaxime the least toxic, dose for dose. Proximal localization of injury is apparently the result of concentration of drug within these cells; the drug readily enters the cell via the OATs, but it is a poor substrate for efflux pumps and most of it accumulates in the cell. Despite these experimental findings, clinically significant cases of renal tubular toxicity are rare at the recommended doses of these agents, and newer agents have even less toxic potential.

In addition, cephalosporins are known to cause hypersensitivity reactions. In some cases, there has been resolution with drug withdrawal and, in a few cases, recurrence on rechallenge (497). The cephalosporins are structurally similar to the penicillins, which produce similar reactions, and cross-reactivity may occur in 1% to 20% of patients. No specific cephalosporin is more likely than others to cause such a reaction.

### IMMUNOSUPPRESSIVE/IMMUNOMODULATORY AGENTS

**Cyclosporine**

Cyclosporine is very lipophilic, circulating in plasma and erythrocytes and accumulating in the liver and adipose tissue. It is extensively metabolized in the liver; its metabolites are minimally nephrotoxic. Most excretion is in the bile. It interacts with many other drugs through the hepatic cytochrome P450-3A system. Cyclosporine binds in cells to cyclophilin, which interacts with calcineurin to inhibit the enzyme, affecting a wide variety of downstream genes via its substrate, nuclear factor of activated T cells (NFAT). The latter in turn regulates transcription of interleukin-2 (IL-2), TNF-α, and granulocyte-macrophage colony-stimulating factor. Calcineurin also regulates transcription of IL-2 receptor, NO synthase, TGF-β, endothelin-1, collagen types I and II, and Bel-2 protein (94,498).

Intrarenal vasoconstriction appears to be the central pathogenetic mechanism for most types of CsA nephrotoxicity (95,499). This vasoconstriction can result from a direct vasoconstrictive effect, endothelin mediation (499), increased local production of angiotensin in renal vessels without the usual compensatory release of vasodilatory prostaglandins (500), activation of the sympathetic nervous system, selective impairment of endothelium-dependent relaxation related to prostaglandins or NO release, or increased thromboxane production (93).
Several lines of evidence implicate the role of endothelin in the vascular effects of CsA. Endothelin plasma and urine levels have been shown to be elevated in CsA-treated patients, and in vitro, CsA causes cultured vascular cells to release endothelin (501,502). Antiendothelin antibody or receptor blockade prevents a CsA-induced fall in the GRF in rats (503). Cyclosporine also up-regulates endothelin receptors in the kidney of rats (93). Thromboxane receptor blockade or modulation of thromboxane metabolism has been shown to reduce CsA toxicity in experimental animal models (93). In addition, inhibition of thromboxane synthetase has been demonstrated to improve renal allograft function in patients taking CsA (93). Platelet-derived growth factor, another vasoconstrictor substance, has been found to be increased in arterioles of CsA-treated rats (504). Another intriguing finding is markedly enhanced immunostaining for vascular clusterin after 4 and 6 weeks of CsA treatment in the rat (505). Clusterin has a variety of effects, including chemotactic effects, in injured and regenerating tissue.

The nephrotoxic effect of CsA appears to be tightly linked to its immunosuppressive effects (241). The mechanisms of action of CsA as an immunosuppressive drug involve binding to cyclophilin, a 17-kD basic cytosolic polypeptide with peptidyl-prolyl cis-trans isomerase activity. This enzyme is involved in protein folding, an activity that is inhibited by immunosuppressive concentrations of CsA. Kidney androgen-regulated protein (KAP) specifically interacts with cyclophilin B; KAP levels are decreased in CsA-treated rats. Overexpression of KAP in proximal tubular cells significantly decreased toxic effects of CsA, a protective stress response (506). The intracellular target of cyclophilin A-CsA is calcineurin, a protein phosphatase required for signaling via the T-cell receptor (93). Calcineurin regulates both baseline and receptor-activated Na/K-ATPase activity (507). There is evidence that CsA also decreases cell levels of the calcium-binding protein calbindin D (508,509), which increases urinary calcium excretion, promoting intratubular calcifications that can be seen with CsA toxicity.

Administration of cyclosporine and also tacrolimus may lead to the development of thrombotic microangiopathy. The main mechanism is through endothelial damage due to ischemia caused by vasoconstriction. Calcineurin inhibitor–mediated hyperaggregation of platelets contributes also to the activation of prothrombin factors (510). Withdrawal of CsA with conversion to tacrolimus or sirolimus is often a sufficient therapeutic measure (511,512). A variety of additional factors may act together to injure the endothelium; these factors include inflammation and hypertension. Moreover, it has been shown experimentally that at high doses, CsA exhibits direct endothelial toxicity in vitro (513). At lower doses, it may inhibit endothelial repair (514).

The hyaline arteriolar lesions observed in humans have been difficult to reproduce in experimental animal models, with the exception of the spontaneously hypertensive rat. However, Young et al. (515) reported such a model in persistently salt-depleted rats. The lesions, first detected at day 10, began with granular eosinophilic transformation of smooth muscle cells in afferent arterioles, followed by vacuolation of smooth muscle cells and discrete hyaline deposits in vessel walls. Immunocytochemistry and electron microscopy revealed accumulation of renin granules in the smooth muscle cells. It is possible that the lesion is more likely to develop clinically if the arterioles are abnormal before CsA treatment. Indeed, CsA nephrotoxicity appears to be much more severe in patients with preexisting kidney disease, and age has been identified as an additional risk factor (93). A more recent study attributed the pathogenesis of the arteriolar hyaline lesions to the important role of calcineurin-NFAT in smooth muscle cells (516).

Tubular injury may be enhanced by the antiproliferative effects of CsA on renal tubular cells, an effect which may be explained, in part, by stimulation of TGF-β expression in renal tubular cells (517). In vivo, CsA significantly inhibits H3-thymidine incorporation in a time- and dose-dependent manner; p53 levels increased coincident with cell cycle arrest (518). Oxidants may play a role in tubular cell injury in CsA toxicity. Renal lipid peroxidation has been shown in vivo and in vitro. Acute calcineurin inhibitor toxicity is often associated with cytoplasmic vacuolization, induced by endoplasmic reticulum enlargement and multiplication of lysosomes (247). Cyclosporine induces endoplasmic reticulum stress in tubular cells and endothelial cells, which can contribute to cell death (519–522). Atrial natriuretic factor reduces toxicity in renal cells via cyclic guanine monophosphate and heme oxygenase (523). Melatonin is also protective in isolated perfused rat kidney (524). In vitro exposure of LLC-PK1 cells to CsA increased glucose consumption and pyruvate production, consistent with a shift to glycolysis; interruption of glucose influx and glycolysis increased lactate dehydrogenase release, whereas the Glut-1 gene was protective (525). In primary cultures of rat renal epithelial cells, CsA-induced increases in mitochondrial Ca2+, reduction in mitochondrial membrane potential, and reduction in ATP have been detected; all these changes may play an important role in CsA-related cell cytotoxicity (526). However, while direct treatment of cells in vitro inhibits mitochondrial respiration, cells isolated from CsA-treated rats showed mitochondrial inhibition only at high dose (75 mg/kg/d), not at immunosuppressive doses (527). Cyclosporine-induced apoptosis has been described in a murine cell line in vitro at relatively low doses. However, despite increased expression of apoptosis-stimulating fragment (Fas) and evidence of endoplasmic reticulum stress, the pathway of apoptosis did not involve apoptosis-stimulating fragment ligand (FasL)-induced mechanisms of caspase-12 but instead involved Bax translocation to the mitochondria and activation of caspases 2, 3, and 9 (528).

Charuk et al. (529) found that CsA has a high affinity for human renal P-glycoprotein and also described enhanced cell accumulation of the drug and other agents transported by P-glycoprotein. The authors postulated that this binding may competitively inhibit excretion of an endogenous P-glycoprotein substrate (529).

Rosen et al. (530,531) described a model of chronic CsA-induced nephropathy in which CsA (12.5 mg/kg) was injected daily into sodium-depleted rats. Histologic assessment revealed focal atrophy of the thick ascending limb and fibroblast proliferation. Structural lesions and renal functional impairment were less severe in animals, which had been fed a normal sodium diet. Based on this model, Heyman et al. (532) proposed a role for medullary ischemia in CsA-induced lesions.

Young et al. (533) used this model to study the pathogenesis of interstitial fibrosis. Proliferation of tubular and interstitial cells was documented in the medulla by day 5. By day 35, proliferation was maximal, and there was increased...
cortical tubular staining for osteopontin, a macrophage adhesion protein. A significant influx of macrophages was detected by day 35, which was associated with maximal corticomedullary fibrosis. These changes correlated with functional abnormalities, and the authors concluded that these cellular events may be important in the pathogenesis of chronic CsA nephrotoxicity. Studies in rats have implicated angiotensin II in effecting fibrosis with prolonged CsA administration (503). Transforming growth factor–β (TGF-β) also likely plays a role in induction of fibrosis in chronic CsA nephropathy (534). In a rat model of chronic CsA toxicity, administration of anti-TGF-β antibodies reversed most of the CsA-induced renal lesions (535). There is evidence that CsA may bind to the promoter for collagen type III, stimulating collagen expression in renal cells (536). Loss of peritubular capillaries has been demonstrated in chronic CsA toxicity; in an experimental model, vascular endothelial growth factor ameliorated the chronic nephropathy (537). Inappropriate apoptosis and the vascular effects described above leading to chronic vasoconstriction also likely contribute to chronic effects of CsA.

**FK506 (Tacrolimus)** Tacrolimus appears to have a mechanism of action similar to that of CsA (538). Like CsA, FK506 binds to an intracellular-binding protein, FKBP12; this complex targets calcineurin within the cell (538). Studies have shown inhibition of renal calcineurin in rats treated with FK506, suggesting that renal toxicity is mediated in part by inhibition of the phosphatase activity of calcineurin (539,540). Tacrolimus also binds to FKBP59, a heat shock protein associated with the nucleus, cytoskeleton, and mitotic apparatus (540). Like cyclosporine, FK506 is bound to proteins and erythrocytes in the blood. Like CsA, FK506 is metabolized by the hepatic cytochrome P450 3A4 system, and there is potential for drug interactions (541). Metabolites are generally inactive, and excretion is largely via the biliary tract.

Studies in mesangial cells cultured in vitro have shown that FK506 induces release of endothelin-1, an effect that may be mediated by FKBP (542). Clinically, endothelin levels in the urine have been shown to rise with FK506 immunosuppression after liver transplantation, whereas 6-keto-PG1α levels fell; the changes in levels of these vasoactive substances persisted for 2 years, over a period when the GFR dropped and renal vascular resistance rose (543). In an experimental rat model, 2 weeks of treatment with FK506 produced a rise in SUN and sCr levels, luminal narrowing of arterioles, increases in plasma renin and urine thromboxane, and a decline in urinary 6-keto-PG1α; the effects were reversible (544). The drug also induces TGF-β in experimental FK506 toxicity (545), suggesting that the drug may induce renal fibrosis by mechanisms analogous to CsA. Tacrolimus-mediated injury is also related to endoplasmic reticulum stress (546).

**Sirolimus** Sirolimus has been shown to impair recovery from experimental ARF. A role for cell cycle arrest and apoptosis of tubular cells has been demonstrated (547). This compound has also been studied in a rat model of CsA toxicity (548). The drug potentiated the renal toxicity of low-dose (5 mg/kg/d) CsA. Sirolimus alone increased TGF-β expression by 44%. In the setting of a combination of sirolimus and low-dose CsA, TGF-β mRNA and protein were increased by 121% and 176%.

Lieberthal et al. (548) found that rapamycin inhibits growth factor–induced proliferation of cultured proximal tubular cells and fosters apoptosis by blocking survival effects of the growth factors. The drug also impaired recovery from experimental ARF caused by renal artery occlusion via increased apoptosis and inhibition of regeneration; these effects were attributable to the inhibition of p70 S6 kinase.

**Intravenous Immunoglobin** The toxicity of IVIG appears to be osmotic. Highly osmotic, sucrose-stabilized formulations have a disproportionately high rate of ARF compared to non-sucrose-stabilized products (124). Rate of infusion may be an important risk factor for renal tubular injury.

**Chemotherapeutic Agents**

**Cis-platinum** Cis-platinum is a highly effective chemotherapeutic drug that is used to treat a variety of cancers both as first-line treatment and as adjuvant therapy. Cisplatin chemotherapy is limited by severe toxic side effects, including nephrotoxicity (549). The susceptibility of the kidney to cisplatin is due to accumulation of high concentrations of cisplatin in tubular epithelial cells (550,551). The intestinal secretion of the drug is minimal. Impairment of renal function is seen in 25% to 35% of patients treated and occurs initially predominantly in the proximal tubule. Recently, active transport systems have gained importance in the understanding of mechanism of cisplatin toxicity. The facilitated transport systems associated with cisplatin toxicity are those mediated by the organic cation transporter OCT2 and the copper transporter Ctr1, which foster intracellular accumulation of cisplatin (552,553). OCT1/2 double knockout mice show only mild cisplatin nephrotoxicity (554).

Cisplatin induces both apoptosis and necrosis in proximal tubular epithelial cells. Both mechanisms have been shown in vivo. Necrosis has been mainly associated with high doses of cisplatin, whereas apoptosis is associated more commonly with therapeutic doses (550). Both the intrinsic and extrinsic apoptotic pathways have been implicated in cisplatin-mediated toxicity (555,556). Moreover, endoplasmic reticulum stress has been implicated in cisplatin-dependent apoptosis (557).

Inflammatory responses initiated by cisplatin have been shown to be associated with enhanced expression of TNF-α (555,556,558). TNF-α has been shown to activate proinflammatory cytokines and chemokines and recruit leukocytes, thereby causing oxidative stress and amplifying renal damage (559). Moreover, the cytokine-like TGF-β, MCP-1, intercellular adhesion molecule (ICAM), and heme oxygenase 1 have been implicated in cisplatin-induced nephrotoxicity (560). Further evidence that cisplatin induces proinflammatory reactions in the kidney is indicated by the observations that anti-CD54 antibody blockade of leukocyte adhesion is protective (561) and that interleukin-10, an anti-inflammatory cytokine, inhibits cis-platinum–mediated nephrotoxicity (562).

**Nitrosoureas** The mechanism of injury appears to be direct renal tubular toxicity. Metabolites of the drug ifosfamide may be responsible for the tubular injury induced by that agent (563). Methotrexate also causes direct toxic injury to the proximal tubule. In addition, precipitation of the drug in renal tubules, with resultant obstruction, has been reported.
**Radiocontrast Agents**

Based on the existing clinical and experimental studies, it appears that the tubules and the vasculature of the kidney are the key targets in the development of RN (radiocontrast nephropathy). Increased tubular protein and enzyme excretion have been detected in the urine of patients undergoing radiocontrast studies (150,151), suggesting a direct tubular toxic effect of contrast media. Rise in urinary levels of markers of oxidative stress has been documented (151). The pattern of amplified enzyme and protein excretion (e.g., more urinary brush border enzymes, folate-binding protein) was suggestive of a primarily proximal tubular injury. Mechanisms have been reviewed (564).

In general, it is difficult to induce ARF with contrast media in most animal species, and contrast media alone are not sufficient to cause renal injury in animal models. The combination of unilateral nephrectomy, salt depletion, and administration of indomethacin and other injurious agents is necessary to cause renal injury in animals after contrast media exposure. In this model, apoptosis of medullary tubular cells has been noted, ascribed to hypoxia (565). Some experimental studies describe proximal tubular vacuolation (260). Other investigators have emphasized the selective injury of the thick ascending limb of Henle in a rat experimental model for RN (225,566). However, this thick ascending limb injury appears to have been the consequence of hypoxia rather than direct toxic damage in this model. The thick ascending limb of Henle is the site where Tamm-Horsfall protein is produced, and some data indicate that contrast media may increase the urinary excretion of Tamm-Horsfall protein, an important cast-forming protein (566). Contrast media may also facilitate the urinary excretion of oxalate and urate, but there is no evidence that urinary obstruction by any form of cast plays a role in RN.

There is both human and experimental evidence that vasoconstriction and subsequent ischemic injury may play an important role in RN (567–570). The injection of contrast media causes a biphasic response in the renal blood flow. There is an initial short phase of increased flow followed by a long phase of reduced flow caused by intrarenal vasoconstriction (568,571). Some experimental studies suggest that high endothelin levels, low NO levels, or both are key mediators of this intrarenal vasoconstriction (566,569,570). However, early results with endothelin receptor blockade in clinical trials have not shown benefit (571). Other factors, such as increased adenosine release and decreased prostanoïd levels (e.g., owing to the concomitant administration of indomethacin or other prostaglandin synthase inhibitors), may also play a part in pathogenesis (566,567).

More recently developed iso-osmolar contrast media are dimers, while the widely used nonionic, low-osmolar contrast media are monomers. The viscosity of these dimers is higher than that of blood, potentially interfering with flow within the kidney. Experimental studies suggest greater perturbation in renal function with the dimers, although clinical trials have yielded conflicting results (564).

Whereas vascular effects are important, in vitro studies demonstrate toxic effects of contrast media on cultured renal epithelial cells (572). Iodinated radiocontrast agents produce cytotoxic effects in glomerular mesangial cells as well as tubular epithelial cells in vitro. Exposure of cultured tubular cells to ionic contrast media induces opening of intercellular junctions and redistribution of surface proteins (573,574). More severe injury is usually characterized by cell shrinking and nuclear fragmentation, consistent with apoptosis (271,575–577). Most studies utilize the Madin-Darby kidney (MDCK) cell line (predominantly distal phenotype), but changes occur in LLCPK-1 cells (proximal phenotype) as well. There are loss of cellular energy stores, disruption of calcium homeostasis, and disturbance of cell polarity. All agents appear to variably affect mitochondrial function (575). Some experimental evidence has accrued that oxidative stress is an underlying mechanism (578). In vitro cell injury is variably correlated with osmolality of the contrast media (576,578).

**Narcotics**

Rhabdomyolysis in drug addicts is associated primarily with the use of opiates and cocaine. The pathogenesis of muscle damage following substance abuse is obscure. Cocaine and opiates may have a toxic effect on the skeletal muscle, but seizures, muscle injury, hyperthermia, and coma-induced ischemic or pressure injury of the muscle may also be important factors (167,273). Once rhabdomyolysis evolves, three major mechanisms are thought to be involved in the development of ARF: direct tubulotoxicity of myoglobin, renal tubular obstructive cast formation, and vasoconstriction/hypoperfusion (for a review, see Zager (167)). Several factors have been implicated in renal infarction induced by narcotics, including intense renal vasoconstriction from adrenergic stimulation, endothelial injury, and platelet activation. Cocaine-induced endothelial injury has also been implicated in the few cases of microangiopathy associated with cocaine use (579).

**Anesthetics**

The toxicity of methoxyflurane may be related to the fluoride ion, but other fluoride-containing anesthetics are not associated with renal failure (580,581).

**Herbal Medications**

Poisoning caused by these formulations may be a result of the presence of undisclosed drugs or heavy metals, interaction with conventional medications, or misidentified herbal species (169).

**Differential Diagnosis**

As indicated previously, the causes of ARF are varied, although a significant portion of cases can be attributed to ATI. A similar clinical syndrome is seen in a variety of primary renal diseases, including rapidly progressive glomerulonephritis and thrombotic microangiopathies, though the presence of hematuria, hematologic abnormalities, and other clinical and laboratory data often provides clues to diagnosis in these settings. “Secondary” ATI may occur in these settings due to ischemia, inflammation, and potentially other mechanisms and may contribute to renal dysfunction and ultimate prognosis. Clinical differentiation between ischemic and toxic ATI may be difficult in some settings, especially in hospitalized patients. Morphologically, toxic injury is more strongly associated with frank cellular necrosis. There are some pathologic features, as discussed above, that may make it possible to identify the mechanism and even occasionally a specific agent.

There may be an inflammatory response in ATI. The single most distinguishing feature between ATI and acute interstitial nephritis is the severity and nature of the interstitial infiltrate. Although eosinophils can be present during the recovery phase of some cases of ATI, they are usually low in number and found only in a scattered distribution. The changes associated
TABLE 26.4 Complications of acute renal failure

<table>
<thead>
<tr>
<th>Renal</th>
<th>Chronic renal failure</th>
</tr>
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<tbody>
<tr>
<td>Metabolic</td>
<td>Hyperkalemia</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>Hypocalcemia</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>Hyperphosphatemia</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>Hypermagnesemia</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Pulmonary edema</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>Pericarditis</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Nausea</td>
<td>Vomiting</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>Gastritis</td>
</tr>
<tr>
<td>Parotitis or pancreatitis</td>
<td>Gastrointestinal ulcers</td>
</tr>
<tr>
<td>Gastropathy</td>
<td>Gastrointestinal bleeding</td>
</tr>
<tr>
<td>Neomuscular irritability</td>
<td>Stomatitis or gingivitis</td>
</tr>
<tr>
<td>Asterixis</td>
<td>Parotitis or pancreatitis</td>
</tr>
<tr>
<td>Seizures</td>
<td>Infectious</td>
</tr>
<tr>
<td>Mental status changes</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>Somnolence</td>
<td>Wound infections</td>
</tr>
<tr>
<td>Coma</td>
<td>Intravenous line infections</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Septicemia</td>
</tr>
<tr>
<td>Anemia</td>
<td>Urinary tract infection</td>
</tr>
<tr>
<td>Bleeding</td>
<td>Other</td>
</tr>
<tr>
<td>Hiccups</td>
<td>Decreased insulin catabolism</td>
</tr>
<tr>
<td>Mild insulin resistance</td>
<td>Elevated parathyroid hormone</td>
</tr>
<tr>
<td>Reduced 1,25-dihydroxy- and 25-hydroxyvitamin D</td>
<td>Low total triiodothyronine and thyroxine</td>
</tr>
<tr>
<td>Normal free thyroxine</td>
<td>Prognosis</td>
</tr>
</tbody>
</table>

Patients who survive an episode of ARF generally recover sufficient renal function and do not usually suffer from overt progressive chronic renal deterioration. However, in addition to increased risk of mortality, a minority of patients with AKI may suffer persistent progressive dysfunction. For example, nearly 10% of patients with radiocontrast nephropathy (RN) become dialysis dependent (585). AKI has been shown to be a risk for end-stage renal disease, especially in the elderly (586). Patients with the greatest impairment of renal hemodynamics have the lowest potential for recovery of renal function long term (587), and an accurate estimate of GFR may be of prognostic significance.

Toxic tubular injury will continue as long as there is exposure to the offending agent. Discontinuation of the drug or adjustment of the dosage will allow recovery of tubular cells and of renal function, although permanent damage has been seen with some toxins, and some drugs such as calcineurin inhibitors, lithium, and herbal medications routinely cause fibrosis. Recovery may be incomplete, with persistent decrease in creatinine clearance and urine concentrating ability in 35% to 71% of patients (588), with some evidence of progression of dysfunction after 1 to 5 years in one follow-up study (588).
Persistent renal dysfunction has been reported in adults and children (589,590). In the newborn, prognosis and recovery are also dependent upon the underlying etiology. Hypoxic/ischemic and nephrotoxic injury to the developing kidney in the perinatal period can result in a reduced number of nephrons, and monitoring for the late developments of chronic renal insufficiency is recommended. Early ischemic injury in the renal allograft has persistently been shown to predispose to later graft injury and loss (see Chapter 29).

Chronic renal failure and fibrosis have been described in animal models when these animals have been followed long term, and although the renal insults in these models are not completely analogous to those in clinical ARF, these studies provide some insights into mechanisms of progression. Both ischemic injury and cisplatin toxicity have been reported to result in centring defects in rats. In the ischemic model, chronic renal insufficiency develops after several months, following recovery of function and morphologic tubular injury, and has been associated with progressive proteinuria (591–593). Early increases in macrophages and myofibroblasts have been documented in early experimental ischemic injury (594) and gentamicin toxicity.

Early postischemia, there are significant alterations in renal blood flow, with reduced and chaotic cortical flow demonstrable by video microscopy (595). Increased capillary leakiness has been documented following ischemia/reperfusion injury by tracking diffusion of fluorescent high molecular weight dextrans by two-photon confocal microscopy (596), associated with disorganization of F-actin in endothelial and vascular smooth muscle cells and loss of E-cadherin-positive tight junction. Late microvascular damage and loss of peritubular capillaries have been documented in animal models with ischemic injury. These changes persist even as tubules recover from the acute insult. In a study using microfil injection, a 30% to 50% reduction in vascular density was demonstrated at 4, 8, and 40 weeks following ischemia/reperfusion injury in the rat (591). It has been hypothesized that rarefaction of peritubular capillaries permanently alters renal function and predisposes to chronic renal insufficiency (592). Other possible mechanisms for progressive decline in renal function include inability of some nephrons to regenerate following ischemic injury (592). Inhibition of B7 costimulatory factor in experimental ischemic injury attenuates the development of progressive renal failure (597), suggesting a role for inflammation, which may be a factor in both ischemic and some types of toxic injury and especially in sepsis (see below). A possible role for endothelin has also been implicated. All of these factors could be interrelated. The hypoxia marker 2-pimonidazole has been used to demonstrate persistent hypoxia in the outer medulla at 5 weeks following experimental ischemia/reperfusion injury, when function and renal tubular structure have recovered. Treatment with L-arginine increased blood flow and attenuated the hypoxia and later interstitial fibrosis (598).

Therapy

Therapy for ARF includes prevention and interventions during or after the insult. Any inciting agents or factors should be removed or corrected. Depending on the toxic agent and severity of injury, recovery may be rapid or prolonged. Careful management of fluid, electrolytes, and acid-base status is critical, especially if renal insufficiency is severe. Renal replacement therapy, including dialysis or other forms of hemofiltration, may be required (599–602). Intermittent hemodialysis is the most common modality. Peritoneal dialysis is not widely used in adults, and use of this modality is decreasing in pediatric patients, except for neonates and very small infants. Hemofiltration is increasingly common in the pediatric population (603). Dialysis dose is the most critical parameter, regardless of modality (604,605). A number of therapeutic agents and strategies have been efficacious in experimental models to prevent or ameliorate ARF, although many have been generally disappointing in clinical trials.

Prevention of ARF is a goal, and some strategies have been developed, including perioperative hydration, maintenance of perfusion pressure, and avoidance of nephrotoxins or minimization of toxic effects of potential nephrotoxins, to lessen occurrence of ARF (606). Many experimental models have focused on therapies administered before the onset of ARF. However, the efficacy of these approaches is limited to scenarios in which development of ATI can be anticipated, including preoperatively, following myocardial infarction, in sepsis/systemic inflammatory response syndrome (SIRS), prior to use of potential nephrotoxic agents, and in renal transplantation. In humans, some of the best results in prevention of ARF have been seen with RN (607); isotonic sodium bicarbonate infusion, N-acetylcysteine combined with hydration (608), and ascorbic acid (609) have been used to prevent RN. However, results have been heterogeneous, and caution is advised in adopting these preventive strategies as standard of care (610). Avoidance of volume depletion and/or volume repletion/expansion may be the most important strategy (611). Prevention of AKI in sepsis focuses on at-risk patients, with prophylactic antibiotics, treatment of hospital-acquired infection, control of blood glucose, and nutritional support. Maintenance of renal blood flow may require support of volume and cardiac output to achieve adequate mean blood pressure and central venous pressure (612,613).

More generally, useful therapies are those that are effective when given during or after the onset of injury and dysfunction. Benefits of low-dose dopamine infusion to produce vasodilation and maintain renal blood flow are equivocal, and some studies have shown worsening of renal perfusion (614). Loop diuretics may reduce the severity of injury and maintain urine output (615), but large clinical trials are needed. A variety of agents, including growth factors, have some efficacy in experimental models. In humans, atrial natriuretic peptide (ANP) has proven efficacious in nonoliguric renal failure (616); however, use of ANP to prevent RN has had variable efficacy, although perhaps with some utility in diabetic patients. Treatment with insulin-like growth factor had no measurable benefit in a randomized clinical trial in ARF patients (617). In general, clinical trials using single agents based on findings in experimental models have not identified significant efficacy. Combination therapies as used in some animal models, for example, use of a vasodilator such as ANP combined with mannitol to maintain tubular flow or ANP and dopamine in combination, could be an optimal approach (618,619).

Removal of inflammatory mediators with plasma therapies and adsorption techniques may have some efficacy in states such as sepsis and multiorgan failure (see Syndromic Acute Tubular Injury below, and see (613) for review). Nutritional support with provision of calories and protein is important in hypercatabolic states such as sepsis. The bioartificial kidney, which combines hemofiltration and a device containing human tubular cells in hopes of replacing some of the metabolic and endocrine...
functions of the renal tubules, has been in development for some years (see 620 for review), with some preliminary evidence of efficacy. However, there are technical issues, and these devices have not been approved for clinical use. More recently, based on experimental evidence that extrarenal cells, including bone marrow–derived cells, may have beneficial effect in recovery and repair following renal tubular injury, there has been a focus on how endothelial cells or stem cells might be used to accelerate recovery from AKI. However, intrarenal cells are the primary source for regeneration and repair of tubular epithelium in AKI (433,621). Future strategies in the treatment of ARF include use of growth factors or stem cells and other novel therapies, including anti-inflammatory therapies, especially relevant in septic AKI (588,622–624).

SYNDROMIC ACUTE TUBULAR INJURY

Acute Renal Failure in Sepsis

Clinical definition of sepsis includes fever, high heart and respiratory rates, and elevation in white blood cells and/or immature white blood cell forms in the setting of infection. Severe sepsis is associated with lactic acidosis, and there may be altered mental status. In septic shock, hypotension persists despite adequate fluid replacement. The incidence of ARF is approximately 19% in moderate sepsis, 23% in severe sepsis, and 51% in septic shock with positive blood cultures (291,625). The combination of ARF and shock is associated with 70% mortality (reviewed in 38,626).

ARF/AKI is one manifestation of acute organ dysfunction occurring in severe sepsis. During sepsis, development of AKI correlates with increased morbidity and mortality, impacts multiple-organ functions, and increases length of stay in the ICU (627). Sepsis is an important contributing factor for AKI in the critically ill (628), and mortality of ARF in sepsis is high. An understanding of mechanisms and development of therapeutic approaches has been hampered by limited histopathologic information and paucity of animal models (626,627).

In an effort to help elucidate mechanisms in sepsis, the pathology of AKI in sepsis has been recently reviewed (201). In a literature review of clinical and experimental studies, while “acute tubular necrosis” occurs, it was seen in only a minority of studies, and “ATN” was described in over 30% of specimens from primates, but in less than 1% of specimens from humans, with rodents intermediate. Human studies were heterogeneous in design, definition of AKI, and histopathology. In one study (629), 82% of biopsied patients showed acute “tubulo-interstitial nephropathy,” 7% had acute glomerulonephritis, 3.5% had acute pyelonephritis, and 7% had classic “ATN.” In another large study of patients with severe sepsis (630), 27.5% had nonspecific tubular or glomerular damage, and 22.5% had vascular involvement. This literature review confirmed the paucity of histopathologic material from septic patients, as only a minority were biopsied in each series. As emphasized earlier in this chapter, mild forms of “ATN” are typical rather than “ATN,” even in these severely ill patients. Biomarkers for sepsis-induced AKI include those discussed above for AKI, though excretion of IL-18 is reportedly higher in septic AKI (631).

Pathophysiology of AKI in sepsis is multifactorial, triggered by sepsis-induced activation of the innate immune response, resulting in cytokine storm, with release of IL-1, IL-6, TNF-α, and other cytokines. This systemic response triggers hemodynamic changes, endothelial dysfunction, infiltration of inflammatory cells, capillary thromboses, and tubular cell injury (reviewed in 627,632). Patients with severe sepsis may develop prerenal failure as a result of septic shock. Renal vasoconstriction plays a role in sepsis-induced prerenal failure, but arterial vasodilation in sepsis and decrease in renal vascular resistance caused in part by cytokine-mediated vascular effects such as induction of NO synthesis are predisposition to ARF and have been demonstrated in septic states in large animal models (633). Acidosis and decrease in vascular smooth muscle ATP lead to alteration in K+ channels and resistance to vasopressin (634). Knockout of eNOS in mice makes the animals very vulnerable to ARF when treated with endotoxin, consistent with a role for endothelial injury in sepsis (635). In a rat model, a specific iNOS inhibitor, L-NIL, protected against ARF (636). The inflammatory cytokine TNF has been implicated in sepsis by studies showing preservation from renal injury in experimental endotoxemia in mice with TNF receptor blockade (637). Other experimental studies have implicated ROS. In animal studies, oxygen radical scavengers, including superoxide dismutase, have been shown to protect against endotoxemia-induced acute renal injury (638). Caspase-1 knockout mice are resistant to ARF induced by endotoxemia (639), implicating this protease in sepsis-associated ARF. A possible role for complement has been proposed in studies documenting the protective effect of blockade of complement component C5a in sepsis (640).

Despite these findings in animal models, clinical trials with anti-TNF antibody and other strategies based on preclinical studies have not shown improved patient survival in these complex patients (641,642). Management of septic AKI includes prophylactic measures, medical and extracorporeal treatment, and support of failing organs (reviewed in 38). Early diagnosis using standardized criteria for AKI is recommended (8), to optimize management.

The Hepatorenal Syndrome

The term hepatorenal syndrome (HRS) is not a definable histopathologic entity of intrinsic renal disease. It describes a clinical syndrome of ARF that may complicate advanced liver disease (643), occurring in up to 40% of cirrhotic patients. Two types have been defined: type 1, with rapid reduction of renal function and frequently associated with failure in other organs and with decreased survival, and type 2, with more progressive decline in renal function. The five criteria for HRS, as defined by the International Ascites Club, include severe cirrhosis with ascites; sCr more than 1.5 mg/dL; failure of plasma expansion and diuretic withdrawal to improve renal function, absence of shock, and no current or recent treatment with nephrotoxic drugs; and absence of proteinuria, hematuria, and/or abnormal renal ultrasound. The syndrome is thought to be common, but the incidence is not known, in part because clinical measurements tend to overestimate renal function in cirrhosis (644). In a multivariate retrospective study of 355 patients with cirrhosis and ARF, 58% had prerenal failure (71 of 206 with type 1, the remainder type 2). Forty-two percent had “acute tubular necrosis.” No cases of ARF owing to acute glomerulonephritis were identified (645). This study confirms that the vast majority of cases of ARF in cirrhosis are caused by hypoperfusion injury.
HRS is characterized physiologically by intense intrarenal vasoconstriction and hypoperfusion, resulting in a primary decrease in the GFR, and is a variant of prerenal failure, because it is associated with diminished effective systemic circulatory volume, and splanchic arterial vasodilatation, with some component of cardiac dysfunction (reviewed in (646)). Urinalysis will usually reveal a benign urinary sediment and concentrated urine. In contrast to the chemical composition of the urine in ATI caused by ischemia or nephrotoxins, the sodium concentration is usually low. This finding could be a useful addition to the five criteria for HRS outlined above, helping to differentiate HRS and ATI. The pathogenetic mechanisms of action of the dramatic hemodynamic alterations accompanying severe hepatic disease are incompletely understood. The presence of ascites and other shifts in total body fluid volume are major contributors. Type 1 HRS usually develops in relationship to precipitating events such as various infections or surgical procedures (647). Gastrointestinal bleeding may underlie the ARF in some of these patients (648). Other risk factors in this setting include vomiting, diarrhea, or diuretic therapy. However, a significant number of cases occur without these antecedents. The renin-angiotensin-aldosterone system, activation of the sympathetic nervous system, and increased ADH activity have all been implicated as possibly playing a role. Treatment of HRS varies between type 1 and type 2 (reviewed in (643,649,650). The treatment for type 1 HRS is vasoconstrictors and albumin; patients with type 1 HRS have improved renal function after therapy with vasoconstrictors such as terlipressin (645). This response could also serve as an additional diagnostic criterion for HRS (643). Treatment for type 2 HRS is transjugular intrahepatic portacaval shunt or large-volume paracentesis; vasoconstrictors and albumin may be effective, but recurrence rate is high. Prevention of HRS using albumin, prophylactic antibiotics, or TNF inhibitors may be possible in some settings such as bacterial peritonitis. Liver transplantation is the most effective therapy; patients with type 1 HRS have high priority for organ allocation. Recent studies have elucidated a role for intra-abdominal hypertension (IAH) in HRS, and relief of the IAH may have some efficacy (see below).

