CHAPTER

13 Renal Biopsy: Indications and Evaluation

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This chapter discusses the indications for performing a renal biopsy, describes the procedure and methods of tissue preparation, and demonstrates the manner in which biopsy specimens are interpreted using a combination of light microscopy, electron microscopy, and immunohistologic microscopy. The technique of percutaneous renal biopsy was introduced clinically in the early 1950s. Iversen and Brun[1] are generally credited with describing its initial use. They believed the technique would be quite useful in obtaining more information about diseases that caused acute kidney injury. At that time, the diseases were referred to as lower nephron nephrosis. The renal biopsy technique was used with increasing frequency during the 1950s, and it has enjoyed wide usage throughout the world since the early 1960s. The technique has provided a wealth of information about the histopathology, pathogenesis, and classification of renal disease that could not have been obtained by any other means.

Proponents of the biopsy procedure employ this technique to diagnose kidney disease, to assess prognosis, to monitor disease progress, and to aid in the selection of a rational approach to therapy. It is used extensively both in younger[2–7] and older patients.[8–14] However, the procedure is not without morbidity and, occasionally, mortality. Therefore, the risk/benefit ratio must be considered carefully in each patient who is being evaluated for a biopsy.

As originally described, the biopsy was performed with the patient in the sitting position, and the procedure involved aspiration of the tissue sample. Brun and Raaschou[15] used the Iversen-Rohlm cannula and syringe, which yielded a cylinder of tissue approximately 1.5 mm in diameter and of variable length. Kark and Muehrcke[16] chose to place the patient in the prone position and initiated the use of the Franklin modification of the Vim-Silverman cutting needle (Popper & Sons, Inc., New Hyde Park, NY) in place of the aspiration technique. Today, most nephrologists position the patient in the prone position and use a spring-loaded, semiautomatic biopsy device. The use of either ultrasonography (US) or computed tomography (CT) to locate the kidneys and to aid in positioning the biopsy needle has greatly simplified the technique and improved its safety.

Adequate tissue samples are obtained in greater than 95% of procedures. In a retrospective study, Bolton and Vaughn[17] reported that renal tissue was obtained in 97% of their patients with the use of image-amplification fluoroscopy, compared with 81% without the use of fluoroscopy. Percutaneous renal biopsies performed with renal imaging using either US or CT were successful in ~98% of patients in several series.[18–21]

The percutaneous renal biopsy is a safe and reliable technique in the hands of the experienced operator. The most common complication is bleeding, which occurs in the majority of patients if they are studied carefully after biopsy using ultrasonography[22] or CT.[23,24] However, the bleeding is self-limited and rarely requires an operative intervention or a blood transfusion. In a survey[25] of the results of over 5,500 percutaneous renal biopsies, the rate of complications, including the need for a blood transfusion or a nephrectomy, the puncture of other organs, or the presence of a clinically evident perinephric hematoma, was 2.1%. The overall mortality is approximately 0.1% to 0.2%,[25–27] which is comparable to that reported for percutaneous liver biopsy or coronary angiography.[25] In a study from a single institution[28] in which 1,000 consecutive percutaneous renal biopsies were analyzed, a total of 94 complications were observed in 81 patients. Gross hematuria, including the passage of blood clots, represented 73% of the complications. Two patients underwent exploration for the evacuation of perirenal hematomas, but no kidneys were lost. One patient died of multiple complications after biopsy.

Multiple factors are associated with an increased risk of complications from the renal biopsy procedure. In one study, the presence of a serum creatinine of at least 5.0 mg per deciliter was associated with a 2.3-fold increase in the risk of a complication.[29] Other studies have identified uncontrolled hypertension, thrombocytopenia, and anemia as predictors of increased risk for complications.[30–32] The simultaneous presence of both hepatitis C and HIV infection is associated with as much as a 5.7-fold increase in complications,[31] but the presence of amyloidosis or monoclonal gammopathy is not.[33,34]

The timing of postprocedure complications has important implications regarding how long patients should be observed prior to discharge. Most studies have shown that the great majority of complications can be identified in the initial 6 to 8 hours after the procedure,[32,35] suggesting that a renal biopsy can be performed safely as an outpatient procedure. However, some studies report that as many as 33% of complications are not identified after 8 hours of observation.[29] Screening tests such as the presence or absence of a postprocedure perirenal hematoma may be helpful in assessing the risk of a clinically significant complication.[36,37]

TECHNIQUES

Prior to an elective renal biopsy, it is important to screen the patient for the presence of bleeding disorders. A careful history should be obtained to determine whether abnormal bleeding occurred during previous surgical procedures. A history of severe menorrhagia, if female, and other evidence of abnormal bleeding, as well as a family history of bleeding disorders should be sought. Screening laboratory studies may include an assessment of the platelet count and bleeding time. In addition, it is advisable to obtain the hematocrit and hemoglobin levels within 24 hours prior to the procedure. Renal imaging, typically by ultrasonography, should be performed prior to a biopsy to assess for the presence of anatomic abnormalities, including solitary kidney, horseshoe kidney, hydronephrosis, small kidneys, or other anatomically abnormal kidneys, which may adversely affect the risk of a renal biopsy. Currently, most percutaneous biopsies are performed with the guidance of US or CT to permit an accurate localization of the kidney. The use of a premedication, such as midazolam (Versed), to help alleviate patient anxiety may make the procedure less unpleasant for the patient. We routinely place an intravenous access in the patient.

Most operators prefer to biopsy the lower pole of the left kidney to reduce the risk of inadvertently passing the biopsy needle through a major renal artery or vein. After the completion of the biopsy, patients are instructed to remain at bed rest for 6 to 8 hours. In our institution, we screen with US or CT in the immediate postprocedure period for the presence or absence of a perirenal hematoma and its size, if present. We assess the blood pressure and pulse every 15 minutes for 1 hour, every 30 minutes for 1 hour, then hourly for the next 4 to 6 hours. The patient is asked to save an aliquot of each voided urine in a separate clear plastic specimen jar labeled with the date and time, which is kept at the patient's bedside for inspection. This provides a visual check for evidence of bleeding into the intrarenal collecting system. The hemoglobin and hematocrit are determined 6 to 8 hours after the biopsy, or earlier if hemodynamic instability or gross hematuria is observed. If the hemoglobin and hematocrit are stable, the patient is relatively pain free and there is no hemodynamic instability or gross hematuria, we discharge the patient home with instructions to call immediately should there be a change in his or her clinical condition. If the patient does not meet these criteria, we admit the patient overnight for further observation.

An outpatient renal biopsy, as described in the previous paragraph, is a component of an ongoing trend to identify approaches to optimize the use of health care resources. An ample amount of literature demonstrates the safety of this approach in both native and transplanted kidney biopsies in both children and adults.[38–40] Ultrasonographic evidence suggests that most episodes of major bleeding occur within the initial 6 hours after a renal biopsy and that the size of perirenal hematomas actually decreases thereafter.[39] These data confirm an earlier report by Carvajal et al.[2] who found only three significant bleeding episodes in 890 consecutive percutaneous biopsies performed in pediatric patients. These data, when linked with the experience in the outpatient setting thus far, suggest that in carefully selected patients in whom the procedure is performed without difficulty, the use of ambulatory percutaneous renal biopsy can be justified. If patients are free of pain at the site of biopsy, have clear urine, and have stable cardiovascular signs for a minimum of 4 to 6 hours after the procedure, they can be safely discharged.[40] Activity should be restricted for at least 24 hours, and patients should be cautioned to seek medical attention immediately if there is macroscopic hematuria or pain over the biopsy site.

Several types of spring-loaded automatic or semiautomatic biopsy guns are employed to perform percutaneous biopsies of both transplanted[21,39–50] and native kidneys.[21,49–63] Based on a sample of almost 2,000 percutaneous biopsy procedures, the rate of complications, including a clinically evident hematoma, nephrectomy, blood transfusion, acute urinary tract obstruction, or biopsy of another organ, was 1%. Adequate samples of tissue were obtained 94% of the time on the initial attempt at biopsy. These data compare very favorably with the published experience with either the Franklin modification of the Vim-Silverman needle or the Travenol Tru-Cut disposable needle (Travenol Laboratories, Deerfield, IL).[17,25] Furthermore, when direct comparisons have been made, the results obtained with the biopsy gun were easily comparable to those achieved with the Travenol disposable needle.[44,48,54,55,60,61] In another study,[21] 1,090 percutaneous kidney biopsies were performed using US guidance and an automated spring-loaded biopsy device. A total of 114 (10.4%) were performed on renal allografts and 976 (89.6%) were performed on orthotopic kidneys. No serious complications, including the loss of kidney, life-threatening hemorrhage, or a persisting hemodynamically relevant arteriovenous (AV) fistula, were encountered. In 98.8% of the patients, sufficient tissue was obtained to make a reliable histopathologic diagnosis.

When combined with real-time US technology, there are several advantages to using the fully automatic biopsy guns. For example, the depth of the biopsy is controlled precisely and can be selected for a particular clinical situation. In the case of one of the most commonly used instruments

(Biopty, Bard Urological Division, C.R. Bard, Covington, GA), the long-throw device has a depth of 2.3 cm, yielding a specimen with a potential length of up to 1.7 cm. The short-throw device has a depth of 1.15 cm and a potential specimen length of 0.9 cm.[64] Fully automatic biopsy guns can be triggered with one hand, thus leaving the operator with a free hand to control the US probe if necessary. Instruction in the use of the biopsy gun is also easier. Many also believe that there is less discomfort with use of the biopsy gun.[21,53,54,60] Some studies have found decreased bleeding with automated biopsy devices,[65] whereas others have not.[60] The use of automated renal biopsy devices has almost completely replaced the use of manual devices.

Currently, there is no universal agreement on the optimum size of the needle that should be used with the various biopsy guns. Many favor the 18-gauge needle, which retrieves almost as many glomeruli per specimen as larger gauge needles.[41–54] This is due, in part, to the fact that the individual specimens have cleaner, sharper edges with less crush artifact. Certainly, in pediatric patients, the 18-gauge needle has been found to be quite adequate.[49,50,52,63] We favor use of a 15- or 16-gauge needle for biopsies in adult patients.

An alternative technique for performing the renal biopsy involves the transjugular approach. In this technique, a guide wire is inserted through the right internal jugular vein, through the vena cava, into the right renal vein, and is then wedged into the lower pole of the right kidney. A transvenous biopsy needle, similar to those used for transjugular hepatic biopsies, is then inserted over the guide wire, advanced into the kidney, and samples are taken. The first description of the procedure is generally attributed to Mal et al.,[66] who reported its use in 50 consecutive patients. All were patients in whom conventional percutaneous renal biopsy was felt to be clinically contraindicated, because of a need for simultaneous hepatic and renal biopsies, severe clotting disorders, respiratory insufficiency, uncontrolled hypertension, morbid obesity, or a solitary kidney. Renal tissue was obtained in 88% of patients, and glomeruli were present in 76% of the samples. Since this initial description, the procedure has become available and is used in a large number of centers. Typically, because of the increased technical difficulty and the cost of the procedure, the transjugular renal biopsy is reserved for patients with contraindications to a percutaneous renal biopsy. Subsequent studies that followed this initial report have confirmed its usefulness in patients in whom a conventional percutaneous approach is contraindicated. In general, adequate tissue is obtained in 85% to 95% of procedures.[67–72] The reported complications include capsular perforation, collecting system puncture, hematuria or loin pain, sufficient bleeding that blood transfusion is necessary, and hypovolemic hemorrhagic shock.[67–71,73,74] Because of the risk of postprocedure complications, most patients should be observed overnight after the procedure. The presence of an underlying clotting disorder is associated with an increased risk of complications,[74] but morbid obesity is not.[70] Thus, the transjugular renal biopsy provides an approach to the renal biopsy in patients in whom a conventional percutaneous approach is contraindicated. The risk of complications, although not inconsequential, is generally considered acceptable if the result of a renal biopsy is important in the patient's management.

Because decreased glomerular filtration rate can lead to platelet dysfunction, which may increase the risk of bleeding, efforts have been made to determine whether specific prebiopsy testing can decrease the risk of clinically significant postrenal biopsy bleeding. Traditional coagulation tests, such as partial thromboplastin time (PTT), prothrombin time (PT), and the International Normalized Ratio (INR), assess coagulation factor-mediated clotting, which is not altered with renal disease. Therefore, such tests are not good predictors of bleeding after a renal biopsy. The bleeding time, sometimes termed the template bleeding time, is more specific for assessing platelet function. Many authors feel that the bleeding time should be a routine component of the pretransplant evaluation,[75,76] whereas others disagree and have instead suggested that failing to measure the bleeding time does not expose the patient to an increased risk of bleeding.[77] Our personal practice is to assess the bleeding time, particularly in individuals with an increased blood urea nitrogen (BUN), in whom the risk of uremic platelet dysfunction is greater.

There are a number of treatment options in patients with uremic platelet dysfunction. Desmopressin (deamino-8-D-arginine vasopressin) rapidly decreases the bleeding time in patients with uremic platelet dysfunction,[78] and can be used to treat patients with a prolonged bleeding time.[75] A recent prospective, randomized clinical trial suggested that the routine use of desmopressin in patients with a serum creatinine less than 1.6 mg per deciliter and normal coagulation parameters, irrespective of bleeding time, decreases both the likelihood of postbiopsy bleeding (treated, 13.7% versus control, 30.5%) and, in those with bleeding, decreases both the size of the hematoma and the duration of hospital stay.[79] Although very intriguing, it is our current belief that confirmatory studies are necessary before adopting routine desmopressin treatment for all renal biopsies. Uremic platelet dysfunction can also be treated either with renal replacement therapy, such as hemodialysis,[80] or with oral estrogen therapy.[81,82] These alternative therapies take longer to improve the bleeding time than is required for desmopressin, and therefore are not routinely used.

INDICATIONS

There is no universal agreement on the precise indications for use of the percutaneous renal biopsy despite almost 60 years of experience with the technique by the nephrology community. The present section describes several clinical situations in which this technique is either routinely or frequently employed to aid in the evaluation and management of a patient with undiagnosed kidney disease.

Acute Kidney Injury

There are many occasions when the etiology of acute kidney injury secondary to intrinsic renal disease is not evident despite a carefully performed history and physical examination and the availability of information gained from various laboratory studies. A biopsy can be very useful in establishing the diagnosis, determining the approach to management, and defining the prognosis in this clinical setting. Retrospective studies from several centers have revealed that the diagnosis of acute tubular necrosis (ATN) cannot be established clinically[76,83–85] in 10% to 25% of patients who present with acute kidney injury. A biopsy in this population can be important because other causes of acute kidney injury are revealed, such as crescentic proliferative glomerulonephritis, interstitial nephritis, Wegener granulomatosis, polyarteritis nodosa, multiple myeloma, amyloidosis, endocapillary proliferative glomerulonephritis, cortical necrosis, hemolytic-uremic syndrome (HUS), systemic lupus erythematosus (SLE), and thrombotic thrombocytopenic purpura, to list just a few. These diseases usually require an approach to management that is different than that normally employed in uncomplicated cases of ATN.

Occasionally, a biopsy can provide helpful clinical information in patients who appear to have ATN on clinical grounds at initial presentation, but who do not regain renal function after 2 to 3 weeks of supportive therapy, including dialysis. The diagnostic possibilities generally are the same as those listed in the preceding paragraph. A careful evaluation of the clinical situation is deemed prudent before a renal biopsy is initiated because this procedure carries a higher risk in the patient with acute uremia.[86]

Nephrotic Syndrome

A renal biopsy in the clinical setting of an acute nephrotic syndrome not associated with systemic disease is influenced greatly by the age of the patient. It is common practice to treat children initially with high-dose corticosteroids, because most younger children have minimal change nephrotic syndrome (MCNS) on a biopsy. The presence of a selective proteinuria and normal renal function and the absence of hypertension strengthen the clinical diagnosis. In children, a biopsy is usually reserved for patients with no response to corticosteroid therapy or in whom the clinical and laboratory features of the illness at the time of initial presentation are distinctly atypical for MCNS. These features would include hypertension, azotemia in the absence of volume depletion, nonselective proteinuria, a highly active urine sediment including red cell casts, and involvement of other organ systems.

Most nephrologists believe that the adult nephrotic patient without signs of systemic disease should undergo a biopsy before therapy is initiated because the majority of these patients, including elderly persons,[87] have a renal disease other than MCNS.[10] The most frequent cause of the nephrotic syndrome in adults is idiopathic membranous glomerulonephritis[10,88]; other frequent causes include focal segmental glomerular sclerosis (FSGS), membranoproliferative glomerulonephritis (MPGN), proliferative glomerulonephritis, immunoglobulin A (IgA) nephropathy, and amyloidosis. Because the optimal treatment differs in different conditions, a renal biopsy can provide helpful clinical information. Moreover, fewer than one-third of adult patients have MCNS. Thus, if the physician elects to administer a short course of high-dose corticosteroid therapy equivalent to that employed in pediatric patients, approximately two-thirds of the patients would not be expected to respond favorably. Despite suggestions to the contrary, [25] we believe the risks associated with the use of corticosteroids or other immunosuppressive agents, such as azathioprine, chlorambucil, cyclosporine A, mycophenolate mofetil, and cyclophosphamide, in this population are too great to justify their use in the absence of a specific histologic diagnosis.

Isolated Proteinuria

Isolated nonnephrotic proteinuria of 1 g or less per 24 hours without hematuria or pyuria in an otherwise asymptomatic patient who does not have diabetes mellitus is a relatively common clinical problem. Often, the proteinuria is first detected during a routine physical examination required for participation in school athletics, during a preemployment examination, or at the time of application for life insurance. In young adults, orthostatic proteinuria is commonly identified in this presentation, carries a benign prognosis, and does not require a renal biopsy.[89] Otherwise, unless the patient requests a kidney biopsy for purposes of reassurance, it is currently our policy to merely monitor the clinical course of such patients at periodic intervals of 6 months to 1 year. There is little evidence to suggest that these patients will progress to renal failure or that they are candidates for any type of specific medical therapy in the absence of impaired renal function.[90] If there is any evidence during follow-up of functional deterioration or the development of additional clinical signs or symptoms suggesting the presence of a primary renal disease or kidney involvement secondary to systemic disease, the patient is thoroughly reevaluated and is often advised to undergo a kidney biopsy for diagnosis and possible therapeutic intervention.

In asymptomatic patients who do not have diabetes mellitus and who remain nonnephrotic but persistently excrete more than 1 g of protein per 24 hours, we advise a renal biopsy. It is this group of patients who are more likely to have an underlying renal abnormality. Some of the more common diagnostic possibilities include early idiopathic membranous glomerulonephritis, FSGS, and IgA nephropathy. Patients with urinary abnormalities such as hyaline and granular casts are even more likely to have an underlying glomerular abnormality.[91]

Hematuria with or without Proteinuria

Asymptomatic hematuria, especially in children and young adults, is a frequent cause of referral to nephrologists. It is important that causes of hematuria due to neoplasms in either

the upper or lower collecting system or due to either cystitis or pyelonephritis be excluded before one considers a renal biopsy. In general, the diagnostic value of a renal biopsy in the setting of idiopathic microscopic hematuria relates directly to the extent of associated clinical and laboratory findings. For example, in a series of 76 pediatric patients with isolated hematuria, Trachtman et al.[92] found that almost three-quarters of all biopsy specimens obtained in patients who had either a first-degree relative with hematuria or a history of at least one episode of gross hematuria were abnormal histologically. IgA nephropathy and Alport syndrome were the two most common findings. Schröder et al.[93] performed renal biopsies in 65 children with isolated hematuria of at least a 1-year duration. Of the group, 95% had histologic abnormalities that included IgA nephropathy (16 patients), Alport syndrome (8 patients), thin glomerular basement membrane (33 patients), and nonspecific mesangial abnormalities (5 patients). In a later report, Topham et al.[94] evaluated 165 children and adults with isolated hematuria using cystourethroscopy and renal biopsy. All had a normal intravenous pyelogram, were normotensive with a normal serum creatinine, and were free of both proteinuria and a urinary tract infection. In this group, 47% had significant histologic findings, including IgA nephropathy in 49 patients, whereas only 5 abnormalities were identified on a cystourethroscopy. Renal biopsy abnormalities were most common among patients under 20 years of age (69%), prompting these investigators to conclude that a renal biopsy should replace a cystoscopy in younger patients as the next step in evaluation if renal imaging yielded normal results. Furthermore, because renal histologic abnormalities are quite frequent in the clinical setting of isolated hematuria, these investigators recommended a kidney biopsy in patients over 45 years of age in whom findings at renal imaging and cystoscopy are normal.

The likelihood of identifying significant glomerular pathology is considerably higher when hematuria is accompanied by proteinuria, with or without an abnormal urine sediment that includes red blood cell, granular, hyaline, or white blood cell casts. We believe it is important to establish the histologic diagnosis of the renal lesion in this clinical setting; although admittedly, a biopsy is not required to identify the source of hematuria. Primary renal diseases that can be seen include IgA nephropathy, acute or resolving postinfectious glomerulonephritis, MPGN, and an occasional example of interstitial nephritis. Heredofamilial and multisystem diseases that may be seen include Fabry disease, sickle cell trait and disease, polyarteritis nodosa, Wegener granulomatosis, diabetes mellitus, SLE, and Henoch-Schönlein disease. Many of these systemic diseases may be evident on clinical grounds if a careful prebiopsy evaluation is undertaken, as discussed in the next section.

Systemic Disease

There are many systemic diseases that involve the kidney, although the extent and frequency of involvement varies considerably in different conditions. Patients often undergo a renal biopsy for diagnosis and management on the basis of either the frequency or severity of the renal lesion. These diseases include SLE, Henoch-Schönlein purpura, polyarteritis nodosa, Goodpasture syndrome, Wegener granulomatosis, and various gammopathies.

In approximately 40% to 50% of all patients with type I insulin-requiring diabetes mellitus and comparable percentages with type II adult-onset diabetes mellitus, renal failure develops during the course of the disease.[95,96] The natural history of renal disease in both types of diabetes mellitus has been well studied and is reasonably predictable[96]; thus, in most patients, a renal biopsy is seldom indicated for a diagnosis or management. However, a biopsy can be helpful in patients whose course may be complicated by the sudden development of renal failure, proteinuria, or nephrotic syndrome, or who have serologic evidence of other causes of renal disease.

Although nephrotic syndrome is observed in approximately 10% of all patients with diabetes, its sudden appearance, especially in the young diabetic without previous evidence of functional renal impairment, should not be ascribed automatically to diabetic nephropathy. This point is well illustrated by the experience of Urizar et al.[97] who described five young diabetic patients with nephrotic syndrome in whom the renal disease was not distinguishable histologically from MCNS. Nephrotic syndrome appeared either simultaneously or shortly after the recognized onset of diabetes in three of the children. Treatment with corticosteroids in four patients resulted in a prompt response, with loss of edema, cessation of proteinuria, and normalization of all serum abnormalities. No patient had abnormalities suggestive of diabetic nephropathy. Other investigators have reported similar experiences.[98,99]

Other types of renal disease also can be seen in association with diabetes mellitus, often in the clinical setting of the nephrotic syndrome. Couser et al.[100] reported the coexistence of dense deposits within the glomerular and tubular basement membranes, resembling those seen in type 2 MPGN and lesions typical of diabetic nephropathy in a 24-year-old nephrotic man with type I diabetes mellitus. Other examples of well recognized renal diseases that have been reported to occur in patients with diabetes mellitus in either the presence or absence of diabetic nephropathy include acute postinfectious proliferative glomerulonephritis,[101,102] crescentic proliferative glomerulonephritis,[101] and membranous glomerulonephritis.[103–105]

The renal biopsy is central to the management of SLE with renal involvement (i.e., lupus nephritis). At present, it is our practice to biopsy all patients who present with clinical evidence of active lupus nephritis unless a medical contraindication exists. Border[106] has suggested that patients with more than six red blood cells (RBCs)/high-power field, a urine protein excretion greater than 200 mg per 24 hours, or an abnormal serum creatinine value are candidates for a biopsy. There is no other way to establish the type of renal lesion that is present, and the management of lupus nephritis varies considerably depending on the specific histologic lesion.

The value of renal biopsy in predicting a prognosis has been debated. The results of earlier studies suggested that the biopsy classification of lupus nephritis was useful in predicting the clinical course[107,108] and this issue was challenged[109–111] from a prognostic standpoint but reaffirmed subsequently.[112–116] Correspondingly, we believe it is important to establish as precise a histologic diagnosis as possible because, in general, patients with diffuse proliferative lupus nephritis with signs of disease activity, such as increased cellularity, segmental necrosis, fibrinoid deposits, and crescents in the glomeruli, have a poorer prognosis than individuals with mesangiopathic, focal proliferative, or membranous lupus nephritis.

Controversy also exists concerning the value of renal biopsy in patients with clinically silent lupus nephritis. In 1977, Mahajan et al.[117] described 12 patients with diffuse lupus nephritis but without clinical or laboratory evidence of renal involvement at the time of renal biopsy. A later report, in which 10 of the original 12 patients were followed from 5 to 11 years, revealed deterioration of renal function in 3 years, with one death as the result of renal failure.[118] All patients received prednisone alone or in combination with azathioprine. These investigators concluded that the prognosis for the preservation of renal function appeared better in patients with clinically silent diffuse proliferative nephropathy as opposed to those with clinically active disease, and recommended a biopsy in patients with SLE even in the absence of overt clinical renal involvement.[118] Woolf et al.[119] described eight patients ranging in age from 6 to 26 years, with clinically silent lupus nephritis, who on biopsy had a variety of histologic lesions indicative of active renal involvement. Although no consensus exists regarding the use of a renal biopsy in patients with SLE who are without clinical evidence of renal involvement, it is currently our policy to withhold a biopsy in this group of patients.

