Review Article

Medical Progress

The Nephrotic Syndrome

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THE nephrotic syndrome is defined by a urinary protein level exceeding 3.5 g per 1.73 m^2 of body-surface area per day. At the turn of the century, clinicians distinguished a nephritic syndrome of inflammatory origin and a nephrotic syndrome of presumed degenerative origin. Today these concepts are outmoded, but the term "nephrotic syndrome" is clinically useful and has persisted, because heavy proteinuria, irrespective of its origin, is associated with a spectrum of clinically important sequelae, particularly sodium retention, hyperlipoproteinemia, and thromboembolic and infectious complications. The definition given above is arbitrary, however, and special significance should not be given to the criteria used to distinguish between nephrotic and non-nephrotic proteinuria.

CAUSES OF NEPHROTIC PROTEINURIA

Diabetic nephropathy is the most common cause of nephrotic proteinuria.[1] Several primary glomerular diseases (Table 1) account for the great majority of cases of the nephrotic syndrome in persons who do not have diabetes. The relative frequency of glomerular diseases accounting for the nephrotic syndrome varies with age.

Idiopathic nephrotic syndrome frequently responds to treatment with corticosteroids and can present either as minimal-change glomerulopathy, when the glomeruli appear normal on light microscopy but exhibit fusion of the foot processes of the epithelial cells (podocytes) on electron microscopy (Fig. 1B and 1C), or as focal segmental glomerulosclerosis (Fig. 2A). It is possible that the two forms represent the extremes of a spectrum in which focal segmental glomerulosclerosis is the more severe and prognostically more sinister variant that frequently progresses to renal failure.[3] This issue is controversial, however.

In adults the most common cause of the nephrotic syndrome is membranous glomerulonephritis (Fig. 2B). Membranoproliferative glomerulonephritis is rare (Fig. 2C), and IgA glomerulonephritis, the most common glomerular disease (Fig. 2D), only occasionally causes a nephrotic syndrome (Table 1). Almost every type of glomerulopathy, but particularly membranous glomerulonephritis, can be linked to neoplasia (carcinoma, sarcoma, lymphoma, or leukemia). Physicians should consider this possibility in older patients. It is also imperative to perform urinary immunoelectrophoresis routinely to rule out myeloma and renal primary (AL) amyloidosis.

The nephrotic syndrome may also be caused by a wide range of relatively rare diseases (Table 2). Human immunodeficiency virus nephropathy typically causes nephrotic proteinuria and renal insufficiency, which are occasionally the first clinical manifestations of the acquired immunodeficiency syndrome.[5] Preeclampsia is often associated with nephrotic-range proteinuria, which is in turn associated with increased fetal loss[6] but not necessarily with a more adverse maternal prognosis.

PATHOPHYSIOLOGY OF GLOMERULAR LEAKAGE OF PROTEIN

Passage of plasma proteins larger than 70 kd across the glomerular basement membrane is believed to be normally restricted by a charge-selective barrier and a size-selective barrier.[7,8] The former is thought to be mainly the result of polyanionic glycosaminoglycans in the glomerular basement membrane, which restrict the passage of small polyanionic plasma proteins (70 to 150 kd), primarily albumin. The size-selective barrier, which is thought to consist of pores in the glomerular-basement-membrane meshwork, restricts the passage of larger plasma proteins (more than 150 kd). Investigations have revealed that the defect in minimal-change glomerulopathy results mainly from a loss of charge selectivity,[9] whereas the defect in membranous glomerulonephritis results mainly from a loss of size selectivity.[10]

What causes the leakage of glomerular protein? When patients with focal segmental glomerulosclerosis relapse after renal transplantation, interventions that adsorb immunoglobulins, such as protein A–affinity[11] or immunoadsorption columns,[12] lead to considerable reduction of proteinuria. A plasma factor, presumably produced by lymphocytes,[13] increases albumin excretion in perfused rat kidneys.[11] It

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TABLE 1. RELATIVE FREQUENCY OF PRIMARY GLOMERULAR DISEASES UNDERLYING THE NEPHROTIC SYNDROME IN CHILDREN AND ADULTS.*

DISEASE	CHILDREN	ADULTS ≤60 YR	ADULTS >60 YR
		percent	
Minimal-change glomerulopathy	76	20	20
Focal segmental glomerulosclerosis	8	15	2
Membranous glomerulonephritis	7	40	39
Membranoproliferative glomerulonephritis	4	7	0
Other diseases	5	18	39

*Data are from Lewis.[2]

raises the permeability of isolated glomeruli to albumin and is associated with the recurrence of disease after renal transplantation.[14]