Because the pathogenesis appears to be primarily hemodynamic, the morphologic changes associated with this syndrome are nonspecific and not distinctive. Although bile-stained casts and crystals can be seen within tubular lumina, the cytologic changes visible in patients with ATI are not consistently present. Relatively few renal biopsy studies have been performed, because the biopsy procedure is often contraindicated in the clinical context of end-stage liver disease. The findings of postmortem studies must be evaluated with consideration of the changes caused by autolysis and other comorbid features. Nevertheless, some authors have emphasized particular histologic findings, including “tubularization” of Bowman capsular epithelium, tubular dilation, interstitial edema, bile-stained intratubular casts, leucine crystals in the tubules and interstitium, and sometimes an interstitial leukocytic infiltrate.

**Acute Renal Failure and Multiple-Organ Failure**

ARF often occurs in the setting of other acute organ dysfunctions. Potential “cross-talk” between affected organs is emerging as an area of interest for nephrology and critical care medicine (see (584,651) for review). For example, mechanical ventilation may initiate or aggravate ARF. Three mechanisms have been invoked: permissive hypercapnia or hypoxemia with compromise of renal blood flow, effects on cardiac output, and barotrauma with pulmonary inflammation and release of inflammatory mediators (652). Conversely, ARF may potentiate acute lung injury. ARF leads to macrophage-mediated increase in pulmonary vascular permeability (653). ARF also leads to dysregulation of lung salt and water channels in bilateral ischemic injury or bilateral nephrectomy, though not in unilateral ischemic injury, suggesting a role for “uremic toxins” (654). Mechanisms underlying combined ARF and acute lung injury in the intensive care unit have been reviewed (655).

**Cardiorenal Syndromes**

The interrelationship between the heart/circulatory system and the kidney is reflected in the cardiorenal syndromes (CRS). The coexistence of cardiac and renal disease increases morbidity and mortality (656–658). A number of definitions and classifications had been developed to describe the syndrome(s) prior to 2008, largely not multidisciplinary (659,660). In 2008, an international multidisciplinary consensus conference was held to consider definition/classification, epidemiology, diagnostic criteria and biomarkers, prevention/protection strategies, management, and therapy. They defined five CRS: type 1 acute cardiorenal, type 2 chronic cardiorenal, type 3 acute renalocardi, type 4 chronic renocardiac, and type 5 secondary CRS (660).

The primary events for type 1 were identified as acute cardiac dysfunction due to acute heart failure/coronary syndrome or cardiogenic shock, resulting in AKI due to hypotension/hypoperfusion and ischemia. Proposed renal biomarkers included serum cystatin C, creatinine and NGAL, and urinary KIM-1, IL-18, NGAL, and NAG. Incidence of this syndrome has been estimated at between 19% and 45% of patients with acute cardiac dysfunction and is associated with increased mortality, hospitalization/readmission, and accelerated progression to CKD (661,662). An association between severity of AKI and risk of death has been noted (663), and even small acute changes in serum creatinine can modify mortality risk (661). Pathology in these cases has not been extensively studied, but is likely that of acute ischemia (see above).

Chronic CRS is due to chronic left ventricular dysfunction, diastolic dysfunction, cardiomyopathy, or other chronic forms of cardiac dysfunction, resulting in chronic kidney disease (CKD). Proposed renal biomarkers for this syndrome include sCr, cystatin C, urea, uric acid, and C-reactive protein. Proposed mechanisms include neurohumoral factors, inflammation, and oxidative injury. Pathology is likely that of chronic ischemia, with “creeping” fibrosis widening interstitial areas between atrophying tubules.

Acute and chronic renocardiac syndromes, CRS types 3 and 4, were also defined. In type 3, acute worsening of kidney function leads to cardiac injury and/or dysfunction. The primary event is AKI, with proposed biomarkers as noted in type 1 CRS. Mechanisms leading to cardiac effects likely include acute sodium and volume overload. In type 4, CKD leads to cardiac injury, disease, and/or dysfunction. Cardiac changes may be due to chronic sodium and volume overload, neurohumoral factors, and/or inflammation, in addition to effects of CKD-associated anemia and mineral/bone abnormalities.

Finally, type 5 (secondary CRS) is due to systemic conditions simultaneously affecting kidney and heart (e.g., sepsis, amyloidosis, autoimmune disease, severe hypertension).
Intra-Abdominal Hypertension and Abdominal Compartment Syndrome

Intra-abdominal hypertension (IAH) is defined as sustained or repeated elevation of intra-abdominal pressure (IAP) to ≥12 mm Hg. Abdominal compartment syndrome (ACS) is defined by sustained elevation of IAP greater than 20 mm Hg with new organ dysfunction (664). IAH/ACS increases morbidity and mortality in many patients in medical and surgical intensive care units. While traditionally seen in trauma, major burns, and postabdominal surgery, IAH/ACS is now recognized in patients with a variety of medical conditions, including septic shock and severe acute pancreatitis. Risk factors include conditions in which there is increase in intra-abdominal volume and/or decreased abdominal wall compliance, including sepsis, large-volume fluid resuscitation, multiple transfusions, high-pressure mechanical ventilation, obesity, acidosis, and in abdominal transplantation (reviewed in [665,666]). In mixed medical-surgical intensive care units, IAH occurs in up to 64% and ACS in up to 12% of patients.

Oliguria and AKI are frequent in IAH/ACS and increase morbidity and mortality. IAH/ACS also contributes to renal dysfunction in cardiorenal and hepatorenal syndromes. In one study in patients with advanced heart failure, higher central venous pressure was associated with development of worsening renal function and was a stronger predictor than cardiac index (667), consistent with a role for IAH. Improved GFR following reduction of IAP via paracentesis (668).

IAP can be measured using transvesical pressure monitoring via an indwelling catheter. Abdominal perfusion pressure (APP), defined as the difference between systemic mean arterial pressure (MAP) and the IAP, falls with drop in MAP and/or rise in IAP. A fall in APP is associated with fall in perfusion to organs in or near the abdomen, including the kidneys (669,670). Renal pathology has not been well defined clinically in this syndrome, but is likely that of hypoperfusion. In one study in pigs using pneumoperitoneum to induce IAH, proximal tubular necrosis was described; fluid resuscitation preserved cardiac output, but did not prevent renal tubular injury (or changes in other organs) (670). In rats with ACS, renal tubular cell apoptosis and bal-2 expression were found, greater with longer duration of ACS. Abdominal decompression has been successful in treatment, and high-volume fluid resuscitation and fluid overload should be avoided or managed with ultrafiltration or diuretics. In general, multidisciplinary integrated management with IAP measurement, preventive measures, and medical and surgical approaches should reduce mortality and costs. Decompressive laparotomy is used if medical treatment is ineffective or if there is rapidly progressive organ dysfunction caused by IAH/ACS. More study is needed by nephrologists and nephropathologists to fully define renal effects of these syndromes.

RENAI CORTICAL NECROSIS

Bilateral RCN is a rare and dramatically unique cause of ARF. The clinical course is similar to that of ATI, except that it almost always presents with anuria or profound oliguria. It most commonly is seen in association with obstetric accidents (671), such as abruptio placentae, placenta previa, or in septic abortion, but has rarely been reported following elective abortion (672). Coagulopathy associated with abruptio placentae, abortion, or placenta previa is reported as being responsible for 50% to 60% of all cases of acute bilateral RCN. Twin-twin or twin-maternal transfusions with resultant activation of the complement cascade can also lead to cortical necrosis (279). RCN may also occur in the context of HUS/TTP (673) and is also seen in instances of severe trauma, systemic sepsis, postoperative shock, and some specific poisonings, including snake venom, diethylene glycol, and arsenic (674–678). Pregnancy-associated HELLP syndrome, with hemolysis, elevated liver enzymes, and thrombocytopenia, is a recognized cause (679,680). Antiphospholipid syndrome has also been associated with RCN (681). A pediatric case has been described in the context of antiprotein S antibodies following varicella infection (682). Acute RCN may also be associated with severe acute pancreatitis (683). In infants and children, the precipitating event is often gastroenteritis with severe vomiting, diarrhea, and dehydration. Overwhelming infection with bacterial sepsis is the other major cause in adults. There are also reports of cortical necrosis related to malarial infection (684). Patchy RCN is also seen in renal allografts, especially with severe antibody-mediated rejection, and is associated with early graft loss (685).

The pathogenesis of cortical necrosis involves microvascular abnormalities. There are several major theories, and they are not mutually exclusive. On the basis of examination of the kidneys from patients who died after abruptio placentae, Sheehan and Davis (22) proposed that vasospasm is the primary event causing cortical necrosis. Alternatively, acute cortical necrosis may result from severe forms of thrombotic microangiopathy, resulting from acute vascular injury followed by activation of coagulation and thrombosis (675,686,687). A third hypothesis suggests that acute cortical necrosis may be the consequence of an immunologic mechanism akin to hyperacute rejection of renal allografts. All of these hypotheses have some supporting evidence, but there is no convincing proof that any one of them fully explains the sequence of events that occurs in human patients.

The clinical course of acute cortical necrosis depends on the extent of involvement. If necrosis is extensive, death occurs within the first few days unless dialysis is undertaken. With timely renal replacement therapy, renal function may recover sufficiently to allow patients to become dialysis independent after a period of 1 to 3 months, and renal function may continue to improve over a period of 1 to 2 years. No specific therapeutic approaches have been successful, although anticoagulants, beta-blockers, cytotoxic drugs, and mannitol have all been tried.

Gross Pathology

Bilateral cortical necrosis in its diffuse form is a condition in which there is widespread destruction of the renal cortex, except for a narrow rim of cortical tissue just underneath the capsule and with relative preservation of the medulla and the adjacent juxtamedullary cortex. This is the most severe form and can be detected on imaging studies (Fig. 26.31A). It is generally recognized on gross examination as large, swollen kidneys in which the necrotic portion of the cortex is pale or yellowish white, with congestion of the
adjacent, relatively well-preserved tissue (see Fig. 26.31B). Patchy and focal forms affect smaller amounts of cortex and appear grossly similar to areas of infarction, except that they are surrounded on all sides by viable tissue and do not have the characteristic wedge-shaped pattern of the classic infarct.

Light Microscopy
By light microscopy, the findings are very similar to those seen with ischemic infarcts. There is coagulation of the central necrotic areas with relative preservation of the architecture of the tubules and the glomeruli but loss of normal cytologic features (Fig. 26.32). The arteries and arterioles are also necrotic.

FIGURE 26.31  A: Radiograph with contrast of a kidney with cortical necrosis showing hypoperfusion and areas of hemorrhage. B: Gross specimen of a kidney with extensive areas of pallor representing the necrotic cortex with intervening areas of congested nonnecrotic parenchyma.

FIGURE 26.32  A: Cortical necrosis, with sparing of the subcapsular cortex and medulla. (H&E; ×64.) B: Cortical necrosis with coagulative necrosis with focal hemorrhage. (H&E; ×200.)
Chapter 26  |  Ischemic and Toxic Acute Tubular Injury and Other Ischemic Renal Injuries

Renal infarction caused by arterial occlusion is not uncommon, largely because there is little collateral circulation available and because complete occlusion of an arterial branch results in absolute ischemia of the distal parenchyma. The majority of infarcts in adults are often clinically silent and are frequently caused by sudden and complete arterial blockage by emboli, potentially originating from ventricular thrombi or from vegetations on heart valves with verrucous or infective endocarditis or due to atheroemboli (see below). Less commonly, arterial obstruction is produced by thrombosis owing to changes in the wall of the vessel associated with atherosclerosis, systemic sclerosis, malignant hypertension, polyarteritis, or aneurysm formation as a result of dysplastic disease of the renal artery. Renal infarction has also rarely been described as a result of cocaine use (690, 691). Cases have also been described with fibromuscular dysplasia involving the renal arteries. Loin or renal fossa pain, hematuria, and/or pyrexia may suggest infection or renal calculi. Renal infarction frequently goes undetected, however, particularly if the area of infarction is small. Large infarcts can be associated with loin pain followed by hematuria and transient proteinuria.

**Gross Pathology**

The gross appearance of a renal infarct depends on the age of the lesion, the size of the vessel obstructed, and the presence or absence of infection. Initially, the infarct is red and pyramidal in shape, with the apex toward the obstructed artery. Within hours, it becomes gray, with a narrow red rim of adjacent congested parenchyma; as intralesional coagulation occurs, the infarcted area develops a yellow coloration (Fig. 26.35). As necrotic tissue is removed and replaced by collagenous tissue, the area of infarct shrinks and eventually becomes a V-shaped scar. The medulla is generally spared in renal infarction, and the lesions are confined to the cortex. Infarcts resulting from septic embolization are associated with the presence of liquefactive necrosis and abscess formation as a result of digestion by leukocytic enzymes.

**Light Microscopy**

Histologically, sterile infarcts show the findings of classic coagulative necrosis. Initially, there is marked congestion, followed by cytoplasmic and nuclear changes, where the tubular and glomerular architecture is preserved but gradual loss of viable cytologic...
structure occurs. The cytoplasm becomes homogeneous and eosinophilic, and the nuclei demonstrate condensation and karyorrhexis (Fig. 26.36). Peripheral to the central area of necrosis is a marginal zone in which there is a gradual transition from frank necrotic changes to sublethal injury in which glomerular and tubular changes are less striking and are similar to those seen in ATI (Fig. 26.37). As the lesion develops, it is in this zone that polymorphonuclear leukocytic infiltration becomes prominent. As the lesion progresses, the central necrotic area becomes smaller, and organization and regeneration occur around the periphery, with eventual collapse of the central necrotic area and replacement by collagenous scarring. As mentioned previously, the lesions are generally confined to the cortical tissue, and the medulla is spared. This picture helps distinguish scars resulting from infarction from those caused by reflux or pyelonephritis, in which medullary involvement is prominent.

**Venous Infarction**

Venous obstruction as a cause of infarction is much less common than arterial obstruction. It is seen in infancy as a complication of severe dehydration stemming from diarrheal diseases. Thrombosis of intrarenal veins and, occasionally, of the main renal vein produces an infarct of the hemorrhagic type (Fig. 26.38), as opposed to the relatively bland ischemic infarction that follows arterial occlusion. Whether infarction occurs in the kidney as a result of venous thrombosis depends on the completeness of the occlusion and the speed at which thrombosis and occlusion take place. Sudden, complete occlusions can be associated with infarction in adults, although this is rare; in most instances, thrombosis of the renal vein does not lead to infarction after infancy.

**ATHEROEMBOLIC DISEASE OF THE KIDNEY**

Embolization of the kidney by fragments of atheromatous plaques is extremely common and is found in nearly 5% of autopsies of men over the age of 50 and 3% of women in the same age group (692–695). Although emboli do appear spontaneously, they more commonly follow invasive arterial procedures, including arteriography, coronary angiography, coronary artery bypass, and repair of aortic aneurysms; they are found in as many as 25% of patients who have undergone such procedures (696). The emboli are usually derived from...
atheromatous lesions of the abdominal aorta that become impacted in intrarenal vessels (Fig. 26.39). Arteriolar and glomerular embolization can also occur (Fig. 26.40). When obstruction is complete, distal areas of infarction and necrosis are evident. Often the obstruction is incomplete, and the distal parenchyma demonstrates only ischemic atrophy (Fig. 26.41).

Cholesterol emboli are identified by the characteristic needle-shaped clefts that remain after the lipid has been dissolved during histologic processing (see Fig. 26.39). In early-stage lesions, the crystals are surrounded by fibrin, occasionally with associated eosinophils. In older embolic lesions, organization is evident, and the crystals are surrounded by fibrous tissue. Renal atheroemboli are frequently part of more generalized atheroembolic disease, resulting from multiple showers of cholesterol-containing microemboli in many organs, including the retina, brain, pancreas, and, in particular, the muscles and skin of the legs in addition to the kidney. Multisystem involvement often mimics systemic vasculitides, such as microscopic polyarteritis. In some instances, showers of emboli may be so extensive as to result in the clinical syndrome of ARF, mimicking the findings of rapidly progressive glomerulonephritis. The presence of eosinophilia, hypocomplementemia, and sometimes eosinophiluria further complicates the clinical recognition of this disease.

REFERENCES

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Bacterial infection outside the kidney can lead to glomerulonephritis either after the infection has been cleared, in which case the glomerulonephritis is appropriately called postinfectious glomerulonephritis, or while the active, persistent infection is still ongoing, in which case the terminology of postinfectious glomerulonephritis is obviously incorrect and the glomerulonephritis is best designated as glomerulonephritis associated with active/persistent bacterial infection. From the clinical point of view, it is relevant to differentiate these two forms of bacterial infection–related glomerulonephritis because, in postinfectious glomerulonephritis, antibiotic treatment is not necessary and immunosuppressive medications can be given. In contrast, if a bacterial infection is still active, the glomerulonephritis should be treated primarily with antibiotics, and immunosuppression should be avoided. If the previous or ongoing infection is known to the clinician and pathologist, the diagnosis is usually easy. However, in real-life situations, it is common that patients with bacterial infection–related immune complex glomerulonephritis do not display obvious clinical symptoms of infection at the time the glomerulonephritis is diagnosed. Such subclinical infections may be easily overlooked, and if the slightest suspicion for an underlying infection emerges, the pathologist has to raise this possibility to avoid immunosuppressive treatment before the infection can be safely excluded (1). There are several publications in the literature where postinfectious glomerulonephritis is defined...
The patient returned at a later time with what we would now regard as chronic renal failure.

With the introduction of microscopic examination of the kidney over the ensuing decades, it became apparent that changes took place in the glomeruli, and Langhans (8) described a category of Bright disease with glomerular inflammation. Schick (9) commented on the similarity of the latent period in serum sickness to that of acute glomerulonephritis.

The first major clinicopathologic treatise on renal disease appeared in 1914 with the publication of the work of Volhard (the clinician) and Fahr (the pathologist), *Die Brightsche Nierenkrankheit* (10). They classified Bright disease into various categories, including inflammatory diseases of the glomerulus. Longcope (11,12) recognized two general forms of glomerulonephritis, the first of which was associated with preceding bacterial infections and had a quick recovery and a good prognosis (acute glomerulonephritis). Ellis (13) also distinguished two types of glomerulonephritis. Type 1 nephritis, usually seen in young patients, was characterized by an abrupt onset, constitutional symptoms, gross hematuria following infection, and a high recovery rate; this condition corresponded to the first type described by Longcope (11).

Scarlet fever was noted to be associated with acute glomerulonephritis in the late 1800s and early 1900s, and it soon became apparent that there was a common association with a previous infection of group A streptococcus (GAS). Varying attack rates of acute glomerulonephritis were noted in patients with scarlet fever, and a greater attack rate of nephritis was found in children compared with adults. These varying rates were probably largely dependent on the strain of *Streptococcus* causing the infection. Ophüls (14), as early as 1917, had suggested that only certain strains of streptococci appeared to have a nephritogenic capacity.

**Nephritogenic Strains and Epidemiology**

Most cases of acute glomerulonephritis seen worldwide are caused by the *streptococcus*, without the clinical signs and symptoms of scarlet fever. In colder northern climates, most cases of acute glomerulonephritis follow upper respiratory tract infections, such as pharyngitis or tonsillitis, but cases also can follow skin infections, especially in warmer climates (15–17). Most cases of PSAGN are caused by group A streptococci, which are also responsible for rheumatic fever. Although rare cases of concomitant rheumatic fever and PSAGN have been noted (18,19), there are many differences between the epidemiology of acute glomerulonephritis and rheumatic fever. A likely explanation for the different patterns is that only certain (nephritogenic) strains of group A streptococci lead to acute glomerulonephritis (20–26). Types 12, 4, and 1 are more likely to cause acute glomerulonephritis after throat infections than other types (25,26). Type 12 is especially common as a strain leading to acute glomerulonephritis. However, even with the same type of streptococcal organism, there are differences in the attack rate. Siegel et al. (27) showed that only 1 of 58 patients with well-documented type 12 streptococcal infection progressed to acute glomerulonephritis; this was a convincing demonstration that not all strains of type 12 are nephritogenic. The attack rate (variably defined and detected) with certain nephritogenic strains ranges from 1% to 33% of patients (28,29). Differences in the host, such as different immune responses, abnormalities in the alternate complement pathway activation, could lead to
this variability. Of all children infected with the various strains of streptococci, it appears that less than 2% show clinically obvious signs of acute glomerulonephritis.

Acute glomerulonephritis resulting from skin infections is not uncommon, especially in warm climates (16,17,22,30–34). Streptococcal infections of the throat are more common in the winter and early spring, whereas streptococcal pyoderm or impetigo tends to occur in temperate climates in the late summer and early fall (34). The seasonal pattern is found for acute glomerulonephritis. When skin infections lead to acute glomerulonephritis, certain serotypes of streptococci are isolated more commonly than others; streptococcal M types 49, 42, 2, 57, and 60 seem to be predominant, and types 49, 42, and 2 are particularly potent (34). The nephritogenic strains from the throat and skin show, in general, comparable attack rates of glomerulonephritis (34). However, type 49 infections of the skin have quite different attack rates of acute glomerulonephritis (24%) than type 49 that appears in the throat (5%) (34). Frequently, the same bacteria are found in the throat and the skin; in these instances, the skin infection typically precedes that in the throat (35).

Many of the important early observations on the epidemiology of acute postinfectious glomerulonephritis were made on the Red Lake Indian Reservation in Minnesota, where outbreaks of acute glomerulonephritis occurred in 1952 and again in 1966 (35,36). A study of the second epidemic (both caused by type 49) showed that all cases occurred in children too young to have been infected in the first epidemic (35) because of the lack of type-specific immunity. Epidemic outbreaks tend to occur in closed communities (20,36,37) or in highly populated areas in which poor hygiene, malnutrition, anemia, and parasites are common (17,20,22,38–40). PSAGN epidemics related to skin infections may be associated with outbreaks of scabies (38). Some epidemics in certain communities tend to recur and are separated by 5 to 7 years (17,20).

From the 1940s to the mid-1980s, the incidence of the suppurative and nonsuppurative complications of group A β-hemolytic streptococcal infections, such as glomerulonephritis and rheumatic fever, all but disappeared in the United States and throughout much of Europe (41,42). However, in 1987, the first of several outbreaks of rheumatic fever was reported (43). The concern about these infections increased when the outbreaks were followed by severe systemic streptococcal illnesses, invasive skin diseases, and a toxic shock–like syndrome (42). Despite these outbreaks and the continued prevalence of certain major nephritogenic strains (M type 12) (44), PSAGN has apparently continued the same sharp decline in incidence it had pursued before the mid-1980s. This decline is not thought to be caused by primary prophylaxis with penicillin but by a changing epidemiology of the disease that may stem from either changes in the nephritogenic potential of certain strains (e.g., M type 12) or changes in susceptibility of the host.

Roy and Stapleton (18) noted a changing perspective in the occurrence of PSAGN in one Tennessee hospital during the course of two decades. Although they noted a marked decline in the prevalence of PSAGN, they also noted a decline in urban patients and an increase in rural patients with PSAGN. In the last decade, they noticed a predominance of antecedent pharyngeal infection in children older than 6 years of age and a predominance of antecedent pyodermia in African American children (18). Postinfectious glomerulonephritis, however, continues to have a high incidence in other parts of the world, especially in areas with tropical climates, where skin infections are common, such as Africa (19), South America (20,38,39), the Caribbean (17), New Zealand (45), India, and in indigenous communities (Aborigines in Australia) (46). Incidence and prevalence of PSAGN in selected countries worldwide, based on biopsy studies published after 1985, are shown in Table 10.1 (68). A Kuwait study described 234 patients over a 9-year period, and these patients showed a high prevalence of certain nephritogenic strains (M types 12 and 49) (67). The possibility of reemergence of poststreptococcal glomerulonephritis in the United States and Europe cannot be excluded (41). In 1995, an epidemic outbreak was reported in Armenia following serious deterioration of the living conditions there. In this epidemic, most children had upper respiratory tract infections or scarlet fever preceding PSAGN, and only 13% of them had skin infections (40). There are two recent reviews describing the global burden of PSAGN/postinfectious glomerulonephritis worldwide, one from Bangkok, Thailand, and the other a collaborative work from the United Kingdom, Australia, and Canada (46,68). The calculations of incidence and prevalence of PSAGN are based on large population-based studies by Carapetis et al. (69) and Rodríguez-Iтурbe et al. (70,71). Carapetis et al. calculated an incidence of approximately 24.3 cases per 100,000 person-years in children and 2 cases per 100,000 person-years in adults in the developing world versus 6 and 0.3, respectively, in the developed world. They calculated a prevalence of GAS disease of at least 18.1 million cases, with 1.78 million new cases each year and 517,000 deaths per year due to severe group A streptococcal (GAS) diseases (acute rheumatic fever, rheumatic heart disease, PSAGN, and invasive infections). There is significant global variation with the highest incidence of 239 per 100,000 in Australian Aborigines and the lowest incidence of 0.04 per 100,000 in an Italian study of people under the age of 60. Still all these statistical calculations are likely to be underestimations since they cannot account for the vast majority of subclinical disease that is thought to be 4 to 19 times more common than symptomatic disease. The estimates are even higher in the reports by Rodríguez-Iтурbe et al. (70,71).

The epidemiology of postinfectious glomerulonephritis in the developed world is undergoing rapid changes. In the United States, most infection-related glomerulonephritis cases occur in adults, and staphylococcal infection–associated glomerulonephritis (usually not postinfectious) is more common than PSAGN (2,3). The type 2 diabetes “epidemic” and rapid increase in obesity substantially contribute to these changes (2,3,68).

**General Properties of Streptococci, Antibody Formation, and Complement Changes**

**Streptococcus Pyogenes**

*Streptococcus pyogenes* (GAS) produces many virulence-enhancing extracellular products and toxins, including erythrogenic toxin, DNase, hyaluronidase, streptokinase, NADase, proteinases, and the hemolysins streptolysin-O (oxygen labile) and streptolysin-S (oxygen stable). GAS is the etiologic agent of a number of suppurative infections, including pharyngitis, cellulitis, necrotizing cellulitis, scarlet fever, erysipelas, pyoderma, puerperal sepsis, toxic shock–like syndrome, and impetigo. Ferretti (72) reviewed the molecular basis of virulence and antibiotic
resistance in GAS. Certain GAS organisms have surface receptors that bind selectively to the key fibrinolytic enzyme, plasmin (73). The bacterium-bound plasmin retains its enzymatic ability to cleave substrates and hydrolyze a fibrin clot, which may in part contribute to its tissue invasive properties (73).

GAS infection can be diagnosed and monitored with many laboratory procedures that detect the organism, its antigens, or its antibodies.

Conventional methods for the identification of viable organisms include finding \( \beta \)-hemolytic colonies on 5% sheep blood agar with a subsequent presumptive identification based on sensitivity to bacitracin on streptococcal-selective agar or hydrolysis of 1-pyrrolidonyl-\( \beta \)-naphthylamide. Serologic procedures to identify \( \textit{Streptococcus} \) include latex agglutination, coagglutination, immunofluorescent antibody staining, and the Lancefield precipitin test, in which cell wall antigens must be extracted by heating or chemical treatment prior to testing. Throat cultures are a reliable method for finding GAS, but they have a long turnaround time (74).

Rapid methods for the detection of organism antigen directly from throat swabs include latex agglutination, coagglutination, and enzyme immunoassay (74,75). These rapid methods are truly helpful only if results are positive; negative results do not necessarily mean that the specimen collection site was free of \( \textit{S. pyogenes} \). In addition, cultures with fewer than 10 colonies (with false-negative rapid test results) have yielded positive serologic test results (i.e., a fourfold or greater rise in antibody titers). Therefore, small numbers of group A streptococci can be meaningful.

There is much information on the biologic characteristics of the streptococcal organism as well as the strains that lead to acute glomerulonephritis. Poststreptococcal glomerulonephritis is almost always caused by strains of the serogroup A; however, several well-documented outbreaks have been caused by group C organisms in patients with septic arthritis, pneumonia, and septicemia (76,77) and to group G streptococci (skin infections) (78). Milk-borne \( \textit{Streptococcus zoonepidemicus} \) infection from unpasteurized milk and cheese has been reported with septicemia and clinical evidence of PSAGN (39,79).

TABLE 10.1 Incidence and prevalence of PSAGN worldwide

<table>
<thead>
<tr>
<th>Country</th>
<th>Ref.</th>
<th>Incidence</th>
<th>Prevalence</th>
<th>Period of study</th>
</tr>
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<tbody>
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<td>Australia</td>
<td>(47)</td>
<td>7.33</td>
<td>0.16</td>
<td>1995 and 1997</td>
</tr>
<tr>
<td>Brazil</td>
<td>(48)</td>
<td>22.86</td>
<td>0.23(^b)</td>
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<td>13.25</td>
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<td>1979–2002</td>
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<tr>
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<td>10.14(^b)</td>
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<td>(^c)</td>
<td>0.78</td>
<td>0.13(^a)</td>
<td>1999–2006</td>
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</table>

\(^a\)Data from children.

\(^b\)Data from adults.

\(^c\)Data provided by Dr Tray Hunley, Division of Pediatric Nephrology, Vanderbilt Children’s Hospital, USA.

Estimates of the incidence and prevalence of postinfectious glomerulonephritis in selected countries, based on data from biopsy studies published after 1985 (68). Incidence is given as cases per year; prevalence is given as cases per 100,000 population.
contained in the most conserved region of the M protein have yet been possible (81,82). Molecular typing of the M protein has been used to investigate the molecular epidemiology of GAS as well as group C and G streptococcal disease. A systematic review of the global distribution of GAS M types revealed that the epidemiology of GAS disease in Africa and the Pacific region seems to be different from that in other regions, particularly the United States and Europe. In Africa and the Pacific regions, there is more diversity of M types. The M types (including 1, 4, 6, and 12) that are more common in the high-income countries were found to be less common in Africa and the Pacific region. This has implications for the development of multivalent GAS vaccines. One vaccine may not provide good coverage worldwide (81). Nontypeable GAS organisms also have been cultured from patients with acute glomerulonephritis, which presumably represent unclassified nephritogenic strains (20). It is likely that multiple factors of the bacteria and the host contribute to the differences in the attack rates for different strains of streptococcal organisms. Numerous proteins/antigens were described that are characteristic of nephritogenic strains of streptococci. These nephritogenic proteins are discussed later in this chapter.

**Antibody Formation**

Both intracellular and extracellular antigens of the *streptococcus* stimulate the production of antibodies in the infected patient. Antibodies against the various streptococcal products are of great help in clinical medicine because their presence provides evidence of a preceding streptococcal infection, although probably not all are involved with conferring immunity. However, the specificity of these antibodies can be questionable. These antibodies include antistreptolysin O (ASO), antistreptokinase (ASK), antihyaluronidase (AH), antideoxyribonuclease-B (anti-DNase-B), antidiaphosphophorydine nucleotidase (anti-DPNase), and anti–nicotinamide adenine dinucleotidase (anti-NADase). The "streptozyme" antibody test was introduced as a latex agglutination method in a kit intended to simultaneously measure antibodies to five streptococcal extracellular antigens (exoenzymes), including streptolysin, streptokinase, hyaluronidase, DNase, and NADase. It should be noted, however, that approximately 20% of healthy children have elevated streptozyme titers. Also, some investigators believe that the reliability of the streptozyme test is not as good as that of conventional methods for single-antibody determinations.

Two of the most useful antibody determinations in the evaluation of patients with recent streptococcal infections are the ASO and anti-DNase-B assays. The ASO assay is the best known and the one most frequently ordered. In one study (83), the ASO titer was greater than 160 units in 92% of patients with acute glomerulonephritis; ASK and AH titers were raised in less than 50%. The ASO titer is usually greater than 250 Todd units, and most patients have a threefold or greater rise. A rising titer provides the best proof of a streptococcal infection. The ASO titer begins to climb within a few days of infection and reaches a peak level after several weeks; as a rule, it then declines. However, the ASO titer does not increase in all patients with streptococcal infections; thus, the absence of a high titer does not exclude a streptococcal infection. This is especially true of patients with skin infections (pyoderma).

Conversely, the ASO titer can be modestly elevated in patients with nonstreptococcal disease, and up to one third of patients with other forms of nonstreptococcal glomerulonephritis may have mild elevations of ASO. Because the ASK or AH titer may be elevated when the ASO titer does not rise (as in skin infections), some researchers have suggested that a combination of all three tests is of advantage in diagnosing PSAGN. False-positive results are caused by β-lipoprotein in liver disease, some other bacteria, and oxidation of streptolysin O. False-negative results may be obtained after antibiotic treatment of the patient. AH and anti-DNase-B titers are commonly raised in patients with skin infections, more so than ASO, as indicated earlier. Anti-DNase-B testing is more sensitive than AH and is the test of choice in the investigation of skin infections. The anti-DNase-B titer remains elevated longer than the ASO titer. Zymogen is the precursor of cationic streptococcal proteinase (erythrogenic toxin B). Researchers in a multicenter study from South America concluded that detecting antibodies to streptococcal zymogen is superior compared with ASO and anti-DNase-B titers in the detection of PSAGN (84).

It is unusual for patients to experience a second attack of poststreptococcal glomerulonephritis. This finding is probably owing to the relatively limited number of nephritogenic strains of streptococci and to the acquisition of type-specific protective immunity to the serotype of *Streptococcus* that elicited the initial attack. Other factors probably contribute to the relative resistance to another nephritogenic attack, such as the presence of antibodies to the specific nephritogenic factor(s). Cross-reacting neutralizing antibodies may be directed at one potential factor but may cross-react with another (85). When second attacks occur (86), they are similar clinically and morphologically to the initial attack. Penicillin interferes with the production of both type-specific antibody and ASO when significant dosages are given (27). Experimental evidence in a rabbit model of poststreptococcal glomerulonephritis using viable group A streptococci suggested that penicillin therapy within the first 3 days of infection prevents the acute nephritic process (87).

