Primary Glomerulonephritis

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Approach to the Patient with Proteinuria and Microscopic Hematuria

Proteinuria and/or microscopic hematuria are typical findings in patients with glomerulonephritis (GN). However, they can also be associated with other renal or extrarenal disorders. Therefore, a stepwise approach is advisable for a proper evaluation (Figures 1 and 2).

When proteinuria (or more appropriately albuminuria) is detected by dipstick, a false positive should first be ruled out. This can be caused by urinary density > 1.025, urinary pH

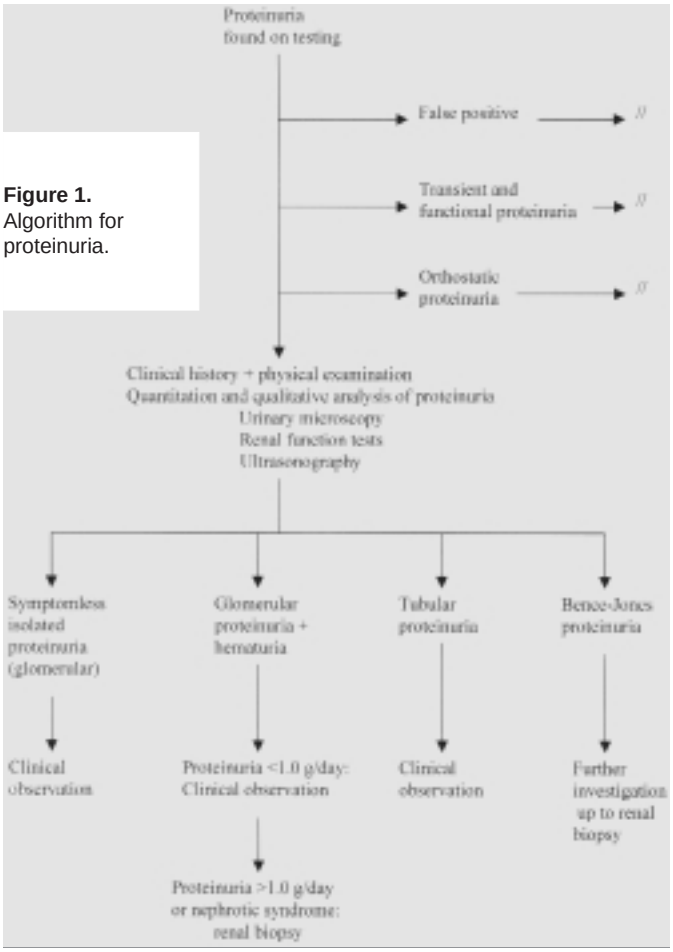

Figure 1. Algorithm for proteinuria.

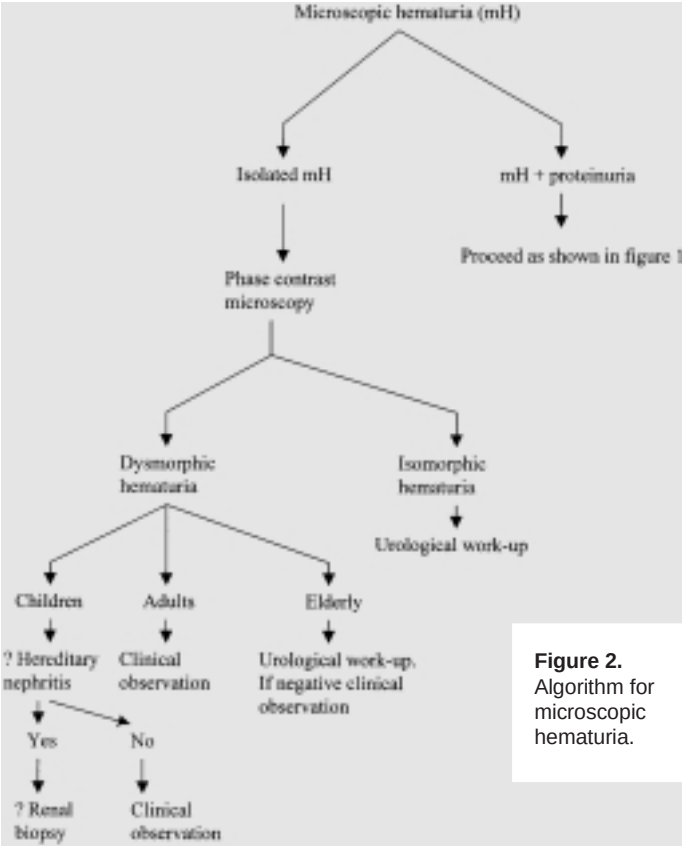

Figure 2. Algorithm for microscopic hematuria.

> 8.0, contamination of urine by quaternary ammonium compounds or phenazopyridine used for disinfection of urine containers, or by immersion of the dipstick in the urine for too long a period of time. It is also important to exclude clinical conditions that can cause transient and functional albuminuria, such as vigorous physical exercise, fever, or acute congestive heart failure (CHF) (Table 1). Especially in adolescents and young males, proteinuria may be purely orthostatic. This condition is characterized by the presence of proteins in urine collected on a standing position and complete absence in urine collected during recumbency. Even when orthostatic proteinuria is quantitatively important, the long-term prognosis is favorable, and no further investigation is needed. Clearly, orthostatic proteinuria differs from the quantitative increase of proteinuria that can be found in most patients with GN while they are standing [194].

If persistent nonorthostatic proteinuria is found, a complete work-up is necessary. This includes clinical history and physical examination, evaluation of renal function, the quantitation of proteinuria in g/24 hours or as albumin/creatinine ratio, the qualitative analysis of proteinuria by electrophoresis on cellulose acetate or agarose, or by sodium dodecyl sulfate-polyacryl-amide gel electrophoresis (SDS-PAGE) or other techniques, other appropriate laboratory tests, and ultrasonography of the kidneys and urinary tract.

In case of glomerular proteinuria, which is by far the most frequent condition seen in clinical practice, the clinical history may be

Table 1. Classification of Proteinuria and Main Clinical Associations

Transient/functional proteinuria
Strenuous physical activity
Fever
Acute congestive heart failure
Orthostatic proteinuria
Glomerular proteinuria
Primary and secondary glomerulonephritis
Isolated symptomless proteinuria
Proteinuria in morbid obesity
Tubular proteinuria
Acute and chronic tubulointerstitial diseases
Toxins and drugs
Primary and secondary glomerulonephritis
Overflow proteinuria
Monoclonal gammopathies (immunoglobulin light chains
Intravascular hemolysis (hemoglobin)
Rhabdomyolysis (myoglobin)
Leukemia (lysozyme)
Tissue proteinuria
Acute inflammation of urinary tract
Neoplasia of urinary tract

characterized by hereditary renal diseases, by a family predisposition to renal or systemic diseases such diabetes mellitus (DM) or systemic lupus erythematosus (SLE), or by allergy. In other cases, there may be a history of exposure to hydrocarbons or solvents, the use of potentially nephritogenic drugs, or a preceding infection. Physical examination may be normal or reveal arterial hypertension, morbid obesity (possibly associated with focal segmental glomerulosclerosis (FSGS) [152]), generalized or local edema with weight gain, weight loss, skin or joint changes, enlarged liver and spleen, macroglossia, lung disease, vascular disease, neurologic abnormalities or other findings. Basic laboratory tests include serum creatinine and/or glomerular filtration rate (GFR), glycemia, total serum proteins and protein electrophoresis, serum cholesterol, hemogram, plasma immunoglobulins, C3 and C4 levels, the search for HBs antigen and of hepatitis C antibodies, and tests for syphilis. More targeted tests are the search for neoplastic markers, antistreptolysin titer (ASO), cryoglobulins, antinuclear (ANA) and/or anti-DNA antibodies, rheumatoid factor (RF), antineutrophilic cytoplasmic antibodies (ANCA), or antiglomerular basement membrane (anti-GBM) antibodies. Ultrasonography may reveal normal or enlarged kidneys or reduction of size with increased hyperechogenicity or scarring.

If glomerular proteinuria does not exceed 1.0 g/24 hours and is associated with normal renal function and there is no hematuria, negative clinical history, negative physical examination, and normal ultrasonography, a diagnosis of symptomless isolated proteinuria can be made. In this case, no immediate further investigation is necessary, although long-term follow-up is indicated. For patients with proteinuria and microscopic hematuria, monitoring over time may be sufficient if proteinuria is < 1.0 g/day, but renal biopsy may be indicated for prognostic or genetic reasons. With proteinuria > 1.0 g/24 hours, renal biopsy is advisable. If proteinuria is in the nephrotic range (i.e. > 3.5 g/24 hours), with or without hematuria, renal biopsy is indicated unless there are unacceptable risks of complications. A frequent exception is represented by children with a selective proteinuria, which is usually caused by minimal change nephropathy responsive to glucocorticoids.

Tubular proteinuria usually does not exceed 1.5 – 2.0 g/24 hours. It may be caused by acute or chronic tubular disorders such as interstitial nephritis or heavy metal nephropathy. Tubular proteinuria is also present in GN with associated tubulointerstitial changes [9]. A pure tubular proteinuria needs to have the

Table 2. The Main Causes of Microscopic Hematuria (modified from [57])

Renal parenchymal disease	*Urinary tract disease*
Primary and secondary glomerulonephritis	Trauma/surgery
Glomerular C3 deposition	Neoplasia
Alport's syndrome	Angioma
Thin glomerular basement membrane disease	Obstructive uropathy
Interstitial nephritis	Cysts
Analgesic nephropathy	Varices/teleangiectasia
Pyelonephritis	Papillary necrosis
Sickle cell disease	Periureteritis
Polycystic kidney	Ureterocele
Loin pain hematuria syndrome	Endometriosis
Trauma/surgery	Infections
Renal biopsy	Infestations
Jogger's nephritis	Radiation
	Diverticulum
Renal vessel disease	Cyclophosphamide-induced cystitis
C3 arteriolar deposition	Ex vacuo hematuria
Arteriolar emboli or thrombosis	Prostatitis
Renal vein thrombosis	Prostatic hypertrophy
Arterial or venous malformations	Urethritis
Arteriovenous fistula (idiopathic, cirsoid, acquired)	Urethral prolapse
Nutcraker's syndrome	Urethral caruncle
	Meatal ulcers
	Condyloma acuminatum
	Foreign bodies
	Catheters
	Long-distance running
	Systemic coagulation disorders
	Platelet defect
	Coagulation protein deficiency
	Scurvy
	Anticoagulant treatment

cause identified. In these cases, clinical history is of particular importance. Tests exploring the function of proximal tubules are necessary. No renal biopsy is usually needed. Observation over time is advisable.

Among the various types of overflow proteinuria, the most clinically relevant is represented by the increased excretion of monoclonal immunoglobulin light chains, better known as Bence-Jones proteinuria. This is caused by monoclonal gammopathies such as multiple myeloma, AL amyloidosis, light chain deposition disease, or some types of cryoglobulinemia. It is worth remembering that dipsticks do not react with immunoglobulin light chains, leading to false negative results. In some of these disorders a glomerular proteinuria can also be found because of the damage caused by the deposition of light chains in the glomeruli. Immunofixation is the best method to characterize the monoclonal component. Further clues to the diagnosis are the search for a monoclonal peak in the blood, quantitation of plasma immuno-

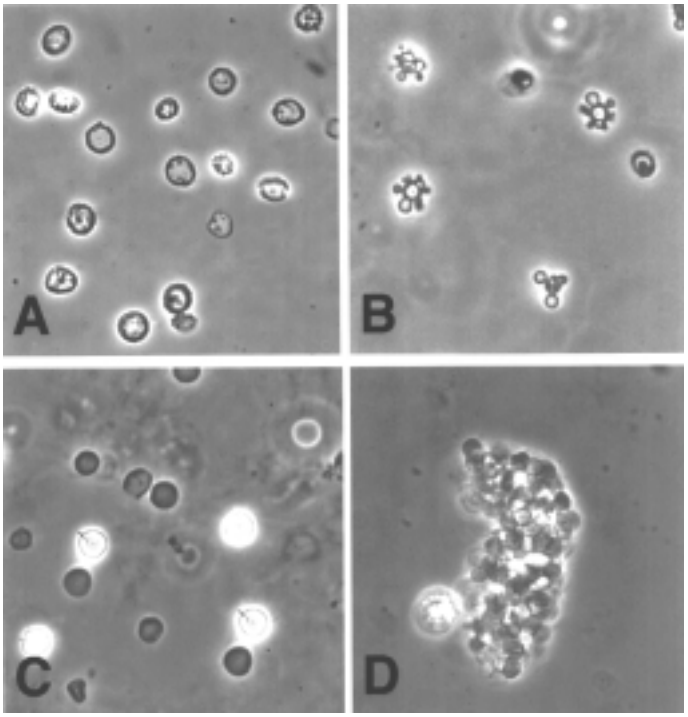

Figure 3. A: dysmorphic urinary erythrocytes. B: acanthocytes. C: isomorphic erythrocytes. D: erythrocyte cast. (Phase contrast microscopy, 400x).

globulins, bone marrow aspiration or biopsy, bone X-rays, abdominal fat pad or rectal biopsy, and renal biopsy.

Microscopic hematuria indicates the presence in the urine of an abnormal amount of erythrocytes, which can be the consequence of a large number of disorders (Table 2). When microscopic hematuria is associated with proteinuria, a diagnosis of GN is likely. The cause of symptomless, isolated, microscopic hematuria can be much less clear. This is usually found by chance by dipsticks, which have a 91 – 100% sensitivity and a 65 – 99% specificity [198]. False negative results can occur with high concentrations of urinary ascorbic acid [22], while false positives are caused by myoglobinuria or bacteriuria [107]. Microscopy is necessary, not only to confirm a positive dipstick, but also to separate a glomerular from a nonglomerular bleeding on the basis of erythrocyte morphology. In fact, when hematuria is caused by a glomerular disease, "dysmorphic" erythrocytes and acanthocytes predominate in the urine (Figures 3A and 3B), while normal or "isomorphic" erythrocytes (Figure 3C) predominate in nonglomerular bleeding [45, 100]. The presence of erythrocyte/hemoglobin casts (Figure 3D) is pathognomonic of bleeding of the renal parenchyma. However, the sensitivity is low, approximately 20 – 30%. Phase contrast microscopy is by far superior to conventional bright field microscopy in revealing these findings.

We consider the analysis of the urinary sediment as a key step in the work-up of patients with isolated microscopic hematuria [57]. When dysmorphic hematuria is found on repeated examination, a diagnosis of chronic glomerular disease is likely. All glomerular diseases can cause symptomless isolated microscopic hematuria, but immunoglobulin A (IgA) nephropathy, non-IgA mesangial or focal proliferative glomerulonephritis (FPGN),

and thin basement membrane disease are the most frequently found when renal biopsy is performed [77, 185]. The work-up of these patients differs according to their age. In children and adolescents, hereditary nephritis such as Alport's syndrome or thin basement membrane disease has to be suspected first. An accurate family history should be taken and family members investigated for microscopic hematuria, renal function impairment, deafness, and/or ocular abnormalities. A renal biopsy should be performed in case there is a suspicion of Alport's syndrome. However, when the family findings suggest benign hematuria the indication for renal biopsy is less definite. If the family history and investigation are negative for hereditary nephritis, renal biopsy is not strictly necessary, and clinical observation may be sufficient. However, ultrasonography of the kidneys and of the urinary tract is always necessary to exclude urological disorders.

In young and middle-aged adults, dysmorphic microscopic hematuria is more likely caused by primary glomerulonephritis such as IgA nephropathy or other less defined glomerular diseases, although thin basement membrane is still a possibility. The measurement of serum immunoglobulins may show increased IgA levels, which are found in 30 – 50% of patients with IgA nephropathy. A persistent decrease of C3 serum level may indicate a type II membranoproliferative glomerulonephritis (MPGN) or, especially in young women, SLE. Rarely, microscopic hematuria may be the only sign of anti-GBM disease, of systemic vasculitis, or of other systemic diseases. Clinical observation is needed, and renal biopsy should be considered in case of appearance of proteinuria, renal function impairment, or definite signs of a systemic disorder. For these patients, ultrasonography of the kidneys and the urinary tract is mandatory in the initial work-up to exclude other causes of microscopic hematuria such as stones, polycystic kidney, and tumors.

In the elderly, especially in males, microscopic hematuria is frequently the first and only sign of tumor of the urinary tract. Thus, even in the presence of a dysmorphic hematuria, a full urological work-up is recommended. If no urological abnormalities are found, an underlying GN is possible, as in the previous categories [185]. Clinical observation is sufficient, although a tumor of the urinary tract can be associated with a glomerular disease.

The prognosis of patients with symptomless isolated microscopic hematuria of renal origin is usually good, as demonstrated by several studies both in children and adults [77, 133, 170]. In fact, most patients continue to have microscopic hematuria, although it completely disappears in other patients. A minority of patients develop hypertension with or without proteinuria, but renal function impairment usually does not occur.

Pathogenesis, Complications, and Treatment of the Nephrotic Syndrome

The term nephrotic syndrome refers to a clinical condition characterized by heavy proteinuria, hypoalbuminemia, edema, and hyperlipidemia. The nephrotic syndrome is often seen with urinary protein excretion > 3.5 g/24 hours and is almost invariably present when proteinuria is > 5 g/24 hours. The nephrotic condition may expose the patient to disabling and even life-threatening complica-

Table 3. Main Complications of the Nephrotic Syndrome

Complication	*Pathogenesis*	*Treatment*
Proteinuria	Alterations in glomerular barrier	Moderate protein restriction ACE inhibitors AT1 receptor antagonists, NSAID
Hypoalbuminemia	Urinary loss Increased catabolism Insufficient liver synthesis	Reduction of proteinuria
Lipid abnormalities (Increased LDL, VLDL, lipoprotein(a))	Increased synthesis Reduced catabolism	CoA reductase inhibitors
Edema	Hypoalbuminemia (underfill mechanism) Resistance to ANP (overfill mechanism)	Thiazide agents Loop diuretics
Hypercoagulability	Increase in prothrombotic factors Decrease of anticoagulant proteins	Oral anticoagulation (?)

tions such as infections, bone disease, intravascular thrombosis, and cardiovascular disease (Table 3). Moreover, the onset of the nephrotic syndrome is a marker for bad prognosis for most glomerular diseases.