CLINICAL SEQUELAE OF NEPHROTIC-RANGE PROTEINURIA

Sodium Retention and Edema Formation

In the past it was thought that reduced plasma oncotic pressure caused hypovolemia and sodium retention. Increased tubular sodium reabsorption was interpreted as a homeostatic response to hypovolemia, mediated by the activation of volume-control and pressor systems, such as the renin–angiotensin–aldosterone, vasopressin, and sympathetic nervous systems. Several observations argue against a primary role of "circulatory underfilling" — that is, hypovolemia. First, although the measurement of plasma volume is beset by methodologic problems, adults with the nephrotic syndrome are often found to have normal or even increased plasma volume,[15] but children with the nephrotic syndrome often have low volume.[16,17] Higher blood-pressure values during the phase of nephrotic proteinuria are also more consistent with hypervolemia.[18] Second, levels of atrial natriuretic peptide are often elevated, suggesting "circulatory overfilling."[19] Third, pharmacologic blockade of the renin–angiotensin–aldosterone system may not cause natriuresis, as one would expect if sodium retention were the result of a compensatory activation of this system.[20] Fourth, edema fails to develop in unusual cases in which urinary protein loss occurs in the absence of intrinsic renal disease through a lymph fistula draining into the renal pelvis.[21] During the initial stages of relapse,[17] sodium retention is seen before massive proteinuria and hypoalbuminemia have developed. Conversely, during the initial phase of remission, natriuresis sets in before urinary protein loss has been reversed.[22] These observations are more in line with primary retention of sodium by the kidney.

The foregoing arguments against the role of hypoalbuminemia and hypovolemia in nephrotic edema are weakened by several other considerations. The nature of homeostasis is such that blood volume may be expected to rise to normal when a patient with hypoalbuminemia approaches salt balance (that is, when the output of salt rises to equal the intake). Conversely, at the very onset of heavy proteinuria leading to edema, a contraction in blood volume may delay the recognition of a decrease in the plasma albumin level. Because the level of other proteins in plasma may vary in patients with the nephrotic syndrome, serum albumin does not always mirror the oncotic pressure of the plasma. Finally, it should be noted that glomerular inflammation can clearly produce primary salt retention and edema without a decrease in serum albumin but with an increase in blood volume, and that in many but not all patients with heavy proteinuria and edema, this so-called nephritic mechanism is likely to be operating. Primary salt retention has been well documented in the rat model of unilateral nephrotic syndrome, in which only one kidney is exposed to puromycin, an agent causing proteinuria. In such animals, sodium reabsorption is increased in the nephrotic kidney. Micropuncture studies show unchanged delivery of filtrate to the distal nephron, pointing to increased sodium reabsorption at more distal sites.[23] Clinical studies show decreased proximal tubular sodium reabsorption, also implying that increased overall sodium reabsorption must be the result of increased distal reabsorption.[24]

Why does the distal nephron reabsorb more sodium? An inappropriately low natriuretic response to atrial natriuretic peptide was shown in clinical[25] and experimental[26] studies. In the model of unilateral proteinuria, impaired natriuretic response to atrial natriuretic peptide was noted in the proteinuric kidney but not in the contralateral kidney, despite unaltered binding of atrial natriuretic peptide to its receptor.[26] Abnormal sodium excretion was ameliorated by renal denervation, suggesting a role of renal nerves. A further abnormality is the hyporesponsiveness to atrial natriuretic peptide caused by a postreceptor defect,[27] as illustrated by subnormal urinary levels of cyclic guanosine monophosphate after the administration of atrial natriuretic peptide.[28] Inhibition of the breakdown of cyclic guanosine monophosphate by specific phosphodiesterase inhibitors reversed the abnormality.[27]

Patients with the nephrotic syndrome may have episodes of hypovolemia, particularly after treatment with diuretics. These episodes result in orthostatic hypotension, tachycardia, peripheral vasoconstriction, abdominal pain and diarrhea, oliguria, and oc-

