- The most common causes are immunologically mediated glomerular injury; lesions are characterized by proliferative changes and leukocyte infiltration.
- **Acute postinfectious glomerulonephritis** typically occurs after streptococcal infection in children and young adults but may occur following infection with many other organisms; it is caused by deposition of immune complexes, mainly in the subepithelial spaces, with abundant neutrophils and proliferation of glomerular cells. Most affected children recover; the prognosis is worse in adults.
- **Rapidly progressive glomerulonephritis** (RPGN) is a clinical entity with features of the nephritic syndrome and rapid loss of renal function.
- RPGN is commonly associated with severe glomerular injury with necrosis and GBM breaks and subsequent proliferation of parietal epithelial cells (forming crescents).
- RPGN may be antibody mediated, caused by autoantibodies to the GBM or as a result of immune complex deposition. It can also occur in the absence of significant antibody deposition, although most affected patients with this type of RPGN have circulating antineutrophil cytoplasmic antibodies (ANCAs).

Nephrotic Syndrome

Certain glomerular diseases virtually always produce the nephrotic syndrome. In addition, many other forms of primary and secondary glomerulopathies discussed in this chapter may underlie the syndrome. Before the major diseases associated with nephrotic syndrome are presented, the causes and pathophysiology of this clinical complex are briefly discussed.

Pathophysiology. **Nephrotic syndrome is caused by a derangement in glomerular capillary walls resulting in increased permeability to plasma proteins.** The manifestations of the syndrome include:

- *Massive proteinuria*, with the daily loss of 3.5 gm or more of protein (less in children)
- *Hypoalbuminemia*, with plasma albumin levels less than 3 gm/dL
- *Generalized edema*
- *Hyperlipidemia and lipiduria*

The various components of nephrotic syndrome bear a logical relationship to one another. The glomerular capillary wall, with its endothelium, GBM, and visceral epithelial cells, acts as a size and charge barrier through which the plasma filtrate passes. Increased permeability resulting from either structural or physicochemical alterations in this barrier allows proteins to escape from the plasma into the urinary space, resulting in proteinuria.

Heavy proteinuria depletes serum albumin levels at a rate beyond the compensatory synthetic capacity of the liver, resulting in hypoalbuminemia. Increased renal catabolism of filtered albumin also contributes to the hypoalbuminemia. The generalized edema is a direct consequence of *decreased intravascular colloid osmotic pressure*. There is also *sodium and water retention*, which aggravates the edema (Chapter 4). This seems to be due to several factors, including compensatory secretion of aldosterone, mediated by the hypovolemia-enhanced renin secretion; stimulation of the sympathetic system; and a reduction in the secretion of natriuretic factors such as atrial peptides. Edema is characteristically soft and pitting, and is most marked in the periorbital regions and dependent portions of the body. If severe, it may also lead to pleural effusions and ascites.

The largest proportion of protein lost in the urine is albumin, but globulins are also excreted in some diseases. The ratio of low- to high-molecular-weight proteins in the urine in various cases of nephrotic syndrome is a manifestation of the *selectivity* of proteinuria. A *highly selective proteinuria* consists mostly of low-molecular-weight proteins (albumin, 70 kD; transferrin, 76 kD molecular weight), whereas a *poorly selective proteinuria* consists of higher molecular-weight globulins in addition to albumin.

The genesis of the hyperlipidemia is complex. Most patients with nephrotic syndrome have increased blood levels of cholesterol, triglyceride, very-low-density lipoprotein, low-density lipoprotein, Lp(a) lipoprotein, and apoprotein, and there is a decrease in high-density lipoprotein concentration in some patients. These defects seem to be due to a combination of increased synthesis of lipoproteins in the liver, abnormal transport of circulating lipid particles, and decreased lipid catabolism. Lipiduria follows the hyperlipidemia, because lipoproteins also leak across the glomerular capillary wall. The lipid appears in the urine either as free fat or as *oval fat bodies*, representing lipoprotein resorbed by tubular epithelial cells and then shed along with injured tubular cells that have detached from the basement membrane.

Nephrotic patients are particularly vulnerable to *infection*, especially staphylococcal and pneumococcal infections, probably due to loss of immunoglobulins in the urine. *Thrombotic and thromboembolic complications* are also common in nephrotic syndrome, due in part to loss of endogenous anticoagulants (e.g., antithrombin III) in the urine. *Renal vein thrombosis*, once thought to be a cause of nephrotic syndrome, is most often a *consequence* of this hypercoagulable state, particularly in patients with membranous nephropathy (see later).

Causes. The incidences of the several causes of the nephrotic syndrome vary according to age and geography. In children younger than 17 years in North America, for example, nephrotic syndrome is almost always caused by a lesion primary to the kidney; among adults, in contrast, it is often associated with a systemic disease. Table 20-7 represents a composite derived from several studies of the causes of the nephrotic syndrome and is therefore only approximate. The most frequent *systemic causes* of the nephrotic syndrome are diabetes, amyloidosis, and SLE. The most important of the *primary glomerular lesions* are *minimal-change disease*, *membranous glomerulopathy*, and *focal segmental glomerulosclerosis*. The first is most common in children in North America, the second is most common in older adults, and focal segmental glomerulosclerosis occurs at all ages. These three lesions are discussed individually in the following sections. Other less common causes of nephrotic syndrome include the various proliferative glomerulonephritides such as MPGN and IgA nephropathy.