Proteinuria

Proteinuria is a consequence of the disruption of the permeselectivity caused by the disease-related functional and/or anatomical damage of the glomerular basement membrane (GBM). Plasma proteins, particularly albumin, are allowed to pass through the glomerular capillary wall, exceeding the tubular reabsorptive capacity. There is now evidence that proteinuria may play a role in the progression of chronic renal failure (CRF). The abnormal filtration of proteins brings them into contact with the mesangium and with the proximal tubular cells. Mesangial accumulation of proteins may produce mesangial cell injury, mesangial cell proliferation, and increased production of mesangial matrix that eventually lead to glomerulosclerosis [158]. The proximal reabsorption of proteins may trigger upregulation of inflammatory and vasoactive genes such as MCP-I and endothelins. The corresponding molecules formed in an excessive amount by renal tubuli are secreted toward the basolateral compartment of the cell and give rise to an inflammatory reaction that leads to renal scarring [158].

Eradication of the underlying glomerular disease represents the best treatment for proteinuria. Some reduction of urinary protein excretion may also be obtained with diet and/or drugs. While a high-protein diet increases proteinuria, a low-protein diet may reduce urinary albumin excretion and increase serum albumin levels, at least in the short-term [93]. ACE inhibitors can have an

antiproteinuric effect, which is dose-dependent. The effect may require some weeks to be complete and is blunted by sodium intake [74]. Angiotensin II (ANG II) receptor AT1 antagonists have a comparable antiproteinuric effect [61]. ACE inhibitors may also slow the progression of chronic renal insufficiency. This beneficial effect may be independent of the blood pressure reduction and is particularly marked in patients with proteinuric glomerular diseases [117]. Diet protein restriction, around 0.8 g per kg/day plus urinary losses, in combination with ACE inhibitors at the highest tolerated doses and restricted sodium intake may be recommended in patients with glomerular diseases to reduce urinary protein excretion and preserve renal function. It is possible but still unproven that the addition of AT1 receptor antagonist may further potentiate the antiproteinuric effect.

Nonsteroidal anti-inflammatory drugs (NSAIDs) may reduce proteinuria by ≥ 50% or more. The effect is rapid (within 1 week) and reverses after cessation of treatment. Indomethacin (150 mg/day) and meclofenamate (200 – 300 mg/day) are the 2 agents used most frequently. These agents can cause hyperkalemia, sodium retention, and acute renal failure (ARF) triggered by vasoconstriction or interstitial nephritis. Thus, careful monitoring of renal function is mandatory during treatment of nephrotic patients. The association with ACE inhibitors potentiates the antiproteinuric effect but increases the risk of renal function deterioration and hyperkalemia.

Hypoalbuminemia

Hypoalbuminemia plays a pivotal role in many complications of the nephrotic syndrome, including edema, malnutrition, hyperlipidemia, and cardiovascular disease. The urinary loss of albumin is not sufficient to explain hypoalbuminemia. There is also an increased catabolism of albumin that might contribute to hypoalbuminemia. However, the most important mechanism is the inability of the liver to increase the albumin synthesis in response to urinary losses and/or increased catabolism [93].

Neither albumin infusion nor a high-protein diet may increase serum levels of albumin because these measures result in increased urinary losses of albumin.

Lipid Abnormalities

In nephrotic patients, there is an increase in low density lipoproteins (LDL), very low density lipoproteins (VLDL), and lipoprotein (a) (Lp(a)) levels while high density lipoprotein (HDL) levels are either normal or decreased. The composition of lipoproteins is also altered with a relative increase in cholesterol. These abnormalities are caused both by an increased hepatic synthesis and by a decreased clearance of lipids and lipoproteins. Experimental and clinical studies showed that cholesterol synthesis increased in response to hypoalbuminemia, serum cholesterol being inversely proportional to serum albumin. In addition to the increased synthesis, there are alterations in catabolism of lipids in nephrotic syndrome caused mainly by a decreased activity of the enzyme lipoprotein lipase. This may be related either to the urinary loss of some activators of the enzyme or to an increase in free fatty acids that are known to inhibit lipoprotein lipase activity. The reduction of HDL levels may be attributed to the urinary loss of lecithin-cholesterol acyltransferase and/or to its inhibition caused by the increased levels of free lysolecithin produced in hypoalbuminemia [73]. There has been controversy in the past about the possible role

of hyperlipidemia in favoring cardiovascular complications. More recently an association between lipid abnormalities and coronary artery disease has been demonstrated in nephrotic patients [138].

A lipid-lowering diet (< 200 mg/day of cholesterol, total fat < 30% of total calories, and polyunsaturated fatty acids about 10% of total calories) is usually recommended as the first therapeutic step in patients with hypercholesterolemia. However, for many nephrotic patients, diet is not sufficient to correct hyperlipidemia. Various lipid-lowering drugs such as probucol, nicotinic acid, resins, and fibric acid derivates have been used with little success because these agents are either poorly tolerated or have little efficacy. At present, hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors are considered the drugs of choice for treating the hyperlipidemia of nephrotic patients. These agents may decrease serum cholesterol 30 – 40%, LDL about 40%, and apolipoprotein B 30%, but do not reduce the elevated levels of the atherogenic LP(a). The tolerance is usually good. Mild and transient increase in serum transaminase is rarely seen. Myositis and myalgias are rare but can occur with large doses.

Edema

Edema is one of the cardinal features of the nephrotic syndrome. Its pathogenesis is incompletely understood. Two main theories have been proposed: the classical underfill theory and the overfill theory. According to the classical view, hypoalbuminemia represents the "primum movens" of edema. Decreased plasma oncotic pressure favors translocation of fluid from the intravascular space into interstitial space. Reduction of plasma volume activates the renin-angiotensin system, secondary salt and water retention, plasma dilution, and further aggravation of hypoalbuminemia. However, only a minority of nephrotic patients have a decreased intravascular volume. The majority show normal or expanded plasma volume. Moreover, the plasma levels of renin, angiotensin, and aldosterone show large variations in nephrotic patients. Finally, maneuvers that increase plasma volume do not always result in a natriuretic response [139]. The overfill theory attributes a key role to the inability of the diseased kidney to excrete salt and water, with consequent intravascular expansion, increase in capillary hydrostatic pressure, and transudation of fluid into the interstitial space. The enhanced tubular NaCl avidity is mainly caused by post-receptor resistance to the action of atrial natriuretic peptide, due to enhanced activity of cyclic GMP phosphodiesterase [80]. Although the overfill theory may account for most cases of nephrotic edema, it is possible that underfill mechanisms are involved in few other cases, especially during the edema acquisition phase.

In milder cases, edema may be handled by restricting dietary sodium intake. Diuretic therapy may be required in patients who do not respond to a low-sodium diet. The first step may consist of administration of hydrochlorothiazide (12.5 – 50 mg/day), preferably in combination with a potassium-sparing agent such as amiloride, triamterene, or spironolactone. Loop diuretics, such as furosemide, ethacrynic acid, or bumetanide are needed for more severe edema. Furosemide is the most-used agent because of its flexibility and good tolerance. The drug may be given by mouth or intravenously, at doses ranging between 25 and 2000 mg/day. Binding of the drug to tubular fluid albumin can blunt the diuretic response. In patients who do not respond to high-dose furosemide, combining it with diuretics acting at different

levels, such as hydrochlorothiazide (25 – 50 mg/day) or metolazone (2.5 – 10 mg/day), may maximize the diuretic response.

Coagulation Abnormalities

In the nephrotic syndrome, there is an imbalance between procoagulant/antithrombotic factors. Usually there is an increase of prothrombotic factors such as fibrinogen, factors V and VIII, factor VII, platelets, and platelet hyperaggregability. Anticoagulant proteins such as active protein S, active protein C, antithrombin III are decreased, due to loss in the urine. In addition, nephrotic patients may show hyperviscosity favored by hyperlipidemia and impaired fibrinolysis, caused by elevated Lp(a) and ANG IV levels that promote the synthesis of plasminogen activation inhibitor. These hemostatic abnormalities promote the synthesis of plasminogen activation inhibitor and determine a hypercoagulable state that may cause thromboembolic complications. Renal vein thrombosis, deep vein thrombosis and pulmonary embolism are the most frequent thrombotic complications of the nephrotic syndrome and are roughly correlated with the magnitude of the depression of serum albumin. Their incidence is lower in children than in adults, but children are more exposed to the risk of arterial thrombosis.

Anticoagulant drugs can reduce the risk of thrombosis. However, because they carry a substantial risk of hemorrhagic complications, their use is generally restricted to situations such as prolonged bed rest, surgery, and episodes of dehydration. On the other hand, decision analysis studies reported that the benefits of prophylactic anticoagulants outweigh the risks, at least in nephrotic patients with membranous nephropathy who are particularly exposed to the risk of intravascular thrombosis [162].

Infections

Nephrotic patients have an increased susceptibility to infections. Several factors may be responsible: urinary loss of immunoglobulins, urinary loss of complement factors B and D, defective cellular immunity caused by the urinary loss of zinc, transferrin and vitamin D, and malnutrition. The concomitant use of high-dose glucocorticoids and immunosuppressive agents may further increase the risk of infections.

Endocrine Abnormalities

Nephrotic patients have significant urinary losses and reduced plasma concentration of $25(OH)D_3$. However, the vitamin D binding protein is also reduced in the nephrotic syndrome, so that the free $1,25(OH)_2D_3$ remains at normal plasma levels. Hypocalcemia is frequently seen in nephrotic patients. In most cases, it may be attributed solely to the reduction in protein-bound calcium secondary to hypoalbuminemia. Thus, while many nephrotic patients may show decreased serum levels of $25(OH)D_3$ and calcium, the serum-free $1,25(OH)_2D_3$ and ionized calcium are normal so that treatment with vitamin D is not necessary. However, vitamin D supplements are indicated in a minority of patients who demonstrate evidence of reduced serum ionized calcium, reduced intestinal calcium absorption, and secondary hyperparathyroidism.

Urinary losses of thyroxin-binding globulin can occur in the nephrotic syndrome. However, the serum levels of T4 and thyrotropin are normal, and clinically most patients are euthyroid.

Table 4. Factors Associated with Minimal Change Nephropathy

Drugs	*Tumors*
Nonsteroidal anti-inflammatory drugs	Hodgkin's lymphoma
Lithium	Non-Hodgkin's lymphoma
Thiola	Leukemia
Gold	Mesothelioma
Trimethadione-paramethadione	Carcinoma of colon, prostate, pancreas, or lung
Mercury	Nephroblastoma
Penicillamine	Waldenstrom's
Ampicillin	
Interferon	
Other diseases	
Diabetes mellitus	*Allergy*
Dermatitis herpetiformis	Pollens
Schistosomiasis	Food allergy
Virus infections	House dust
Immunizations	Bee stings

Minimal Change Disease (MCD)

MCD, also called minimal change nephropathy, nil disease or, lipoid nephrosis, is the most common cause of the nephrotic syndrome in children but may also occur in adults and the elderly. Clinically, MCD is characterized by a pure nephrotic syndrome. There are few or no abnormalities on light microscopy and immunofluorescence. The typical lesion is represented by a diffuse effacement of the foot processes of the podocytes on electron microscopy. The disease usually responds to glucocorticoids. In many patients the course is punctuated by alternating remissions and relapses of the nephrotic syndrome. Although there is evidence that MCD and FSGS may represent the 2 extremes of the same disease, we will treat these entities separately as they have a different histologic picture, clinical presentation and outcome, and response to therapy.

Etiology and Epidemiology

MCD may affect siblings in 3.5% of cases. An indication for a possible genetic predisposition is the reported association with certain HLA antigens such as B12, B8, and Drw 7. However, not all studies confirm this association [169]. Atopic diseases such as asthma, eczema, and hay fever may be present in almost one-third of patients with MCD. In a number of patients MCD may develop after allergic episodes.

Although MCD is usually idiopathic, rare cases occurring in association with drugs or other diseases have been reported (Table 4). MCD and acute interstitial nephritis may develop after the use of NSAIDs. Most of the affected patients are elderly and develop a nephrotic syndrome with ARF while taking the drug. Renal signs usually improve after discontinuing the drug with or without glucocorticoids [161]. Lithium and thiola, a drug used for treating cystinuria, may also cause MCD. Some cases of nephrotic syndrome and MCD have been observed during administra-

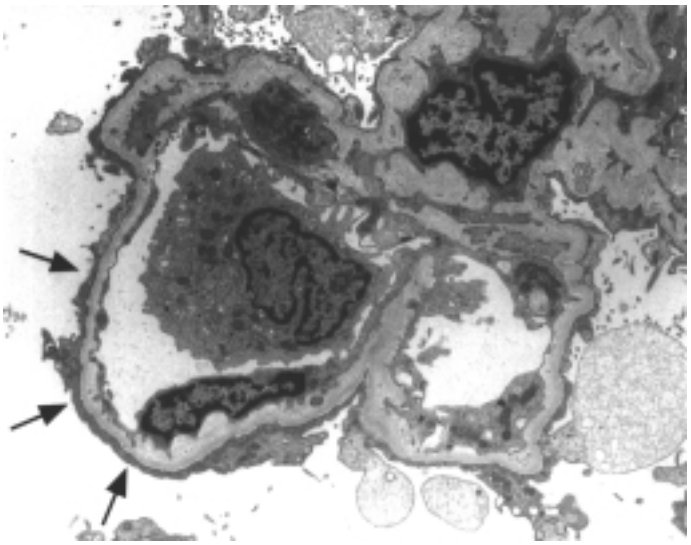

Figure 4. Minimal change nephropathy. Severe effacement of foot processes (arrows)(electron microscopy, 7,500x).

tion of interferon [44]. Usually nephrotic syndrome reverses after discontinuation of the drug. MCD may also be associated with DM, schistosomiasis, and other diseases, including neoplasias. The most frequent association with malignancy is with Hodgkin's lymphoma, while the association with non-Hodgkin's lymphoma or solid tumors is rare.

Pathology

On light microscopy, glomeruli may be completely normal with normal capillary walls and cellularity. However, a mild and focal mesangial hypercellularity may be noted. On morphometric analysis, glomerular hypertrophy may be seen in some cases. This finding may predict the progression to focal glomerulosclerosis [58]. Immunofluorescence is usually negative, but mesangial IgM deposition may be seen in some cases, with or without a slight increase in mesangial matrix. Some investigators have proposed that the presence of IgM deposits could identify a separate entity, but affected patients can neither be differentiated clinically from patients without IgM deposition nor have a different outcome and response to treatment. Also, the presence of mesangial IgG should be considered as nonspecific.

Electron microscopy shows the typical features of MCD consisting of an effacement of the foot processes of podocytes (Figure 4). The GBM is mostly normal; no parietal deposits are present. The endothelial cells are often swollen.

Pathogenesis

A number of studies have suggested that alterations in glomerular charge sites play an important role in MCD. A decreased glomerular negative charge has been found in rats with nephrotic syndrome caused by puromycin aminonucleoside [15]. Intrarenal arterial infusion of polycations causes selective proteinuria and foot processes effacement [8], and a decreased staining for glomerular polyanions has been observed in renal biopsies from patients with MCD [21]. The loss of

anionic charges on glomerular structures prevents the electrostatic repulsion between negatively-charged structures, which is a fundamental constituent of glomerular filtration barrier. As a consequence, there is retraction and effacement of foot processes, which are normally negatively charged, and there is a passage of lower macromolecules, such as serum albumin, into the urine. However, it is possible that the disturbance in charge is not confined to the glomerulus. Ghiggeri et al. showed that the charge and conformation of serum albumin were modified in the nephrotic phases of MCD but returned to near normal values after steroid-induced remission of proteinuria [62]. Levin et al. found an early reduction of surface negative charge on red blood cells (RBCs) and platelets preceding reduction of serum albumin during relapses [111]. Thus, MCD may result both from loss of negative glomerular charge (due to a loss of glomerular polyanions) and from a generalized electrochemical disorder with increased positive charge of some extrarenal structures, including serum albumin (Figure 5).

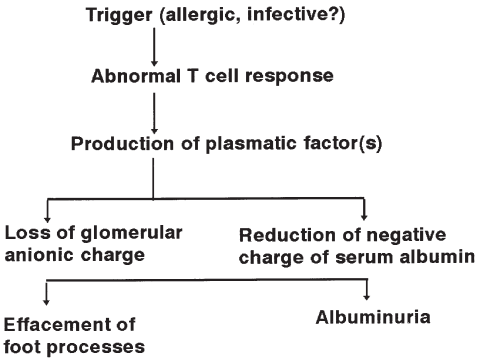

Figure 5. Possible pathogenesis of minimal change nephropathy.

What is the primary cause of these electrostatic defects? The abnormalities might be a consequence of failure to synthesize the charged group, loss of anionic charges due to degradative process, or neutralization. These mechanisms might arise from a circulating charge-neutralizing factor that could be produced by T cells in response to an infective or allergic trigger. A number of studies reported that during MCD relapses, lymphocytes have impaired responses to polyclonal activators, probably caused by prostaglandins secreted by macrophages. The response returns to normal during remission. On the other hand, there is an increase in T-suppressor activity during relapse that reverses after treatment. However, it is still unclear whether these and other abnormalities of the cell-mediated immunity are the cause or the consequence of the nephrotic syndrome and/or of circulating factor(s). Several lymphokines, including interleukin-2, and vascular permeability factors were isolated in the supernatant of cultured lymphocytes. These factors might be responsible of the loss of anionic charges and increased glomerular permeability, but their pathogenic role is still far from being established.