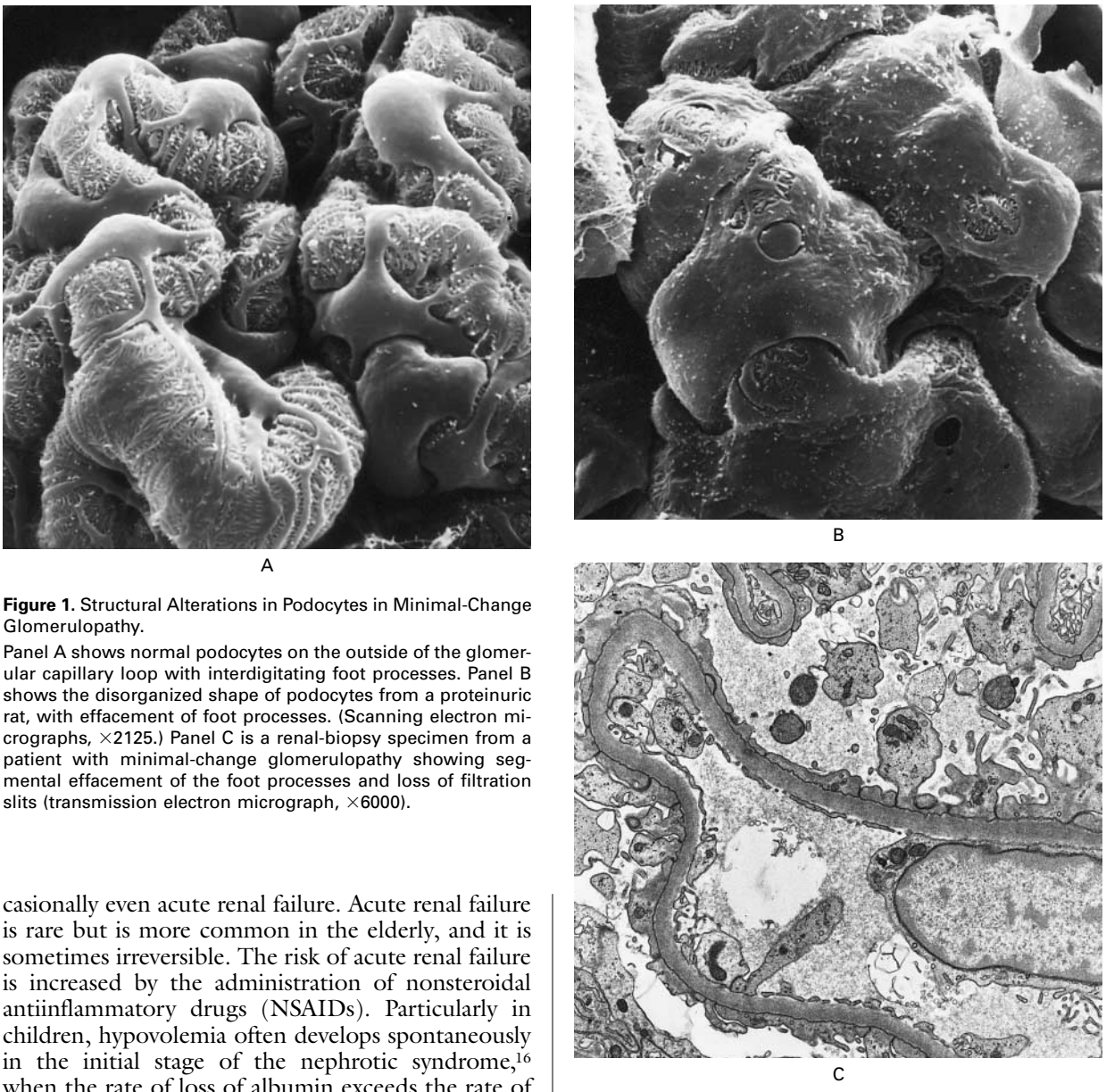

Figure 1. Structural Alterations in Podocytes in Minimal-Change Glomerulopathy.

Panel A shows normal podocytes on the outside of the glomerular capillary loop with interdigitating foot processes. Panel B shows the disorganized shape of podocytes from a proteinuric rat, with effacement of foot processes. (Scanning electron micrographs, ×2125.) Panel C is a renal-biopsy specimen from a patient with minimal-change glomerulopathy showing segmental effacement of the foot processes and loss of filtration slits (transmission electron micrograph, ×6000).

casionally even acute renal failure. Acute renal failure is rare but is more common in the elderly, and it is sometimes irreversible. The risk of acute renal failure is increased by the administration of nonsteroidal antiinflammatory drugs (NSAIDs). Particularly in children, hypovolemia often develops spontaneously in the initial stage of the nephrotic syndrome,[16] when the rate of loss of albumin exceeds the rate of compensatory mobilization of albumin from extravascular compartments, its synthesis by the liver, or both. Infusion of albumin reverses the clinical signs of hypovolemia,[29] but it may cause dangerous increases in blood volume if continued during the normovolemic phase.[30,31]

Treatment of Patients with Nephrotic Edema

Generalized edema implies that the sodium content of the body is increased. Edema can be reversed only if a negative sodium balance is induced.[32] During the initial phase of edema formation, sodium excretion may be as low as 10 mmol per day.[17] Dietary sodium intake cannot be reduced to such low levels, but the induction of a negative sodium balance by diuretics is facilitated if sodium intake is lowered; a value that can reasonably be achieved is 50 mmol of sodium (approximately 3 g of sodium chloride) per day. Because of the avidity of the kidney for sodium in patients with the nephrotic syndrome, potent loop diuretics, such as furosemide, are indispensable. They act in the ascending thick loop of Henle. At the same time, it is advisable to reduce sodium reabsorption in the distal nephron, where sodium reabsorption is increased in patients with the nephrotic syndrome. This can be achieved by combining loop diuretics with thiazides[33] and potassium-sparing diuretics.

