The primary glomerulopathies are those disorders that affect glomerular structure, function, or both in the absence of a multisystem disorder. The clinical manifestations are predominantly the consequence of the glomerular lesion (such as proteinuria, hematuria, and reduced glomerular filtration rate). The combination of clinical manifestations leads to a variety of clinical syndromes. These syndromes include acute glomerulonephritis; rapidly progressive glomerulonephritis; chronic renal failure; the nephrotic syndrome or “asymptomatic” hematuria, proteinuria, or both.
CLINICAL SYNDROMES OF GLOMERULAR DISEASE

Acute glomerulonephritis
Rapidly progressive glomerulonephritis
Chronic glomerulonephritis
Nephrotic syndrome
“Asymptomatic” hematuria, proteinuria, or both

PRIMARY GLOMERULAR LESIONS

Minimal change disease
Focal segmental glomerulosclerosis with hyalinosis
Membranous glomerulonephritis
Membranoproliferative glomerulonephritis
Mesangial proliferative glomerulonephritis
Crescentic glomerulonephritis
Immunoglobulin A nephropathy
Fibillary and immunotactoid glomerulonephritis
Collagenofibrotic glomerulopathy
Lipoprotein glomerulopathy

FIGURE 2-1
Each of these syndromes arises as a consequence of disturbances of glomerular structure and function. Acute glomerulonephritis consists of the abrupt onset of hematuria, proteinuria, edema, and hypertension. Rapidly progressive glomerulonephritis is characterized by features of nephritis and progressive renal insufficiency. Chronic glomerulonephritis features proteinuria and hematuria with indolent progressive renal failure. Nephrotic syndrome consists of massive proteinuria (>3.5 g/d in adults), hypoalbuminemia with edema, lipiduria, and hyperlipidemia. “Asymptomatic” hematuria, proteinuria, or both is not associated initially with renal failure or edema. Each of these syndromes may be complicated by hypertension.

FIGURE 2-2
Age-associated prevalence of various glomerular lesions in nephrotic syndrome. This schematic illustrates the age-associated prevalence of various diseases and glomerular lesions among children and adults undergoing renal biopsy for evaluation of nephrotic syndrome (Guy’s Hospital and the International Study of Kidney Disease in Children) [1]. Both the systemic and primary causes of nephrotic syndrome are included. (Diabetes mellitus with nephropathy is underrepresented because renal biopsy is seldom needed for diagnosis.) The bar on the left summarizes the prevalence of various lesions in children aged 0 to 16 years; the bar on the right summarizes the prevalence of various lesions in adults aged 16 to 80 years. Note the high prevalence of minimal change disease in children and the increasing prevalence of membranous glomerulonephritis in the age group of 16 to 60 years. FSGS—focal segmental glomerulosclerosis; MCGN—mesangiocapillary glomerulonephritis. (From Cameron [1]; with permission.)

FIGURE 2-3
The primary glomerular lesions.
Minimal Change Disease

**FIGURE 2-4**
Light and electron microscopy in minimal change disease (lipoid nephrosis). **A**, This glomerulopathy, one of many associated with nephrotic syndrome, has a normal appearance on light microscopy. No evidence of antibody (immune) deposits is seen on immunofluorescence. **B**, Effacement (loss) of foot processes of visceral epithelial cells is observed on electron microscopy. This last feature is the major morphologic lesion indicative of massive proteinuria.

Minimal change disease is considered to be the result of glomerular capillary wall damage by lymphokines produced by abnormal T cells. This glomerulopathy is the most common cause of nephrotic syndrome in children (>70%) and also accounts for approximately 20% of adult patients with nephrotic syndrome. This glomerulopathy typically is a corticosteroid-responsive lesion, and usually has a benign outcome with respect to renal failure.

**FIGURE 2-5**
Therapeutic response in minimal change disease. This graph illustrates the cumulative complete response rate (absence of abnormal proteinuria) in patients of varying ages in relation to type and duration of therapy [1]. Note that most children with minimal change disease respond to treatment within 8 weeks. Adults require prolonged therapy to reach equivalent response rates. Number of patients are indicated in parentheses. (From Cameron [2]; with permission.)