Renal biopsy can often aid the clinician in selecting an appropriate therapy for the treatment of vasculitis when renal involvement is present. Polyarteritis nodosa and Wegener granulomatosis require aggressive combination therapy with cyclophosphamide and prednisone. The prognostic value of crescents in antiglomerular basement membrane (GBM) disease and other conditions is discussed in later paragraphs. Other systemic diseases that often exhibit renal involvement and, therefore, can be diagnosed with the aid of a renal biopsy when other diagnostic tests have failed or have not been employed include multiple myelomas, kappa light-chain disease,[120] amyloidosis,[121] fibrillary glomerulonephritis, and mixed cryoglobulinemia with renal failure.[85,122]

Transplant Kidney

Renal biopsies are a valuable diagnostic tool in the management of the transplant recipient. A biopsy of an allograft represents the major clinical exception to avoidance of a percutaneous biopsy of a single functioning kidney. Numerous studies confirm the value and relative safety of a renal biopsy in this setting.[41,42–48,123,124] A biopsy is the most accurate means of determining the presence of lesions, such as cellular or humoral rejection, ATN, drug-induced or viral (especially BK virus) interstitial nephritis, hemorrhagic infarction, calcineurin inhibitor toxicity, and de novo or recurrent glomerulonephritis in the allograft. There are several clinical settings in which a biopsy of the allograft is often indicated. These include failure of the graft to function within the initial 7 to 10 days after surgery, a rapid deterioration in function of unknown etiology after the initial good function, an absence of a response to an adequate antirejection therapy within a reasonable period of time, and an unexplained nephrotic syndrome or nephrotic-range proteinuria.

A large number of cadaveric kidneys are engrafted, and ischemia-reperfusion injury is a frequent complication. Failure to achieve improved renal function within 7 to 10 days after surgery raises the possibility of a more severe form of renal injury, such as an infarction or a superimposed episode of acute rejection. A biopsy is often invaluable in determining the etiology of the renal failure, in guiding subsequent therapy, and in establishing a prognosis. For example, Kiaer et al.[125] reported a 100% graft loss when infarction, capillary thrombosis, and arterial or arteriolar thrombosis were found either singly or in combination on a biopsy. Thus, the presence of these lesions in the clinical setting of an acute kidney injury would obviate the necessity for the continued use of antirejection therapy.

The incidence of acute rejection, characterized by a sudden decrease in renal function, is greatest during the first 6 months after transplantation. In most instances, the suspicion of acute rejection can be made on clinical grounds. However, acute rejection often occurs in the absence of clinical features, such as graft tenderness or fever, and a patient believed to have acute rejection may not respond to a reasonable course of antirejection therapy. It may be desired to tailor the antirejection therapy to vascular versus tubulointerstitial rejection or antibody versus cellular rejection. A biopsy can be extremely helpful at this juncture in the patient's therapy. In particular, the presence of peritubular C4d deposition suggests the presence of acute humoral rejection, whereas its absence is typical in cell-mediated rejection.[126,127] A confirmation of acute humoral rejection involves the demonstration of morphologic evidence of acute tissue injury in combination with circulating antibodies to either donor human leukocyte antigen (HLA) or to other antidonor endothelial antigens.[128] Other complications, such as ATN, drug-induced nephrotoxicity, or overt renal infarction may be diagnosed.

As noted previously, C4d staining of biopsies has been a valuable tool. C4d is produced by the activation of the classic and lectin complement pathways. Thus, ischemia reperfusion (I/R), necrosis, lupus nephritis, and other conditions may exhibit C4d staining and must be considered in a biopsy interpretation.[129–133] Current guidelines recommend the exclusion of loci of I/R, necrosis, and fibrosis when using C4d staining to evaluate for possible humoral rejection.[128,134,135]

The occurrence of the nephrotic syndrome or nephrotic-range proteinuria in a transplant recipient suggests the possibility of either recurrent or de novo glomerulonephritis.[136,137] Those forms of disease that are most likely to recur in the transplant kidney include MPGN, FSGS, diabetic nephropathy, and IgA nephropathy.[136,137] To date, the most common de novo disease reported is membranous glomerulonephritis.[136] Although some would take exception, we believe it is worthwhile to establish the lesion that is responsible for proteinuria, especially if the proteinuria is associated with a decrease in renal function.

Renal Mass or Neoplasm

In addition to a percutaneous kidney biopsy for traditional medical indications, as introduced previously, the past decade has seen renewed interest in percutaneous (core) biopsies for renal masses and other neoplasms. The technique fell into disfavor in previous decades because of bleeding, false-negative results, and other less common complications.[138] Regardless, there is a driving force for tissue diagnosis because 50% of renal neoplasms are now identified as incidental to abnormal imaging for other reasons. A percutaneous renal mass biopsy is often performed to evaluate for a possible lymphoma, a renal abscess, or metastatic disease due to a known extrarenal malignancy. It may also be performed to confirm the diagnosis of a primary renal neoplasm in a patient with known disseminated disease or an unresectable retroperitoneal tumor in whom surgical treatment is contraindicated.[138–144] Although there was initial concern regarding the potential for seeding the biopsy tract with malignant cells, only a total of six cases have been reported, and multiple case series published since 1999 have reported no such events.[145]

CONTRAINDICATIONS

Both the relative and the absolute contraindications for a renal biopsy vary among nephrologists. However, most agree that the risk of complications increases in the presence of severe uncontrolled hypertension, sepsis, known or suspected renal parenchymal infection, a hemorrhagic diathesis, a solitary ectopic or horseshoe kidney (except in the case of a transplanted kidney), or when the patient is unable to cooperate during the procedure.

In 1958, Kark et al.[146] published the results from their initial 500 percutaneous renal biopsies and listed 11 contraindications. These included an uncooperative patient, large cysts, a renal neoplasm, a renal artery aneurysm, marked calcific arteriosclerosis, a hemorrhagic diathesis, a single kidney, a perinephric abscess, hydronephrosis or pyonephrosis, a terminal state of illness, and a rising blood nonprotein nitrogen level greater than 100 mg per deciliter. Hypertension was viewed as a relative contraindication, depending on the importance of the biopsy and the skill of the operator.

Certainly, the presence of a single kidney (except a renal allograft), including a horseshoe kidney, sepsis, or a hemorrhagic diathesis, remain important contraindications to percutaneous renal biopsy.[147] However, in some patients, an open or laparoscopic biopsy may well be justified if the clinical situation warrants the risk. This also holds true for the patient with a renal artery aneurysm or calcific arteriosclerosis and an undiagnosed parenchymal renal disease. Many times, a coagulation disorder can be corrected, thus allowing the biopsy to be performed. In most clinical situations, there is little or no reason to perform a biopsy if the patient has large multiple cysts or a terminal illness. The same is true in the presence of a perinephric abscess, acute pyelonephritis, hydronephrosis, or pyonephrosis. Today, a rising BUN or a BUN greater than 100 mg per deciliter is not considered a contraindication if the rise is sudden or unexplained and quite likely due to an acute and potentially reversible process, as discussed earlier in this chapter. The presence of normal-sized or large kidneys increases the likelihood that an acute rather than a chronic form of renal failure is present.

When a patient is hypertensive, we delay the biopsy until the blood pressure is brought under adequate control. Thus, the presence of hypertension should be considered, at most, a relative contraindication. It is important that blood pressure control is obtained because it is well documented that hypertensive patients are more prone to bleeding after a percutaneous renal biopsy.[17,28] Diaz-Buxo and Donadio[28] not only found a significantly greater incidence of complications in hypertensive patients (11.6%) as compared with normotensive subjects (7.1%) undergoing percutaneous renal biopsy, but the higher incidence also correlated positively with both the severity and the duration of the hypertension.

GROSS INSPECTION AND TISSUE PROCESSING

An evaluation of a kidney biopsy includes both a gross and a histologic examination of the specimen. A standard histologic examination includes light microscopy, immunohistology, and transmission electron microscopy. Other less frequently used techniques include scanning electron microscopy, microbiologic cultures, tissue and cell cultures, quantitative or qualitative chemical analyses, enzyme assays, and molecular pathology. Most of the remainder of this chapter is concerned with the preparation, histologic examination, and actual evaluation of the biopsy specimen for clinicopathologic interpretation.

Gross Examination

The general purpose of a gross examination is to determine adequacy and to divide the specimen into the appropriate portions for subsequent processing. The overall dimensions, color, and consistency should be noted. In particular, the area of viable cortex should be identified and delineated from the medulla, which is generally paler. Areas of infarction, other necrosis, or pyogenic inflammation that are often pale and highlighted by a hyperemic border may be evident by a gross examination. Ischemia with reflow also may be

hyperemic throughout. In general, if the specimen contains both the cortex and the medulla, the medulla is the deeper tissue as it is removed from the needle, although there are several exceptions. If the needle is thrust deeply into the kidney before the core is taken, the cortex may be missed altogether, or if the direction of the needle is obtuse to the pelvis, the needle may pick up the medulla first and then the cortex as it passes completely through the medulla. We have observed specimens that contain the cortex, the medulla, and then more of the cortex. Chronic disease will make it more difficult to delineate the cortex.

Allografts have additional notable characteristics. First, in older grafts, a thick rind of fibrous tissue surrounds the graft. This area may be quite pale and should not be confused with the cortex. In newer grafts, the surface may be deeply colored from a hemorrhage or the presence of granulation tissue. Second, the outermost rim of the cortex may be pale from ischemic atrophy or necrosis. The deeper cortex is of interest for the diagnosis of an additional disease. Many laboratories employ a dissecting microscope or hand lens to identify glomeruli in the cortex and to guide division of the specimen at the time of the biopsy.

Processing for Histologic Examination

Despite considerable effort, it has not been possible to develop a single method of tissue fixation and processing that is optimal for light, immunofluorescence, and electron microscopy. Therefore, it is customary to divide the cortical portion of the biopsy into three parts (Fig. 13.1). We prefer to divide the tissue core along its short axis, as illustrated, to minimize tissue damage. For longer cores, the largest part is taken for light microscopy, a smaller portion is taken for immunofluorescence microscopy, and the smallest portion is taken for electron microscopy. The exact proportions of this division are variable and depend on the total amount of cortex and the clinical setting (e.g., native versus allograft biopsy). The basic consideration in the division of the specimen depends on the definition of an adequate sample for each type of histologic examination. Six glomeruli generally are considered an adequate number in a native kidney for light microscopic evaluation. However, in exceptional circumstances, the limits are broad. For example, in the evaluation of a patient with nephrotic syndrome, a disease that is diffuse and generalized such as uncomplicated idiopathic membranous glomerulonephritis may be diagnosed with a single glomerulus. On the other hand, in the early stages of a focal proliferative disease or with the variable pattern of involvement often observed in lupus nephritis, the diagnosis may not be appreciated with six or more glomeruli. We prefer a core of tissue sufficient in length to provide 12 glomeruli for light microscopic examination. The extent or degree of severity of chronic atrophy also is determined best on larger specimens and is especially important for the assessment of permanent nephron loss.

The factors that determine the adequacy of a sample for immunohistology are somewhat different. The principal role of immunohistochemistry is to evaluate the type, location, and distribution of serum proteins, particularly those commonly identified in immune complexes or directed against a specific antigen, such as seen in anti-GBM disease. The biology of these immune diseases is such that the distribution of immune mediators is more diffuse and generalized, even though the light microscopic pattern may be focal and segmental; therefore, sections containing four to six glomeruli usually are adequate.

Electron microscopy is most useful in diffuse and generalized diseases. It is preferable to examine two or three glomeruli as well as tubules and small vessels whenever possible. After the viable cortex has been divided, any remaining tissue such as the medulla is also processed for light microscopy.

When only a few millimeters of cortex are obtained, we process the entire specimen for electron microscopy. During the examination for electron microscopy, the tissue also is evaluated by light microscopy so that the maximum amount of information can be obtained. In addition, electron microscopic processing is technically most suited for handling small pieces of tissue, and the overall preservation of the tissue is much better. If the core of the cortex is 4 to 8 mm in length, we process equal parts for the electron microscopy and the immunofluorescence microscopy (Fig. 13.1).

Two tissue cores are recommended for allograft biopsies because of the variable nature of rejection.[148] We also modify the division of tissue from transplant biopsies. This is done to expedite the diagnosis when rejection is suspected. Approximately half the cortex is submitted for frozen sections. Most of the remainder is processed for routine light microscopy. Small (1-mm) portions are saved for electron microscopy. Frozen sections are taken immediately for light microscopy stains, hematoxylin and eosin (H&E) and periodic acid-Schiff (PAS), and immunohistology microscopy. These procedures can be completed within 1 to 2 hours. Rejection can be determined from the frozen sections in many patients. The final evaluation has to wait

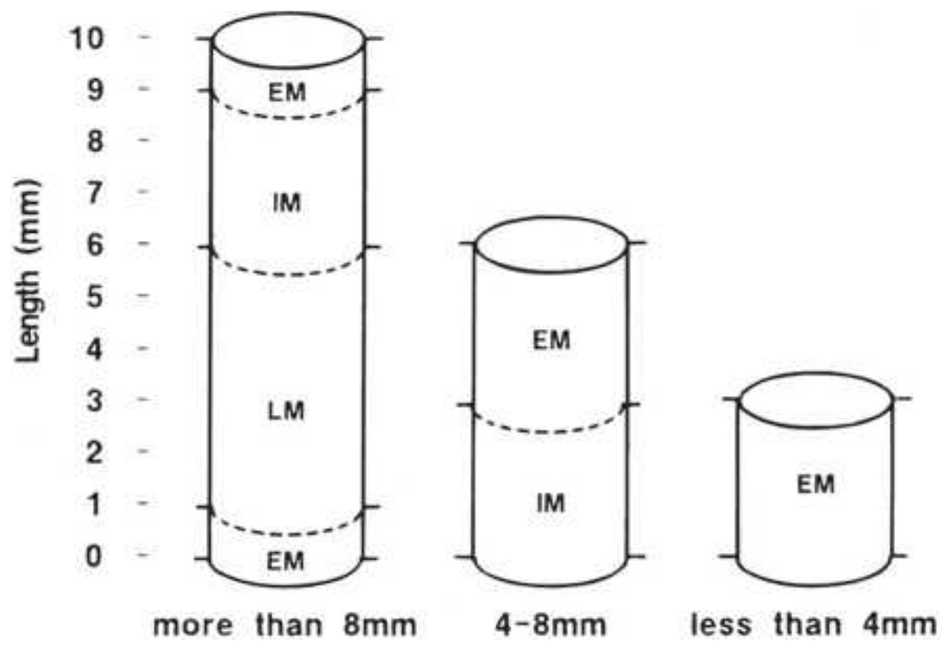


FIGURE 13.1 The methods of dividing cores of native cortical renal tissue obtained by a percutaneous biopsy based on the sample size. *EM*, electron microscopy; *IM*, immunofluorescence microscopy; *LM*, light microscopy.

for routine processing in subtle or complex situations, but rapid processing produces permanent sections in 4 hours.

There is a diversity of opinion regarding the optimal tissue fixation for light microscopy. In part, this is because several fixatives are available that yield generally acceptable results. The fixative for use in general pathology has a formaldehyde base; a 4% solution of formaldehyde in neutral phosphate buffer is acceptable in most situations. Other common fixatives include Zenker, Van de Grift, Helly, and Bouin solutions.[149] Variations in fixation and other processing steps make less and less difference with time and experience.

There are circumstances when a standard fixation and tissue processing should be supplemented with special handling of the tissue. Urate, uric acid, other water-soluble crystals, and glycogen may be dissolved from the tissue during processing in aqueous solutions. Ethanol is the fixative of choice for preservation when the presence of urates and uric acid are suspected. Lipids are extracted from the tissue during the later stages of processing for routine paraffin sections; therefore, frozen sections are preferable for the demonstration of lipids. Some fixatives degrade antibody binding and nucleic acid hybridization to tissue or tissue extracts; therefore, processing must be appropriate for these tests. Because special handling is required in only a few cases, it is important to have a high index of suspicion when these situations arise and to alert the pathologist and the laboratory before the biopsy is actually performed.

After fixation, the tissue is dehydrated and embedded using one of several techniques. We prefer wax embedding because it is automated and permits the use of the greatest variety of special stains. We normally prepare seven slides with 2-μm thick sections. The first, fourth, and seventh slides are stained with H&E, the second and fifth are stained with PAS, and the third and sixth are stained with periodic acid-methenamine silver (PAMS).[149] Additional stains, such as Congo red, are used as necessary. Some laboratories use plastic materials for embedding, which produce very clean, thin, crisp sections that also can be stained with the H&E, PAS, and PAMS procedures. Specimens processed in this manner require separate handling and, in our experience, additional special stains often demonstrate poor contrast.

Many types of fixatives are available for electron microscopy, and several are acceptable for the evaluation of a kidney biopsy within certain limits. We recommend either of two initial fixatives for electron microscopy. The first is buffered formaldehyde. In its early use, formalin solution was maligned as a fixative for electron microscopy because of poor tissue preservation. This was not because formaldehyde is actually a poor fixative, but because formaldehyde produces a highly acidic solution in water and the increased acidity produces many artifacts. Buffered formaldehyde (pH 7) is a good fixative, is inexpensive, and is readily available. It has a long shelf life, and tissue can remain in the fixative for months if necessary before additional processing.

Glutaraldehyde is commonly employed to preserve kidney biopsy specimens for an electron microscopy and is our choice as a primary fixative for ultrastructural preservation, although it may be less readily available in routine histology laboratories. Regardless of the fixative, it is important that the tissue to be processed for electron microscopy is divided into pieces less than 1 mm in any dimension to ensure good penetration of the fixative and all other solutions used in subsequent processing. This is not a problem with needle biopsies, but wedge biopsies must be divided accordingly. After the primary fixation, the tissue is ready for additional processing, which should be performed in a dedicated electron microscopy laboratory.

Tissue for immunohistology can be handled in several ways. For frozen sections, the tissue is placed between gauze sponges, moistened with saline, and taken directly to the laboratory. It is important that the tissue not be allowed to float in saline because tissue specimens left in aqueous solutions absorb water, which distorts the architecture. Ideally, the transit time to the laboratory should be less than 30 minutes. If transport is delayed, the tissue should be kept on ice, but should not be frozen. Alternatively, a second method can be employed. Michel et al.[150] developed a holding solution composed of buffered ammonium sulfate and N-ethylmaleimide, which is used at room temperature for the preservation of biopsy specimens for immunofluorescence microscopy. The original solution has been modified slightly and is even more broadly applicable than originally described.[151] Michel's medium remains valuable for holding the tissue at room temperature or for shipping kidney specimens without refrigeration, provided certain guidelines are followed. First, the tissue pieces should be 2 mm or less in thickness. Second, the tissue should not be kept in the solution for longer than 1 week before it is rinsed and frozen as described for fresh tissue. We block the tissue in gelatin, as described by Burkholder et al.,[152] or routine cryomicrotomy solution, after which it is snap frozen in isopentane or Freon cooled with liquid nitrogen or an electrical refrigeration unit, or in a slurry of dry ice and acetone. Rapid freezing is important to reduce the formation of large ice crystals because they result in tissue distortion and sectioning artifacts. Tissue that is stored frozen before and after sectioning should be protected to prevent desiccation and denaturation artifacts.

Frozen sections are cut and stained according to any of several immunohistologic procedures. Direct immunofluorescence staining for serum proteins with fluoresceinated heteroantisera or monoclonal antibodies remains the standard procedure. Antibodies to IgG, IgM, IgA, C1q, C3, and albumin are used most frequently. With the appropriate interpretation, this panel of antisera allows for the successful identification of most clinical diseases. Staining for selected amyloid proteins and κ and λ light chains is helpful or necessary in many adult cases. A variety of other antigens have been used in special or experimental situations; however, most are not necessary in everyday clinical practice. After staining, the slides are cover-slipped with buffered glycerol at pH 8.2 in preparation for viewing.

A fluorescence microscope equipped with epifluorescence is convenient to use and should be outfitted with adequate illumination, a primary interference filter, and an appropriate secondary filter.

A number of methods employing other fixatives or embedding procedures for the immunohistochemical demonstration of serum proteins in kidney biopsies have been described, including the use of wax sections. Some of these alternative procedures are unreliable, but others[153] are suitable for the demonstration of antibodies and some complement proteins in paraffin sections.

Several other tests are occasionally required that can be performed only on frozen sections. These include neutral fat stains and most enzyme histochemistry. The use of immunohistochemistry, combined with a host of specific monoclonal antibodies, has produced a highly specific and sensitive system for the identification of cell and tissue antigens. The impact of this methodology has been most noticeable in our ability to identify lymphohistiocytic cell infiltrates and to classify cellular immune responses in the kidney such as cellular rejection, interstitial nephritis, and posttransplant lymphoproliferative disease (PTLD). We have found that the avidin biotin complex (ABC) procedure yields the best combination of sensitivity, specificity, quality control, and time for the completion of the test.[154] There are excellent monoclonal antibodies commercially available for the identification of B cells, T-cell subsets, and monocytes. Many of these may be used in tissues following the fixation in buffered formalin.

Immunoperoxidase staining of frozen sections can also be used in addition to or instead of immunofluorescence staining. The advantage of immunoperoxidase techniques over immunofluorescence microscopy includes a greater sensitivity and permanence of the staining when diaminobenzidine is used as the substrate for color development. The disadvantages of immunoenzyme staining for immunoglobulin localization include the increase in preparation time and the added expense. Endogenous peroxidase and endogenous biotin may produce a bothersome high background and should be blocked.[155]

Molecular Biology

In situ hybridization has been a powerful tool for a host of investigational studies.[156,157] A variety of molecular probes have been used to study gene expression at the level of messenger RNA (mRNA)[158–160] and for the detection of viral sequences.[161,162] For example, Epstein-Barr virus (EBV) probes may be useful in the diagnosis of PTLD. Renal biopsy specimens also can be used as a source of DNA or RNA for extraction and nucleic acid blotting or for polymerase chain reaction (PCR)-based techniques.[161,164–167] Although the potential for molecular diagnosis of renal disease by microarray analysis and other techniques is near at hand, there are few standard applications for clinical renal biopsy diagnosis at the present time.[168] Proteomic studies (e.g., mass spectroscopy) have been used in the subclassification of amyloids in tissue blocks[169,170] and have additional potential.

THE HISTOLOGIC EVALUATION

Light Microscopy

The purpose of this section is to present a systematic approach to the histologic interpretation of a kidney biopsy. The discussion also includes the role of several special stains in a biopsy diagnosis. The evaluation should begin with a review of all tissue that is present on the light microscopic sections at a relatively low magnification to assess the adequacy of the specimen and to identify any major abnormalities. This is followed by a systematic evaluation of the glomeruli, tubules, the interstitium, and the vasculature. It is preferable to establish the histopathologic findings before the clinical history is known to avoid a bias in the final biopsy interpretation. Nevertheless, the biopsy findings must ultimately be reconciled with the clinical presentation, course, and prognosis.

It is important that certain terms be carefully defined before continuing. There are four principal definitions that have evolved largely from light microscopic evaluation of kidney biopsies to describe glomerular disease. Focal denotes a process in which only some of the glomeruli are altered histologically. The majority of glomeruli are spared. Generalized indicates the majority of glomeruli on the biopsy are altered by some process; for instance, proliferation or sclerosis. A local, or segmental, lesion is one in which only a portion of a glomerulus exhibits an alteration. A segmental sclerotic process involves only a portion of a glomerulus. The opposite of a segmental process is one that is global in nature and generally affects the entire glomerulus. The term diffuse has been used ambiguously in the literature. Sometimes it has meant global and other times it has meant generalized; therefore, care must be taken when interpreting this term. We will avoid the term diffuse for these reasons. Glomerular lesions are generally focal and segmental or are generalized and global, but important exceptions exist (e.g., generalized and segmental in lupus nephritis).

The initial evaluation of the specimen is intended to determine the specific regions of the renal parenchyma that are present on the section, which might include the cortex and the outer and inner medulla. If only the cortex is seen, the presence of the renal capsule can aid in the orientation of the specimen. The glomeruli should be counted to provide a rough estimate of the sample size. This is generally accomplished best with the PAS-stained sections, in which the glomeruli (including those that are globally sclerotic) can be identified readily. All the tissue on each slide should be evaluated because certain features may not be present in all sections. Next, the overall condition of the renal architecture is evaluated to differentiate between

chronic or irreversible nephron loss and acute or reversible nephron damage. The type, distribution, and intensity of cellular infiltration are accurately established on the H&E and PAS sections. The PAS and PAMS stains are well suited to evaluate the degree of interstitial fibrosis, tubular atrophy, and glomerulosclerosis. In general, the degree of tubular and interstitial injury relates to the reduction in creatinine clearance when the sample size is adequate and the process producing the injury is uniform. The latter feature is important because, with approximately 1 million nephrons in each kidney, a needle biopsy specimen that contains 10 glomeruli only provides a sample of 1 in 100,000. As a first approximation, we employ a simple procedure to estimate the extent of chronic nephron loss in a biopsy. Using a PAS-stained section, the total number of glomeruli is counted and the percentage that is sclerotic is determined. Sclerotic glomeruli are generally shrunken in appearance because of the complete collapse of the capillary bed and the paucity of cells. In a study of chronic glomerulonephritis, we have shown that global glomerular sclerosis of up to 50% is associated with the maintenance of the serum creatinine near the normal range.[171] However, an increase in glomerular sclerosis of the global type above 50% to 60% is associated with increases in the serum creatinine. This estimate of chronic nephron loss is based on an interpretation of the intact nephron hypothesis.[172] When one portion of the nephron is lost to disease or injury, the remainder of the nephron undergoes atrophy. Thus, the accompanying tubule undergoes atrophy in the presence of global sclerosis. The converse also is true. Tubular atrophy is characterized by a decrease in the outer diameter of the tubule, thickening and wrinkling of the tubular basement membrane, simplification and a decrease in thickness of the tubular epithelium, and an increase in the interstitial connective tissue that surrounds the tubule. However, it is also true that one part of the nephron may take longer than another to atrophy. It is also important to estimate the percentage of atrophic tubules in the specimen because there may be significant tubular atrophy in the absence of glomerular sclerosis. These changes all lead to disruption of the normal architecture of the renal parenchyma. Because some nephrons are destroyed or atrophy, the remaining nephrons may hypertrophy, showing tubules with larger diameters and cells with increased cytoplasm. This picture of atrophy and hypertrophy is visualized in Figure 13.2. In this setting, hyperfiltration is associated with glomerular changes of increased size and mesangial matrix and segmental sclerosis.[173–177] These features are the harbingers of the point of no return or of continued deterioration in renal function.[178] The normal architecture also can be disrupted by more acute changes, such as edema and inflammation. In this setting, there is separation without evidence of atrophy of the renal tubules. Depending on the etiology of the injury, these latter changes may be reversible, as seen in ATN, or occasionally they may progress to the loss of the entire nephron.

