

*Medical Progress***GLOMERULONEPHRITIS**DONALD E. HRICK, M.D., MOONJA CHUNG-PARK, M.D.,
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DISEASES involving the renal glomeruli are encountered frequently in clinical practice and are the most common causes of end-stage renal disease worldwide. In the United States alone, glomerular diseases accounted for 51 percent of the 305,876 cases of treated end-stage renal disease that were reported to the U.S. Renal Data System between 1991 and 1995, including 115,938 cases of diabetic nephropathy (37.9 percent) and 41,333 cases of nondiabetic glomerular disease (13.5 percent).¹ Some common glomerular diseases do not cause progressive renal failure but are important causes of morbidity and sources of considerable medical expense.

Glomerulonephritis is defined here as a disease characterized by intraglomerular inflammation and cellular proliferation associated with hematuria. This definition excludes several important nonproliferative or sclerosing glomerulopathies such as membranous glomerulopathy, focal segmental glomerulosclerosis, and diabetic nephropathy (Table 1). Hematuria in patients with glomerulonephritis is typified by the presence of dysmorphic red cells² or red-cell casts in the urine, findings that differentiate hematuria of glomerular origin from extraglomerular bleeding. However, the presence of urinary red-cell casts or dysmorphic red cells cannot be used to discriminate proliferative from nonproliferative glomerulopathies. Patients with glomerulonephritis generally present with one of five clinical syndromes: asymptomatic hematuria, acute glomerulonephritis, rapidly progressive glomerulonephritis, the nephrotic syndrome, or chronic glomerulonephritis. Recognizing that there

is considerable overlap in the clinical presentation of each of the diseases to be discussed, we will review the pathophysiology, natural history, and treatment of the forms of glomerulonephritis that are commonly or prototypically associated with these five syndromes.

MECHANISMS OF GLOMERULAR INFLAMMATION

Both humoral and cell-mediated immune mechanisms play a part in the pathogenesis of glomerular inflammation (Fig. 1).³ Two basic mechanisms of antibody-mediated glomerular injury have been identified. First, antibodies can bind either to a structural component of the glomerulus or to material that is not intrinsic to the glomerulus but is there because of its physicochemical characteristics. The best example of a structural nephritogenic antigen is the Goodpasture autoantigen, which has been identified in glomerular basement membrane as two discontinuous epitopes within the noncollagenous domain of the $\alpha 3$ chain of type IV collagen.⁴ In patients with systemic lupus erythematosus, histone-DNA complexes, which can bind to glomerular cell surfaces and basement membrane, are examples of "planted" antigens that could be a target of anti-DNA antibodies.⁵ Second, circulating antigen-antibody complexes form, escape clearance by the reticuloendothelial system, and are deposited in the glomerulus. A number of exogenous and endogenous antigens have been identified in circulating immune complexes and implicated in the pathogenesis of human glomerulonephritis.⁶

Several studies have suggested that the activation of cell-mediated immunity can also induce glomerular injury. First, adoptive transfer of sensitized T lymphocytes to rats treated with subnephritogenic doses of antibody results in glomerular hypercellularity due to the proliferation of resident glomerular cells and an influx of mononuclear leukocytes.⁷ Second, in chickens unable to mount an antibody response because of chemical bursectomy, severe proliferative nephritis develops after immunization with glomerular basement membrane.⁸ Finally, granulomatous nephritis induced by a hapten can be reproduced in previously unexposed recipients by adoptive transfer of T cells but not by passive administration of antibody.⁹ In humans, T cells have been identified in both proliferative and nonproliferative glomerulopathies.¹⁰ Treatment with cyclosporine, an inhibitor of T-cell function, is effective for some glomerular diseases, suggesting that the experimental findings also apply to glomerular injury in humans.¹¹

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TABLE 1. CLASSIFICATION OF GLOMERULAR DISEASES ACCORDING TO THE PRESENCE OR ABSENCE OF PROLIFERATIVE CHANGES.

TYPE OF DISORDER	PROLIFERATIVE CHANGES	NO PROLIFERATIVE CHANGES
Primary renal disorder	IgA nephropathy	Focal segmental glomerulosclerosis
	IgM nephropathy	Membranous glomerulopathy
	Other mesangioproliferative glomerulonephritides	Minimal-change disease
	Crescentic glomerulonephritis	Thin basement membrane disease
	With immune deposits	
	Pauci-immune	
	Membranoproliferative glomerulonephritis	
Secondary disorder	Lupus nephritis	Diabetic nephropathy
	Postinfectious glomerulonephritis	Amyloidosis
	Glomerulonephritis related to hepatitis B or C	Light-chain nephropathy
	Systemic vasculitides	Human immunodeficiency virus nephropathy
	Wegener's granulomatosis	Alport's syndrome
	Polyarteritis nodosa	Drug-induced glomerulopathies
	Henoch-Schönlein purpura	
	Idiopathic	