**FIGURE 2-6**
Cyclophosphamide in minimal change disease. One of several controlled trials of cyclophosphamide therapy in pediatric patients that pursued a relapsing steroid-dependent course is illustrated. Note the relative freedom from relapse when children were given a 12-week course of oral cyclophosphamide. An 8-week course of chlorambucil (0.15–0.2 mg/kg/d) may be equally effective. (From Arbeitsgemeinschaft für pädiatrische nephrologie [3]; with permission.)
2.4 Glomerulonephritis and Vasculitis

Cyclosporine in minimal change disease. One of several controlled trials of cyclosporine therapy in this disease is illustrated. Note the relapses that occur after discontinuing cyclosporine therapy (arrow). Cyclophosphamide was given for 2 months, and cyclosporine for 9 months. Probability—actuarial probability of remaining relapse-free. (From Ponticelli and coworkers [4]; with permission.)

Focal Segmental Glomerulosclerosis

Light and immunofluorescent microscopy in focal segmental glomerulosclerosis (FSGS). Patients with FSGS exhibit massive proteinuria (usually nonselective), hypertension, hematuria, and renal functional impairment. Patients with nephrotic syndrome often are not responsive to corticosteroid therapy. Progression to chronic renal failure occurs over many years, although in some patients renal failure may occur in only a few years. A, This glomerulopathy is defined primarily by its appearance on light microscopy. Only a portion of the glomerular population, initially in the deep cortex, is affected. The abnormal glomeruli exhibit segmental obliteration of capillaries by increased extracellular matrix–basement membrane material, collapsed capillary walls, or large insudative lesions. These lesions are called hyalinosis (arrow) and are composed of immunoglobulin M and complement C3 (B, IgM immunofluorescence). The other glomeruli usually are enlarged but may be of normal size. In some patients, mesangial hypercellularity may be a feature. Focal tubular atrophy with interstitial fibrosis invariably is present.
THE PRIMARY GLOMERULOPATHIES

FIGURE 2-9
Electron microscopy of focal segmental glomerulosclerosis. The electron microscopic findings in the involved glomeruli mirror the light microscopic features, with capillary obliteration by dense hyaline “deposits” (arrow) and lipids. The other glomeruli exhibit primarily foot process effacement, occasionally in a patchy distribution.

CLASSIFICATION OF FOCAL SEGMENTAL GLOMERULOSCLEROSIS WITH HYALINOSIS

Primary (Idiopathic)
- Classic
- Tip lesion
- Collapsing

Secondary
- Human immunodeficiency virus-associated
- Heroin abuse
- Vesicoureteric reflux nephropathy
- Oligonephronia (congenital absence or hypoplasia of one kidney)
- Obesity
- Analgesic nephropathy
- Hypertensive nephrosclerosis
- Sickle cell disease
- Transplantation rejection (chronic)
- Vasculitis (scarring)
- Immunoglobulin A nephropathy (scarring)

CLASSIFICATION OF MEMBRANOUS GLOMERULONEPHRITIS

Primary (Idiopathic)

Secondary
- Neoplasia (carcinoma, lymphoma)
- Autoimmune disease (systemic lupus erythematosus, thyroiditis)
- Infectious diseases (hepatitis B, hepatitis C, schistosomiasis)
- Drugs (gold, mercury, nonsteroidal anti-inflammatory drugs, probenecid, captopril)
- Other causes (kidney transplantation, sickle cell disease, sarcoidosis)

FIGURE 2-10
Note that a variety of disease processes can lead to the lesion of focal segmental glomerulosclerosis. Some of these are the result of infections, whereas others are due to loss of nephron population. Focal sclerosis may also complicate other primary glomerular diseases (e.g., Immunoglobulin A nephropathy).

FIGURE 2-11
Most adult patients (75%) have primary or idiopathic disease. Most children have some underlying disease, especially viral infection. It is not uncommon for adults over the age of 60 years to have an underlying carcinoma (especially lung, colon, stomach, or breast).
Two important variants of FSGS exist. In contrast to the histologic appearance of the involved glomeruli, with the sclerotic segment in any location in the glomerulus, the glomerular tip lesion (A) is characterized by segmental sclerosis at an early stage of evolution, at the tubular pole (tip) of all affected glomeruli (arrow). Capillaries contain monocytes with abundant cytoplasmic lipids (foam cells), and the overlying visceral epithelial cells are enlarged and adherent to cells of the most proximal portion of the proximal tubule. Some investigators have described a more favorable response to steroids and a more benign clinical course.