Clinical Presentation and Course

MCD is the major cause of the nephrotic syndrome in children, accounting for 90% of cases under the age of 6. The disease is not limited to children, however. It may occur in adulthood and also in the elderly.

Patients with MCD generally present with full-blown nephrotic syndrome. The onset of the disease is usually acute and frequently follows a viral upper respiratory infection, an allergic episode, or a vaccination. The degree of pedal and periorbital edema may be variable, but most patients have a severe fluid retention that can also result in ascites and pleural effusion. Blood pressure is usually in a normal range but is higher than in normal

Table 5. Definitions of Responses and Relapses in Patients with Minimal Change Nephropathy

Complete remission	Proteinuria < 4 mg/m^2/day in children or < 0.2 g/day in adults for 3 consecutive days
Partial remission	Proteinuria between 4 and 40 mg/m^2 day in children or between 0.21 and 3.5 g/day in adults for 3 consecutive days
Relapse of proteinuria	Proteinuria > 4 mg/m^2/day in children or > 0.2 g/day in adults for at least one week in patients who were in complete remission
Relapses of nephrotic syndrome	Proteinuria > 40 mg/m^2/day in children or > 3.5 g/day in adults for at least one week in patients who were in remission
Frequent relapsers	Patients with ≥ 2 episodes of the nephrotic syndrome in 6 months or ≥ 3 episodes of the nephrotic syndrome in 12 months
Steroid-dependent	Reappearance of the nephrotic syndrome within 2 weeks after reduction or discontinuation of glucocorticoids

subjects of the same age. About 20 – 30% of patients are hypertensive. On the other hand, hypovolemic shock may sometimes occur as a consequence of massive urinary loss of albumin. Proteinuria ranges between 3 and 20 g or more per day. It is typically selective with heavy loss of smaller macromolecules, such as albumin and transferrin, while proteins of higher molecular weight are retained. Severe hypoalbuminemia and hypercholesterolemia are common. Microscopic hematuria can be found in about one-third of cases. Renal function is usually normal. However, moderate to severe renal failure can occur, particularly in older patients.

It is difficult to assess the natural course of MCD because today most patients are treated with glucocorticoids and other effective drugs. Before the use of these agents, the 5-year mortality rate in children was as high as 67%, with the remaining patients undergoing spontaneous remission [6]. The major causes of death were infection, particularly peritonitis and pneumonia, and renal failure. A beneficial alteration in the course of MCD was achieved with glucocorticoids (see below). Approximately 95% of children and 80% of adults can obtain complete remission of proteinuria under glucocorticoid therapy. In those who respond, the remission is permanent in only about 20 – 25%. Another 20 – 25% of patients will have infrequent relapses, while the rest become frequent relapsers or steroid-dependent (see Table 5). The risk of relapse seems to be inversely correlated with age, being higher in children younger than 6 years than in older children [186]. The risk is lower in adults [60] and even lower in the elderly [113]. The risk of frequent relapses and/or steroid dependency is lower in patients who had a good response to glucocorticoids, a prolonged initial treatment [24], and a prolonged remission after the first episode [112]. As already mentioned, the presence of glomerular hypertrophy on morphometric analysis is a bad prognostic sign, because it may herald progression to FSGS [58]. Although in the past mesangial hypercellularity

and mesangial IgM deposits were thought to be associated with a decreased response to glucocorticoids and steroid dependency, the current opinion is that these findings are not associated with outcome or response to treatment different from those of patients with classic MCD. Eventually, about 65 – 75% of patients may enter a prolonged remission within 10 years from clinical onset, but some children need 20 – 30 years before attaining a definitive remission.

Progression to CRF is exceptional in children but may occur in adults and particularly in elderly patients. Sporadic cases of ARF have also been reported. These can be due to hypovolemia, renal vein thrombosis, or interstitial nephritis, but are more often caused by diuretics or hemodynamic factors [177]. ARF is more frequent and severe in elderly patients but can also rarely occur in children. MCD patients are exposed to the complications of the nephrotic syndrome, such as infections and intravascular thrombosis, or its treatment. Some patients may die as a result of these complications. The mortality rate ranges around 2% for children [112], 65 – 10% for adults [167], and 35 – 45% for elderly patients [113]. Death is particularly frequent in patients with renal dysfunction and in those untreated or refractory to treatment [135].

Diagnosis

MCD may occur in the first year of life but this is rare. In these cases, it is difficult to distinguish MCD from the Finnish type of congenital nephrotic syndrome and diffuse mesangial sclerosis. Congenital nephrotic syndrome is more common in Finland but has also been observed in other countries. It is an inherited autosomal recessive disease characterized by a severe nephrotic syndrome from the first days of life. There are no definite histopathologic criteria that allow differentiation between it and MCD. Diffuse mesangial sclerosis is another entity which also has an early onset and a severe nephrotic syndrome but differs in its rapid progression to end-stage renal failure and by histopathologic lesions characterized by a combination of thickened basement membranes and expansion of mesangial matrix with no increase in the number of mesangial cells [25].

It is difficult to differentiate MCD from other glomerular diseases on clinical grounds. Selective proteinuria is more frequent in MCD but can also be found in the initial stages of membranous nephropathy and FSGS. Hypertension, hematuria, and renal insufficiency are more common in other glomerular diseases, but there is considerable overlap. Because MCD is responsible for most cases of nephrotic syndrome in children, treatment with glucocorticoids is usually initiated on empirical grounds, and renal biopsy is performed only if an 8-week trial does not induce remission of proteinuria. In adults MCD is a rarer cause of the nephrotic syndrome. A trial with glucocorticoids is not helpful for an early diagnosis, as only 50 – 60% of adults show disappearance of proteinuria after 8 weeks of prednisone. Thus, renal biopsy is required in adults.

Treatment

MCD is very sensitive to treatment with glucocorticoids. Although remission may occasionally be obtained with relatively moderate doses, most authorities suggest an aggressive initial treatment. In children the standard treatment for the first episode of nephrotic syndrome consists of prednisone at a dose of 60 mg/m^2/day for 4 weeks, followed by 40 mg/m^2 given on alternate days for 4 more weeks [24]. With such a regimen, proteinuria

can be expected to disappear in about 50% of children within one week, in 80 – 85% within 4 weeks, and in 90 – 95% within 8 weeks. In a few children, however, complete remission of proteinuria occurs only after more prolonged treatment or after intravenous (IV) high-dose methylprednisolone [25].

Adults are usually treated with lower doses of prednisone, i.e. 1 mg/kg body weight/day. Proteinuria disappears only in 50 – 60% of adults within 8 weeks. However, about 80% of patients become free of proteinuria if treatment is prolonged to ≥ 16 weeks [60, 134]. Thus, it is now clear that the concept of steroid resistance, which was previously applied to patients who did not respond to high-dose prednisolone within 4 – 8 weeks, should be reviewed. Many adults and some children who were considered as steroid resistant in the past were simply undertreated.

There is, however, a small proportion of patients with the histological appearance of MCD who do not respond even to a prolonged treatment with steroids. These patients usually show FSGS on repeated biopsy and should be treated accordingly.

After remission is obtained, some 20 – 30% of patients do not relapse, and a similar number have only infrequent relapses. Patients with infrequent relapses are usually treated with high-dose prednisone until remission, followed by 4 weeks of alternate-day prednisone at a dose of 40 mg/m^2 in children and 0.75 mg/kg in adults [147]. Spontaneous remission is also possible, particularly when relapse follows an intercurrent infection.

Unfortunately, many initial responders either become frequent relapsers or show steroid dependency. There is some evidence that the risk of relapse is greater in children given a short course of treatment for the initial attack than in children given long-term treatment [24]. Thus, after remission has been obtained, it is advisable to prolong treatment to prevent further relapses. If well tolerated, low-dose prednisone can be given every other day for 6 – 12 months. The doses of steroid should be tapered gradually to prevent relapses that may be triggered by secondary hypoadrenalism.

The treatment of frequently relapsing or steroid-dependent patients is difficult. For inducing remission, schedules based on alternate-day prednisone, low-dose hydrocortisone, and IV high-dose methylprednisolone followed by low-dose prednisone can reduce iatrogenic toxicity. However, in spite of these schedules, a number of patients develop steroid-related side effects, including obesity, diabetes, osteoporosis, Cushingoid features, hypertension, infection, and growth retardation in children.

Levamisole, cytotoxic agents, and cyclosporin have been suggested as potential alternative treatments. Levamisole is an antihelminthic drug with immunomodulating properties. Some retrospective studies reported that this agent could reduce the risk of relapses. Conflicting results have been obtained with controlled trials. In one study [23], 61 steroid-dependent children, in whom remission had been achieved with prednisone, were randomly assigned to receive placebo or levamisole at a dose of 2.5 mg/kg every other day. After 112 days, 4 of 30 patients given placebo vs. 14 of 31 given levamisole maintained remission, the difference being significant. However, another controlled trial could not find any significant difference in the median duration of remission between children given placebo and those given levamisole [41].

Cytotoxic agents, such as cyclophosphamide and chlorambucil, can produce more lasting remission than steroids. Remission seems to be more stable in adults than in children. More than 60% of adults given cyclophosphamide because of multiple relapses remained in remission for at least 5 years [115,

134], while a pediatric review reported that the rates of remission at 5 years in children ranged from 36 – 66% [25]. Duration of treatment is also important. Pennisi et al. reported complete remission at one year in 92% of children given cyclophosphamide for 10 – 12 weeks vs. 42% of children treated for 6 – 8 weeks [141].

Alkylating agents may cause leukopenia, hemorrhagic cystitis, oncogenic effects, and gonadal toxicity, testes being more vulnerable than ovaries. Therefore, their use should be limited to those patients who are at risk of developing steroid toxicity. To prevent leukopenia, high daily doses should not be used (we suggest 2 mg/kg/day for cyclophosphamide and 0.1 – 0.15 mg/kg/day for chlorambucil). To prevent azoospermia, cumulative doses of 200 – 250 mg/kg for cyclophosphamide or 10 – 15 mg/kg/day for chlorambucil should not be exceeded. With these cumulative doses, the oncogenic risk is minimal. Forced diuresis and/or 2-mercaptoethanesulphonate (MESNA) can protect from the bladder toxicity of cyclophosphamide.

Cyclosporin is another therapeutic option. Most steroid-dependent patients can be maintained in remission with cyclosporin, which is usually started after remission has been induced with steroids [145]. After cyclosporin is stopped, an early relapse of nephrotic syndrome usually occurs, but some patients may maintain remission, particularly if cyclosporin dosing has been tapered gradually after prolonged treatment. A number of side effects may be associated with the use of cyclosporin. Hypertrichosis, gum hyperplasia, gastrointestinal symptoms, and hypertension are the most frequently reported. There has been much concern about the potential nephrotoxicity of cyclosporin. In patients with nonrenal autoimmune diseases, a cyclosporin-related nephropathy characterized by interstitial fibrosis and progressive renal disease can develop. This is usually preceded by a typical arteriolopathy with either nodular proteinaceous deposits in the arteriolar wall or mucinoid thickening of the intima. Older age, high doses of cyclosporin, and an increase in plasma creatinine to > 75% over the basal values are the most important variables associated with the risk of developing irreversible cyclosporin nephropathy [55]. The importance of the size of the dose in inducing nephropathy is confirmed by some studies based on iterative renal biopsies in patients with MCD [70, 123]. On the other hand, there is evidence that cyclosporin arteriolopathy, which precedes the development of interstitial fibrosis, can be reversible if cyclosporin is stopped or given at lower doses [129]. Thus, cyclosporin can be used in patients with resistant disease, but careful monitoring is needed with its use in patients with renal diseases. We suggest as an initial dose 4 mg/kg/day of the new microemulsion in adults and 100 mg/m^2/day in children. Trough blood levels should be maintained between 75 and 200 ng/mL. The doses should be reduced if plasma creatinine rises > 30% over the basal values. The drug should be stopped if plasma creatinine rises > 75% over the basal values.

In summary, we suggest the following approach in MCD. An aggressive and prolonged (if tolerated) course of glucocorticoids should be used to treat the first episode of nephrotic syndrome in an attempt to achieve remission and prevent relapse. Infrequent relapses can be treated with shorter courses of glucocorticoids. In frequently relapsing/steroid-dependent patients, levamisole may be tried in an attempt to reduce steroid doses in responders. Although the efficacy of this drug is controversial, the tolerance is usually good. If levamisole is not successful, patients may be treated with continuous alternate-day prednisone and IV methylprednisolone pulses dur-

ing relapses. Those patients who do not tolerate steroids may be given a trial with a cytotoxic agent for 12 weeks at cumulative doses not exceeding 250 mg/kg for cyclophosphamide or 12 mg/kg for chlorambucil. If further relapses occur, cytotoxic therapy should not be repeated, as potential toxicity may be cumulative. Those patients can be switched to cyclosporin at an initial dose of 4 mg/kg/day in adults and 100 mg/m^2 in children, trying to gradually taper off the drug after 1 – 2 years.

Table 6. Causes of Secondary Focal Glomerulosclerosis

Elderly	Malignancy
Morbid obesity	Familial dysautonomia
Reduced renal mass	IgA nephritis
Reflux nephropathy	Membranous nephropathy
Obstructive uropathy	Segmental hypoplasia
AIDS	Diabetes mellitus
Heroin addiction	Sickle cell disease
Analgesic nephropathy	Transplantation
Hypertension	Oligomeganephronia

Focal Segmental Glomerulosclerosis (FSGS)

FSGS is a clinicopathologic entity characterized by proteinuria, often in nephrotic range, and by focal and segmental sclerosis, which initially predominates in the juxtamedullary glomeruli and then spreads to the outer cortex. The primary form of FSGS affects both children and adults. It may represent an evolutionary stage of MCD. A morphologically similar lesion to FSGS may result from a number of disorders and may create problems of differential diagnosis with the primary form. Most patients with FSGS and the nephrotic syndrome develop renal failure within 10 – 15 years.

Etiology

The current opinion is that MCD and FSGS represent the 2 extremes of the same disease. Both entities are characterized by massive proteinuria as well as by the effacement of the foot processes of epithelial cells on electron microscopy and insignificant deposition of immunoglobulins and complement. The etiology of primary FSGS is unknown as it is for MCD.

Segmental sclerosing lesions may also develop in different clinical instances and can even complicate other glomerular diseases (Table 6). In a number of cases, these secondary forms of FSGS are caused by maladaptive glomerular hemodynamic alterations, leading to glomerular hyperfiltration and hypertension, with eventual development of segmental glomerular scars. FSGS may be a rare complication of obesity and can also develop in heroin addicts and in patients with the aquired immunodefeciency syndrome (AIDS), where the variant of collapsing glomerulopathy seems to be particularly frequent.

Pathology

The initial lesions develop in a portion (segmental) of some glomeruli (focal) (Figure 6). Early lesions affect the deeper juxtamedullary glomeruli. The segmental lesions affect a few capillary loops that stick together, either at the

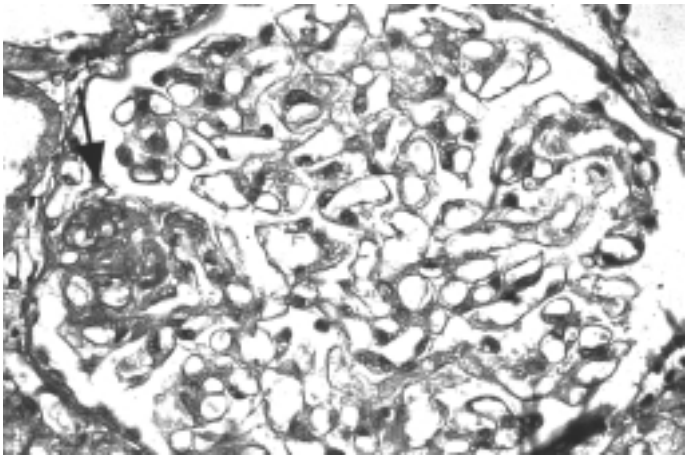

Figure 6. Focal segmental glomerulosclerosis. Typical sclerosis (arrow) of a circumscribed area of the glomerular tuft (500x).

periphery of the tuft (tip lesions) of at the hilum. Hyaline material is often present in the sclerosed areas, which are usually surrounded by a clear halo and always lined by a layer of severely altered and effaced podocytes. Initially, the rest of the tuft and the other glomeruli show only minimal changes, but mesangial hypercellularity may be present. Immunofluorescence is usually negative, but some deposition of IgM and C3 may be seen in the sclerotic areas. Electron microscopy usually reveals diffuse effacement of podocytes and their detachment from the GBM. A form of collapsing glomerulopathy has also been described. It is characterized by glomerular capillary collapse, visceral epithelial swelling, and hyperplasia. It seems to be more frequent in black patients.

Sclerosis progressively destroys the glomerulus, evolving to widespread sclerosis of the whole tuft. With progression of the disease, the lesions extend to the deeper cortex first and then to the outer cortex. Besides the glomerular lesions, there are also tubular and interstitial changes. Initially, there are focal tubular lesions, and foam cells may be seen in the interstitium. In more advanced phases, there is atrophy and interstitial fibrosis of various degree. Interstitial fibrosis is particularly severe in collapsing glomerulopathy, out of proportion to the glomerular process.

Pathogenesis

The pathogenesis of FSGS is similar to that proposed for MCD. The disease could represent a T cell-mediated disorder in which an aberrant clone of T cells secretes a circulating factor that impairs the negative charges of the glomerular structures and probably also of serum albumin and other extrarenal material. Podocytes could be the primary target in FSGS. The initial alterations consisting of an effacement of foot processes may lead to their detachment from the basement membrane. This could result in hyperfiltration, accumulation of subendothelial protein, capillary occlusion, and the formation of synechia between the tuft and the capsule [110]. Massive production of circulating factor(s), genetic predisposition, hyperlipidemia, and hypercoagulation may contribute to the development of FSGS. Another factor that may favor the development of FSGS is an excessive produc-

tion of fibrogenic growth factors. In the animal model, platelet-derived growth factor B and transforming growth factor beta have been implicated in the induction and progression of glomerulosclerosis [90].