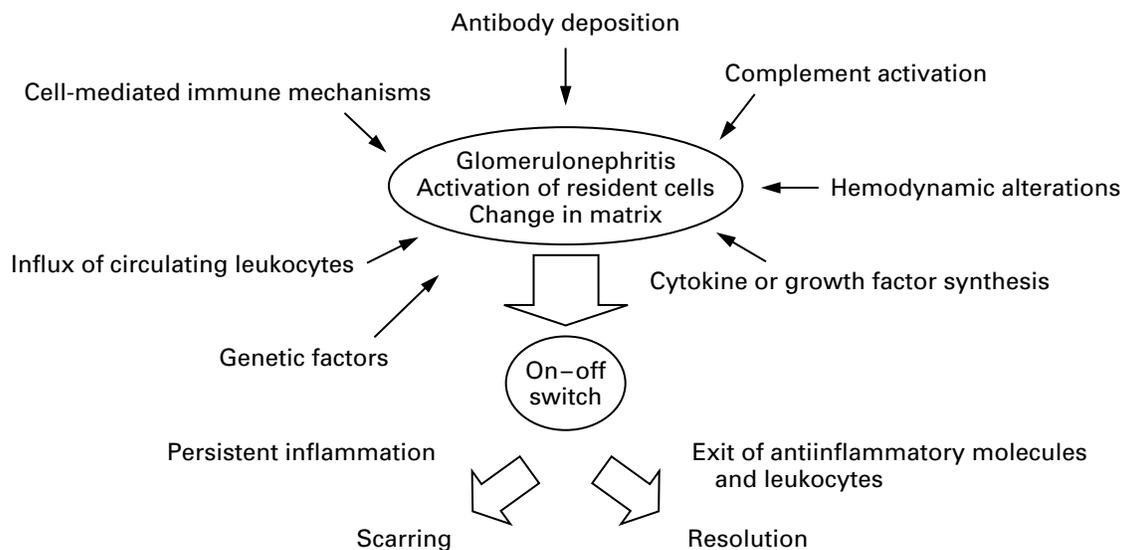


Figure 1. Mechanisms of Glomerulonephritis.

A number of pathogenetic processes have been implicated in the induction, resolution, and progression of glomerular inflammation. Antibody deposition has been the most thoroughly studied of these processes, but other mechanisms of tissue injury clearly cause glomerular injury. The mechanisms that control whether there is progression to scarring or resolution with maintenance of glomerular function (the “on-off switch”) remain unclear. The elucidation of these regulatory processes may lead to more specific and efficacious therapy.

After the initiation of glomerular injury, a number of proinflammatory mediator pathways are activated in both infiltrating cells and resident glomerular cells.³ Complement activation, influx of circulating leukocytes, cytokine synthesis, release of proteolytic enzymes, activation of the coagulation cascade, and generation of proinflammatory lipid mediators have

been demonstrated in experimental glomerulonephritis and, to a more limited degree, in human disease.^{12,13} Resident cells within the kidney become activated after injury and participate in subsequent destructive and restorative processes.¹³⁻¹⁵ In addition, the amount and composition of extracellular matrix are modified.¹³ Matrix remodeling in response to in-

jury generates signals that are different from those transmitted by normal glomerular matrix and may facilitate the activation and proliferation of both resident and infiltrating glomerular cells.

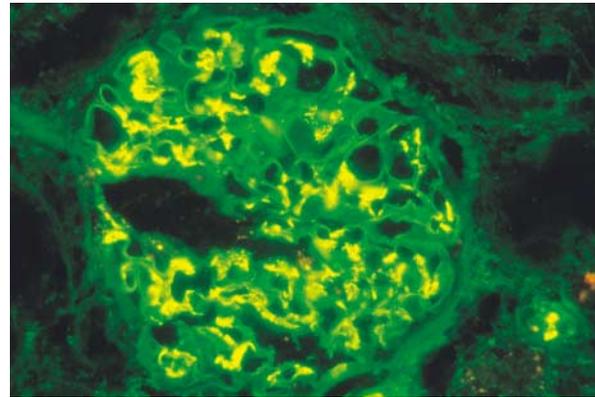
Other processes control the amplification, progression, or resolution of glomerulonephritis. Adaptive hemodynamic alterations in the remaining functional glomeruli cause hyperfiltration, intraglomerular hypertension, and abnormal intravascular stress and shear. These altered physical forces can exacerbate ongoing glomerular injury.^{13,16} Depending on the cells affected, apoptosis, or programmed cell death, may have a crucial role either in the resolution of glomerulonephritis or in glomerular scarring.¹⁷

CLINICAL SYNDROMES

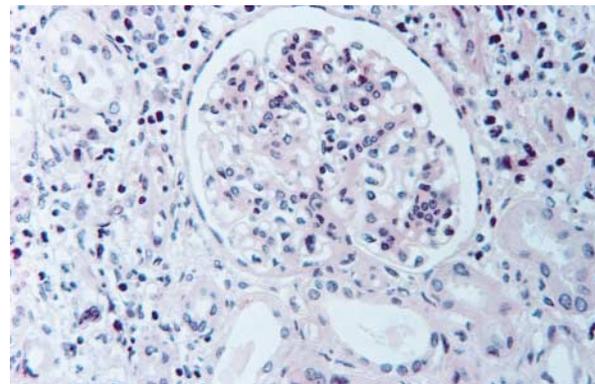
Asymptomatic Hematuria

Asymptomatic hematuria refers to either macroscopically or microscopically detected blood in the urine of patients who have normal glomerular filtration rates and no evidence of a systemic disease known to affect the kidneys. The differential diagnosis of asymptomatic hematuria includes a large number of urologic conditions beyond the scope of this review. Many, but not all, patients with asymptomatic hematuria resulting from glomerulonephritis also have proteinuria (urinary protein excretion is usually less than 1.5 g per day). Renal biopsies in such patients most commonly show one of two patterns of proliferative inflammation: focal proliferative glomerulonephritis, in which less than 50 percent of glomeruli have increased numbers of mesangial, endothelial, or epithelial cells, or mesangioproliferative glomerulonephritis, either focal or diffuse (involving 50 percent or more of glomeruli), in which mesangial-cell proliferation is the dominant abnormality.

IgA nephropathy, an example of mesangioproliferative glomerulonephritis, is the most common form of glomerulonephritis worldwide¹⁸ and a common cause of asymptomatic hematuria. The pathological hallmark of primary IgA nephropathy is the demonstration by immunofluorescence microscopy of mesangial deposition of IgA (Fig. 2A) in association with various degrees of mesangial-cell proliferation and expansion of mesangial matrix on light microscopy¹⁹ (Fig. 2B). The morphologic appearance of the glomerulonephritis associated with Henoch–Schönlein purpura is so similar to that of primary IgA nephropathy that these disorders often are considered to be related components of a pathophysiologic spectrum. The prevalence of IgA nephropathy varies considerably between and within countries, with high rates in the western Pacific Rim and relatively low rates in the United States and Europe.²⁰ Geographic variations in prevalence may reflect differences in national health screening practices or local indications for renal biopsy. IgA nephropathy occurs in all age groups, with a peak incidence in the sec-



A



B

Figure 2. IgA Nephropathy.