The other variant, known as collapsing glomerulopathy, most likely represents a virulent form of FSGS. In this form of FSGS, most visceral epithelial cells are enlarged and coarsely vacuolated and most capillary walls are wrinkled or collapsed (B). These features indicate a severe lesion, with a corresponding rapidly progressing clinical course of the disease. Integral and concomitant acute abnormalities of tubular epithelia and interstitial edema occur.

**FIGURE 2-12**

Histologic variations of focal segmental glomerulosclerosis (FSGS). Two important variants of FSGS exist. In contrast to the histologic appearance of the involved glomeruli, with the sclerotic segment in any location in the glomerulus, the glomerular tip lesion (A) is characterized by segmental sclerosis at an early stage of evolution, at the tubular pole (tip) of all affected glomeruli (arrow). Capillaries contain monocytes with abundant cytoplasmic lipids (foam cells), and the overlying visceral epithelial cells are enlarged and adherent to cells of the most proximal portion of the proximal tubule. Some investigators have described a more favorable response to steroids and a more benign clinical course.

The other variant, known as collapsing glomerulopathy, most likely represents a virulent form of FSGS. In this form of FSGS, most visceral epithelial cells are enlarged and coarsely vacuolated and most capillary walls are wrinkled or collapsed (B). These features indicate a severe lesion, with a corresponding rapidly progressing clinical course of the disease. Integral and concomitant acute abnormalities of tubular epithelia and interstitial edema occur.

**FIGURE 2-13**

Evolution of focal segmental glomerulosclerosis (FSGS). This graph compares the renal functional survival rate of patients with FSGS to that seen in patients with minimal change disease (in adults and children). Note the poor prognosis, with about a 50% rate of renal survival at 10 years. (From Cameron [2]; with permission.)

**FIGURE 2-14**

The outcome of focal segmental glomerulosclerosis according to the degree of proteinuria at presentation is shown. Note the favorable prognosis in the absence of nephrotic syndrome. Spontaneous or therapeutically induced remissions have a similar beneficial effect on long-term outcome. (From Ponticelli, et al. [5]; with permission.)
Membranous Glomerulonephritis

A. At all stages immunofluorescence discloses the presence of uniform granular capillary wall deposits of immunoglobulin G and complement C3.
B. In the early stage the deposits are small and without other capillary wall changes; hence, on light microscopy, glomeruli often are normal in appearance.
C. On electron microscopy, small electron-dense deposits (arrows) are observed in the subepithelial aspects of capillary walls.
D. In the intermediate stage the deposits are partially encircled by basement membrane material.
E. When viewed with periodic acid-methenamine stained sections, this abnormality appears as spikes of basement membrane perpendicular to the basement membrane, with adjacent nonstaining deposits. Similar features are evident on electron microscopy, with dense deposits and intervening basement membrane. Late in the disease the deposits are completely surrounded by basement membranes and are undergoing resorption.

Membranous glomerulonephritis is an immune complex–mediated glomerulonephritis, with the immune deposits localized to subepithelial aspects of almost all glomerular capillary walls. Membranous glomerulonephritis is the most common cause of nephrotic syndrome in adults in developed countries. In most instances (75%), the disease is idiopathic and the antigen(s) of the immune complexes are unknown. In the remainder, membranous glomerulonephritis is associated with well-defined diseases that often have an immunologic basis (e.g., systemic lupus erythematosus and hepatitis B or C virus infection); some solid malignancies (especially carcinomas); or drug therapy, such as gold, penicillamine, captopril, and some nonsteroidal anti-inflammatory reagents. Treatment is controversial.