The role of circulating factor(s) in eliciting the pathogenesis of FSGS has been further substantiated by experience with renal transplantation. A number of patients who lost their native kidney function because of FSGS show recurrence of proteinuria and the typical lesions of FSGS at renal biopsy after transplantation. Plasmapheresis and/or immunoadsorption with protein A may reduce proteinuria in these cases [39], suggesting that the recurrence of FSGS may be caused by a plasmatic factor. Recently, Savin et al. isolated a circulating factor from patients with recurrence of FSGS after renal transplantation [164]. This factor has a molecular weight of about 50 kd, larger than any known lymphokine, and does not precipitate with immunoglobulins. It might be a nonimmunoglobulin protein or a fragment of an immunoglobulin. However, it is unlikely that this factor neutralizes the anionic-charge barrier, because it is not strongly cationic. Its activity, in very small amounts, might be compatible with that of a cytokine-like molecule that directly injures podocytes.

Clinical Presentation and Course

FSGS accounts for up to 20% of glomerular lesions in children and adults presenting with proteinuria. It is more frequent in the black than in the white population. The clinical presentation is similar at any age, although nephrotic syndrome is more frequent in children and hypertension is more frequent in adults [103]. Some 70 – 90% of patients have a nephrotic syndrome at presentation. Microhematuria is found initially in about half of cases, while macroscopic hematuria is rare. Renal insufficiency may be present in about 20 – 25% of cases at clinical onset.

The disease is usually progressive, and about two-thirds of cases develop end-stage renal disease (ESRD) within 10 – 15 years. A few patients with severe nephrotic syndrome may progress rapidly to renal failure, often associated with arterial hypertension and thrombotic complications. Spontaneous remission of the nephrotic syndrome is exceptional. Complete remission can occur in less than 3% of untreated patients [103].

Several factors may have prognostic significance. The 2 most important clinical features are the level of proteinuria and serum creatinine. Patients with nephrotic range proteinuria reach ESRD within 6 – 8 years in 50% of cases, while the 10-year renal survival is > 90% for patients with non-nephrotic proteinuria [31]. The presence of massive proteinuria, (> 10 g/day, is associated with a particularly poor prognosis, with half of patients reaching ESRD within 3 years [31]. There is also general agreement that impaired renal function at presentation indicates a poor prognosis. Among histologic features, location of sclerotic lesions at hilar pole, glomerular hypertrophy, mesangial hypercellularity, and collapsing glomerulopathy have been considered to be associated with poorer prognosis, by some investigators but not by all. Interstitial fibrosis is universally considered as the strongest prognostic predictor among the histologic features. The response to therapy is also a useful clinical indicator of outcome. A review of the literature showed that < 3% of patients who attained complete remission with therapy developed ESRD by 5 years compared with 55% of nonresponding patients [103]. Even a partial remission is associated with a more favorable course compared to persisting nephrotic syndrome.

Diagnosis

As with most other primary glomerulonephritis, the diagnosis of FSGS also requires renal biopsy. The presence of a single glomerulus with segmental hyalinosis is sufficient to make a diagnosis of FSGS. In the initial phases, however, the diagnosis may be impossible if only the glomeruli of the outer cortex are represented in the histologic sample.

In some instances it can be difficult to recognize whether FSGS is idiopathic or secondary to other diseases or conditions. The forms caused by maladaptive glomerular hemodynamic alterations may be distinguished by the absence of hypoalbuminemia, hypercholesterolemia, and edema in spite of nephrotic levels of proteinuria. Human immunodeficiency virus (HIV) and heroin-associated forms rapidly progress to ESRD within a few months. At renal biopsy, the secondary forms may have large glomeruli with hilar lesions, while tip lesions recall idiopathic FSGS. The presence of mesangial hypercellularity is more typical of the idiopathic form. Probably the most reliable sign for idiopathic FSGS is represented by the effacement of foot processes at electron microscopy.

Treatment

Almost all the studies of FSGS treatment are retrospective. A review of uncontrolled trials reported that 29% of children and 17% of adults [167] treated with glucocorticoids entered complete remission of proteinuria. The majority of these patients were given glucocorticoids for no more than 4 – 8 weeks. Better results have been obtained when patients were given more prolonged glucocorticoid therapy. A review of the literature indicated that 51% of patients treated with prednisone for ≥ 6 months entered complete remission of proteinuria [144]. Most responders maintained normal renal function over time. Unfortunately, no clinical or histologic feature can predict the response to glucocorticoids.

The potential role for immunosuppressive agents is even less clear. The results of retrospective studies suggest that, as with prednisone, the longer the treatment the higher the rate of response, but the cumulative rate of remission is similar to that obtained with glucocorticoids [7]. A randomized trial in children did not show differences between alternate-day prednisone alone or combined with cyclophosphamide for 3 months [184]. On the other hand, at least in adults, the length of remission in responders seems to be longer in patients given cyclophosphamide or chlorambucil. In our own retrospective experience, only 18% of patients who responded to cytotoxic therapy had one or more relapses of nephrotic syndrome vs. 40% of patients who responded to glucocorticoids [7].

Mendoza et al. have proposed an aggressive approach for steroid-resistant children [121a]. Their regimen consisted of high-dose IV methylprednisolone pulses given initially every other day, then at progressively longer intervals for more than one year. The children were also given prednisone, 2 mg/kg every other day. If no response was obtained, cyclophosphamide or chlorambucil was added. Their most recent analysis showed that at the end of a mean follow-up of 6 years, 21 out of 32 children treated were in complete remission, 3 were in partial remission (non-nephrotic proteinuria), 5 had reduced creatinine clearance, and 3 had progressed to ESRD [187]. These results were not confirmed by Waldo et al. who gave a similar regimen to 10 children with FSGS [192]. After 47 months, 6 patients had developed ESRD, 2 had developed renal insufficiency, and the other 2 pa-

tients were still nephrotic. However, 8 of their 10 patients were black, and this may have affected the response rate because blacks may have more severe disease than white patients.

Cyclosporin has also been used in FSGS. A review of the literature found that 40% of patients treated with cyclosporin could be maintained in remission from nephrotic syndrome, the response being similar in children and in adults [103]. Ingulli et al. treated 21 children with cyclosporin for a mean period of 27 months [83]. Proteinuria and cholesterol significantly decreased. When compared with a historical population, the rate of patients who progressed to ESRD was lower in cyclosporin-treated children (24% vs. 78%). This apparent benefit of cyclosporin on proteinuria was also supported by an Italian controlled trial [149]. Nephrotic patients who had not responded to a 6-week course of high-dose prednisone were randomly assigned to supportive therapy or to cyclosporin (5 mg/kg/day in adults and 6 mg/kg/day in children) for 6 months. In the first year, 32% of treated patients entered complete remission, another 27% had partial remission, and only 16% of untreated controls had a partial and transient remission. The mean levels of creatinine clearance did not differ between the 2 groups. However, 66% of patients had a relapse in nephrotic syndrome after cyclosporin was stopped. Thus, a prolonged treatment is needed to avoid nephrotic syndrome. Is this approach safe? Worsening of kidney lesions at repeat renal biopsy has been reported in cyclosporin-treated patients with FSGS [124]. It is not clear however, whether the renal lesions seen on repeat biopsy represent progression of the underlying FSGS in nonresponders or represent cyclosporin toxicity. Whatever the mechanism, the risk of severe tubulointerstitial lesions in patients treated with cyclosporin for FSGS seems to be particularly high when there is an abnormal baseline serum creatinine, when a high proportion of glomeruli with sclerosis is seen at renal biopsy, or when the initial dose of cyclosporin is high. On the basis of the available knowledge, we do not recommend prescribing cyclosporin to patients with abnormal renal function, severe hypertension, tubulointerstitial lesions, or extensive glomerular sclerosis.

In spite of some evidence that a prolonged treatment with glucocorticoids, cytotoxic agents, or cyclosporin may bring about remission and protect renal function in a subset of patients, the optimal treatment regime for FSGS is still unclear. There is general agreement that no specific therapy is needed for patients with asymptomatic proteinuria. There is also consensus about using an 8-week course of high-dose prednisolone in nephrotic patients in order to recognize the few early responders.

What to do with nephrotic patients who do not respond to short-treatment is controversial. Many clinicians do not give any specific therapy, whereas others are quite aggressive and give prolonged steroid and/or cytotoxic treatments. Our practice is that, unless steroid toxicity develops, prednisone should be continued for another 4 – 6 months. One alternative is to give an alkylating agent for 6 months or alternate steroids and an alkylating agent every other month for 6 months, with a schedule similar to that used in membranous nephropathy (MN) [150] in order to reduce the risk of steroid toxicity and to induce a longer remission in responders. If nephrotic syndrome persists, a trial with cyclosporin (initial doses with the new microemulsion 4 mg/kg/day in adults or 100 mg/m^2/day in children) may be offered provided that creatinine clearance and blood pressure are normal and that a recent renal biopsy does not show severe tubulointerstitial lesions. If no improvement of proteinuria is seen within 3 months, cyclosporin should be stopped, as it

Table 7. Causes of Secondary Membranous Nephropathy

Infections	*Association with other diseases*
Malaria	Carcinoma
Schistosomiasis	Non-Hodgkin's lymphoma
Hepatitis B	Hodgkin's disease
Hepatitis C	Chronic lymphocytic leukemia
Syphilis	Systemic lupus erythematosus
Tuberculosis	Autoimmune thyroiditis
Leprosy	Sarcoidosis
Filariasis	Sjögren's syndrome
Streptococcal infection	Sickle cell disease
HIV infection	Diabetes mellitus
Rectal abscess	Dermatitis herpetiform
	Bullous pemphigoid
Drugs and Toxins	Psoriasis vulgaris
Non-steroidal anti-inflammatory drugs	Primary biliary cirrhosis
Captopril	Guillain-Barré syndrome
Penicillamine	Mixed connective tissue disease
Gold	Periaortic fibrosis
Mercury	Myasthenia gravis
Hydrocarbons	Rheumatoid arthritis
Formaldehyde	Renal transplantation

is unlikely that more prolonged treatment will result in remission. In patients who respond, cyclosporin can be continued for another 1 – 2 years at the minimal effective dose. If nephrotic syndrome reappears after stopping cyclosporin, a renal biopsy may be repeated before deciding whether or not therapy with cyclosporin should be continued.

Membranous Nephropathy (MN)

MN is a glomerular disease characterized clinically by proteinuria and histologically by a diffuse thickening of the GBM due to deposition of subepithelial immune-complexes. MN is idiopathic in the majority of cases, but in some instances it is secondary to well-defined causes. The course of the disease may be variable. Some patients maintain normal renal function with or without remission of proteinuria, but others progress to renal failure or die from complications related to the nephrotic syndrome.

Etiology

Exceptionally, MN may affect siblings. An association between MN and human leukocyte antigen (HLA)-DR3 antigen has been reported by many studies in white patients. In Japanese patients there is an increased incidence of HLA-DR2 [174].

In most cases of MN no etiological factor can be identified. However, in about one-fourth to one-third of cases, MN is associated with identifiable causes (Table 7). The overall prevalence of secondary MN appears to be

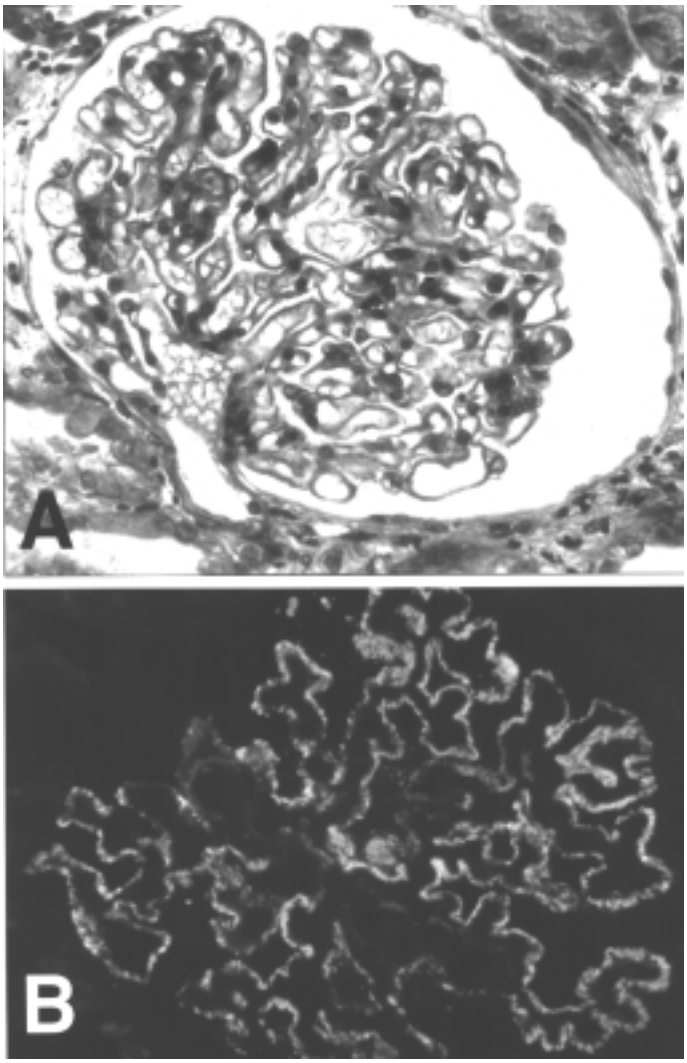

Figure 7. Membranous nephropathy. A: diffuse and homogeneous thickening of the glomerular capillary walls (500x). B: granular deposition of IgG as seen by immunofluorescence (500x).

higher in children and in older adults. Worldwide, malaria and schistosomiasis are the most common causes of secondary MN. Hepatitis B and C are also frequent causes of MN, particularly in endemic areas [106]. MN may be the first manifestation of SLE and may precede serological abnormalities by several years. In some 10% of patients, MN is associated with malignancy. In 40 – 45% of these cases, renal disease may antedate the initial manifestations of the underlying cancer by months or even years [29]. In a number of cases, MN can be secondary to toxic agents or drugs. Penicillamine and gold are 2 well-known causes of MN, but NAIDs are probably the most frequent etiologic drugs of secondary MN. In a recent report, these drugs were responsible for 10% of stage I MN [155]. Recognition of the toxic agent or drug as a cause of MN is important because proteinuria usually remits after the removal of the offending agent.

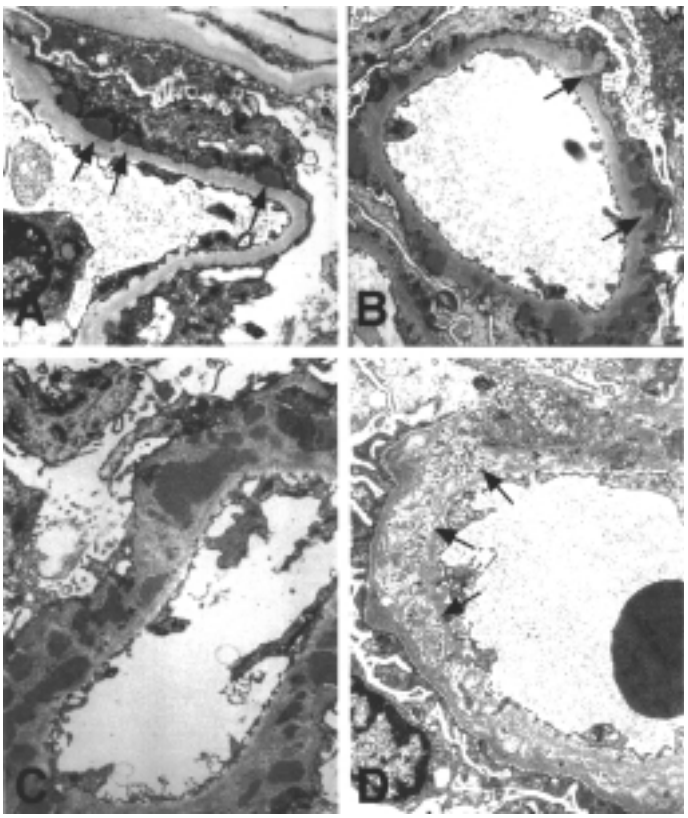

Figure 8. Membranous nephropathy as seen by electron microscopy. A: stage I, with few electron-dense deposits (arrows) on the subepithelial side of the GBM. B: stage II, with projections of the GBM (arrows) around the electron-dense deposits. C: stage III, with electron-dense deposits incorporated within a thickened GBM. D: stage IV, with partially reabsorbed deposits (arrows) and irregular thickening of the GBM. (7,000 – 8,000x)

Pathology

MN is characterized by typical alterations of the GBM caused by subepithelial deposition of immune deposits (Figure 7). Ehrenreich and Churg described 4 glomerular stages of the disease (Figure 8) [52]. In stage I, the glomeruli appear almost normal at light microscopy, but at electron microscopy there are small, spaced, subepithelial electron-dense deposits and diffuse foot process fusion. Immunofluorescence shows diffuse granular deposits of IgG and C3 along the capillary loops. In stage II, light microscopy shows a diffuse, uniform thickening of the GBM, with characteristic spikes on silver stain. By electron microscopy, these are due to projections of the GBM. The deposits are larger, more uniform, and numerous. In stage III, the deposits are incorporated within the GBM, which appears thickened at light microscopy. In stage IV, the GBM is markedly but irregularly thickened. By electron microscopy there is rarefaction of deposits due to resorption. The intensity of the deposits at immunofluorescence may be rather low. These stages are common to all forms of MN, but in secondary forms subendothelial deposits as well as mesangial proliferation may be present. They are not usually found in idiopathic MN. The finding of IgA or C1q by immunofluorescence also suggests a secondary MN.