**Clinical and Laboratory Findings**

PSAGN most commonly affects children and young adults, although no age group is exempt. Although the peak incidence is in the first decade of life, occurrence in older patients has been noted, particularly in the diabetic population (2,3,38,68,88,89). According to an epidemiologic study of the Italian Registry of Renal Biopsy, the incidence of PSAGN in the elderly is higher than in the adult general population (90). Haas et al. (91) reviewed 259 renal biopsies from elderly patients with acute renal insufficiency at the University of Chicago and found that 5.5% of them had some ultrastructural evidence of possible postinfectious glomerulonephritis. Males are affected more commonly than females, the ratio often being 2:1 (92). This ratio is in marked contrast to that for patients with rheumatic fever, which affects both sexes equally. The distribution of PSAGN glomerulonephritis is worldwide. In North America, it affects groups equally in the northern and southern parts, also in contrast to rheumatic fever. PSAGN may appear in either sporadic or epidemic form; children are the group most usually affected in the epidemic forms.

For diagnosis of “acute postinfectious glomerulonephritis,” clear evidence that infection preceded the glomerulonephritis
is the result of sodium and water retention, studies by Parra and normalization of the plasma volume. Plasma renin activity is usually transient with a rapid return to normal levels of more common in adults, especially in elderly patients (99).

In patients with severe proliferative glomerulonephritis, progression of the lesion may result in oliguria or even anuria. This is particularly common in elderly patients with PSAGN. Oliguria may either be short lived or persistent, and it is possible indicative of a severe form of glomerular disease (i.e., the crescentic glomerular form). Oliguria tends to be transient, with diuresis usually occurring within 1 to 2 weeks. Anuria is less common. During the onset of oliguria/anuria, proteinuria may actually diminish because of a decrease in the glomerular filtration rate (GFR) (98). With resolution of the glomerular inflammation, increasing proteinuria may parallel an increasing GFR or even precede it.

Hypertension occurs in half of the children (98) but is more common in adults, especially in elderly patients (99). It is usually transient with a rapid return to normal levels of blood pressure on normalization of the GFR, loss of edema, and normalization of the plasma volume. Plasma renin activity is usually low. Although hypertension is generally thought to be the result of sodium and water retention, studies by Parra et al. (100) have suggested that inhibition of the angiotensin-converting enzyme by captopril could be an effective short-term treatment of low-renin hypertension in this disease. However, hypertension may persist, and when it does, it indicates either progression to a more chronic stage (the likelihood of this happening is discussed later) or that the disorder is not acute postinfectious glomerulonephritis.

Hypertensive encephalopathy is noted in no more than 5% to 10% of patients. There is usually clinical improvement without any neurologic deficit. Despite sodium retention during the acute phase of PSAGN, investigators (101) have found increased plasma levels of atrial natriuretic peptide. This finding suggests unresponsiveness of the kidneys to atrial natriuretic peptide in this condition. The accompanying increased plasma levels of endothelin may also contribute to this condition (53,60). Endothelin-1 not only is a potent vasoconstrictor but also facilitates sodium reabsorption in the proximal tubule that results in increased blood volume. Patients with PSAGN have experienced successful pregnancies (48).

Subclinical forms of PSAGN are probably more usual than symptomatic disease (21,102–106). In a prospective study of 248 children with GAS infections, Sagel et al. (103) measured serum complement levels and ASO titers and performed urinalysis. They found that subclinical disease was almost 20 times more common than overt acute glomerulonephritis. Over a 6-week period, 54 children showed either transient depression of serum complement (19 children) or mild urinary abnormalities (proteinuria, hematuria, or leukocyturia—15 children) or both (20 children). All patients were asymptomatic, except for one who had edema; hypertension was present in half the patients. Renal biopsy was performed in 20 patients in whom depressed complement and urinary abnormalities were present, and a proliferative glomerular change, ranging from mild to severe, was noted. A granular glomerular immunofluorescence pattern for complement C3 was noted in 15 of the 20 biopsies.

Few patients may develop left ventricular dysfunction during the acute congestive and convalescent phases of PSAGN. This dysfunction may not be associated with hypertension or pericardial/pleural effusions (107). PSAGN rarely shows initial signs of pulmonary hemorrhage (108,109). PSAGN may be seen in alcoholics with or without cirrhosis (110). PSAGN has often been reported to be superimposed on diabetic nephropathy (412). A number of other diseases have been associated with PSAGN, but these case reports probably describe by chance associations.

Elevations in blood urea nitrogen (BUN) and serum creatinine levels reflect the decrease in GFR, and they are often noted during the acute stages. Lack of normalization of these values within several weeks or a few months suggests that one may not be dealing with a true case of acute postinfectious glomerulonephritis. Elderly patients have a higher rate of major elevations of serum creatinine (90,99). BUN and serum creatinine levels may remain elevated in those patients who have the crescentic form of postinfectious glomerulonephritis (111,112).

Proteinuria may be mild or so severe as to cause hypoalbuminemia and severe edema. Proteinuria is less than 3 g/24 hours in most cases. Nephrotic syndrome occurs in approximately 5% to 10% of patients (113); in one series (114), it was noted in 20%. Proteinuria usually disappears within 6 months and cleared with clinical healing in all but 4 of the 23 patients in the studies.
of Jennings and Earle (115). Proteinuria may persist for longer periods, but complete clinical recovery has been noted after proteinuria has been maintained for as long as 26 months (115). McCluskey and Baldwin (114) described a well-documented case of one patient with disappearance of proteinuria after 6 years. Symptoms, including proteinuria, hypertension, and renal insufficiency, are more severe in adults and, in particular, in the elderly with postinfectious glomerulonephritis (2).

The urine of patients with PSAGN has a high specific gravity. The brown/smoky color is caused by hemolysis of erythrocytes that have penetrated the GBM and have passed into the tubular system. Both are particularly common in patients in whom urine volume is reduced. The urinary sediment has red blood cells, red blood cell casts, granular casts, and sometimes leucocyte casts. Microscopic hematuria often persists longer than proteinuria and may be present in patients in whom the disease has otherwise completely disappeared clinically (115). Hematuria may persist for as long as 18 months, and in a few patients, it persists for much longer periods, even up to 5 years. The presence of red blood cell casts is of great importance because they indicate that the bleeding is of glomerular origin. Such casts are best discovered in first early morning urine specimens studied by the physician shortly after voiding. Dysmorphic red blood cells are also indicative of glomerular disease. A report on 152 patients with PSAGN from Turkey indicates that microscopic hematuria is more common than gross hematuria in patients with severe systemic manifestations (defined by the authors as pulmonary edema, cardiac failure, and severe hypertension with signs of encephalopathy), and, in contrast, gross hematuria is more than three times more common than microscopic hematuria in patients with renal symptoms only (116).

Albuminuria and microhematuria can be detected in the interval between infection and nephritis in up to half the patients with streptococcal upper respiratory tract infections and are thought by some to be more likely to occur in patients who progress to acute glomerulonephritis. In renal biopsies taken shortly after the onset of infection, only mild focal hypercellularity of the glomeruli was noted (92). The serum albumin level is sometimes low because of the loss of albumin in the urine in those patients with severe proteinuria. The serum cholesterol level may be elevated in some children as well as adults.

As noted earlier, antibodies to various streptococcal products can be found in patients with acute glomerulonephritis and are used diagnostically to establish the presence of a preceding streptococcal infection. Comparisons of acute and subsiding titers are of importance clinically. A rise in serum titer of two or more dilution increments between the acute and the convalescent serum is usually considered significant regardless of the magnitude of the titer. The upper limit of the normal range varies with the season, geographic area, and age of the patient; thus, each laboratory should establish its own reference range. Patients who are treated with antibiotics early in the course of the infectious episode or elderly patients may not exhibit a significant rise in antibody titer; thus, the diagnosis may be difficult to make in the absence of positive cultures.

Anemia is commonly noted in the early stages. This feature is thought to be primarily a dilutional phenomenon as a consequence of the expanded extracellular fluid, although cases of hemolytic anemia (117) and hemolytic uremic syndrome have been reported (118–121).

Serum complement is decreased during the acute episode in almost all patients with PSAGN (52,65,118) and is considered evidence in favor of the diagnosis and of an antigen-antibody reaction. Serum complement levels usually return to normal within 6 weeks of the acute onset of the nephritis. In patients in whom the serum complement level is apparently normal, serial determinations will often show an increase during the recovery stage, suggesting that there was in fact a decrease associated with the glomerulonephritis. There is activation of both the classic and the alternative pathways of the complement cascade. Levy et al. (57) suggested that although both pathways are implicated in the early stages of the disease, continued C3 depression is probably through the alternative pathway. Serum complement abnormalities in PSAGN will be discussed more in detail later in this chapter (see Pathogenesis).

Pathologic Findings
As with most of the glomerulonephritides, our early knowledge of the pathology of acute glomerulonephritis was derived mostly from autopsy material. With the advent of renal biopsy, it became possible to compare the morphologic pattern of the glomerular involvement in the living patient with that seen in patients dying with glomerulonephritis. Renal biopsy studies have shown that the morphologic picture described from autopsy material is virtually identical to that found on renal biopsy. This is probably because death in patients with acute postinfectious glomerulonephritis was attributable to congestive heart disease, not to renal injury. Recently, fewer biopsies showing acute glomerulonephritis have been available, since the clinician (especially the pediatric nephrologist) is less likely to conduct a biopsy on a patient with classic or typical signs and symptoms of acute postinfectious glomerulonephritis.

Indications for considering renal biopsy in children with acute nephritic syndrome include (a) persistent severe (gross) hematuria longer than 1 month or persistent hypocomplementemia longer than 6 weeks, (b) progressive deterioration of the GFR, (c) hypertension persisting longer than 2 months, (d) extrarenal manifestations of systemic disease, (e) family history of renal disease, (f) age younger than 2 years, (g) onset of nephritis within 48 hours of pharyngitis (54,55), or (h) nephrotic syndrome (Table 10.2). The indications for renal biopsy in adults are not as clear but are probably more liberal because of the less common occurrence of PSAGN in the adult. A number of glomerular diseases may appear in a manner clinically resembling PSAGN, including C3 glomerulopathy (including dense deposit disease and C3 glomerulonephritis), membranoproliferative glomerulonephritis (MPGN), IgA nephropathy, IgA vasculitis (Henoch-Schönlein purpura), and renal-limited forms of anti-GBM (antiglomerular basement membrane) disease and ANCA (antineutrophil cytoplasmic autoantibody) disease. The most typical examples of disease processes masquerading as acute postinfectious glomerulonephritis in a child are C3 glomerulonephritis and MPGN, which may present with acute nephritis and hypocomplementemia.

Gross Appearance
The kidneys are symmetrically enlarged, generally 25% to 50% larger than normal. They are pallid in appearance, and the cut surfaces bulge because of interstitial edema. The main thickening is in the cortex. The glomeruli may stand out as reddish or gray translucent dots. The capsular and cut surfaces...
may have tiny red speckles caused by red blood cells in the lumens of the Bowman space and tubules.

**Microscopic Findings**

**GLOMERULI**

**Hypercellularity and Other Common Findings**

The glomeruli are all affected (diffuse involvement) and usually to an approximately equal degree (Figs. 10.1 to 10.3). The glomerular tufts are larger than normal, and the cells are more numerous. Many cell types contribute to the hypercellularity, including proliferating endothelial and mesangial cells from the tuft itself and influx of inflammatory cells, among them polymorphonuclear leukocytes and monocytes (Figs. 10.4 and 10.5). The extent to which native endocapillary cells contribute to the hypercellularity is a subject of debate and is discussed later. In most specimens with acute disease, polymorphonuclear leukocytes are the most easily identified cells and may be present in large numbers—hence the term *exudative glomerulonephritis* (although many of the neutrophils are margined in the lumens of capillaries rather than exuding from the capillaries). In other cases, they are inconspicuous. It has been suggested by Jennings and Earle (115) that polymorphonuclear leukocytes may be more frequently found in biopsies performed shortly after the clinical onset of the disease. Obviously, as the acute inflammation resolves, the number of neutrophils will decline progressively. Occasionally, other inflammatory cells, such as eosinophils (59,98) and lymphocytes, are noted, but this is unusual. Necrosis in the glomerular tuft is rare (Fig. 10.6).

The individual lobules of the glomeruli are wider than normal and sometimes assume a clubbed appearance. The glomerular capillary lumina are often reduced by the hypercellularity so that erythrocytes may be difficult to see. The stalk region of the mesangium may be quite hypercellular (115). The glomerular capillary walls are generally not thickened, although there may

**TABLE 10.2**

Atypical features that suggest a need for renal biopsy

<table>
<thead>
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<th>Feature</th>
<th>Atypical features during presumed recovery</th>
</tr>
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<td>Absence of evidence of streptococcal infection or immune complex disease</td>
<td>Failure of normalization of GFR by 4 wk</td>
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<tr>
<td>No rise in antistreptococcal antibodies</td>
<td>Depression of serum complement level longer than 6 wk</td>
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<tr>
<td>Normal serum complement level</td>
<td>Persistence of proteinuria longer than 6–8 mo</td>
</tr>
<tr>
<td>Atypical early features</td>
<td>Persistence of hematuria longer than 18 mo</td>
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<td>No latent period</td>
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</tr>
<tr>
<td>Anuria</td>
<td></td>
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<td>No improvement or continued decrease in GFR at 2 wk</td>
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<td>Persistence of hypertension longer than 2 wk</td>
<td></td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td></td>
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<tr>
<td>Persistence of proteinuria longer than 6–8 mo</td>
<td></td>
</tr>
<tr>
<td>Persistence of hematuria longer than 18 mo</td>
<td></td>
</tr>
</tbody>
</table>

GFR, glomerular filtration rate.

Modified from Nash M. Renal Biopsy in Medical Diseases of the Kidney. New York: Postgraduate course, Department of Pathology, Columbia-Presbyterian Medical Center, 1989.
sometimes be mild thickening visible on light microscopy. The combination of expansion of the lobules, hypercellularity of the tuft, and localized thickening of the glomerular capillary walls may produce a picture mimicking MPGN. Ultrastructural and immunofluorescence studies and clinical findings at the time of biopsy and follow-up allow easy separation of these morphologically and clinically distinct entities.

In some patients, it is possible, especially with the oil immersion lens, to detect tiny nodules on the epithelial side of the glomerular capillary wall. These nodules can be identified as fuchsinophilic dots with the trichrome stain (Masson or Mallory) either on thin (3-μm) sections or on 0.5-μm plastic-embedded sections stained with toluidine blue (Fig. 10.7). These minute structures correspond to the subepithelial deposits (humps) noted by electron microscopy. For optimum detection, it is important to study these renal biopsies with the oil-immersion lens and the trichrome stain because these small deposits may be overlooked on casual examination with the high-dry (40× or 60×) objective alone. Detection of those deposits by light microscopy is especially useful if there are no materials (i.e., glomeruli) for study by electron microscopy or immunofluorescence. Although the glomerulonephritis is diffuse (involving all or almost all glomeruli equally), there may be focal and segmental variability of the lesions among glomeruli, but this is unusual (Fig. 10.8).

In some patients, there may be crescent formation (2,66) or small adhesions (synechiae) (Fig. 10.9). In a few patients, crescent formation is so prominent that the term crescentic glomerulonephritis may be used, but usually only a small percentage of glomeruli are affected by crescents. The Bowman space may contain erythrocytes, which is evidence in a percutaneous renal biopsy that hematuria is caused by glomerular bleeding. Polymorphonuclear leukocytes also may be seen in the Bowman space.

**Cell Types** Both infiltrating leukocytes (neutrophils and monocytes) and proliferating glomerular cells (mesangial, endothelial, and epithelial cells) contribute to the glomerular

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**FIGURE 10.3** Silver stain of a glomerulus from a patient with PSAGN. Note that all the hypercellularity is confined within the glomerular tuft (endo-capillary hypercellularity). (Jones silver methenamine, ×600.)

**FIGURE 10.4** This glomerulus shows a broadening of the lobules, increase in cellularity with moderate numbers of neutrophils with segmented nuclei, and reduction of the capillary lumens. (PAS, ×400.)

**FIGURE 10.5** Acute diffuse proliferative glomerulonephritis with considerable infiltration of the glomerulus by neutrophils, which is common in acute postinfectious glomerulonephritis. (PAS, ×1000.)

**FIGURE 10.6** A glomerulus from a patient with clinically classic PSAGN. Note the focal segmental fibrinoid necrosis at approximately 10 o’clock as well as the endocapillary hypercellularity. (Masson trichrome, ×600.)
hypercellularity. The old term *proliferative glomerulonephritis* implies that the increased cellularity is restricted to native glomerular cells, either endocapillary cells (endothelial or mesangial) or extracapillary cells (visceral and parietal epithelial cells). However, current evidence suggests that much of the glomerular hypercellularity (as well as some of the crescent formation in the Bowman space) stems from infiltrating leukocytes from the peripheral circulation. Langhans (8) initially proposed that the major cause of the cellular increase in the glomerular tuft was a proliferation of endothelial cells. This concept was responsible for the designation *endocapillary proliferative glomerulonephritis*.

Jennings and Earle (115) favored the notion that hypercellularity was owing to native intraglomerular cells because of the presence of mitotic figures in “cells inside and attached to the glomerular capillary basement membrane (by definition, endothelial cells).” These authors also used electron microscopy to strengthen their view and described cells in the resolving phases of the disease process that had inclusions of electron-dense material resembling GBM. They stated that such inclusions were not evident in mononuclear inflammatory cells (115). This argument, however, did not resolve the question regarding which endocapillary cells (mesangial or endothelial) participate in the proliferation. Ia (MHC class II antigen)-bearing mesangial cells (53), which might be resident macrophages, also could play a role in hypercellularity, but studies in humans have not been forthcoming.

Grishman and Churg (60) described proliferation of cells in the mesangium but did not commit themselves as to the nature of the cells. Many other investigators have mentioned the great difficulty in distinguishing between endothelial and mesangial cells in light microscopy of a hypercellular glomerulus.

Experimental studies also confirmed the idea that mononuclear phagocytes appear in the glomerular tuft in various forms of experimentally induced glomerulonephritis. Although most of these studies used models of Masugi nephritis and Habu snake venom, some used acute serum sickness models in the rabbit (48,63). Monocytes were found to be present in the latter model of acute glomerulonephritis by Hunsicker et al. (63) and by Holdsworth et al. (48), using electron microscopy and staining for nonspecific esterase. Thus, it appears that bone marrow–derived mononuclear cells play a significant part in the hypercellularity noted in the glomeruli of certain experimental diseases.

In human studies using staining for nonspecific esterase and electron microscopy, monocytes are identified in less than half the biopsies of acute glomerulonephritis examined, especially in the early stages of the disease (50,58). Specimens with...
mesangial hypercellularity, but less exudative change, had fewer esterase-positive cells. It was suggested that early glomerular hypercellularity is owing to an influx of blood-borne cells, but at a later stage, it is caused mainly by proliferation of intrinsic glomerular cells (62,64). Magil et al. (62,64) verified the presence of glomerular intraluminal monocytes that correlated positively with the presence of deposits. They also described dissection of the glomerular endothelium from the capillary wall adjacent to deposits by the monocytosis. Ferrario et al. (58) showed that the degree of proteinuria correlated well with the degree of glomerular mononuclear cell infiltration.

Chung and Kim (47) performed immunohistochemical studies with a monoclonal antibody to Ki-67 (a cell proliferation marker) on renal biopsies from 21 children with PSAGN. They found that the active phase of the disease was associated with more prominent glomerular Ki-67 expression compared with the convalescent phase of PSAGN. However, one has to note that even if in the active disease group, only 11 of 13 biopsies showed Ki-67–positive glomerular cells. Therefore, their results clearly indicate that although some degree of proliferation of endogenous glomerular cells takes place, the bulk of the hypercellularity is secondary to infiltrating inflammatory cells (47). Unfortunately, the study does not clarify the exact cell populations that undergo proliferation in these biopsies with PSAGN.

Inflammatory cells in acute diffuse proliferative glomerulonephritis have been studied by immunophenotyping, but only a few studies concentrated on PSAGN. Hooke et al. (56) found significantly increased numbers of glomerular monocytes and granulocytes, but no significant increase in the number of glomerular T cells or B cells in cases of acute postinfectious glomerulonephritis when compared with normal glomeruli. There was a rise in the number of interstitial T lymphocytes compared with the normal interstitial cell population, but the OKT4/OKT8 ratio was the same as in normal cell populations (56).

Parra et al. (51) studied the cell populations in glomeruli of patients with PSAGN using monoclonal antibodies and indirect immunofluorescence. They found infiltration of the glomeruli by monocytes, granulocytes, and lymphoid cells. T cells were noted adjacent to the Bowman capsule. CD4+ (helper/inducer) lymphocytes were found in the glomeruli early in the course of the disease, whereas CD8+ (cytotoxic/suppressor) cells were found later. Yoshizawa et al. (61) evaluated the role of the cell-mediated immune response in the kidneys of 22 patients with PSAGN. They found a substantial increase in the total number of granulocytes and monocytes/macrophages with only a slight rise in T cells. The number of cells correlated well with time after clinical onset. A positive linear correlation was confirmed between helper/inducer T cells and monocytes/macrophages. As with the study of Parra et al. (51), helper T cells tended to increase to a higher proportion early on, although suppressor T cells remained constant throughout the course of the disease. Although there were fewer total leukocytes than in patients with clinically overt disease, in asymptomatic patients with PSAGN, the proportions of infiltrating cells were similar (61).

Polymorphonuclear leukocytes are often numerous, although large numbers of these cells do not indicate a poor outcome. The leukotactic properties of complement have been verified. Lewy et al. (98) documented a case with a predominantly polymorphonuclear leukocytic reaction in which there were large numbers of glomerular subepithelial humps. These authors commented that in other cases, the greatest numbers of polymorphonuclear leukocytes were found when there were large numbers of humps.

**Other Mesangial Changes** Several probes have found increases in some naturally occurring substances in the glomeruli in postinfectious glomerulonephritis. Actomyosin has been shown to be mildly elevated in the mesangial regions (49), but the significance of this finding is unclear. Likewise, fibronectin has been demonstrated in the mesangial areas (122,123). This protein is present in the normal mesangium and is significantly elevated in a variety of conditions associated with mesangial increase. Mosquera and Rodriguez-Iiturbe (124) found glomerular-binding sites for fluoresceinated peanut agglutination lectin in renal biopsies showing evidence of PSAGN. Peanut agglutination lectin has specificity for galactosyl radicals that are exposed after sialic acid removal, as one would see with neuraminidase. These findings suggested to the authors that sialic acid–depleting material (probably neuraminidase) was present in glomeruli early in the course of the glomerulonephritic process.

Several immunopathologic studies have been performed on renal biopsy material taken from patients with PSAGN. Parra et al. (125) confirmed enhanced expression of intraglomerular ICAM-1 (intercellular adhesion molecule 1) in early-stage biopsies; this expression decreased with time. The numbers of cells expressing lymphocyte function–associated antigen 1 (LFA-1) in glomeruli were also elevated in early biopsies. Levels of VCAM-1 (vascular cell adhesion molecule 1) were not higher. This study suggested that ICAM-1 (and possibly other adhesion molecules) is important in the recruitment/influx/localization of leukocytes in acute postinfectious glomerulonephritis. The study by Lhotta et al. (126) of ICAM-1 expression in various proliferative glomerulonephritides demonstrated that the changes in staining intensity were observed mainly on the glomerular endothelial cells with less mesangial staining. However, it should be noted that induction of E-selectin (ELAM-1) is not invariable in acute glomerulonephritis (127).

**Subclinical and Resolving Glomerulonephritis** Renal biopsies in patients with minimal urinary changes have been performed (usually in prospective studies) and show differing results. Some find no substantial abnormalities. Increased cellularity of the glomeruli also has been noted, as have changes indistinguishable from characteristic acute diffuse proliferative poststreptococcal glomerulonephritis (105,128,129). In renal biopsies taken several weeks after the clinical onset of disease, there is diffuse hypercellularity in mesangial regions of the glomeruli; the glomerular capillaries are patent, and the capillary walls appear thin and delicate (130) (Fig. 10.10). Some degree of resolution of the hypercellular process takes place, and the number of polymorphonuclear leukocytes is diminished. Mesangial hypercellularity appears to persist for many months in patients who eventually experience complete resolution of the glomerular lesion (131).

An old term for this morphologic picture is **chronic latent glomerulonephritis**. However, caution needs to be exercised for two reasons. First, an unusually thick paraffin section may give the false appearance of diffuse mesangial hypercellularity.
Second, many cases termed *chronic latent glomerulonephritis* may not be resolving/resolved PSAGN, in our opinion, but rather represent a nonspecific histologic pattern associated with various renal injuries unrelated to previous infections (132). In one long-term follow-up study (more than 5 years) of 26 patients suffering from PSAGN, Buzio et al. (133) found diffuse mesangial hypercellularity in those patients with persisting urinary albumin or proteinuria.

It has been proposed that patients with well-documented PSAGN who show a mesangial proliferative picture on subsequent biopsy have a worse renal prognosis than those with typical resolving streptococcal glomerulonephritis. Patients with isolated mesangial C3 deposits in association with mesangial proliferative glomerulonephritis may actually have poststrep-tococcal glomerulonephritis, but there is little proof in most patients. Multiple entities may show this pattern, since the kidney responds in a limited fashion to many different injurious stimuli. The recently characterized entity, C3 glomerulopathy, should be considered in proliferative glomerulonephritis with isolated C3 deposits, particularly in the absence of an obvious preceding infection (134). Also, patients with underlying abnormalities of the alternative complement pathway activation may have an atypical course of postinfectious glomerulonephritis (135). Complete morphologic resolution occurs following PSAGN, but follow-up biopsies in such patients, obviously, are not performed. In fact, “incidental healed” postinfectious glomerulonephritis may be more common than anticipated. Haas (136), in a study from the Johns Hopkins Hospital, reviewed 1112 consecutive renal biopsy specimens and found 57 biopsies in which ultrastructural findings indicated resolving/healed PSAGN. According to Haas, resolving or largely healed postinfectious glomerulonephritis was present in 10.5% of renal biopsy specimens, excluding biopsies with a primary diagnosis of immune complex glomerulonephritis (136). The study was based on ultrastructural findings (subepithelial deposits in glomerular mesangial notch regions); therefore, this incidence may be somewhat overestimated because subepithelial deposits in the mesangial notch region are not specific for resolving postinfectious glomerulonephritis because they can be seen in other glomerular diseases, for example, in C3 glomerulopathy (including dense deposit disease and C3 glomerulonephritis). Interestingly, in Haas’ study, 50% of the biopsies showing some evidence of incidental healing postinfectious glomerulonephritis had evidence of mesangial hypercellularity (136).

**Tubules**

The tubular changes are not as pronounced as those involving the glomeruli. When proteinuria is present, there may be hyalin droplets (protein reabsorption droplets, phagolysosomes) or vacuoles (dissolved lipid droplets) in the proximal convoluted tubular epithelium. Erythrocytes may be seen in the lumen of the tubules, and they are sometimes mixed with eosinophilic cast-like material. Polymorphonuclear leukocytes also can be present in the lumens, especially in the first portions of the proximal tubules. This feature is most commonly seen in patients with severe exudation or infiltration of polymorphonuclear leukocytes in the glomeruli. In a few patients, polymorphonuclear leukocytes can be seen between the tubular basement membrane (TBM) and the overlying tubular epithelial cells (Fig. 10.11). In patients who develop severe renal insufficiency, classic changes of acute tubular necrosis (ATN) are usually evident. With serial renal biopsies, these changes resolved. There was no apparent relationship between the morphologic tubular changes and $\text{TPA}_\text{PAH}$. In the most florid cases of acute glomerulonephritis with extensive crescent formation, there may be progressive tubular injury with tubular atrophy and loss, as well as tubulitis characterized by inflammatory cells between the TBMs and the tubular epithelium or within the tubular epithelium.

**Interstitium**

The degree of interstitial involvement is variable. The interstitial areas may show edema with separation of the tubules from one another. Scattered foci of inflammatory cells, made up of mixtures of polymorphonuclear leukocytes, monocytes, and lymphocytes, are sometimes present (Fig. 10.11). There may occasionally be severe interstitial mononuclear cell infiltration...
and scattered regions of interstitial fibrosis. Usually, however, the interstitial changes are not remarkable or severe. As noted earlier, interstitial changes may be found in relation to tubular changes (137). Bohle et al. (138), using morphometric methods on tissue sections, showed that the level of serum creatinine correlated with the increase in interstitial volume. They explained this finding on the basis of a reduction of renal blood flow and, hence, the GFR, brought about by compression of the postglomerular vasculature.

**Blood Vessels**

The arteries and arterioles generally do not show changes. In older patients, preexisting vascular abnormalities, such as arterial and arteriolar sclerosis, may be seen, and, according to Gallo et al. (139), these may be accentuated and lead to greater renal parenchymal injury. Arteritis has been described (140), but in such cases, systemic necrotizing vasculitis must be excluded. There are other accounts of arteritis (141,142) as well, but they are rare. Fibrinoid necrosis of the arterioles may be associated with severe hypertension. As noted earlier, in rare instances, vascular changes of thrombotic microangiopathy (TMA) may be seen (143,144).

**Immunofluorescence Findings**

Immunofluorescence studies have been reported by many investigators (59,96,131,145–152). Classically, in biopsies taken early in the clinical course (first 2 or 3 weeks) of the illness, small, granular deposits are noted along the glomerular capillary walls following immunofluorescence studies with anti-IgG and anti-C3 fluoresceinated antisera (Figs. 10.12 and 10.13). The pattern is granular (“lumpy-bumpy”) and usually more coarse than in patients with membranous glomerulonephritis. Large, coarsely granular immune complex deposits are usually easy to visualize using immunoperoxidase methodology as well on paraffin sections (Fig. 10.14). These deposits may assume a somewhat linear or band-like (garland) pattern in some areas, owing to the confluence of subepithelial deposits. The granular deposits correspond to the glomerular subepithelial deposits evident on electron microscopy, although there has been controversy over this feature in the past (153).

Sorger et al. (147–149) have described different immunofluorescence microscopy patterns called the garland pattern (Fig. 10.15), the starry sky pattern (Fig. 10.16), and the mesangial pattern (Figs. 10.17 and 10.18). The garland pattern has a discrete, more densely packed and sometimes confluent heavy disposition of IgG and C3, corresponding to numerous humps noted on the subepithelial side of the glomerular capillary wall (147,149). This arrangement is most often seen in patients with acute glomerulonephritis who have severe proteinuria (often with the nephrotic syndrome) (see Fig. 10.15). Other glomerular deposits are rare. The starry sky pattern has a more irregular, finely granular pattern, with the deposits (IgG, IgM, C3, IgA) being smaller and often situated on the GBM overlying the mesangial regions. This arrangement was most commonly seen in early cases (see Fig. 10.16). Only a few large, typical humps were noted in these cases. This picture may turn into the mesangial pattern, characterized by a granular deposition of IgG and C3 (usually with predominance of C3). It seems to be most closely related to a resolving pattern (see
Fig. 10.17). The deposits are generally noted in the mesangial matrix of the glomerulus and are accompanied by mesangial hypercellularity.

Edelstein and Bates (154) studied 42 adult patients with characteristic acute postinfectious glomerulonephritis and divided the biopsies into these three subtypes. There was no significant difference among the three subgroups of patients with regard to age, blood pressure, serum creatinine, ASO titers, or decreased serum C3 levels at presentation. Patients with the garland pattern had significantly more proteinuria, whereas the renal biopsies with the mesangial pattern had a lesser degree of glomerular hypercellularity and leukocytes.
FIGURE 10.16  A: Immunofluorescence shows a starry sky pattern. There are diffuse and irregularly distributed fine and coarse granular deposits in the glomerular capillary walls and in the glomerular mesangial regions. (C3, ×704.)  B: The accompanying electron micrograph shows a segment of a glomerular capillary loop from a patient with a starry sky pattern. The lumen of the glomerular capillary is totally occupied by a monocyte and by endothelial cells with prominent nuclei and swollen cell bodies. Numerous subendothelial deposits are present. (×5280.)  **Inset:** A pointed, arch-like glomerular subepithelial deposit with sparse areas of higher electron density. (×17,600.) From a 56-year-old man with a 3-week history of poststreptococcal glomerulonephritis. (From Sorger K. Postinfectious Glomerulonephritis. Stuttgart, Germany: Gustav Fischer Verlag, 1986.)
FIGURE 10.17  A: Immunofluorescence shows a mesangial pattern. Granular deposits are found in the mesangial regions, although the glomerular capillary wall remains largely negative. (C3, ×704.) B: The accompanying electron micrograph shows the corresponding ultrastructural appearance. A portion of the glomerulus shows marked proliferation of mesangial cells but free and open glomerular capillary lumens. Mesangial deposits are located in the mesangial matrix, and individual subepithelial deposits are present in the region of the mesangial waist (arrow). Less frequently, glomerular subendothelial deposits are situated along the loop. (×5280.) Inset: A glomerular subepithelial deposit with an almost homogeneous, comparatively pale density. (×17,600.) From an 18-year-old boy with a 5-week history of illness. (From Sorgor K. Postinfectious Glomerulonephritis. Stuttgart, Germany: Gustav Fischer Verlag, 1986.)
The starry sky pattern was noted in four of five patients with a crescentic pattern and six of seven patients with a chronic course (154). There is no evidence so far that different etiologic factors are responsible for these three subtypes (148). The individual immune response of the host and the stage of the disease are likely to play a role in their genesis. A diffuse granular pattern for IgG and, usually, C3 is also found in patients with subclinical glomerulonephritis (146,150,151) and in those with minimal urinary changes.

There is usually more intense and more constant staining with anti-C3 than with anti-IgG (145,146,150,151). In fact, it is common to see granular glomerular C3 without any demonstrable IgG. Some authors have noted the combination of granular and patchy, interrupted linear staining along the glomerular capillary wall and in the mesangial regions (59,88). At times, there seems to be an exclusively patchy, interrupted linear pattern for C3 along GBMs close to the mesangium as well as in the mesangium, with no staining for IgG (154). This interrupted linear deposits of C3 in the absence of IgG could be the result of a direct toxic effect of the organism (i.e., *Streptococcus*) on the glomerulus and that only a certain percentage of patients (especially those destined to experience severe acute nephritis) proceed to nodular deposits. As we will discuss briefly later, another explanation for the absence of IgG is that PSAGN may represent a transient form of C3 glomerulonephritis induced by streptococcal infection/antigens. In C3 glomerulonephritis, the glomerular deposits do not truly represent immunoglobulin-containing immune complexes.