The changes by light and electron microscopy mirror one another quite well and represent morphologic progression that is likely dependent on duration of the disease. A. At all stages immunofluorescence discloses the presence of uniform granular capillary wall deposits of immunoglobulin G and complement C3. B. In the early stage the deposits are small and without other capillary wall changes; hence, on light microscopy, glomeruli often are normal in appearance. C. On electron microscopy, small electron-dense deposits (arrows) are observed in the subepithelial aspects of capillary walls. D. In the intermediate stage the deposits are partially encircled by basement membrane material. E. When viewed with periodic acid-methenamine stained sections, this abnormality appears as spikes of basement membrane perpendicular to the basement membrane, with adjacent nonstaining deposits. Similar features are evident on electron microscopy, with dense deposits and intervening basement membrane. Late in the disease the deposits are completely surrounded by basement membranes and are undergoing resorption.
FIGURE 2-16  
Evolution of deposits in membranous glomerulonephritis. This schematic illustrates the sequence of immune deposits in red; basement membrane (BM) alterations in blue; and visceral epithelial cell changes in yellow. Small subepithelial deposits in membranous glomerulonephritis (predominately immunoglobulin G) initially form (A) then coalesce. BM expansion results first in spikes (B) and later in domes (C) that are associated with foot process effacement, as shown in gray. In later stages the deposits begin to resorb (dotted and crosshatched areas) and are accompanied by thickening of the capillary wall (D). (From Churg, et al. [6]; with permission.)

FIGURE 2-17  
Natural history of membranous glomerulonephritis. This schematic illustrates the clinical evolution of idiopathic membranous glomerulonephritis over time. Almost half of all patients undergo spontaneous or therapy-related remissions of proteinuria. Another group of patients (25–40%), however, eventually develop chronic renal failure, usually in association with persistent proteinuria in the nephrotic range. (From Cameron [2]; with permission.)
Membranoproliferative Glomerulonephritis

FIGURE 2-18 (see Color Plate)
Light, immunofluorescence, and electron microscopy in membra-
noproliferative glomerulonephritis type I. In these types of
immune complex-mediated glomerulonephritis, patients often
exhibit nephrotic syndrome accompanied by hematuria and
depressed levels of serum complement C3. The morphology is var-
ied, with at least three pathologic subtypes, only two of which are
at all common. The first, known as membranoproliferative
(mesangiocapillary) glomerulonephritis type I, is a primary
glomerulopathy most common in children and adolescents. The
same pattern of injury may be observed during the course of many
diseases with chronic antigenemic states; these include systemic
lupus erythematosus and hepatitis C virus and other infections. In
membranoproliferative glomerulonephritis type I, the glomeruli
are enlarged and have increased mesangial cellularity and variably
increased matrix, resulting in lobular architecture. The capillary
walls often are thickened with double contours, an abnormality
resulting from peripheral migration and interposition of
mesangium (A). Immunofluorescence discloses granular to confluent
granular deposits of C3 (B), immunoglobulin G, and
immunoglobulin M in the peripheral capillary walls and mesangial
regions. The characteristic finding on electron microscopy is in the
capillary walls. C. Between the basement membrane and endothe-
lial cells are, in order inwardly: (1) epithelial cell, (2) basement
membrane, (3) electron-dense deposits, (4) mesangial cell cyto-
plasm, (5) mesangial matrix, and (6) endothelial cell. Electron-
dense deposits also are in the central mesangial regions.
Subepithelial deposits may be present, albeit typically in small
numbers. The electron-dense deposits may contain an organized
(fibrillar) substructure, especially in association with hepatitis C
virus infection and cryoglobulnia.
known as dense deposit disease, the glomeruli may be lobular or may manifest only mild widening of mesangium. A, The capillary walls are thickened, and the basement membranes are stained intensely positive periodic acid–Schiff reaction, with a refractile appearance. B, On immunofluorescence, complement C3 is seen in all glomerular capillary basement membranes in a coarse linear pattern. With the use of thin sections, it can be appreciated that the linear deposits actually consist of two thin parallel lines. Round granular deposits are in the mesangium. Coarse linear deposits also are in Bowman's capsule and the tubular basement membranes. C, Ultrastructurally, the glomerular capillary basement membranes are thickened and darkly stained; there may be segmental or extensive involvement of the basement membrane. Similar findings are seen in Bowman's capsule and tubular basement membranes; however, in the latter, the dense staining is usually on the interstitial aspect of that structure. Patients with dense deposit disease frequently show isolated C3 depression and may have concomitant lipodystrophy. These patients also have autoantibodies to the C3 convertase enzyme C3Nef.
## SERUM COMPLEMENT CONCENTRATIONS IN GLOMERULAR LESIONS