Because of its short elimination half-life, furosemide must be administered in two or three doses per

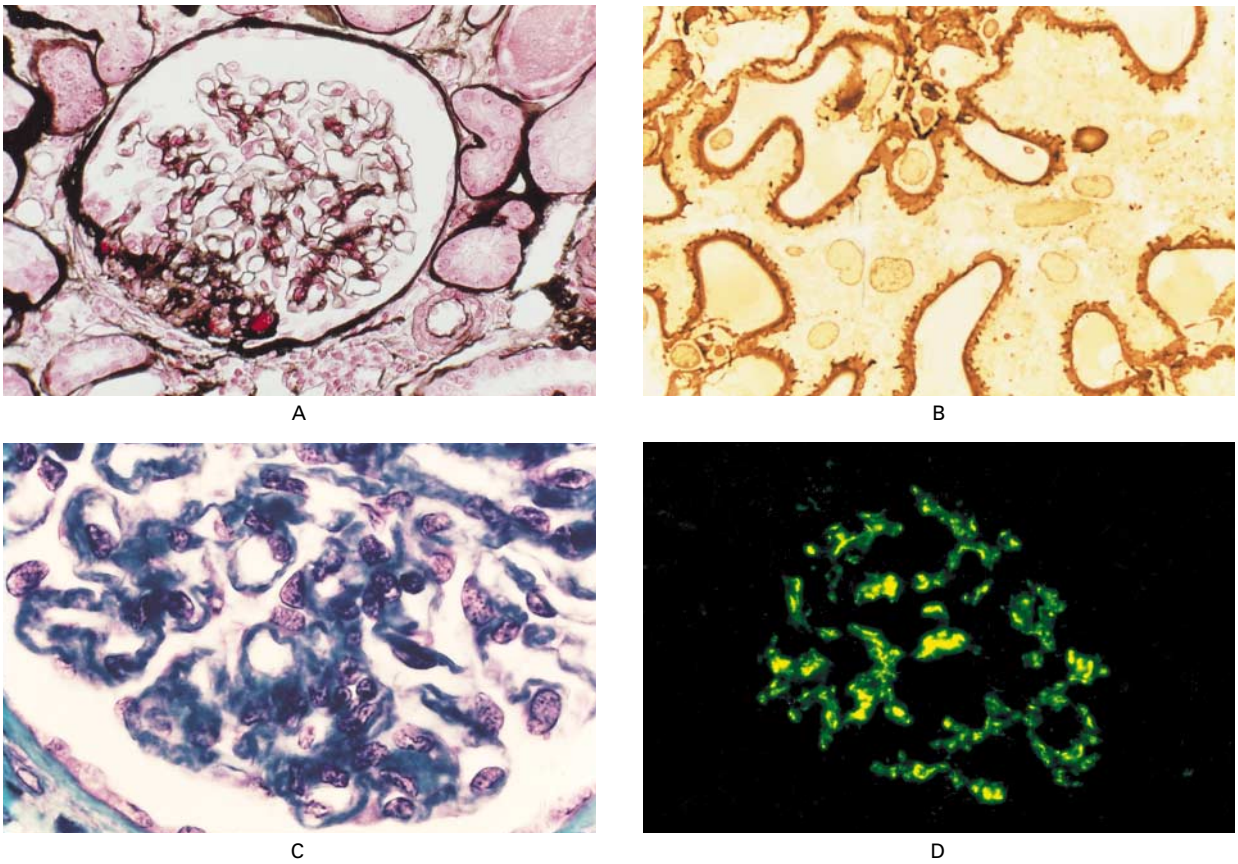

Figure 2. Histopathological Features of Some Primary Glomerular Diseases That Can Cause the Nephrotic Syndrome.

Panel A shows segmental glomerulosclerosis. There is segmental obliteration of the capillary lumina adjacent to the vascular pole with an increase in mesangial matrix, capsular adhesion, and a large hyaline deposit (red) (chromotrope 2R–silver methenamine stain, ×230). Panel B shows membranous glomerulonephritis, stage 2. Subepithelial immune deposits are separated by argyrophilic basement-membrane projections ("spikes") (silver methenamine stain, ×575). Panel C shows membranoproliferative glomerulonephritis type II (dense deposit disease). Peripheral capillary walls have marked thickening of the basement membrane (Masson trichrome stain, ×575). Panel D shows mesangial IgA glomerulonephritis. Immunofluorescence microscopy demonstrates diffuse granular deposits of IgA in the mesangium (×230).

day. High doses are often required. Not only is the avidity of the kidney for sodium high, but furosemide and other diuretics are also bound to albumin in the tubular lumen of patients with proteinuria. Binding to albumin competes with binding to the target molecules — the sodium transporters.[34] Higher doses are therefore needed to achieve effective intratubular concentrations of non–protein-bound diuretic.