Glomeruli

The next step in the interpretation of the biopsy is a detailed evaluation of the glomeruli, which includes a careful assessment of the various structures that comprise the glomerulus or renal corpuscle. The glomerulus is composed of the visceral epithelial cells, the endothelial cells, the mesangial cells with the mesangial matrix and the basement membranes of the capillary loops, the Bowman capsule and the

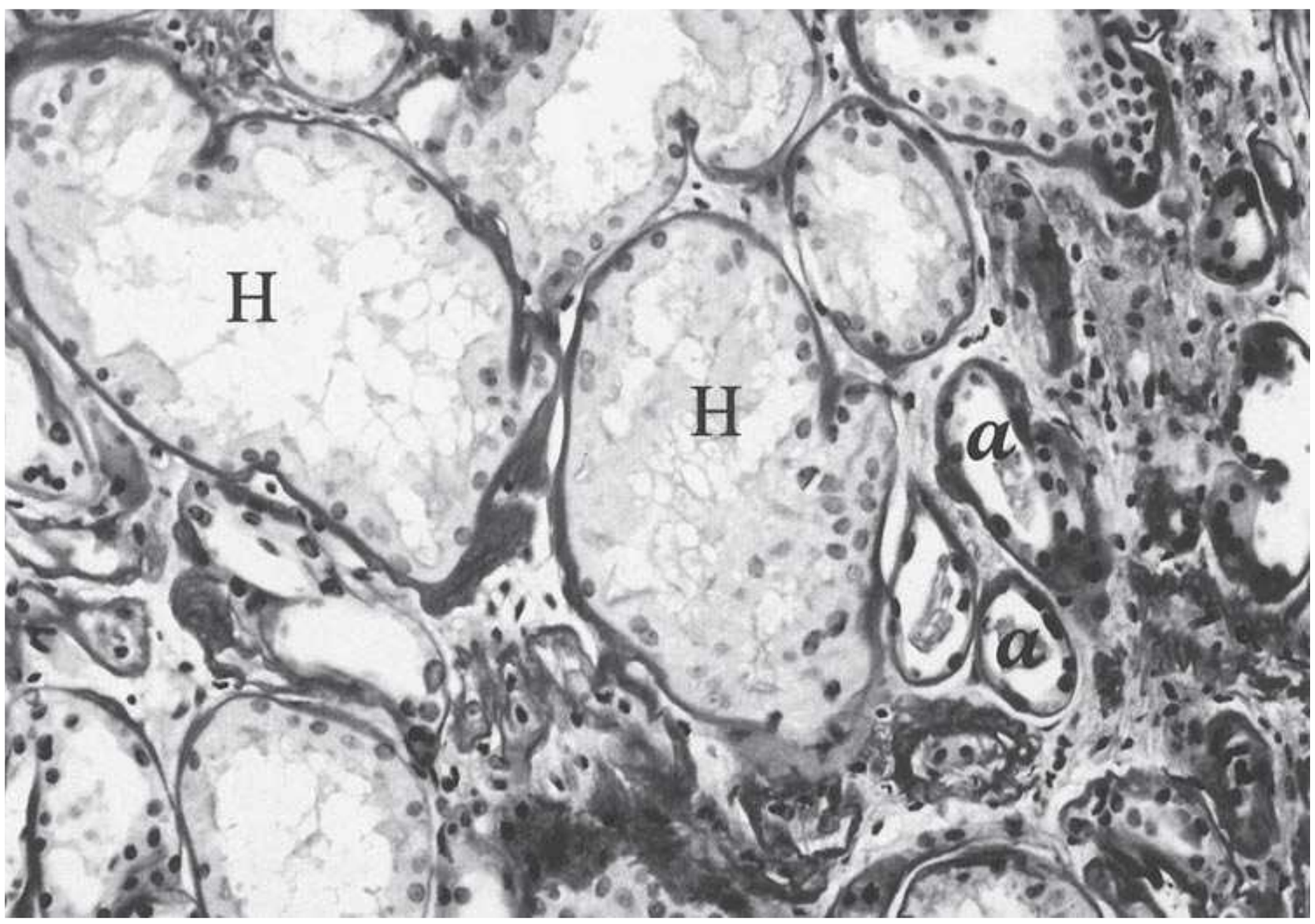


FIGURE 13.2 This figure shows shrunken atrophic tubules *(a)* and hypertrophic tubules *(H)* (PAS, magnification ×210.)

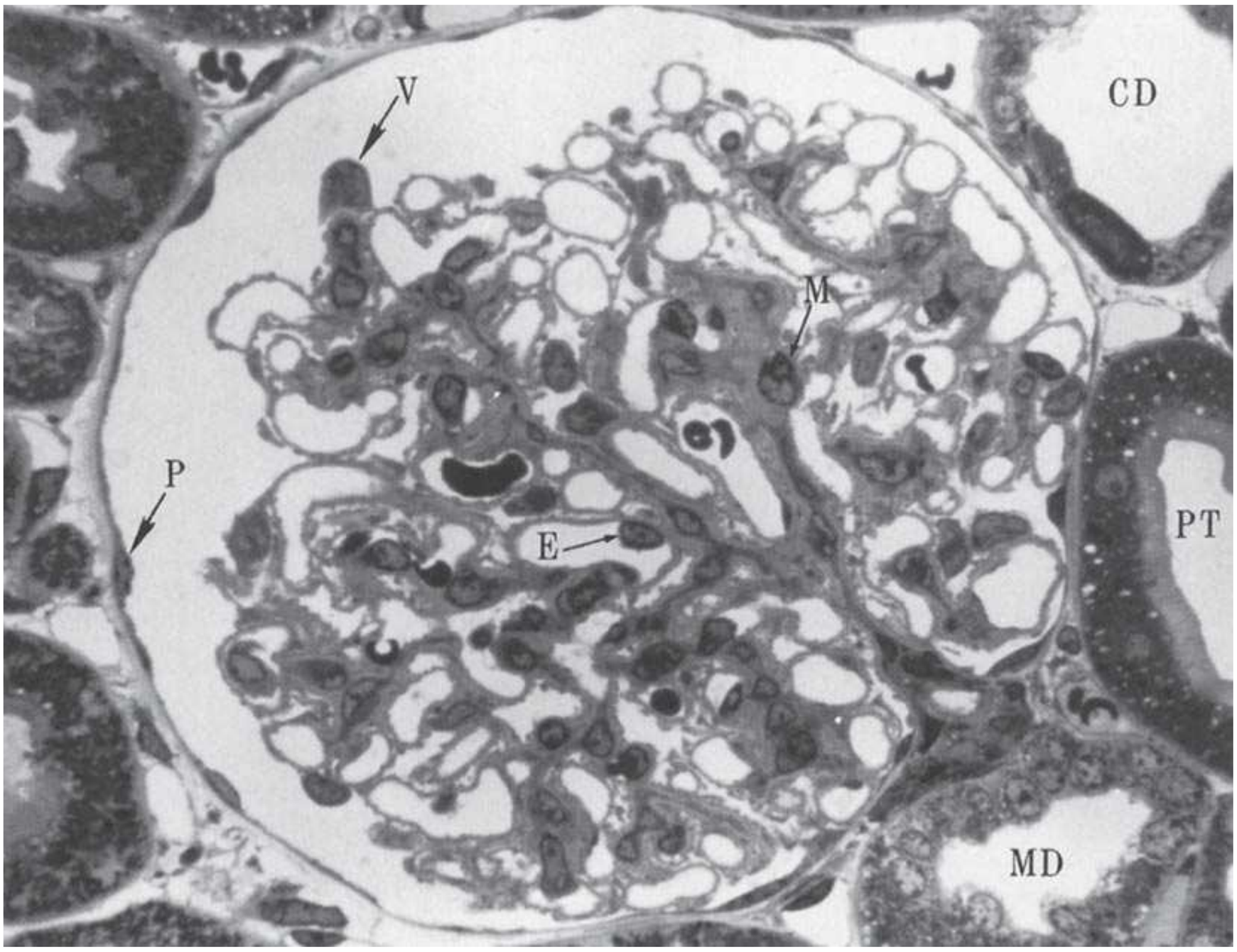
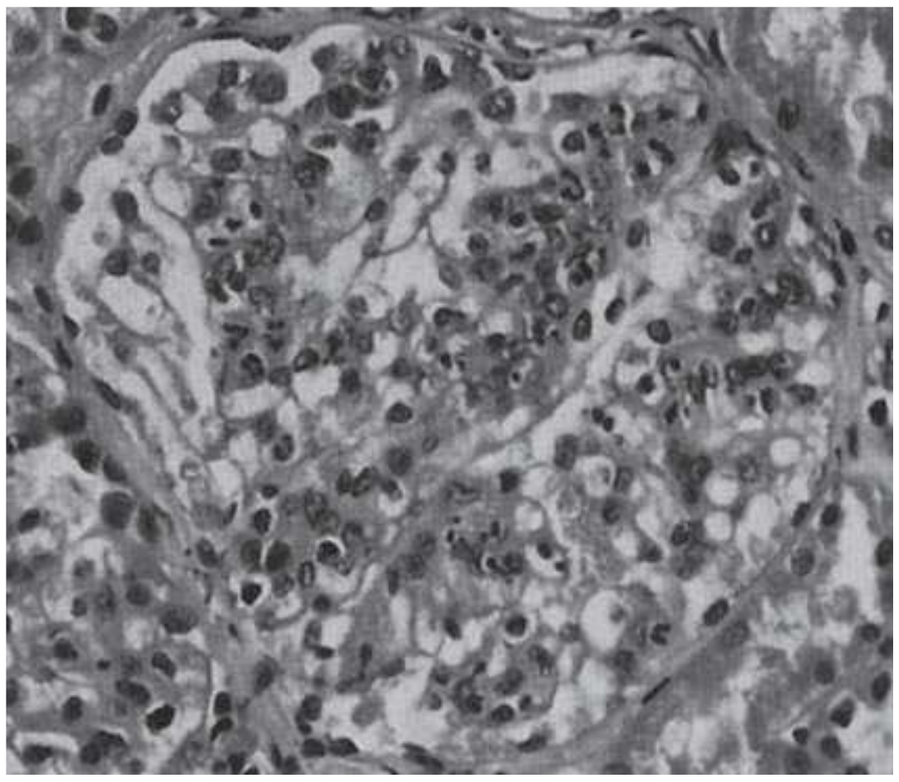


FIGURE 13.3 A photomicrograph of the glomerulus (renal corpuscle) depicting the major cell types and anatomic regions. *V,* visceral epithelial cell; *M,* mesangial cell; *P,* parietal epithelial cell; *E,* endothelial cell; *MD,* macula densa; *CD,* collecting duct; *PT,* proximal tubule (magnification ×750). (From Brenner BM, Rector FC Jr, eds. *The Kidney,* 3rd ed. Philadelphia: Saunders; 1986, with permission.)

overlying parietal epithelial cells, the extraglomerular mesangium, and the afferent and efferent arterioles (Fig. 13.3). The first assessment is a determination of the overall glomerular cellularity, which is evaluated using H&E-stained sections (Fig. 13.4A). The cell type should be established if the glomeruli are hypercellular. This includes an estimate of the number of cells normally present in the glomerulus, including the mesangial, endothelial, visceral epithelial, and parietal epithelial cells; and the inflammatory cells that migrate into the glomerulus, including neutrophils, lymphocytes, and monocytes (Fig. 13.5). Most pathologists principally rely on a qualitative assessment of the cellular composition in sections 2- to 3-μm thick and stained with H&E. There are several guidelines for this assessment. Under normal conditions, a typical cross-section through the mesangium contains one to three mesangial cell nuclei. An entire glomerulus may contain one to two neutrophils, but more than two is abnormal. There are also a small number (1%) of mononuclear cells (monocytes) in the normal glomerular mesangium,[179] but these cells cannot be identified with certainty on routine H&E sections. Similarly, it may not be possible to distinguish monocytes from large lymphocytes or even epithelial cells without immunohistochemistry or electron microscopy. Some cells within the glomerulus may contain inclusions, inspissated material, or numerous vacuoles, such as those that are present in foam cells.

Next, the glomerular capillaries are examined to determine whether they are patent, collapsed, or obstructed with fibrin, platelets, or cells. The PAS and PAMS stains are important in the evaluation of the capillary walls (Fig. 13.4B,C). Both stains will label normal as well as have an abnormally thickened basement membrane. If the basement membrane is thickened, it is important to establish the nature of the changes. Both the epithelial and endothelial surfaces are smooth under normal conditions. If one surface is shaggy or irregular or exhibits projections, often referred to as spikes when present on the epithelial surface, it is distinctly abnormal (Fig. 13.4C). Occasionally, both surfaces of the basement membrane are irregular in configuration. In necrotizing glomerulonephritis owing to virtually any cause, the capillary wall, including the basement membrane, may be ruptured, discontinuous, or completely lost (Fig. 13.6). This histologic picture usually is associated with fibrin deposition. Fibrin deposition associated with necrosis should be distinguished from fibrin deposits that distend the capillary in the presence of an intact basement membrane. Larger immune complexes can be seen on Masson or PAS stains. These deposits can also be identified on 1-μm thick plastic sections stained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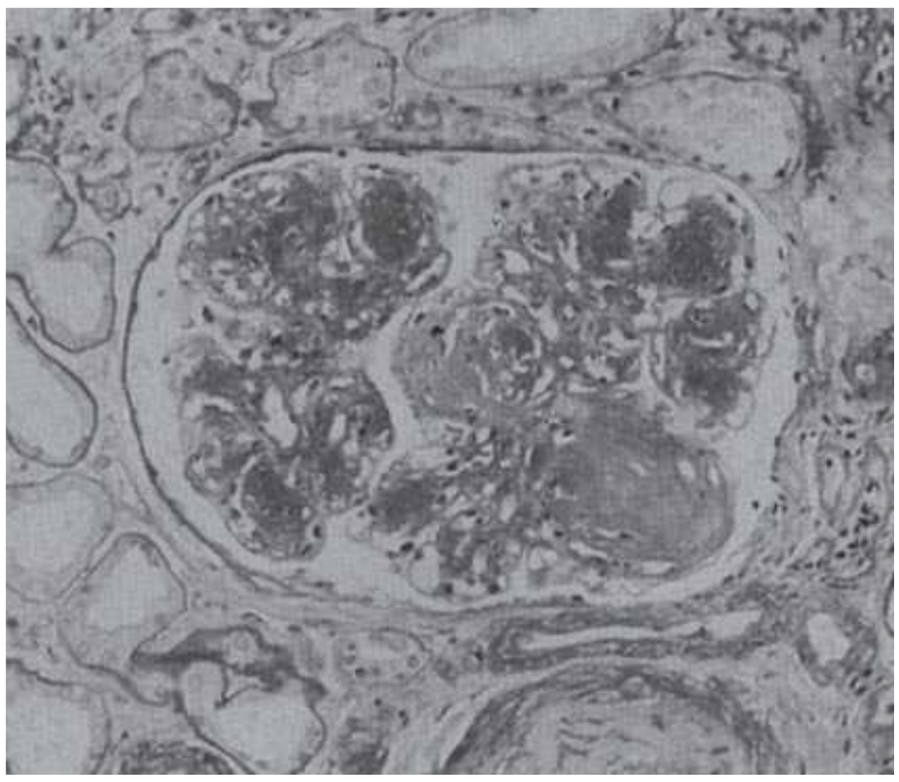
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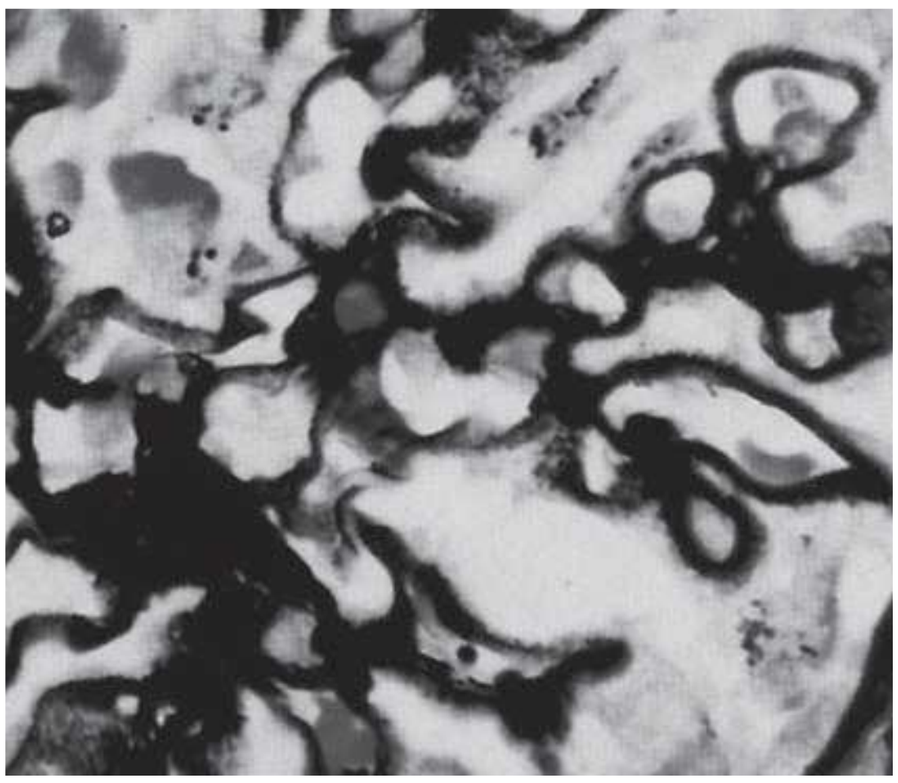
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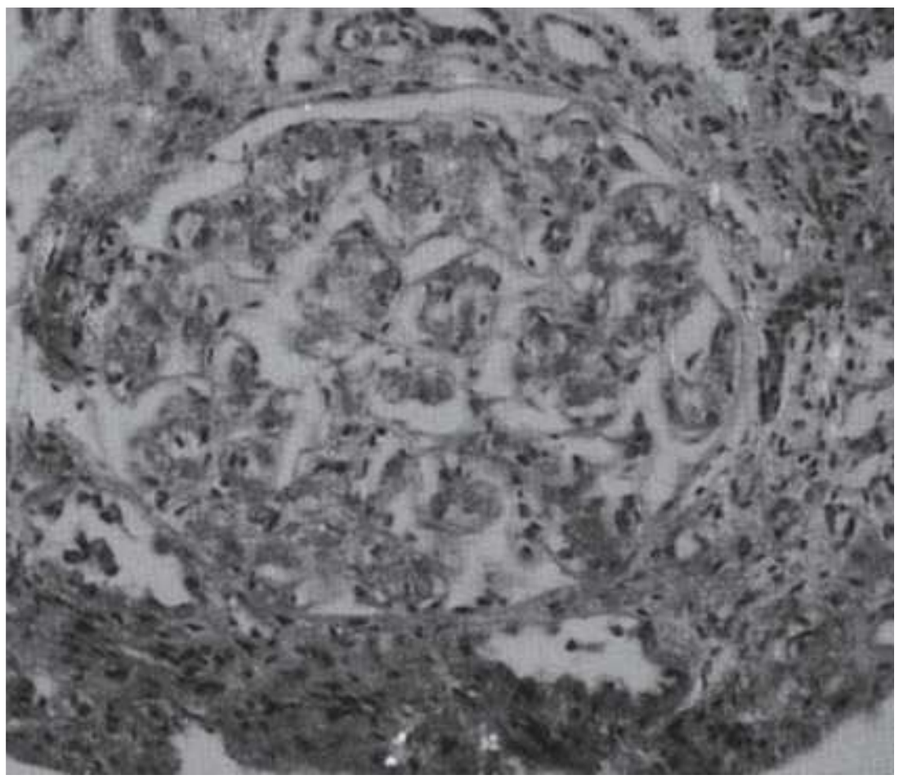
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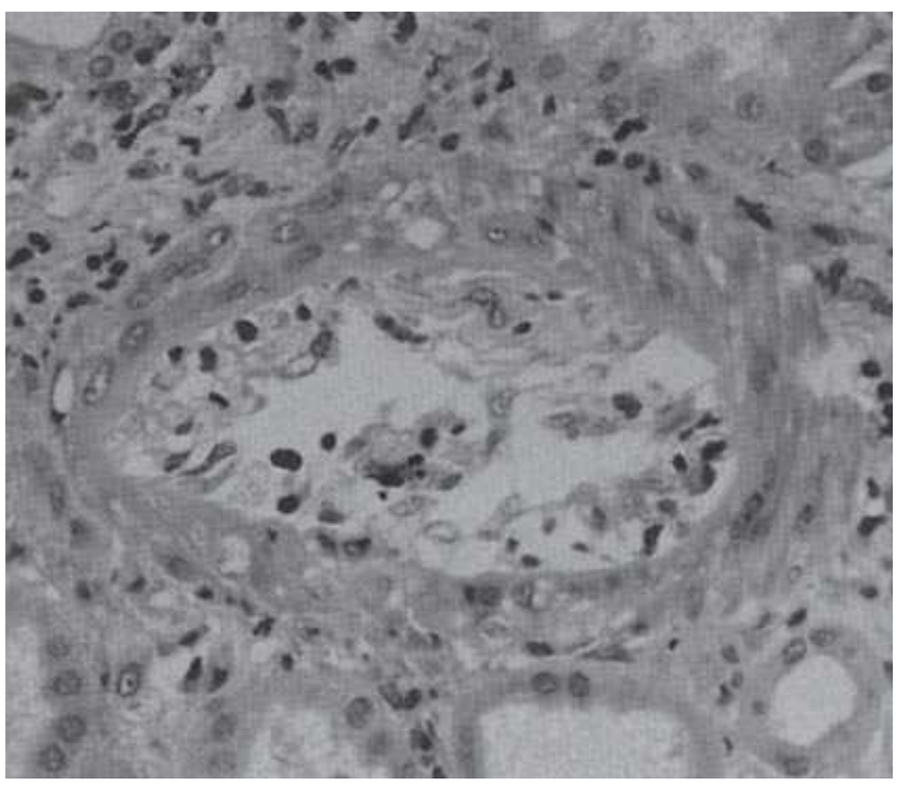
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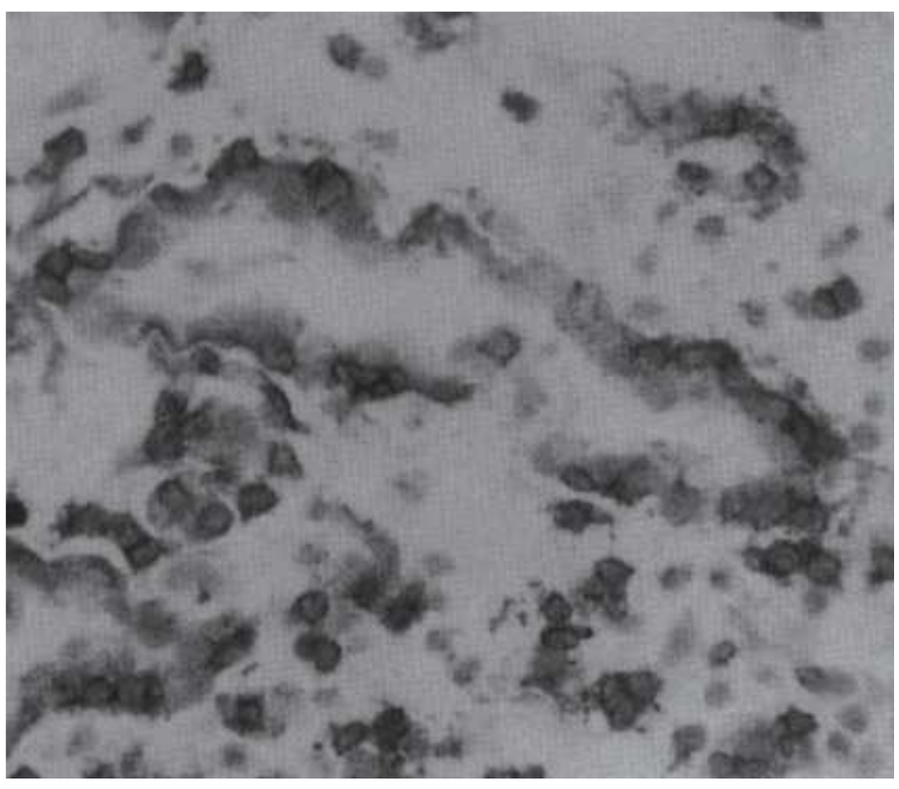
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FIGURE 13.4 **A:** An H&E stain of a glomerulus with moderate neutrophilic infiltrate in acute poststreptococcal glomerulonephritis (magnification ×200). **B:** A PAS stain of a glomerulus, illustrating an early and late nodular mesangial expansion typical of nodular intercapillary glomerulosclerosis of diabetic nephropathy (magnification ×200). **C:** A PAMS stain depicting a portion of a capillary tuft with spikelike projections extending outward from the capillary basement membrane. This picture is characteristic of stage II idiopathic membranous glomerulonephritis (magnification ×1,000). **D:** A depiction of the yellow-green birefringence of the amyloid when stained with Congo red. Other tissue structures (particularly fibrous tissue) may appear white when viewed with the polarizing microscope and should be distinguished from the amyloid (Polarization optics; magnification ×200). **E:** This interlobular artery exhibits inflammation primarily in the intima, which is seen commonly in acute vascular rejection. Compare with the immunofluorescence pattern in Figure 13.22F, which demonstrates the transmural nature of the process (H&E; magnification ×400). **F:** A photomicrograph of an immunoperoxidase preparation using LEU 2A antibody, an antibody to cytotoxic T cells, and diaminobenzidine. Several cross-sections of tubules and interstitium are shown from a typical example of acute cellular rejection. The T cells infiltrate both the interstitium and the tubular epithelial cells (magnification ×200). (See Color Plate.)