<table>
<thead>
<tr>
<th>Lesion</th>
<th>C3</th>
<th>C4</th>
<th>C'H50</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal change disease</td>
<td>Normal</td>
<td>Normal</td>
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<td>–</td>
</tr>
<tr>
<td>Focal sclerosis</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>–</td>
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<td>Membranous glomerulonephritis (idiopathic)</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>–</td>
</tr>
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<td>Immunoglobulin A nephropathy</td>
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<td>Normal</td>
<td>Normal</td>
<td>–</td>
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<td>Membranoproliferative glomerulonephritis:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type I</td>
<td>Moderate decrease</td>
<td>Mild decrease</td>
<td>Mild decrease</td>
<td>C3 nephritic factor+</td>
</tr>
<tr>
<td>Type II</td>
<td>Severe decrease</td>
<td>Normal</td>
<td>Mild decrease</td>
<td>–</td>
</tr>
<tr>
<td>Acute poststreptococcal glomerulonephritis:</td>
<td>Moderate decrease</td>
<td>Normal</td>
<td>Mild decrease</td>
<td>Anti–double-stranded DNA antibody+</td>
</tr>
<tr>
<td>Lupus nephritides:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(World Health Organization Class IV)</td>
<td>Moderate to severe decrease</td>
<td>Moderate to severe decrease</td>
<td>Mild decrease</td>
<td>anti–double-stranded DNA antibody+</td>
</tr>
<tr>
<td>(World Health Organization Class V)</td>
<td>Normal or mild decrease</td>
<td>Normal or mild decrease</td>
<td>Normal or mild decrease</td>
<td>anti–double-stranded DNA antibody+</td>
</tr>
<tr>
<td>Cryoglobulinemia (hepatitis C)</td>
<td>Normal or mild decrease</td>
<td>Severe decrease</td>
<td>Moderate decrease</td>
<td>Cryoglobulins; hepatitis C ab</td>
</tr>
<tr>
<td>Amyloid</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>–</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>Normal or increased</td>
<td>Normal or increased</td>
<td>Normal</td>
<td>Antineutrophil cytoplasmic antibody+</td>
</tr>
</tbody>
</table>

C'H50—serum hemolytic complement activity.

**FIGURE 2-20**

The serum complement component concentration (C3 and C4) and serum hemolytic complement activity (C'H50) in various primary and secondary glomerular lesions are depicted. Note the limited number of disorders associated with a low C3 or C4 level.

## CLASSIFICATION OF MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS TYPE I

<table>
<thead>
<tr>
<th>Primary (Idiopathic)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary</td>
<td></td>
</tr>
<tr>
<td>Hepatitis C (with or without cryoglobulinemia)</td>
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</tr>
<tr>
<td>Hepatitis B</td>
<td></td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td></td>
</tr>
<tr>
<td>Light or heavy chain nephropathy</td>
<td></td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td></td>
</tr>
<tr>
<td>Sjögren’s syndrome</td>
<td></td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td></td>
</tr>
<tr>
<td>Shunt nephritis</td>
<td></td>
</tr>
<tr>
<td>Antitrypsin deficiency</td>
<td></td>
</tr>
<tr>
<td>Quartan malaria</td>
<td></td>
</tr>
<tr>
<td>Chronic thrombotic microangiopathy</td>
<td></td>
</tr>
<tr>
<td>Buckley’s syndrome</td>
<td></td>
</tr>
</tbody>
</table>

**FIGURE 2-21**

Note that although there is the wide variety of underlying causes for the lesion of membranoproliferative glomerulonephritis hepatitis C, with or without cryoglobulinemia, accounts for most cases.
Mesangial Proliferative Glomerulonephritis

![Image A](image1)

![Image B](image2)

![Image C](image3)