Although some investigators have found that patients with stage I – II glomerular lesions are unlikely to develop renal failure [52], others did not find any correlation between the glomerular stage and the renal out-

come [97, 150, 196]. An unfavorable prognostic role has been attributed to the finding of a superimposed focal glomerulosclerosis [191]. There is general agreement, however, that interstitial fibrosis and tubular atrophy, rather than glomerular changes, are the histologic findings more strictly associated with a poor prognosis [97, 150, 196].

Pathogenesis

As shown by immunofluorescence and electron microscopy, MN is characterized by the subepithelial deposition of immune complexes. Two hypotheses regarding the immune deposits formation have been considered. First, circulating immune complexes of intermediate size escape phagocytosis from the reticuloendothelial system, pass the GBM, and deposit in the subepithelial space. This mechanism might be operating in some cases of secondary MN. Circulating complexes have been detected in MN associated with SLE, hepatitis B, or neoplasia; and in some cases the antigen has been eluted from glomeruli [183]. However, such a pathogenesis is unlikely in idiopathic MN, as a number of clinical studies failed to detect circulating immune complexes. Second, immune complexes could form in situ by antibody reacting with antigens planted in the glomeruli or with endogenous glomerular antigen.

The Heymann nephritis model has been largely used to understand the pathogenesis of idiopathic MN. There are 2 models of Heymann nephritis. Both of them lead to an autoimmune-mediated glomerulonephritis that has functional and immunopathologic features similar to human idiopathic MN. Active nephritis is induced by immunization of susceptible strains of rat with crude proximal tubular brush border extract. The passive Heymann nephritis is induced by injecting antibodies against this extract. Two main antigenic determinants have been identified in Heymann nephritis: megalin and receptor-associated protein. Megalin, previously called gp 330, is a member of low-density lipoprotein receptors located in the brush border of tubular cells and, in lower amounts, in glomerular epithelial cells. The receptor-associated protein binds to megalin and may serve as its intracellular chaperon [54]. There is now evidence that in Heymann nephritis subepithelial deposits do not derive from trapped circulating immune complexes but are caused by in situ complex formation [95]. Antibodies penetrate the GBM and bind to antigens located at the base of the epithelial cells. The immune deposits grow in size by repeated cycles of immune complex formation and new formation of megalin. A similar mechanism is thought to be operating in human idiopathic MN, although the target antigen has yet to be identified.

The subepithelial deposition of immune complexes activate the complement system with formation of the C5b – C9 complex (membrane attack complex). This results in release of potential inflammatory mediators such as prostaglandins, oxidants, and proteinases leading to damage of the glomerular epithelial cells and altered glomerular barrier function [36]. An important role in the progression of renal disease has been attributed to cytokines, particularly transforming growth factor β, which can stimulate the synthesis of collagens, fibronectin, and proteoglycans and contribute to the accumulation of extracellular matrix material within the damaged kidney [18, 173].

Clinical Presentation and Course

Idiopathic MN is rare in children while it occurs in adults usually between 30 and 50

years. In people aged > 60 years MN has an annual incidence 2.5 fold higher than in younger population [175]. Overall there is a predominance of males at 2 : 1 ratio [79]. Proteinuria, usually non-selective, is the hallmark of the disease. Some 70 – 80% of patients have a nephrotic syndrome at presentation and others may become nephrotic later. Microscopic hematuria is found in about half of patients. Gross hematuria and red blood cell casts are rare. Arterial hypertension and renal dysfunction may be present at clinical onset.

Idiopathic MN may have a variable outcome. Some patients may show spontaneous reduction or even disappearance of proteinuria over time, others may remain nephrotic with stable renal function, and others may slowly progress to ESRD or die from extrarenal complications. It is difficult to assess the natural course of the disease and the relative importance of these events because the inclusion criteria in the available studies were very different. Moreover, most studies included both treated and untreated patients, and the length of follow-ups was quite different. Some studies that considered both patients with and without nephrotic syndrome at presentation and followed for 5 – 6 years concluded that MN is a benign disease with a high rate of spontaneous remission [32, 50, 168]. Other series that included only nephrotic patients with longer follow-up reported a 10-year kidney survival of around 50% [51, 81].

A number of studies tried to identify which clinical and/or histologic factors could predict the renal course at presentation. The conclusions were often contradictory. With univariate analysis, male sex, age > 50 years, HLA-DR3 genotype, superimposed glomerulosclerosis, heavy proteinuria, and arterial hypertension at presentation were found to be associated with a poorer prognosis by some investigators but not by others. When multivariate analyses were performed, the factor more strongly associated with renal failure was the presence of interstitial fibrosis and tubular atrophy at initial renal biopsy [97, 150, 196].

More information may be obtained by the follow-up of the patients. It has been pointed out that most patients who progress to renal failure have some increase in plasma creatinine after 2 – 3 years [195]. Pei et al. described a model that predicted outcome in a semiquantitative fashion by evaluating the persistence of certain levels of proteinuria over time [140]. The risk of chronic renal failure was 66% for patients with proteinuria ≥ 8 g/day for at least 6 months, 55% when proteinuria exceeded 6 g/day for ≥ 9 months, and 47% for proteinuria > 4 g/day for ≥ 18 months. These data were recently validated by extending the study to 360 MN patients from 3 different countries who were followed for a mean of > 6 years [34]. Complete remission of proteinuria, whether spontaneous or induced by treatment, probably represents the most reliable clinical predictor of a favorable outcome in the long term. The published data show that only 1 of 157 patients who attained complete remission had to undergo dialysis [146].

It is even more difficult to predict which patient may have spontaneous remission of proteinuria. We studied the influence of several factors on the development of remission. Among the numerous variables taken into consideration, only treatment with steroids and cytotoxic agents and glomerular stage I – II at initial biopsy significantly increased the probability of remission [148].

Patients with MN are also exposed to extrarenal complications. Thrombotic events are frequent in nephrotic patients. Among primary glomerulonephritides, idiopathic MN has the highest risk of renal vein thrombosis. This may occur in about 10% of patients and is frequently complicated by pulmonary em-

boli [203]. Deep vein thrombosis may develop in about 11% of patients with MN [10]. Arterial occlusion may also complicate the course of this disease. MacTier et al. reported 14 cases of arterial occlusion in 37 untreated patients with MN followed for a mean period of 64 months [114].

Diagnosis

The diagnosis of MN may be suspected on clinical grounds but requires renal biopsy to be confirmed. After the histologic diagnosis has been obtained, efforts should be made to identify possible causes of MN. In most instances, a thorough history and clinical examination are sufficient to recognize the secondary cause. Because hepatitis may be occult, a serological screening for hepatitis virus B and C (HBV and HCV) is mandatory. Two underlying diseases may pose diagnostic problems: SLE and neoplasia. MN may be the first manifestation of SLE and may precede serologic abnormalities even by years. The diagnosis of lupus MN may be suspected whenever IgA and C1q as well as subendothelial and mesangial deposits are found, but only the presence of virus-like particles or tubular basement deposits at electron microscopy may be considered to be specific for SLE [87]. In some 10% of cases, MN may be associated with cancer and in 40 – 45% of patients with cancer, neoplasia may antedate the initial manifestations of cancer by months or years [29]. It is still debated how extensively an underlying cancer should be investigated. We feel it is appropriate to recommend a stool guaiac examination, renal ultrasonography, chest X-ray, and prostatic antigen. Mammography and colonoscopy should also be performed in patients older than 50 years. Aged patients should be closely followed because neoplasia is more frequent in the elderly and may be undetectable on initial screening.

Treatment

Patients with idiopathic MN and subnephrotic proteinuria do not need any specific treatment because the risk of developing renal failure is minimal [50, 51]. Moreover, these patients are asymptomatic and are not exposed to the risk of nephrotic complications. The only treatment we suggest is the use of ACE inhibitors or antagonists of Ang II receptors that may reduce proteinuria.

Whether or not patients with nephrotic syndrome should receive specific treatment is still a matter of debate. A meta-analysis of controlled studies with glucocorticoids concluded that these agents are of no benefit either in favoring remission or in improving kidney survival [79]. Controlled trials with cytotoxic agents gave conflicting results although generally showing a favorable effect on proteinuria [146]. Unfortunately, most studies were performed on small groups of patients and follow-ups were short. A combination of steroids and chlorambucil was assessed in an Italian controlled trial. Patients with idiopathic MN and nephrotic syndrome were randomly assigned to receive symptomatic therapy or methylprednisolone (1 g for 3 days IV, then 0.4 mg/kg/day orally for 1 month) alternated every other month with chlorambucil (0.2 mg/kg/day for 1 month) for 6 months. The actual probability of surviving without developing ESRD at 10 years was significantly better in patients given steroids and chlorambucil (92%) than in untreated controls (60%). The slope of the reciprocal of plasma creatinine was also significantly better in treated patients than it was in controls. The probability of having complete or partial re-

mission as a first event was significantly better for treated patients (88% vs. 47%). Among the numerous variables taken into consideration, only treatment was significantly associated with remission. At the last follow-up visit 17 of 42 treated patients vs. 2 of 39 untreated patients were without proteinuria. Four of 41 patients had to stop therapy because of adverse events, which were reversible. No disquieting morbidity was observed in the long term [151]. On the basis of available studies, we feel that a 6-month regimen alternating glucocorticoids with an alkylating agent (either chlorambucil or cyclophosphamide) offers good chances of obtaining remission and preserving renal function. Some 10% of patients may develop side effects that are usually reversible. Leukopenia and infection are the most frequent side effects. Thus, it is recommended that the blood cell count be checked at least every 10 days during cytotoxic treatment. The alkylating agent should be halved when leukocytes fall < 5,000/mm^3 or stopped if they fall < 3,000/mm^3. A main concern with the use of cytotoxic agents is the possible development of cancer. We pooled all patients who were treated with chlorambucil in our controlled studies. We observed 3 cases of malignancy (one probably preexisting) out of 662 patient-years, with a cumulative risk of 4.5/1000 per year similar to the 4.3/1000 per year observed in the white general population. Thus, it would seem that there is little if any oncogenic risk of a cumulative treatment of 3 months with chlorambucil.

On the basis of these results, we feel that patients with MN and persisting nephrotic syndrome can benefit from a 6-month course with steroids alternated with a cytotoxic drug. In patients who have contraindications to glucocorticoids, a 6- to 12-month course with cyclophosphamide alone may be tried, although the oncogenic risk as well as the bladder and gonadal toxicity increase with more prolonged cytotoxic treatment. Cyclosporin can also be used. In a review it was found that of 73 adults with MN treated with cyclosporin, 20% entered complete remission and 25% had partial remission [123]. Remission was usually obtained within 6 months. However, most patients relapse after cyclosporin is stopped.

Table 8. Therapeutic Decisions in Patients with Idiopathic Membranous Nephropathy and Slowly Progressive Renal Insufficiency

	Treat	Do not treat
Pl. creatinine	< 5 mg/dL	> 5 mg/dL
Ultrasonography		
size	Normal	Reduced
Hyperechogenicity	+/++	+++
Renal biopsy		
Tubulointerstitial lesions	+/++	+++
Immune deposits	yes	No

In patients with renal insufficiency, a rapid decline of renal function may be caused by an acute renal vein thrombosis, by a superimposed extracapillary glomerulonephritis, by an interstitial nephritis caused by diuretics, nonsteroidal anti-inflammatory drugs or other drugs, or simply by dehydration. Thus, whenever a sudden increase in plasma creatinine occurs, efforts should be made to recognize and appropriately treat any possible superimposed complications. For patients with slowly progressive renal failure, the indication to treatment depends on the degree of renal dysfunction, the characteristics of kidney at ultrasonography, and the histologic findings at renal biopsy (Table 8). In fact, as patients with renal insufficiency are more exposed to the risk of side effects caused by glucocorticoids and cytotoxic drugs, treatment should be lim-

ited to those cases having actual chances of improving. Several therapeutic approaches have been used. The best results have been obtained with 1 – 2 years of cyclophosphamide associated with low-dose prednisone [27, 88] or with a 6-month course with methylprednisolone and chlorambucil [26, 119, 157].

Most investigators reported numerous and sometimes severe treatment side effects in patients with renal insufficiency. In order to reduce iatrogenic morbidity, the doses of the chosen agents should be reduced. If a schedule based on prolonged cyclophosphamide is chosen, the daily dose should not exceed 1.5 mg/kg/day. If the methylprednisolone-chlorambucil regimen is preferred, the pulses of methylprednisolone should be 0.5 g each, and the daily dosage of chlorambucil should be around 0.1 mg/kg.

Membranoproliferative Glomerulonephritis (MPGN)

MPGN or mesangiocapillary glomerulonephritis is a disease characterized by mesangial hypercellularity and proliferation with broadened capillary loops. Four types of primary MPGN have been described. The clinical expression of these types is similar, with nephritic or nephrotic syndrome, hypertension, and often hypocomplementemia. Some 50 – 60% of patients develop renal failure within 10 years from clinical onset. The treatment of idiopathic MPGN is still controversial.

Table 9. Disorders Associated with Membranoproliferative Glomerulonephritis

Autoimmune diseases	*Neoplasias*
Lupus nephritis	Lymphomas
Mixed cryoglobulinemia	Leukemia
Sjögren syndrome	Nephroblastoma
Sarcoidosis	Light-chain disease
Complement deficiencies	
Rheumatoid arthritis	*Miscellaneous*
	Sickle cell disease
Infectious diseases	Castleman's disease
Hepatitis B and C	Thrombotic microangiopathy
Visceral abscesses	
Shunt nephritis	
Quartan malaria	
Schistosomal infection	
Mycoplasma infection	
HIV	

Etiology

Idiopathic MPGN is a rare disease. The incidence of type I MPGN is decreasing in the developed world but remains relatively common in underdeveloped countries. The incidence of type II has remained unchanged. Children and adolescents are affected more frequently than adults, but there is not a substantial difference between sexes. It has been reported that the haplotype HLA-B8, DR3, SC01, GL02 is more frequent in patients with type I MPGN [197]. Some familial cases of type I and II have also been described. An association with partial lipodystrophy has been reported in some cases of type II MPGN. Among the 4 types of MPGN, type I is by far the most common, accounting for almost 80% of cases; type II represents 15 – 20% of cases; type III accounts for < 5% of cases; and type IV is very rare. A histologic pattern of MPGN may be observed in a number of autoimmune diseases, chronic infections, paraproteinemias, and neoplasia (Table 9). Lupus nephritis and mixed cryoglobulinemia are the most frequent causes of secondary MPGN.

Table 10. Main Histological Features in Membranoproliferative Glomerulitis

Common features: increase in mesangial cells and matrix, thickening of capillary walls.

	Location of deposits	Immunofluorescence pattern
Type I	Mesangial and subendothelial	IgG and C3 (C1q – C4) granular pattern
Type II	Mesangial and dense intramembranous	C3 (early complement components and IgG usually negative)
Type III – IV	Mesangial, subepithelial and subendothelial	C3 (early complement components and IgG usually negative)

Pathology

The 4 major types of MPGN have been identified with different findings, particularly on electron microscopy and immunofluorescence. Light microscopy is similar in each type with increase in mesangial cells and matrix and thickening of the capillary walls (Table 10).

Type I is also called subendothelial MPGN (Figure 9A). In type I the cellular increase is due to mesangial cells and infiltrating neutrophils. The thickening of the capillary wall is caused by the interposition of mesangial cells and matrix as well as neutrophils into the capillary wall. In many cases the silver staining shows a typical aspect of double contour ("tram-track"), caused by the staining of the true basement membrane and of a false membrane produced by mesangial interposition. The mesangial increase may accentuate the lobular form of the glomeruli leading to a lobular appearance. A nodular form has also been described. It is characterized by centrolobular sclerosis associated with dilation of glomerular capillaries. Although the changes are generally diffuse, focal and segmental abnormalities have been described in a few cases. Immunofluorescence shows granular deposits of C3 (Figure 9B) often associated with IgG and less frequently IgM. C1q and C4 may be present in about half of cases while properdin is always present. These components deposit along the internal side of the capillary walls and less prominently in the mesangium. In a few cases there is a lobular pattern. The deposits outline a lobulated tuft while there are no deposits in the mesangium. Electron microscopy confirms the lesions observed by light microscopy and shows typical electron-dense deposits mainly located in the subendothelial areas (Figure 9C).