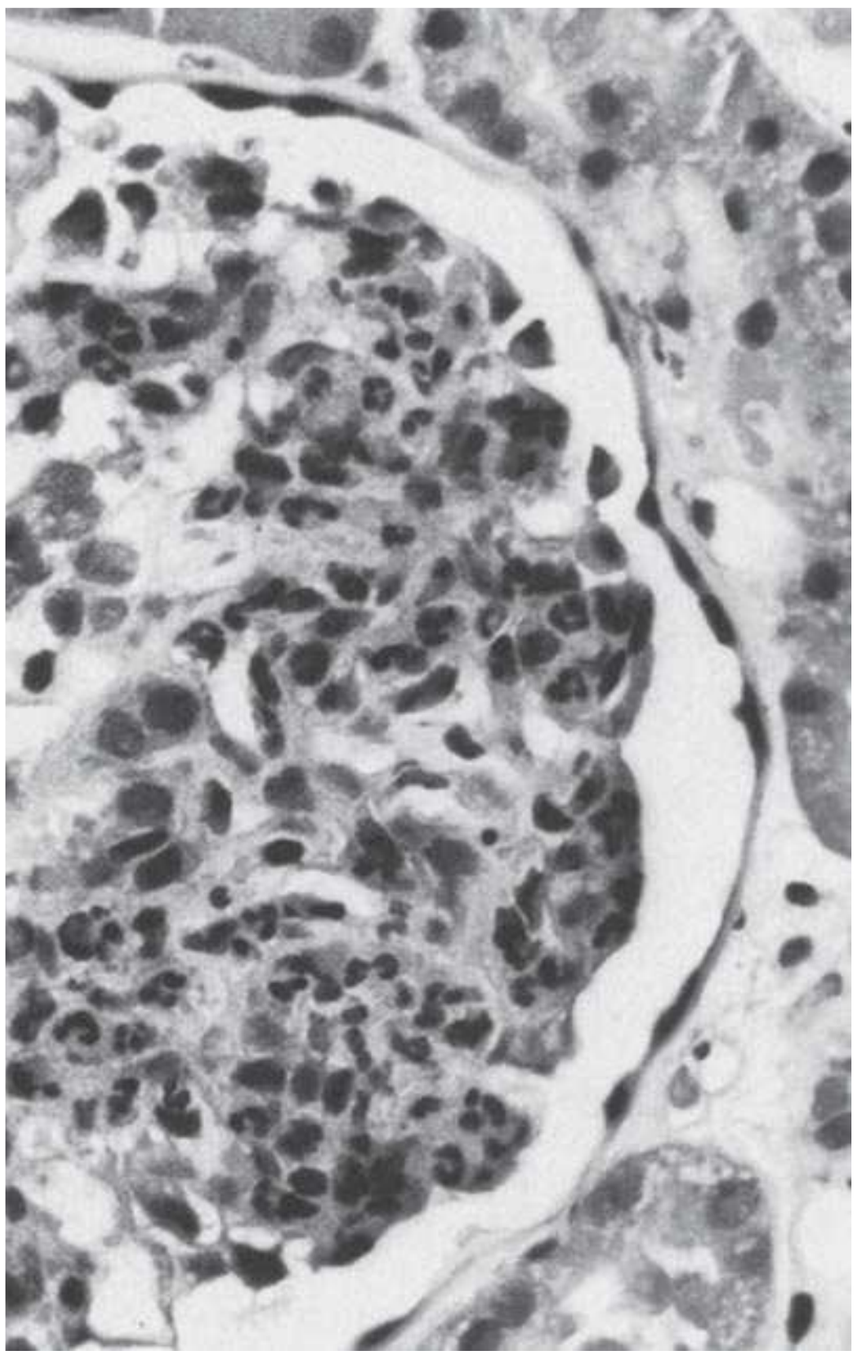


FIGURE 13.5 A photomicrograph of a glomerulus illustrating large numbers of neutrophils and mononuclear cells within peripheral capillary loops in a biopsy from a patient with post-streptococcal glomerulonephritis (H&E; magnification ×560).

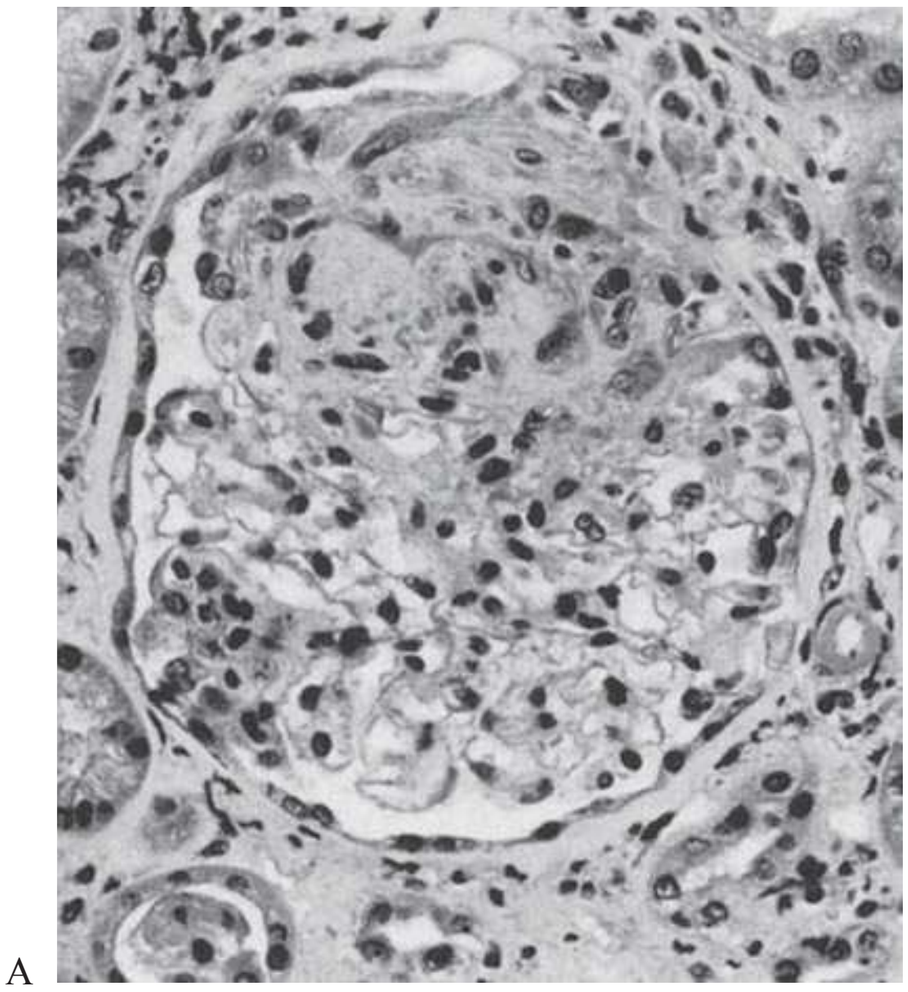
with toluidine blue[180] that are cut from tissue that has been prepared for electron microscopy (Fig. 13.7). The capillary (visceral) epithelial cells may exhibit hypertrophy, atrophy, or hyperplasia.

In addition to the mesangial cellularity, there may be an increase in mesangial matrix material with or without an increase in cells. This is evaluated best with the PAS and PAMS stains (Fig. 13.4B). Mesangial expansion may be global and may involve the entire glomerular tuft; it may be segmental (Fig. 13.8); or it may involve only the stalk region, which is designated the extraglomerular mesangium and forms part of the juxtaglomerular apparatus. Mesangial matrix expansion may extend into the capillary or may be observed in association with subendothelial capillary basement membrane thickening, so-called mesangial interposition.

Mesangiolysis is an alteration of the mesangium that is characteristic of thrombotic microangiopathies, but can be observed in patients with diabetes and other conditions.[181] The lesion appears as a relaxation or a disruption of the attachment of the capillary basement membrane to the mesangium. The basement membrane balloons outward in early lesions. The potential space is filled with disrupted mesangial matrix material, fibrin or platelet thrombi, fragmented erythrocytes, and other material (Fig. 13.9). Eventually, the mesangiolytic lesions sclerose and sclerosis is associated with worsening renal function.

The basement membrane of Bowman's capsule is thicker than the capillary basement membrane in the normal state and, like the capillary basement membrane, may increase in thickness with injury. The parietal epithelium lining the Bowman capsule can respond to injury with hypertrophy or hyperplasia or can exhibit infiltration with monocytes, resulting in the formation of crescents.[182]

The arterioles of the juxtaglomerular apparatus may be markedly abnormal because of the presence of glassy eosinophilic hyaline material (Fig. 13.10), edema, fibrin, other inflammatory changes; hypertrophy; or sclerosis. They may



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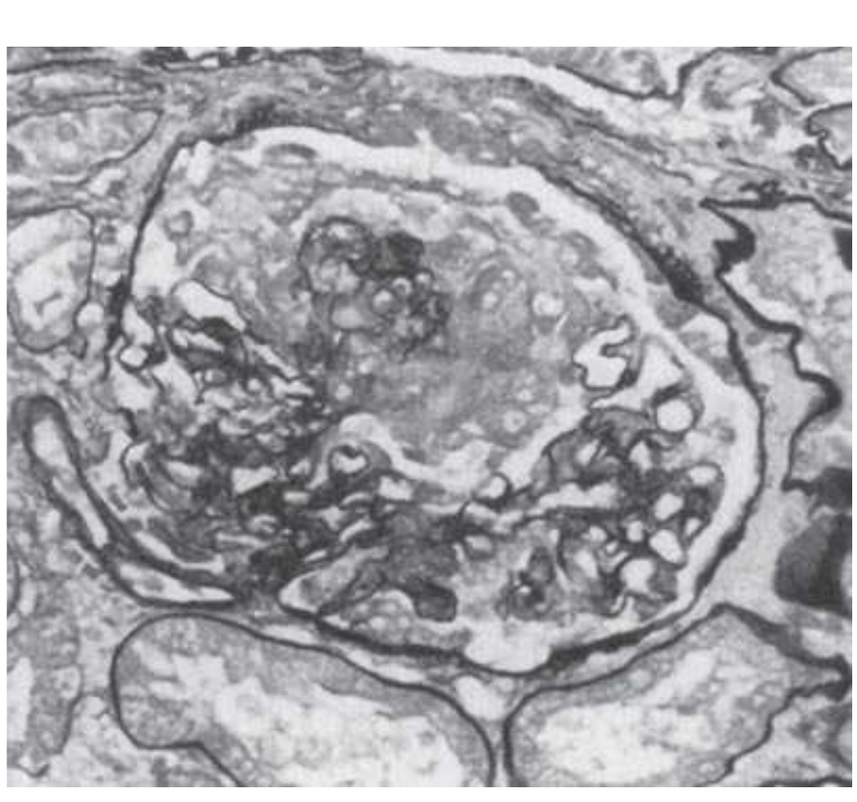


B

FIGURE 13.6 Photomicrographs demonstrating a segmental necrosis of a glomerular tuft in a biopsy from a 60-year-old man with a clinical diagnosis of Wegener granulomatosis (**A:** H&E stain; ×340; **B:** PAMS stain; ×300).

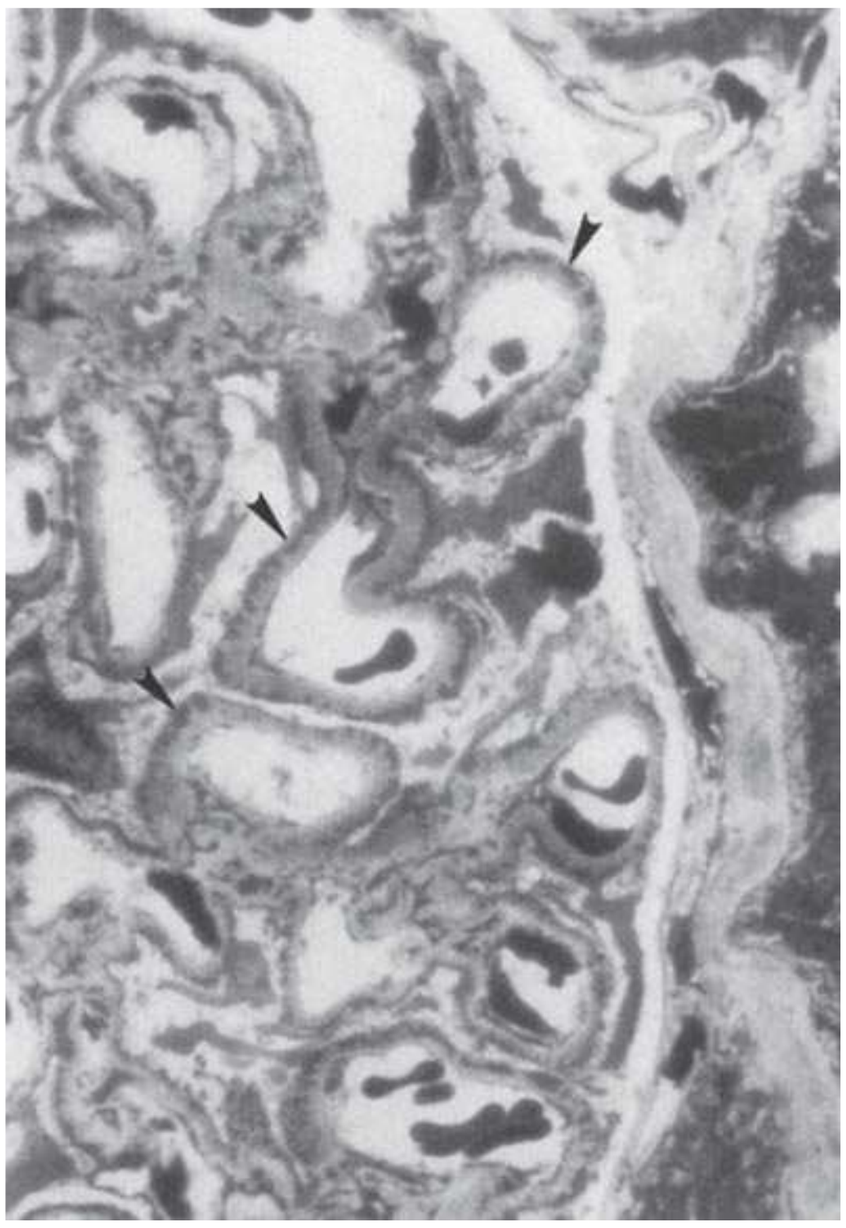


FIGURE 13.7 A micrograph of an Epon section stained with toluidine blue, illustrating subepithelial immune complexes (*arrowheads*) along capillary basement membranes in a patient with idiopathic membranous glomerulonephritis (magnification ×1,050).

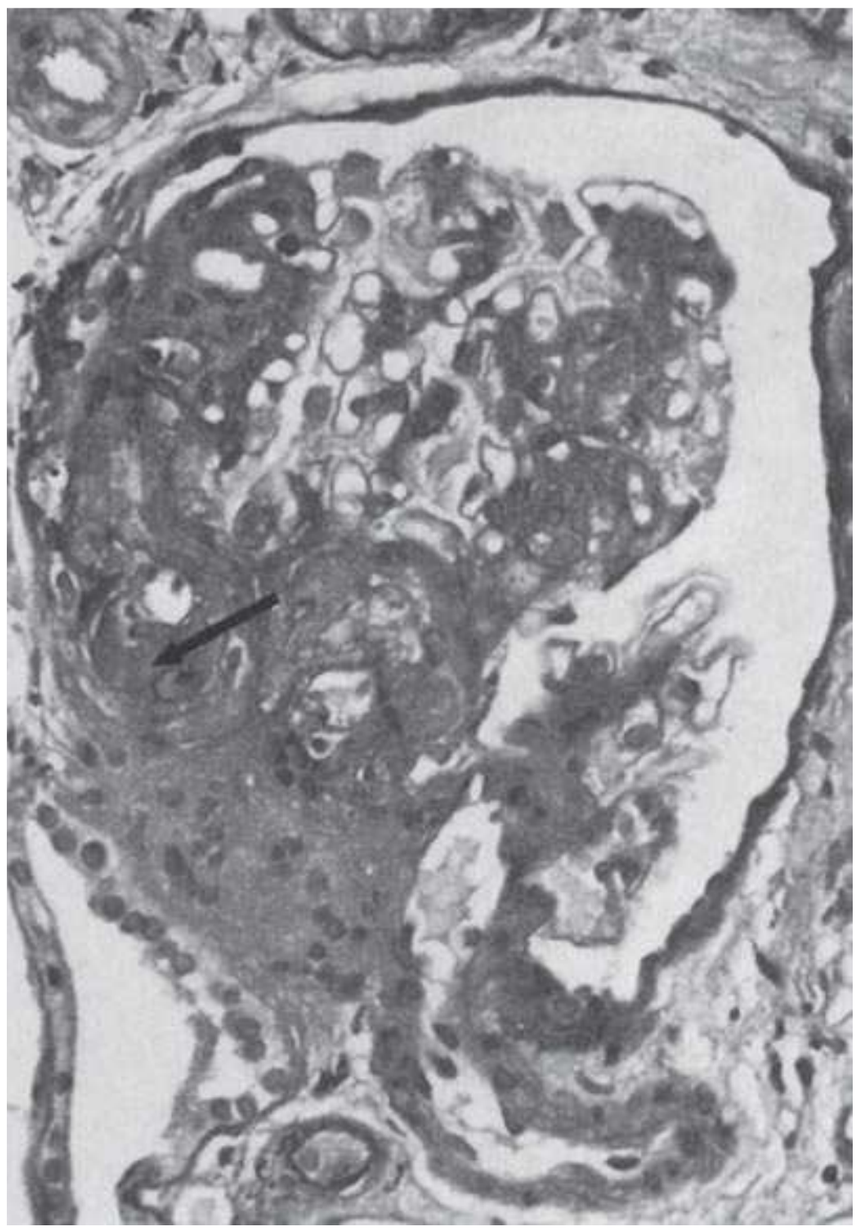


FIGURE 13.8 A glomerulus from a patient with focal segmental glomerular sclerosis, illustrating segmental sclerosis and hyalinosis (*arrow*) (PAS; magnification ×360). (From Newman WJ, Tisher CC, McCoy RC, et al. Focal glomerular sclerosis: contrasting clinical patterns in children and adults. *Medicine* 1976;55:67, with permission.)

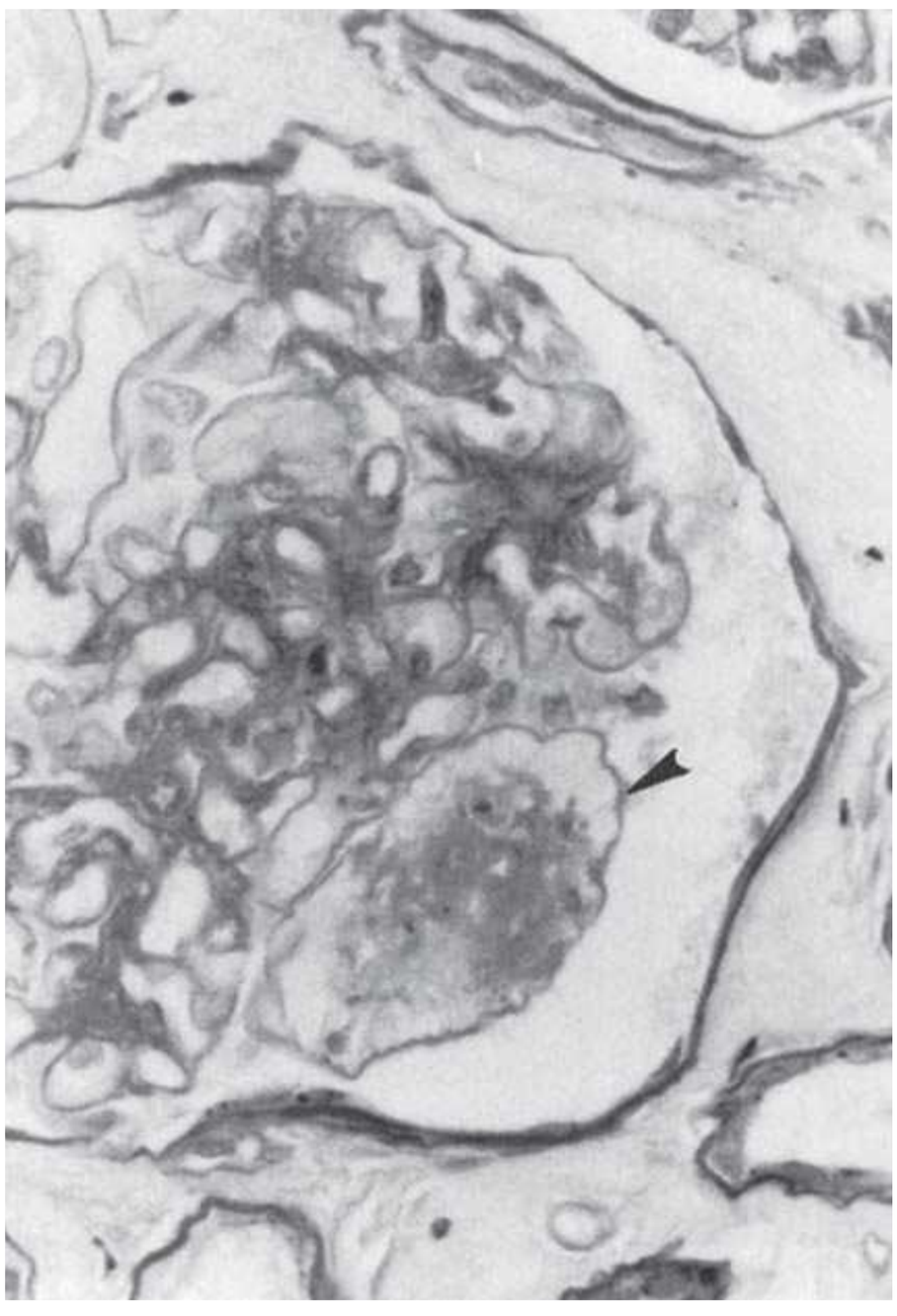


FIGURE 13.9 A light micrograph depicting mesangial lysis (*arrowhead*) in a glomerular tuft (PAS; magnification ×500).

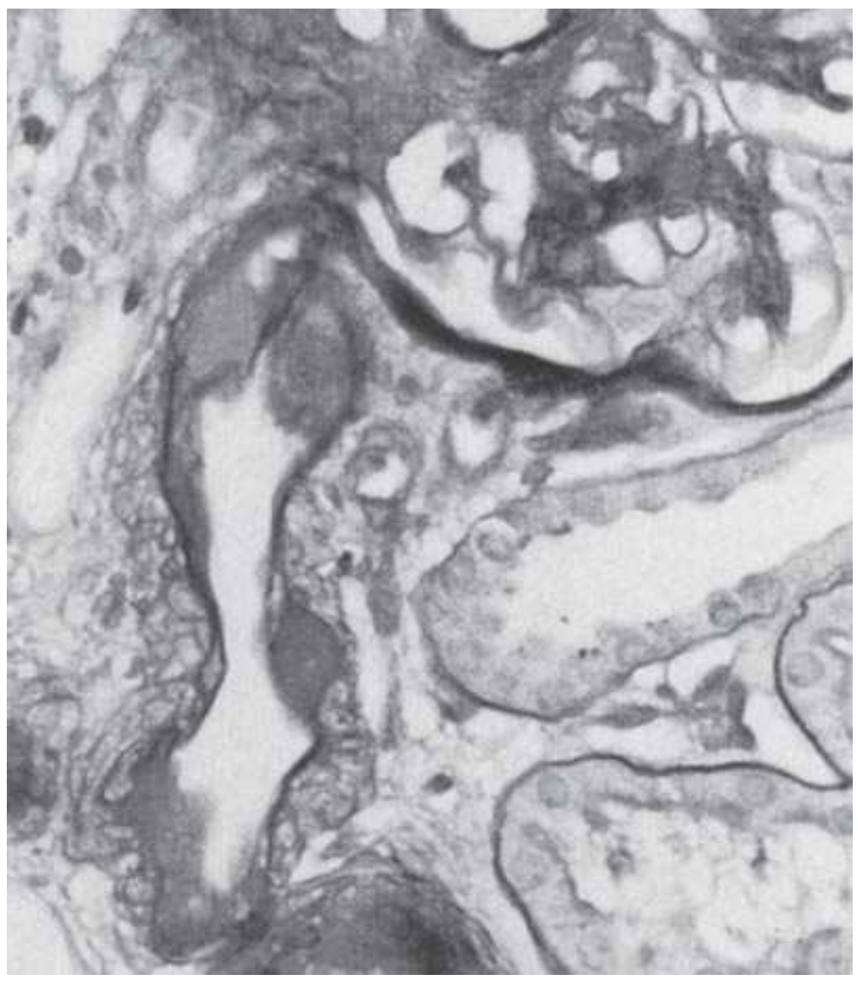


FIGURE 13.10 An arteriole with marked subintimal hyaline arteriolosclerosis from a patient with diabetic nephropathy (PAS; magnification ×460). (From Suki WN, Eknoyan G, eds. *The Kidney in Systemic Disease,* 2nd ed. New York: Wiley-Liss; 1981, with permission.)