IgM is frequently present and was recorded in more than 50% of cases in one series (131). Other authors (146) have not found IgM. IgA is usually absent (59,145,146), but it has been noted from time to time (131,150,151). If IgA immunofluorescence is strong in postinfectious glomerulonephritis, the possibility of an underlying staphylococcal infection has to be considered irrespective of presence or absence of diabetes mellitus (section on Glomerulonephritis associated with staphylococcal infections). IgE has seldom been sought; in one series of 10 patients, it was present in 5 biopsies (151). Fibrin/fibrinogen-related antigen also can be detected in the mesangial regions (as well as in the Bowman space in the crescentic form) (59,131,146).

Westberg et al. (155) noted properdin in the glomeruli in eight cases of postinfectious glomerulonephritis. In three of these patients, the pattern was granular along the glomerular capillary walls, whereas in five, it was noted in the mesangium together with C3. Various other authors (146,150) have also found properdin in several biopsies. Classic pathway components of complement, such as C1q and C4, are generally lacking (146,150,151). These various observations support the role of the alternative pathway of complement activation in postinfectious glomerulonephritis (151).
Parra et al. (51) studied the membrane attack complex in glomeruli of patients with PSAGN using monoclonal antibodies and indirect immunofluorescence. Membrane attack complex was noted along the GBM early and within the mesangial regions later in the course of the disease (a distribution similar to the deposition of C3 and C5). Rarely, immunoglobulins and complement components may be detected in renal arteries, especially in those rare patients with necrotizing arteritis. Immunohistochemical studies by Kamitsuki et al. (156) localized intraglomerular deposits of fibrin and cross-linked fibrin in the proliferative glomerulonephritides.

As noted earlier, attempts to identify and localize the streptococcal antigen have usually failed. However, studies by Seegal et al. (157) demonstrated streptococcal antigen in over half the cases studied. Andres et al. (158), using ferritin-conjugated antibodies to type 12 streptococcal products, confirmed the presence of labeled antibody in the GBM, mesangium, and arterioles. No staining was noted in the glomerular subepithelial deposits. Some studies identify the streptococcal pyrogenic exotoxin B (SPEB) and nephritis-associated plasmin receptor (NAPr) in the glomeruli of biopsies with PSAGN (159–161). The discrepancy between the results of various studies suggests that either the wrong antibody or the wrong antigen is being studied or that the antigen is being lost or masked in the glomeruli in these studies or that streptococcal antigens are not present in the glomerular deposits at all.

Deposits of immunoglobulins and, especially, complement may be detected in the glomeruli for months to years after apparent clinical resolution (136). The intensity of the immunofluorescence staining usually correlates with the severity of the glomerular lesion, although severe diffuse glomerulonephritis may be accompanied by unimpressive or negligible deposits.

**Electron Microscopic Findings**

There are many reports of the ultrastructural findings in acute glomerulonephritis (59,136,149,162–164). Many of the findings merely confirm what has long been noted at the light microscopic level, that is, increased numbers of endocapillary and infiltrative inflammatory cells in the glomerular tuft. There is swelling of both endothelial and mesangial glomerular cells, with closure of the capillary lumens by the increased numbers of cells, or swelling of the native glomerular cells. The GBMs generally appear normal in contour, thickness, and texture, although patchy thickening may occasionally be noted. There may be widening of the lamina rara interna by subendothelial electron-lucent "fluff" or fibrillar/finely granular amorphous material. The outer layer of the GBM may show "scalloping" or irregularity of the lamina rara externa and lamina densa. The GBM may contain lucent areas that may represent resolving deposits that are described and discussed later. Often, the glomerular endothelium is focally disrupted and denuded, with polymorphonuclear leukocytes directly adjacent to the denuded GBMs.

The most consistent classic diagnostic change is the presence of glomerular subepithelial electron-dense deposits, often referred to as “humps” (Figs. 10.19 and 10.20). A “hump” is a term used in renal pathology to describe subepithelial electron-dense immune-type deposits that bulge outward toward the Bowman capsule beyond the boundary of the glomerular basement membrane. They can be large or small in size. Typically, they are more unevenly distributed and more heterogeneous in size than the subepithelial deposits of membranous glomerulopathy. They are especially abundant in the first few weeks of acute postinfectious glomerulonephritis, and they decline in number afterward. They are usually less than 1 μm wide and long, but they sometimes are up to 3 μm wide and 6 μm long. In the study of Lewy et al. (98), two patients had quite elongated cigar-shaped glomerular subepithelial humps; these patients also had the nephrotic syndrome. The subepithelial humps are sometimes separated from the lamina densa by a zone of translucence that is continuous with the lamina rara externa; on other occasions, they merge with the underlying lamina densa. The deposits often bulge or project toward the cytoplasm of the overlying podocyte that often shows effacement of foot processes just above the deposit. There is frequently condensation of the microfilaments (especially actin) at the base of the effaced podocyte adjacent to the hump. The electron density of the deposits is variable, and the granularity may range from fine to coarse (165) (Figs. 10.21 and 10.22). Occasionally, the subepithelial deposits are markedly variegated with an irregular admixture of dense and less dense zones. Although there is no direct correlation between the fine ultrastructural appearance of the deposit and the clinical or nonultrastructural morphologic findings, Torroth (164) has suggested that electron-lucent regions in the deposit may represent regions of resolution.

The deposits are usually plentiful and discrete and are most commonly found on that part of the GBM overlying the mesangial regions (i.e., the paramesangial GBM). West and McAdams (166) described a population of pediatric patients with PSAGN who had prominent hypoaalbuminemia and edema with no or only very few subepithelial deposits along the glomerular basement membrane covering the mesangium. At times, the subepithelial deposits may be confluent along short stretches of the basement membranes. Similar discrete electron-dense immune-type deposits may be seen in the lamina densa and the subendothelial regions (59,66,149,163,164) (Fig. 10.23). Although the glomerular subepithelial hump is the most characteristic lesion by electron microscopy, similar subepithelial deposits are seen in various other glomerular disorders, such as membranous glomerulonephritis, MPGN, systemic lupus erythematosus, IgA vasculitis (Hench-Schönlein purpura), and especially C3 glomerulopathy (including dense deposit disease and C3 glomerulonephritis). The subepithelial humps of C3 glomerulopathy have the greatest resemblance to the humps of PSAGN.

Discrete, electron-dense, immune-type deposits collect in the mesangial regions in classic postinfectious glomerulonephritis (149,167) (see Fig. 10.18B). The mesangial regions contain large numbers of cells whose identity is often elusive. In addition to native mesangial cells, there appear to be varying quantities of infiltrating inflammatory cells. Polymorphonuclear leukocytes are the easiest cells to identify in the glomerular mesangial regions, and they may be extensive in the exudative form of glomerulonephritis. There may be a mild increase in the amount of mesangial matrix. The Bowman space may contain debris, fibrin, large epithelial cells, erythrocytes, and polymorphonuclear leukocytes, particularly if crescents are present.

During the recovery phase (based on observations of patients undergoing serial biopsy), the glomerular subepithelial humps usually disappear within 6 weeks of the clinical
FIGURE 10.19 Electron micrograph and drawing showing the ultrastructural features of PSAGN. A: This electron micrograph shows a number of discrete electron-dense osmiophilic deposits in the subepithelial portions of the glomerular capillary walls. Some of the glomerular capillaries are narrowed or compressed, but one is patent. (Uranyl acetate and lead citrate, ×6930.) (Courtesy of Drs. William Murphy and Lillian Gaber.) B: Drawing depicting a single glomerular capillary with features of PSAGN including variably sized subepithelial, small subendothelial, and multiple mesangial electron-dense deposits (black), mesangial hypercellularity (red), endothelial hypercellularity (yellow), capillary margination of neutrophils (dark green), and effacement of podocyte foot processes (light green). Compare this drawing with features in the electron micrographs in Figures 10.15 to 10.23.
FIGURE 10.20  Glomerular capillary wall from a patient with PSAGN. There is a large, discrete, electron-dense (osmiophilic) immune-type deposit in the glomerular subepithelial region of the capillary wall. This hump, or deposit, is large and abuts on the glomerular capillary wall. There is effacement or fusion of the glomerular visceral epithelial cell over the deposit. (Uranyl acetate and lead citrate, ×10,125.) (Courtesy of Drs. Tito Cavallo and Srinivasan Rajaraman.)
onset of disease (162). Sometimes, they persist for longer periods of time (163), but the clinical course in such cases is not clear. The fate of the glomerular subepithelial deposits has been studied by Tornroth (164), who has shown that the electron density (osmiophilia) of the deposits diminishes with time, so that electron-lucent regions are formed in the subepithelial zone that eventually disappear. The deposits may disappear by dissolution and passage into the blood or urinary ultrafiltrate or by pinocytotic removal by podocytes. Glomerular intramembranous electron-lucent regions have been seen in later biopsies (after 1 month) and, in some cases, these regions protruded toward the epithelium and were covered on that side by a thick layer of basement membrane–like material.

**FIGURE 10.21** Electron micrograph of a segment of the glomerular capillary wall shows large, discrete, subepithelial electron-dense deposits. Note the heterogeneous or variegated appearance of these humps (i.e., varying degrees of osmiophilia or electron density). There is loss of the glomerular endothelium, and a polymorphonuclear leukocyte abuts the naked, or denuded, GBM. Polymorphonuclear leukocytes are often found near these glomerular subepithelial deposits. (Uranyl acetate and lead citrate, \( \times \)14,400.)
FIGURE 10.22  A: Electron micrograph of a segment of the glomerular capillary wall from a patient with typical PSAGN. Note that the electron density (i.e., osmiophilia) of the glomerular subepithelial deposit is not homogeneous. B: A similar variegated appearance of the deposit. These regions of greater electron lucency suggest to some investigators that the deposit is being “washed out” or is in the process of dissolution. (Uranyl acetate and lead citrate. A, x20,100; B, x23,450.) (Courtesy of Drs. William Murphy and Lillian Gaber [A] and Drs. Conrad L. Pirani and Vivette D’Agati [B].)
Other deposits were found deeper in the lamina densa, giving it a somewhat mottled appearance (164). Kobayashi et al. (163) showed that the deposits became buried in the GBM and also acquired a fine granularity with an electron density less than that of the original humps. Glomerular subendothelial deposits that were present early disappeared with time (163,164). The GBM became irregular in thickness and contour. Increased cellularity may persist in the mesangial regions for many months, even in those patients in whom the clinical picture and urinary sediment have returned to normal. In patients who have chronic proteinuria, an increase in mesangial matrix is often found. It appears that there are more subepithelial humps in those patients with a severe, protracted clinical picture than in those with immediate clinical recovery (163). Size of the deposits does not seem to correlate with clinical course or outcome (168).

Haas (136) emphasized the significance of scattered intramembranous and subepithelial remnant deposits following possible history of PSAGN. Using careful ultrastructural studies, Haas identified 57 renal biopsies with such deposits out of 543 biopsies that did not have a primary diagnosis of immune complex glomerulonephritis. Haas emphasizes the diagnostic significance of subepithelial deposits in the mesangial notch region. The mesangial notch region represents a fold of the glomerular basement membrane overlying the mesangium. Interestingly, 40% of the biopsies that, according to Haas, revealed incidental healed postinfectious glomerulonephritis also showed evidence of diabetic nephropathy (136). The author recognizes that the shortcoming of the study is that the diagnosis of incidental healed postinfectious glomerulonephritis was entirely based on morphologic (ultrastructural) findings. Authors of this chapter agree that scattered intramembranous deposits of variable electron density and deposits in the mesangial notch region occur in biopsy specimens, but these deposits are not specific for postinfectious glomerulonephritis.
Ultrastructural studies in prospective series of patients with minimal urinary findings have shown either a lack of electron-dense deposits (169) or glomerular subepithelial or subendothelial deposits. In one case, the deposits were confined to the glomerular subendothelial zone. In another series, the ultrastructural findings in patients with subclinical glomerulonephritis were studied (103). The only biopsies in which glomerular subepithelial deposits were documented were from cases overt acute glomerulonephritis by light microscopy.

Focal disruptions or gaps of the GBM have been identified (170–172) and, rarely, mononuclear cells and erythrocytes can be seen migrating through these gaps (171). Usually, however, the gaps are covered by glomerular endocapillary cells and podocytes. Bonsib (170) conducted interesting scanning electron microscopic studies following the selective removal of glomerular visceral epithelial cells by a sequence of lytic and solubilization procedures. The changes seen in acute postinfectious glomerulonephritis are illustrated in Figure 10.24. There are several distinct crater-like GBM formations (Fig. 10.24B).
that are empty, reflecting the solubilization of the subepithelial immune complexes. The craters are uniform in size and shape. Every glomerulus studied contained at least several craters that were located at various sites within the glomerular tuft. The case from which Figure 10.24C was prepared was unique because of the presence of subepithelial humps several years after the acute nephritic episode and because of the large size of GBM craters.

**Etiology and Pathogenesis**
The relationship between streptococcal infection and acute glomerulonephritis is well established and much has been learned about the mechanism of action by which the infection leads to the characteristic glomerular changes (173). It has been known for a long time that the blood and urine are sterile in patients with acute glomerulonephritis (11), and the kidney parenchyma is also sterile. The renal changes in acute glomerulonephritis were noted to be unlike those in patients with streptococcal septicemia, in which the major changes are interstitial nephritis and abscess formation. However, some studies have shown that streptococcal septicemia can lead to proliferative glomerulonephritis, a finding that is especially common in patients with acute bacterial endocarditis. Although streptococcal toxins could play a role in acute glomerulonephritis, it is unlikely, because the renal injury would be expected to occur at the height of the infection (whereas it takes place during the subsidence of the infection). Moreover, acute proliferative glomerulonephritis is not the type of morphologic change usually noted in patients with various circulating toxins; additionally, it would be anticipated that the renal changes would be proportional to the severity of the infection, which is the opposite.

**Immune-Mediated Disease and Experimental Studies—Historical Perspective**
It is now widely accepted that acute poststreptococcal and other forms of postinfectious or infection-associated glomerulonephritis stem from an immunologic phenomenon. There is much to support an immune complex mechanism of action. Schick (9) noted the latent interval between clinical signs of infection and the onset of acute glomerulonephritis and likened it to the course of events in acute serum sickness and other allergic states. The latent interval after infection has been well documented a long time ago and usually ranges between 7 and 21 days (average, approximately 10 to 11 days).

Much of the support for immune complex pathogenesis comes from the analogy to acute “one-shot” serum sickness in the rabbit. When human acute postinfectious glomerulonephritis is compared with acute serum sickness, there are obvious similarities. Von Pirquet (174), in 1911, thought that the similarities between postinfectious glomerulonephritis and acute serum sickness syndrome supported his concept of allergy. Longcope (175) showed that parenteral administration of foreign protein in experimental animal models could induce glomerulonephritis. There is a latent interval between the injection of foreign protein and development of acute glomerulonephritis that is quite similar to the latent interval between streptococcal infection and the clinical onset of human renal disease. By immunofluorescence microscopy techniques, it is possible to demonstrate antigen, antibody, and complement in the glomeruli. This finding correlates with the formation of a variety of circulating immune complexes.

Ultrastructural studies in both human beings and experimental animal models also show similar glomerular subepithelial electron-dense “immune-type” deposits (176–179). Low levels of serum complement are found in both instances. As in the human counterpart, experimental acute serum sickness is a self-limited disease that generally resolves over a period of weeks.

Unfortunately, there is no perfect animal model for PSAGN. Many attempts have been made to induce an animal model of PSAGN by the injection of intact streptococci (180–183), crude culture supernatants (94), or specific components of the streptococci (47–66, 85–116, 122–127, 130–186).
Although some of these experimental manipulations produced histologic lesions somewhat similar to the disease pattern in man, most called for the periodic administration of the putative factors thought to be involved; this, of course, does not precisely mimic the gradual release of streptococcal products that probably occurs at the site of infection in the clinical condition in humans (85). Also, many of the experimental studies were performed at a time when electron and immunofluorescence microscopy and other biochemical determinations were not available, making it difficult to carry out an adequate comparison (85).

Holm (85) and Nordstrand et al. (187) developed animal models in rabbits and mice that permitted the establishment of a focal infection using subcutaneous tissue cages and continuous monitoring of the infection and the release of streptococcal factors. According to the authors, these models simulate PSAGN clinically, histologically, and immunologically; however, not all investigators agree that this is a solid model of the human disease. Yoshizawa et al. (188) developed a rabbit model with the infusion of a peculiar streptococcal antigen called preabsorbing antigen (PA-Ag). After infusing 18 mg of this antigen into rabbits for 8 days, the animals developed proliferative immune complex glomerulonephritis with glomerular deposition of C3 without deposition of immunoglobulins. Electron microscopy revealed hump-like subepithelial deposits. Burova et al. (189) induced proliferative glomerulonephritis in the rabbit following repeat infusions of GAS strains bearing IgG-binding M family proteins. The animals had glomerular IgG and C3 deposition. Infusion of mutant bacterial strains, lacking the IgG-binding proteins, did not result in glomerulonephritis. The authors postulate that streptococcal IgG-binding proteins have an important role in triggering PSAGN in their model (189).

**Search for the Antigen**

The identity of the nephritogenic fractions of the bacteria is the subject of controversy. Rodriguez-Iturbe (20) has suggested two major possibilities: that the nephritogenic antigen is a specific component of some streptococci or that the streptococcal infection itself triggers an autoantigenic reactivity in the host. However, as noted later, it has been very difficult to establish the presence of streptococcal antigen either within the presumed immune complexes in the glomeruli or in the circulating immune complexes. The potential nephritogenic streptococcal antigens that have been proposed to play a causative role are summarized in Table 10.3.

Treser et al. (194) described how IgG fractions from the serum of patients with acute postinfectious glomerulonephritis caused staining of the glomerular capillaries and mesangium of patients with early-stage acute glomerulonephritis. This staining was abolished if the serum fraction had been previously absorbed with frozen and thawed nephritogenic -hemolytic streptococcal organisms. The plasma membrane appeared to be the fraction responsible. This staining activity was not abolished by absorption with other bacteria, and the antiserum against streptococcal plasma membranes had staining properties similar to those of the sera of the patients with acute postinfectious glomerulonephritis. The conclusion drawn was that the streptococcal plasma membrane constituents were present in the glomeruli of patients with PSAGN (195). These same workers (195) were able to show antigenic sites in the mesangial matrix and on the glomerular subendothelial region using immunoferretion ultrastructural techniques (195). There is some evidence that antibodies to streptococcal cell membrane antigens may cross-react with antigens in the glomerular basement membrane (221). Studies by Lange et al. (196) and others (158,222,223) have suggested that free antigen may be found in situ in the glomeruli and is available for the deposition of circulating antibodies. Cationic antigens, which are able to penetrate the fixed glomerular polyanionic charge barrier of the capillary wall, could be candidates for triggering an in situ immune complex reaction (119,224,225).

**Table 10.3 Potentially nephritogenic streptococcal antigens**

<table>
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<th>Antigen</th>
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<td>Streptococcal M protein and its fractions</td>
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<td>Endostreptosin</td>
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<tr>
<td>Streptokinase</td>
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<tr>
<td>Nephritis strain–associated protein or streptococcal pyrogenic exotoxin exotoxin B or Nephritis plasmin binding protein</td>
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<tr>
<td>Nephritis-associated plasmin receptor or streptococcal glyceraldehyde 3-phosphate dehydrogenase</td>
<td>(161,213–217)</td>
</tr>
<tr>
<td>Preabsorbing antigen</td>
<td>(188,218–220)</td>
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Streptococcal M protein is a strong candidate for the relevant antigenic bacterial fraction (190). M protein fractions can complex with fibrinogen and localize in glomeruli (226), and glomerulonephritis can be induced with injection of M protein–M protein/fibrinogen complexes. M protein may be antigenically cross-reactive with the GBM (191). However, Treser et al. (227) have suggested that the nephritogenic fraction is different from the M protein. Serum from patients convalescing from poststreptococcal glomerulonephritis, when labeled, could identify free antigenic sites in renal biopsy specimens showing poststreptococcal glomerulonephritis; the fact that this serum had these antibodies independent of the M type of the original infection suggested that a non–M antigen was present in the glomerulus. In contrast, Mori et al. (192) found that IgG titers against the C region of the M protein of group A streptococci are elevated in patients with PSAGN compared with patients with uncomplicated streptococcal pharyngitis, chronic glomerulonephritis, and healthy controls. IgG titers against the A and B regions of streptococcal M protein were not different between these groups.

Several streptococcal fractions have been studied in search of the trigger for glomerulonephritis. One streptococcal fraction, endostreptosin, has been extensively studied (194–201). This antigen is demonstrable in the glomerulus only during the initial phase of acute glomerulonephritis and reacts with antibodies present in the convalescent sera of patients with acute glomerulonephritis. In the late phases of the disease, the antigen can no longer be detected, presumably because all the previously noted antigenic sites have been covered by the specific antibody.

Endostreptosin’s molecular weight is between 40 and 50 kDa (186) and is most likely derived from the streptococcal cytoplasm. Seligson et al. (200) have suggested that acute
elevations of endostreptosin titers are generally diagnostic of PSAGN. Although low titers of antibody have been found in as many as 70% of normal individuals, significantly higher titers of antibodies are found in patients with poststreptococcal glomerulonephritis (200). Most patients with acute rheumatic fever do not have these high levels of antibody titer. Thus, Lange et al. (198) believe that elevated levels of antibody to endostreptosin are diagnostic of postinfectious glomerulonephritis and correlate well with the course of the pathologic disease process. Experimental studies by Cronin and Lange (197), using Wistar Furth rats, showed deposition of endostreptosin along the GBMs 1 day after injection of immunoaffinity-isolated endostreptosin. Rats killed on days 8 to 12 showed increasing deposition of IgG and C3 with diminished staining for endostreptosin. No antiendostreptosin antibodies were detected in the sera in the first 3 days, whereas rats from day 4 onward had low levels of these antibodies. According to these authors, endostreptosin does not appear to be immunologically related to streptococcal exoenzymes or the streptococcal cell wall (197). Endostreptosin is similar to the preabsorbing antigen described by Yoshizawa et al. (188,201,218) and Holm et al. (228).

Yoshizawa et al. (218) isolated a 43-kDa protein from nephritogenic streptococci ("preabsorbing antigen") and noted identical precipitation lines by immunodiffusion between rabbit antisera against preabsorbing antigen and the sera of patients with PSAGN. Antibodies to preabsorbing antigen were found in 30 of 31 patients with acute glomerulonephritis but only very rarely in control groups. The preabsorbing antigen is present in the glomeruli in the early phases of human PSAGN and appears to activate C3 by the alternate pathway (factor B). These authors developed a rabbit glomerulonephritis model by administering preabsorbing antigen for 8 days (188). Light microscopy revealed proliferative glomerulonephritis; immunofluorescence showed glomerular capillary and mesangial C3 deposits; and electron microscopy revealed occasional subepithelial hump-like deposits. Interestingly, IgG and preabsorbing antigen were not detected in the glomerular deposits (188).

Villarreal et al. (206) identified an extracellular protein unique to nephritogenic strains from cultures of type 12 organisms. This fraction (called nephritis strain-associated protein, NSAP) was noted in 56% of renal biopsies with signs of poststreptococcal glomerulonephritis; it was not found in biopsies from patients with other forms of nonstreptococcal glomerulonephritis or rheumatic fever. The vast majority of patients with glomerulonephritis had serum antibodies to the fraction (205). Holm et al. (85,207) suggested that the ability of NSAP to convert plasminogen to plasmin (possibly in situ) might be related to many of the pathologic events taking place in PSAGN. The plasmin formed by the interaction between NSAP and plasminogen splits the C3 molecule and activates the alternative pathway of complement activation, thereby initiating the inflammatory glomerular response. Interaction with plasmin or plasminogen can cause glomerular damage by degrading the GBM through the activation of latent metalloproteinases or collagenases. The circulating or in situ immune complexes can then move across the altered GBM and accumulate as subepithelial “humps.” NSAP (also called streptococcal pyrogenic protease exotoxin B [SPEB] or nephritis plasmin-binding protein [NPBP]) can directly cause tissue destruction by cleaving extracellular matrix proteins including fibronectin and vitronectin and might aggravate inflammation via superantigenic effects on the immune system, similar to staphylococcal enterotoxins A and C. SPEB can directly bind to class II MHC molecules on antigen-presenting cells and specific Vβ chain of T-cell receptors causing proliferation and massive activation of T cells, liberating copious amounts of Th1 cytokines. Antibodies to streptococcal glyceraldehyde 3-phosphate dehydrogenase (GADPH) and SPEB (NSAP) have been found specifically in patients with poststreptococcal glomerulonephritis and persist for 10 years and 1 year, respectively, after acute attack, thought to give long-lasting immunity (208). The genes for both these proteins are highly conserved among isolates of group A streptococci. Studies using double immunofluorescence staining methods for NSAP and collagen type IV demonstrate that NSAP localizes to the inner side of the glomerular capillary walls (209,210,229).

NSAP has a subunit of 46 kDa. The molecule has been isolated and purified (186); it has an antigenic, biochemical, and structural similarities to streptokinase from group C streptococcal organisms, and it binds to plasmin and is a plasminogen activator. This protein is not related to group A streptokinase (230) or to a recently described streptococcal dehydrogenase protein according to these authors (213,230). Amino acid sequence analysis and immunologic reactivity studies suggest that this protein is the SPEB precursor (previously termed zymogen streptococcal proteinase precursor) (213).

Vogt et al. (214,231) isolated and identified a number of different cationic proteins from nephritogenic streptococci. Cationic moieties are known to have affinity for the GBM. Publications from the group at the Rockefeller University indicate that the cationic protein described by Vogt et al. (214,231) is structurally identical to SPEB (159). This group and other investigators suggest an important role of SPEB in PSAGN (159,232). Cu et al. (159) found that SPEB antibodies were present in the sera of patients with PSAGN significantly higher than in patients with acute renal failure, scarlet fever, and normal sera. Following injection of SPEB into male Sprague-Dawley rats, Romero et al. (232) found that inflammatory cells are accumulated in the glomeruli and in the interstitium. The same authors also found elevated levels of apoptosis in human SPEB-treated leukocytes (233). Savill (234) also proposes a role of apoptosis in the pathogenesis of PSAGN.

Glurich et al. (235) found that a number of surface proteins from nephritogenic streptococcal strains (M type 12) bind to the rabbit kidney in vitro and in vivo. Streptococcal components bound in vitro to several constituents of the glomerular capillary walls (heparan sulfate, laminin, and collagen IV), suggesting that bacterial proteins, when released by these bacteria during infection, become planted antigens that contribute to the pathogenesis of acute glomerulonephritis.

Some promising studies have suggested that streptokinase is the most important bacterial product leading to PSAGN (202–204). Holm et al. (202), in a steel net tissue cage model of “slow release” in a rabbit model of acute glomerulonephritis, showed loss of nephritogenic potential by deletion of a streptokinase gene (in a nephritogenic type 49 strain) in a molecular construct prepared by electrottransformation.

Nordstrand et al. (203,204) demonstrated an important role for streptokinase in the pathogenesis of PSAGN in their mouse model. Nephritogenic group A streptococci could cause glomerulonephritis only if they contained the nephritis-associated...
streptokinase gene (SKA1). Strains with deleted SKA1 gene did not cause glomerulonephritis in their mouse model (203,204). Studies conducted by Mezzano et al. (236) and others (237,238) have failed to make a strong connection between streptokinase and PSAGN. Mezzano et al. (236) did not find any unique reactivity to group A streptokinase in the sera of patients with PSAGN, and they also failed to establish the presence of streptokinase in renal biopsies early in the course of disease in 10 patients with PSAGN. Okada et al. (238) studied the major variable region of streptokinase genes of \textit{S. pyogenes} strains isolated from patients with and without PSAGN. The major variable region of the streptokinase gene did not show any apparent relationship to poststreptococcal glomerulonephritis, suggesting that unique classes of streptococcal streptokinase do not play a role in the pathogenesis of PSAGN (238).

Considerable attention has been given to NAP1r in PSAGN (213,214,217). NAP1r is proved to be homologous to streptococcal glyceraldehyde-3-phosphate dehydrogenase (GAPDH). Yoshizawa et al. (161) found that 92% of patients with early PSAGN had anti-NAP1r in their serum and 80% of the renal biopsies of early cases showed deposits of NAP1r. In a subsequent study, authors showed that distribution of glomerular plasmin-like activity and glomerular NAP1r is identical and postulated that NAP1r traps and maintains plasin in the active form in the glomeruli, which, in turn, induces glomerular damage (215). Those authors propose that following infection with a nephritogenic strain of group A streptococci, NAP1r will be released into the circulation, which will bind to the glomerular mesangium and the glomerular basement membrane. This bound NAP1r traps plasin and maintains its activity, which in turn may degrade the glomerular basement membranes by itself or through activation of matrix metalloproteinases (216). Plasmin activity may also attract neutrophils and macrophages to the site of inflammation. The circulating immune complexes, therefore, can easily pass the damaged glomerular basement membrane and accumulate along the subepithelial surface as large subepithelial deposits (215). Although these studies and the hypothesis are very attractive, Rodriguez-Iturbe points out that Yoshizawa et al. studied patients with upper respiratory infection; therefore, the results may not be applicable to PSAGN following skin infections (239). Transient immunostaining for NAP1r antigen has been demonstrated in the glomeruli during the early stages of PSAGN, and the staining diminishes within several months. This antigen is reported to be localized in mesangial cells, endothelial cells, and neutrophils, similar to the localization of SpeB antigen (215,239). However, glomerular NAP1r deposition has also been found in other glomerular diseases including IgA vasculitis (Henoch-Schönlein purpura), lupus glomerulonephritis, and dense deposit disease (240,241). Therefore, the specificity of this nephritogenic antigen for PSAGN is somewhat questionable.

In summary, the search for antigens responsible for the development of PSAGN continues. In fact, there is still no proof that immune complexes containing streptococcal antigens are causing PSAGN. A large number of streptococcal proteins have been hypothesized to be important in the causation of PSAGN, through their binding to plasin, release of matrix metalloproteinases, destruction of glomerular capillary basement membranes, and recruitment of inflammatory cells. Lack of specificity of these proteins to PSAGN alone is what plagues the findings. Another important obstacle is the fact that not only \textit{Streptococcus} but a large number of other infectious agents can cause immune-mediated glomerulonephritis, suggesting that not one but a large spectrum of bacterial proteins may be capable of binding to glomerular matrix and basement membranes and causing tissue injury, complement activation and recruitment of inflammatory cells to the site.

Circulating Immune Complexes and Cryoglobulins

Ninety percent of patients with PSAGN have elevated serum levels of IgG and IgM. Various techniques have been used to detect circulating immune complexes (201,242–246). Circulating immune complexes (as measured by C1q-binding activity) are found in the serum of two thirds of patients in the 1st week of the disease. After 4 weeks, they are evident in approximately 20% of patients (246,247). It has been suggested that circulating immune complexes correlate with the severity of renal disease and with the detection of renal immune deposits (224). Rodriguez-Iturbe et al. (83,239) and others (245), however, did not find a correlation between this assay and the intensity of the clinical manifestations. Lin (244) found that patients with poststreptococcal glomerulonephritis had significantly elevated levels of circulating immune complexes during the acute phase; 6 months later, the levels were only slightly elevated, and by 9 months after the initial attack, no circulating immune complexes were detectable. In patients who had persistent hematuria and proteinuria, however, immune complexes continued to be detected during this time.

Cryoglobulins (usually type III) are frequently found in patients with PSAGN (131,145,248). In fact, Rodriguez-Iturbe (20) noted cryoglobulins in two thirds of patients in the first 2 weeks of the disease. Most of these studies have found that the cryoglobulins contain combinations of IgG, C3, and/or IgM. IgA is less commonly found in precipitates. Streptococcal antigens are not generally evident in the cryoprecipitates (248). McIntosh et al. (248) suggested that the detection of serum cryoglobulins is a better indicator of clinical and morphologic renal disease than measurement of serum complement.

Serum from patients with PSAGN contains components of mesangial cell and GBMs (194–196,221,223), and nephritogenic antigens have been observed in circulating immune complexes in patients with PSAGN (but not in patients with acute rheumatic fever) (219,248). Yoshimoto et al. (249) noted high levels of antibodies to streptococcal cell membrane antigens. Kefalides et al. (223) recorded that the sera from patients with postinfectious glomerulonephritis contained antibodies against major macromolecular components of the GBM (i.e., type IV collagen, laminin). Because circulating immune complexes of various types have been observed in patients with streptococcal infections alone (without glomerulonephritis), it is possible that these complexes represent a systemic inflammatory response rather than being the cause of glomerular damage (201).

Complement and Complement Receptors

The fact that PSAGN is associated with low levels of serum complement has been proven by many investigators (98,106,199,250–252). Serum complement levels are almost always low in the acute stages of PSAGN. Rodriguez-Iturbe (20) noted depressed levels in 93% of patients. Lange et al. (196) suggest that in the acute stage of a clinical disease thought
to be PSAGN, the absence of a low complement level indicates that the patient does not have PSAGN. It is worth noting that patients with postinfectious glomerulonephritis, not related to streptococcal infection, may have normal serum complement levels more commonly than patients with PSAGN (2). Serum complement levels rise to normal levels after several weeks and almost always return to normal within 6 weeks. In more than half the patients of Fischel and Gajdusek (251), normal serum complement levels had been attained within 3 weeks of the acute clinical onset of disease. All 32 patients studied by Cameron et al. (250) had regained normal serum complement levels within 4 months and all but 2 within 2 months.

It has been suggested that the persistence of low serum complement levels is associated with a poor prognosis (252); however, in such patients, renal biopsy must be performed to exclude other glomerular diseases, such as MPGN or C3 glomerulopathy. Most authors have not found a correlation between the level of serum complement and the degree of proteinuria (251), indicating that complement was not diminished because of loss of complement in the urine. As noted earlier, the low serum complement level is evidence in favor of an antigen-antibody reaction. Because the serum complement level rises soon after the acute phase of the disease, it is generally not thought that there is a generalized disorder in the synthesis of complement (251). One study (253), however, did show that children with postinfectious glomerulonephritis had depressed synthesis of C3 relative to normal subjects. Serum complement levels are low even in patients with subclinical glomerulonephritis (103,106).

The serum complement studies have measured either total hemolytic complement or components of the complement cascade, such as C3. Many studies have shown that although serum levels of C3 are depressed, the classical pathway components of the complement cascade, such as C1q, C2, or C4, have been normal or only slightly depressed (52,65,250). These studies suggest that the alternative pathway of complement activation is operating, a suggestion strengthened by immunofluorescence studies that show the deposition of properdin in the glomeruli (131,155). Other studies that reveal C3 deposition, but no apparent IgG (59,145,150,151,254), also suggest that the alternative pathway often operates in acute postinfectious glomerulonephritis. Matsell et al. (255) have found terminal complement complex activation and the local generation of terminal complex in patients with PSAGN. All patients had elevated plasma C5b-9 concentrations at the onset of clinical nephritis; there was an inverse linear relationship with time after onset of clinical disease. Renal biopsies of five patients established colocalization of C5b-9, S-protein, and C3 deposition along the glomerular capillary walls and mesangial areas (255).