**FIGURE 2-22** (see Color Plate)

Light, immunofluorescence, and electron microscopy in mesangial proliferative glomerulonephritis. This heterogeneous group of disorders is characterized by increased mesangial cellularity in most of the glomeruli associated with granular immune deposits in the mesangial regions. Little if any increased cellularity is seen, despite the presence of deposits. In this latter instance, the term mesangial injury glomerulonephritis is more properly applied. The disorders are defined on the basis of the immunofluorescence findings, rather than on the presence or absence of mesangial hypercellularity. There are numerous disorders with this appearance; some have specific immunopathologic or clinical features (such as immunoglobulin A nephropathy, Henoch-Schönlein purpura, and systemic lupus erythematosus). Patients with primary mesangial proliferative glomerulonephritis typically exhibit the disorder in one of four ways: asymptomatic proteinuria, massive proteinuria often in the nephrotic range, microscopic hematuria, or proteinuria with hematuria. A. On light microscopy, widening of the mesangial regions is observed, often with diffuse increase in mesangial cellularity commonly of a mild degree. No other alterations are present. B. Depending on the specific entity or lesion, the immunofluorescence is of granular mesangial deposits. In the most common of these disorders, immunoglobulin M is the dominant or sole deposit. Other disorders are characterized primarily or exclusively by complement C3, immunoglobulin G, or C1q deposits. C. On electron microscopy the major finding is of small electron-dense deposits in the mesangial regions (arrow). Foot process effacement is variable, depending on the clinical syndrome (eg, whether massive proteinuria is present).
Crescentic Glomerulonephritis

Crescentic glomerulonephritis. A crescent is the accumulation of cells and extracellular material in the urinary space of a glomerulus. The cells are parietal and visceral epithelia as well as monocytes and other blood cells. The extracellular material is fibrin, collagen, and basement membrane material. In the early stages of the disease, the crescents consist of cells and fibrin. In the later stages the crescents undergo organization, with disappearance of fibrin and replacement by collagen. Crescents represent morphologic consequences of severe capillary wall damage. A, In most instances, small or large areas of destruction of capillary walls (cells and basement membranes) are observed (arrow), thereby allowing fibrin, other high molecular weight substances, and blood cells to pass readily from capillary lumina into the urinary space. B, Immunofluorescence frequently discloses fibrin in the urinary space. C, The proliferating cells in Bowman’s space ultimately give rise to the typical crescent shape. Whereas crescents may complicate many forms of glomerulonephritis, they are most commonly associated with either antiglomerular basement membrane (抗基底膜抗体) antibodies or antineutrophil cytoplasmic antibodies (ANCA s). The clinical manifestations are typically of rapidly progressive glomerulonephritis with moderate proteinuria, hematuria, oliguria, and uremia. The immunomorphologic features depend on the basic disease process. On light microscopy in both AGBM antibody-induced disease and ANCA-associated crescentic glomerulonephritis, the glomeruli without crescents often have a normal appearance. It is the remaining glomeruli that are involved with crescents. D, Anti-GBM disease is characterized by linear deposits of immunoglobulin G and often complement C3 in all capillary basement membranes, and in approximately two thirds of affected patients in tubular basement membranes. The ANCA-associated lesion typically has little or no immune deposits on immunofluorescence; hence the term pauci-immune crescentic glomerulonephritis is used. By electron microscopy, as on light microscopy, defects in capillary wall continuity are easily identified. Both AGBM- and ANCA-associated crescentic glomerulonephritis can be complicated by pulmonary hemorrhage (see Fig. 2-25).
### CLASSIFICATION OF CRESCENTIC GLOMERULONEPHRITIS

<table>
<thead>
<tr>
<th>Type</th>
<th>Serologic Pattern</th>
<th>Primary</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Anti-GBM + ANCA-</td>
<td>Anti-GBM antibody–mediated crescentic glomerular nephritis</td>
<td>Goodpasture’s disease</td>
</tr>
<tr>
<td>II</td>
<td>Anti-GBM - ANCA-</td>
<td>Idiopathic crescentic glomerular nephritis (with or without immune complex deposits)</td>
<td>Systemic lupus erythematosus, immunoglobulin A, MPGN cryoimmunoglobulin (with immune complex deposits)</td>
</tr>
<tr>
<td>III</td>
<td>Anti-GBM - ANCA+</td>
<td>Pauci-immune crescentic glomerular nephritis (microscopic polyangiitis)</td>
<td>Drug-induced crescentic glomerulonephritis</td>
</tr>
<tr>
<td>IV</td>
<td>Anti-GBM + ANCA+</td>
<td>Anti-GBM antibody–mediated crescentic glomerular nephritis with ANCA</td>
<td>Goodpasture’s syndrome with ANCA</td>
</tr>
</tbody>
</table>

ANCA—antineutrophil cytoplasmic antibody; anti-GBM—glomerular basement membrane antibody; MPGN—membranoproliferative glomerulonephritis.