Type II MPGN is also called dense deposits disease. The cardinal feature is a ribbon-like aspect of the basement membranes of glomeruli, tubules, peritubular capillaries, and Bowman's capsules (Figure 9D). Subepithelial humps similar to those seen in post-streptococcal glomerulonephritis may be seen in about one-third of cases. In some patients, however, the dense deposits may be missed at light microscopy. Immunofluorescence shows linear staining of C3 along the capillary walls and bright granules in the mesangial regions. Deposits of C1q, C4, properdin, and IgG are rare. The intramembranous deposits are negative for immunofluorescence. Electron microscopy clearly shows dense amor-

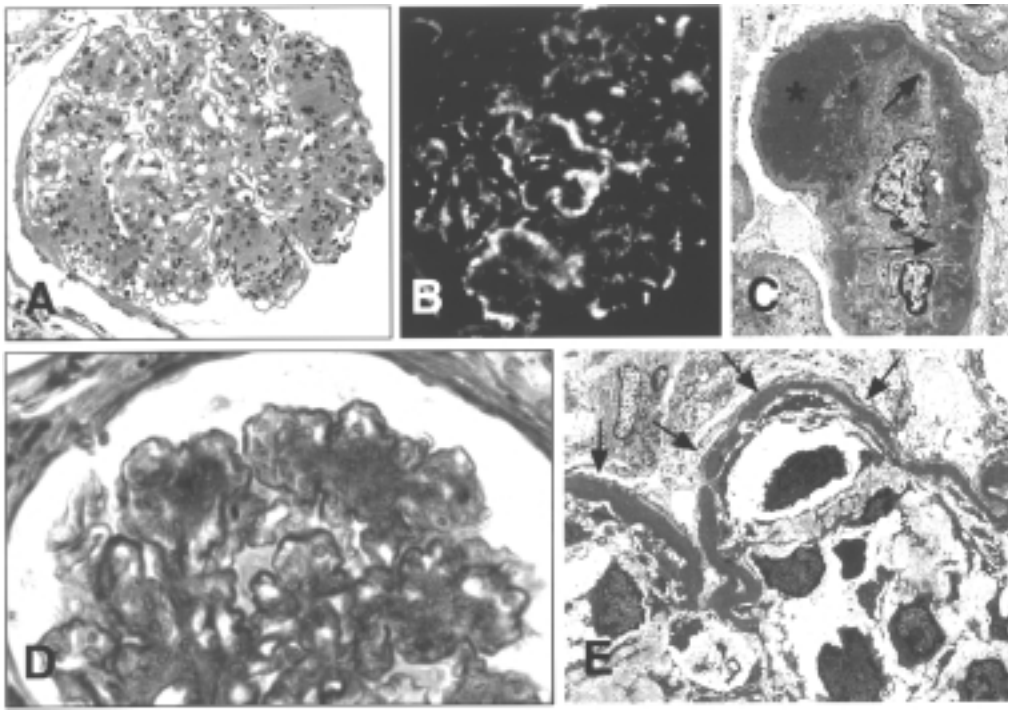

Figure 9. Membranoproliferative glomerulonephritis. A: type I MPGN with a typical lobular appearance (400x). B: typical coarse deposits of C3 along the glomerular capillary walls as seen by immunofluorescence (500x). C: large (*) and small (arrows) subendothelial electron-dense deposits as seen by electron microscopy (3,500x). D: type II MPGN with the typical ribbon-like appearance of the glomerular capillary loops (630x). E: type II MPGN with continuous electron-dense deposits in the context of the GBM as seen by electron microscopy (3,500x).

phous osmiophilic deposits in the basement membrane and in the mesangium (Figure 9E). The deposits are not continuous, and some capillary walls may appear normal.

Type III MPGN is also called mixed membranous and proliferative glomerulonephritis. The main lesions are similar to those observed in type I MPGN. However, the deposits are subepithelial rather than subendothelial, with interspersed projections of basement membrane. Immunofluorescence shows C3 but no or minimal deposition of immunoglobulins.

Type IV MPGN is characterized by a disruption of the basement membranes. Both subendothelial and subepithelial deposits may be seen. Whether types III and IV should actually be considered as separate entities or variants of type I is still controversial.

Pathogenesis

The findings of immunofluorescence and electron microscopy strongly support the hypothesis that type I MPGN is an immune-complex mediated disorder. The demonstration of circulating complexes and the frequent hypocomplementemia with a classic activation pathway are also consistent with this hypothesis. However, the nature of the anti-

gen(s) involved remains unknown. Also, it is unclear whether the complex deposition is actually the triggering event leading to endothelial damage, mesangial activation and expansion, and peripheral interposition of mesangial material.

The pathogenesis of type II MPGN is even less understood. A role for immune complexes can be excluded, because immunoglobulin deposits are usually absent and dense deposits do not show any of the typical characteristics of immune-complex deposits. The frequent recurrence of the disease after transplantation also excludes a primary defect of the GBM. Rather, it suggests that type II MPGN is a systemic disorder that causes the aggregation of basement membrane-like material on renal basement membranes. In patients with type II MPGN, a circulating IgG called C3 nephritic factor can activate the alternative pathway of complement. This has raised the hypothesis that complement abnormalities may play a primary pathogenetic role. However, despite much study the importance of serum C3 nephritic factor remains undefined, as there is no relationship between the serum levels of C3 nephritic factor or complement and the clinical course. It is possible that hypocomplementemia may represent the consequence rather than the cause of the capillary wall damage. The increased consumption of complement could be triggered by complement binding to the abnormal basement membranes. The presence of large deposits of lipids in the dense deposits suggests that this material is the result of a deposition of substances of extrarenal origin [130]. Immunological mechanisms, still poorly elucidated, might contribute in amplifying the damage to the membranes and in sustaining hypocomplementemia.

The pathogenesis of types III and IV MPGN is also unclear. The presence of discrete deposits on electron microscopy may suggest an immune-complex mechanism, although there are minimal deposits of immunoglobulins on immunofluorescence.

Clinical Presentation and Course

MPGN may present with the abrupt onset of hematuria, heavy proteinuria, and hypertension sometimes preceded by an infection of the upper respiratory tract. In other cases, the disease is discovered because of the insidious appearance of edema or because of the finding of microscopic hematuria and proteinuria on a routine urinalysis. At least half of patients have a nephrotic proteinuria, one-third have arterial hypertension, and 20% have renal insufficiency at presentation. Hematuria and cellular and granular casts are usually found on urinalysis. Hypocomplementemia is present in about 50% of cases with type I MPGN and in 70 – 80% of cases with type II MPGN. In type I, complement is activated by the classic pathway, possibly in response to the immune-complex formation. As a consequence, there is a moderate reduction of serum C3 associated with low levels of the early components of complement, such as C4. In type II, there is an activation of the alternate pathway, probably caused by C3 nephritic factor, which induces the cleavage of C3. In the serum of these patients, the early components of complement are normal but there is a profound reduction of C3.

Most patients have a progressive course. This is usually slow so that many patients show normal or subnormal renal function in the first few years after clinical onset. By 10 years, however, some 40% of patients with type I and 50% with type II MPGN [31, 64] have reached ESRD. In a few patients there is a rapidly progressive course. A superimposed crescentic glomerulonephritis may be seen at renal biopsy in some of these cases. Other

patients may show acute nephritic episodes triggered by infections of the upper respiratory tract, with rapid deterioration of renal function, which is sometimes reversible.

Several clinical and histologic features affect the likelihood of progressing to renal failure. A large amount of proteinuria, arterial hypertension, and increased serum creatinine at presentation are usually associated with a poor prognosis [37]. On the contrary, the pattern of complement levels and their fluctuations have little impact on prognosis. As for other glomerular diseases, severe tubulointerstitial lesions at initial renal biopsy represent the most important prognostic factor among morphologic features. Superimposed crescents may also affect the prognosis adversely.

Diagnosis

The acute nephritic presentation of MPGN may mimic poststreptococcal glomerulonephritis (PSGN), lupus nephritis, IgA nephritis, and cryoglobulinemic nephritis. A differential diagnosis may be made on certain clinical clues. Distinguishing between MPGN and PSGN may be difficult because both disorders can be triggered by upper respiratory infections. Usually in PSGN there is a longer free interval between infection and the first renal signs, the nephrotic syndrome and renal failure are more rare, and hypocomplementemia returns to normal within 6 – 8 weeks.

If present, hypocomplementemia can rule out a suspicion of IgA nephritis. Serum cryoglobulins may be found in idiopathic MPGN, but the presence of purpura, arthralgias, positivity for HCV, and high levels of RF allow the diagnosis of mixed cryoglobulinemia. The simultaneous decrease of serum C3 and C4 indicates an activation of complement through the classic pathway, which can be found in type I MPGN, while low levels of C3 with normal serum levels of C4 express an activation by the alternative pathway characteristic of type II MPGN.

In most cases, however, the diagnosis of MPGN can be made only by renal biopsy. The histologic material should be investigated by optic microscopy, immunofluorescence, and electron microscopy to obtain an adequate classification. An extensive search for underlying disease should be done to evaluate whether MPGN is primary or secondary. This should include anti-DNA antibodies, cryoglobulins, serum and urine protein immunoelectrophoresis, serology for hepatitis B and C, and in older patients investigations for malignancy. Blood cultures should be performed in case of bacterial infections [64].

Treatment

Several therapeutic approaches have been tried in MPGN. The Cincinnati group for many years has used long-term, high-dose, alternate-day prednisone therapy in children. Prednisone is begun at a dose of 2 – 2.5 mg/kg (maximum dose 80 mg) every other day and slowly reduced it to 1 – 1.5 mg/kg every other day after 2 years and 0.2 – 1.0 mg/kg every other day after 4 years. Of 71 pediatric patients, survival at 10 and 20 years from the time of diagnosis was 82% and 56%, respectively. Steroids were usually well tolerated [120]. The efficacy of this regimen has been evaluated by a randomized, placebo-controlled trial organized by the International Study of Kidney Diseases in Children [183b]. A total of 80 children with primary MPGN were randomly assigned to receive placebo or prednisone 40 mg/m^2 every other day for a mean duration of 41 months. Only 12% of placebo patients had stable renal function over the first 10 years vs. 61% of treated patients. However, the difference was not significant. Repeat re-

nal biopsy showed no important differences between treated and placebo patients. Unfortunately, the power to detect substantial differences was small. Many patients stopped either treatment or placebo because of renal failure or side effects. Differences in renal function were observed only after 90 months, but at that time only 18 patients were still under observation. Other uncontrolled studies suggested that the results with glucocorticoids in children may be improved if treatment is started early after diagnosis and if it is tailored to the severity of the disease. Ford et al. used IV methylprednisolone pulses followed by high-dose oral prednisone in patients with creatinine clearance < 50 mL/min, while low-dose alternate day prednisone was given in children with normal renal function [59]. The average creatinine clearance increased from 78 to 126 mL/min after a mean follow-up of 6.5 years and a mean duration of treatment of 38 months. Repeat renal biopsies showed reduced inflammatory activity in the majority of cases. The results with glucocorticoids in adults are limited. An analysis of the available trials concluded that glucocorticoids do not show any benefit in adults [49].

Immunosuppressive drugs, alone or in combination with anticoagulants or indomethacin, have been claimed to be of benefit in some noncontrolled studies. However, a controlled trial failed to show favorable effects of a combination of cyclophosphamide with oral anticoagulants and dipyridamole [32].

Donadio et al. found that a combination of aspirin (975 mg/day) and dipyridamole (225 mg/day) could significantly delay the deterioration of renal function over the first 4 years, although there was no modification of proteinuria or hematuria [46]. However, this advantage was lost in the long-term, the 10-year renal survival being 49% in treated patients and 41% in untreated patients [49].

In summary, the treatment of MPGN remains elusive. We do not recommend any specific treatment in patients with normal renal function and asymptomatic proteinuria. A trial with alternate-day glucocorticoids may be attempted in patients with severe nephrotic syndrome who usually have a bad prognosis. Oral prednisone may be given at a dose of 2 mg/kg every other day for 2 months with gradual decrease in the following period. If proteinuria does not vary within 4 – 6 months, the steroid should be stopped. If there is considerable reduction of proteinuria, the steroid may be continued at the minimal effective doses. In patients with rapidly progressive decline of renal function, a renal biopsy should be obtained. In the presence of an extracapillary glomerulonephritis or a superimposed interstitial nephritis, an aggressive treatment with high-dose IV methylprednisolone pulses, oral prednisone, and cyclophosphamide may obtain a recovery of renal function in several patients.

IgA Nephritis (IgAN)

IgAN, also called Berger disease [13], is the most common primary glomerulonephritis in the world. It may present with macroscopic hematuria or with microscopic hematuria and mild proteinuria. In other cases, the diagnosis is made on the occasion of the discovery of renal insufficiency. In spite of intensive investigation, the pathogenesis of IgAN is unclear, and there is not yet a definite treatment.

Etiology and Epidemiology

The cause of IgAN is still unknown. Even though in a number of cases it may be associ-

Table 11. Main Conditions Associated with Mesangial IgA Nephropathy

Primary
IgA nephropathy (Berger disease)
Systemic
Henoch-Schönlein purpura
Secondary
Chronic liver disease
Crohn's disease
Celiac disease
Dermatitis herpetiformis
Psoriasis
Episcleritis
Sjögren syndrome
IgA monoclonal gammopathy
Carcinomas (lung, pancreas, mucin-secreting)
Mycosis fungoides
Ankylosing spondylitis
Reiter's disease
Leprosy
Toxoplasmosis
HIV infection
Thin basement membrane disease

ated with other conditions (Table 11), IgAN is mainly a primary renal disease. In about 50% of patients, IgAN presents after upper respiratory infections, either viral or bacterial. Much less frequently IgAN may be preceded by other infections (e.g. intestinal or urinary) or by surgery, vaccination, or heavy physical efforts. In the remaining cases, precipitating factors cannot be found.

IgAN is ubiquitous, but its prevalence varies in different geographical areas. Of all patients with glomerulonephritis, IgAN constitutes approximately 8% in Canada, 12% in the United States, 20 – 27% in Southern Europe, 40% in Japan, and > 50% in Singapore [82]. At least in part, this distribution reflects different attitudes towards the screening of renal diseases and different indications for renal biopsy in patients with only mild urinary changes.

IgAN can affect any age, but the highest prevalence is in the second and third decades of life. Males are more frequently affected than females, with a ratio ranging from to 2:1 to 6:1 according to race. All races are affected, but IgAN is less common in blacks than in Caucasians and Asians.

Occasionally, IgAN can affect several members of the same family [91, 172]. In some families one member can suffer from IgAN and another from Henoch-Schönlein purpura (HSP) [121], which is an additional element in favor of the common pathogenesis of the 2 conditions. Immunogenetic studies have shown that IgAN may be associated with different HLA antigens, even in the same country [165].

Pathology

By light microscopy, a large spectrum of patterns can be found, from almost normal kidneys to diffuse proliferative or sclerosing forms. In most cases the typical pattern consists of focal and segmental proliferation of mesangial cells associated with expansion of the mesangial matrix (Figure 10A). Although small epithelial crescents are frequent, a true crescentic form is rare [1]. In a minority of cases focal-segmental glomerulosclerosis can be seen [69]. In patients with gross hematuria, acute tubular necrosis (ATN), thought to derive from tubulotoxic effects of erythrocyte components, can superimpose to the glomerular lesions [56, 98]. At a cellular level, increased numbers of macrophages can be observed in the glomeruli in the initial phases of the disease [132]. Increased numbers of monocyte/macrophages and T lymphocytes as well as myofibroblasts can be found in the

interstitium, especially in progressive cases [3, 68].

Immunohistology is mandatory for the diagnosis of IgAN. IgA is the dominant glomerular antigen, which is present in *all* glomeruli, including those that are normal by light microscopy. In typical cases, IgA deposits located in the mesangium appear as confluent masses with moderate-to-high intensity stain (Figure 10B). Extension to the paramesangial areas is frequent, but deposits in peripheral areas of the glomerular capillaries are less common. Other immunoglobulins such as IgG and IgM can also be found, the latter being observed especially in the areas of sclerosis. C3 is almost as frequent as IgA, with a similar pattern but lower intensity stain. C4 and C1q are negative, which is useful to distinguish IgAN from other proliferative nephritis [84]. Fibrinogen can also be observed in the mesangium.

The IgA deposited in the glomeruli belongs to IgA1 subclass [131] and contains mostly lambda light chain [105]. The finding of the J chain, which is a subunit of dimeric and polymeric immunoglobulins, suggests that the glomerular IgA is polymeric [126].

Electron microscopy shows mesangial cell proliferation, increased mesangial matrix, and electron-dense deposits in the mesangium. Electron-dense deposits can also be seen at the periphery of the glomerular capillaries, either in the subendothelial or subepithelial location, often in association with irregularities of the GBM. Some patients have abnormally thin basement membrane (< 264 nm) [14].

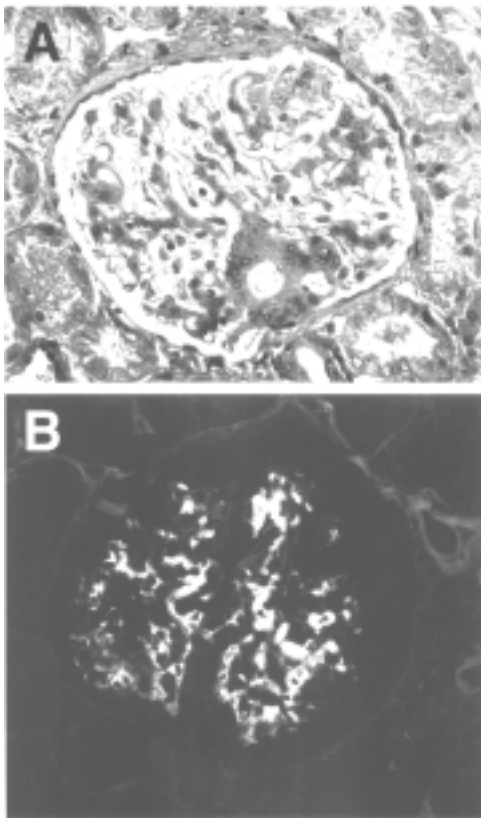

Figure 10. IgA nephropathy. A: mesangial enlargement and hypercellularity (400x). B: coarse and confluent mesangial deposits of IgA (immunofluorescence, 500x).

Pathogenesis

Many aspects of the pathogenesis of IgAN are still unclear. A number of factors that might be involved have been identified, but the data are often conflicting or uncertain. Several abnormalities have been described, not only in the kidneys, but also in the circulation and in other organs.

The findings of immunohistology and of electron microscopy support the hypothesis of an immune-complex disease. Furthermore, the frequent recurrence of the disease in transplanted kidneys and the finding of IgA1 in the glomeruli together with increased amounts of circulating IgA1 and IgA1-containing immune complexes suggest that the immune complexes derive from the circulation.