In Panel A, immunofluorescence microscopy reveals mesangial IgA in a 23-year-old man with recurrent hematuria ($\times 320$). In Panel B, light microscopy shows moderate expansion of the mesangial matrix with mild hypercellularity in the same patient (hematoxylin and eosin, $\times 156$).

ond and third decades.¹⁹ The disease is uncommon in blacks.²⁰⁻²² Most studies indicate a male predominance of at least 2:1.^{20,23}

Several lines of evidence indicate that IgA nephropathy results from altered regulation of the production or structure of IgA. The common association of gross hematuria with infections of the respiratory or gastrointestinal tract suggests that abnormal production of IgA is triggered by exposure of the mucosa to exogenous antigens. Plasma concentrations of IgA are elevated in up to 50 percent of patients with IgA nephropathy.²⁴ In vitro studies indicate that the production of IgA and other immunoglobulins by the B lymphocytes is increased in patients with this disorder.^{25,26} Circulating IgA immune complexes are detectable in many patients, and their levels roughly parallel the severity of the disease.²⁷ Glomerular immune deposits in patients with IgA nephropathy consist primarily of polymeric forms of the isotype subclass IgA1²⁸ that are aberrantly gly-

cosylated.²⁹ Abnormal glycosylation of IgA allows IgA immune complexes to escape clearance by asialoglycoprotein receptors expressed in the reticuloendothelial system³⁰ and may promote the deposition of IgA in glomeruli. Deposits of IgG or IgM are also present in the majority of patients, with isolated deposition of IgA occurring in only 15 percent of patients.¹⁹ C3 and terminal complement components are nearly always present, whereas C1 and C4 are uncommon,^{19,31} suggesting that IgA-mediated activation of the alternative complement pathway may be important in the pathogenesis of this form of mesangioproliferative glomerulonephritis. Because hypocomplementemia is typically not observed in IgA nephropathy, it is probable that complement activation occurs in the kidney and not systemically.

The most common clinical presentation of IgA nephropathy (occurring in 50 to 60 percent of cases) consists of episodic gross hematuria, frequently in association with a simultaneous respiratory or gastrointestinal tract infection.^{19,20} In this clinical presentation, most often observed in male patients under the age of 25 years, proteinuria tends to be minimal. Persistent microscopic hematuria, typically discovered on routine or screening urinalysis and associated with various degrees of concomitant proteinuria, occurs in 30 percent of cases and is the more common clinical presentation in patients of either sex who are over the age of 25.^{19,20} Finally, 10 percent of patients present with either acute glomerulonephritis or the nephrotic syndrome (see below). Although patients with IgA nephropathy commonly present with asymptomatic, or benign, hematuria, end-stage renal disease ultimately develops in 20 to 40 percent 5 to 25 years after diagnosis.^{18,32,33} Risk factors for progression to end-stage renal disease include older age, male sex, hypertension, persistent proteinuria, impaired renal function at the time of diagnosis, the absence of macroscopic hematuria, and the presence of glomerulosclerosis or interstitial fibrosis on renal biopsy.³²⁻³⁴

Although curative therapy for IgA nephropathy is lacking, a variety of therapies have been used in an attempt to retard the progression of this disease in patients deemed to be at high risk for end-stage renal disease. Trials of glucocorticoids with or without adjunctive cytotoxic agents have yielded mixed results. A meta-analysis of randomized, controlled trials of such agents concluded that they reduce urinary protein excretion in patients presenting with severe proteinuria,³⁵ but whether the drugs beneficially influence long-term renal function remains unclear. On the basis of the premise that n-3 fatty acids may limit the production or actions of cytokines and eicosanoids induced by the glomerular deposition of IgA, fish oil has been prescribed, with some benefit, in randomized trials.^{36,37} In one multicenter study, serum creatinine concentrations doubled with-

in four years in 6 percent of patients treated with fish oil, as compared with 33 percent of patients given placebo.³⁷

Angiotensin-converting-enzyme inhibitors have proved to be more effective than other antihypertensive agents in delaying the progression of renal failure and reducing proteinuria in patients with IgA nephropathy³⁸; these drugs may be particularly beneficial in patients who are homozygous for the deletion polymorphism of angiotensin-converting enzyme.³⁹ Several other treatments, including phenytoin, antiplatelet agents, urokinase, dapsone, plasma exchange,⁴⁰ tonsillectomy,⁴¹ and high-dose immune globulin therapy,⁴² have been attempted without conclusive results.

Acute Glomerulonephritis

Acute glomerulonephritis is a syndrome characterized by the abrupt onset of macroscopic hematuria; oliguria; acute renal failure, manifested by a sudden decrease in the glomerular filtration rate; and fluid retention, manifested by edema and hypertension. Urinary protein excretion varies widely in this syndrome, but the rate is generally less than 3 g of protein per day. Edema probably results from renal sodium retention caused by the sudden decrease in the glomerular filtration rate, rather than occurring as a consequence of hypoalbuminemia.

Poststreptococcal glomerulonephritis usually presents with the features of acute glomerulonephritis and is representative of a larger group of postinfectious glomerulonephritides in which acute glomerular injury results from immune events triggered by a variety of bacterial, viral, and protozoal infections. Poststreptococcal glomerulonephritis predominantly affects children between the ages of 2 and 10 years, with a slight predominance of males; fewer than 5 percent of patients are under 2 years of age, and fewer than 10 percent are over the age of 40 years.^{43,44} Only certain nephritogenic strains of streptococci have been associated with poststreptococcal glomerulonephritis. The more common sporadic variety of poststreptococcal glomerulonephritis usually follows type 12 streptococcal infection of the pharynx.⁴⁴ Epidemics of the disorder have been linked to several strains causing either throat or skin infections.⁴⁵