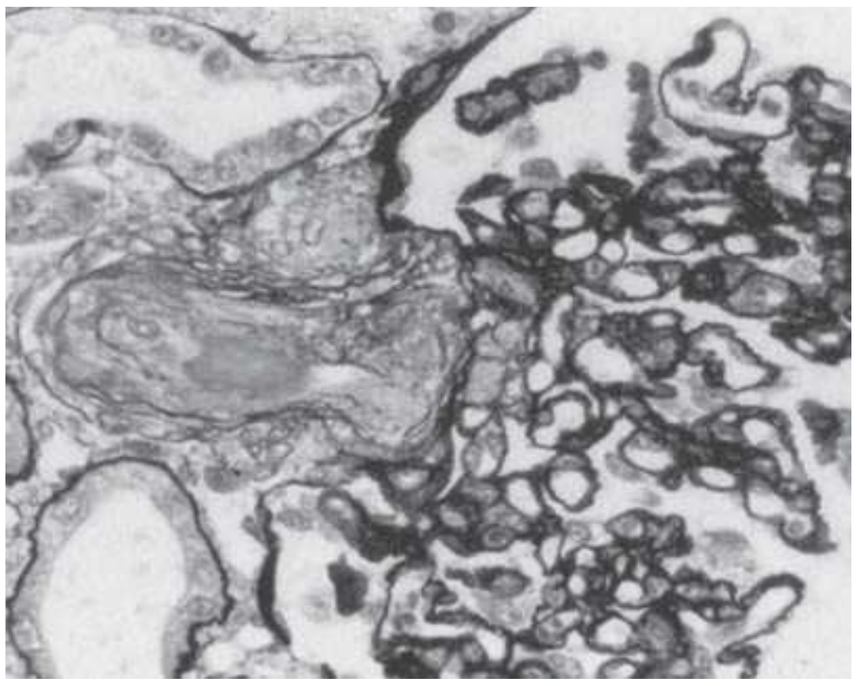


FIGURE 13.11 A fibrin thrombus in an afferent arteriole of a kidney biopsy from a 62-year-old woman with acute kidney injury and a stigmata of a hemolytic-uremic syndrome (PAMS; magnification ×415).

contain fibrin thrombi (Fig. 13.11) or may exhibit segmental fibrinoid necrosis. The pericytes surrounding the arterioles should be examined carefully for evidence of hypercellularity and increased granularity. The PAMS stain is used to screen for the latter feature.

Tubules

Next, the tubules are examined in detail. The proximal tubule epithelium should be tall, columnar, and should possess a PAS-positive brush border and display a deeply eosinophilic cytoplasm. Acute signs of ischemic or toxic injury include swelling of the cell cytoplasm and disruption of the brush border. Cytoplasmic vacuolization is followed by cell necrosis. Later stages include the flattening of the remaining cells with irregular staining of nuclei, and evidence of early regeneration (Fig. 13.12). Apoptosis[183,184] follows a variety of stimuli, including cell-mediated cytotoxicity[185–187] with pyknosis of the nucleus, condensation of the cytoplasm, and extrusion of the tubular cells into the lumen. Characteristic PAS-positive droplets that represent lysosomes are present in increased numbers with proteinuria. Additional findings include lipid droplets and cytoplasmic vacuoles. Large irregular vacuoles are seen with severe hypokalemia (Fig. 13.13); whereas fine, diffuse cytoplasmic vacuoles are observed with exposure to osmotic agents, such as mannitol (Fig. 13.14). Vacuoles are observed in calcineurin inhibitor toxicity (Fig. 13.15). Inflammatory cells may infiltrate the tubule and, if present, the type of inflammatory cell should be characterized (Fig. 13.4F). The lumen may contain extracellular material, such as casts or white or red blood cells. The basement membrane may be thickened by atrophy or the presence of immune deposits, or it may exhibit breaks.

Interstitium

Normally, the tubules are separated by an inconspicuous interstitium, which contains peritubular capillaries and a few interstitial cells. The interstitium may be abnormally thickened or expanded by a variety of extracellular materials, including collagen, other proteins, crystals, or edema. The type of inflammatory cells should be characterized if inflammation is present. Inflammatory cells may display a specific distribution, such as perivascular or periglomerular, marginated in peritubular capillaries, or scattered uniformly throughout the biopsy. Monocytes may aggregate and assume an epithelioid appearance, giving rise to granulomas. Normally, the interstitium is more prominent in the medulla and around the muscular arteries.

Vasculature

Finally, the larger vessels should be examined. The medium-sized renal arteries have a histology typical of arteries elsewhere; however, intrarenal veins have minimal smooth muscle compared to veins of similar caliber in other organs. The most common arterial change is intimal thickening in association with irregular reduplication of the internal elastic lamina, a finding that is seen best with the PAMS stain. The lumen may contain fibrin thrombi, embolized material, or inflammatory cells (Fig. 13.4E). The walls of the arteries

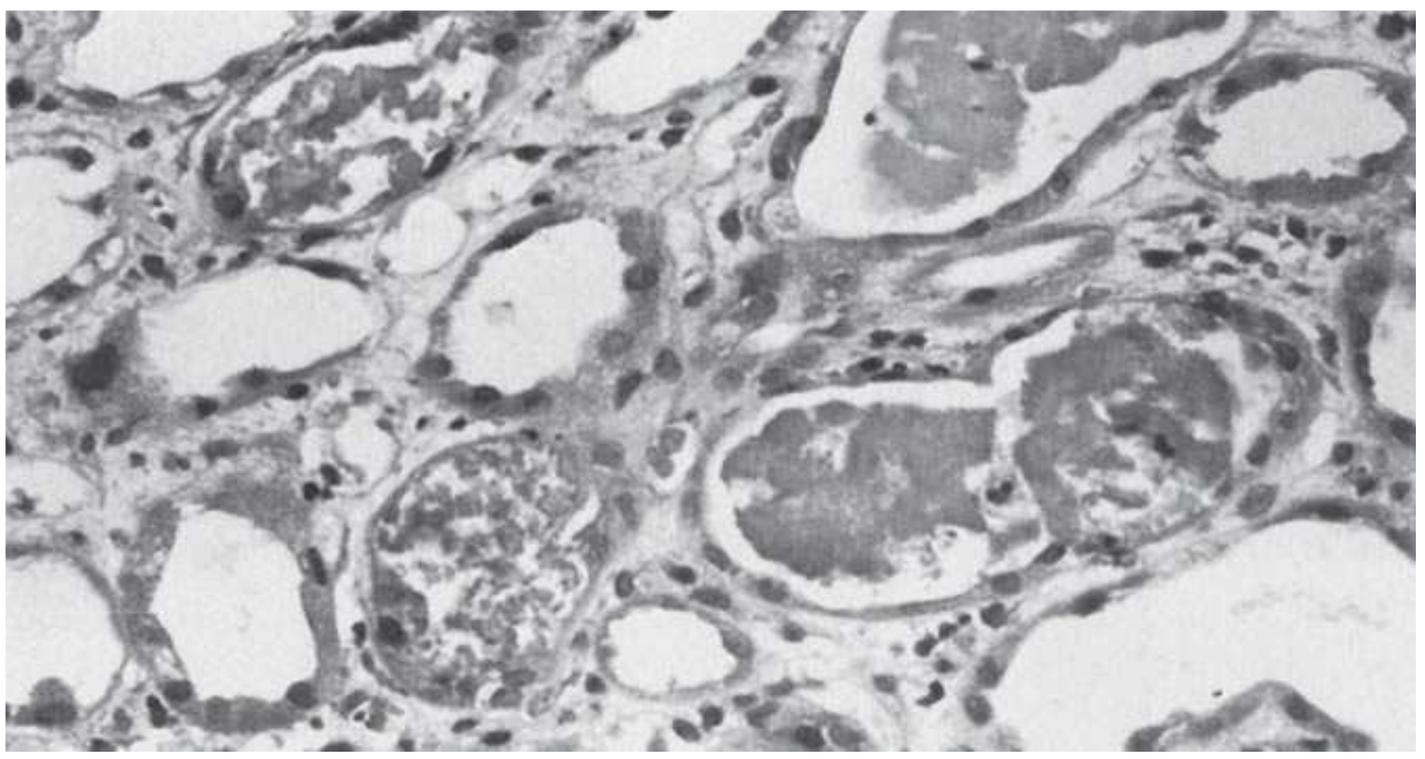


FIGURE 13.12 A photomicrograph depicting acute tubular necrosis (H&E; magnification ×440).

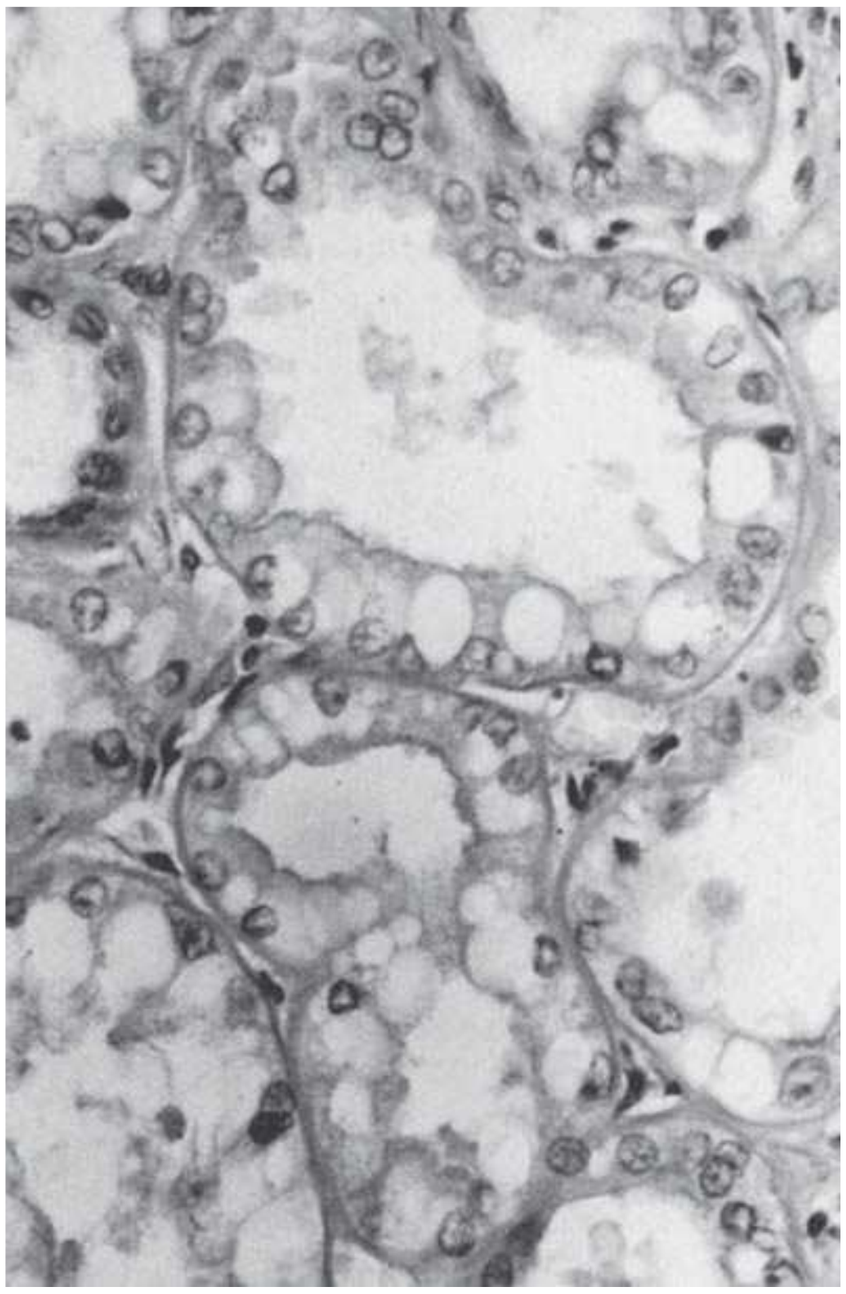


FIGURE 13.13 An example of severe hypokalemic nephropathy. Large irregular vacuoles are evident in the proximal tubule epithelium (H&E; magnification ×460).

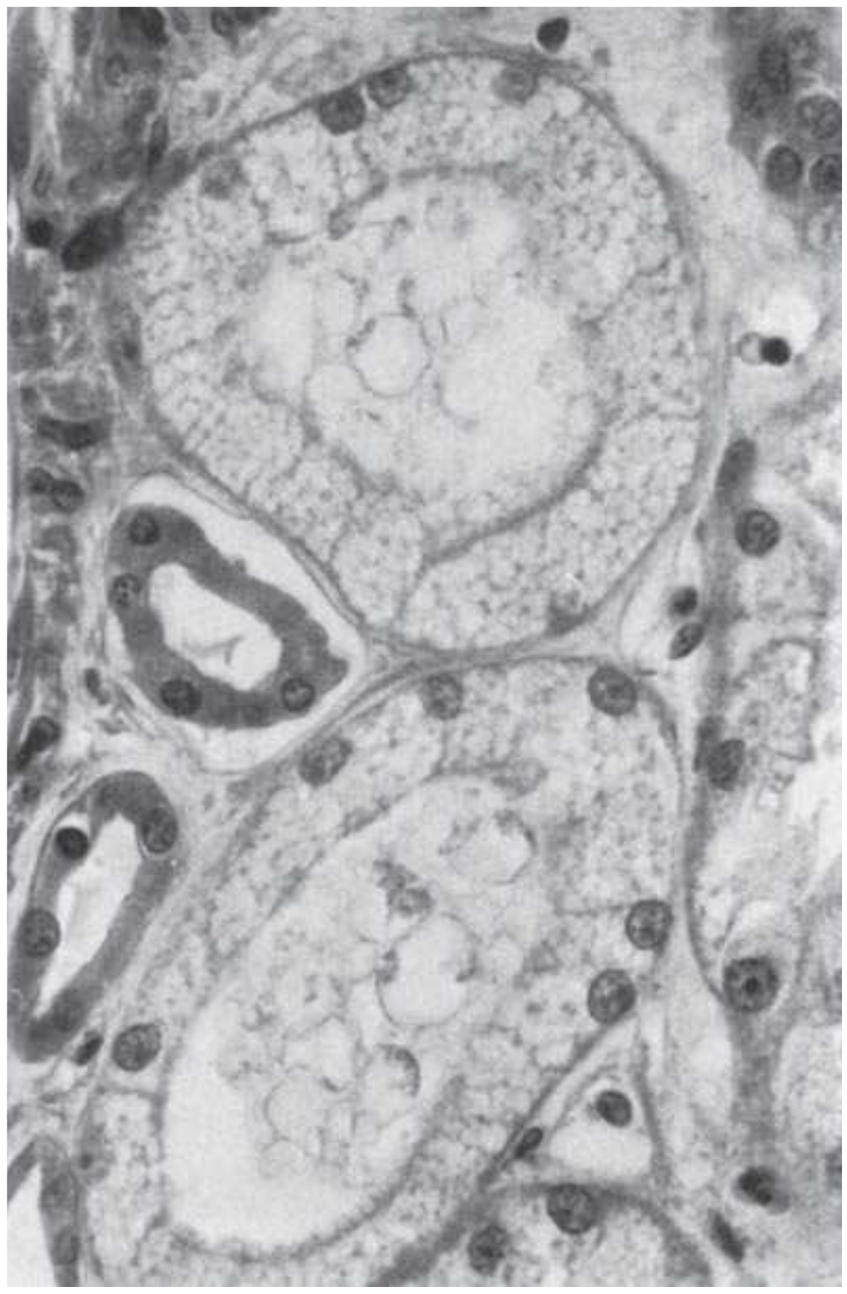


FIGURE 13.14 A photomicrograph illustrating osmotic nephrosis characterized by fine vacuolization of the proximal tubule epithelium (H&E; magnification ×540).

also may be thickened as the result of edema, fibrin, other exogenous material, or inflammation. Similar, although less extensive, changes may be observed in the renal veins.

At this point, it is useful to compare the relative degree and type of involvement of each of the cortical structures. As discussed in the preceding text, when one portion of the nephron is diseased, the remainder of the nephron eventually is affected. The site of the initial insult usually demonstrates the earliest and most severe changes. Thus, in glomerulonephritis, the glomeruli usually exhibit the most

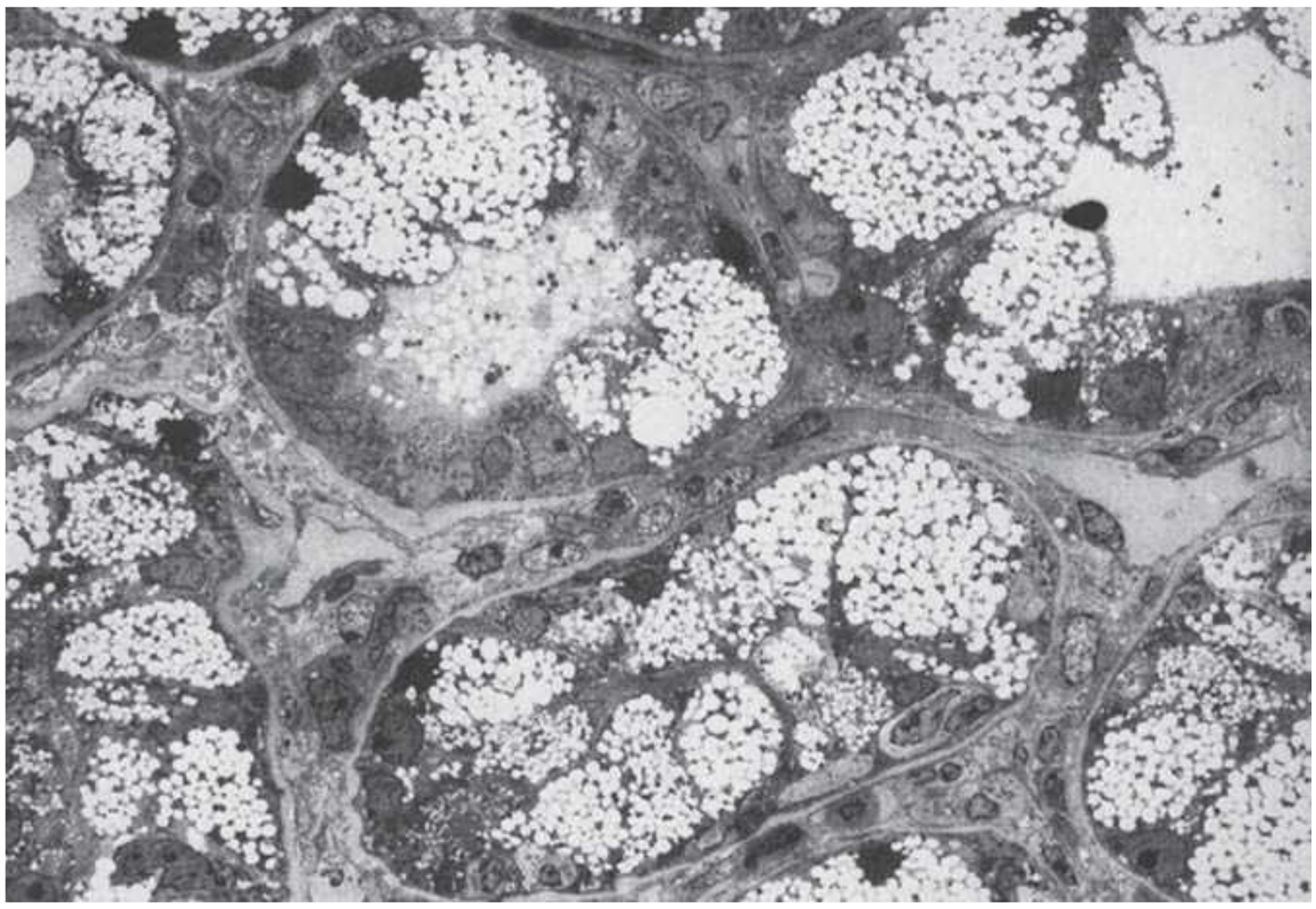


FIGURE 13.15 An electron micrograph illustrating severe tubular vacuolization secondary to calcineurin inhibitor toxicity. The nuclei are pyknotic, and the brush border is often disrupted or lost (magnification ×4,900). (From Tisher CC, Brenner BM, eds. *Renal Pathology with Clinical and Functional Correlations*. Philadelphia: Lippincott; 1989, with permission.)

striking changes, whereas less severe alterations in the form of interstitial inflammation and tubular injury accompany the primary lesion. The interstitium shows the most inflammation in interstitial nephritis, whereas the glomeruli may exhibit secondary involvement. If a process is severe enough and of a sufficient duration, all structures will atrophy and sometimes leave few clues to the etiology of the original disease. One is then left with a diagnosis of end-stage renal disease.

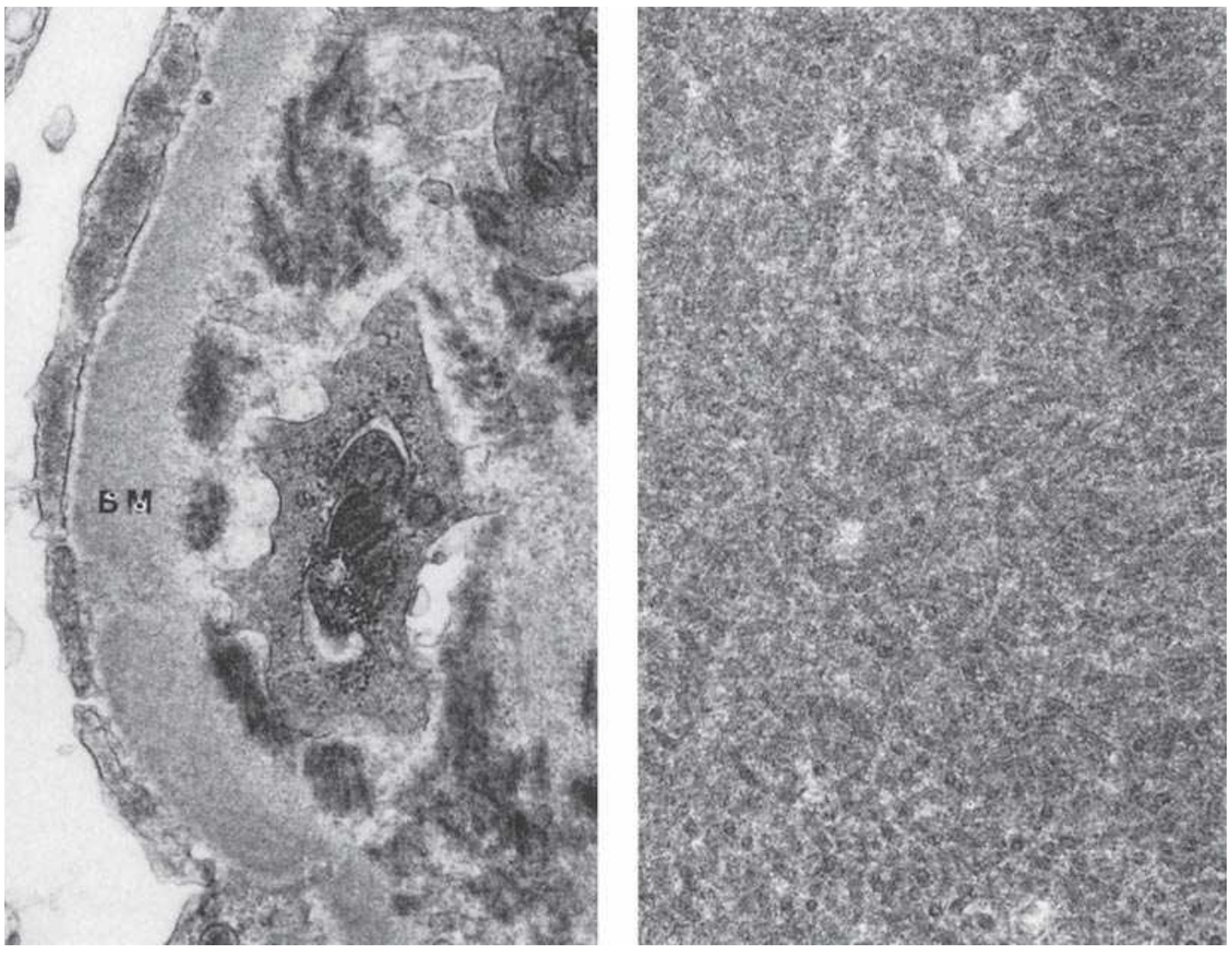
Electron Microscopy

The major advantage of electron microscopy is its greater resolving power when compared with light microscopy. In a kidney biopsy interpretation, electron microscopy is most useful in the examination of glomerular lesions. Immune complexes can be identified by electron microscopy when they are too small to be evident on light microscopy or when the immunofluorescence findings lack specificity. Electron microscopy gives the most definitive localization of immune complex deposits, thus making it possible to subcategorize their location as mesangial, subendothelial, subepithelial, or intramembranous. Some deposits have a characteristic substructure, such as those observed in light-chain disease,[188] amyloidosis,[121] cryoglobulinemic glomerulonephritis (Figs. 13.16A, B),[122] immunotactoid glomerulopathy,[189] or fibrillary glomerulonephritis (Fig. 13.17A, B).[190]

The basement membrane of the glomerular capillary loops may be uniformly thickened, as seen in diabetes mellitus,[191] or may be thin or irregular in appearance, as in Alport hereditary nephritis (Fig. 13.18)[192] or thin basement membrane disease.