Edema should be reversed slowly. Abrupt natriuresis may cause hypovolemia and potentially even acute renal failure, as well as hemoconcentration, increasing the risk of thromboembolic complications. The prophylactic administration of heparin or anticoagulants and the use of support stockings are therefore indispensable.

Infusion of hyperoncotic albumin to expand plasma volume should be tried only if symptomatic hypovolemia is present. Otherwise, its use is neither effective (because infused albumin is rapidly excreted into the urine) nor safe (because it may provoke an increase in blood pressure and even pulmonary edema in patients with hypervolemia).[17,30]

In particularly severe cases, plasma ultrafiltration may be tried. As an extreme approach in patients with severe proteinuria and renal failure, renal ablation by bilateral nephrectomy or embolization of the renal artery may be indicated to avoid the serious risks of severe hypoproteinemia and hypovolemia.[35]

Thromboembolic Complications

Thromboembolic complications have emerged as a major hazard of the nephrotic syndrome. Renal-vein thrombosis is particularly frequent in patients with membranous glomerulonephritis,[36] as documented by retrospective[37,38] and prospective[39,40] stud-

TABLE 2. RARE CAUSES OF THE NEPHROTIC SYNDROME.

Fibrillary glomerulopathy
Several forms of amyloidosis
Light-chain deposit disease
Preeclampsia
Infectious diseases
Bacterial (poststreptococcal glomerulonephritis, infectious endocarditis, syphilis)
Viral (hepatitis B and C, human immunodeficiency virus)[4]
Protozoal (quartan malaria)
Helminthic (schistosomiasis, filariasis, toxoplasmosis)
Cancer (mostly associated with minimal-change glomerulopathy or membranous glomerulonephritis)
Systemic diseases (mostly systemic lupus erythematosus)
Heredofamilial syndromes (e.g., Alport's syndrome, nail–patella syndrome)
Proved or suspected immune reactions
Drugs (e.g., gold, penicillamine, nonsteroidal antiinflammatory drugs, captopril, interferon alfa)
Environmental antigens (e.g., poison ivy, inhalational antigens, bee sting)
Illicit drugs (e.g., heroin)

TABLE 3. MAJOR FACTORS CONTRIBUTING TO THE HYPERCOAGULABLE STATE IN THE NEPHROTIC SYNDROME.

Low zymogen factors: factor IX, factor XI
Increased procoagulatory cofactors: factor V, factor VIII
Increased fibrinogen levels
Decreased coagulation inhibitors: antithrombin III (but protein C and protein S increased)
Altered fibrinolytic system (α_2-antiplasmin increased, plasminogen decreased)
Increased platelet reactivity
Thrombocytosis
Increased release reaction in vitro (adenosine diphosphate, thrombin, collagen, arachidonic acid, epinephrine)
Increased factor IV and β-thromboglobulin in vivo
Altered endothelial-cell function

ies. It is seen in 20 to 30 percent of adult patients with membranous glomerulonephritis. Only 10 percent of patients with renal-vein thrombosis present with symptoms: flank pain, gross hematuria, increased renal size,[39] and loss of renal function. Another serious hazard is pulmonary embolism, which is frequently clinically silent[39] and is manifested in no more than one third of patients. Deep venous thrombosis is also frequent,[36] but it is less so in children. Again, only a minority of patients are symptomatic. Venous thrombosis may also occur in other vascular beds.

In adults with the nephrotic syndrome, arterial thrombosis is less common than venous thrombosis, but it is a serious complication causing important morbidity. Although there has been controversy in the past,[41] an increased risk of coronary events in patients with the nephrotic syndrome has been documented in a retrospective, controlled study.[42] After adjustment for age, sex, hypertension, and smoking, the relative risk of myocardial infarction in these patients was 5.5 and the relative risk of death from coronary thrombosis was 2.8. The causal roles of dyslipidemia and a procoagulatory state remain to be elucidated.

The cumulative incidence of thromboembolic complications in patients with the nephrotic syndrome is nearly 50 percent,[36] raising the issues of prophylaxis and therapy. Unfortunately, there are few reliable predictors of individual risk, but low serum albumin levels (less than 25 g per liter), high rates of protein excretion (more than 10 g per 24 hours), high fibrinogen levels, low antithrombin III levels (less than 75 percent of normal), and hypovolemia[43] are significantly associated with an excessive risk of thromboembolic complications.