**FIGURE 2-24**
Note that the serologic findings allow for a differentiation of the various forms of primary and secondary (eg, multisystem disease) forms of crescentic glomerulonephritis.

**FIGURE 2-25**
Chest radiograph of alveolar hemorrhage. This patient has antiglomerular basement membrane-mediated glomerulonephritis complicated by pulmonary hemorrhage (Goodpasture’s disease). Note the butterfly appearance of the alveolar infiltrates characteristic of intrapulmonary (alveolar) hemorrhage. Such lesions can also occur in patients with antineutrophil cytoplasmic autoantibody–associated vasculitis and glomerulonephritis, lupus nephritis (SLE), cryoglobulinemia, and rarely in Henoch-Schönlein purpura (HSP).
Evaluation of rapidly progressive glomerulonephritis. This algorithm schematically illustrates a diagnostic approach to the various causes of rapidly progressive glomerulonephritis (Figure 2-24). Serologic studies, especially measurement of circulating antiglomerular basement membrane antibodies, antineutrophil cytoplasmic antibodies, antinuclear antibodies, and serum complement component concentrations, are used for diagnosis. Serologic patterns (A through D) permit categorization of probable disease entities.

**Figure 2-26**

Evaluation of rapidly progressive glomerulonephritis. This algorithm schematically illustrates a diagnostic approach to the various causes of rapidly progressive glomerulonephritis (Figure 2-24). Serologic studies, especially measurement of circulating antiglomerular basement membrane antibodies, antineutrophil cytoplasmic antibodies, antinuclear antibodies, and serum complement component concentrations, are used for diagnosis. Serologic patterns (A through D) permit categorization of probable disease entities.

**Figure 2-27**

Antineutrophil cytoplasmic autoantibodies (ANCA). Frequently, ANCA are found in crescentic glomerulonephritis, particularly type III (Figure 2-24). Two varieties are seen (on alcohol-fixed slides). A, C-ANCA are due to antibodies reacting with cytoplasmic granule antigens (mainly proteinase-3). B, P-ANCA are due to antibodies reacting with other antigens (mainly myeloperoxidase).
Immunoglobulin A Nephropathy

Light, immunofluorescence, and electron microscopy in immunoglobulin A (IgA) nephropathy. IgA nephropathy is a chronic glomerular disease in which IgA is the dominant or sole component of deposits that localize in the mesangial regions of all glomeruli. In severe or acute cases, these deposits also are observed in the capillary walls. This disorder may have a variety of clinical presentations. Typically, the presenting features are recurrent macroscopic hematuria, often coincident with or immediately after an upper respiratory infection, along with persistent microscopic hematuria and low-grade proteinuria between episodes of gross hematuria. Approximately 20% to 25% of patients develop end-stage renal disease over the 20 years after onset. A, On light microscopy, widening and often an increase in cellularity in the mesangial regions are observed, a process that affects the lobules of some glomeruli to a greater degree than others. This feature gives rise to the term focal proliferative glomerulonephritis. In advanced cases, segmental sclerosis often is present and associated with massive proteinuria. During acute episodes, crescents may be present. B, Large round paramesangial fuchsinophilic deposits often are identified with Masson’s trichrome or other similar stains (arrows). C, Immunofluorescence defines the disease; granular mesangial deposits of IgA are seen with associated complement C3, and IgG or IgM, or both. IgG and IgM often are seen in lesser degrees of intensity than is IgA. D, On electron microscopy the abnormalities typically are those of large rounded electron-dense deposits (arrows) in paramesangial zones of most if not all lobules. Capillary wall deposits (subepithelial, subendothelial, or both) may be present, especially in association with acute episodes. In addition, capillary basement membranes may show segmental thinning and rarefaction.
The Primary Glomerulopathies