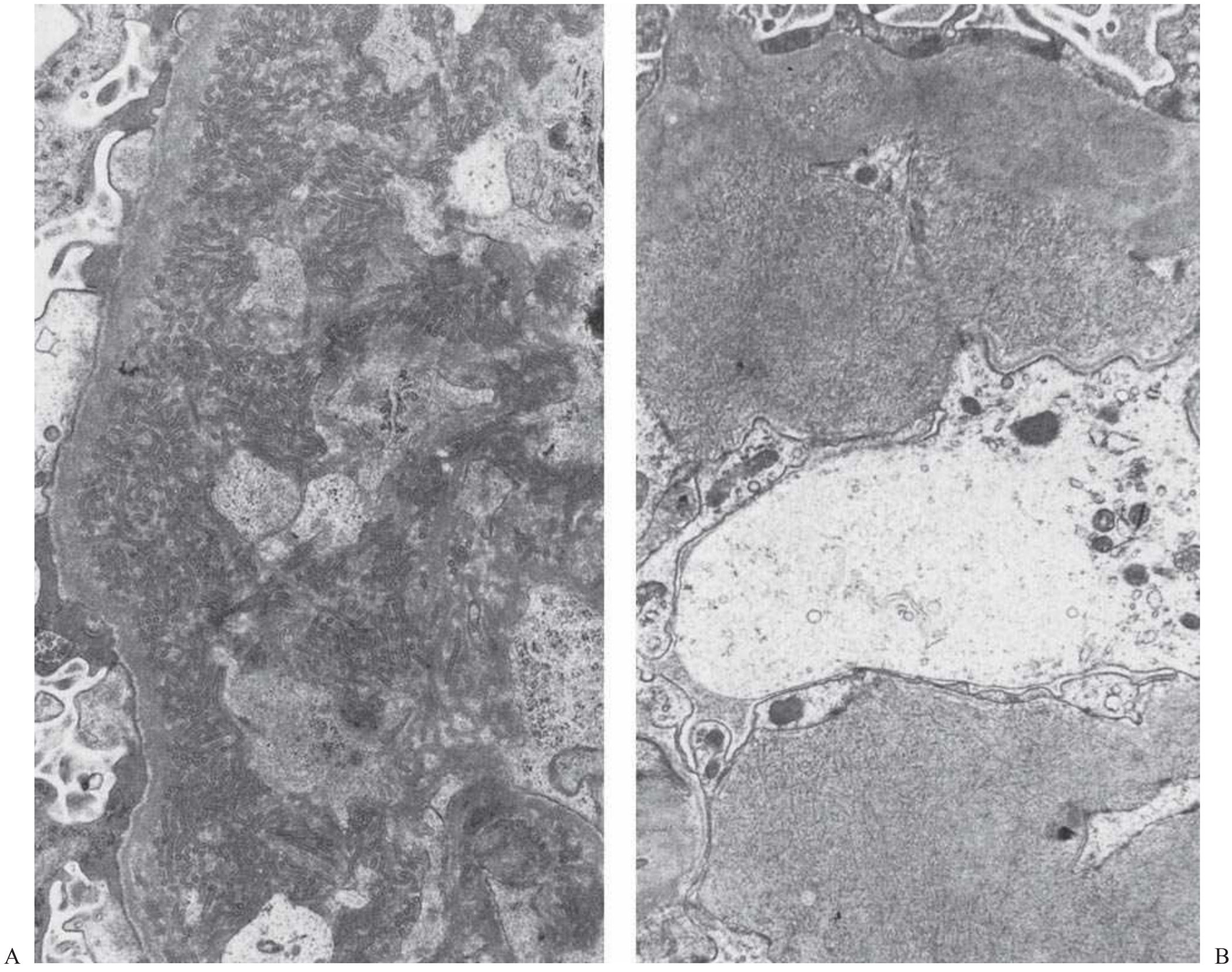
Metabolic abnormalities may be identified by the presence of characteristic accumulations of lipids, such as seen in Gaucher disease.[193] Tubuloreticular arrays may be present in the endoplasmic reticulum of endothelial cells and are characteristic of lupus nephritis when seen in large numbers (Fig. 13.19), although they may be observed in other conditions, such as in HIV-associated nephropathy (Fig. 13.20). Endothelial cell injury is characteristic of thrombotic microangiopathy and vascular allograft rejection. Immune deposits can also be identified along the tubular basement membrane (TBM) in lupus nephritis (Fig. 13.21) and light chain deposition disease.[194]

Recently, the importance of electron microscopy in the evaluation of native kidney biopsies was reaffirmed. In a series of 233 biopsies, Haas[195] found that electron microscopy was necessary to arrive at a final diagnosis in 50 biopsies, representing 21% of the total cases. In another 48 cases, the



A B

FIGURE 13.16 Electron micrographs illustrating cryoglobulin deposits in a glomerular capillary. **A:** A basement membrane with electron-dense subendothelial deposits (magnification ×15,000). **B:** A high-magnification view of the characteristic substructure of cryoglobulin deposits (magnification ×41,000). (Illustrations from Silva F, Eigenbrodt E, with permission.)



A B

FIGURE 13.17 Electron micrographs depicting the characteristic appearance of immunotactoid glomerulopathy (**A:** magnification ×21,000) and fibrillary glomerulonephritis (**B:** magnification ×18,400). (From Alpers CE. Immunotactoid (microtubular) glomerulopathy: an entity distinct from fibrillary glomerulonephritis? *Am J Kidney Dis* 1992;19:185, with permission.)

ultrastructural data were felt to provide important confirmatory information.

One disadvantage of electron microscopy is the limitation in the size of the sample; therefore, ultrastructural findings must be interpreted in the context of other histologic features. In addition, tissue processing for electron microscopy generally takes longer than that for light microscopy. Although rapid processing methods are available, they require special handling and therefore are more costly. Scanning electron microscopy has been used for biopsy investigation, but it is not incorporated into the processing of kidney biopsy specimens for routine clinical evaluation.

Immunohistology

Immunofluorescence and immunoenzyme staining have overlapping but different uses, as discussed previously. Standard immunofluorescence microscopy (as compared to confocal microscopy) is a more rapid but less sensitive technique. It is ideally suited for the detection of immune complex deposits. The major advantages of the immunoperoxidase technique are the greater sensitivity and the ability to examine the tissue with the light microscope, which makes the spatial relationships between tissue structures easier to identify.

There are four major immunoglobulin-staining patterns in glomeruli, which may occur singly or in various combinations (Fig. 13.22). They include linear staining along the basement membrane, granular subepithelial capillary wall staining, granular subendothelial capillary wall staining, and mesangial staining. Paramesangial deposits also may be seen alone, but as a rule, they are observed in association with one of the other granular patterns. Intramembranous deposits also are observed, but their exact location is difficult to determine. The granular deposits may be large and coarse (Fig. 13.22B) or fine (Fig. 13.22C). This difference is readily appreciated when comparing the coarse

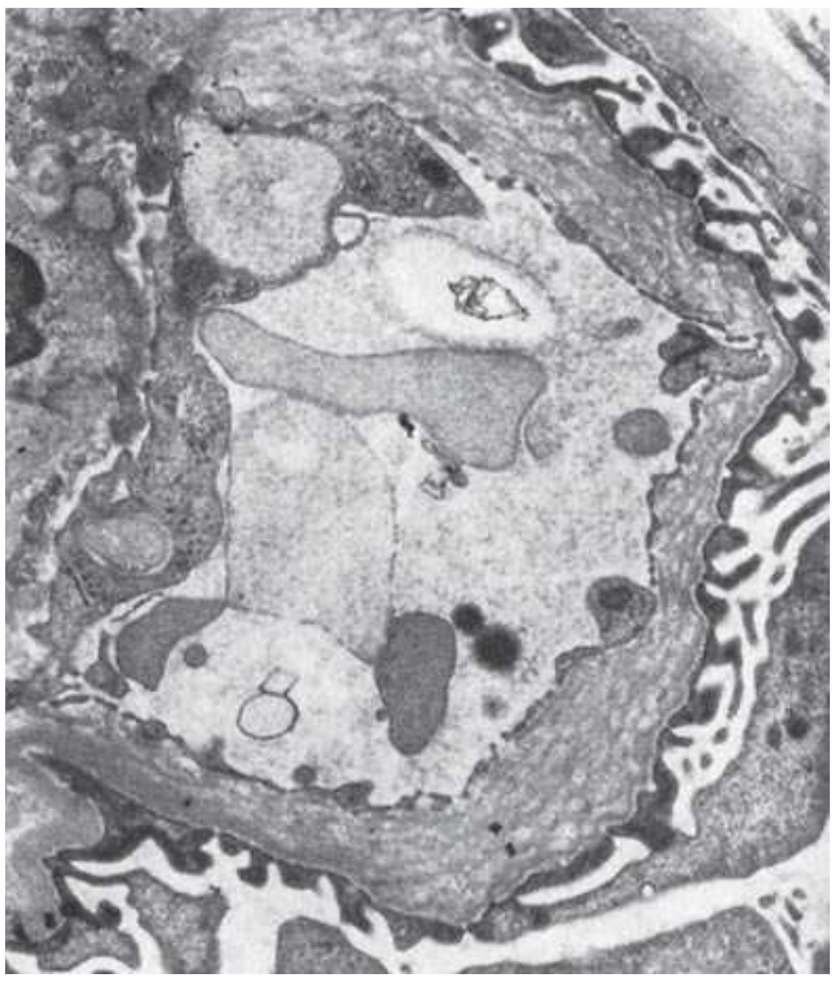


FIGURE 13.18 An electron micrograph of a portion of a glomerular capillary loop from a patient with Alport hereditary nephritis. The typical multilaminated appearance of the thickened basement membrane is evident (magnification ×3,800). (Illustration from Silva F, with permission.)

subepithelial deposits of poststreptococcal glomerulonephritis (Fig. 13.22B) with the subepithelial deposits of an early idiopathic membranous glomerulonephritis (Fig. 13.22C). Immune complex deposits may contain IgG, IgM, or IgA in any combination. C1q or C3 staining may be present in any of the same patterns as seen with immunoglobulins, or they may be observed separately. Linear staining requires careful interpretation. First, finely granular capillary wall staining can appear as a confluence of granules yielding a pseudolinear pattern. Electron microscopy resolves any doubt in this situation. Second, diseases such as diabetes mellitus and most other chronic renal diseases, including chronic allograft nephropathy, cause a thickening of the basement membrane. This is associated with increased staining of the capillary wall for serum proteins, particularly IgG4 and albumin, owing to electrostatic attraction.[196] These situations must be distinguished from the linear capillary basement membrane staining that is specific for IgG as observed in anti-GBM disease (Fig. 13.22A). In anti-GBM disease, the IgG staining clearly exceeds the albumin staining in intensity.

Epithelial cells, especially in the glomerulus and the proximal tubule, commonly have cytoplasmic droplets of protein in proteinuric conditions. Immune complexes also may be seen in the vessels, the interstitium, or along the tubular basement membranes. Vascular or tubular basement membrane staining for C3 in the absence of immunoglobulin is a common and often nonspecific sign of injury.

The use of immunoperoxidase staining with monoclonal antibodies directed against different antigens has made it possible to identify cell populations in tissue sections with great clarity and discrimination.[197] Immunofluorescence microscopy also can be used,[198] but the spatial discrimination is not as good. Most nonspecific inflammatory infiltrates are an approximately equal mixture of B and T cells, with a predominance of T-helper cells (CD4) over T-suppressor or cytotoxic (CD8) cells.[197–199] These cells form nodular aggregates in interstitial areas. Cellular allograft rejection predominantly has T cells (Fig. 13.4F)[197–199] and monocytes (macrophages).

In some cases, a viral cytopathic effect may be seen by standard histology (e.g., nuclear inclusions) and the viral pathogen inferred from the clinical situation or serologic tests. However, the virus can be specifically identified by immunohistochemistry or in situ nucleic acid hybridization. Common examples in the transplant setting are BK virus, cytomegalic virus (CMV), and EBV.

Other enzyme systems can be used to replace peroxidase in immunoenzyme staining. However, immunostaining

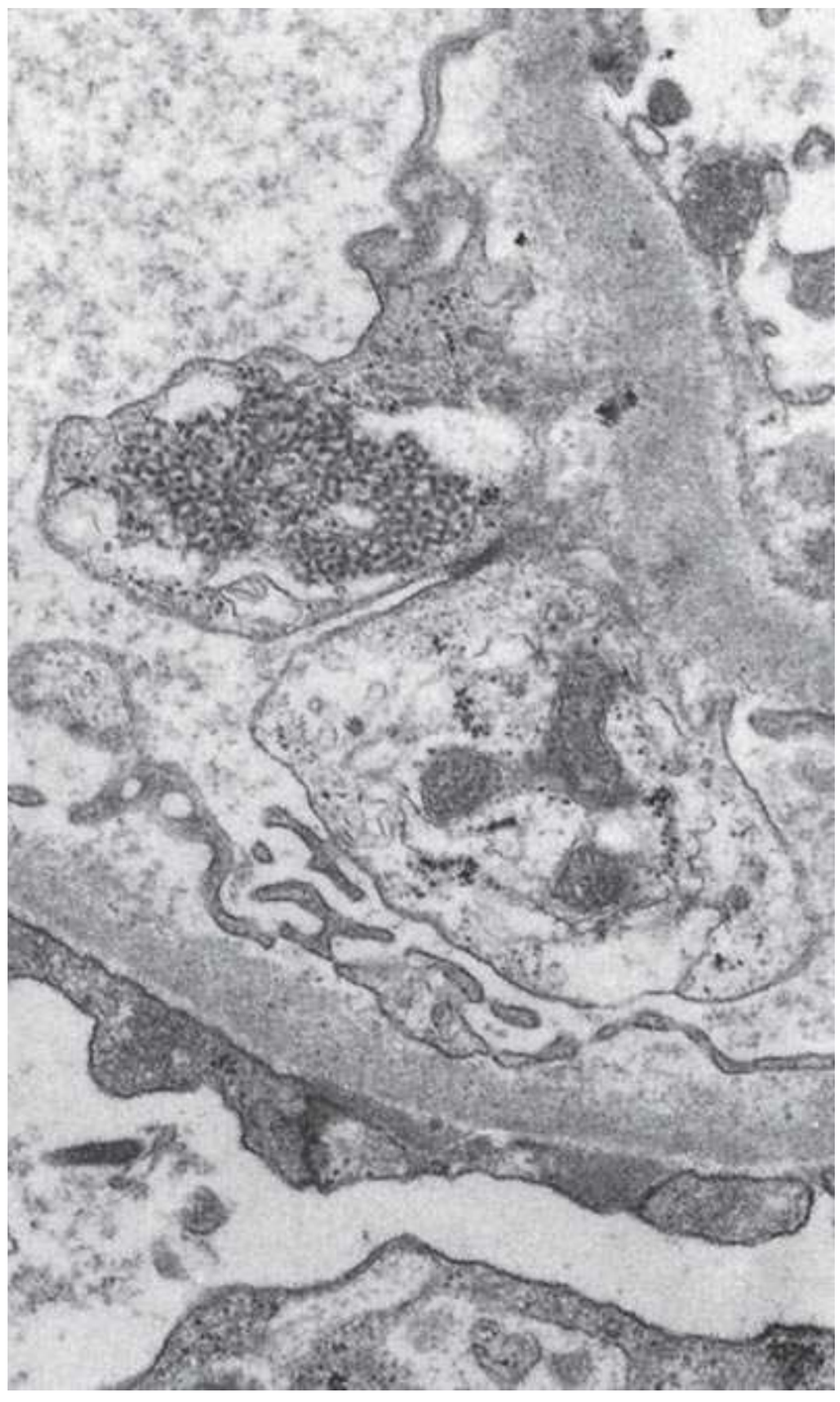


FIGURE 13.19 An electron micrograph depicting tubuloreticular arrays in a smooth-surfaced endoplasmic reticulum of a glomerular capillary endothelium from a patient with lupus nephritis (magnification ×24,000). (From Tisher CC, Kelso HB, Robinson RR, et al. Intraendothelial inclusions in kidneys of patients with systemic lupus erythematosus. *Ann Intern Med* 1971;75:537, with permission.)

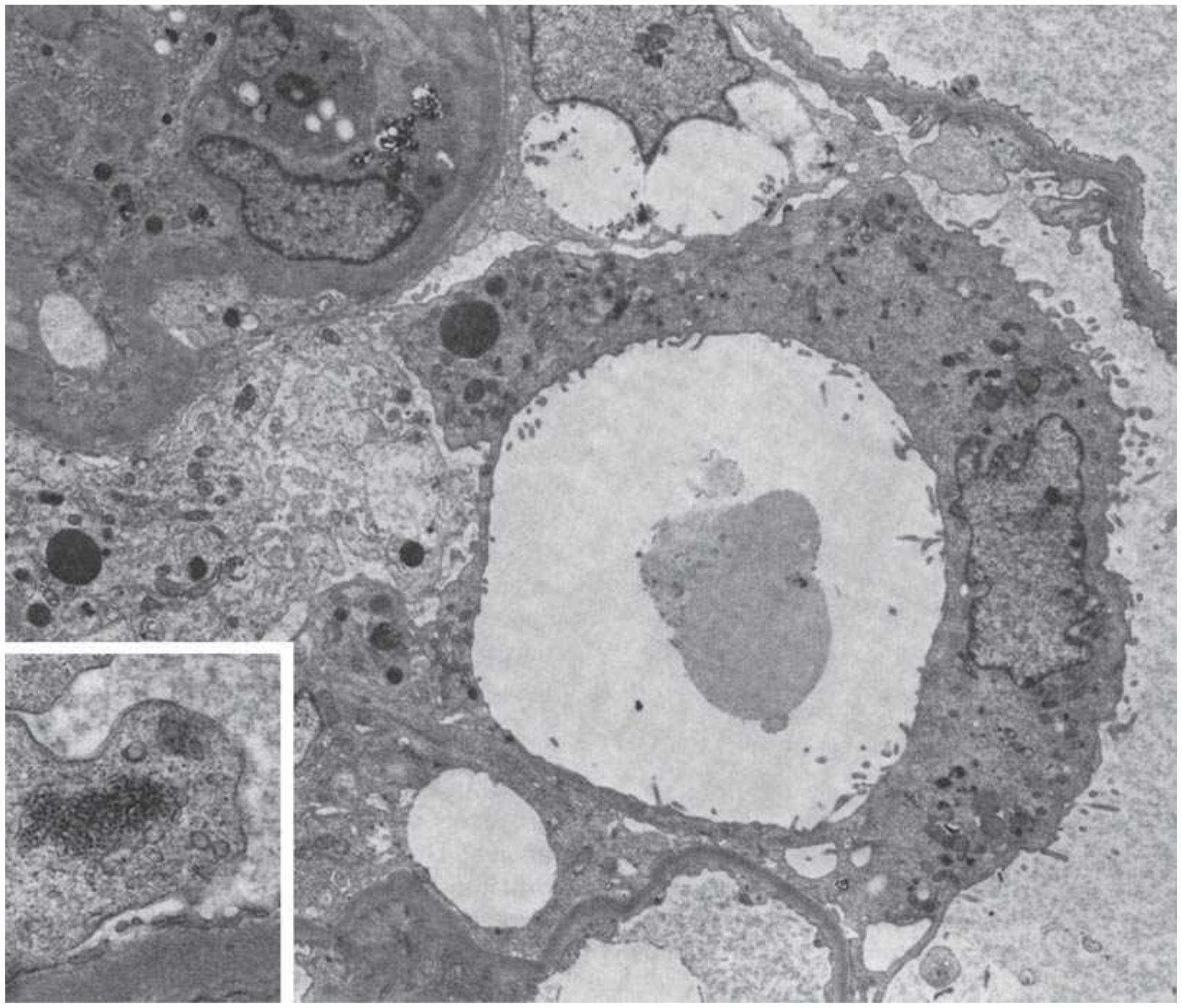


FIGURE 13.20 An electron micrograph illustrating focal and segmental glomerulosclerosis in HIV-associated nephropathy. The inset depicts the characteristic tubuloreticular arrays located within the endoplasmic reticulum of glomerular endothelial cells that are typically observed in this condition (magnification ×4,000; *inset,* magnification ×16,250). (Illustration from Cohen AH, with permission.)

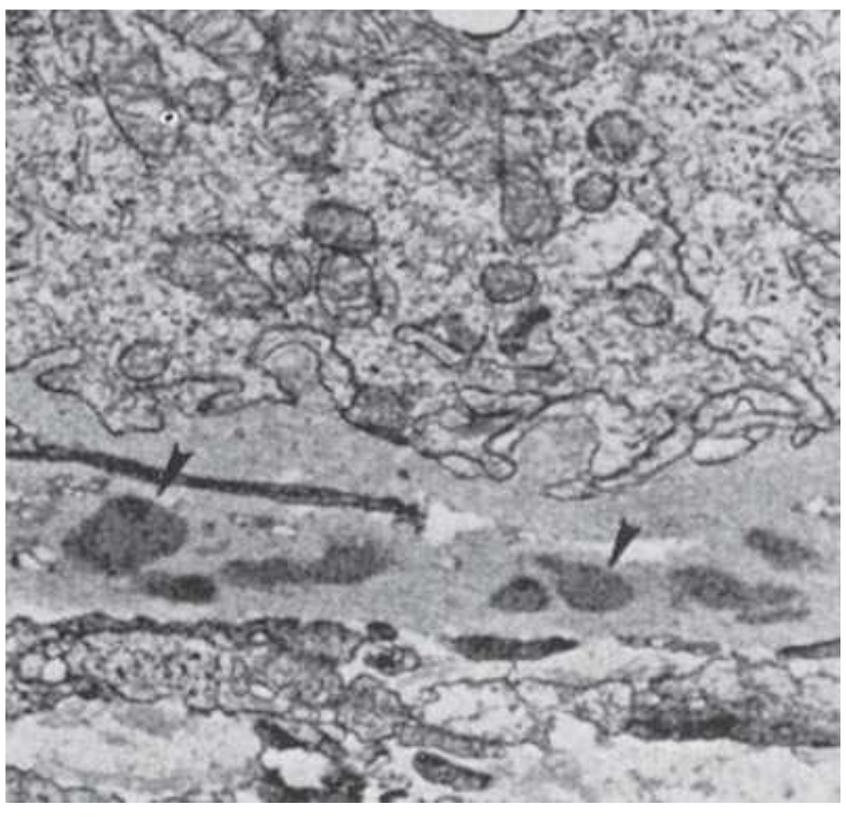


FIGURE 13.21 An electron micrograph illustrating immune complex deposits (*arrowheads*) along a tubular basement membrane in a renal biopsy from a 14-year-old boy with lupus nephritis (magnification ×2,500). (Biopsy specimen from Nash ML, with permission.)

using horseradish peroxidase and diaminobenzidine as the substrate is the best combination currently available because the staining is crisp and the slides are permanent. Diaminobenzidine is a carcinogen and must be handled with caution. Immunohistochemistry has great diagnostic potential, which is limited primarily by the antibody specificity.

The vision of gene expression in kidney disease has progressed in two paradigms for kidney transplant pathology. The first is in "for cause" biopsies where the microarray transcriptiosome signature may help clarify the ambiguous Banff subclassification of "Borderline (Suspicious) for rejection" and various chronic renal allograft pathology states[200] known as chronic rejection, chronic allograft nephropathy, or interstitial fibrosis/tubular atrophy (IFTA).[201,202] The second paradigm is to monitor gene expression in biopsies to evaluate the adequacy of immunosuppresion in terms of determining which gene signature profiles are predictive of chronic progression.[203] Biopsy studies are supplemented by minimally invasive peripheral blood profiles.[204–206]

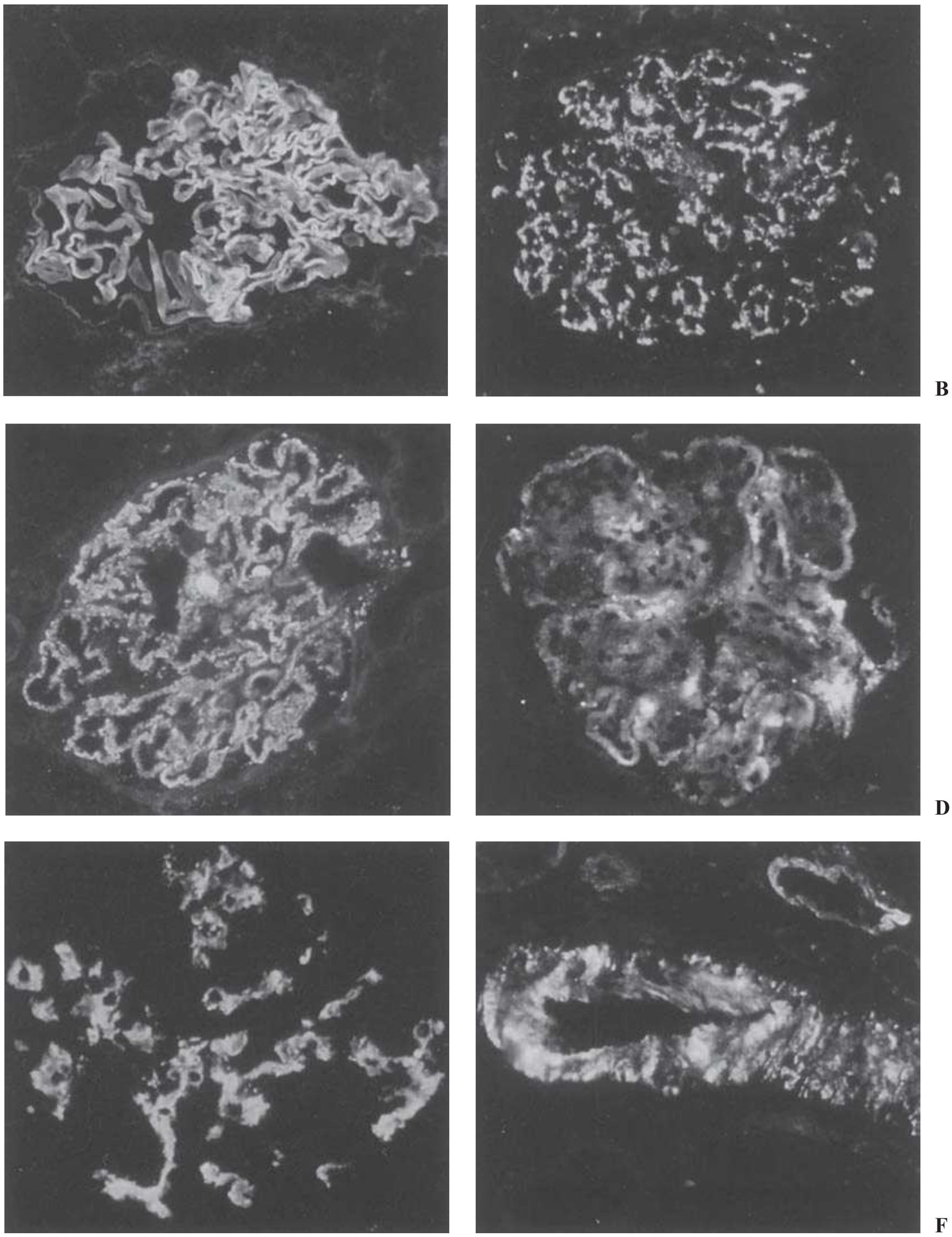


FIGURE 13.22 **A:** A glomerulus with fine, ribbonlike basement membrane staining with IgG indicative of anti-glomerular basement membrane disease (magnification ×200). **B:** A glomerulus exhibiting coarse granular deposits of IgG distributed irregularly along the glomerular basement membranes. This pattern is typical of poststreptococcal glomerulonephritis. C3 is usually present in the same pattern (magnification ×200). **C:** A glomerulus with fine IgG granules evenly deposited along the glomerular basement membrane. This pattern is typical of the subepithelial deposits of idiopathic membranous glomerulonephritis (magnification ×200). **D:** A glomerulus demonstrating the typical pattern of subendothelial immune complex deposits. The outer edge of the deposits abuts the inner surface of the glomerular basement membrane and is relatively smooth. The inner aspect of the deposits is shaggy and irregular and may merge with the mesangium, which is expanded. This pattern is characteristic of membranoproliferative glomerulonephritis (IgM; magnification ×200). **E:** A glomerulus exhibiting the typical pattern of IgA mesangial immune deposits. Note the absence of basement membrane localization. The dark spaces in the midst of the deposits represent mesangial cells, not capillary lumina. This pattern is typical of IgA nephrology, Henoch-Schönlein purpura, and mesangiopathic lupus nephritis (magnification ×200). **F:** An arteriole with transmural staining for IgM. This pattern is characteristic of relatively mild, acute vascular lesions of vascular rejection. In more severe lesions, there is a greater disruption of the vessel wall, which also can be seen by light microscopy. This pattern should be distinguished from the subintimal glossy deposits of hyaline that are seen in chronic vascular disease (magnification ×400). (See Color Plate.)