Other studies, by Tanuma et al. (256), suggest the possibility of accelerated decay of the cell-bound C4b2a complex by serum of patients with both PSAGN and MPGN. This accelerated decay of C42 convertase might interfere with the clearing and processing mechanism(s) of circulating immune complexes. C3 nephritic factor (C3NeF) autoantibody activity (which stabilizes the alternative pathway convertase complex) has been detected in the serum of children with PSAGN. This finding was associated in the acute phase with decreased plasma levels of C3. C3NeF activity declined within weeks as the plasma levels of C3 progressively returned to normal.

C3NeF activity was undetectable within 1 to 4 months following normalization of the plasma C3 levels (257).

Neuraminidase (sialidase) has been implicated in the pathogenesis of PSAGN. Neuraminidase-treated leukocytes preferentially accumulate in the kidneys with PSAGN and a large number of the infiltrating inflammatory cells represent desialized leukocytes (255). Interestingly, Fujita et al. (258) indicate that neuraminidase plays a potentially important role in the activation of the alternative complement pathway. Based on their in vitro data and on in vivo experience, they postulate that increased neuraminidase levels may be responsible for complement activation and subsequent low complement levels in PSAGN (258). Furthermore, they also found that free sialic acid might have an inhibitory effect on complement activation and may be implicated in the improvement of hypocomplementemia, if neuraminidase levels decrease (258).

Somedown related to neuraminidase-mediated complement activation is the third pathway of complement activation, the lectin pathway (259). Lectin pathway activation starts with molecules consisting of mannose-binding lectin (MBL) and two associated serine proteases (259). In many forms of infections, the lectin pathway of complement activation is a very important first line of host defense because of its immunoglobulin-independent opsonizing ability. Ohsawa et al. (219) postulated that the lectin pathway is also important in PSAGN and detected MBL in the glomeruli in kidney biopsies from patients with PSAGN. Mannose-binding lectin recognizes mannose and N-acetylgalactosamine residues and, to a lesser degree, also galactosamine residues. Group A streptococci carry N-acetylgalactosamine in the cell wall polysaccharides, which can be recognized by molecules containing MBL with subsequent complement activation. A study from Sweden (193) examined sera from 56 children and 17 adults with PSAGN and found no or minor concentrations of MBL in these patients, which does not support a role of the lectin pathway of complement activation in the pathogenesis of PSAGN.

The Relationship of Abnormal Alternate Pathway Complement Activation, C3 Glomerulopathy, and PSAGN

C3 glomerulopathy is a recently described entity associated with abnormalities in alternate pathway complement activation. C3 glomerulopathy includes dense deposit disease as well as a histopathologic spectrum of disease called C3 glomerulonephritis. C3 glomerulonephritis lacks the diagnostic intramembranous deposits of dense deposit disease but has extensive deposits of C3 with little or no accompanying IgG. The light microscopic features of C3 glomerulonephritis vary from focal or diffuse proliferative to MPGN. The disease is detailed in Chapter 9 of this book. Obviously, C3 glomerulonephritis and PSAGN have many similarities. In both diseases, the serum C3 levels are low, and both are associated with alternative complement pathway activation. IgG deposits are not seen in the glomeruli in C3 glomerulonephritis, but they are also frequently absent in PSAGN. Theoretically, PSAGN may represent a transient acute form of C3 glomerulopathy with direct alternative pathway complement activation induced by streptococcal infection without the need for mediation by immune complexes. As detailed above, streptococcal antigen can activate the alternate complement pathway, and it is
Theoretically possible that in patients who have mild underlying complement regulatory deficiency, streptococcal infection could evoke an acute glomerulonephritis. There were several reports supporting this hypothesis (260–262). Vernon et al. report a 7-year-old female who clinically developed typical symptoms of PSAGN following streptococcal pharyngitis. However, she developed persistent hematuria, proteinuria, and persistently low C3 levels, and the kidney biopsy performed 1 year after presentation revealed proliferative glomerulonephritis with prominent glomerular capillary C3 deposits. Ultrastructural examination showed intramembranous subendothelial and occasional hump-like subepithelial deposits. The patient was found to be heterozygous for factor H–related protein V deficiency, which is responsible for one form of C3 glomerulopathy. Authors postulate that the streptococcal infection and the heterozygous complement factor H–related protein V deficiency were responsible for the glomerular disease (262). Sandhu et al. (260) described a similar clinical course in a 63-year-old man; however, in their patient, genetic workup was not performed. Sethi et al. from the Mayo clinic reported on 11 patients with atypical postinfectious glomerulonephritis. These patients had a clinical presentation suggestive of acute postinfectious glomerulonephritis; however, their symptoms proved persistent. They found a variety of defects in complement-regulating proteins and antibodies to the C3 convertase in their patients. They also suggest that after bacterial infections, a so-called postinfectious glomerulonephritis may turn into an overt C3 glomerulonephritis if patients have an underlying deficiency in regulation of the alternate pathway activation. These included the presence of C3 nephritic factor, factor H gene mutation, as well as complement factor H–related protein V mutation (261). These authors also indicate that, following bacterial infection and subsequent alternate pathway complement activation, a persistent glomerulonephritis consistent with C3 glomerulonephritis can develop if the patients have an abnormality in the proteins regulating alternate complement pathway activation. These are intriguing data that will need further in-depth investigation. It is theoretically possible that at least a subset of patients with PSAGN has a mild genetic or acquired deficiency in one of the alternate pathway complement regulatory proteins that could trigger uncontrolled complement activation with subsequent glomerulonephritis. Apparently, most patients, particularly children, recover from the disease, but if the complement regulatory protein abnormality is more prominent, the glomerulonephritis may become persistent and progressive. This theory might explain why significant amounts of immunoglobulins are frequently absent from the glomerular deposits and why no reliable pathogenic antigen has been identified in spite of extensive research.

**Other Pathogenic Mechanisms of Postinfectious Glomerular Inflammation**

In addition to the classic concept that streptococcal organisms produce a protein fraction that is immunogenic and causes an antibody response, there is also a theory that the streptococcal organism may trigger an autoimmune disease by inducing antigenic modification of normal autologous proteins (143,263–266). Some authors proposed that acute postinfectious glomerulonephritis is in part or totally an autoimmune immune complex disease in which autologous IgG is modified by a number of streptococcal enzymes or products of the bacterial organism released during infection (e.g., neuraminidase). In this way, IgG becomes autoimmunogenic and stimulates the production of anti-IgG antibodies (205,263,264).

Marin, Mosquera, and Rodriguez-Iturbe (254,264) reported that nephritogenic streptococci are frequently neuraminidase producers. Others have described similar findings (267), although not all researchers agree (268). Circulating anti-immunoglobulins have been detected in half of patients (20), and glomerular fixed antiglobulins have been encountered in renal biopsy specimens from patients with poststreptococcal glomerulonephritis (202,248,263). IgG clutred from the kidney shows anti-IgG reactivity (259). Rheumatoid factor also has been noted in patients with PSAGN. Vilches and Williams (269) found persistent anti-DNA antibodies and DNA-anti-DNA complexes in two patients with poststreptococcal glomerulonephritis. Fillit et al. (270) noted that sera from patients with poststreptococcal glomerulonephritis contained antibodies to glomerular heparan sulfate proteoglycan. Kemenyi et al. (220) demonstrated intact linear GBM staining with monoclonal antibodies to heparan sulfate proteoglycan in patients with acute poststreptococcal glomerulonephritis (as seen in normal kidneys) in contrast to most other forms of glomerulonephritis in which the staining was lost.

An experimental rabbit model of streptococcal infection–induced glomerulonephritis emphasizes the role of streptococcal IgG FC-binding proteins. These authors postulate that after streptococcal infection, human IgG will bind to the streptococcal FC receptors and will elicit an anti-IgG antibody response. This antibody response will then result in the glomerular deposition of IgG and complement-containing immune complexes (189). They were able to inhibit this glomerulonephritis with the administration of IgG FC but not with FAB fragments supporting the importance of FC-mediated pathogenesis in this form of experimental glomerulonephritis.

Certain molecules of virulent GAS contain structural elements that appear to be capable of evoking cross-reacting auto-immune reactions with certain host tissues (271,272). Heart reactive antibodies are produced in rabbits immunized with GAS, and these antibodies bind to certain cardiac components. These antibodies are different from those detected in patients with other nonstreptococcal, nonrheumatic cardiac disorders. The titer of antibodies to heart sarcolemmal sheath proteins is also higher in children with PSAGN (211). Antimyosin antibodies, found in patients with acute rheumatic fever, have also been discovered in patients with PSAGN. Antimyosin antibodies in acute rheumatic fever share a common determinant or idiotypic with antibodies in poststreptococcal glomerulonephritis. Kraus and Beachey (220) have identified a renal autoimmune epitope in the M protein molecule of streptococci. The work of Kraus and Beachey (271) and others incriminates certain proteins (M protein) of streptococci in molecular mimicry between *Streptococcus* and host tissues. Thus, immune complex deposition in tissues expressing antigens cross-reactive with infectious agents could be important in the pathogenesis of PSAGN.

Cell-mediated mechanisms have traditionally not been considered an important factor in the initiation of acute glomerular injury. Increasingly, however, they have been studied and are now thought to play an ancillary role in the progression of acute glomerulonephritis to a chronic stage (273–276).
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They also may be important in those patients with severe acute postinfectious glomerulonephritis who have few immune deposits. Zabriskie et al. (275,276) have suggested that proteins from nephritogenic streptococci may deposit in the glomerulus and release a glycopeptidase capable of altering the composition of the GBM and exposing new antigens. Progression might take place through antibodies on sensitized lymphocytes directed against the “new” GBM antigens. The same researchers demonstrated that lymphocytes from patients with nonresolving poststreptococcal glomerulonephritis showed significant inhibition of cell migration and increased DNA synthesis in the presence of GAS antigens; lymphocytes from patients with unrelated renal diseases showed lesser degrees of reactivity (275,276).

Altered lymphocyte transformation using streptococcal protoplast membrane antigens in 12 patients known to have had PSAGN with persistent renal disease has been noted by Bhat et al. (277). A depressed immune response was found in these patients compared with normal subjects. The authors concluded that the depressed cellular immune response could be responsible for the chronic renal disease by facilitating the persistence of a humoral immune mechanism. Reid et al. (275) also suggested that the percentage of T lymphocytes (especially T gamma, the T cells bearing Fc receptors for IgG) is reduced. Some patients with a well-documented history of postinfectious glomerulonephritis and end-stage renal disease (ESRD) respond to altered basement membrane antigens, whereas patients with ESRD stemming from other renal conditions do not (278). None of these patients respond to native GBM antigens (278).

Reactive oxygen species produced by glomerular macrophages have been shown to contribute to GBM injury in a rabbit model of diffuse proliferative glomerulonephritis (279), but macrophages also can contribute to the glomerular handling of circulating immune complexes (280).

Various authors have investigated interleukin (IL) production in patients with PSAGN (212,266,267,281,282). There was enhanced IL-1 and tumor necrosis factor–alpha secretion by peripheral blood monocytes from patients with PSAGN. This secretion was found in unstimulated and lipopolysaccharide-stimulated monocytes (281) and by monocytes stimulated with soluble immune complexes (212). IL-6 and IL-8 have been demonstrated in the urine of patients with various renal diseases (including PSAGN) (282,283). IL-8 and TGF-beta were localized to the glomeruli in biopsies from patients with PSAGN. Increased TGF-beta expression was also seen in the tubulointerstitium (267). Urinary IL-8 levels were higher in patients with glomerular leukocyte infiltration than in those patients without infiltration, and IL-8 was detected immunohistochemically in diseased glomeruli, suggesting its local production (283). Increased urinary levels of IL-8 and monocyte chemoattractant protein-1 were found in the acute phase of PSAGN (266).

Fibrin/Fibrinolysis

Various studies on coagulation have been performed in patients with acute glomerulonephritis (156,284). One study showed that during the acute phase, there was evidence of fibrin formation as judged by an increase in plasma high molecular weight fibrinogen complexes and the development of either hypofibrinogenemia or hyperfibrinogenemia, an elevation in fibrin degradation (split) products in the urine (284). With recovery, these abnormalities diminished. There is no correlation between the levels of serum C3 and serum fibrinogen degradation products (285). Platelets may play a role in various forms of glomerulonephritis (286), and glomerular platelet antigens have been noted in a variety of human glomerular diseases (287). Ultrastructural evidence of platelets in PSAGN in humans is unusual; however, platelets are thought to be evanescent at sites of acute injury and may be missed by electron microscopic studies, especially if the biopsy is done late in the course of the disease. Investigators have found evidence of the participation of platelets in PSAGN (288); diminished platelet survival time in these patients is considered an index of platelet activation. Also, Mezzano et al. (289) found platelet-activating factor in the plasma of 49 of 50 patients with PSAGN.

As listed previously, TMA, including hemolytic uremic syndrome, complicating acute postinfectious glomerulonephritis has been reported (143,144,290,291). Interestingly, the TMA in patients with concomitant PSAGN is generally benign, and most patients recover from both TMA and PSAGN. It is possible that the TMA in these patients is secondary to endothelial injury that is caused by circulating antibodies that cross-react with endothelial cells and subsequent complement activation. A popular theory is that removal of sialic acid from the cell membranes of endothelial cells, red blood cells, platelets, and inflammatory cells by streptococcal neuraminidase will result in the exposure of the Thomsen–Friedenreich antigen. The exposed Thomsen-Friedenreich antigen will react with an anti-T IgM antibody, present in the plasma, which in turn will cause endothelial injury and subsequent activation of the coagulation cascade. If this is true, it is puzzling why so few patients with PSAGN develop TMA.

Genetic Predisposition

PSAGN occurs in siblings of patients with this disease (292). Dodge et al. (102,292) reported that 20% of index patients had siblings with subclinical or clinical acute glomerulonephritis. Rodriguez-Iturbe et al. (21) noted an attack rate for siblings in affected families in nonepidemic conditions of 38.5%. This rate is even higher than the attack rate in epidemic conditions; thus, a familial susceptibility to the disease was presumed (21,104). Lange et al. (199) also found a high rate of asymptomatic glomerulonephritis (detected by urinalysis, hypocomplementemia, or elevated antibody titers to streptococcal antigens) in the family members of patients with symptomatic poststreptococcal glomerulonephritis (22%). It is conceivable, of course, that these findings could be explained on the basis of shared environments and shared infections. Layrisse et al. (217) suggested that HLA-DRw4 is more common in patients with PSAGN, but at present, no firm conclusions can be reached about the association between certain HLA antigens and the development of PSAGN. As indicated previously, patients who have mild genetic form of alternate complement pathway regulatory protein deficiency may be predisposed for the development of PSAGN, including atypical protracted forms of the disease (260,261).

Differential Diagnosis

Acute Postinfectious Glomerulonephritis of Nonstreptococcal Origin

The morphology of the various nonstreptococcal postinfectious or infection–related glomerulonephritides vary somewhat, according to the underlying pathogen. Glomerular subepithelial
humps are usually less prominent, and one can find more intramembranous or subendothelial and mesangial deposits, such as in staphylococcal infection–related glomerulonephritis or in shunt nephritis. In staphylococcal infection–associated glomerulonephritis, the glomerular deposits, in addition to C3, frequently also contain IgA. Glomerular IgA deposits do not occur in PSAGN. However, in many biopsies, based on morphologic examination alone, it is impossible to determine whether the etiologic agent is GAS or a nonstrepococcal pathogen. Only detailed clinical history and identification of the exact pathogen enables the definitive diagnosis. These entities will be discussed in more detail later in this chapter.

C3 Glomerulopathy
C3 glomerulopathy (particularly the hypercellular C3 glomerulonephritis) can be very difficult to differentiate from PSAGN based on morphologic findings alone. C3 glomerulopathy, as discussed in Chapter 9, is associated with congenital or acquired dysregulation of the alternate pathway complement activation with glomerular C3 deposits in the absence of immunoglobulin deposits (134). C3 glomerulopathy encompasses C3 glomerulonephritis in which proliferative renal lesions are seen with C3 deposits but with little or no immunoglobulin deposits, dense deposit disease, familial MPGN type III and familial complement factor H–related protein 5 abnormality nephropathy (134). Differentiating PSAGN from C3 glomerulopathy, particularly C3 glomerulonephritis, can be difficult, because C3 glomerulonephritis, just like PSAGN, may show glomerular endocapillary and mesangial hypercellularity (sometimes including numerous neutrophils) and C3 containing mesangial and glomerular capillary deposits, including occasional subepithelial humps (261). If the biopsy in PSAGN is performed in the resolving phase, the glomerular hypercellularity is mostly seen in the mesangium and the C3 deposits may also be mainly mesangial. Serum C3 levels are usually low both in PSAGN and in C3 glomerulopathy/glomerulonephritis. There are two major differences between PSAGN and C3 glomerulonephritis: PSAGN is preceded by streptococcal infection and almost always is a self-limiting benign disease with recovery without intervention. In contrast, C3 glomerulopathy is usually not preceded by an infection and the disease is associated with persistent proteinuria/hematuria, persistently low serum C3 levels and usually slow disease progression. Differentiating dense deposit disease from PSAGN pathologically is relatively straightforward because of the characteristic intramembranous dense deposits, seen by electron microscopy. The other familial forms of C3 glomerulopathy can potentially cause a diagnostic and problem, but the family history of renal disease and the persistent clinical symptoms should provide a clue. As indicated above, the differential diagnosis can be particularly complex if an infection such as a streptococcal infection invokes the alternate pathway complement regulatory abnormality, which can happen in patients who have otherwise subclinical mild form of dysregulation of the alternate complement pathway activation (260,261). The classification and definition of C3 glomerulopathy/glomerulonephritis are discussed in more detail in Chapter 9.

Membranoproliferative Glomerulonephritis
The differentiation of MPGN (MPGN type I with C3 and IgG deposits) from PSAGN is not a challenge for an experienced renal pathologist, if the case is typical. Unfortunately, “typical” cases are becoming more and more an atypical occurrence in our renal biopsy material. Therefore, this differential diagnosis may cause a dilemma. In early stages of active MPGN type I, the glomerular hypercellularity can be quite striking and endocapillary polymorphonuclear leukocytes may be prominent. Immunofluorescence reveals granular glomerular C3 deposition with IgG, which can be seen in both MPGN and PSAGN, and occasionally, it is difficult to decide whether the immunofluorescence findings represent a garland pattern in PSAGN or subendothelial deposits in MPGN. Ultrastructurally, MPGN is characterized by subendothelial deposits, but the presence of subepithelial humps in MPGN is not unusual, and occasionally, quite a few humps can be identified. In PSAGN, usually subepithelial humps predominate, but in many cases, subendothelial deposits are also seen. Mesangial deposits are present in both MPGN and PSAGN. Based on the above, it is evident that there are morphologic overlaps between PSAGN and MPGN type I. The clinical presentation can also be quite similar because both diseases frequently present with nephritic syndrome and variable degrees of proteinuria and hypocomplementemia. Proteinuria occasionally can be quite prominent in PSAGN. Serum complement levels (in particular, C3 levels) are low in both diseases. C3NeF is not always present in MPGN and may occasionally be seen in PSAGN. We have encountered a few renal biopsies in which we were unable to decide whether the biopsy represented an early active stage of MPGN type I or PSAGN. In such cases, only careful follow-up will establish the diagnosis because the great majority of PSAGN cases will gradually improve and resolve, whereas MPGN type I, if untreated, usually progresses.

Cryoglobulinemic Glomerulonephritis
In a typical case, the differential diagnosis is obvious because of the intracapillary hyalin thrombi, which represent cryoglobulin precipitates in the glomerular capillaries. However, particularly in a small biopsy specimen or in atypical cases, these hyalin thrombi are not present, and cryoglobulinemic glomerulonephritis may merely show the pattern of endocapillary proliferative glomerulonephritis. Glomerular intracapillary cryoglobulin precipitates may appear rapidly, and it is likely that they can also disappear rapidly. The predominant endocapillary cells in cryoglobulinemic glomerulonephritis are monocytes and macrophages, but numerous neutrophils are not unusual. The immunofluorescence pattern in cryoglobulinemic glomerulonephritis is distinctive (particularly in type I and type II cryoglobulinemia) if the intraluminal cryoglobulin deposits (hyaline thrombi) are present. Unfortunately, as any glomerular disease, cryoglobulinemic glomerulonephritis also represents a disease spectrum and cases with little or no intraluminal cryoglobulin deposits in the glomerular capillaries occur. This is more likely if the tissue for immunofluorescence contains only a few glomeruli. The distinctive IgG- and IgM-positive globules of type II cryoglobulinemia, which usually also stain for complement, may not be evident in such cases. Electron microscopy usually reveals numerous monocytes and macrophages with unusually large secondary phagolysosomes. Ultrastructural examination at high magnification often reveals the characteristic organized microtubular substructure in the cryoglobulin deposits, but this could be missed, particularly if not enough glomeruli are examined under the electron microscope under high magnification.
occasional cases will have no ultrastructural substructure in the immune deposits. One important differential diagnostic hint is that in cryoglobulinemic glomerulonephritis, humps are usually absent. We always consider cryoglobulinemic glomerulonephritis in the differential diagnosis if we see an endocapillary proliferative glomerulonephritis with no or only few immune complex deposits. The clinical history may be quite helpful in differentiating PSAGN from cryoglobulinemic glomerulonephritis. Similarly to PSAGN, C3 levels may be low in cryoglobulinemic glomerulonephritis, but unlike in PSAGN, the C4 levels are usually quite low in cryoglobulinemic glomerulonephritis. Cryoglobulinemic glomerulonephritis is typically associated with normal or slightly low serum C3 levels and very low C4 levels. A positive cryoglobulin test may be helpful, but unfortunately, this test is unreliable, and cryoglobulins occur in some patients with PASGN. Another useful test in the differential diagnosis is rheumatoid factor, which is detectable in most patients with cryoglobulinemic glomerulonephritis. Positive serology for hepatitis C also supports a diagnosis of cryoglobulinemic glomerulonephritis. Rarely, even the clinical history may be misleading because cryoglobulinemic glomerulonephritis may undergo spontaneous remission giving the impression of a resolving postinfectious glomerulonephritis.

Membranous Glomerulonephritis

In our experience, this is not a problematic differential diagnosis; however, in a review, Sotsiou et al. (293) described two patients with presumed postinfectious glomerulonephritis who had spike formation on methenamine silver stain, endocapillary hypercellularity with neutrophils, granular deposits of IgG and C3 along the glomerular capillaries, and elevated ASO titers. Unfortunately, no follow-up data are provided, and it is difficult to exclude the possibility that these cases in fact represented atypical membranous glomerulonephritis rather than atypical postinfectious glomerulonephritis. Three cases are reported that showed transformation of an acute proliferative and exudative glomerulonephritis into a membranous glomerulonephritis (294). These are very unusual, and the pathogenesis is debatable. Wu et al. (295) described a patient who developed PSAGN superimposed on membranous glomerulonephritis.

Diffuse Proliferative (Class IV) Lupus Nephritis

Class IV lupus nephritis shows a diffuse endocapillary proliferative pattern, frequently with the presence of glomerular polymorphonuclear leukocytes. Therefore, if immunofluorescence and electron microscopy are not available, the differential diagnosis, based on light microscopy alone, may be difficult. One has to remember that in proliferative lupus nephritis, large hump-like subepithelial deposits may be seen by electron microscopy. Still, because of the characteristic immunofluorescence and ultrastructural findings and the clinical history, the differential diagnosis is obvious in most cases.

Clinicopathologic Correlations

Many studies have been performed to correlate various clinical and pathologic aspects of PSAGN. There is no correlation between the presence of hematuria or proteinuria and the severity of the glomerular lesion. This finding is not surprising, because histologic evidence of glomerulonephritis has been noted in patients with minimal or absent hematuria and proteinuria (186) and because it is known that considerable hematuria can be present with no changes or only trivial changes in glomeruli by light microscopy.

Jennings and Earle (115) found some correlation between the light microscopic appearances of the glomeruli and various clinical parameters, certain exceptions were noted; there was a greater tendency for patients with the more severe glomerular changes to have hypertension, although this correlation was not absolute. These patients also tended to have high BUN (115). Parrish et al. (296) showed that the ratio of glomerular to tubular functions gave a good indication of the progress of the renal disease, since the renal histologic picture improved in those patients whose ratio rose during the course of the disease but remained unchanged in those whose ratio was low.

Lewy et al. (98) carried out extensive clinicopathologic correlations. They found that glomerular tuft hypercellularity showed a significant inverse correlation with creatinine clearance and a good relationship with BUN. Glomerular tuft hypercellularity did not correlate with the ASO titer, oliguria, or hypertension and also showed a significant correlation with serum complement levels. However, the greatest degree of glomerular hypercellularity was associated with the lowest levels of serum complement. There was no correlation between the number of glomerular humps by electron microscopy and the level of serum complement. Total morphologically evident tubular damage related directly to creatinine clearance and BUN. This is not surprising, since there may be a good correlation between the glomerular and tubular damage.

Haen et al. (297) showed with morphometric studies that there is a direct correlation between serum creatinine and interstitial volume. Even with severe glomerular changes, the serum creatinine level was usually not higher unless the interstitial volume was increased by 15%. Bohle et al. (138) and Hooke and Atkins (298) also found a close relationship between the severity of interstitial inflammation and the GFR. The number of glomerular humps (by electron microscopy) was associated with a more severe and protracted clinical picture (138). There was no apparent difference in the glomerular lesion or in the clinical course when patients with and without hypocomplementemia were compared. Some authors state that up to 10% to 20% of patients may have normal serum complement levels (65); others disagree (199,252). There is no doubt that large numbers of crescents are associated with oliguria and rise in the BUN and serum creatinine levels.

Several investigators have suggested that initial and/or persistent nephrotic syndrome is a harbinger of a poor renal prognosis (299,300). As noted earlier, there may be difficulty in distinguishing between exacerbations of nonstreptococcal chronic glomerulonephritis and true de novo attacks of PSAGN (301). An added problem is the lack of evidence of a streptococcal cause in many cases studied (296). Renal biopsies of patients with low creatinine clearance, microscopic hematuria, and proteinuria usually show moderate to advanced glomerulosclerosis, mesangial hypercellularity, and intense immunofluorescent staining for IgG and C3 (22). However, patients without clinical or laboratory evidence of disease can have moderate segmental mesangial sclerosis and positive glomerular immunofluorescent findings of IgG and C3 (22). As noted earlier, the studies of Sorger et al. (147,149) and others (152) indicate that the garland pattern of immunofluorescence is associated with more severe proteinuria. West and McAdams
(166) found that children with PSAGN and hypoalbuminemia had no subepithelial deposits (humps) on the paramesangial portion of the glomerular basement membrane. Children who had subepithelial deposits, not only along the peripheral glomerular capillary loops but also along the paramesangial basement membrane, had significantly higher serum albumin levels. Unfortunately, quantification of the proteinuria was not performed in this retrospective study, and the meaning of this association is unclear.

Patients older than 60 years of age tend to have a worse renal prognosis than younger adults according to some authors (2,302). When adult patients with oliguria/anuria and crescent formation are considered, the prognosis is especially poor; as many as 50% of them progress to end-stage renal failure (299,303). The prognosis for adult patients with oliguria/anuria may be related to the availability and use of dialysis and other medical support and is taken from the older literature.

Correlation of Light, Electron, and Immunofluorescence Microscopy

There is usually concordance between the light and the electron microscopic findings. The number of glomerular subepithelial deposits is directly correlated with the degree of polymorphonuclear leukocytic infiltration in theglomeruli, however, humps can be seen in sections without neutrophils (98). Those patients with the greatest extent of glomerular tuft hypercellularity generally have the most numerous humps.

There is generally good correlation between the light microscopic appearance of diffuse glomerular hypercellularity and the characteristic diffuse granular staining along the glomerular capillary walls for IgG and C3 (59). In certain cases, however, lesions thought by light microscopy to be well developed may not have glomerular staining for IgG and may show only staining for C3 (59). In biopsies in which light microscopy shows complete resolution of hypercellularity, there may be loss of staining for both IgG and C3 (59). In biopsies in which mesangial prominence persists many months after the initial biopsy, there is commonly only complement in the mesangium.

There is usually granular immunofluorescent staining along the glomerular capillary walls corresponding to the humps noted in ultrastructural studies from the same biopsy. This, however, is not always the case, and some researchers believe that the number and location of the immunofluorescent granules best match the various sites of the glomerular subendothelial deposits (153).

As noted earlier, Sorg et al. (149) have provided detailed immunofluorescence studies. They described three patterns, termed stary sky, garland, and mesangial. In the stary sky type, there is a granular deposition of IgG and C3 along the glomerular capillary walls and mesangium. The garland pattern consists of densely packed, sometimes confluent or continuous deposits of IgG and C3 along the glomerular capillary walls. The mesangial pattern consists of the presence of C3 in the mesangial regions. When these three patterns were compared with ultrastructural findings, the stary sky pattern corresponded, in general, to the glomerular subendothelial deposits, the garland pattern to the classic glomerular subepithelial deposits that tended to be elongated or confluent, and the mesangial pattern to electron-dense deposits in the mesangium and in a subepithelial pattern on the GBM overlying the mesangium (see Figs. 10.15 to 10.17). In summary, the correlations are good, although there are some anomalies. Chief among them is the occasional lack of concordance between immunofluorescence and electron microscopic studies.

Correlation of Morphologic Changes With Clinical Outcome

The most controversial facet of PSAGN is its long-term outcome. This is a question on which there are strong opinions and incomplete data. The difficulty in demonstrating with certainty that the glomerulonephritis in the individual patient is related to the streptococcal infection has made it difficult to interpret follow-up studies on progression to a chronic stage. Information about the correlation of morphologic changes with clinical outcome was scanty before the days of renal biopsy, although it was known that certain patients pursued a variable course ending with death owing to renal failure within a few months. Most of these are poststreptococcal cases in which crescent formation is abundant. The presence of a large number of crescents is an ominous sign. However, it is quite common to see cases of acute postinfectious glomerulonephritis with a few crescents where complete recovery is generally the rule (98). Clinical recovery has been noted in half of patients with less than 40% crescents (98) as well as in certain patients with a greater percentage of crescents (304).

Crescentic glomerulonephritis as a severe manifestation of a postinfectious episode has been noted by many researchers (66,88,111,113,295,299,304–308). The significance of crescentic glomerulonephritis in children with PSAGN remains the subject of controversy (111,112,305,309). In a comprehensive review of the natural history of glomerulonephritis, Cameron (310) described the actuarial survival of patients with severe crescentic glomerulonephritis based on the experiences of himself and Drs. Habib, Kincaid-Smith, and Morel-Maroger. He concluded that the prognosis of such patients (with all forms of nephritis) is “almost entirely dependent on the large numbers of crescents and that the prognosis normally associated with the underlying glomerular disease is no longer operative, because the prognosis of the crescent formation is so bad.” He also furthered the argument that the apparently good prognosis in patients with PSAGN and extensive crescents has been misrepresented, because most of the patients in this group have had relatively minor degrees of crescent formation. In the investigation of the Southwest Pediatric Nephrology Study Group (SPNSG) (304), six patients were found to have poststreptococcal glomerulonephritis and crescent formation in 51%, 60%, 87%, 90%, 92%, and 100% of their glomeruli. The crescents were generally cellular rather than fibrocellular or fibrous, and there was a low percentage of large crescents with little evidence of chronic histologic changes, such as global glomerulosclerosis and interstitial fibrosis. In the absence of constant or progressive injury to the glomerulus, these cellular crescents can resolve without major side effects. Indeed, the five patients who had adequate follow-up in the SPNSG series had normal GFRs at last evaluation, irrespective of whether treatment was given (304).

As the above data indicate, PSAGN is usually fully reversible, even in crescentic forms. Still, long-term follow-up studies indicate that after many years, or decades, some patients who
had a history of PSAGN develop renal failure or even ESRD (293,311–315). Unfortunately, most of these studies do not specify whether the cases that show poor long-term outcome had crescents or not. Tasic et al. (316) report a pediatric patient who developed chronic renal failure 12 years following an episode of PSAGN from which the patient seemed to have recovered fully. Moroni et al. (315) followed 50 adult patients with PSAGN and found that the presence of crescents is an indicator of unfavorable long-term outcome. Interestingly, these authors found the presence of interstitial inflammatory cell infiltrate as the most important histologic indicator predicting a poor long-term outcome (315). Ardiles et al. (317) examined serum from 210 patients with PSAGN for the presence of ANCA. They found that 9% of the patients had ANCA, which was associated with crescent formation.

The study of Roy et al. (112) suggests that the outcome is unaffected by therapeutic intervention and that such patients should receive only supportive measures to control the consequences of their renal insufficiency and hypertension until a spontaneous remission occurs. Cunningham et al. (111) noted that 7 of 13 children with PSAGN and crescentic glomerulonephritis progressed to chronic renal failure. In some of their patients, anticoagulant and antiplatelet therapy appeared to improve survival rates. Srivastava et al. (318), in a study of 43 children with crescentic glomerulonephritis, found 11 patients with evidence of poststreptococcal glomerulonephritis. Seven of these eleven children progressed to ESRD, and two additional children had chronic renal failure by the end of the study (318). Thus, the renal prognosis in this set of patients is still somewhat debatable.

Jennings and Earle (115) have suggested that the severely exudative form of PSAGN with a large number of polymorphonuclear leukocytes is the forerunner of the most severe type of PSAGN; however, the mere presence of polymorphonuclear leukocytes in the glomerular tuft does not portend a poor prognosis. Polymorphonuclear leukocytes are often present in the glomeruli of patients who recover completely (292).

Several authors have attempted to use other morphologic markers as prognostic indicators. Some suggest that the overall degree of glomerular tuft hypercellularity is related to either the degree of persistent proteinuria (319) or outcome (320), but other authors have stated that there does not seem to be a good correlation between excessive glomerular hypercellularity and outcome (98). Lesser degrees of hypercellularity also have been found to be associated with irreversible renal changes (320). There are so many exceptions to the suggested correlations that a rule of thumb probably does not exist. It is likely that several of these morphologic features taken together may be of greater prognostic value than any single finding, but this type of study has not been performed. Some investigators have ascertained that glomerular necroses, adhesions, glomerular capillary thromboses, crescent formation, and interstitial nephritis have been found more commonly in those patients whose disease progresses (302,320).

A study by Lien et al. (321) addressed the issue of obsolescent glomeruli in 57 patients (mostly adult) with PSAGN followed for 1 to 4 years. Twenty-six percent of these patients had combinations of hypertension, microscopic hematuria, proteinuria, and elevations in the serum creatinine level; 9% died. These authors raised the important point that one must exclude underlying clinically covert glomerular disease that is brought to clinical attention because of a superimposed acute postinfectious glomerulonephritis.