FIGURE 2-29
Natural history of immunoglobulin A (IgA) nephropathy. The evolution of IgA nephropathy over time with respect to the occurrence of end-stage renal failure (ESRF) is illustrated. The percentage of renal survival (freedom from ESRF) is plotted versus the time in years from the apparent onset of the disease. Note that on average about 1.5% of patients enter ESRF each year over the first 20 years of this nephropathy. Factors indicating an unfavorable outcome include elevated serum creatinine, tubulointerstitial lesions or glomerulosclerosis, and moderate proteinuria (>1.0 g/d). (Modified from Cameron [2].)

Fibrillary and Immunotactoid Glomerulonephritis

FIGURE 2-30 (see Color Plate)
Light, immunofluorescent, and electron microscopy in nonamyloid fibrillary glomerulonephritis. Fibrillary glomerulonephritis is an entity in which abnormal extracellular fibrils, typically ranging from 10- to 20-nm thick, permeate the glomerular mesangial matrix and capillary basement membranes. The fibrils are defined only on electron microscopy and have an appearance, at first glance, similar to amyloid. Congo red stain, however, is negative. Patients with fibrillary glomerulonephritis usually exhibit proteinuria often in the nephrotic range, with variable hematuria, hypertension, and renal insufficiency. A, On light microscopy the glomeruli display widened mesangial regions, with variable increase in cellularity and thickened capillary walls and often with irregularly thickened basement membranes, double contours, or both. B, On immunofluorescence, there is coarse linear or confluent granular staining of capillary walls for immunoglobulin G and complement C3 and similar staining in the mesangial regions. Occasionally, monoclonal immunoglobulin Gκ deposits are identified; in most instances, however, both light chains are equally represented. The nature of the deposits is unknown. C, On electron microscopy the fibrils are roughly 20-nm thick, of indefinite length, and haphazardly arranged. The fibrils permeate the mesangial matrix and basement membranes (arrow). The fibrils have been infrequently described in organs other than the kidneys.
Glomerulonephritis and Vasculitis

2.18

Light, immunofluorescent, and electron microscopy in immunotactoid glomerulopathy. Immunotactoid glomerulopathy appears to be an immune-mediated glomerulonephritis. On electron microscopy the deposits are composed of multiple microtubular structures in subepithelial or subendothelial locations, or both, with lesser involvement of the mesangium. Patients with this disorder typically exhibit massive proteinuria or nephrotic syndrome. This glomerulopathy frequently is associated with lymphoplasmacytic disorders.

A. On light microscopy the glomerular capillary walls often are thickened and the mesangial regions widened, with increased cellularity.

B. On immunofluorescence, granular capillary wall and mesangial immunoglobulin G and complement C3 deposits are present. The ultrastructural findings are of aggregates of microtubular structures in capillary wall locations corresponding to granular deposits by immunofluorescence.

C. The microtubular structures are large, ranging from 30- to 50-nm thick, or more (arrows).
Collagenofibrotic Glomerulopathy

Collagenofibrotic glomerulopathy (collagen III glomerulopathy). The collagens normally found in glomerular basement membranes and the mesangial matrix are of types IV (which is dominant) and V. In collagenofibrotic glomerulopathy, accumulation of type III collagen occurs largely in capillary walls in a subendothelial location. It is likely that this disease is hereditary; however, because it is very rare, precise information regarding transmission is not known. Collagenofibrotic glomerulopathy originally was thought to be a variant of nail-patella syndrome. Current evidence suggests little relationship exists between the two disorders. Patients with collagen III glomerulopathy often exhibit proteinuria and mild progressive renal insufficiency.

For reasons that are not clear, hemolytic-uremic syndrome has evolved in a small number of pediatric patients. A. On light microscopy the capillary walls are thickened and mesangial regions widened by pale staining material. These features are in sharp contrast to the normal staining of the capillary basement membranes, as evidenced by the positive period acid–Schiff reaction. With this stain, collagen type III is not stained and therefore is much paler. Amyloid stains (Congo red) are negative.

B. On electron microscopy, banded collagen fibrils are evident in the subendothelial aspect of the capillary wall.

References