CLINICOPATHOLOGIC CORRELATIONS

Once the light, immunohistologic, and electron microscopic findings are completed, they should be integrated to derive a histologic diagnosis that is indicative of the disease process. The histologic diagnosis then is related to the clinical findings to give a clinicopathologic diagnosis that can be used to plan a course of therapy, establish the prognosis, or both. We do not try to describe all of the many histologic patterns of kidney disease in this section, because they are discussed in considerable detail in other chapters of this book. Instead, we briefly discuss selected examples in which the approach we have outlined is used.

Several renal diseases fail to reveal significant changes or only nonspecific changes on a histologic examination. For instance, in MCNS, the findings are principally the result of proteinuria and include foot-process simplification in the glomerulus and evidence of increased protein resorption by the proximal tubule. The only abnormality in benign recurrent hematuria may be the presence of red blood cells in the tubules. The differential diagnosis should include Alport disease early in its course and thin basement membrane disease. Differentiation requires a thorough electron microscopic examination of the specimen and the appropriate clinical studies.

Mesangial Expansion

In many conditions, mesangial expansion may be the only abnormality observed on light microscopy. The immunofluorescence findings separate a group of immune complex diseases that exhibit mesangial involvement. For instance, if IgA is the predominant immunoglobulin that localizes to the mesangium (Fig. 13.22E), the differential diagnosis should include IgA nephropathy and Henoch-Schönlein disease. If IgG is the principal immunoglobulin, then lupus nephritis should be considered and a careful search should be made by electron microscopy for subendothelial and subepithelial deposits or fibrillary glomerulonephritis. If the predominant immunoglobulin is IgM, then the differential diagnosis should include IgM nephropathy and the mesangiopathic form of lupus nephritis. Mesangial localization of C3 in the absence of immunoglobulins may represent a resolving immune complex disease. Evidence of resolving immune complexes may be seen by electron microscopy. The mesangial expansion may represent early diabetic nephropathy, arteriolonephrosclerosis, or FSGS if no complexes are noted on electron microscopy. If the material responsible for the mesangial expansion is negative or only weakly positive with the PAMS and PAS stains, it is important to examine additional sections after staining with Congo red in search of evidence of amyloid. On light microscopy, the most specific indication of amyloid is a green birefringence that occurs when the Congo red stain is viewed under polarized light (Fig. 13.4D). Occasionally, electron microscopy may be necessary to establish the diagnosis because it is the most sensitive technique to detect amyloid. Other, less common immune deposits that are also demonstrated easily with electron microscopy include κ light-chain disease, cryoglobulinemic glomerulonephritis, fibrillary glomerulonephritis, and immunotactoid glomerulopathy (Figs. 13.16A,B and 13.17A,B).

Neutrophilic Exudates

A neutrophilic exudate may be observed in a variety of renal diseases. The most prominent neutrophilic exudate is typically seen in poststreptococcal glomerulonephritis (Fig. 13.5),[207] a disease that does not usually require a biopsy for diagnosis. Occasionally, the typical clinical features are obscured, however, and a kidney biopsy is required. The patient may not seek medical attention until later in the disease course, when the light microscopic and immunofluorescence microscopic findings of coarse granular IgG deposits (Fig. 13.22B) may not be present. Often, however, C3 deposits remain. Again, electron microscopy may demonstrate typical large humplike subepithelial deposits that are in various stages of resolution. Numerous neutrophils also may be seen in other forms of postinfectious glomerulonephritis, in MPGN (Fig. 13.23),

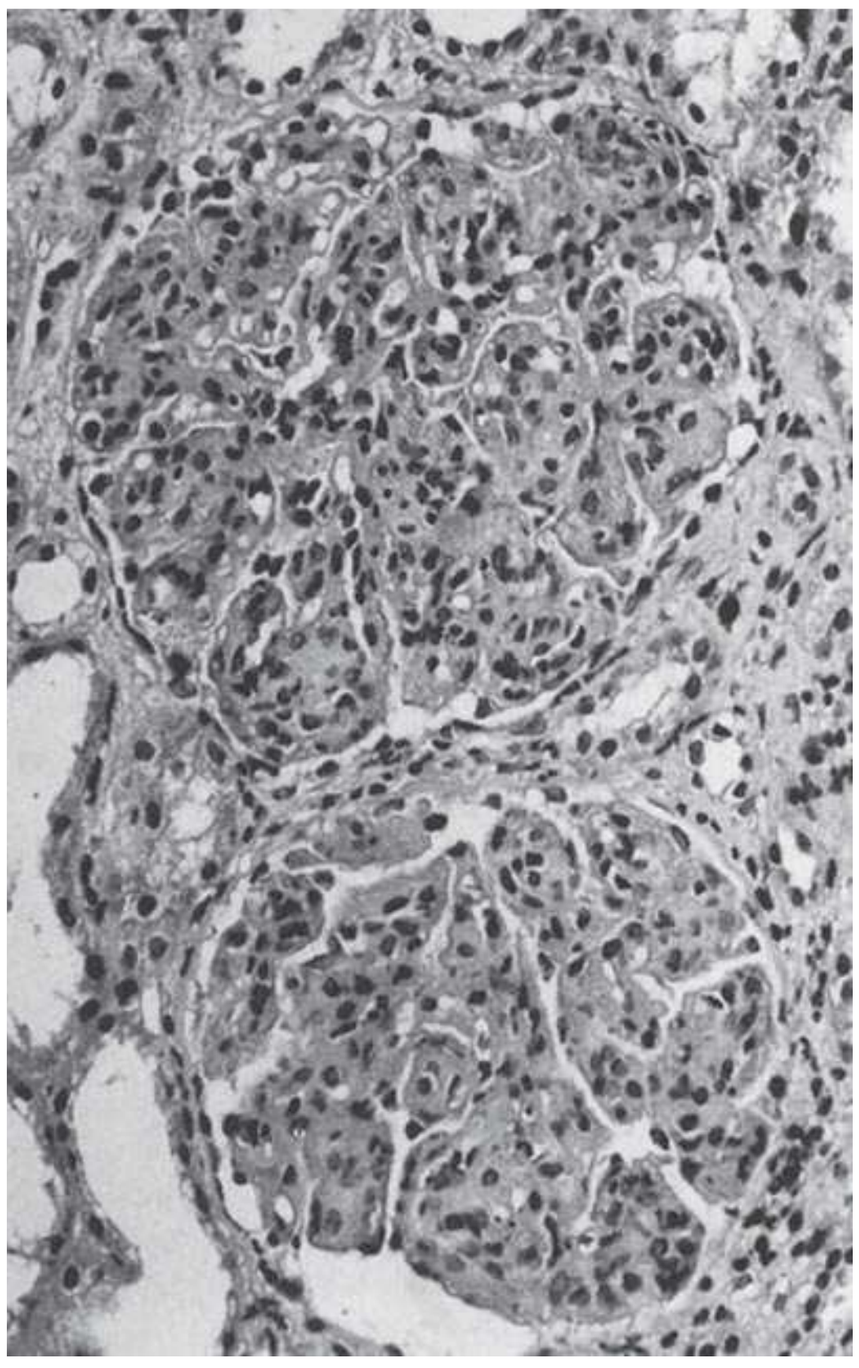


FIGURE 13.23 A photomicrograph demonstrating a mesangial hypercellularity and neutrophilic infiltrates in two glomeruli from a patient with type II membranoproliferative glomerulonephritis (H&E; magnification ×300). (From Lamb V, Tisher CC, McCoy RC, et al. Membranoproliferative glomerulonephritis with dense intramembranous alterations. A clinicopathologic study. *Lab Invest* 1977;36:607, with permission.)

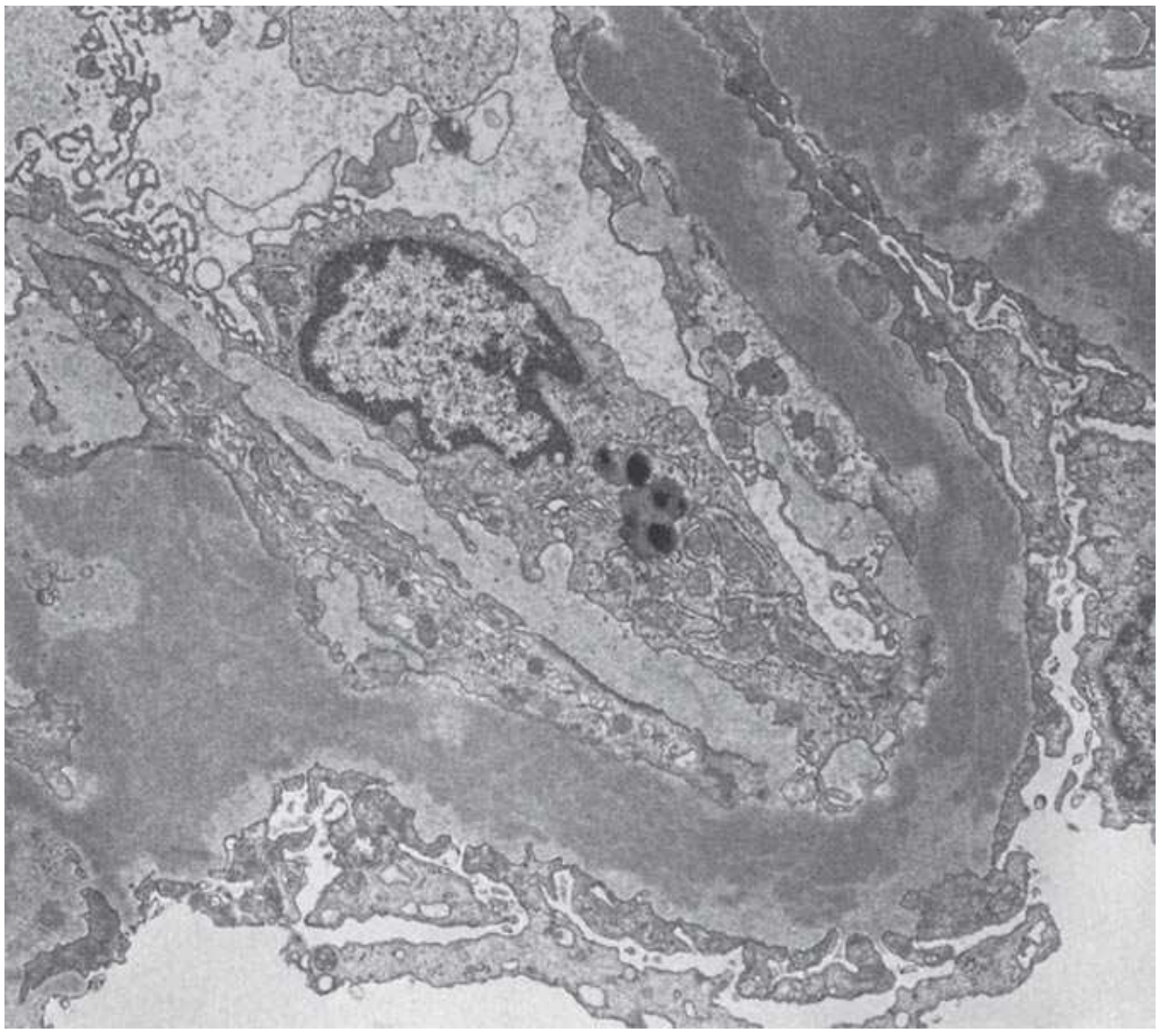


FIGURE 13.24 An electron micrograph of a peripheral capillary loop from the glomerulus of a patient with type II membranoproliferative glomerulonephritis. Intramembranous electron-dense deposits are present throughout the widened basement membrane (magnification ×9,650). (From Lamb V, Tisher CC, McCoy RC, et al. Membranoproliferative glomerulonephritis with dense intramembranous alterations. A clinicopathologic study. *Lab Invest* 1977;36:607, with permission.)

and in the proliferative forms of lupus nephritis. Membranoproliferative glomerulonephritis may be identified by its characteristic pattern of mesangial interposition and the electron-dense deposits that are primarily subendothelial in location in type I disease and intramembranous in location in type II disease (Fig. 13.24) when observed by electron microscopy. The proliferative forms of lupus nephritis are often characterized by the prominent variability in their histologic appearance from one part of a glomerular tuft to another and from one glomerulus to another.

Crescents

Crescents may be present in every type of immune-mediated glomerulonephritis; therefore, they are not diagnostic. Most types of glomerulonephritis associated with crescents can be identified by their characteristic patterns of immunoglobulin localization with immunofluorescence microscopy. These include the more severe forms of IgA nephropathy and Henoch-Schönlein purpura (IgA deposits), lupus nephritis, anti-GBM disease, and MPGN. Serologic studies for antineutrophil cytoplasmic antibodies (ANCA) have helped clarify the diseases with sparse immune deposits (pauci-immune glomerulonephritis) and fibrinoid necrosis or crescents.[208] These glomerular changes are indistinguishable from the glomerular involvement observed in the microscopic form of polyarteritis nodosa or Wegener granulomatosis. In the absence of a vasculitis involving the muscular arteries in the biopsy specimen, these conditions can be separated by the presence or absence of other systemic organ involvement.[209]

The association of crescents and the clinical outcome is typified by the findings in anti-GBM disease. Several authors have noted the generally benign course of anti-GBM disease in those few patients who do not develop crescents over the course of their disease even with minimal therapy.[210–212] A close follow-up is prudent in this group because, rarely, a patient has been shown to progress from noncrescentic to crescentic glomerulonephritis.[211] A graded response in renal and patient survival is dependent on the percentage of crescents. Five studies in the literature[210,212–215] had comparable results that could be combined to evaluate the relationship between the percentage of crescents in the biopsy and renal survival in a total of 133 patients. If the percentage of crescents was less than 85%, most patients (48 of 61) had independent renal function, that is, did not require renal replacement therapy, at follow-up (78%). If the percentage of crescents was 85% or greater, most patients (61 of 72) progressed to renal failure (85%) (Table 13.1). Similar results are found correlating serum creatinine values at presentation with renal survival in anti-GBM disease (Table 13.1).[210,212,214–216] There also is a correlation between serum creatinine and the percentage of crescents at presentation.[212]

In general, the presence of crescents in glomeruli is associated with a worse prognosis. Exceptions include poststreptococcal glomerulonephritis in children where the crescents may resolve without adverse sequelae.[217,218] ANCA-associated glomerulonephritis does not have as clear an association between crescents and renal survival.[208] Therefore, it is preferable to separate the various causes of crescentic glomerulonephritis for the determination of prognosis and treatment.

13.1 Survival in Anti-GBM Disease[241]

	Patient Survival		Renal Survival[a]	
	1 year	5 year	1 year	5 year
Initial creatinine < 5.66 mg/dL (500 μmol/L)	100%	94%	95%	94%
Creatinine > 5.66 mg/dL (500 μmol/L) but no dialysis	85%	80%	69%	50%
Dialysis dependent	67%	44%	5%	13%

[a]Renal survival is defined as the absence of the need for dialysis or renal transplantation.

Glomerulosclerosis

Glomerulosclerosis may be the result of scarring from a prior proliferative or immune complex lesion, or it can be primary in nature.[219] Two common examples of the latter are diabetes mellitus and FSGS. FSGS is commonly associated with hyalinosis and foam cells within the glomerular tuft and hyperplasia of the parietal epithelium in the area adjacent to the sclerosis (Fig. 13.8); however, these features may be absent in a given biopsy specimen. In the early stages of FSGS, only a few glomeruli are affected and these are usually located deep in the cortex.[220] Not infrequently, a biopsy may miss glomeruli with segmental lesions and the histology will resemble MCNS. With time, the segmental sclerosis progresses to global sclerosis and involves a greater number of glomeruli throughout the cortex. Although diabetic nephropathy and FSGS are not considered immune complex diseases, the globally or segmentally sclerotic glomeruli usually have staining for IgM and C3. Segmental glomerulosclerosis may also be the end result of any disease that progresses toward chronic renal failure. Therefore, FSGS as a primary disease must be differentiated from the end-stage process of focal glomerulosclerosis. To make a diagnosis of FSGS, one must exclude other causes of segmental sclerosis that produce hyperfiltration and secondary changes of glomerular sclerosis. The diagnosis cannot be made with certainty in the presence of advanced nephron destruction or severe vascular disease.

Capillary Wall Thickening

Thickening of the glomerular capillary walls can be seen in a variety of renal diseases. In its early stages, diabetes is characterized by thickening of the lamina densa, which may be visualized by electron microscopy. It may occur as a consequence of glomerulosclerosis and take on a wrinkled, ribbonlike appearance in association with other evidence of glomerular tuft ischemia or atrophy. Localized thickening can be seen in postinfectious proliferative glomerulonephritis because of the presence of subepithelial, humplike, immune-complex deposits. In idiopathic membranous glomerulonephritis, discrete granular immune-complex deposits are localized to the subepithelial surface of the capillary wall and are associated with subepithelial extensions of basement membrane material, referred to as spikes (Fig. 13.4C). These progress to form bridges to completely enclose the subepithelial deposits, yielding a tram-track configuration. In type I MPGN, subendothelial immune-complex deposits are often seen in association with a reduplication of the peripheral glomerular basement membrane (mesangial interposition, Fig. 13.25). Similar changes can be seen in type II MPGN, in which electron-dense material expands the original basement membrane of the peripheral capillary loop and is also associated with mesangial interposition (Fig. 13.24). In both type I and II MPGN, this combination of histologic changes can give rise to a double contouring of the peripheral portion of the glomerular capillary wall.

Regardless of the particular glomerular alteration, it is often important for a diagnostic and prognostic evaluation to note whether the lesion is segmental versus global or focal versus generalized. An example of this distinction is emphasized in the most recent classification of lupus nephritis,[221] which divided the World Health Organization class IV into segmental (class IV-S, Fig. 13.26) and global (class IV-G) subdivisions. There is a presumption or hypothesis that the segmental subclass may have a different pathogenesis, and one published study[222] shows a difference in outcome when compared with the global subclass.

Interstitial Inflammation

The differential diagnosis of interstitial inflammatory infiltrates poses some interesting diagnostic problems for the nephropathologist. Kidneys with nephron atrophy may have fibrosis and associated dense nodular lymphocytic infiltrates composed of mixtures of B cells and T cells. Interstitial infiltrates in the absence of nephron atrophy or acute glomerulonephritis suggest a primary interstitial

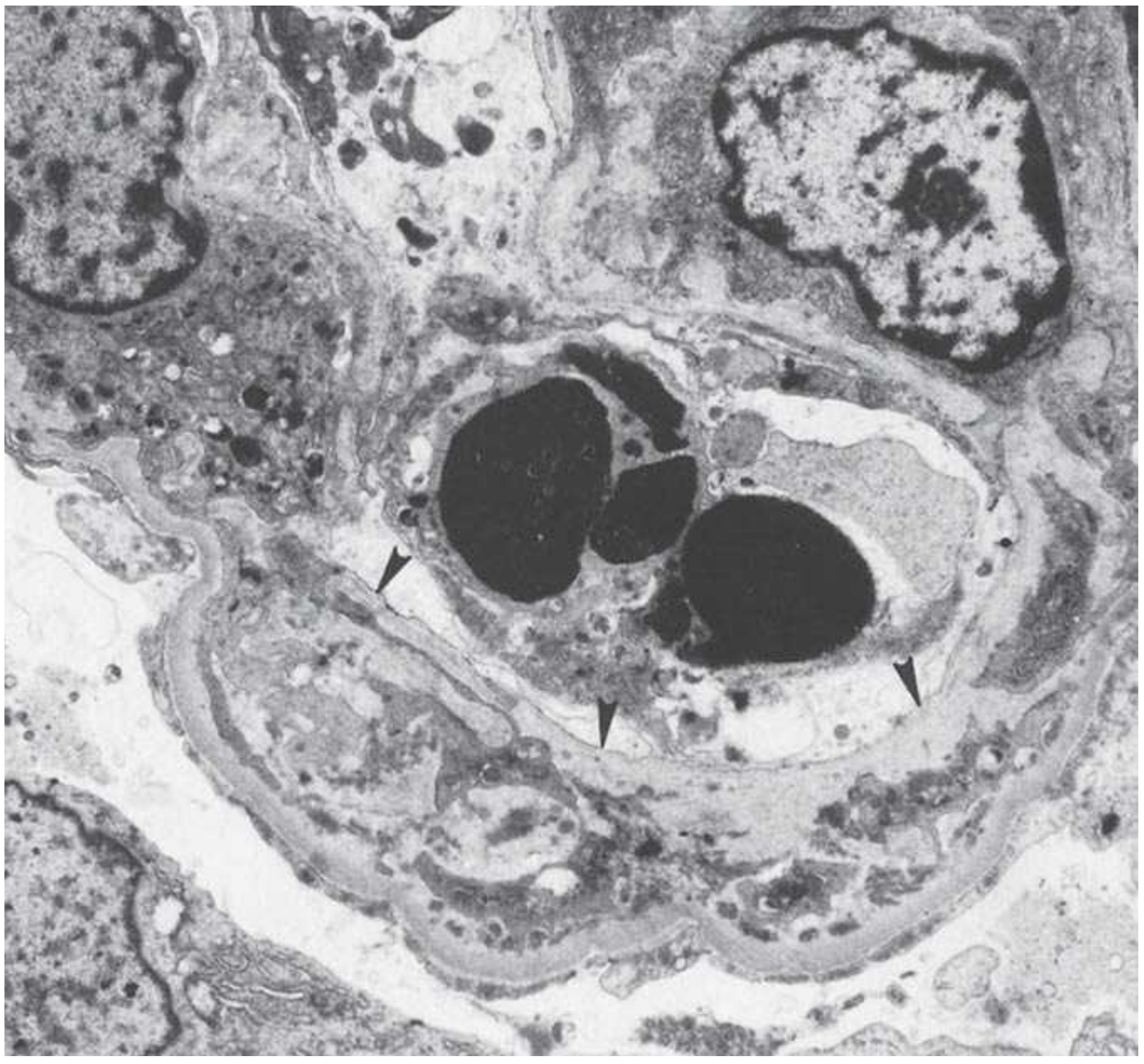


FIGURE 13.25 An electron micrograph illustrating typical mesangial interposition (*arrowheads*) in type I membranoproliferative glomerulonephritis (magnification ×3,200). (Illustration from Silva F, with permission.)

nephritis. The presence of large numbers of neutrophils in the tubules (neutrophilic tubulitis), the Bowman space, and the interstitium suggests a diagnosis of acute bacterial interstitial nephritis, whereas an occasional tubule with neutrophils may be seen in ATN. Cellular infiltrates composed of lymphocytes and plasma cells, with or without eosinophilia, commonly are the result of a drug allergy or are idiopathic in nature. Urinary outflow obstruction and renal vein thrombosis may cause interstitial edema and mild inflammation, but these changes are relatively nonspecific. Acute tubular necrosis is also associated with mild interstitial infiltrates in the region of the straight portion of the proximal tubule. A more chronic interstitial nephritis can result from an adverse response to nonsteroidal anti-inflammatory drugs. A pattern of nephron atrophy that affects the tubules before the glomeruli and vessels is consistent with, but is not pathognomonic of, chronic interstitial nephritis. Rarely, a lymphocytic lymphoma or leukemia may be seen on a kidney biopsy.

Vascular Lesions

Arteriosclerosis is the most common vascular lesion observed in kidney biopsies. It may represent a primary vascular disease such as that seen with long-standing hypertension, or it may be observed in association with progressive nephron loss that occurs with end-stage renal disease of any etiology. Extensive hyaline arteriolosclerosis suggests the presence of diabetes mellitus (Fig. 13.10). Milder hyaline lesions are seen in FSGS and, sporadically, in hypertension and other conditions. Necrotizing vasculitis is rarely seen in kidney biopsies in the absence of the glomerular lesions of polyarteritis, lupus nephritis, or Henoch-Schönlein purpura. Thrombotic microangiopathy is a distinctive lesion of small arteries and glomerular capillaries. It is characterized by an insudation of fibrin and RBCs, the latter of which is often in the form of schistocytes, into the walls of the small arteries and glomerular capillaries. The latter may appear as mesangiolysis. These acute changes often progress to renal ischemia and atrophy. This lesion can be seen in varying degrees of severity in several clinical settings, including the hemolytic–uremic syndrome, malignant hypertension, progressive systemic sclerosis, lupus nephritis, and anti-GBM disease.