Vascular changes, such as arteriolar sclerosis and arte-
rial sclerosis, have been suggested to be a harbinger of a poor prognosis (114,139). A direct correlation was noted between the presence of thickening of the vessel wall with narrowing of the lumen and the percentage of globally sclerotic glom-
eruli. Hypertension tended to develop in those patients with global glomerulosclerosis and morphologic evidence of vascular disease.

Ultrastructural changes, such as large and confluent glomerular subepithelial electron-dense deposits, have been thought to be indicators of a poor prognosis (319). These atypical humps have invariably been associated with renal fail-
ure following the initial attack, according to one report (319). Persistence of immunoglobulins and complement, primarily in the glomerular mesangial regions, has been considered to be evidence of continuing immunologic involvement and injury (194). Those patients who progress to a chronic stage have this feature. However, some authors have noted the final loss of immunoglobulins and complement as long as 5 years after the initial acute attack; therefore, the persistence of these immuno-
reactants beyond the acute stage of disease cannot be univer-
sally regarded as an infallible sign of a poor prognosis.

Linear immunofluorescence for IgG was noted in certain patients who progressed to chronic renal failure (320). Anti-
GBM antibodies were searched for but were not found. The long-term study of Baldwin et al. (114) showed similar linear immunofluorescence in subsequent renal biopsies with a sig-
nificant number of globally sclerotic glomeruli; renal failure had not yet developed in these patients. Whether these changes are truly specific and portend a poor prognosis is unclear; mild linear glomerular capillary staining for IgG is a common non-
specific immunofluorescence finding, particularly in diabetic patients.

The outcomes of patients with acute postinfectious glo-
merulonephritis are shown in Table 10.4, but many important points need to be made before considering these outcomes. In many of the series quoted, renal biopsies were not performed; thus, histologic proof of acute postinfectious glomerulonephritis is lacking. Without pathologic categorization of nephritis, the outcome might be altered by diseases erroneously diag-
nosed clinically as postinfectious glomerulonephritis, such as IgA nephropathy with onset or exacerbation initiated by strep-
tococcal pharyngitis. The criteria used for making the diag-
nosis of acute postinfectious glomerulonephritis were clinical and variable. Lengths of follow-up vary among the series, but they were often short. The outcome indicators used are also different; some authors used the presence of mild proteinuria and microscopic hematuria, whereas others relied on BUN and serum creatinine levels and the presence of hypertension. As Heptinstall stated (168), “It is a human failing to include as many cases in a series as possible, yet the task of assessing prog-
nosis from published series would be made much easier if a smaller number of cases, all with a minimum follow-up period of, say, 5 or 10 years, were described.”

Short-term follow-up data can give an erroneous impres-
sion, because the disease resolves more slowly in some patients than in others, with the net result that the number of patients in the latent stage is exaggerated. Studies with short-term follow-up provide fewer opportunities for some patients with
<table>
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<th>Author</th>
<th>Follow-up period (years)</th>
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<tr>
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<td>7–12</td>
<td>Adult and child</td>
<td>722</td>
<td>0</td>
<td>See text</td>
<td>—</td>
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</tr>
<tr>
<td>Garcia et al. (329)</td>
<td>11–12</td>
<td>Adult and child</td>
<td>71</td>
<td>21v</td>
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<td>79</td>
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</tr>
<tr>
<td>Chugh et al. (303)</td>
<td>2–10</td>
<td>Adult and child</td>
<td>146</td>
<td>14m</td>
<td>31</td>
<td>27</td>
<td>28</td>
</tr>
<tr>
<td>Potter et al. (317)</td>
<td>12–17</td>
<td>Adult and child</td>
<td>534</td>
<td>0r</td>
<td>3.5</td>
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<td>96.5</td>
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<tr>
<td>Guild (330)</td>
<td>1–12</td>
<td>Child</td>
<td>34</td>
<td>0</td>
<td>18</td>
<td>0</td>
<td>82a</td>
</tr>
<tr>
<td>Gachet (331)</td>
<td>&gt;1</td>
<td>Child</td>
<td>114</td>
<td>7</td>
<td>9</td>
<td>0</td>
<td>91f</td>
</tr>
<tr>
<td>Davis and Faber (332)</td>
<td>&gt;2</td>
<td>Child</td>
<td>102</td>
<td>6</td>
<td>13m</td>
<td>0</td>
<td>81</td>
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<tr>
<td>Burke and Ross (333)</td>
<td>2</td>
<td>Child</td>
<td>90</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>94</td>
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<tr>
<td>Åkeråen and Lindgren (5) (334)</td>
<td>—</td>
<td>Child</td>
<td>57</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>McCory et al. (335)</td>
<td>2</td>
<td>Child</td>
<td>35</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>97</td>
</tr>
<tr>
<td>Perman et al. (336) (337)</td>
<td>10</td>
<td>Child</td>
<td>52</td>
<td>1.6</td>
<td>0</td>
<td>0</td>
<td>98.4</td>
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<tr>
<td>Dodge et al. (102)</td>
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<td>Child</td>
<td>20</td>
<td>0</td>
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<td>0</td>
<td>55</td>
</tr>
<tr>
<td>Lewy et al. (98)</td>
<td>5</td>
<td>Child</td>
<td>21</td>
<td>0p</td>
<td>24</td>
<td>0</td>
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<tr>
<td>Schacht et al. (320)</td>
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<td>Child</td>
<td>54</td>
<td>0v</td>
<td>38</td>
<td>0</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Child</td>
<td>31</td>
<td>0u</td>
<td>45</td>
<td>0</td>
<td>55</td>
</tr>
<tr>
<td>Travis et al. (338)</td>
<td>&gt;3</td>
<td>Child</td>
<td>54</td>
<td>2</td>
<td>8</td>
<td>0</td>
<td>92h</td>
</tr>
<tr>
<td>Roy et al. (18)</td>
<td>4–12</td>
<td>Child</td>
<td>35</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>97</td>
</tr>
<tr>
<td>Drachman et al. (339)</td>
<td>1/2–2</td>
<td>Child</td>
<td>155</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Popovic-Roloviz et al. (340)</td>
<td>5–9</td>
<td>Child</td>
<td>40</td>
<td>0</td>
<td>5v</td>
<td>85aa</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>10–17</td>
<td>Child</td>
<td>88</td>
<td>0</td>
<td>6.8aa</td>
<td>69aa</td>
<td>93.2</td>
</tr>
<tr>
<td>Clark et al. (341)</td>
<td>5.4–22</td>
<td>Child</td>
<td>36</td>
<td>0</td>
<td>20 (persistent urinary abnormalities) 3 (hypertension)</td>
<td>0</td>
<td>80–97</td>
</tr>
<tr>
<td>White et al. (313)</td>
<td>6–18</td>
<td>Child</td>
<td>63</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Kasahara et al. (342)</td>
<td>4</td>
<td>Child</td>
<td>138</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Cleper et al. (314)</td>
<td>46</td>
<td>Child</td>
<td>36</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Sarkissian et al. (40)</td>
<td>1</td>
<td>Child</td>
<td>474</td>
<td>1</td>
<td>5</td>
<td>0</td>
<td>97</td>
</tr>
</tbody>
</table>

aOlder than 10 y of age.
bSeen within 3 mo of onset.
c Died from etiologic disease or incidental cause.
d Died in rapidly progressive phase.
e Died in acute stage or later.
f Died from unrelated disease; time was not given.
g "Quiescent" cases (latent).
h Percentage of those who survived acute attack.
i Uncertain.
j Some followed for <1 y.
k All had recovered on discharge.
l Those who survived the acute phase.
m Includes 5% who died from chronic nephritis.
n Includes three with orthostatic proteinuria.
o Of nine patients, two had persistent and seven had intermittent proteinuria.
p Three deaths in the initial 46 patients.
q Includes one death from chronic renal failure at 5 y.
r Mainly children.
s Nine percent in children, 37% in adults.
t By histologic outcome.
u Two had crescentic glomerulonephritis and became uremic.
w One patient with chronic renal failure.
x Died of uremia within 2 yr.
y Half progressed to renal failure.
z Only one patient died in renal failure 6–10 yr after the initial illness.
{Hypertension plus proteinuria in both patients.
{Hypertension, proteinuria, or microhematuria. (All patients had normal creatinine clearances.)
{From original 271 patients seen.
{Three patients of the original 134 died; they were released from the study.
{Thirty percent had renal insufficiency, and 48% had that or persistent proteinuria or hematuria.
{Albuminuria or hematuria was present in 13% and 21% of patients, respectively.
{Normal GFR with reduced renal functional reserve.
asymptomatic proteinuria to progress to the chronic stage, with hypertension and raised levels of BUN and serum creatinine, or for other patients to recover completely.

It is important to remember that selection or entry bias plays a major role in the interpretation of these series. Patients studied in the hospital represent a highly selective population, and it is likely that most mild cases may not be hospitalized or undergo biopsy. Hospitalized patients are likely to have the most severe clinical course. Renal biopsy is usually reserved for those whose clinical picture is not one of a classic or typical form of acute postinfectious glomerulonephritis. Despite these reservations, most investigators believe that the prognosis in children is good in both the epidemic and sporadic cases. The mortality rate for children in the acute stage is generally low, although some workers have noted higher death rates than others (331). These high mortality rates are usually the result of severe infection, cardiac failure, or hypertensive encephalopathy, not the nephritic process itself.

A review of 22 series confined to children noted that 0% to 45% of children were found to have latent or chronic disease, usually defined as asymptomatic or intermittent proteinuria. As mentioned previously, it is likely that short follow-up periods, highly selective admission policies, and misdiagnoses contribute to this high figure. The morphologic findings in the series, of Travis et al. (338), were described 3 or more years after the acute attack. Of the 54 children whose diagnosis of acute postinfectious glomerulonephritis was confirmed by biopsy, 1 died from a crescentic form of glomerulonephritis, 4 failed to show histologic healing, 3 had latent glomerulonephritis, and 1 had chronic glomerulonephritis. The authors thought that the three patients with latent glomerulonephritis were capable of spontaneous resolution of the glomerular process. If we take that to be true and the patient with the crescentic form of acute glomerulonephritis is excluded, then the probability of recovery from the acute attack of postinfectious glomerulonephritis would be 98%. If resolution of disease in the three with latent glomerulonephritis were not to take place, the probability of recovery would be 92%.

In a prospective study of children followed for 4 to 12 years after the onset of acute glomerulonephritis with sequential renal biopsies, healing occurred in 20% at 2 years, 46% at 4 years, 77% at 6 years, 94% at 10 years, and 97% at 12 years (86). Although there was a very high rate of healing, it can be considerably delayed. There was less than perfect correlation between the morphologic findings and the results of the Addis counts of hematuria; for example, six patients (17%) had abnormal Addis counts at a time when histologic healing and resolution had occurred (327).

A study from Japan on 138 children with PSAGN reports a 100% recovery rate including the disappearance of clinical symptoms (342). The serum complement levels were normalized within 12 weeks, the proteinuria disappeared within 3 years, and the hematuria disappeared within 4 years in all children. The authors emphasize their usage of strict criteria for diagnosing PSAGN to avoid the possibility of selection bias. They included only children who had hematuria, proteinuria, evidence of streptococcal infection, transient hypocomplementemia, and no clinical or histologic evidence of previous renal disease (342).

The patients with epidemic forms of poststreptococcal glomerulonephritis have almost uniformly shown excellent outcomes, and only a few have persisting renal abnormalities, as determined by clinical and laboratory examinations (hematuria/proteinuria) (22,93,268,337,339,343–345). This is exemplified by long-term follow-up of an epidemic in Trinidad of 760 patients, 87% of whom were younger than 15 years of age. The excellent results at 2 to 6 years (345) were surpassed in the 7- to 12-year study by Nissenson et al. (93), in which, of the 722 patients followed, persistent urinary abnormalities were present in only 0.8%, hypertension in 2.3%, and serum creatinine levels greater than 1.2 mg/100 mL in as few as 3 patients. In the 12- to 17-year follow-up of 534 patients undertaken by Potter et al. (268), only 3.5% had urinary abnormalities, 3.7% were hypertensive, and no patient had a serum creatinine level greater than 1.25 mg/100 mL. These figures did not differ from expected values in surveys of the normal population.

In an 11- to 12-year follow-up of an epidemic in children conducted by Drachman et al. (339), no persistent urinary or serologic abnormalities (BUN, creatinine) were noted. Drukker et al. (346) studied the renal sodium handling (i.e., the natriuretic response to intravenous saline loading) in 11 patients (both children and adults) several years after PSAGN and found no evidence of exaggerated natriuresis.

A few series (300,303,347) suggest that children do not do as well as generally believed and that a high proportion have at least minor clinical or laboratory abnormalities at follow-up; however, clinically significant renal failure is rare. It is also believed that patients who once had poststreptococcal glomerulonephritis in childhood have an increased propensity or susceptibility to chronic glomerulonephritis as adults (102,115,320,348). In a series of 83 children who were followed for periods of up to 17 years (with renal biopsy performed in only 36 of them), proteinuria, hypertension, and decreased GFRs were noted in 38% of the 54 children followed for 2 years or more, 45% of 31 children followed for 5 years or more, and 47% of 17 children followed for more than 10 years (347). Two of the patients, who had uremia from onset, showed progression from diffuse proliferative glomerulonephritis with crescents to proliferative and sclerosing chronic glomerulonephritis. A study of 35 patients by Rodriguez-Iiturbe (20) indicated that patients followed for up to 13 years after an episode of poststreptococcal glomerulonephritis had diminished renal functional reserve capacity, as determined by a lower GFR after challenge by acute oral protein load. A study from Israel reports on the follow-up of 36, mainly pediatric, patients after an episode of PSAGN (314). The investigators calculated the renal functional reserve in these patients and found it to be significantly decreased compared to control patients, even though they had similar creatinine clearances. Interestingly, in 69% of patients who had PSAGN more than 10 years ago, the renal functional reserve was reduced compared with reduction in only 26% of the patients who had PSAGN less than 10 years ago (314). These data indicate progressive but subtle underlying injury that is not evident by measuring serum creatinine or GFR only.

Thus, these studies indicate that although uremia is rare, there is evidence of depressed renal function in some children. This finding dictates the need for continued follow-up. The following features have an adverse effect on clinical outcome: underlying renal disease, persisting proteinuria with or without the nephrotic syndrome, impaired renal function, oliguria/anuria, extensive crescent formation, atypical humps on electron
microscopy, and the garland pattern on immunofluorescence. The prognosis for children with these features is worse than for those without them (111,149,293,300,303,349). Children with the crescentic form of postinfectious glomerulonephritis may or may not have a poor renal prognosis (111,304,305,318). As we pointed out above, one has to consider the possibility that the relatively low full recovery rate in some of these publications could be explained by the possibility that in children with progressive renal disease, streptococcal infection initiated the development of C3 glomerulonephritis (260–262).

The prognosis for adults is even more controversial, and many authors consider that it is not as favorable as for children (2–4,114,236,242). The proportion of complete recoveries ranges from 53% to 76% (see Table 10.4), and death in the adult stage has been recorded in up to 9% of adults (14). A more recent paper of Nasr et al. (2,3) describes 109 elderly (≥65 years old) patients with postinfectious glomerulonephritis. The complete remission rate was only 22% after a mean follow-up of 29 months. However, only 16% of these patients had PSAGN; most of them (46%) had staphylococcal infection. Also, many of them had preexisting chronic renal disease, including diabetic nephropathy. In contrast, another recent publication from China (89) reports an 85.7% remission rate in adults with acute postinfectious glomerulonephritis. The remission rate in the 43 patients with PSAGN was higher (94.7%) than in the 21 patients (66.7%) with nonstreptococcal infection–associated glomerulonephritis (89). The good outcome is probably related to the relatively young age of patients (29 ± 14 years) and the low prevalence of underlying chronic renal conditions. It should be noted that several of the series quoted in Table 10.4 that indicated a high mortality rate in the acute stage were compiled many years ago. In those series comprising only adults, the figures for chronicity range up to 36% (13,350). The percentages might vary in part because of different durations of follow-up and uncertainty as to whether to include patients whose sole abnormality is hematuria or proteinuria. It has been suggested by Mezzano et al. (323) that there are age-related changes in the mononuclear phagocyte system fragment crystallizable receptor function in patients with poststreptococcal glomerulonephritis and that this could help explain prognostic differences between children and adult patients (351).

The studies of Baldwin et al. (114,328) and Schacht et al. (320) are of great importance in determining prognosis in a predominantly adult population. In one of their series (114) of 89 adults and 37 children, 9 patients died within the first 6 months, and 6 of them had the crescentic form of acute glomerulonephritis. Two others died from renal failure (one at 2 years and the other at 6 years); both showed extensive evidence of glomerular sclerosis at that time. Proteinuria was noted in half the patients followed from 5 to 7 years, and hypertension was seen in one fourth to one half. Subsequent renal biopsies showed subsidence of glomerular hypercellularity and an increase in the degree of glomerular sclerosis. The severity of glomerular sclerosis correlated with reductions in the GFR. Baldwin (328), in a later study, noted that 56% of renal biopsies obtained 3 years or more after the onset of the acute attack showed signs of segmental to global glomerular sclerosis of 10% or more of glomeruli (an abnormally high percentage for patients younger than 40 years of age. Of the 95 patients followed for more than 2 years in this study, 46% had proteinuria, 42% had hypertension, and 38% had reduced GFRs. Some patients died from chronic renal failure (320), which suggests that although improvement in renal function can take place after acute onset of the initial illness, chronic renal failure might nevertheless develop several years later. All the deaths were among adult patients.

In Baldwin’s largest study (328), involving 168 patients who were followed for periods of up to 18 years, the author noted proteinuria or hypertension in 50% (clinical uremia occurred in 6). Thus, Baldwin maintains that an appreciable number of patients had irreversible sclerotic glomerular changes. The mechanism of such progression is unclear, although ischemia or enhancement by vascular disease was proposed as an answer. These results, however, have been widely challenged. It has been suggested that there is an inordinately high proportion of adult patients in the studies and that the patients are somewhat atypical of patients with PSAGN. Moreover, the population had a much higher incidence of the nephrotic syndrome and was clinically different from those with typical acute postinfectious glomerulonephritis. Indeed, reports from other investigators (321,329) fail to support the findings of Baldwin (328) and others and suggest that progression to chronicity is a rare event. One has to take into consideration that a proportion of adult patients may have a preexisting underlying renal condition, and the prognosis of infection-related glomerulonephritides in these patients is inferior (2,315).

In summary, acute postinfectious (mostly poststreptococcal) glomerulonephritis has an excellent prognosis in children, although the outcome of the crescentic form is less clear, especially in epidemics. Complete clinical recovery usually takes place in children. It is difficult to determine whether patients with skin infections have a different prognosis from patients with throat infections, although the prognosis for either type of infection appears good in the epidemic variety (95). Death may occur in the acute stage from infections, heart disease, or kidney failure (98,331). The outcome in adults is worse than in children. However, many infection-associated glomerulonephritides in adults are not poststreptococcal glomerulonephritis; many of them are associated with other infections such as staphylococcal infections (see subsequent section). Also, many of the infected adults have underlying comorbidities such as diabetes, hypertension, and obesity.

### ACUTE POSTINFECTIOUS AND INFECTION-ASSOCIATED GLomerulonephritis of Nonstreptococcal Origin

GAS organisms are not the only organisms with the ability to cause acute diffuse proliferative glomerulonephritis. Various bacterial, viral, and fungal infections are thought to give rise to acute glomerulonephritis (Table 10.5), and antigens generated by these infections have been demonstrated in the glomeruli of affected patients. Many of these patients have initial signs of acute nephritic syndrome, but signs of this syndrome are less common than in those patients with nephritogenic streptococci (407,408). The glomerular diseases related to these nonstreptococcal antigens are associated with a broader spectrum of morphologic changes than typical PSAGN (2). There are also a number of patients with acute diffuse proliferative glomerulonephritis (appearing to be postinfectious) in whom no evidence of infection can be found at the time glomerulonephritis is
TABLE 10.5 Glomerulonephritis with other infections

<table>
<thead>
<tr>
<th>Bacterial</th>
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<tr>
<td>Endocarditis</td>
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<td>Shunt nephritis(^a)</td>
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<tr>
<td>Deep-seated visceral abscesses(^a)</td>
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<tr>
<td>Staphylococcal infections(^a)</td>
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<tr>
<td>Pneumococcal pneumonia and other pneumococcal infections (352–362)</td>
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<tr>
<td>Syphilis (363)</td>
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<td>Salmonellosis (364)</td>
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<td>Neisseria gonorrhoeae (365)</td>
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<td>Brucellosis (366)</td>
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<td>Mycobacterial infection (367)</td>
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<td>Campylobacter enteritidis (368)</td>
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<tr>
<td>Nocardia (369)</td>
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<td>Actinobacillus actinomycetemcomitans (370)</td>
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<tr>
<td>Yersinia infections (371)</td>
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<td>Borrelia burgdorferi (372)</td>
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<td>Bartonella henselae (362,373,374)</td>
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<td>Propionibacterium acnes (375–380)</td>
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<td>Q fever (Coxiella burnetii) (381)</td>
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<td>Legionnaires disease (382)</td>
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<td>Mycoplasma infection (383–386)</td>
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<td>Coxsackie (391)</td>
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<td>Measles (393)</td>
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<td>Hepatitis C (see Chapter 8)</td>
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<tr>
<td>ECHO (391,397,399,400)</td>
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<td>Adenovirus (391,397,401)</td>
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<td>Parvovirus B19 (402,403)</td>
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<td>Herpes (399,405,406)</td>
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<td>Schistosoma (see Chapter 5)</td>
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<td>Malaria (see Chapter 5)</td>
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\(^a\) Detailed references provided in text.

The epidemiology of infection-associated or postinfectious glomerulonephritis has changed considerably from decades ago. Recent studies show that the bacteria causing glomerulonephritis are often staphylococcal or gram-negative strains rather than streptococci, which predominated decades ago (3,4,68). Almost one half of the patients in recent studies were alcoholics, diabetics, or intravenous illicit drug users. The origin of infection was the oropharynx, skin, and lung (in that order of frequency). Renal biopsy disclosed signs of acute endocardial proliferative glomerulonephritis in over one half of the patients, crescentic glomerulonephritis in one third, and a membranoproliferative pattern in almost 10% of biopsies. The glomerulonephritis persists until the infection has been eradicated, but despite therapy, the prognosis is poor (3,4,68,410).

As we already emphasized earlier in this chapter, many glomerulonephritides associated with bacterial infections other than streptococci are not truly postinfectious (1). The bacterial infection causing the glomerulonephritis is frequently persistent, and the pathogenic bacteria are in the body at the time the glomerulonephritis is diagnosed. This has important therapeutic implications with respect to the use of immunosuppressive drugs. In our experience, it is a frequent mistake to consider an infection-associated glomerulonephritis postinfectious.

Glomerulonephritis Associated With Staphylococcal Infections

In the past, most glomerulonephritides associated with staphylococcal infections were secondary to endocarditis, deep-seated visceral abscesses, or ventriculoatrial shunts. In the older literature, studies have been published on only a few patients with staphylococcal glomerulonephritis in whom the glomerulonephritis was not secondary to the above conditions (120,121,131,411–414). Interestingly, in more recent years, a number of publications have drawn attention to the association of staphylococcal infection and glomerulonephritis not related to endocarditis or ventriculoatrial shunts (415–431). The earliest reports came from Japan and were subsequently followed by reports from the United States (4,13,415–431). Most of these staphylococcal organisms are coagulase-positive S. aureus, but rarely even coagulase-negative Staphylococcus epidermidis infection can be associated with acute glomerulonephritis. Many of these infections caused by methicillin-resistant strains of Staphylococcus aureus (MRSA) or Staphylococcus epidermidis (MRSE) are difficult to treat. Staphylococcal enterotoxins acting as superantigens have been implicated in the pathogenesis, and mild to prominent glomerular IgA immune complex deposits are seen, warranting the term “IgA-dominant staphylococcal infection–associated glomerulonephritis.”

IgA-Dominant Staphylococcal Infection–Associated Glomerulonephritis

There is increasing focus on staphylococcal infection–associated glomerulonephritis because of the following:

1. In developed countries, the incidence of PSAGN has declined because of successful treatment of acute streptococcal infections. On the other hand, staphylococcal

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...
infection–related glomerulonephritis is on the rise because of emerging drug-resistant staphylococcal strains and increase in nosocomial and community-acquired staphylococcal infections (2–4,68).

2. The elderly population (above 60), particularly those with underlying diabetes mellitus, malignancy, and other comorbidities, are increasingly diagnosed with infection-associated glomerulonephritis. Staphylococcus is the leading cause of infection-related glomerulonephritis in this population (1–4).

3. Patients with staphylococcal infection–associated glomerulonephritis frequently have active ongoing infection at the time the glomerulonephritis is diagnosed. This is different from the prototypical "postinfectious" (post-streptococcal) glomerulonephritis that develops after the infection (upper respiratory tract or skin infection with *Streptococcus*) has completely resolved, either naturally or after antibiotic treatment. In glomerulonephritis of active staphylococcal infection, the infection does not resolve naturally but is commonly persistent and difficult to treat (e.g., infected foot ulcers in diabetic patients, postsurgical wound dehiscence, endocarditis, deep-seated visceral abscess, osteomyelitis). These patients frequently suffer from comorbidities, and they sometimes may have mixed (multibacterial) infections. Overt signs of infection may not be clinically evident, and sometimes the infection comes to attention only after the renal biopsy (1). There is general agreement that the prognosis in cases of "glomerulonephritis with active infection" is guarded in sharp contrast to the acute "postinfectious" glomerulonephritis in children (2–4,420,428–430).

4. IgA-dominant or codominant immune complex deposits (along with C3, occasionally with IgG) are commonly seen in *Staphylococcus* infection–associated glomerulonephritis; therefore, the differential diagnosis from IgA nephropathy (and Henoch-Schönlein purpura) can be difficult. This has important treatment implications because giving immunosuppressive medications to patients infected with *Staphylococcus* can have dire consequences (418,432–436).

Recent literature has described this condition under different names, such as IgA-dominant postinfectious or poststaphylococcal glomerulonephritis (in fact, most of these cases are not truly postinfectious) (426,427,429,430), staphylococcal infection–associated glomerulonephritis mimicking IgA nephropathy (428), or staphylococcal superantigen–associated glomerulonephritis (415).

**Prevalence**

The exact incidence and prevalence can be difficult to calculate, because bacterial culture results are unavailable in a large percentage of patients whose kidney biopsies show features of ongoing infection associated IgA-dominant glomerulonephritis. This could be because many of these patients are elderly with several comorbidities and are treated empirically with antibiotics (without culture studies) with resultant negative blood cultures. We previously reported eight patients with staphylococcal infection–associated glomerulonephritis over a period of 1 year from October 2004 to October 2005, based on the renal biopsy material at The Ohio State University (428). Over the following years, we have expanded our experience. During the period 2004 to 2011, out of 5192 native kidney biopsies, a total of 37 (0.7%) biopsies with (culture-proven) staphylococcal infection–related glomerulonephritis were seen. In addition, there were at least thirty other biopsies, with histologic features of infection-associated glomerulonephritis as well as clinical signs of infection in the patient, but no definitive culture results available (so the prevalence is probably higher). In the series by Nasr, et al. (427) among 4600 biopsy samples processed from 2000 to 2002, five cases had IgA-dominant *Staphylococcus* infection–associated glomerulonephritis (0.1%). In the report by Haas, et al. (429), of the 6334 renal biopsies examined over a period of 4 years (2004 to 2007), 13 (0.2%) showed IgA-dominant infection–associated glomerulonephritis. Documented staphylococcal infection was present in 6 of 13 cases. In the report by Worawichawong et al. (430), 0.8% (7 of 905) of the biopsies fulfilled the clinical and pathologic criteria for IgA-dominant infection-associated glomerulonephritis, and 4 of 7 had proven staphylococcal infection. These patients usually have an underlying debilitating condition, such as diabetes (32% in our series of 37 patients), malignancy, severe trauma, extensive surgery, chronic infections such as Hepatitis C or severe coronary artery disease requiring catheterization, bypass arterial grafting or stent placements. Multiple simultaneous bacterial infections can occasionally be present.

Nasr et al. from the Mayo Clinic focused on infection–related glomerulonephritis in the elderly population that included staphylococcal as well as nonstaphylococcal infections (3). They report a biopsy incidence of 0.9% (93 of 10,080) over a period of 11 years from 2000 to 2010 of "postinfectious" glomerulonephritis in adults (age above 50 years). In addition to staphylococcci, other infectious agents such as streptococci, pneumococci, pseudomonas, enterococci were implicated (3). In 41.9% of the patients in the series by Nasr et al., the infectious agent was unknown.

The types of infection described in these publications include osteomyelitis (430), septic arthritis (412), discitis (422), pneumonia (121,427), infected leg ulcers (424), rectal abscess, other deep-seated abscesses, peritonitis, and pancreatitis (412,414,428), as well as undiagnosed primary site of infection with positive blood cultures (414–416). Many of these infections were associated with MRSA (412,414–419).

Positive blood cultures are commonly found with staphylococcal endocarditis infection. However, in other sites of infection, blood cultures are often negative. Culture studies from the actual site of infection tend to be more useful. Out of the 37 cases in our series with confirmed staphylococcal infection by culture results, 19 patients had MRSA infection, 13 patients had methicillin sensitive *Staphylococcus aureus* (MSSA) infection and 1 patients had MRSE (methicillin resistant *S. epidermidis*); in the remaining patients, the exact speciation was not available. Six patients had endocarditis, five had osteomyelitis, one had septic arthritis, four had pneumonia, nine had infected leg ulcers, five had postsurgical site infection, two had skin wounds from motor vehicle accident, one had groin abscess, one patient had scrotal abscess, one had abdominal abscess, one patient had staphylococcal urinary tract infection, and three had bacteremia with unknown site of infection. Two of the patients had multiple sites of infection at the same time including endocarditis, pneumonia, and paraspinal abscess or pneumonia and abdominal abscess. One patient developed abdominal wound dehiscence after
Clinical Presentation and Laboratory Findings  The most common presentation is acute renal failure with microscopic hematuria and proteinuria. Proteinuria can be quite severe and in the nephrotic range (even above 10 g/d). Eight of the ten patients described by Koyama et al. (415) had nephrotic range proteinuria at one point during their disease course. Gross hematuria is not very common but can occur. Patients usually have active urine sediment with microscopic hematuria. In our short series of eight patients, one patient (who also had the morphologic pattern of cryoglobulinemic glomerulonephritis with IgA/IgG deposits) had a positive cryoglobulin test (428). Hypertension is common, but this may be multifactorial, due to other co-morbidities. Clinical and laboratory findings in our series of 37 patients with culture-proven staphylococcal infection–associated glomerulonephritis over a span of 8 years are shown in Table 10.6.

Serum complement levels are lowered in a small percentage of patients (up to 30% in our series), but interestingly they can also be normal. Among our 37 patients, low C3 levels were seen in only 9 patients, low C4 was seen in 2 patients (one in combination with low C3). Nasr et al. (3) report hypocomplementemia in up to 72% of the patients in their series. Low C3 is more common than low C4. History of infection in the recent past is usually present even though the specific infective agent may have not been identified at the time of the renal biopsy. In some cases, however, infection may not even be suspected. The signs of active ongoing infection in elderly patients may be masked by other comorbidities such as congestive heart failure and diabetic complications. In some instances, potential sites of infection may be overlooked, most commonly diabetic foot ulcers. Practically, all patients have at least transient staphylococcal bacteremia, which may or may not be detected on blood cultures. In our series of 37 patients with proven staphylococcal infection only, 16 (43%) had positive blood culture results. According to the largest series from Japan (417), the average duration from the detection of the infection to the glomerulonephritis is 5.4 weeks. In some cases, it is difficult to determine when the infection exactly began. This is most common in diabetic patients with chronic leg ulcers and also in patients with surgical complications and multiorganism infections. Often such patients have already received multiple antibiotics (on an empiric basis). We have encountered biopsies from diabetic patients, in whom the foot infection was so persistent that amputation of the infected limb was required to bring the infection under control and to rescue kidney function. In our experience, in diabetic patients with leg or foot ulcers, gangrene, and amputation, osteomyelitis can be a sometimes-overlooked complication.

Up to 30% of patients may present with purpuric skin rash mimicking IgA vasculitis (Henoch-Schönlein purpura) (IgAV) (418,432–436). Eight of the thirty-seven patients in our series presented with petechial skin rash (432) (Table 10.7). Skin biopsy shows leukocytoclastic vasculitis with mild IgA deposits. Kidney biopsies reveal endocapillary proliferative glomerulonephritis with varying degrees of IgA and C3 deposits, which is indistinguishable from IgAV. This is a potential diagnostic pitfall (see Differential Diagnosis section). Four of our eight patients were initially treated with high-dose steroids for presumed IgAV and at least one patient developed sepsis.