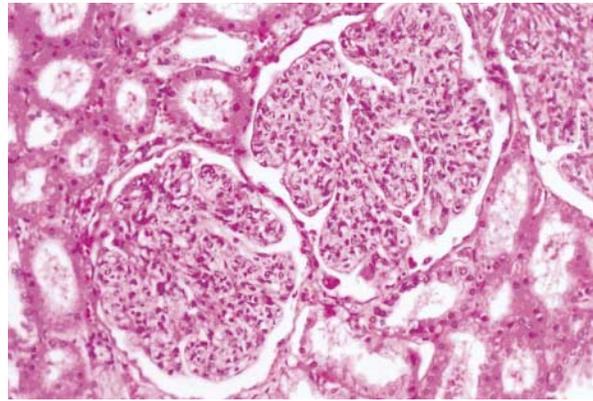
The mechanisms of renal injury in poststreptococcal glomerulonephritis have not been delineated completely. Deposits of IgG and C3 are regularly found within glomeruli and suggest that immune-complex formation is involved. However, it remains unclear whether the associated inflammation is mediated by circulating immune complexes, complexes formed *in situ*, or both.⁴⁶ Recent evidence has been found to support the notion that one or more streptococcal antigens with an affinity for glomerular structures are "planted" in the glomerulus during the

early phase of streptococcal infection, followed 10 to 14 days later by a host immune response in which antibody attaches to the antigen.⁴⁷ The most plausible candidate antigens include endostreptosin,⁴⁸ nephritic strain-associated protein (which exhibits streptokinase activity),⁴⁹ and nephritis plasmin-binding protein (a precursor of pyrogenic exotoxin B).⁵⁰ Although concentrations of circulating immune complexes do not correlate with the severity of the disease, they may contribute to the generation of massive intraglomerular immune deposits after the initial immune complexes formed in situ have altered the permeability of the glomerular basement membrane.

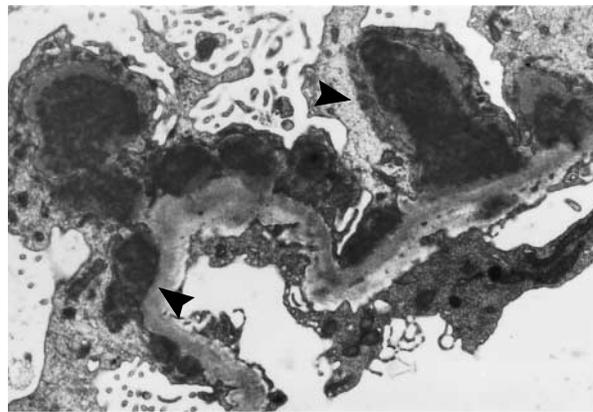
On light microscopy, poststreptococcal glomerulonephritis is seen to be a diffuse proliferative process with increased numbers of mesangial cells and endothelial cells, often accompanied by infiltration of capillary lumina and the mesangium by polymorphonuclear cells, monocytes, and eosinophils (Fig. 3A). In severe cases, epithelial cells and macrophages accumulate in Bowman's space and form crescents, also a hallmark of rapidly progressive glomerulonephritis. Immunofluorescence microscopy typically reveals a coarse granular pattern of deposits of IgG and C3 in mesangial stalks and in capillary loops.⁵¹ Subendothelial immune deposits are probably responsible for the local influx of inflammatory cells, but they are rapidly cleared and may not be seen on renal-biopsy specimens obtained relatively late in the course of the disease. Large subepithelial immune deposits referred to as "humps" are best seen on electron microscopy (Fig. 3B) during the first two weeks of the disease and tend to diminish by week 4 to 8.^{52,53}

Poststreptococcal glomerulonephritis is an acute, reversible disease characterized by spontaneous recovery in the vast majority of patients. Typically, gross hematuria and edema develop 7 days to 12 weeks after the streptococcal infection. Spontaneous resolution of the clinical manifestations is generally rapid: diuresis usually ensues within one to two weeks, and the serum creatinine concentration returns to base line within four weeks.⁴⁴ The rate at which urinary abnormalities disappear is more variable. Hematuria usually resolves within 6 months, but mild proteinuria is still present in 15 percent of patients after 3 years and in 2 percent of patients after 10 years.⁵⁴

Serial measurements of complement components can be helpful in the diagnosis of this disorder. Total hemolytic complement activity and C3 concentrations are depressed early in the course of the disease and, in most cases, return to normal in six to eight weeks.⁵⁵ The finding of persistently low concentrations of C3 more than eight weeks after presentation should alert the clinician to the possibility of lupus nephritis or membranoproliferative glomerulonephritis. The detection of antibodies to streptococcal an-



A



B

Figure 3. Poststreptococcal Glomerulonephritis.

In Panel A, glomeruli from a 10-year-old girl with acute post-streptococcal glomerulonephritis show marked, diffuse hypercellularity, with infiltration of polymorphonuclear cells (hematoxylin and eosin, $\times 156$). In Panel B, large, nodular, variegated subepithelial deposits referred to as "humps" (arrowheads) are present on electron microscopy ($\times 9350$).

tigens provides evidence of recent infection but is not diagnostic of poststreptococcal glomerulonephritis itself. Antibodies to streptolysin O, streptokinase, hyaluronidase, and nicotinamide dinucleotidase are the ones that are most often measured.⁵⁶ However, as many as one third of the streptococci of the type 12 strain do not produce streptolysin,⁴⁴ thus limiting the diagnostic value of antistreptolysin O titers in patients with recent pharyngeal infections.

The long-term prognosis of patients with post-streptococcal glomerulonephritis has been a subject of controversy. Although most patients eventually have a complete recovery, hypertension, recurrent or persistent proteinuria, and chronic renal insufficiency develop in some.⁵⁷ The reported incidence of chronic renal insufficiency ranges from 0 to 20 percent.^{44,57,58} It has been suggested that misdiagnosis, racial differences in the risk of progression of renal

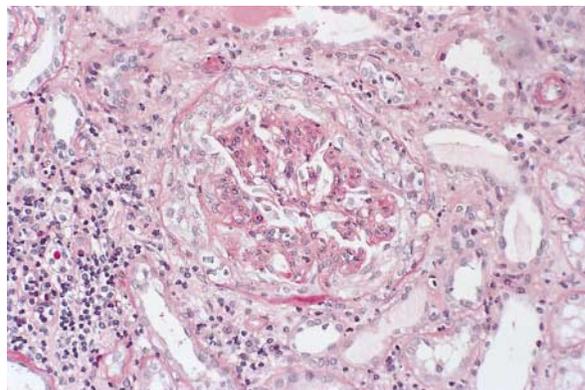
disease, and differences in the natural history of sporadic and epidemic glomerulonephritis may account for these discrepancies. Treatment of poststreptococcal glomerulonephritis is supportive, focusing on the short-term management of fluid overload and hypertension with diuretics and other antihypertensive agents as needed.