Renal Allograft Pathology

Percutaneous biopsies of renal allografts introduce another set of diagnostic challenges for the pathologist. Virtually any lesion that occurs in the native kidney also can be found in the allograft in addition to the histologic picture of rejection.[137] An absence of function in the immediate postoperative period, especially in a cadaveric kidney, is usually due to ischemic tubular damage or rejection. A pathogenetic classification of rejection is given in Table 13.2, which incorporates features of immunologic mechanisms and the clinical setting. A hyperacute rejection may occur in a small percentage of patients and has a very distinctive morphology

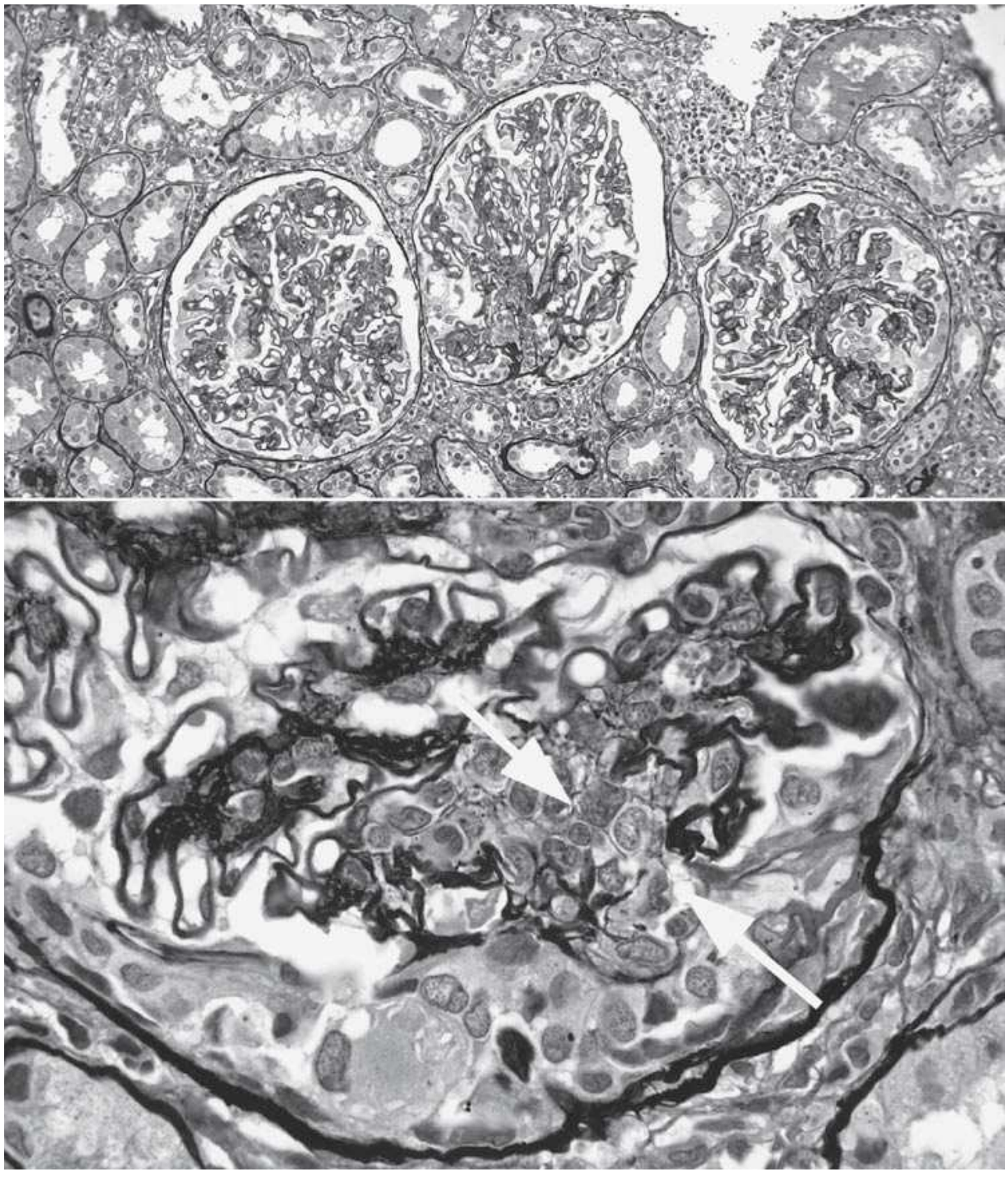


FIGURE 13.26 A segmental class IV lupus nephritis. **A:** This figure shows three glomeruli with segmental involvement (PAMS; magnification ×200). **B:** This is a higher magnification (×500) of a segmental lesion with increased cellularity and fragmentation and disruption of the GBM between the arrows (PAMS).

characterized by the presence of extensive fibrin thrombi and neutrophils in glomerular capillaries. This form of rejection is thought to be secondary to the presence of a preformed circulating antibody in the recipient that was not detected with the usual screening procedures.

Acute vascular rejection can occur from the first week of engraftment. It may be antibody or cell-mediated. It resembles the histologic picture of a low-grade vasculitis, with intimal proliferation or disruption and exudation in the walls of arteries and glomerular capillaries (Color Fig. 13.4E). The vascular lesions usually are patchy and are more frequently missed by light microscopy in biopsies with few arteries. The immunofluorescence findings of IgM, C1q, and C3 in the walls of vessels are more sensitive indicators of vascular rejection (Fig. 13.22F). Immunoperoxidase staining for the complement component, C4d (Fig. 13.27), is a marker for antibody-mediated rejection and is more widely distributed.[223] Electron microscopy reveals a swelling of the glomerular endothelium and the lamina rara interna.

Tubulointerstitial rejection is another type of acute rejection and is a form of acute interstitial nephritis. In most cases, the infiltrate is composed of large active cytotoxic T cells.[224] The cytotoxic T cells identified by immunohistochemical staining (Fig. 13.4F) infiltrate the tubular cytoplasm, a process termed emperipolesis, to produce lymphocytic tubulitis.[225] The differentiation of acute cellular rejection from other forms of interstitial nephritis can be difficult in certain settings, especially when characterized by a delayed-type hypersensitivity (DTH) response with CD4 T cells and macrophages.[198,199,225]

It is also important to note the distribution of the cellular infiltrate. Both native and allograft kidneys may have nodular infiltrates. These are often located in the adventitia of blood vessels and are composed predominantly of T4 cells and B cells. This type of cellular infiltrate is nonspecific.

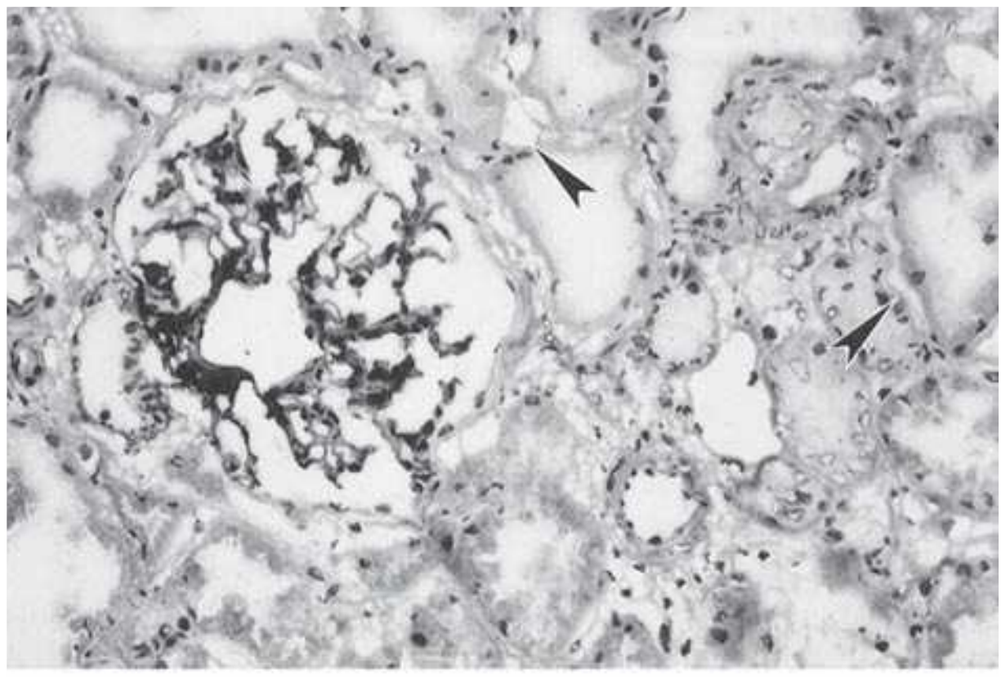
13.2 Immunopathogenic Mechanisms Associated with Renal Allograft Rejection

Type	Onset of Clinical Manifestation	Morphology	Mechanism
Acute Rejection			
Antibody-mediated (Vascular)			
Hyperacute	0–72 hr	Intracapillary PMN inflammation and thrombosis	Preformed antibody with complement and fibrinogen activation
Accelerated acute	3–7 d	Endovascular inflammation similar to above but histologically less intense	Memory antibody response
Acute rejection	7 d or more	Endovasculitis with PMN but without lymphocytes	De novo antibody response
Cell-mediated			
Vascular	7 d to 3 mo	Endovasculitis with varying proportions of CD4 + CD8 lymphocytes and macrophages	May be any of several cell-mediated mechanisms
Tubular		Lymphocytic tubulitis with predominately CD8 cells	Cytotoxic lymphocytes
Interstitial		Mononuclear interstitial inflammation with predominately CD4 lymphocytes and macrophages	Delayed type hypersensitivity
Chronic rejection (3 mo or longer)			
Vascular		Intimal proliferation	Antibody
Cell-mediated		Interstitial nephritis	Continued DTH and cytotoxic responses
Innate response			
Acute		Intrinsic cell activation	Oxidative and other stress injury
Chronic		Chronic interstitial nephritis	Macrophage activation and fibrogenesis

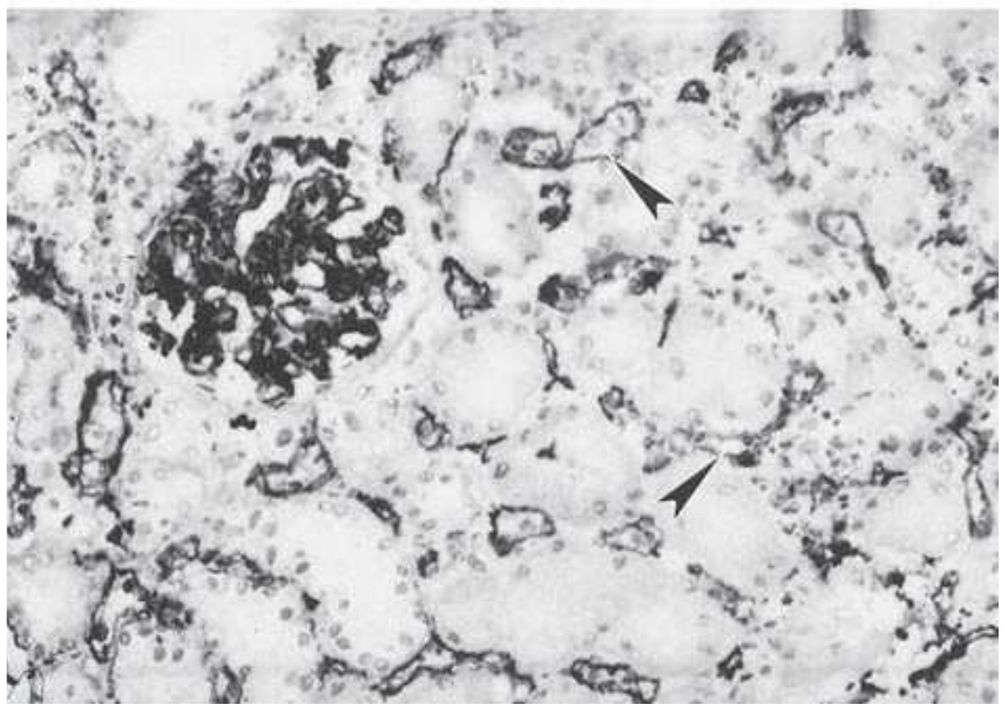
PMN, polymorphonuclear leukocyte; DTH, delayed type hypersensitivity.

In cellular rejection, allografts often exhibit a superimposed diffuse interstitial and tubular cytotoxic T-cell infiltrate.[225] An increase in cytotoxic T cells during cellular rejection has been confirmed in these infiltrates by fine-needle aspiration.[226] B-cell infiltrates suggest PTLD, particularly in the presence of EBV and destructive nodules. The BK virus also produces interstitial nephritis and is indicated by nuclear inclusions and is confirmed by electron microscopy, immunostaining, or molecular studies (Fig. 13.28).[227]

An immunohistochemical examination of the renal biopsy is also beneficial. In particular, the presence of alloantibodies, which classically localize to peritubular and glomerular capillaries, suggests the presence of antibody-mediated rejection.[126] The most commonly employed tests evaluate the presence of C4d deposition in renal transplant biopsies. Feucht et al.[228] initially showed that peritubular capillary C4d deposition predicated a worse prognosis. This was followed by numerous studies demonstrating



A



B

FIGURE 13.27 This figure shows C4d staining. **A:** An allograft with acute tubular necrosis. Peritubular capillaries (*arrowheads*) are unstained (immunoperoxidase, C4d; magnification ×210). **B:** An allograft with antibody-mediated rejection. Peritubular capillaries (*arrowheads*) are staining (immunoperoxidase, C4d; magnification ×210).

an interrelationship between C4d deposition, circulating donor-specific antibodies, and renal histopathologic findings.[126,127] Activation of the classic complement pathway generates C4b, of which C4d is a biologic fragment; C4d does not have a known biologic function, but because it is tightly bound to tissue, it serves as an excellent marker of complement-fixing, circulating antiendothelial antibodies. Peritubular capillary C4d deposition can be seen in hyperacute rejection, acute humoral rejection, and chronic humoral rejection.[126,127] In addition, C4d deposition can be observed in the kidneys of patients who received transplantation across ABO barriers, using special protocols to deplete naturally occurring anti–blood group antibodies, in whom circulating anti–blood group antibodies return but do not cause obvious graft rejection,[126] a state termed accommodation.[229] In addition, C4d deposition can occur in a number of different conditions, including I/R injury, necrosis, and lupus nephritis.[129–133] Correlating findings of C4d deposition with the clinical presentation, the renal histology, and the serologic evidence of anti-donor HLA antibodies is essential to guide appropriate therapy.

Calcineurin inhibitor toxicity is an important cause of decreased renal function in the allograft. The tubular changes were noted in an earlier section (Fig. 13.14). The most widely accepted demonstrations of calcineurin inhibitor-related renal vascular changes have been observed in the setting of transplantation of solid organs other than the kidney (e.g., the heart)[230] or inflammatory diseases of other organs (e.g., type I diabetes).[231]

Although acute changes in renal function are established in many systems,[232] the current data suggest that morphologic changes associated with long-term calcineurin inhibitor use are characteristic, but are not pathognomonic, of this class of drugs.[233] Those features include hyalinosis of arterioles (Fig. 13.29), interstitial fibrosis, and tubular atrophy.[230,231,234] When these lesions are noted in the allograft biopsy, calcineurin inhibitor toxicity should be considered in the differential diagnosis.

Systemic cytomegalovirus infection continues to be a significant cause of morbidity and mortality among recipients of renal transplants.[157] Cytomegalovirus may be detected in the biopsy, whereas viremia is determined best by peripheral blood studies.

Traditionally, rejection has been defined as an immune response directed against the graft antigens or alloimmune response. In more recent years, it has become evident that a

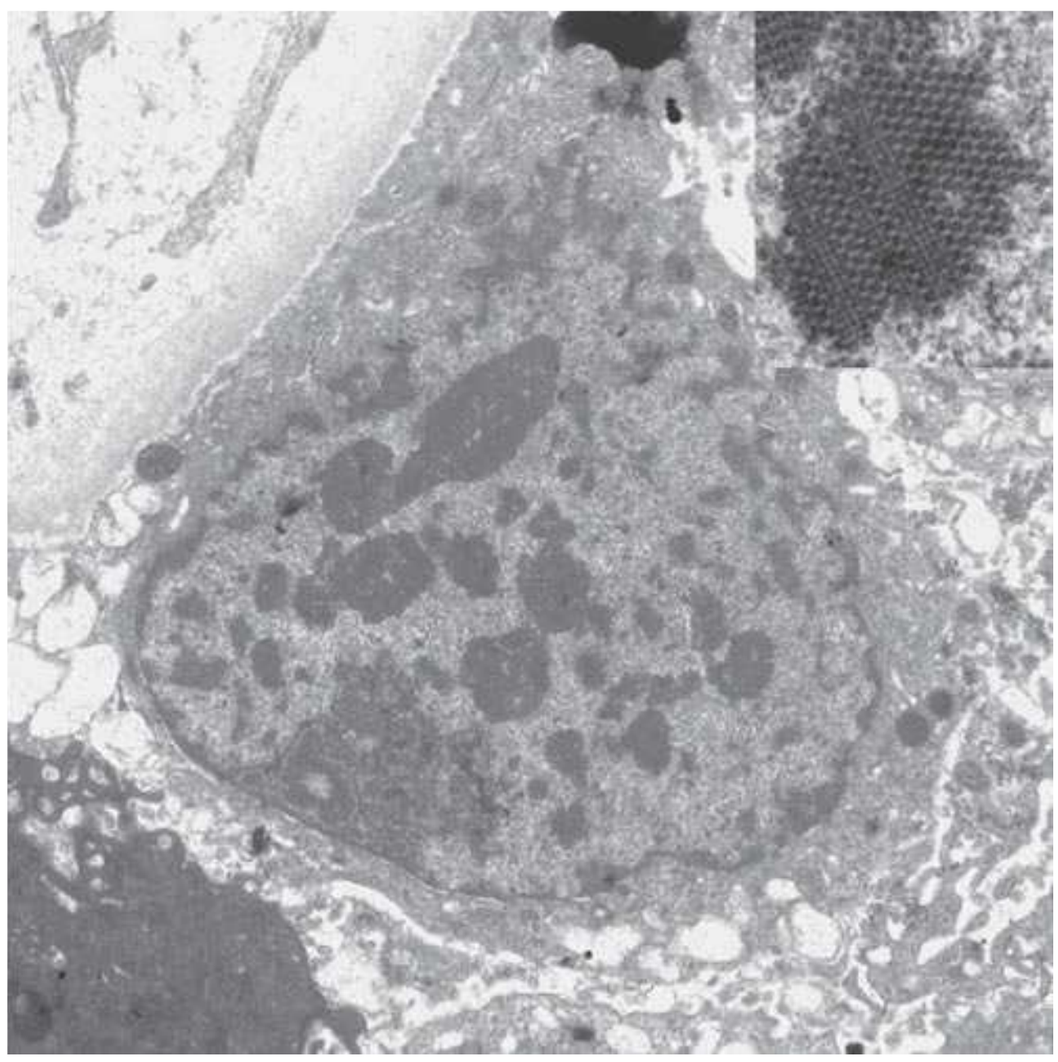


FIGURE 13.28 An electron micrograph of a tubular epithelial cell showing coarse clusters of nuclear material. The identification of the virus is not obvious at this magnification (magnification ×7,500). **Inset:** A higher magnification of nuclear densities (magnification ×33,000) showing the polyoma virus in a crystalloid array.

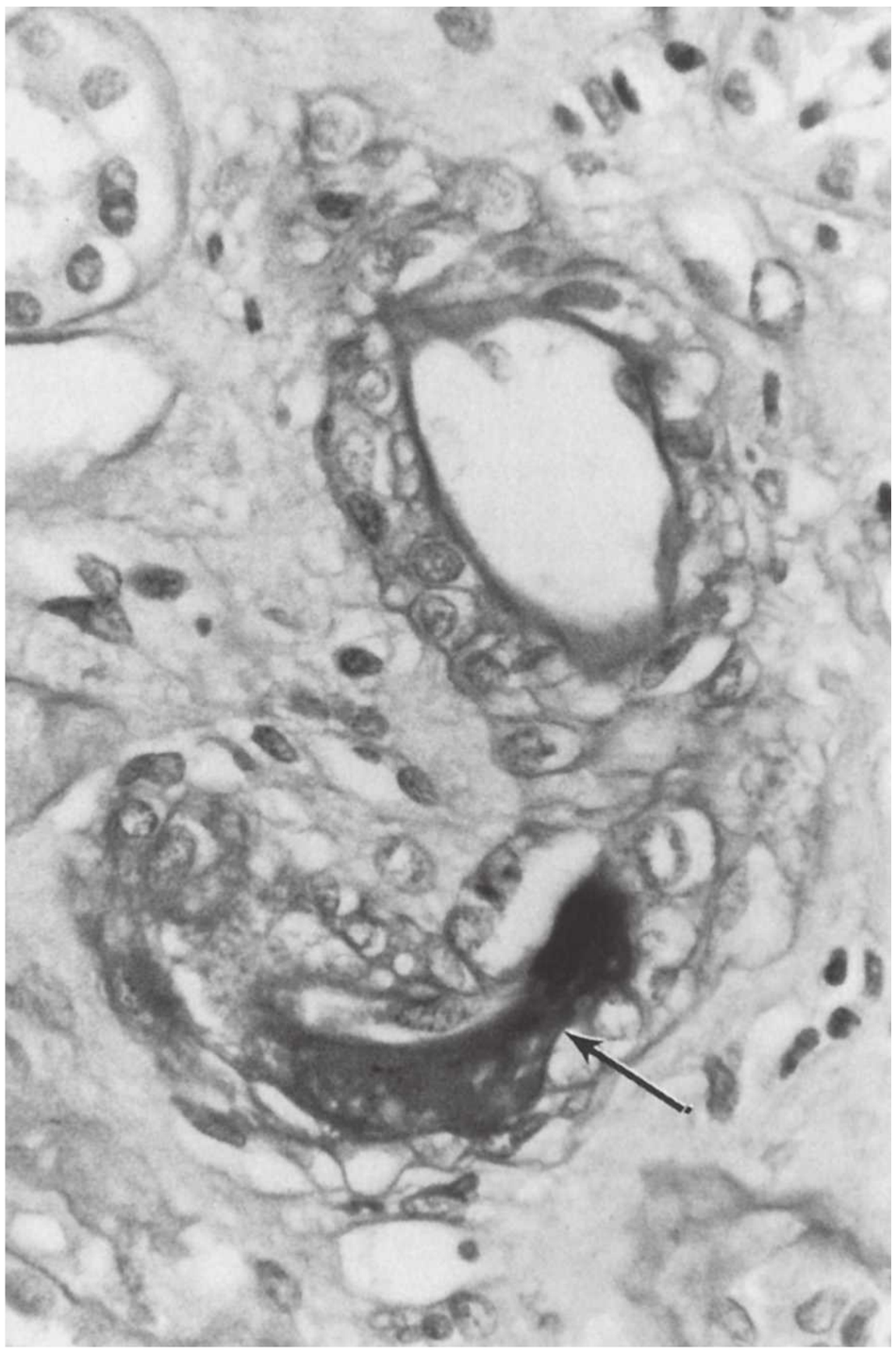


FIGURE 13.29 A photomicrograph illustrating calcineurin inhibitor toxicity in a terminal interlobular artery. Degenerative changes are evident in the muscularis in association with a large dense hyaline deposit (*arrow*) (PAS; magnification ×750).

variety of factors affect graft survival that are unrelated to traditional antigen driven B- and T-cell responses. They include donor factors such as age and gender, and events coincident to organ procurement such as cadaveric donation and ischemia time.[235,236] The kidney response in these settings recapitulates the responses of innate immunity (Table 13.2).

Finally, late irreversible changes in the graft that are associated with chronic azotemia may represent the sequelae of chronic rejection. This is not necessarily a separate entity, but may be the result of repeated episodes of acute rejection and innate immunity. Therefore, the term chronic transplant nephropathy is preferred, rather than chronic rejection, to identify the nonspecific pathologic changes. The morphologic features are those of severe tubular atrophy, glomerulosclerosis, interstitial fibrosis, and arteriosclerosis with varying degrees of chronic inflammation.

In addition to the pathogenetic classification (Table 13.2) noted in the preceding sections, several schemes for the histologic classification of rejection have been developed to facilitate interinstitutional studies and therapeutic trials. The Banff schema[237] was specifically designed toward this end and is based on light microscopic features with readily available histologic stains. With the experience of experimental validation and clinical trials, the original Banff schema was modified in 1995,[238] 1997,[239] and 2003.[128] The National Institute of Health-sponsored Combined Clinical Trials in Transplantation (CCTT) classification[240] is simpler but similar in structure for acute rejection. Clinical correlation in the CCTT study indicated that mononuclear cell margination of the vascular endothelium was an indicator for clinical severity. Although more complex, the strength of the Banff schema is that it captures fundamental histologic data. Although acute rejection continues to be a significant problem, a greater problem (as noted in the preceding section) is chronic rejection and chronic allograft nephropathy. Structural relationships remain the cornerstone for understanding these processes and developing the molecular genomic, the functional proteomic, and the genetic basis for graft failure versus survival continues. Using a classification that incorporates these elements is essential for understanding and categorizing the many features of renal allograft pathology. Any classification must also be flexible to accommodate morphologic changes that may be associated with new therapeutic measures in this rapidly changing field.

CONCLUSION

We have presented a time-tested, step-by-step approach to the use and evaluation of the kidney biopsy. An in-depth discussion of specific diseases that affect the kidney can be found in other chapters of this text. We have selected some common diseases that are amenable to a diagnosis on a kidney biopsy in an effort to demonstrate the necessity and advantage of using a combination of light, electron, and immunohistologic microscopy to obtain the maximum amount of information from a biopsy specimen to aid in the clinical management of the patient. We expect that molecular genetic, functional genomic, and proteomic studies will eventually augment the classic structural and functional approach outlined in this chapter.

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