Pathologic Findings
Light Microscopy
Various light microscopic patterns are observed, and the morphology of staphylococcal infection–related glomerulonephritis represents a spectrum. The light microscopic findings are
<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Ethnicity</th>
<th>Sex</th>
<th>Diabetes</th>
<th>Other comorbidities</th>
<th>Site of Infection</th>
<th>Positive cultures</th>
<th>Organism</th>
<th>Rash</th>
<th>Antibiotics</th>
<th>Corticosteroids Given</th>
<th>S. cr. before onset of ARF</th>
<th>S. cr. at biopsy</th>
<th>Follow-up period</th>
<th>S. cr. at follow-up</th>
<th>C3</th>
<th>C4</th>
<th>Hematuria</th>
<th>Proteinuria</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>66</td>
<td>C</td>
<td>F</td>
<td>Present</td>
<td>None</td>
<td>Leg ulcers, osteomyelitis</td>
<td>Wound</td>
<td>MRSA</td>
<td>Vasculitic rash</td>
<td>Linezolid, Amoxicillin Clavulanate</td>
<td>Yes</td>
<td>Not known</td>
<td>9.7</td>
<td>1 mo</td>
<td>3.5</td>
<td>69*</td>
<td>30</td>
<td>&gt;50/hpf</td>
<td>&gt;200 mg/dL</td>
<td>CRF</td>
</tr>
<tr>
<td>2</td>
<td>72</td>
<td>C</td>
<td>M</td>
<td>Present</td>
<td>Prostate cancer, s/p radiation, CHF, pneumonia</td>
<td>Leg ulcers</td>
<td>Wound</td>
<td>MRSA</td>
<td>Papular/purpuric</td>
<td>Yes</td>
<td>No</td>
<td>1</td>
<td>4.5</td>
<td>8 mo</td>
<td>1.4</td>
<td>Not known</td>
<td>Not known</td>
<td>3+</td>
<td>2+</td>
<td>Partial recovery</td>
</tr>
<tr>
<td>3</td>
<td>90</td>
<td>C</td>
<td>M</td>
<td>Absent</td>
<td>None</td>
<td>Groin abscess</td>
<td>Abscess</td>
<td>MSSA</td>
<td>Rash after antibiotics; eosinophilia</td>
<td>Erythematous nodular bullous lesions on the legs, LCV with IgA on biopsy</td>
<td>Yes</td>
<td>Not known</td>
<td>4.6</td>
<td>0</td>
<td>Dialysis</td>
<td>11*</td>
<td>Normal</td>
<td>Present</td>
<td>Present</td>
<td>No recovery</td>
</tr>
<tr>
<td>4</td>
<td>44</td>
<td>C</td>
<td>F</td>
<td>Absent</td>
<td>Dental problems</td>
<td>Tricuspid valve endocarditis</td>
<td>Blood</td>
<td>MRSA</td>
<td>Erythematous nodular bullous lesions on the legs, LCV with IgA on biopsy</td>
<td>Daptomycin, vancomycin</td>
<td>No</td>
<td>Not known</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>104</td>
<td>18</td>
<td>50/mg/dl</td>
<td>Urine protein/creatinine ratio 4</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>48</td>
<td>C</td>
<td>M</td>
<td>Absent</td>
<td>MVA</td>
<td>Skin, blood</td>
<td>Wound, blood</td>
<td>MRSA</td>
<td>Purpuric lesions, maculo-papular vasculitic rash, LCV with C3 on biopsy</td>
<td>Vancomycin, piperacillin and tazobactam</td>
<td>Yes</td>
<td>0.7</td>
<td>1.9</td>
<td>1 mo</td>
<td>3.7</td>
<td>163</td>
<td>25</td>
<td>large</td>
<td>1.2 g/24 h</td>
<td>CRF</td>
</tr>
<tr>
<td>6</td>
<td>51</td>
<td>C</td>
<td>M</td>
<td>Absent</td>
<td>Wrist injury, swelling, pain, osteomyelitis of the wrist</td>
<td>Bone</td>
<td>MSSA</td>
<td>Burning purpuric rash LE and flanks, back, upper extremities; LCV with IgA, C3 on biopsy</td>
<td>Vancomycin, nafcillin</td>
<td>Yes</td>
<td>0.9</td>
<td>2.8</td>
<td>8 mo</td>
<td>1.3</td>
<td>144</td>
<td>24</td>
<td>Present</td>
<td>Trace</td>
<td>Partial recovery</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>48</td>
<td>C</td>
<td>M</td>
<td>Absent</td>
<td>Colon cancer, hemicolectomy</td>
<td>Fistula and abdominal abscess, mesh infection</td>
<td>Blood</td>
<td>MRSE</td>
<td>Pseudo nodular LE rash, LCV with IgA, C3 on biopsy</td>
<td>Piperacillin and tazobactam, linezolid, cefturoxime</td>
<td>No</td>
<td>1</td>
<td>2.3</td>
<td>3 yr, 6 mo</td>
<td>2 to 5</td>
<td>169</td>
<td>43</td>
<td>Present</td>
<td>Present</td>
<td>CRF</td>
</tr>
<tr>
<td>8</td>
<td>57</td>
<td>C</td>
<td>M</td>
<td>Present</td>
<td>Obese, hypertensive</td>
<td>Skin wounds after working with colored mulch</td>
<td>Wound</td>
<td>MRSA; mixed infection</td>
<td>Vasculitic LE rash, blisters, LCV on biopsy</td>
<td>Multiple</td>
<td>No</td>
<td>1.2</td>
<td>2.8 mg/dL</td>
<td>2 mo</td>
<td>2.3</td>
<td>Normal</td>
<td>Normal</td>
<td>Present</td>
<td>10 g/24 h</td>
<td>CRF</td>
</tr>
</tbody>
</table>

C, Caucasian; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; MRSE, methicillin-resistant *Staphylococcus epidermidis*; S. cr., serum creatinine; LCV, leukocytoclastic vasculitis; CRF, chronic renal failure; LE, lower extremity; *, low C3 levels; exact antibiotics for patients 2, 3 and 8 not known; MVA, motor vehicle accident.
usually that of mesangioproliferative (mesangial hypercellularity without closure of the capillary loops) or endocapillary proliferative immune complex glomerulonephritis with or without crescents. The morphology may be similar to that in PSAGN or other infection-related glomerulonephritis. In our series of 37 patients, 16 cases (43%) showed enlarged glomeruli and diffuse endocapillary hypercellularity with polymorphonuclear leukocytes resembling PSAGN (2,3,427–430) (Figs. 10.25A and 10.26A). Some biopsies show a membranoproliferative (MPGN) pattern of injury with thickening and duplication of capillary loops. In other biopsies, the endocapillary hypercellularity may be focal and segmental in distribution as seen in 9 (24%) of our biopsies. Crescent formation occurs occasionally (2,3,428–430). Twelve of our thirty-seven biopsies (32%) showed crescents/necrotizing lesions of the capillary loops (Fig. 10.27). These varied from small subtle segmental necrotizing lesions (Fig. 10.28A) to large cellular crescents. Few admixed fibrocellular crescents may also be seen, but they are unusual given the acute nature of the disease. In a minority of biopsies (5 of 37), despite the presence of crescents and/or necrotizing glomerular lesions, the remaining glomeruli appeared unremarkable, a histologic pattern reminiscent of ANCA-associated glomerulonephritis. In four of five cases, the immune complex deposition also tended to be quite mild (see Fig. 10.28B). We have seen three biopsies in which, in addition to extensive endocapillary hypercellularity, few glomerular “hyalin thrombi” were evident (Fig. 10.29) suggestive of cryoglobulinemia, but these deposits did not show microtubular substructure on electron microscopic examination.

Overall, glomerular mesangial hypercellularity is common and can vary from mild segmental to prominent and diffuse. The mesangial hypercellularity may in some cases be masked by nodular mesangial matrix expansion secondary to underlying...

**FIGURE 10.25** A 48-year-old male with MSSA endocarditis. **A:** Diffuse endocapillary hypercellularity with numerous polymorphonuclear leukocytes. (H&E, ×400.) **B:** Immunofluorescence showed bright granular C3 deposits (bright IgG, but less intense IgA were also noted) (×400). **C:** Electron micrograph showed mesangial deposits (asterisk) and small, scattered subendothelial deposits (arrow). (Uranyl acetate and lead citrate, ×44,000.)
diabetic glomerulosclerosis (Fig. 10.30A). Interestingly, in many patients, the histologic findings are relatively unremarkable with only mild mesangial expansion and mesangial hypercellularity (Figs. 10.31A and 10.32A) (120,121,414). Based on the literature review and on our experience, the light microscopic appearance of the glomeruli, including the degree of glomerular hypercellularity, and the clinical activity do not show a good correlation. ATN is commonly seen. Red blood cells in tubules can be present on the biopsy. Red blood cell casts may also be evident and were numerous and conspicuous in 24% of our biopsies. Interstitial inflammation tends to be quite mild in our experience. Interstitial fibrosis and tubular atrophy depend on the underlying condition of the kidney. A moderate degree of interstitial fibrosis and tubular atrophy was present in 35% of our biopsies. It was mild to absent in the remaining biopsies.

**Immunofluorescence Microscopy**

The most characteristic finding is the IgA dominance or codominance in the glomerular deposits, resembling the staining pattern in primary IgA nephropathy (Berger disease) or IgA vasculitis (Henoch-Schönlein purpura) (see Figs. 10.26B and 10.30B). IgA and IgG staining in *Staphylococcus*-related glomerulonephritis was noted already in 1980 by Spector et al. (121). Most of the recent literature agrees that IgA is either the predominant or the codominant immunoglobulin in these deposits (1,2,4,120,121,414,418,423,424,427–430). However, occasionally, the IgA staining can be mild and segmental. Weak or absent IgA deposits (in the presence of appropriate clinical history and morphologic findings) does not exclude the possibility of *Staphylococcus* infection–associated glomerulonephritis (see Fig. 10.28B). C3 is almost always present even when IgA staining is weak (see Figs. 10.25B and 10.30C). Early components of the complement cascade, such as C1q and C4, are usually not seen. In rare instances, immunofluorescence reveals a pauci-immune pattern (no significant deposits) (336). These patients usually also have crescents and therefore mimic ANCA–associated pauci-immune crescentic and necrotizing glomerulonephritis (see Figs. 10.28B and 10.31B) (336). History of recent or ongoing infection, especially endocarditis, should be carefully investigated in such cases.

The intensity and extent of IgA immunofluorescence staining can vary widely from trace to bright. Granular IgA staining is seen predominantly in the mesangium but can also be seen scattered along segments of the glomerular capillary loops. Sometimes, the staining can be bright, by electron microscopy, the deposits appear scant and seen only along
peripheral capillary loops around the expanded nodular mesangium of glomeruli in diabetic patients. IgA staining was absent in 3 of our 37 cases with *staphylococcus* infection–associated glomerulonephritis. In such cases, C3 staining alone can be very helpful. C3 tends to be bright, coarsely granular, and quite abundant (similar to that seen in PSAGN). Also, the extent of IgA immunofluorescence can vary from one glomerulus to the other within the same biopsy. Rarely, staining for all three immunoreactants IgG, IgA, and C3 can be weak (5 biopsies in our series of 37 patients). Moderate to prominent codominant granular IgG immunofluorescence was seen in 6 and mild granular IgG staining in 12 of our 37 biopsies. Smudgy IgG staining in the mesangium or linear staining along the glomerular capillary loops is often noted in diabetic patients; this IgG staining pattern is common in the kidneys with diabetic glomerulosclerosis and is considered nonspecific (the glomerular staining for albumin is similar). We encountered three biopsies with globular cryoglobulin-like glomerular capillary hyaline thrombi (without microtubular substructure on electron microscopy). In two of these three biopsies, the deposits showed strong staining for IgA and C3 with no IgG, and one of the patients tested positive for cryoglobulins. One biopsy with glomerular capillary hyaline thrombi showed strong IgG and C3 staining with no IgA; this patient was negative for cryoglobulins. Mesangial granular fluorescence for lambda light chain tends to be stronger than for kappa light chain in
most cases (similar to that seen in idiopathic IgA nephropathy). Immunofluorescence staining for IgM and C1q tends to be quite inconspicuous, but segmental IgG deposits (probably nonspecific) are not unusual. Bright fibrinogen staining can help to identify focal segmental necrotizing lesions or crescents.

**Electron Microscopy**

The degree of electron-dense immune complex deposition tends to vary from case to case. Electron-dense deposits are described in the mesangium in most publications that detail morphologic findings; however, subepithelial and occasional subendothelial deposits can also occur (2–4,420,424,428). In our experience, mesangial electron-dense deposits are present but can vary from few scattered deposits to several easily identified deposits (see Figs. 10.25C and 10.31C). These may be accompanied by small scattered intramembranous and/or subendothelial deposits (Fig. 10.32 B). Subendothelial electron-dense immune-type deposits tend to be few and small. Numerous subendothelial deposits may be seen, albeit rarely. In our series of 37 biopsies, 6 showed several subendothelial deposits, out of which 3 biopsies contained large subendothelial deposits (see Fig. 10.26C). In one of these patients, large intraluminal and subendothelial cryoglobulin-like deposits were noted but without microtubular substructure (428).

“Humps” (large subepithelial deposits bulging outward from the boundary of the glomerular capillary basement membrane toward the Bowman space) may occur (Fig. 10.33), resembling PSAGN, but it is more common to see intramembranous and smaller subepithelial deposits rather than true “humps,” and the latter are not a prerequisite for making this diagnosis. Some case series describe “humps” occurring very commonly in *Staphylococcus* infection–associated glomerulonephritis (2). In fact, it has been listed as one of the criteria for diagnosis (2). We emphasize, however, that these are not specific to this condition, and its absence does not exclude the possibility of infection–associated glomerulonephritis. Subepithelial humps can be seen in other diseases like MPGN, C3 glomerulopathy, and rarely lupus glomerulonephritis. Also, subepithelial humps may be seen in infection–associated glomerulonephritis caused by other pathogens as well, such as gram-negative bacteria and nonbacterial pathogens (2).

**Etiology and Pathogenesis**

Antibodies against staphylococcal antigens have been proposed in the pathogenesis already in the 1970s. Sato et al. (414) detected antistaphylolysin antibodies in 71 patients with acute glomerulonephritis, and in four of these patients, the staphylococcal antigen was visible in the glomerular mesangium by immunofluorescence. Polyclonal elevation of serum IgA and IgG, as well as circulating immune complexes, is frequently detected (120,414,418). One hypothesis is that staphylococcal enterotoxins act as superantigens (120,414–417,419).
FIGURE 10.31  This patient developed acute glomerulonephritis secondary to MRSA infection of the graft site following coronary artery bypass surgery. A: Note the mild mesangial and endocapillary hypercellularity. (H&E, ×400.) B: Diffuse granular mesangial fluorescence was noted for IgA. (×400.) C: Rare electron-dense deposits were identified in the mesangium (arrows). No glomerular capillary cell deposits were present. (Uranyl acetate and lead citrate, ×4400.)

FIGURE 10.32  Renal biopsy findings in a 66-year-old male with femoral catheter wound infection, MSSA sepsis, and endocarditis. A: The glomeruli showed only mild mesangial hypercellularity and occasional intracapillary polymorphonuclear leukocytes. (H&E, ×400.) B: Electron micrograph shows prominent intramembranous and subepithelial electron-dense immune-type deposits. (Uranyl acetate and lead citrate, ×17,000.)
The enterotoxin is usually staphylococcal enterotoxin C, A, or the toxic shock syndrome toxin-1. Superantigens can directly bind to MHC class II molecules on antigen-presenting cells without intracellular antigen processing to form peptides that can fit into the MHC molecule groove on the surface of the antigen-presenting cell. Also, the superantigen can directly bind to the T-cell receptor V beta region of a large percentage of the total T-cell population, irrespective of the antigen specificity of the receptor. These superantigens are strongly mitogenic for the T cells causing marked T-cell proliferation, and subsequent release of large amounts of lymphokines/cytokines. These cytokines, in turn, will cause polyclonal B-cell activation and immune complex formation and, eventually, glomerulonephritis. Hirayama et al. (434) in their series of six patients with staphylococcal infection–induced HSP-like (IgA vasculitis) clinical syndrome with acute glomerulonephritis have demonstrated increased number of T cells bearing specific Vβ chain of T-cell receptor (Vβ 5.2, 5.3 and 8) compared to normal controls and to patients whose Staphylococcus infection had improved. Serum levels of cytokines (ILs 1β, 2, 6, 8, and tumor necrosis factor–alpha) were also significantly higher than in normal individuals, and these normalized after staphylococcal infection had healed. They conclude that in addition to superantigens, conventional Staphylococcus antigens also play a role in the pathogenesis of glomerulonephritis. Staphylococcal enterotoxins acting as superantigens are also implicated in other diseases such as staphylococcal toxic shock syndrome. Minute concentration of superantigens can activate the immune system receptors because they bind with strong avidity to T-cell antigen receptors and class II MHC molecules. Koyama et al. (422) expanded this hypothesis and proposed that the Staphylococcus cell envelope antigen is a crucial pathogenic factor in the development of IgA nephropathy. These investigators found this antigen in 68% of renal biopsy specimens from patients with IgA nephropathy. The same group from Japan developed an experimental model of IgA nephropathy in mice following biweekly immunization of the animals with antigens derived from Staphylococcus aureus mixed with Freund adjuvants (437). Of course, these data will need further confirmation.

**Differential Diagnosis**

As detailed above, the morphologic findings can resemble various conditions, including PSAGN, other infection-related glomerulonephritides, MPGN type I, C3 glomerulopathy, IgA nephropathy (or IgA vasculitis), and pauci-immune ANCA-associated crescentic glomerulonephritis. The differential diagnosis is possible only if detailed clinical data, particularly bacterial culture results and serologies, are available. In PSAGN, the presence of IgA in the immune deposits is unusual; therefore, if in an infection-associated glomerulonephritis codominant or dominant glomerular IgA deposits are seen, an underlying staphylococcal infection has to be considered. The differential diagnosis from idiopathic IgA nephropathy or IgA vasculitis can be quite difficult. If no bacterial culture results are available, a staphylococcus infection–associated glomerulonephritis could easily be diagnosed as a primary IgA nephropathy. Of course, as indicated above, theoretically, it is possible that a subset of IgA nephropathy cases are related to staphylococcal infection (422). Also, up to 30% of patients with staphylococcus-related acute glomerulonephritis may develop purpuric skin lesion; therefore, the clinical presentation may mimic Henoch-Schönlein purpura (425,432–436). Adult Henoch-Schönlein purpura is a rare disease. In our experience, it is more common to see adult IgA-dominant glomerulonephritis associated with purpuric skin lesions in patients with staphylococcal infection. Therefore, if an adult patient presents with symptoms of IgA vasculitis and a renal biopsy shows IgA-dominant glomerulonephritis, an underlying staphylococcal infection should always be taken into consideration.

The clinical presentation can be quite helpful in making the differential diagnosis. As pointed out above, just based on morphologic findings, the diagnosis of IgA nephropathy will likely be made. However, if a patient’s kidney biopsy shows IgA and C3-dominant/codominant immune complex deposits with active glomerular lesions and the patient presents with acute kidney injury, including active urine sediment, heavy proteinuria, and even the slightest signs of infection, one has to consider the possibility of an underlying staphylococcus infection. As pointed out above, blood cultures are frequently positive and the site/origin of infection may be quite difficult to identify. We always raise the possibility of an underlying staphylococcus infection if we see IgA and C3 codominant glomerulonephritis with an acute clinical presentation. Although IgA nephropathy can show exacerbations with episodic gross hematuria following upper respiratory tract infections, most of these patients do not develop acute kidney injury or heavy proteinuria, and sometimes, C3 staining is mild or even absent. In typical cases of progressive IgA nephropathy, the patients have a protracted, slowly progressive clinical course with persistent microscopic hematuria, hypertension, and gradually worsening proteinuria. Renal biopsy findings usually show a mixture of chronic and active glomerular lesions, including segmental or global glomerular sclerosis, glomerular scars, adhesions, and old fibrous crescents. In acute staphylococcus infection–associated glomerulonephritis, chronic glomerular lesions are
unusual, and if they are present, they may not be related to the infection (they could be secondary to diabetic nephropathy, for example).

Rare cases of pauci-immune crescentic and necrotizing glomerulonephritis have been reported in association with staphylococcal infection (417,422). In fact, the possibility that *S. aureus* infection may play a role in the pathogenesis of ANCA-associated granulomatosis polyangiitis (previously known as Wegener granulomatosis) has been proposed (431). Fortunately, such cases are rare, but the clinical management can be quite problematic because if a pauci-immune crescentic and necrotizing glomerulonephritis is secondary to *staphylococcus* infection, treatment with cyclophosphamide and steroid may be contraindicated.

MPGN, particularly MPGN type I, may be difficult to differentiate, particularly because *S. epidermidis* infections can “cause secondary MPGN” (see section on ventriculotraial shunts). Fortunately, in most instances, the obvious clinical history of infection, fever, and positive cultures make the differential diagnosis relatively easy. A subset of MPGN cases would now be classified under the recently described entity C3 glomerulopathy, in which C3 deposits are the predominant finding on immunofluorescence staining with absence of immunoglobulin components. As mentioned above, IgA staining can be weak to absent in few cases of *Staphylococcus* infection–associated glomerulonephritis, but these tend to have strong staining for C3. Such cases may be confused with the disease entity of C3 glomerulopathy. Rarely, hyaline thrombi resembling cryoglobulin deposits can be seen in association with bacterial infections, and the patients may have mixed type III cryoglobulinemia. This should be differentiated from noninfectious causes of cryoglobulinemia.

**Clinical Course and Outcome**

In contrast to children with postinfectious glomerulonephritis, in whom complete remission occurs in the vast majority of patients, the prognosis in adults with staphylococcal infection–associated glomerulonephritis is much more guarded. A significant proportion of adults does not recover and have persistent renal dysfunction or progress to ESRD. Persistent renal dysfunction develops in 8% to 54% of patients and progression to ESRD in 4% to 33% of patients as described in several case series (2–4,315,410,428). Poor prognostic indicators in adults include older age, higher serum creatinine at biopsy, tubulointerstitial scarring, and presence of underlying debilitating conditions (2,3,428–430). The goal of treatment should be eradication of the infection and management of additional comorbidities that these elderly patients commonly have, such as diabetes, hypertension, congestive heart failure, and surgical complications (2,167,410). Appropriate antibiotics (for methicillin-resistant or methicillin-sensitive *staphylococcus*), surgical debridement of the infected wounds, or infection sites such as cellulitis, osteomyelitis, are important (421,438). In severe cases of diabetes, even amputation of the infected lower extremity may be required to bring the infection under control. Some antibiotics (such as high doses of vancomycin) used for staphylococcal infections can themselves be nephrotoxic and can cause acute tubular injury and interstitial nephritis. In such instances, it can be difficult to determine the cause(s) of the renal dysfunction. Antibiotic levels, especially vancomycin levels in the blood, may have to be monitored, and the antibiotic may have to be changed to reverse the drug-induced nephrotoxicity. The role of immunosuppressive therapy in adult patients with ongoing *Staphylococcus* infection–associated glomerulonephritis is highly controversial and considered contraindicated in most instances. There are no randomized prospective clinical trials on the role of steroids in this condition. The available data are based on retrospective studies. Steroid use is common in patients with accompanying leukocytoclastic vasculitic skin rash because it can mimic IgA vasculitis (Henoch-Schönlein purpura) (432–435). Sometimes, the rash may even disappear following administration of steroids. However, the patients subsequently may develop sepsis without improvement in renal function (432). Despite few case reports describing good results after the use of steroids in adults with infection-associated glomerulonephritis (with or without crescents) and renal dysfunction (308,349), none of the case series with statistical analyses have found a beneficial effect of steroids on outcome (2–4,315,410,428,432). Based on the absence of any proven benefit and the potential risk of sepsis, immunosuppressive therapy is not recommended in most adults with staphylococcal infection–associated glomerulonephritis.

**Glomerulonephritis Associated With Other Infectious Agents**

Pneumococcal infections may cause acute proliferative glomerulonephritis (352–362) as well as other morphologic patterns (352,354,355), such as pure mesangial proliferative glomerulopathy. The clinical signs are hematuria, proteinuria, edema, and renal insufficiency. Glomerular subepithelial humps are found, and C3 and pneumococcal antigens can be detected in the mesangial regions and along the glomerular capillaries by immunofluorescence (354,355). Properdin also has been found to be present in a similar distribution (352), and C3, C3 proactivator, and pneumococcal antigen are sometimes evident focally along the TBMs (355). In view of these findings, it was suggested that the alternative pathway of complement activation had been stimulated by the pneumococcal polysaccharide. Complete recovery has been noted.

Meningococcal infections may cause acute proliferative glomerulonephritis (358,359). Patients with this infection may not have clinical evidence of glomerulonephritis, but they undergo biopsy because of laboratory evidence of circulating immune complexes. Immunofluorescence and electron microscopic studies reveal changes similar to those noted in typical PSGN.

There are many other causes of acute infection–associated glomerulonephritis (see Table 10.5). Proliferative glomerulonephritis has been reported in patients with pneumonia owing to *Klebsiella* and *Mycoplasma* organisms (360,383–386). This disease may manifest in the form of hematuria, proteinuria, or renal insufficiency, but it may also be clinically occult (360,383–386). *Klebsiella* capsular polysaccharide antigens, immunoglobulins, and complement have been demonstrated in the glomerular capillaries and in the mesangial regions of a patient with focal proliferative glomerulonephritis and pneumonia caused by *Klebsiella* organisms (360). In this case, the eluate of the glomerular-bound IgG had antibody specific to *Klebsiella*. Similar evidence of diffuse proliferative glomerulonephritis, with mycoplasma antigen, immunoglobulin, and complement deposition along the glomerular capillary wall and mesangium, was noted in a patient with pneumonia caused by
**Mycoplasma** organisms (383). In **Mycoplasma-associated** glomerulonephritis, renal biopsy most frequently shows diffuse endocapillary proliferative glomerulonephritis with low serum complement levels and primarily mesangial immune complex deposition (383–386). One patient had findings of characteristic glomerulonephritis. **Mycobacterium gordonae**– and **Coxiella burnett**–associated glomerulonephritis also has been reported (367,381).

Bookman et al. (373) reported three patients with **Bartonella henselae** endocarditis–associated crescentic and necrotizing glomerulonephritis. The patients all had crescentic and necrotizing glomerulonephritis mimicking a vasculitis; however, they had mesangial or subendothelial immune complex deposits by electron microscopy and C3 deposits on immunofluorescence. A very similar case was presented at the 2004 meeting of the American Society of Nephrology in St. Louis, MO, by Dr. Helen Liapis (Fig. 10.34). These cases may mimic crescentic glomerulonephritis secondary to a vasculitis; however, the correct diagnosis is important to make because treatment is antibiotics instead of immunosuppression.

**Salmonella typhi** has been noted to trigger glomerulonephritis with glomerular deposition of immunoglobulins and complement (364,439), although the clinical evidence of glomerular disease has usually been slight. Various protozoan and viral organisms can produce glomerulonephritis, although the glomerular changes by light microscopy are not as marked as those in classic acute postinfectious glomerulonephritis (see Table 10.5).

Viruses have been incriminated in the evolution of acute immune complex–mediated glomerulonephritis (391,397, 401,440–443). Smith et al. (391) prospectively studied 240 previously healthy military personnel with nonstreptococcal upper respiratory tract infections to find evidence of asymptomatic glomerulonephritis. Nine patients were found to have red blood cell casts in the urine and focal or diffuse mesangial hypercellularity (with mesangial deposits of C3) on renal biopsy. Five of these nine patients had serologic evidence of viral infection with adenovirus or influenza A or B, and four of nine had hypocomplementemia. Subsequent renal biopsies showed histologic improvement or loss of immunofluorescent staining.

### POSTSTREPTOCOCCAL AND OTHER INFECTION-RELATED GLOMERULONEPHRITIDES SUPERIMPOSED ON DIABETIC NEPHROPATHY

In the United States, diabetic nephropathy has become the most common cause of ESRD. Therefore, the incidence of glomerular disease superimposed on diabetic nephropathy is also on the rise. Because diabetic patients are susceptible to infections, they also develop infection-related renal disease more commonly. In our biopsy material, an increasing proportion of adult infection-related glomerulonephritides occur in diabetic patients and many of them have underlying diabetic nephropathy. The same tendency is reported in the literature (2–4,68,427,444–446). Nasr et al. (4) studied 86 adult patients with postinfectious glomerulonephritis. Twenty-five (29%) of them had diabetes and 16 (18.6%) had diabetic nephropathy with diabetic glomerulosclerosis. The same authors later published 109 elderly patients with postinfectious glomerulonephritis and found that 49% of them were diabetic (3). Haas (446), at the Johns Hopkins Hospital, found some ultrastructural evidence (subepithelial deposits in the glomerular mesangial notch region) of postinfectious glomerulonephritis in 23 of 104 kidney biopsy specimens with the primary pathologic diagnosis of diabetic nephropathy (22% of all biopsies with diabetic nephropathy). Although this number represents the high end of the spectrum, one must not underestimate the significance of the problem. It is quite possible that in many cases of unexplained deterioration of renal function in patients with underlying diabetic nephropathy, an undiagnosed postinfectious glomerulonephritis may be in the background. A large study from Italy by Mazzucco et al. (445), describing 393 renal biopsies from diabetic patients, reports 37 biopsies with postinfectious glomerulonephritis. Twenty six of these biopsies were from patients who had evidence of diabetic nephropathy and only eleven of them from patients who had no histologic evidence of diabetic nephropathy (445). Most of these cases represent PSAGN; however, any kind of infection, particularly staphylococcal infections, may induce a proliferative glomerulonephritis superimposed on diabetic nephropathy (427).

The diagnosis of infection-associated glomerulonephritis superimposed on diabetic nephropathy may not be easy because the underlying changes of diabetic glomerulosclerosis may alter the typical histologic manifestations (Fig. 10.35). Some degree of mesangial hypercellularity may occur in diabetic nephropathy. One has to look carefully for intracapillary accumulation of inflammatory cells, which is frequently not diffuse in infection-associated glomerulonephritis superimposed on diabetic glomerulosclerosis. Immunofluorescence frequently shows various nonspecific staining patterns in diabetic nephropathy, including linear staining for albumin and IgG along the glomerular and TBMds and smudgy or coarsely granular, frequently somewhat...
segmental, fluorescence for C3. Therefore, using immunofluorescence alone may not be sufficient to make the diagnosis. One has to review carefully the electron micrographs in search for subepithelial humps as well as mesangial, intramembranous, and subendothelial deposits. Unfortunately, in many biopsies with diabetic glomerulosclerosis, electron-dense deposits, representing hyalin change, are abundant and can be difficult to differentiate from true immune complex deposits. As also indicated earlier, Haas (136) emphasizes careful electron microscopic studies to diagnose a so-called incidental healed postinfectious glomerulonephritis. In his opinion, subepithelial deposits in the mesangial notch region (between folds of the glomerular basement membrane overlying mesangial regions) are of particular diagnostic value. The importance of this finding needs further confirmation. We encounter occasional subepithelial deposits in mesangial notch regions. Such deposits frequently (but not always) have a microspherical substructure (Fig. 10.36) and, in our opinion, represent a nonspecific degenerative change with no proven diagnostic specificity.

The prognosis of postinfectious glomerulonephritis in patients with underlying diabetic nephropathy appears to be much worse than that of postinfectious glomerulonephritis without any underlying renal disease. In the study of Nasr et al. (4) on adult postinfectious glomerulonephritis, 9 of 11 patients (81.8%) with underlying diabetic glomerulosclerosis progressed to ESRD. Their extended study on a larger number of elderly patients showed similarly dismal outcome; 55% of patients with diabetic glomerulosclerosis progressed to ESRD during the short follow-up period in contrast to the 19% progression rate in patients without diabetic glomerulosclerosis (3). As pointed out above, it is not uncommon that an otherwise relatively mild postinfectious or infection-associated glomerulonephritis may represent the last “hit” to the kidney with underlying diabetic nephropathy. Because of the prominent microvascular disease, frequent hypertension, cardiac disease, and other complications of diabetes, renal function in these patients may never recover.

GLOMERULONEPHRITIS ASSOCIATED WITH DEEP-SEATED VISCERAL ABSCESES

Clinical Features
Whitworth et al. (447) and Beaufils et al. (447, 448) first described the association of glomerulonephritis and visceral suppuration in the absence of infective endocarditis. The temporal association between deep-seated infection and glomerulonephritic immune-type lesions suggests an etiologic relationship between these two conditions. Serum cryoglobulins and circulating...
immune complexes are often present (447,448) and usually disappear when the infection is cured. Hypocomplementemia is not generally a feature unless infective endocarditis is also present (380); however, the data suggest activation of the alternative pathway of complement activation.

Deep suppurative infections are caused by either gram-positive or gram-negative organisms; as noted previously, bacterial endocarditis also can be present. Bacteremia may not be documented in all patients. Two patients with Entamoeba histolytica liver abscess–related proliferative immune complex glomerulonephritis have been reported (449,450). A recent case report describes MPGN with glomerular C3 and IgG deposits in a patient with nocardial cerebral abscess (451). Most cases are owing to intrathoracic abscesses, but wound infections, subphrenic abscess, abscess of the appendix, abdominal abscess, rectal abscess, septic abortion, cutaneous abscess, mediastinitis, osteomyelitis (including mastoiditis), and infection of vascular and vascular Dacron prostheses have all been reported (120,411,423,448,452–454). Lung abscesses were most commonly noted in those with the crescentic form of the disease (447). In our experience, staphylococcus infection–associated osteomyelitis in diabetic patients is becoming a more and more common disease underlying a glomerulonephritis. The duration of the deep-seated abscess ranges from a few weeks to a few years (409,448). The morphologic picture correlates somewhat with the duration of the preceding infection. Those patients with infection of less than 2 months’ duration had only mesangial hypercellularity, whereas patients experiencing more than 2 months of infection had either acute diffuse glomerulonephritis with crescents or crescentic glomerulonephritis (409,448).

The patients are febrile and generally quite ill. Microhematuria is present in all patients, and gross hematuria is noted in approximately half of them. Proteinuria is usually present and may be marked. Hypertension is found in about one fourth of patients, and oliguria is evident in almost half. Rapid progression of renal insufficiency can occur (408,447). Some three fourths of patients require dialysis. Extrarenal manifestations include purpura, arthralgia, and cutaneous necrosis, especially if there is cryoglobulinemia.

**Pathologic Findings**

A number of morphologic patterns have been noted, including crescentic glomerulonephritis (447), MPGN with or without crescents (409,444,447,448), acute diffuse endocapillary proliferative glomerulonephritis (411,423,427,454) with or without crescents (409,448), and mild mesangial hypercellularity (121,413,421). Immunofluorescence staining for immunoglobulins and complement is positive in the glomeruli in a granular pattern. As pointed out earlier, if the abscess is secondary to staphylococcal infections, the immunofluorescence may reveal predominant or codominant IgA fluorescence, in addition to C3 and occasionally IgG. In other cases, the predominant immunoreactant is usually C3 with some IgG. Electron microscopy most commonly demonstrates glomerular mesangial deposits; glomerular subepithelial deposits have been noted in patients with S. aureus infection–associated glomerulonephritis (427–430). Small intramembranous and subendothelial deposits may also occur. Magil (454) reported eight patients with remote visceral infections who all had diffuse proliferative glomerulonephritis; the sites of infection included the lung, blood, and retroperitoneal space. Histochemical staining with the α-naphthyl acetate stain for nonspecific esterase showed numerous intraglomerular monocytes/macrophages (fewer than are seen with cryoglobulinemia but more than are evident in other types of proliferative glomerulonephritis, such as systemic lupus erythematosus or cases of MPGN).

**Prognosis and Outcome**

Deep-seated abscess–associated glomerulonephritis is not postinfectious glomerulonephritis, and the treatment should focus on the eradication of the infection (1,438). When there is complete eradication of the deep-seated infection (through surgical means and/or aggressive antibiotic treatment), renal function generally recovers (409,447). Subsequent renal biopsies show morphologic evidence of healing, with only mild residual mesangial hypercellularity, capillary wall thickening, and a few globally sclerotic glomeruli (409,447). If the infection cannot be controlled, the glomerulonephritis persists (as demonstrated on subsequent biopsies) and patients progress to renal failure (409,447). Incomplete therapy (delayed or suboptimal) results in moderate to severe renal insufficiency that may require dialysis. Persistent microhematuria or proteinuria may be found in those who otherwise appear to have recovered normal renal function (409,447).

**GLOMERULONEPHRITIS ASSOCIATED WITH INFECTIVE ENDOCARDITIS**

Infection of the heart valves historically has been divided into subacute bacterial endocarditis, which usually affects a previously damaged heart valve that is susceptible to bacterial organisms...
of low virulence, and acute bacterial endocarditis, which usually affects a previously normal heart valve that is infected by a virulent bacterial organism. Infection of a rheumatic heart by organisms of the Streptococcus viridans group is an example of the former, whereas S. aureus infection in an intravenous drug abuser is an example of the latter. The natural history of glomerulonephritis owing to infectious endocarditis has been dramatically influenced and altered by the advent of antibiotic therapy and changing epidemiologic patterns. Although some authors have discontinued use of this subdivision of terminology (subacute and acute), we retain it in this chapter for historical purposes.