Although it is not yet established whether there is a reduced clearance of circulating

IgA1 and IgA1-containing immune complexes, it is accepted that there is a an overproduction of IgA1, which is likely to occur in the bone marrow [72]. It is also possible that some abnormalities in the IgA1 molecules may play a pathogenetic role. These might have an abnormal reactivity against specific exogenous or endogenous antigens. Moreover, the deposition of IgA in the mesangium might be favored by a more negative electric charge or by an abnormal *O*-linked glycosylation of the IgA1 [4]. On the other hand, the mesangial cells can have an active role in producing the glomerular and interstitial damage because they can synthesize a number of inflammatory cytokines in response to IgA deposits.

Several other factors might also be involved in the progression of the disease. For example, the angiotensin-converting enzyme (ACE) DD genotype is associated with renal function deterioration [71]. Also, the presence of myofibroblasts in the interstitium may stimulate progressive fibrosis [68], or the peritubular deposition of the complement complex C5b-9 may recruit and activate a number of inflammatory substances [2].

Clinical Presentation and Course

Some patients present with gross hematuria of variable duration. This presentation is more frequent in children than in adults and varies in different geographical areas, being more frequent in North American and European than in Asian-Pacific countries. In about 50% of cases, gross hematuria occurs 24 – 72 hours after a precipitating factor such as pharyngitis, gastroenteritis, urinary infection, fever or strenuous physical effort. Usually gross hematuria is asymptomatic and is not associated with renal function impairment, hypertension, or edema. In some cases, however, there is loin pain, malaise, or myalgia. Rarely, there is a rapid decline of renal function caused by either extracapillary proliferation [1] or by ATN induced by hematuria itself [98]. Recognizing these 2 conditions is important, because patients with the crescentic form require aggressive immunosuppressive treatment, while patients with ATN have a spontaneous recovery of renal function after clearing of gross hematuria.

Asymptomatic microscopic hematuria, either isolated or associated with proteinuria, is the other most frequent presentation in patients with IgAN. This is often found by chance during screening performed for any reason. Microscopic hematuria can be mild or severe and is mixed or dysmorphic by morphology. It is worth remembering that among glomerular diseases IgAN is the most frequent cause of isolated microscopic hematuria [185]. Proteinuria, when present, is mild in the initial phases, < 1 g/day. Exacerbations are possible during infections.

About 5 – 8% of patients present with the nephrotic syndrome. Usually this is associated with renal insufficiency, hypertension, and chronic damage at renal biopsy. However, in rare patients renal function and blood pressure are normal, and at renal biopsy only minor changes are found [182].

Approximately 15 – 20% of patients already have chronic renal insufficiency and hypertension at presentation. However, it is likely that the real prevalence of renal failure caused by IgAN is underestimated due to the reluctance to perform renal biopsies in hypertensive patients with renal insufficiency and hyperechoic kidneys.

IgAN is a chronic disease with variable course. Some patients may do well for many years, while others develop ESRD in short periods of time. The renal survival at 10 years after biopsy varies among different countries, being 67% in North America, 74% in Japan,

81% in Germany, 83% in the United Kingdom, 86% in Australia, and 94% in France [48]. Hypertension, elevated serum creatinine concentration, and increased protein excretion are considered the most important clinical risk factors for renal survival [48]. Among the biopsy finding, glomerular hyalinosis, interstitial fibrosis, and extension of IgA deposits to the peripheral capillary walls are the more reliable indicators of a poor outcome [38].

IgAN can recur after transplantation and, in contrast with a previous view, recurrence is now considered a cause of late graft loss in a considerable number of cases [96, 136].

Diagnosis

The diagnosis of IgAN is based on renal biopsy with the typical finding of dominant IgA at immunohistology. The absence of arthralgia, bloody diarrhea, abdominal pain, and purpura rules out HSP. However, one must be aware that in the latter disease the extrarenal symptoms may rarely develop even months after the renal disease. Recurrent bouts of gross hematuria associated with pharyngitis are rather typical of IgAN but can occasionally also occur in patients with thin basement membrane disease. Asymptomatic microscopic hematuria and proteinuria may suggest a diagnosis of IgAN, but most other glomerular diseases can have a similar presentation. Increased levels of serum IgA, which belong to IgA1 subclass, are observed in 30 – 50% of patients. Usually the serum levels of IgA, either normal or increased, are stable over time. Circulating immune complexes, IgA RF, or circulating levels of some C3 fragments may be found in some cases, but their measurement is more important for research than for clinical practice.

Treatment

The observation that IgAN can lead to renal failure has stimulated a large number of therapeutic trials based on many different approaches, including gluten-free diet, tonsillectomy, phenytoin to reduce serum IgA levels, danazol to dissolve immune complexes, sodium chromoglycate to reduce the mucosal permeability to antigens, antiplatelet/anticoagulant agents and others [108]. These treatments may obtain some reduction of hematuria, serum IgA levels, and/or circulating immune complexes, but there is no clear evidence that any of these treatments could interfere with the progression of the disease.

Uncontrolled trials conducted in small groups of patients showed that glucocorticoids given daily or on alternate days for > 1 year stabilized renal function and reduced proteinuria both in children [193] and in adults [99], with few major side effects. A retrospective study reported that long-term azathioprine at the dose of 2 mg/kg/day together with small amounts of prednisolone preserved renal function [67]. Severe side effects were observed in 3% of patients. Unfortunately, no controlled studies with either glucocorticoids or azathioprine are yet available.

Fish oil, which limits the production or action of eicosanoids and cytokines released during inflammation, has been given with contrasting results in recent controlled studies. Bennet et al. and Petterson et al. did not obtain positive results [11, 142]. However, in a recent, large, multicenter, controlled trial, 12 g/day of fish oil were given for 2 years to IgAN patients with a proteinuria of ≥ 1 g/day or with an increase in serum creatinine of ≥ 25% in the 6 months preceding entry into the study [47]. At an average follow-up of 3 years, renal function was significantly better in the 55 treated patients than in the 56 patients of the placebo group. Compliance to

fish oil was high and side effects minimal. It is possible that the difference with the negative results of the previous controlled trials is due to the higher dosage of fish oil and to the more prolonged treatment used by Donadio et al. It is worth remembering that with this approach the treatment cost is higher.

Several papers showed that ACE inhibitors have a protective effect on renal function and can frequently, but not always, reduce proteinuria [74, 117]. Fosinopril 20 mg once daily or placebo were randomly administered in 4-month sequences to adult patients with normal renal function and normal blood pressure but persistent proteinuria of > 1 g/24 hours [118]. At the end of the period with fosinopril, there was a significant decrease of mean blood pressure, proteinuria, and fractional clearance of albumin and IgG, but there was no effect on creatinine clearance. Recent studies have shown that the response to treatment with ACE inhibitors may be influenced by ACE polymorphism [201].

Considering the available knowledge, we feel that treatment should be limited to the cases at risk of renal failure, namely patients with proteinuria > 1 g/day and/or hypertension. ACE inhibitors are usually well tolerated and can represent the drug of choice in these patients. The results of ongoing controlled studies will be forthcoming. In the meantime, a 6- or 12-month trial with glucocorticoids and/or azathioprine may be attempted to reduce the risk of renal insufficiency. We usually give IV methylprednisolone pulses (0.5 – 1 g each) for 3 consecutive days followed by oral prednisone, 0.5 mg/kg every other day, for 2 months. This course is repeated 3 times for a cumulative treatment of 6 months. Clearly, careful monitoring of side effects is mandatory so that a treatment with still unproven efficacy can be stopped, if necessary.

For 2 subgroups of patients with IgAN, there is a sound indication for treatment. Patients with nephrotic syndrome and minimal change disease at biopsy usually respond well to glucocorticoids, in spite of frequent relapses that remain steroid-sensitive [182]. Patients with rapid decline of renal function due to extensive extracapillary proliferation have a high risk of a poor outcome in the short-term. In these cases, therapy must be aggressive and based on IV methylprednisolone pulses and cytotoxic agents [108]. However, one must be aware that even with this approach the evolution can be unfavorable.

Poststreptococcal Glomerulonephritis (PSGN)

PSGN is characterized by the abrupt onset of hematuria and proteinuria, often in association with edema, hypertension, and mild/moderate renal insufficiency. The disease usually develops several days after a pharyngeal or cutaneous infection caused by group A beta-hemolytic streptococci. The prognosis of PSGN is usually good in the short and long term, but some patients have excessive salt and water retention, and others may slowly progress to renal failure.

Etiology and Epidemiology

PSGN is associated with infections caused by a limited number of strains of group A beta-hemolytic streptococci. These nephritogenic streptococci may be identified by serotyping of a cell wall antigen called M protein. In most cases, streptococcal infection occurs in the upper respiratory tract or in the skin.

Less commonly, PSGN may be preceded by otitis or endocarditis, and may be triggered by other streptococci such as *Streptococcus viridans, Streptococcus mitis* or *Streptococcus mutans*. It must be remembered that in several cases acute GN is not caused by streptococci but is associated with a bacteremic state or with viral or parasitic diseases.

PSGN is the most common primary GN in developing countries, while in the Western world it has become an uncommon disease [166, 175], suggesting that it is favored by low socioeconomic status and poor hygienic conditions. This is also confirmed by the cases occurring in clusters and epidemics, which at times may be even cyclic.

All ages can be affected by PSGN. However, most patients are between 2 and 12 years old. PGN is twice as common in males as in females.

Pathology

In the early phases, there is diffuse mesangial and endothelial cell proliferation, associated with infiltration of the capillary lumens by polymorphonuclear leukocytes and mononucleated cells (Figure 11A). Extracapillary proliferation may involve a few glomeruli, while diffuse and extensive circumferential crescent formation is uncommon, although possible. Cells expressing interleukin-8 (IL-8) and transforming growth factor-beta (TGF-β) [125], as well as cells with increased expression of intercellular adhesion molecule-1 (ICAM-1) can be found both in glomeruli and interstitium [156]. IL-8 correlates with glomerular neutrophil infiltration, while TGF-β correlates with mesangial matrix expansion. The tubulointerstitial compartment is usually normal, but in the most proliferative forms acute cellular infiltrates can be seen.

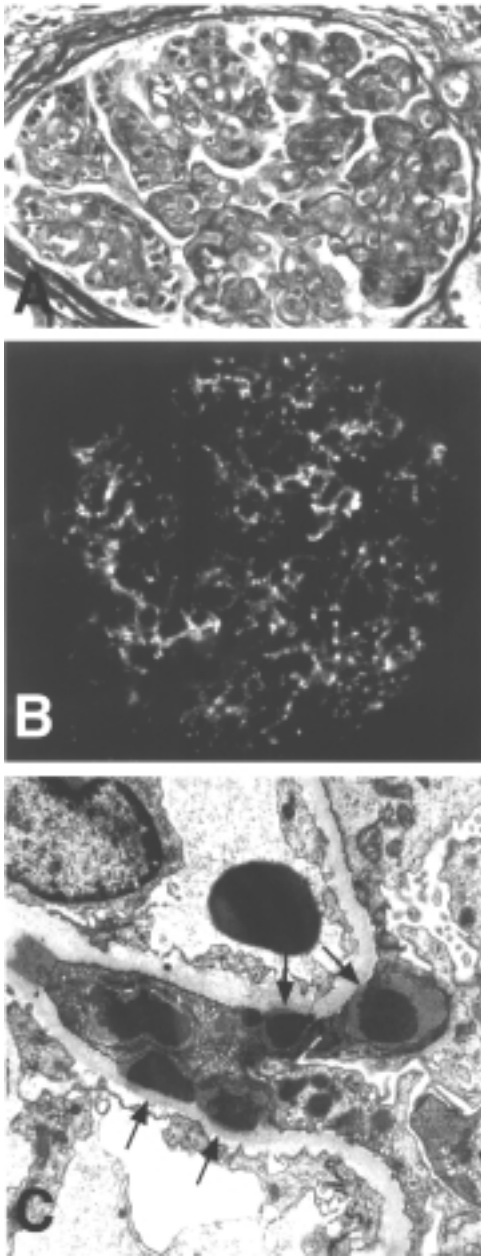

Figure 11. Poststreptococcal glomerulonephritis. A: typical endocapillary proliferation and lobular appearance (400x). B: typical "starry sky" pattern of C3 by immunofluorescence (500x). C: several "humps" (arrows) in subepithelial location (electron microscopy, 7,000x).

The typical immunohistologic pattern is characterized by abundant and well-defined granular deposits of C3 along the outer aspects of the glomerular capillary walls. These deposits confer the appearance known as "starry sky" (Figure 11B). IgG and IgM are present in 60 – 70% of cases. C1q and C4 are generally lacking. Fibrinogen is seen only in crescents.

By electron microscopy, coarse electron-dense subepithelial deposits are the distinguishing feature of PSGN. Due to their shape, the deposits are defined as humps (Figure 11C). However, intramembranous and subendothelial deposits, as well as mesangial deposits, can also be found.

In later phases of the disease, endocapillary proliferation and polymorphonuclear infiltration are less evident, and prominent mesangial deposits can be observed [179]. In other cases, subepithelial deposits are confluent, so that the humps are replaced by apparently elongated deposits, which confer a garland-like pattern at immunohistology [178]. In cases without complete resolution, the typical endocapillary disease can transform, over time, into a mesangiocapillary pattern.

Pathogenesis

Some data suggest that PSGN is an immune-complex disease, in which some components of nephritogenic streptococci are likely to act as antigens. Cell membrane antigens, streptococcal cationic proteinase, extracellular plasmin-binding protein, and endostreptosin or preabsorbing antigen have been proposed as possible triggers for the formation of the immune complexes. On the other hand, anti-immunoglobulin antibodies could be involved in the pathogenesis of PSGN, as demonstrated by the high titers of rheumatoid factor and by the presence of anti-immunoglobulin deposits in the renal biopsy of some patients [159]. An important role in conferring antigenicity to immunoglobulins can be played by another streptococcal component, the neuraminidase. This, in fact, can cause desialization and consequent modifications of autologous immunoglobulins. Moreover, neuraminidase can desialize leukocytes and favor their deposition in the glomeruli and interstitium [116].

Cellular immunity may also be involved in the pathogenesis of PSGN, as suggested by glomerular and interstitial infiltration of granulocytes, monocyte/macrophages, and T lymphocytes [156], increased IL-8 and TGF-β in the kidneys [125], and increased IL-6 and tumor necrosis factor-α (TNF-α) in the circulation [180].

Clinical Presentation and Course

The typical presentation of PSGN is an acute nephritic syndrome, i.e. oliguria, edema, hypertension, and gross hematuria 10 – 21 days after an upper respiratory tract or a skin infection. Nonspecific symptoms such as malaise, weakness, and nausea are frequent. Dull lumbar pain is present in 5 – 10% of patients. Although rare, an extrarenal disease is possible in patients with PSGN, as demonstrated by the association with scleritis or cerebral vasculitis. Decreased GFR and salt and water retention are the main causes of edema and hypertension, as documented by the finding of increased plasma volume and cardiac output in most patients with PSGN. In children, edema is usually generalized, while in adolescents and adults it is more frequently confined to face and legs. Hypertension is observed in > 80% of patients, but in only 50% of cases require treat-

ment. In rare cases, however, hypertension may be severe and cause hypertensive encephalopathy. Especially in elderly patients, oliguria and fluid retention can cause heart failure and death. Proteinuria is common in PSGN; however, nephrotic proteinuria is rare, especially in children.

In other patients, PSGN can be asymptomatic and cause only transient serum complement decrease and/or mild urinary abnormalities such as isolated microscopic hematuria [202], with or without hypertension. Prospective studies in families have shown that this presentation is more frequent than the overt clinical presentation described above [160]. Very rarely, PSGN is not associated with urinary abnormalities in spite of clinical symptoms and the presence of endocapillary glomerulonephritis at biopsy.

Usually the nephritic symptoms spontaneously reverse 4 – 7 days after the onset. However, urinary changes, mild renal function impairment, or hypertension can persist or develop months or years after the acute episode. These abnormalities can be found in approximately 20% of patients 1 – 2 decades after the onset. Usually children do better than adults. Patients with a nephrotic syndrome at presentation and those with extensive deposits in the peripheral capillary loops have a poorer prognosis [190]. Patients with crescentic disease may recover spontaneously. However, the prognosis is poor when crescents involve > 60% of glomeruli [127]. In some patients with subclinical presentation, persistent or intermittent microscopic hematuria may be seen at long-term follow-up [202].

Diagnosis

Several renal and systemic diseases can present with an acute nephritic syndrome: IgA nephropathy (IgAN), mesangiocapillary glomerulonephritis, anti-GBM disease, SLE, cryoglobulinemia, HSP, and systemic microscopic vasculitis. However, the finding of a preceding infection of the upper respiratory tract or of the skin, increased antistreptolysin (ASO) titers, decreased C3 levels, and the lack or rareness of extrarenal symptoms strongly suggest a diagnosis of PSGN.

In PSGN the infection typically precedes the nephritis by 10 – 21 days, while the episodes of gross hematuria in IgA nephropathy usually follow infections by hours or only a few days. In addition, while IgA nephropathy tends to cause repeated episodes of gross hematuria, PSGN is rarely recurrent.

Increased ASO titers are observed in 40 – 90% of patients with PSGN. This is much less common in other conditions. In PSGN, > 90% of patients have a decrease of C3 and normal C4 serum levels, indicating an activation of the alternative pathway of complement. In most cases C3 returns to normal in < 8 weeks, even though a prolonged decrease of C3 is possible [42]. The behavior of complement distinguishes PSGN from lupus nephritis in which both C3 and C4 are usually reduced in active phases. In type II cryoglobulinemic nephritis, usually only C4 is strongly decreased. In type II MPGN, similar to PSGN, C3 is low while C4 is normal. However, C3 remains persistently low because of the presence of C3 nephritic factor.

Usually there are no extrarenal symptoms in PSGN besides edema and hypertension. This differentiates PSGN from systemic diseases causing acute nephritic syndrome. However, it should be remembered that in occasional patients with PSGN extrarenal symptoms such as scleritis and cerebral vasculitis may be present, and that even a positive ANCA is possible [5].