Rapidly Progressive Glomerulonephritis

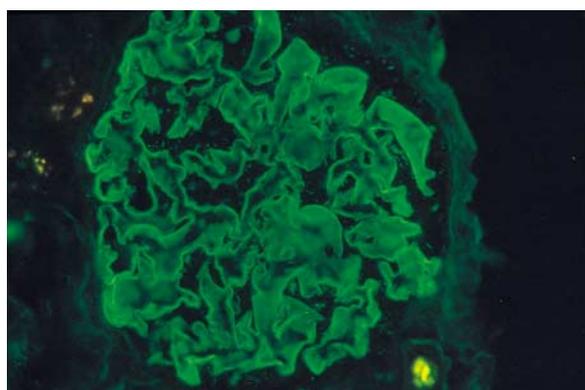
Rapidly progressive glomerulonephritis is a clinical syndrome characterized by signs of glomerulonephritis (hematuria, proteinuria, and red-cell casts) and a rapid decline in renal function that can lead to end-stage renal failure within days to weeks. Fortunately, the disorders associated with this syndrome are rare, so that rapidly progressive glomerulonephritis makes up only 2 to 4 percent of all cases of glomerulonephritis. The pathological hallmark of this syndrome is the presence of cellular crescents surrounding most glomeruli⁵⁹ (Fig. 4A). Crescents result from the proliferation of parietal epithelial cells and mononuclear phagocytes within Bowman's capsule⁶⁰ and, perhaps, from the recruitment of fibroblasts.⁶¹

Rapidly progressive glomerulonephritis can occur as a primary disorder in the absence of other glomerular or systemic diseases and is classified pathologically according to the presence or absence of immune deposits and their character on immunofluorescence microscopy. Linear deposition of immunoglobulin along the glomerular basement membrane (Fig. 4B) is detected in approximately 20 percent of patients with primary rapidly progressive glomerulonephritis, and granular immune-complex deposition is detected in an additional 30 percent.⁶⁰ In the remaining patients, no immune deposits are detectable in glomeruli ("pauci-immune" disease). Over the past several years, the association between antineutrophil cytoplasmic antibodies and pauci-immune glomerulonephritis has been delineated.⁶⁰⁻⁶⁴ Rapidly progressive glomerulonephritis associated with glomerular crescent formation can be superimposed on primary glomerular diseases, including membranoproliferative glomerulonephritis, membranous nephropathy, IgA nephropathy, and hereditary nephritis,^{59,60} and it has been associated with infectious and multisystem diseases, including vasculitides, cryoglobulinemia, and systemic lupus erythematosus.

Unless complicated by systemic disease, rapidly progressive glomerulonephritis typically has an insidious onset, with nonspecific symptoms such as malaise and lethargy. Urinalysis invariably demonstrates hematuria (usually dysmorphic red cells) and moderate proteinuria; nephrotic-range proteinuria occurs in less than 30 percent of patients.⁶⁰ Clinicians must seek evidence of multisystem diseases known to cause rapidly progressive glomerulonephritis by using the symptoms and signs to direct



A



B

Figure 4. Rapidly Progressive Glomerulonephritis.

Panel A shows a glomerulus from a patient with rapidly progressive glomerulonephritis with a large crescent and compressed glomerular capillary tufts (hematoxylin and eosin, $\times 250$). In Panel B, there is linear deposition of IgG along the glomerular basement membrane on immunofluorescence microscopy in a patient with circulating antibodies to glomerular basement membrane ($\times 320$).

the laboratory assessment. The detection of circulating antibodies to glomerular basement membrane is important in the diagnosis of glomerular basement membrane disease (limited to the kidney) or Goodpasture's syndrome (involving pulmonary hemorrhage). However, antibody titers cannot be used prognostically, nor do they correlate with disease activity.

Antineutrophil cytoplasmic antibodies are present in approximately 80 percent of patients with pauci-immune crescentic nephritis, in which the symptoms may be limited to the kidney or systemic vasculitides may be present.⁶² The most common vasculitides associated with antineutrophil cytoplasmic antibodies are Wegener's granulomatosis, microscopic polyangiitis, and Churg–Strauss syndrome.⁶⁵ Like the titers for glomerular basement membrane antibody, antineutrophil cytoplasmic antibody titers cannot be used to differentiate between disease limited to the

kidney and systemic disease,⁶² and in the long-term management of small-vessel vasculitis associated with antineutrophil cytoplasmic antibodies, changes in antibody concentrations should not be used as the sole basis for altering therapy.⁶⁶

Rapidly progressive glomerulonephritis should be treated aggressively. A delay in the diagnosis and initiation of therapy increases the risk of end-stage renal disease, and the likelihood of renal recovery is poor without therapy.^{63,67,68} Glucocorticoids and cyclophosphamide are the main agents in the treatment of this syndrome.^{64,69} Plasma exchange is commonly used in an effort to remove circulating pathogenic autoantibodies in patients with glomerular basement membrane disease and has recently been advocated as therapy for pauci-immune crescentic glomerulonephritis in patients who present with renal failure requiring dialysis.⁶⁹ Trials evaluating the efficacy of plasma exchange have been small, and a benefit has often been identified only in secondary analyses. However, in view of the high risk of renal failure,⁷⁰ plasma exchange may be an appropriate therapeutic option for some patients with rapidly progressive glomerulonephritis.