The potential benefit of prophylactic anticoagulant therapy for patients with membranous glomerulonephritis has been examined by decision analysis.[36,44] Prophylactic anticoagulation was shown to be safer than ad hoc anticoagulant treatment.[36] Uncontrolled series show high mortality from pulmonary embolism among patients not receiving anticoagulant therapy and very low rates of renal-vein thrombosis and pulmonary embolism in patients receiving anticoagulant therapy. A Markov-based decision-analysis model[44] documented that the number of fatal emboli prevented by prophylactic anticoagulation exceeded the number of fatal bleeding events.

Anticoagulant therapy should be administered as long as the patient has nephrotic proteinuria, an albumin level below 20 g per liter, or both. In patients with other causes of chronic nephrotic syndrome, a more cautious approach may be indicated, and prophylactic anticoagulation should be considered only if the risk is high. Anticoagulant therapy is imperative, however, once thromboembolic events have been documented. In patients with the nephrotic syndrome, pulmonary-artery thrombosis and thromboembolism have been successfully treated by thrombolytic therapy with intravenous urokinase or with streptokinase infused into the pulmonary artery.[45-47] In patients presenting with symptomatic thromboembolic complications, heparin should be given, although its effect is attenuated because antithrombin III levels are decreased.[48] Platelet function is consistently increased.[48] Consequently, platelet-aggregation inhibitors, particularly low-dose aspirin,[37] are a rational choice, although no information from controlled studies is available.

The hypercoagulable state has also been related to abnormalities in coagulation factors (Table 3). Low levels of factor XII (the initial factor in the intrinsic system) lead to a prolonged partial-thromboplastin time on routine coagulation screening but are not

associated with a tendency to bleed. Because the hemostatic cascade after injury is triggered by the extrinsic system, renal biopsy can be safely performed.[49]

Infection

In the past, many children with the nephrotic syndrome died of bacterial infections, particularly pneumococcal peritonitis. This has become rare, but infection continues to be a problem in patients receiving immunosuppressive treatment, in whom viral infections (measles and herpesvirus infections) are frequent. Recently, pneumococcal vaccine has been used successfully.[50] The susceptibility to bacterial infection has been related to decreased levels of IgG and of the alternative complement factor B. An uncontrolled study found a reduction in the rate of bacterial infections after the intravenous administration of IgG.[51]

Hyperlipidemia

Hyperlipidemia undoubtedly constitutes a risk factor for vascular disease. There is a variable increase in the levels of very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and low-density lipoprotein (LDL) fractions, resulting in elevated serum cholesterol alone or in simultaneous elevation of serum cholesterol and triglyceride.[52] The high-density lipoprotein (HDL) fraction is usually normal. The lipoprotein classes IDL and LDL tend to be enriched in cholesterol ester. In addition, Lp(a) lipoprotein is increased, irrespective of the apolipoprotein A isoform class,[53] and this increase is reversed after remission of the nephrotic syndrome or after symptomatic antiproteinuric treatment.[54]

Two mechanisms contribute to nephrotic dyslipidemia: overproduction and impaired catabolism of apolipoprotein B–containing lipoproteins. The pathologic mechanisms differ in patients with hypercholesterolemia alone and in those with hypercholesterolemia plus hypertriglyceridemia (combined hyperlipidemia).[55] Decreased catabolism of chylomicrons and VLDL has been documented in the nephrotic syndrome.[56,57] The fractional catabolic rate of LDL apolipoprotein B is low in patients with hypercholesterolemia alone and high in patients with combined hyperlipidemia.[55] Low plasma albumin levels and low oncotic pressure play a part (as shown by the reversal of hyperlipidemia by dextran infusion) but do not fully explain the lipid abnormalities, since the lipid changes in the nephrotic rat are only partially reproduced in the analbuminemic rat.[56] A causal link between altered glomerular permselectivity and reduced lipid metabolism is likely: an α_1-acid glycoprotein was isolated from the urine of patients with the nephrotic syndrome that corrected impaired lipolysis in nephrotic rats.[58,59] It is probable that abnormal lipoprotein catabolism results, at least in part, from urinary loss of some substance. So far, however, none of the compounds isolated from the urine of patients with the nephrotic syndrome fully explain all lipid abnormalities.