**Glomerulonephritis in Subacute Bacterial Endocarditis**

Renal complications of subacute bacterial endocarditis include glomerulonephritis, renal infarction, abscesses, and therapy-related or therapy-induced tubulointerstitial nephritis and acute tubular epithelial injury. We shall consider only glomerulonephritis here. *Embolia nonapparutivae* focal nephritis was the name given by Löfflein at the turn of the century (454) to the renal lesions noted in seven patients with subacute bacterial endocarditis. Baehr (455) and Bell (456) described glomerulonephritis at autopsy in patients with subacute and acute endocarditis. The lesion in subacute endocarditis was characterized by a number of glomeruli with segmental or focal necrosis, often also with segmental hypercellularity or sclerosis. Polymorphonuclear leukocytes and nuclear fragments also were present. Thus, different stages of segmental lesions appeared to be represented. Most of the glomeruli were histologically normal.

The term *focal embolic nephritis* implied that the renal disease was caused by embolization of infectious material. Although most investigators do not accept this pathogenetic mechanism, a few authors have described embolization of infectious material to glomeruli in endocarditis (457). Because it is now apparent that the mechanism is virtually always immunologic, the term *focal* and *segmental* proliferative, *necrotizing, or sclerosing* glomerulonephritis is preferred. The most common organisms leading to this pattern are the *S. viridans* group and coagulase-negative staphylococci, including *S. epidermidis*, although *Actinobacillus actinomycetemcomitans*, *Streptococcus mitis*, *Haemophilus influenzae*, *Neisseria gonorrhoeae*, *enterococci*, and *Chlamydia psittaci* have all been reported.

Glomerulonephritis associated with subacute bacterial endocarditis is becoming rare because of the declining incidence of subacute bacterial endocarditis, but the true incidence is difficult to determine because most reports do not come from prospective and consecutive examinations of clinical and morphologic material from unselected patients.

**Clinical Presentation**

Renal involvement occasionally is the initial manifestation of subacute bacterial endocarditis, especially when the diagnosis of endocarditis is not considered or when blood cultures show negative results. However, the clinical findings of renal involvement may be mild and are usually overshadowed by the cardiac features and the effects of systemic infection. Gross hematuria may be present, but the microscopic hematuria is more commonly noted. Hematuria may persist or resolve, only to appear again on several occasions. Gross hematuria may be caused by renal infarctions rather than by glomerular lesions (168). Proteinuria (mild) and granular casts may be detected in the urine. The nephrotic syndrome and hypertension are unusual. Depression in serum complement level is frequent but not always present, nor is it specific to renal involvement (458–462). Before the era of antibiotic therapy, hypocomplementemia was noted in 90% of patients with diffuse glomerulonephritis and 60% of patients with focal glomerulonephritis in subacute bacterial endocarditis. Most patients appear to have activation of the classic complement pathway (463).

When the BUN and serum creatinine are elevated, the renal lesion is more likely to be the diffuse form of glomerulonephritis rather than the focal form (367,455,464–466). Focal glomerulonephritis may occur in the absence of any clinical renal involvement (466). Uremia was present in approximately 5% to 10% of patients with endocarditis in the era before antibiotics (467). Following the introduction of antibiotics, this figure fell to 3% to 4% (467). No uremic deaths were found in penicillin-treated patients with fatal subacute bacterial endocarditis in the series of Spain and King (468). Among the 52 untreated patients in the same series, 8 patients with diffuse glomerulonephritis and 1 patient with focal glomerulonephritis had uremia.

Glomerulonephritis is common in patients with subacute and acute endocarditis with high titers of ANCA and may be crescentic (336,469–473). Such cases can be problematic for diagnosis because the glomerulonephritis may be “pauci-immune” with few or no detectable glomerular immune complex deposits (336). Differentiating such ANCA-positive endocarditis-associated crescentic glomerulonephritis cases from pauci-immune crescentic glomerulonephritis associated with small vessel vasculitis can be very difficult. From the management point of view, the correct diagnosis is crucial because treatment options are quite different. The differential diagnosis is complicated even more by the fact that, rarely, ANCA-associated small vessel vasculitis may cause cardiac valvular involvement (ANCA-associated noninfectious endocarditis) (472). The ANCA in subacute and acute endocarditis is usually antiproteinase 3 (Pr3-ANCA) (472), but dual ANCA positivity (antiproteinase 3 and antitymelyloperoxidase) has also been reported (473). Rarely, ANCA and crescentic glomerulonephritis may be the first manifestation of infectious endocarditis (474). A recent review of the literature by Uh et al. (475) indicates that after successful treatment of the endocarditis, the titers returned to normal in 10 of 15 patients with available follow-up. Some authors advocate immunosuppression, in addition to antibiotics, but this is controversial. The review of Uh et al. (475) indicates that two of the six patients treated with immunsuppression died.

**Pathologic Findings**

**Gross Pathology**

The kidneys are either normal size or enlarged. The largest kidneys are in patients who have widespread or diffuse glomerulonephritis. There are petechial hemorrhages and red blood cells within tubular lumens that can be seen as red dots on the surface of the kidney (hence the description “flea-bitten”) (471); two thirds of the 30 patients studied by Heptinstall (168) had this appearance. Either fresh or healed renal infarcts were identified in 57% of the cases; the infarcts were either single or multiple and were of a size suggesting obstruction of arcuate or large interlobular arteries.
**LIGHT MICROSCOPY**

The infarcts noted grossly show various ages. They are sterile and are not different from any other type of sterile infarct.

**GLOMERULI**

A number of light microscopic glomerular patterns are noted. Focal and segmental glomerulonephritis is often present (210,455,456,459,465,468,476). This type of lesion was noted in 50% to 84% of patients studied (349,465,468). Bell (456) found diffuse proliferation in over half his patients and focal glomerulonephritis in 18%. Diffuse glomerulonephritis often had more destructive focal segmental lesions. As mentioned above, crescents may occur, sometimes associated with ANCA (129,336) (Fig. 10.37).

Acute or chronic lesions are observed. Acute, or fresh, lesion consists of fibrinoid necrosis or intracapillary thrombosis confined to one or two glomerular lobules. Polymorphonuclear leukocytes and nuclear debris may be present. There is usually segmental hypercellularity in the affected segment, but it is not always present. Cellular crescent formation may be evident. The active segmental lesions are indistinguishable at the light microscopic level from other forms of focal segmental proliferative or necrotizing glomerulonephritis. A few authors have reported organisms in some of the involved segments (455), but this is very unusual. It is important to remember that even in the focal and segmental form of glomerulonephritis (by light microscopy), there are widespread (diffuse global) deposits throughout all glomeruli when they are studied by electron microscopy or immunofluorescence.

Chronic sclerotic lesions are usually situated at the periphery of one or several lobules. There is usually an adhesion or synchia between the sclerotic region and the Bowman capsule. There may be an adjacent fibrocellular crescent. Layers of fibrotic capsular bands encircling the involved glomerular tufts may be noted, but this is not a specific change. This advanced, or scarred, lesion is most common in those cases of longer duration and is the exclusive lesion found in Libman's healed, or bacterial-free, stage (477). The focal segmental sclerotic change may be difficult to distinguish from idiopathic focal segmental glomerulosclerosis (478).

The focal and segmental glomerular changes are evenly distributed throughout the kidney. Baehr (455) noted that in his patients, 2% to 75% of the glomeruli were involved. In more than 70% of patients, the segmental glomerular lesions affected from 10% to 40% of the glomeruli (455,464,479,480). Among 15 patients with focal and segmental glomerulonephritis in the series of Heptinstall (168), 15% or more of the glomeruli had lesions in 6 patients, 5% to 14% were affected in 7, and less than 4% were involved in 2. Villarreal and Sokoloff (206) described patients in whom more than 95% of glomeruli were affected. These authors noted the difficulty in distinguishing widespread glomerulonephritis caused by endocarditis from chronic glomerulonephritis when the lesions show evidence of "advanced healing." Acute diffuse endocapillary proliferative glomerulonephritis also may be encountered (456,459,461,462,479,481).

By light microscopy, it may be indistinguishable from typical PSAGN. There may be segmental necrosis, thrombosis, or sclerosis superimposed on the generalized hypercellularity (461,462). Crescents also may be present, but they are generally not so numerous as to warrant the designation of crescentic glomerulonephritis (146,461,471,482).

Baehr and Lande (479) have noted greater incidence of generalized diffuse glomerular changes in the so-called bacteria-free stage, and most of the patients studied by Gutman et al. (461) who had repeated negative results on blood cultures showed widespread glomerular involvement. However, diffuse glomerulonephritis can be seen in patients with positive blood cultures, and not all patients with negative cultures have the diffuse lesion. Bell (456) noted diffuse proliferative glomerular lesions in 65% of his patients. The exact incidence of this pattern is difficult to determine because most series are small and the large series are based on autopsy findings. Most studies were performed many years ago when the value of thin sections was not appreciated, and many of the sections shown in these articles were quite thick, thereby exaggerating the cellularity of the glomerular tufts. Marked focal segmental glomerular hypercellularity with closure of the capillaries may coexist with mild diffuse global hypercellularity (456,461,483).

Another glomerular pattern noted is membranoproliferative (mesangiocapillary) glomerulonephritis (484,485). Most of the older studies are not detailed, and it is not possible to determine the precise characteristics of the lesion. The finding of membranoproliferative pattern is not surprising, considering that it is one of the most commonly encountered lesions in patients with shunt nephritis, which also is caused by a nidus of persistent bacterial infection in contact with the circulation.

**INTERSTITIUM**

There is interstitial inflammation regardless of the type of glomerulonephritis, and it can be present even in treated patients with quiescent disease (146).

**TUBULES**

There is acute tubular injury and/or tubular atrophy commensurate with the degree of glomerular damage. Tubular casts (granular and red blood cell) are common.
ARTERIES
Arterial intimal thickening may be present (146). It may be noted in quite young individuals, and the cause is uncertain.

IMMUNOFLUORESCENCE MICROSCOPY
Immunofluorescence microscopy studies in both the focal and the diffuse forms of glomerulonephritis usually show widespread glomerular distribution of immunoglobulins and/or complement, even in the normal-appearing glomeruli. The glomerular staining is located in the mesangial regions and along the glomerular capillary walls. Morel-Maroger et al. (466) described a series of patients, most treated with antibiotics, and reported diffuse granular immunofluorescence along the glomerular capillaries for C3 and, in some patients, for IgG, IgM, and IgA in the mesangial regions. Other investigators have reported a granular pattern for immunoglobulins and C3 along the glomerular capillary walls (459,465) and in the mesangial regions (168,459) cite a case in which most glomeruli were normal by light microscopy although others showed segmental sclerosis. There was mesangial IgG, IgM, and C3, with less intense granular staining along the glomerular capillary walls. Immunofluorescence studies in the diffuse glomerulonephritic form, as noted, show diffuse granular deposition of immunoglobulins and C3 along the glomerular capillary walls and in the mesangial regions (461,462,486). Perez et al. (481) described granular deposition of IgM and C3 in the glomeruli in addition to bacterial antigen demonstrated by the corresponding antiserum. A recent case of proliferative glomerulonephritis with “full house” immunofluorescence in a patient with subacute endocarditis was reported from Taiwan. The patient did not have systemic lupus erythematosus and gradually recovered renal function following treatment with penicillin and gentamicin (487). Rarely, few or no immune complex deposits are seen. This is problematic in patients who are ANCA positive, because differentiation from ANCA-positive small-vessel vasculitis is difficult (336,472).

ELECTRON MICROSCOPY
Ultrastructural studies show discrete electron-dense deposits in the mesangial regions, often very near the endothelium of the glomerular capillary. Boulton-Jones et al. (459) and others (461) have reported glomerular subendothelial and mesangial deposits. Nast et al. (488) encountered immune complex deposits not only within glomeruli but also in the splenic venous sinus basement membranes, substantiating the systemic nature of the immune complex deposition in this disorder.

Etiology and Pathogenesis
Löhlein (476) was the first to describe the renal changes in this condition when he reported seven patients with endocarditis in some of whom organisms of the S. viridans group were cultured. He observed streptococci in an embolus in an artery that had led to infarction. This finding suggested to him that the glomerulonephritis was caused by bacterial emboli. This idea was further supported by Baehr (479,489), who noted bacterial emboli in the glomeruli in 5 of 25 patients. The segmentally scarred (sclerotic) lesion was thought to represent a later lesion resulting from healing of the necrotic lesion. Bell (456) considered that the acute glomerular lesion was an intracapillary thrombus that in the larger, but not the smaller, lesions led to necrosis of the glomerular capillaries. Thörig et al. (457) came to the same conclusion after induction of bacterial endocarditis by intravenous injection of live streptococci into rabbits with nonbacterial thrombotic endocarditis.

Longcope (175) suggested that the glomerulonephritic lesion was immunologic rather than infectious. Bell (456) did note in 1932 that “the fact that a certain duration of the infection is necessary suggests that immune bodies may play a role in the formation of the glomerular lesions.” It is now apparent that both focal and segmental glomerulonephritis and acute diffuse glomerulonephritis are manifestations of an immunologic reaction and that glomerular immune complexes or ANCA play the major role in the pathogenesis of glomerular injury. Bacterial cultures from kidneys show no growth. It is now recognized that focal glomerulonephritis can be seen in diseases in which there are no sources of emboli, such as systemic lupus erythematosus and microscopic polyangiitis. Patients with known true septic emboli do not generally have this type of glomerular response.

Williams and Kunkel (490) demonstrated depression in the level of serum complement in patients with subacute infective endocarditis. Subsequently, patients with focal or diffuse glomerulonephritis owing to infectious endocarditis also were noted to have hypocomplementemia (462,481,490). The degree of complement depression is directly correlated with the severity of renal involvement. Persistent hypocomplementemia is associated with a failure to control the infection and prevent continuing renal insufficiency (483), whereas normalization of the serum complement takes place with successful antibiotic therapy and the return of renal function (463).

Circulating immune complexes have been found in patients with infectious endocarditis (458,459,462,490). High levels of circulating immune complexes have been noted in patients with less virulent bacteria, right-sided cardiac involvement, and hypocomplementemia. Many of these patients also had extracardiac manifestations of endocarditis (458,460). Circulating immune complexes are persistent or rise when it is not possible to control the infection (460,461,486). Successful antibiotic therapy leads to falling levels of circulating immune complexes (458). Rheumatoid factor also may be present (470), and the titer falls quickly after successful antibiotic therapy (470).

Mixed cryoglobulinemia has been identified in the serum of most patients with infectious endocarditis (460). The levels of cryoglobulinemia (like the levels of rheumatoid factor and circulating immune complexes) fall with control of the infection (460). However, the level of serum cryoglobulinemia (and rheumatoid factor) is not directly correlated with the presence or absence of renal involvement (460).

Some studies have shown that the eluate from a kidney with focal glomerulonephritis caused by infectious endocarditis reacted specifically with bacteria cultured from the patient’s blood (465,488). Immunofluorescence studies have demonstrated bacterial antigens in glomerular deposits in endocarditis owing to streptococcal infection (481). It is uncertain, however, whether the glomerular deposits form locally, with the binding of circulating antibodies to planted (possibly bacterial) or native glomerular antigens, or result from the deposition of circulating immune complexes. In summary, in patients with subacute bacterial endocarditis, there is much evidence in support of an immune complex pathogenesis of glomerulonephritis with glomerular immunoglobulin and complement deposits. ANCA may have a pathogenic role in patients with a
paucity of immunoglobulin and complement in glomeruli and circulating ANCA.

**Effect of Treatment on Renal Lesions**

Most studies indicate that there is partial to total resolution of the renal disease after successful antibiotic therapy (467); however, repeated biopsies are generally not performed. Treatment with antibiotics alone has resulted in renal recovery with loss of proteinuria, circulating immune complexes, and cryoglobulinemia (482). Observations on the incidence of glomerulonephritis in the early years of antibiotic therapy are few and contradictory. Spain and King (468) studied 77 patients with subacute bacterial endocarditis: 52 were not treated, whereas 25 were given penicillin, with treatment starting on average within 1 to 2 months after the clinical onset of the disease. The incidence of focal glomerulonephritis was reduced by half. Diffuse glomerulonephritis was noted in a third of untreated patients, but no case of diffuse glomerulonephritis was noted in the treated patients. Great numbers of sclerotic or healed lesions were identified in the treated group. The efficacy of antibiotic treatment with regard to glomerular damage is, therefore, apparent and has been confirmed by others (146,438,477,482).

**Glomerulonephritis in Acute Infective Endocarditis**

Antibiotic therapy and prophylaxis, the decline in rheumatic fever, and the marked increase in intravenous drug abuse have all altered the picture of infective endocarditis (483). The routes of infection, types of organisms, and clinical manifestations have undergone major changes. Although the frequency of infection with organisms of the *S. viridans* group has diminished (468), *S. aureus* has become a major cause of bacterial endocarditis (336,483). Infection with this organism has a strong likelihood of causing glomerulonephritis, especially in patients who are intravenous drug abusers. *S. aureus* is the etiologic agent in more than a third of the fatal cases and is responsible for more than half the cases of all types of endocarditis-associated glomerulonephritis in recent series (336,460,463,483). Glomerulonephritis may develop in intravenous drug abusers with *S. aureus* infections following a clinical illness of only 1 week (463). More recently, other microorganisms, including *B. henselae* (373) and *Enterococcus*, have been reported in association with glomerulonephritis (470). With the growing prevalence of intravenous drug abuse, right-sided endocarditis is becoming more common. In fact, in a recent series from referral centers in Little Rock, Arkansas, and the Mayo Clinic, 28% of patients with endocarditis-related glomerulonephritis had tricuspid valve involvement (336).

Irrespective of the infecting organism, glomerulonephritis is uncommon in patients with acute bacterial endocarditis when it is defined as infective endocarditis lasting less than 6 weeks. However, a study by Neugarten et al. (483), conducted at a large metropolitan hospital from 1965 to 1979, found glomerulonephritis in 22% of patients with infective (mostly acute bacterial) endocarditis. Glomerulonephritis was focal in 8% and diffuse in 14% of patients. Before the advent of antibiotics, glomerulonephritis appeared to occur less frequently in cases of acute than in those of subacute bacterial endocarditis (455,456,464,479,480,483). Bell, earlier on (456), noted an incidence of 7% for focal glomerulonephritis in patients with what he termed the primary acute form (i.e., those forms that seemed to begin as a bacteremia) and of 6% in patients with the secondary acute form (his expression for those patients in whom bloodstream bacterial invasion comes from a known focus, such as acute endocarditis or lobar pneumonia). The incidence of focal glomerulonephritis in the subacute form was 53%. Bell (456) found diffuse proliferative or exudative glomerulonephritis in 29% and 33% of patients with primary and secondary acute forms, respectively. Patients with infections caused by organisms of the *S. viridans* group of less than 6 weeks’ duration did not have focal glomerulonephritis. The experiences of other workers are similar (168).

The combination of acute infective endocarditis and diffuse glomerulonephritis is usually the result of infection by coagulase-positive staphylococci (*S. aureus*). Largely as a result of drug addiction, however, other organisms are being seen more frequently. They include coagulase-negative staphylococci (*S. epidermidis* and *Pseudomonas aeruginosa*). A wide range of other bacterial and fungal organisms has been found in those patients. Pulmonary hemorrhage as an initial symptom (at first clinically confused with Goodpasture syndrome) has been reported (490). A study from Birmingham, England, examined 20 renal biopsy specimens and 42 autopsy specimens from patients with endocarditis (470). Interestingly, only 9 patients in the renal biopsy group had acute glomerulonephritis and, according to those authors, 6 of them did not have immune complex deposits, but only crescent formation and necrosis (a pauci-immune pattern). The second most common morphologic pattern in the renal biopsies was acute interstitial nephritis. The most common findings in the autopsy material were localized infarction (19 cases), acute tubular damage (8 cases), glomerulonephritis (7 cases), and cortical necrosis (6 cases). Unfortunately, the morphologic description of the biopsies and of the autopsy specimens is not detailed, and no ultrastructural studies were performed (470). In the section on subacute endocarditis, we briefly addressed the diagnostic challenge in patients with pauci-immune crescentic glomerulonephritis related to endocarditis (336,472). Several of those patients are ANCA positive, and they can be misdiagnosed with small vessel vasculitis. Treating a patient with infectious endocarditis with immunosuppressive medications can have disastrous consequences.

**Clinical Presentation**

Diffuse proliferative glomerulonephritis is well documented in patients with acute endocarditis caused by coagulase-positive staphylococci (*S. aureus*) (461,490–493). The clinical picture may be dominated by the underlying infectious process, but oliguria may herald the onset of renal involvement. There is often a nephritic process with red blood cells and casts in the urine. Gross hematuria may stem from glomerulonephritis, renal infarction, or drug-related interstitial nephritis. Proteinuria is also often noted, but the nephrotic syndrome is unusual (438,490). Most of the patients have been intravenous drug abusers with *S. aureus* infections. The BUN level is often elevated, and the serum complement level is diminished (461,493). Hypertension is unusual; when it is found, it may have been present before the acute onset of infective endocarditis (485,493).

These laboratory findings may show considerable resolution or improvement (within days to weeks) after the institution
of antibiotic therapy. Renal insufficiency may be relatively mild or may lead to the need for dialysis (483). The degree of renal insufficiency does not correlate with the clinical duration of infective endocarditis. In most patients, the serum creatinine level reaches its peak at or just into the beginning of successful antibiotic therapy and soon declines with therapy. Patients who show signs of renal failure fare less well than those in whom it is absent (483). One group (494) has suggested that addition of plasmapheresis and steroids aids in renal recovery, but additional studies are needed to confirm these findings. The problem of ANCA positivity (usually antiproteinase 3) can provide a differential diagnostic dilemma. The prevalence of ANCA in patients with infective endocarditis is unknown, but it is very well documented (336,472–474). In patients with infectious endocarditis, in addition to ANCA, other autoantibodies, such as rheumatoid factor, cryoglobulins, ANA, and anticardiolipin antibodies, may be observed (472).

Although a transient worsening of renal function may occur before recovery (495), mild to moderate renal insufficiency almost always resolves with proper antibiotic therapy (461,495). Even severe renal failure may heal with antibiotic therapy, although it may take weeks or months to achieve (37). Subsequent biopsies have shown almost complete morphologic resolution in those patients with clinical recovery; the only renal parenchymal changes noted were persistence of mesangial sclerosis and the presence of globally sclerotic glomeruli.

Occasionally, renal insufficiency may persist despite proper antibiotic therapy and dialysis (459). Marked residual morphologic changes have been noted long after apparent cure (459). Progressive renal failure and uremic deaths have been reported occasionally even today, when antibiotics are commonly administered (459,483). This is not a typical outcome, and once infectious endocarditis has been effectively treated, complete renal healing should take place. There may be persistent proteinuria or hematuria in some patients despite effective therapy (146,483). Some ANCA-positive patients are given immunosuppressive therapy. In our opinion, this should be avoided or done very carefully. Uh et al. (475) reviewed the literature and found that two of six ANCA-positive patients with subacute bacterial endocarditis who were immunosuppressed died.

Pathologic Findings

**Light Microscopy**

Acute diffuse proliferative glomerulonephritis is the pattern of injury observed most often with acute bacterial endocarditis. The light microscopic features of acute diffuse proliferative glomerulonephritis are a proliferation of endocapillary cells as well as an infiltration by mononuclear and polymorphonuclear leukocytes (Fig. 10.38). Crescents are often evident, but they usually affect less than 50% of glomeruli (Fig. 10.39). The light microscopic changes closely resemble those already described in patients with acute postinfectious (poststreptococcal) glomerulonephritis.

**Immunofluorescence Microscopy**

Immunofluorescence methods show granular deposits of IgG and C3 along the glomerular capillary walls and, often, in the mesangial regions (455,491–493). In *staphylococcus* infection–induced endocarditis, IgA staining may also be seen. Sometimes, the mesangium is predominantly involved, with less conspicuous deposits along the capillary walls (461,493). Immunofluorescence studies have confirmed the presence of bacterial antigens in the glomerular deposits in patients with infective endocarditis owing to *S. aureus* (491,493); staphylococcal antigens were also demonstrated along TBM in some patients (491). As pointed out, a proportion of patients have few or no glomerular immune complex deposits.

**Electron Microscopy**

Ultrastructural studies always show discrete electron-dense glomerular deposits, and subepithelial (including humps) and intramembranous deposits are the most common (483,484, 491–493) (Fig. 10.40). Glomerular subendothelial deposits...
Etiology and Pathogenesis

Immunofluorescence and electron microscopic findings, along with the depression of serum C3, suggest an immune complex etiologic source and pathogenesis. The continued antigenemia with the depression of serum C3, suggest an immune complex probably provides a propitious background for the development of these immune complexes. Most of the cases of infective endocarditis now seen stem from drug addiction (455,492). In some of these studies (461), glomerular subepithelial humps did not disappear on subsequent biopsy as they do in classic PSAGN. The persistence of these humps suggests either that immune complexes containing staphylococcal antigens disappear more slowly than those of streptococcal origin or that the source of the antigen has not been completely eliminated.

GLOMERULONEPHRITIS WITH INFECTED VENTRICULOATRIAL SHUNTS AND CENTRAL VENOUS CATHETERS

Infection of ventriculoatrial shunts (inserted for the relief of hydrocephalus) may lead to glomerulonephritis (375–379, 489,497–510). This finding was first described by Black et al. (498) in two children with the nephrotic syndrome and gross hematuria in whom bacterial colonization of a ventriculoatrial shunt had developed. The infecting organism is usually a coagulase-negative staphylococcus (S. epidermidis) that has been introduced either intraoperatively, probably from a skin source, or as a result of transient bacteremia to which the shunt is exposed. S. epidermidis accounts for approximately 75% of shunt infections (505). The exact way in which the shunt becomes infected is not clear (377,497). Coagulase-negative staphylococcus sometimes forms a biofilm around the catheter tips in vivo, which is thought to shield the organism from the effects of antibiotics (378). Other reported organisms include Listeria monocytogenes (503), peptococcus (509), Corynebacterium bovis, Bacillus subtilis, micrococcus, diphtheroid species, and gram-positive anaerobic rods, such as Propionibacterium acnes (375–379,505–507,511).

Between 6% and 27% of ventriculoatrial shunts have evidence of bacterial colonization (375,509), and low-grade bacteremia may persist for years before the onset of clinical symptoms (497). Cultures of the blood and cerebrospinal fluid may be sterile, and bacterial identification may be achieved only on removal of the shunt (497). Clinically overt glomerulonephritis occurs in approximately 4% to 5% of infected patients (377). The true incidence is not known and would require prospective urinalysis to identify patients with subclinical renal involvement. The latent period between shunt placement and the onset of clinical symptoms ranges from 1 month to 15 years (mean, 4 years). Renal involvement is noted almost exclusively in patients with ventriculoatrial or
ventriculojugular shunts. Renal symptoms in patients with ventriculoperitoneal shunts are uncommon, but they have been reported and are similar to those seen with ventriculoatrial shunts (499,511,512). Ventriculoatrial shunts have been almost totally replaced by ventriculoperitoneal shunts as a form of therapy for hydrocephalus.

Although shunt nephritis is becoming a rare diagnosis, we encounter occasional patients with glomerulonephritis associated with infected central venous catheters (513–515). Although the published cases are still limited, this glomerulonephritis appears very similar to shunt nephritis. The most common pathogen is *S. epidermidis*, colonized to the central venous catheters. Patients have symptoms of acute glomerulonephritis with low serum complement (C3) levels. The morphologic findings are those of an immune complex glomerulonephritis with an MPGN pattern with C3 containing mesangial and glomerular capillary deposits with or without IgG and IgM. Crescents may occur (see below) (513–515).

**Clinical Presentation**

The clinical features include anorexia, anemia, malaise, and fever (all probably the result of the bacteremia). Fever is noted in more than four fifths of patients. Most of the patients are children, although cases among adults have been reported (age ranges from 2 months to older than 50 years). Patients usually show signs and symptoms of bacteremia and sepsis, although renal involvement may be the first manifestation (375). Serum C3 levels are low in 85% to 94% of patients (505). Purpura, arthralgias, lymphadenopathy, hepatosplenomegaly, hypergammaglobulinemia (IgA, IgM, and IgG), and anemia are common. Less common manifestations are leukocytosis, leukopenia (499), thrombocytopenia (502,516), elevation of the erythrocyte sedimentation rate (375), cryoglobulinemia, and hypertension. Just like patients with infectious endocarditis-associated glomerulonephritis, some patients with shunt nephritis may be positive for ANCA (anti–proteinase 3 antibodies) (511). Renal findings include edema, hematuria (gross in half of patients), and proteinuria (375,489,500–504,509,512,517,518). The proteinuria may be pronounced, and the nephrotic syndrome has been described in about half of patients. One patient even had 38 g of proteinuria per 24 hours (504). Acute oliguric renal failure has been noted (509). Apparent recovery takes place in most patients whose infected shunts or central venous catheters are removed (375,497,499,502,504,505,513–515), although there may be persistent proteinuria or hematuria (499,505). Death may result from complications following removal of the shunt or from the original neurologic disease for which the shunt was inserted (502).

**Pathologic Findings**

**Light Microscopy**

Renal biopsies typically show evidence of diffuse proliferative glomerulonephritis or the pattern of MPGN (Fig. 10.41) (501,503,505,509,519). Polymorphonuclear leukocytes are often present within glomeruli. There is typically an increase in the amount of mesangial matrix (498,499,504), and one reported case was referred to as lobular glomerulonephritis (499). There is almost always accentuation of the lobular pattern. Crescents may be present (499,501,514). A membranoproliferative glomerulonephritic pattern is found in approximately one half of patients, diffuse (nonlobular) proliferative glomerulonephritis in about one third, and pure mesangial proliferative glomerulonephropathy in the remainder. Focal segmental proliferative glomerulonephritis and crescentic glomerulonephritis have been noted, but less commonly (497).

**Immunofluorescence Microscopy**

Immunofluorescence shows a granular to coarse broken linear pattern along the glomerular capillary walls and in the mesangial regions (497–499,501,503,504,509). Peripheral glomerular capillary wall immunofluorescent deposits are noted in more than four fifths of patients, whereas mesangial deposits are seen in slightly more than one half. IgG, IgM, C3, and the early complement components (C1q and C4) are present. IgG is found in about two thirds of patients (497), but IgM is sometimes the predominant immunoglobulin (377,499,520). It was found in 84% of patients in one study (497). IgA, usually less intense than IgG or IgM, is present in less than one half of cases (497). Bacterial antigens have been demonstrated (377,499,520). IgM and C1q have been described in peritubular capillaries (499), and immune complexes have been found along the TBM.

**Electron Microscopy**

Ultrastructural studies demonstrate discrete electron-dense immune-type deposits on the subendothelial portions of the glomerular capillary walls and in the mesangial regions (499,501,503,504). Glomerular intramembranous and subepithelial deposits also have been detected, but they are rare (497,509). Increased mesangial matrix and circumferential mesangial cell interposition with creation of a new inner basement membrane–like material also can be identified. Subsequent renal biopsy, after successful treatment, reveals complete disappearance of the deposits found by electron microscopy and immunofluorescence techniques (518).

**Etiology and Pathogenesis**

There is evidence that the renal disease is caused by immune complex deposition. As noted previously in the case of other infectious diseases, there is frequently a depression of the serum complement level (375,499,503,504). Decreases in serum C3
levels are noted in more than 85% of patients (505). Half of patients with acute glomerulonephritis have reduced levels of C4, indicative of activation of the classic complement pathway. Evidence of activation of the alternative pathway is noted in only a few patients (499,503,516). Patients with shunt infections without glomerulonephritis do not have hypocomplementemia. Serum levels of C3 and C4 generally normalize after effective therapy (i.e., antibiotic therapy or shunt removal) (497,516). If therapy is inadequate and the glomerulonephritis persists, the serum complement level remains depressed (516).

Cryoglobulinemia has also been noted (503,509). Cryoglobulins are able to activate the classic complement pathway in vitro (503). Circulating immune complexes and rheumatoid factors are found in most patients (521). Circulating immune complexes, serum cryoglobulins, and serial titers of antibody to bacterial antigen all abate with removal of the shunt, control of the infection, and remission of the glomerulonephritic process (522). IgG, IgM, and C3 are present in the cryoglobulins, and there was evidence in one study of the presence of both antibody to the bacterial organism and the bacterial antigen (503).

**Clinical Course and Outcome**

Serial renal biopsies have been performed before and after removal of the shunt; complete resolution of the glomerulonephritic process has been confirmed (518). The only residual may be mild mesangial hypercellularity (523) or focal global glomerular sclerosis (523). In most patients, the immunofluorescent and electron microscopic deposits completely disappear (504,523). However, disease in patients in whom crescentic glomerulonephritis develops may not resolve despite adequate therapy (523,524). Occasionally, patients with underlying MPGN with crescent formation may also show a steady decline (514,524). Full clinical recovery with normalization of the serum and urine abnormalities is noted in about two thirds of patients, sometimes within a month or two (519); renal disease persists in the remaining third, as manifested by proteinuria, microhematuria, hypertension, or renal insufficiency. Rarely, complete clinical recovery can take place after several months of proteinuria or hematuria (485). Delay in diagnosis and treatment may prevent complete recovery (500) and lead to irreversible renal insufficiency (489).

The glomerulonephritic process may develop as long as 5 years after the apparent colonization of a shunt and the onset of low-grade bacteremia (498,502,509,522). In some of these reports, culture of the blood and of cerebrospinal fluid obtained from the shunt was found to be sterile, and identification of a bacterial infection was possible only on removal of the shunt or central venous catheter (497,513); in other cases, the organism was erroneously regarded as a contaminant (375) or the infection was thought to have been controlled by antibiotic therapy (502). If the shunt infection is not treated properly and the bacteria persist, mild renal involvement may progress to severe renal impairment (501,523). Later renal biopsies in these cases have shown an increase in glomerular tuft hypercellularity, crescent formation, sclerotic glomeruli, and the number of glomerular electron-dense deposits (501). As noted earlier, eradication of the bacteremia (usually by removal of the shunt or the catheter) leads to subsidence of the glomerulonephritis. Although removal of the shunt or catheter is almost always needed to permanently eliminate the infection (497,501), remission of bacteremia and kidney disease has been achieved by antibiotic therapy alone (377,504).

In summary, infected ventriculoatrial shunts and central venous catheters may lead to immune complex glomerulonephritis with the morphologic pattern of type I MPGN, although other phenotypes of immune complex glomerulonephritis are seen less frequently. It is of considerable interest that there can be complete clinical cure following eradication of shunt infection. In contrast, most patients with the idiopathic form of type I MPGN progress inexorably toward ESRD (525–528).

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