The prognosis and response to therapy of patients with glomerular basement membrane disease or Goodpasture's syndrome have not been studied in large trials. Data from a number of trials with similar treatment strategies suggest that the survival rates are high (70 to 90 percent) but that at one year only 40 percent of patients do not require dialysis.⁶⁹ Renal survival is particularly poor in patients with glomerular basement membrane disease who present with advanced renal insufficiency (i.e., a creatinine concentration of more than 6 mg per deciliter [53 μ mol per liter]).^{69,70}

Treatment responses have recently been reported for a cohort of 107 patients with glomerulonephritis and microscopic polyangiitis with associated antineutrophil cytoplasmic antibodies.⁶⁴ Approximately 75 percent of the patients entered remission, and 43 percent of these patients remained in remission after almost four years. The serum creatinine concentration at presentation is a strong predictor of renal survival in patients with antineutrophil cytoplasmic antibodies.⁶⁴ However, some patients who are receiving dialysis at presentation have a response to therapy; therefore, dialysis should not be an absolute contraindication to treatment.

The Nephrotic Syndrome

Patients with the nephrotic syndrome present with "heavy" proteinuria (protein excretion, >3 g per day), hypoalbuminemia, edema, and varying degrees of hyperlipidemia and lipiduria. This syndrome occurs as a complication of a wide variety of systemic diseases, including diabetes mellitus, systemic lupus erythematosus, and amyloidosis. In addition, renal dis-

ease precipitated by certain drugs, cancer (especially Hodgkin's disease and non-Hodgkin's lymphoma), and infectious agents (e.g., hepatitis B virus, hepatitis C virus, and human immunodeficiency virus) is often manifested as the nephrotic syndrome. In adults, the most common histologic lesions associated with primary nephrotic syndrome are focal segmental glomerulosclerosis, membranous glomerulopathy, minimal-change disease, and membranoproliferative glomerulonephritis.^{71,72} Although membranoproliferative glomerulonephritis is the least common of these entities, it is one of the few proliferative glomerulonephritides that is regularly seen with the nephrotic syndrome.

The association of membranoproliferative glomerulonephritis with disparate disorders such as partial lipodystrophy, sickle cell disease, complement deficiencies, cryoglobulinemia, and infections with either hepatitis B or hepatitis C suggests that this disorder is not a single pathogenic entity. The recent recognition of a causal relation between hepatitis C infection and membranoproliferative glomerulonephritis has led to the suggestion that this virus may be responsible for as many as 60 percent of cases previously deemed to be idiopathic.⁷³ Although they have similar clinical manifestations, two major types of idiopathic membranoproliferative glomerulonephritis have been recognized on the basis of differences in ultrastructural morphology: type I, characterized by subendothelial deposits, and type II (dense deposit disease), characterized by the deposition of dense deposits within the glomerular basement membrane.⁷⁴ Idiopathic membranoproliferative glomerulonephritis generally affects persons between the ages of 5 and 30 years, with a slight female predominance.

In type I membranoproliferative glomerulonephritis, light microscopy reveals an increased number of mesangial cells, expansion of the mesangial matrix, and diffuse enlargement of glomerular tufts, which give a lobular appearance to the glomeruli (Fig. 5A). Glomerular capillary walls appear thickened because of the insertion of mesangial matrix between the glomerular basement membrane and the endothelium. With the use of special stains such as periodic acid-Schiff or methenamine silver, the pattern made by the insertion of the mesangial material, referred to as "splitting" or "tram-tracking," can be seen (Fig. 5B).^{74,75} Immunofluorescence microscopy reveals granular deposits of C3 in the mesangium and in peripheral capillary loops in all patients. Deposits of immunoglobulins and other complement components in capillary loops are present in some patients. Type II membranoproliferative glomerulonephritis differs from type I histologically because the dense, refractile immune deposits create a ribbon-like thickening of the glomerular capillary wall on light microscopy.^{74,76} On electron microscopy, these deposits

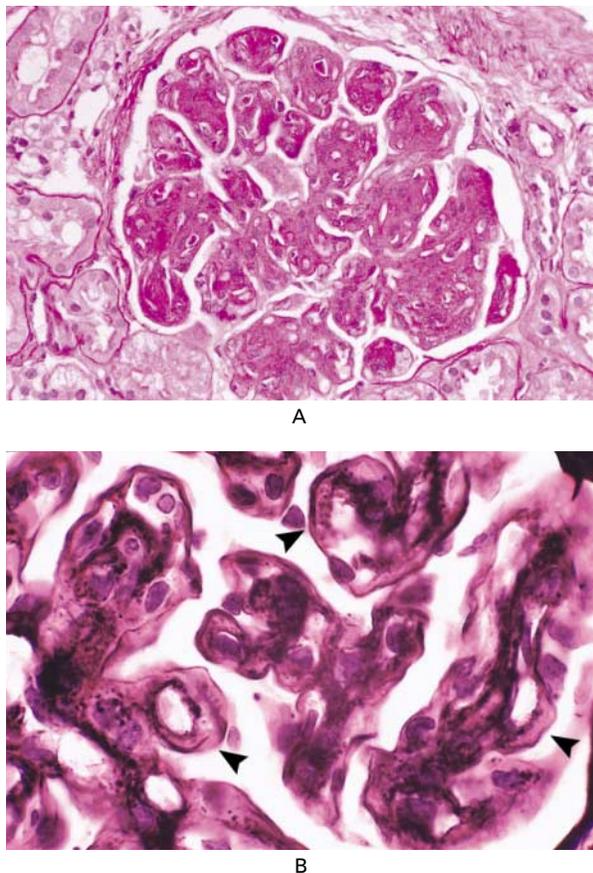


Figure 5. Membranoproliferative Glomerulonephritis.

Panel A shows a typical glomerulus with lobular accentuation due to global expansion of the mesangial matrix and mesangial hypercellularity (periodic acid-Schiff, $\times 320$). In Panel B, under an oil-immersion lens, the double-contoured peripheral glomerular basement membrane (arrowheads), which is caused by the insertion of mesangial matrix between the glomerular basement membrane and the endothelium and is referred to as "tram-tracking" or "splitting," can be seen (periodic acid-Schiff-methenamine silver, $\times 800$).

are seen as strongly electron-dense material distributed homogeneously within the glomerular basement membrane. C3 and other complement components are detected in the mesangium and capillary loops, but immunoglobulins are generally not seen on immunofluorescence microscopy.