Increased synthesis of lipoprotein is suggested by several findings. In the liver of nephrotic rats the levels of apolipoproteins and rate-limiting enzymes of lipogenesis and their messenger RNAs were increased,[60,61] but cholesterol synthesis was not increased in patients with the nephrotic syndrome.[62] The rates of synthesis and turnover of LDL apolipoprotein B were variable, depending on the presence or absence of hypertriglyceridemia.[55]

In view of the effect of dyslipidemia on cardiovascular risk and possibly on the progression of renal disease,[63] treatment seems sensible, although evidence from controlled studies is not available. There is some role for nonpharmacologic intervention. A soy-protein diet caused a significant decrease in cholesterol, LDL, and apolipoprotein B, whereas serum triglyceride levels did not change.[64] Treatment with fish oil decreased triglycerides and VLDL but increased LDL cholesterol.[65] In randomized, prospective, double-blind, placebo-controlled trials, a major decrease in total cholesterol (22 percent) was seen with a dose of 20 mg of pravastatin (there was no further change at 40 mg), with a trend for HDL to increase and triglycerides to decrease.[66] Similarly, simvastatin caused decreases of 33 and 31 percent, respectively, in total and LDL cholesterol.[67] A meta-analysis showed that dietary therapy reduced cholesterol levels, but the pooled effect of diet on LDL did not reach statistical significance.[68] Angiotensin-converting–enzyme (ACE) inhibitors, by reducing urinary protein levels, also reduce cholesterol and LDL levels.[68]

Protein Binding of Endogenous and Exogenous Substances

Many binding proteins are lost in the urine.[69] Consequently, in patients with the nephrotic syndrome, the plasma levels of many ions (iron, copper, and zinc), vitamins (vitamin D metabolites), hormones (thyroid and steroid hormones), and drugs are low, because the levels of protein-bound ligands are reduced. Urinary loss of protein-bound ligands can theoretically cause depletion of the ligands, but there is little convincing clinical evidence of this, with the possible exception of vitamin D.[70]

Many drugs are bound to albumin. Hypoalbuminemia reduces the number of available binding sites and increases the proportion of circulating free drug, but in the steady state this is counterbalanced by faster metabolism. Higher levels of free drug may be toxic, as shown with prednisolone[71,72] and possibly warfarin. When plasma drug levels are monitored, low total levels of highly protein-bound drugs do not necessarily indicate low effective levels. The

level of free drug may be normal or even elevated. The same consideration applies to protein-bound hormones (thyroid hormones and sex hormones).

TREATMENT OF THE NEPHROTIC SYNDROME

Symptomatic Reduction of Proteinuria

Heavy proteinuria is a predictor of rapid progression of renal failure. This relation is arguably causal,[73] so reduction of proteinuria is a therapeutic goal. Three interventions are available to reduce proteinuria: ACE inhibitors,[74-76] NSAIDs,[77] and a low-protein diet.[75]

ACE Inhibitors

An attempt to reduce proteinuria with ACE inhibitors is indicated even in normotensive patients. There is a temporal dissociation between the hemodynamic and antiproteinuric effects of ACE inhibitors.[78] Blood-pressure lowering is maximal within hours, whereas it takes up to 28 days for the antiproteinuric effect to be maximal, suggesting the involvement of nonhemodynamic mechanisms. ACE inhibitors lower urinary protein excretion more than can be explained by the lowering of systemic blood pressure.[74,76] A reduction in proteinuria is seen even in the absence of any effect on systemic blood pressure.[79] The antiproteinuric response may be related to the ACE genotype,[80] but this remains controversial. At least in experiments in animals, enhanced kinin activity seems to contribute to the antiproteinuric action,[81] but in humans only inhibition of the renin–angiotensin–aldosterone system has been proved.[82] The antiproteinuric effect depends on sodium balance and can be increased by a low-salt diet, diuretic treatment, or both,[83] or by a low-protein diet.[75]

NSAIDs

Several studies documented that NSAIDs reduce proteinuria[77,84] more than can be explained by the reduction in the glomerular filtration rate.[85] Because of the drugs' potential side effects, particularly gastrointestinal complications, this approach has not gained wide popularity.

Low-Protein Diet

It is difficult to define the appropriate level of protein restriction in patients with nephrotic proteinuria. In the past, high protein intakes and even amino acid supplements were recommended. More recently, however, it was shown that high protein intake may fail to increase serum albumin levels.[86,87] It may even increase the rate of protein catabolism and urinary excretion of protein.[87] The latter, apparently paradoxical, finding can presumably be explained by the known increase in the glomerular filtration rate caused by dietary protein. However, isocaloric low-protein diets containing 0.6 to 0.8 g of protein per kilogram of body weight per day have not been shown consistently to reduce proteinuria,[88] in contrast to the effect of ACE inhibitors.[74-76] Nevertheless, a remarkable benefit with respect to urinary protein excretion and serum lipid changes has been observed with a low-fat soy-protein diet providing 0.7 g of protein per kilogram per day.[64] Protein-restricted diets may cause malnutrition unless they are well supervised and provide adequate calories. Malnutrition is the most potent predictor of death in end-stage renal failure. Therefore, many nephrologists, for fear of the risks of low-protein diets in the nephrotic syndrome, recommend normal protein intake.