PSGN can be easily diagnosed in epidemic or family cases, even when there are only

transient and minor clinical and urinary changes. However, for sporadic cases with only persistent urinary abnormalities, distinguising between IgA nephropathy, thin basement membrane disease, or other conditions can be difficult without renal biopsy.

Is renal biopsy indicated for patients with acute nephritic syndrome caused by PSGN? For patients presenting with a typical history and clinical picture, the diagnosis is easy and does not need a confirmatory biopsy. However, renal biopsy may be indicated for patients with atypical history or presentation, and especially for cases with severe or prolonged renal failure, which can be caused by crescentic disease.

Table 12. Classification of Crescentic Glomerulonephritis

Type I: Anti-GBM disease
(linear deposition of IgG along the BM)
Renal disease only
Renal and pulmonary disease (Goodpasture's disease)
Type II: Immune-complex associated disease
(granular immunodeposits in the glomeruli)
Primary glomerular diseases
Secondary glomerular diseases
Type III: Pauci-immune disease
(no or scanty immunodeposits in the glomeruli)
ANCA-associated disease
Idiopathic crescentic glomerulonephritis

Treatment

Patients with oliguria, edema, and hypertension need close observation and care. Restriction of sodium and fluid intake are mandatory. Furosemide or other loop diuretics are frequently needed. In many patients, hypertension reverses with the correction of fluid overload and edema. However, in some patients antihypertensive agents are needed. Antistreptococcal antibiotics such as penicillin, cephalosporins, erythromycin or derivatives should be given to patients with positive throat or skin cultures.

Glucocorticoids or immunosuppressive agents are not indicated in PSGN because of spontaneous resolution of the disease in most cases. However, in patients with extensive crescent formation and slow resolution of symptoms, a short course of high-dose glucocorticoids may be considered.

Crescentic Glomerulonephritis (CGN)

CGN encompasses several diseases with different etiologies and pathogenetic mechanisms that have in common a rapid deterioration of renal function and the presence of crescents in > 50% of glomeruli at renal biopsy. The natural course is usually poor. However, early and vigorous treatment can significantly improve the prognosis of these disorders.

According to the immunopathology findings, the various forms of CGN can be grouped into 3 categories (Table 12).

Type I CGN

The hallmarks of type I CGN, or anti-GBM disease (anti-GBM disease), are the presence of anti-GBM autoantibodies in the circulation

and their linear fixation along GBMs. When these antibodies also fix to the basement membrane of pulmonary alveoli, a pulmonary-renal disorder ensues, which is known as Goodpasture's disease.

Anti-GBM disease accounts for approximately 10% of all CGN [86].

Etiology and Epidemiology

Genetic factors play a role in the etiology of the disease, as demonstrated by several familial cases [176]. Immunogenetic studies have shown a linkage with HLA-DR2 and -DR4 antigens, as well as a negative association with HLA-DR7 and -DR1 [28].

Environmental factors are also important. The disease can appear or recur after infections or exposure to organic solvents, hydrocarbons, or cigarette smoking [94, 200]. The clustering of cases in different geographic areas further supports the role of environmental factors.

Anti-GBM disease can be associated with a number of other disorders including lymphoma, crescentic membranous nephropathy [104], and ANCA-positive vasculitis [19].

Anti-GBM disease is rare, but occurs more commonly in Caucasians than other races. Males are more frequently affected than females. All ages can be involved, the peaks being in the third, sixth, and seventh decades of life. Children are more rarely and less severely affected than adults [63].

Pathology

In the early phases, renal biopsy may show focal or diffuse mesangial proliferative GN. In the most typical cases, there are extensive crescents and necrosis of the glomerular tufts (Figure 12). Crescent formation is initiated by

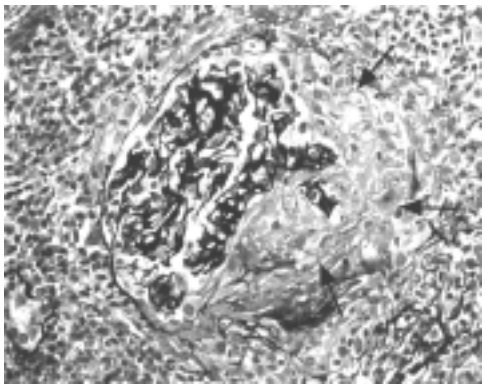

Figure 12. Extracapillary glomerulonephritis with a large fibro-cellular crescent (arrows) occupying the Bowmans space (400x).

holes in the GBM, caused by the antibody attack [17]. Leakage of intravascular content into Bowman's space follows, with consequent fibrin generation and cell recruitment. Several types of cells are found in crescents including visceral and epithelial cells, monocytes, and T lymphocytes [20]. Collagen is then produced, either by the cells forming the crescents of by fibroblasts invading the Bowman's space from ruptured Bowman's capsules [181]. This is followed by fibrotic transformation of the crescents and permanent glomerular damage.

Interstitial inflammation is frequent. Its severity is correlated with the extent of antibody fixation to the tubular basement membranes of the distal tubules. Vasculitis of the kidney is also possible [199].

By immunohistology, linear staining of IgG along the basement membrane of glomeruli (Figure 13), distal convoluted tubules, and collecting ducts is a typical and constant feature of anti-GBM disease. In 60 – 70% of cases, linear deposits of C3 can also be seen.

By electron microscopy, irregularities and breaks of the GBM are the most typical findings.

In the lungs there is often intra-alveolar hemorrhage associated with thickening,

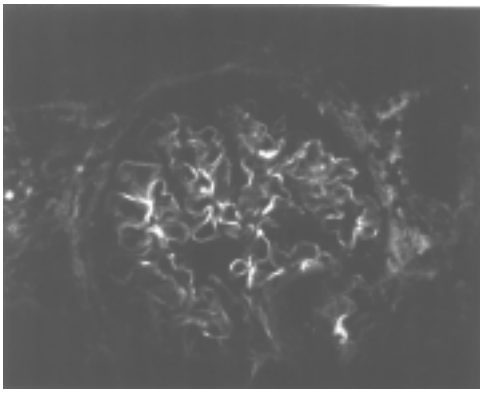

Figure 13. Anti-glomerular basement membrane disease. Linear IgG along the GBM (immunofluorescence, 500x).

edema, and fibrosis of the alveolar membrane. In addition, there are siderin-containing macrophages, deposits of fibrin, and leukocyte infiltration. By immunohistology, there is a typical linear fixation of IgG along the alveolar basement membranes with a patchy distribution.

Pathogenesis

Anti-GBM disease is due to the production of autoantibodies directed against the so-called Goodpasture antigen. The autoantibodies belong to IgG1 and IgG4 subclasses of IgG. However, autoantibodies of IgA class may rarely be found in both the circulation and in tissues [163]. Goodpasture antigen is located on the 230 amino-acid, carboxyterminal, noncollagenous domain of the α-3 chain of type IV collagen, which is one of the main components of the basement membrane [189].

As in other antibody-mediated conditions, there is activation of cell-mediated immunity. T-lymphocytes of patients with anti-GBM disease proliferate when exposed to purified or recombinant Goodpasture antigen [43], and there are a number of T-lymphocytes among the cells infiltrating the kidney [135].

Clinical Presentation and Course

Two-thirds of patients with anti-GBM disease have both renal and lung disease at presentation, while one-third apparently have only renal disease. Lung disease is more common in younger patients and in men. Renal disease is more common in older patients and in women [188].

Malaise, mild arthralgia, and mild weight loss can precede the renal and lung manifestations. These symptoms can be more severe in patients with associated vasculitis and positivity for ANCA. However, some ANCA-positive patients do not have systemic symptoms.

In sporadic cases the renal disease may be mild, causing only minor urinary abnormalities such as isolated microscopic hematuria. Occasionally there may be a history suggesting a subacute or chronic GN. However, in most cases the renal disease is severe and rapidly progressive, so that many patients present with renal failure associated with a nephritic urinary sediment and/or oliguria. Gross hematuria is also common. Proteinuria is constant but is rarely in the nephrotic range. Hypertension is uncommon.

Hemoptysis, trivial or severe, is the most typical sign of lung disease. However, there may be patients without hemoptysis who have life-threatening alveolar bleeding. This can cause microcytic anemia, which is frequent in patients with anti-GBM disease.

If treated promptly and vigorously, anti-GBM disease can subside without recurrences, but in some patients the disease may lead to irreversible renal lesions. Usually lung disease resolves without persistent damage. In other cases, the course may be marked by

remission and recurrences of either renal or lung disease or both, months to years after the first manifestation. Recurrences may be favored by infections or exposure to organic solvents. The reappearance of circulating anti-GBM antibodies without clinical symptoms is also possible [76].

After renal transplantation, anti-GBM antibodies can deposit on transplanted kidneys but frequently without clinical consequences. To reduce the probability of recurrence, transplantation should be postponed until 6 months or more after the disappearance of circulating antibodies. Rarely, an anti-GBM crescentic GN without lung involvement may develop in renal transplant recipients with Alport syndrome [137]. Patients with Alport's syndrome are unable to synthesize α-5 chains of type IV collagen, due to a mutation in the gene COL4A5 on the X chromosome. After renal transplantation, the α chains are recognized as foreign antigen by the recipient immune system, with consequent production of anti-GBM antibodies and development of renal disease [92].

Diagnosis

The presence of a rapidly progressive renal disease with active urinary sediment, hemoptysis, and sideropenic anemia should always raise the suspicion of an anti-GBM disease. Circulating IgG antibodies are the clue for differential diagnosis with other diseases that an also cause a similar clinical picture, such as SLE, HSP, cryoglobulinemia, and pauciimmune systemic vasculitis. Radioimmunoassays or enzyme-linked immunosorbent assays (ELISA) are sensitive and specific methods to detect and titer these antibodies. While antibody titers correlate with the severity of renal damage [75], no correlation has been found with the severity of lung disease.

ANCA can be positive in a number of patients with anti-GBM disease [19]. In most cases, positivity is perinuclear by indirect immunofluorescence (p-ANCA). However, cytoplasmic positivity (c-ANCA) is also possible. As in systemic vasculitis, ANCA titers can be used to monitor the activity of the disease [85]. Because of their possible association, ANCA and anti-GBM antibodies should always be sought in either disorder.

Chest X-rays show symmetrical or asymmetrical lesions of variable size, which can clear 48 hours after bleeding. Increase of carbon monoxide uptake by the lungs, caused by the presence of free hemoglobin in the alveoli, is typical of Goodpasture's disease [53]. The patchy distribution of linear IgG in the pulmonary alveoli makes the diagnosis of anti-GBM disease by transbronchial biopsy unreliable [89].

Treatment

In the last 3 decades, patient and renal survival has dramatically improved. The 1-year mortality rate decreased from 96% in 1964 [12] to 7% to 11% in the 1990s [75, 122], and renal survival increased from 4% to about 40%. Improvement of supportive therapies, such as dialysis and artificial ventilation, and a more refined specific treatment have both contributed to the improved prognosis.

The aim of therapy should be to remove circulating antibodies, prevent the formation of new antibodies, and reduce the inflammatory consequences of antibody deposition on basement membranes. Today, the specific treatment of anti-GBM disease is based on plasma exchange associated with immunosuppressive agents [188]. A suggested schedule for patients with lung and renal disease includes oral prednisolone 1 mg/kg/day, oral cyclophosphamide 3 mg/kg/day, and daily

plasma exchange for 14 days or until the circulating antibodies are suppressed. High-dose IV methylprednisolone pulses can also be used at the beginning of therapy in patients with rapidly a progressive course, but when given alone they are of little efficacy. With such an approach, pulmonary hemorrhage is generally arrested in 24 – 48 hours, and substantial improvement of renal function is usually achieved. However, for patients who present with oliguria and/or a serum creatinine of > 6.8 mg/dL (600 μM) and/or a high percentage of crescents at biopsy, renal survival is still poor despite aggressive therapy [75, 89]. The duration of treatment should be decided on the basis of the clinical data and of circulating antibody titer. After remission, prednisone can be progressively reduced, and therapy may be withdrawn in about 3 months [188]. If severe renal or pulmonary disease recurs, the full treatment should be reinstituted. However, the risk of potentially life-threatening infections favored by immunosuppression must always be kept in mind.

Type II CGN

Type II CGN accounts for approximately 30% of cases of CGN [86]. This type includes a heterogeneous group of renal diseases characterized by glomerular deposits of immunoglobulins and/or complement at immunohistology (Table 13).

Etiology

The majority of the disorders causing type II CGN belong to primary or secondary proliferative glomerular diseases. However, non-proliferative forms, such as membranous nephropathy (MN) [104] and amyloidosis [128], can sometimes be complicated by severe extracapillary proliferation.

Table 13. Main Immune Complex Glomerular Diseases that can be Associated with Extensive Extracapillary Proliferation

Primary Glomerular Diseases
Acute post infectious glomerulonephritis
IgA nephropathy
Mesangiocapillary glomerulonephritis
Membranous nephropathy
Secondary Glomerular Diseases
Lupus nephritis (especially class IV)
Henoch-Schönlein purpura nephritis
Cryoglobulinemia
Amyloidosis
Light chain deposition disease
Glomerular diseases associated with malignancies

Pathology

As a general rule, type II CGN shows fewer necrotizing glomerular lesions on light microscopy than type I and type III CGN. On the other hand, immune complex-mediated CGN has more prominent intracapillary proliferation, mesangial expansion, and thickening of the glomerular capillaries.

Clinical Presentation and Course

The clinical presentation is characterized by rapidly progressive renal failure associated with active urinary sediment, possible oliguria or gross hematuria, and hypertension. In secondary renal diseases, the development of a crescentic form can be associated with an exacerbation of the extrarenal symptoms and/or an abrupt increase of serological markers.

The outcome of untreated forms is usually poor. As in type III CGN, reversal of renal failure and other symptoms can be achieved by early treatment based on high-dose corticosteroids and immunosuppressive drugs (see type III CGN).

More information about the forms belonging to this group is found in Volume 1 Chapter I.8.

Type III CGN

Type III CGN accounts for about 60% of all cases of CGN [86], and includes renal diseases with scanty or absent immune deposits at immunohistology or on electron microscopy.

Etiology

Some patients only have renal symptoms while others have features suggesting a systemic disorder. More than 80% of patients with type III CGN are ANCA-positive, especially p-ANCA [153]. In addition, most patients with type III CGN, even those without extrarenal symptoms, have small vessel vasculitis, such as microscopic polyarteritis, Wegener's granulomatosis, Churg-Strauss syndrome, or other more rare forms.

It is not clear whether the minority of patients without any clinical or laboratory signs of vasculitis actually have an idiopathic CGN or are affected by a vasculitis with negative serological markers and only renal disease [65].

Pathology

By light microscopy, there is extracapillary glomerulonephritis often associated with segmental fibrinoid necrosis of the glomerular tuft. At immunohistology there are no immune deposits. In some cases, scanty granules of immunoglobulin or complement can be seen. No specific findings are observed by electron microscopy.

Clinical Presentation and Course

At presentation, most patients have constitutional symptoms that include fever, weight loss, and malaise. Renal function is variably impaired, with or without reduced urine output. Urinalysis indicates nephritic urinary sediment and variable proteinuria. Normochromic anemia, leukocytosis, and thrombocytosis are common.

Treatment

Irrespective of the presence of systemic symptoms and ANCA antibodies, type III CGN deserves early treatment.

The treatment of type III and type II CGN is based on the association of high-dose IV methylprednisolone pulses with immunosuppressive agents, while the role of plasma exchange is less established.

Even though no controlled therapeutic trials are available, methylprednisolone pulses represent the mainstay therapy for type III CGN. About 75% of patients with type III and almost 90% of patients with type II CGN can obtain improvement of renal function with IV methylprednisolone pulses [16]. The response is usually rapid, and failure to respond within 2 weeks can be considered as a sign of advanced nonresponsive disease [65]. Methylprednisolone pulses are usually well tolerated, even though transient side effects such as tremor, flushing, dysgeusia, epigastric pain, seizures, hyperglycemia, renal function

impairment, cardiac arrhythmias, or hypercoagulability can occur [143]. Usually a course includes 3 – 5 IV pulses of methylprednisolone of 0.5 – 1 g each given daily or every other day. Repeated courses can be given to relapsing patients. After an IV pulse course, oral prednisone is started at a dose of 0.5 – 1 mg/kg/day. Tapering of the dosage is also empirical, being modulated on the evaluation of the general clinical conditions and the severity of the disease.

Glucocorticoids are usually combined with cyclophosphamide, which proved to be efficacious in patients with vasculitis [78]. The drug is preferably given orally at a dosage of 2 – 3 mg/kg/day, which should be halved in patients with renal failure to reduce side effects. In CGN the IV route (500 – 1000 mg/m^2 every month or every 3 months) is usually limited to patients who do not tolerate oral administration. As for oral prednisone, the duration of treatment is based on the evaluation of the clinical situation. Some physicians prefer to switch from cyclophosphamide to azathioprine after 3 months to reduce the risk of myelotoxicity, hemorrhagic cystitis, and neoplasia. Others prefer to give cyclophosphamide for more prolonged periods of time to maximize the chances of renal function recovery [65].

While plasma exchange has a key role in the treatment of anti-GBM disease, its role in type II and type III CGN is still debated. In 2 randomized trials comparing plasma exchange plus immunosuppressive agents vs. immunosuppressive agents alone in non-anti-GBM disease patients, no difference could be seen between the 2 treatments [35, 66]. A third controlled study has reported that the addition of plasma exchange to immunosuppressive agents can more frequently obtain a partial recovery of renal function in dialysis-dependent patients [154]. However, even in the latter trial the beneficial effects of plasma exchange were short lived, because most patients in whom renal function improved had to start dialysis or died at further follow-up. Thus, it seems reasonable to limit plasma exchange to severely ill patients who have not responded to more conventional treatment.

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