Type I membranoproliferative glomerulonephritis may be mediated by the deposition of immune complexes capable of activating complement both systemically and within the kidney. Serum complement concentrations tend to fluctuate. However, serial determinations reveal at least an intermittent decrease in the concentrations of C3, C1q, and C4 in the vast majority of patients, suggesting activation of complement through both the classic and alternative pathways.^{77,78} The composition of the dense in-

tramembranous deposits in type II membranoproliferative glomerulonephritis remains unknown, but there is little evidence of an immune-complex pathogenesis in this disorder. In patients with this histologic variant, serum concentrations of C3 tend to be persistently low while concentrations of early components of the classic pathway are usually normal, suggesting that complement activation occurs primarily through the alternative pathway.⁷⁸ Virtually all patients with type II membranoproliferative glomerulonephritis have high serum concentrations of C3 nephritic factor, an autoantibody that activates the alternative pathway.⁷⁹

Approximately half of patients with membranoproliferative glomerulonephritis present with the nephrotic syndrome, whereas the remainder present with either acute glomerulonephritis or asymptomatic urinary abnormalities. Some degree of renal functional impairment is evident in half of patients at presentation. Spontaneous remissions are rare, and the disease generally has a chronic, progressive course. However, reported outcomes have varied widely, with 10-year renal-survival rates ranging from 16 to 82 percent.^{80,81} Factors associated with an increased risk of progression include renal insufficiency at the time of diagnosis, an age of more than 50 years, hypertension, and glomerular crescents.^{74,80} The use of cytotoxic drugs has not proved to be consistently beneficial. The best long-term renal outcomes have been reported in children treated with glucocorticoids every other day for long periods.^{80,82}

Chronic Glomerulonephritis

Chronic glomerulonephritis is a syndrome manifested by progressive renal insufficiency in patients with glomerular inflammation, hematuria, and often, hypertension. The kidney is the organ most commonly affected by systemic lupus erythematosus, and lupus nephritis is one of the most serious manifestations of this autoimmune disease. In a substantial minority of patients with this disorder, chronic progressive glomerulonephritis ultimately develops that culminates in renal failure. In a large series of patients with lupus nephritis who were studied by the Gruppo Italiano per lo Studio della Nefrite Lupica (GISNEL), the probability of renal survival 5 and 10 years after the diagnosis was 87.7 percent and 80.5 percent, respectively.⁸³ These findings are similar to those of other studies with fewer patients.⁸⁴⁻⁸⁶ In contrast, another series of 89 patients studied by the Glomerular Disease Collaborative Network reported a renal survival rate of 71 percent at five years.⁸⁷ Women, particularly black women, have the highest rates of lupus nephritis,^{84,88} and renal survival is significantly poorer in blacks than in whites.^{87,89}

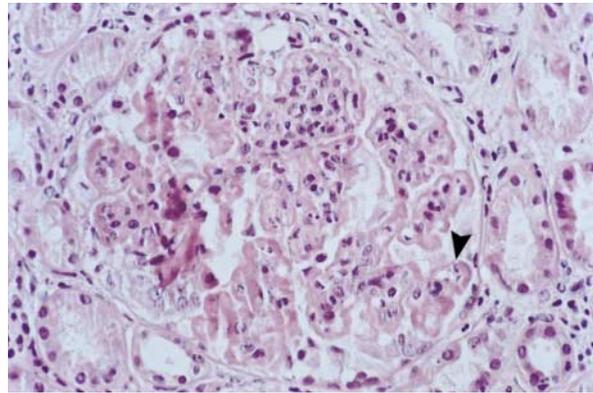
The clinical spectrum of lupus nephritis ranges from mild urinary abnormalities to acute and chronic renal failure. Clinically significant nephritis devel-

ops most commonly within three years after diagnosis and rarely develops after five years.⁸⁴ Asymptomatic hematuria or non-nephrotic proteinuria may be the only clues to renal involvement and should prompt further tests for other evidence of glomerular disease. Low serum concentrations of C3, low total hemolytic complement activity, and elevated levels of antibodies to DNA or antinuclear antibody have been reported to correlate with the presence of active glomerulonephritis, but serologic evidence of increasing disease activity may precede the development of serious renal inflammation by months.⁹⁰ At best, findings of serologic abnormalities should alert the clinician to the possibility of organ involvement and may indicate the need for closer monitoring, but they should not be used as a basis for therapy.

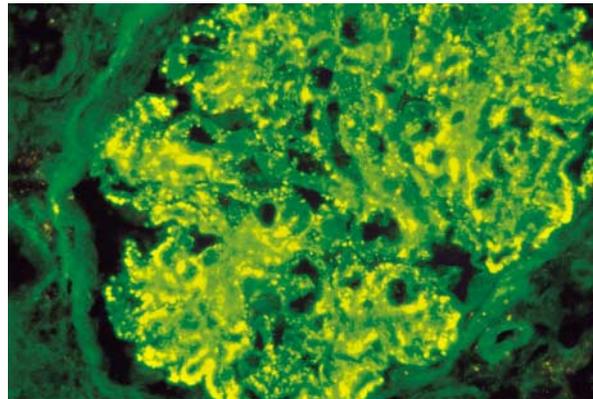
Although tubulointerstitial nephritis can be a prominent component of lupus nephritis, immune-complex glomerulonephritis is the primary histopathological finding. The clinical presentation and the histopathological findings often, but not always, correlate. The World Health Organization (WHO) classification,⁹¹ which is based on five distinct categories of glomerular pathological findings, has been used for prognosis, treatment, and outcome in most trials. WHO class I represents normal kidney. WHO class II (mesangial nephritis) is characterized by few changes on light microscopy but by mesangial deposits on both immunofluorescence and electron microscopy. The capillary loops are generally spared. The results of urinalysis may be normal, but they may also reveal mild-to-moderate proteinuria and occasional red cells. WHO class III (focal proliferative nephritis) is characterized on light microscopy by mesangial and endocapillary hypercellularity in less than 50 percent of glomeruli. Patients with focal proliferative glomerulonephritis have abnormal urinary sediments and proteinuria, although progressive renal failure is uncommon.