Immunologic Interventions

Specific Interventions

Specific immunologic interventions are available for only a few causes of the nephrotic syndrome. For example, colchicine prevents the progression of renal disease in patients with familial Mediterranean fever.[89] Other examples include interferon alfa treatment for hepatitis B–associated nephrotic syndrome[90] or for membranoproliferative glomerulonephritis associated with hepatitis C[91] and cryoglobulinemia (although in rare cases interferon may cause the nephrotic syndrome[92]); treatment of infections causing the nephrotic syndrome, such as hydatid disease[93]; omission of medication causing immune-mediated nephrotic syndrome; and chemotherapy or resection of tumors in the nephrotic syndrome associated with cancer.

Nonspecific Interventions

In all other cases, nonspecific immune intervention is the only option available unless renal function is markedly impaired, with serum creatinine levels above approximately 2 mg per deciliter (177 μmol per liter), in which case immunosuppression carries a high risk of toxicity.

On the basis of decision analysis, the value of renal biopsy before a trial of steroid therapy has been questioned for patients with idiopathic nephrotic syndrome, since blind treatment appears to be as effective as treatment based on renal histologic results.[94] It was reported that even after unsuccessful steroid treatment in children with the nephrotic syndrome, experienced pediatric nephrologists did not resort to renal biopsy.[95] For adult patients, this approach has not been universally accepted,[96] because brief courses of steroid treatment are considerably less likely to yield a therapeutic response than prolonged (and potentially more dangerous) courses[97]; in skilled hands ultrasound-guided renal biopsy (the Biopty technique) poses minimal risk[98]; and renal biopsy provides important prognostic information (for example, on the presence of tubulointerstitial fibrosis).

TABLE 4. IMMUNE THERAPY FOR SOME COMMON PRIMARY GLOMERULAR DISEASES CAUSING THE NEPHROTIC SYNDROME.

DISEASE	THERAPY*
Minimal-change glomerulopathy	Corticosteroids (alkylating agents, cyclosporine)
Focal segmental glomerulosclerosis	Corticosteroids (alkylating agents, cyclosporine); immunoabsorption
Membranous glomerulonephritis	Corticosteroids plus alkylating agents; cyclosporine

*Second-line agents are given in parentheses.

The first controlled trial of treatment of the idiopathic nephrotic syndrome in adults was reported in 1970.[99] Twenty-eight years and several dozen trials later, there is still no consensus on the treatment of the different varieties of the nephrotic syndrome. In Table 4 we provide a brief review of the current state of knowledge.

In adults with minimal-change glomerulopathy, we administer 1 mg of prednisolone per kilogram per day for at least eight weeks, and even longer in selected patients.[97] If the patient has no response or has frequent relapses or if steroid dependence develops, we administer cyclophosphamide (1 to 2 mg per kilogram per day) for a period of eight weeks if the patient is symptomatic or has characteristics associated with an adverse renal prognosis (male sex, hypertension, smoking, elevated serum creatinine level, massive proteinuria, or interstitial fibrosis). Leukocyte counts must be monitored, fluid intake should be high, and adequate contraception in women must be ensured. The same approach is taken in patients with focal segmental glomerulosclerosis, although a good response is less frequent.[100] In children[101] or adults,[102] cyclosporine is an option for those with no response. Nephrotoxic effects from cyclosporine are relatively infrequent when moderate doses are administered and when drug concentrations are monitored,[103] but one must consider that glomerular lesions may progress despite a reduction in proteinuria. Severe hypercholesterolemia interferes with the efficacy of cyclosporine.[104] We hesitate to administer recently proposed aggressive immunosuppressive regimens.[105]

In the patient with membranous glomerulonephritis in whom secondary causes have been excluded, who is symptomatic, and who is at high risk for progression, we use the regimen proposed by Ponticelli et al.,[106] consisting of three alternating monthly cycles of methylprednisolone and chlorambucil. The outcome data for this approach are conflicting and have recently been the subject of controversies and meta-analyses. Selection of therapy can be put on a more rational basis by applying decision analysis.[107] Evidence of a beneficial effect of cyclosporine in a controlled trial has also been reported.[108]

A number of novel approaches, such as the use of high-dose intravenous immunoglobulin and immunoadsorption, are currently under investigation. So far, however, the results are too preliminary for comment.

Considerable progress has been made in understanding the pathogenesis and consequences of the nephrotic syndrome. This has led to some rational therapeutic strategies. Nevertheless, current therapy is far from satisfactory, as illustrated by the completely nonspecific nature of immune interventions.

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