WHO class IV (diffuse, proliferative glomerulonephritis) is characterized by mesangial and endocapillary hypercellularity, areas of necrosis, and occasionally, crescent formation. Subendothelial deposits can cause thickening of the basement membrane so that it looks like a wire loop on light microscopy (Fig. 6A). Immunofluorescence microscopy can demonstrate extensive granular deposition of IgG, IgA, IgM, and complement (Fig. 6B); electron microscopy shows that the deposits are predominantly in subendothelial and mesangial areas. Subepithelial immune deposits are also common. Patients with diffuse proliferative glomerulonephritis generally have an abnormal urinary sediment (hematuria, red-cell casts, and leukocytes) and proteinuria, and they may have the nephrotic syndrome. Azotemia is common.

Diffuse thickening of the basement membrane with normal glomerular cellularity on light microscopy characterizes membranous lupus nephropathy



A



B

Figure 6. Lupus Nephritis.

Panel A shows a glomerulus from a 26-year-old woman with systemic lupus erythematosus with irregular thickening of glomerular basement membrane, giving it the appearance of a wire loop (arrowhead), and endocapillary-cell proliferation, with segmental necrosis and neutrophilic infiltration (hematoxylin and eosin, $\times 320$). In Panel B, direct immunofluorescence shows diffuse, global, coarse, granular deposits of IgG along the glomerular basement membrane and in the mesangium ($\times 320$).

(WHO class V). Electron-dense deposits are found predominantly in the subepithelial portion of the basement membrane but may involve the mesangium and appear as granular IgG deposits on immunofluorescence microscopy. Affected patients usually have the nephrotic syndrome. The disease in an individual patient may fall into more than one WHO class, and multiple glomerular histopathological patterns may be apparent in an individual biopsy specimen.^{84,85,91} Of 659 patients described by the GISNEL investigators, 7 percent had mesangial lupus (WHO class II), 12 percent had focal proliferative glomerulonephritis (WHO class III), 45 percent had diffuse proliferative glomerulonephritis (WHO class IV), 14 percent had lupus membranous nephropathy (WHO class V), 6 percent had mixed histologic findings, and 16 percent did not undergo renal biopsy.

The results of randomized, controlled trials conducted by the National Institutes of Health (NIH)^{92,93} and the Lupus Nephritis Collaborative Study (LNCS)⁹⁴ have provided information about factors that predict the progression of renal disease in patients with biopsy-demonstrated, severe lupus nephritis. These trials have focused on patients with severe lupus nephritis, as evidenced by active glomerular inflammation on biopsy. The LNCS reported that the risk of renal failure was highest among patients with an initial serum creatinine concentration of more than 1.2 mg per deciliter (106 μmol per liter). Similarly, the NIH series identified a serum creatinine concentration of more than 2.4 mg per deciliter (212 μmol per liter) as the best clinical indicator of progressive renal disease.⁸⁹ The GISNEL study identified hypertension at diagnosis as a poor prognostic factor, but the patients with hypertension also had higher serum creatinine concentrations.⁸³ In the NIH, LNCS, and GISNEL studies, the mean length of follow-up was no more than five years. In one study of 70 patients who were followed up for a mean of 10.7 years, the long-term prognostic value of an elevated creatinine concentration at presentation was not confirmed.⁸⁶ Rather, the occurrence of a nephritic flare, male sex, and a hematocrit below 36 percent were better predictors of poor long-term renal outcome.⁸⁶

The prognostic value of renal pathological findings has been controversial. Several^{83,89,95-97} but not all^{86,94,98} studies have demonstrated that these findings help clarify predictions of outcome that are based on clinical and laboratory findings. The NIH group has devised composite scoring systems to quantify active inflammation and scarring and has found that these indexes enhance the prognostic information obtained from the biopsy.⁹⁹ However, others have been unable to confirm the validity of these indexes as predictors of renal outcome.¹⁰⁰

Patients with mesangial lupus (WHO class II) generally require no specific therapy; because the lesion may evolve into a more aggressive form, however, some investigators have advocated prednisone treatment for these patients.¹⁰¹ Regardless of the approach, these patients should be closely monitored for signs that the lesion is evolving to a more aggressive form. Aggressive therapy, consisting of glucocorticoids and cytotoxic immunosuppressive drugs,^{94,102} is usually reserved for patients with severe lupus nephritis (WHO classes III and IV).⁹⁴ In the NIH trials, patients treated with prednisone alone had a higher probability of losing renal function than those treated with intravenous pulsed cyclophosphamide for at least one year after remission.^{92,93,102} Two meta-analyses have confirmed that immunosuppressive therapy administered concomitantly with oral prednisone is more efficacious in preventing end-stage renal disease than glucocorticoid therapy alone.^{103,104}

The appropriate duration of immunosuppressive therapy for patients with lupus nephritis remains to be determined. Plasmapheresis does not improve the clinical outcome in patients with severe lupus nephritis.¹⁰⁵

The appropriate therapy for patients with the membranous variant of lupus nephritis is less clear. In one retrospective analysis of patients with membranous lupus nephropathy who were treated primarily with prednisone, the renal prognosis was excellent.⁹⁶ Another recent study suggested that the combination of chlorambucil and prednisone may induce a more stable remission than prednisone alone.¹⁰⁶

CONCLUSIONS

During the past three decades, epidemiologic studies have defined the clinical characteristics and natural history of patients with glomerulonephritis as well as risk factors for progression to end-stage renal disease. At the same time, our understanding of the immunopathogenesis and genetic basis of the common glomerulonephritides has greatly improved. Unfortunately, treatment is currently limited to supportive therapy with or without nonspecific immunosuppressive drugs. Continued efforts to unravel the pathogenesis of glomerulonephritis may identify new possibilities for treatment of a group of common diseases that still have few effective and no specific therapies.

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