

substantially explains the increased burden of end-stage renal disease among African Americans. Associated risk factors for progression to end-stage kidney disease include increased age, male gender, race, smoking, hypercholesterolemia, duration of hypertension, low birth weight, and preexisting renal injury. Kidney biopsies in patients with hypertension, microhematuria, and moderate proteinuria demonstrate arteriosclerosis, chronic nephrosclerosis, and interstitial fibrosis in the absence of immune deposits (see Fig. 62e-21). Today, based on a careful history, physical examination, urinalysis, and some serologic testing, the diagnosis of chronic nephrosclerosis is usually inferred without a biopsy. Treating hypertension is the best way to avoid progressive renal failure; most guidelines recommend lowering blood pressure to <130/80 mmHg if there is preexisting diabetes or kidney disease. In the presence of kidney disease, most patients begin antihypertensive therapy with two drugs, classically a thiazide diuretic and an ACE inhibitor; most will require three drugs. There is strong evidence in African Americans with hypertensive nephrosclerosis that therapy initiated with an ACE inhibitor can slow the rate of decline in renal function independent of effects on systemic blood pressure. Malignant acceleration of hypertension complicates the course of chronic nephrosclerosis, particularly in the setting of scleroderma or cocaine use (see Fig. 62e-24). The hemodynamic stress of malignant hypertension leads to fibrinoid necrosis of small blood vessels, thrombotic microangiopathy, a nephritic urinalysis, and acute renal failure. In the setting of renal failure, chest pain, or papilledema, the condition is treated as a hypertensive emergency. Slightly lowering the blood pressure often produces an immediate reduction in GFR that improves as the vascular injury attenuates and autoregulation of blood vessel tone is restored.

#### CHOLESTEROL EMBOLI

Aging patients with clinical complications from atherosclerosis sometimes shower cholesterol crystals into the circulation—either spontaneously or, more commonly, following an endovascular procedure with manipulation of the aorta—or with use of systemic anticoagulation. Spontaneous emboli may shower acutely or shower subacutely and somewhat more silently. Irregular emboli trapped in the microcirculation produce ischemic damage that induces an inflammatory reaction. Depending on the location of the atherosclerotic plaques releasing these cholesterol fragments, one may see cerebral transient ischemic attacks; livedo reticularis in the lower extremities; Hollenhorst plaques in the retina with visual field cuts; necrosis of the toes; and acute glomerular capillary injury leading to *focal segmental glomerulosclerosis* sometimes associated with hematuria, mild proteinuria, and loss of renal function, which typically progresses over a few years. Occasional patients have fever, eosinophilia, or eosinophiluria. A skin biopsy of an involved area may be diagnostic. Since tissue fixation dissolves the cholesterol, one typically sees only residual, biconvex clefts in involved vessels (see Fig. 62e-22). There is no therapy to reverse embolic occlusions, and steroids do not help. Controlling blood pressure and lipids and cessation of smoking are usually recommended for prevention.

#### SICKLE CELL DISEASE

Although individuals with SA-hemoglobin are usually asymptomatic, most will gradually develop hyposthenuria due to subclinical infarction of the renal medulla, thus predisposing them to volume depletion. There is an unexpectedly high prevalence of sickle trait among dialysis patients who are African American. Patients with homozygous SS-sickle cell disease develop chronic vasoocclusive disease in many organs. Polymers of deoxygenated SS-hemoglobin distort the shape of red blood cells. These cells attach to endothelia and obstruct small blood vessels, producing frequent and painful sickle cell crises over time. Vessel occlusions in the kidney produce glomerular hypertension, FSGS, interstitial nephritis, and renal infarction associated with hyposthenuria, microscopic hematuria, and even gross hematuria; some patients also present with MPGN. Renal function can be overestimated due to the increased tubular secretion of creatinine seen in many patients with SS-sickle cell. By the second or third decade of life, persistent vasoocclusive disease in the kidney leads to varying degrees of renal failure, and some patients end up on

dialysis. Treatment is directed to reducing the frequency of painful crises and administering ACE inhibitors in the hope of delaying a progressive decline in renal function. In sickle cell patients undergoing renal transplantation, renal graft survival is comparable to African Americans in the general transplant population.

#### THROMBOTIC MICROANGIOPATHIES

*Thrombotic thrombocytopenic purpura* (TTP) and *hemolytic-uremic syndrome* (HUS) represent a spectrum of thrombotic microangiopathies. Thrombotic thrombocytopenic purpura and hemolytic-uremic syndrome share the general features of idiopathic thrombocytopenic purpura, hemolytic anemia, fever, renal failure, and neurologic disturbances. When patients, particularly children, have more evidence of renal injury, their condition tends to be called HUS. In adults with neurologic disease, it is considered to be TTP. In adults there is often a mixture of both, which is why they are often referred to as having TTP/HUS. On examination of kidney tissue, there is evidence of *glomerular capillary endotheliosis* associated with platelet thrombi, damage to the capillary wall, and formation of fibrin material in and around glomeruli (see Fig. 62e-23). These tissue findings are similar to what is seen in preclampsia/HELLP (hemolysis, elevated liver enzymes, and low platelet count syndrome), malignant hypertension, and the antiphospholipid syndrome. TTP/HUS is also seen in pregnancy; with the use of oral contraceptives or quinine; in renal transplant patients given OKT3 for rejection; in patients taking the calcineurin inhibitors, cyclosporine and tacrolimus, or in patients taking the antiplatelet agents, ticlopidine and clopidogrel; or following HIV infection.

Although there is no agreement on how much they share a final common pathophysiology, two general groups of patients are recognized: childhood HUS associated with enterohemorrhagic diarrhea and TTP/HUS in adults. Childhood HUS is caused by a toxin released by *Escherichia coli* 0157:H7 and occasionally by *Shigella dysenteriae*. This shiga toxin (verotoxin) directly injures endothelia, enterocytes, and renal cells, causing apoptosis, platelet clumping, and intravascular hemolysis by binding to the glycolipid receptors (Gb3). These receptors are more abundant along endothelia in children compared to adults. Shiga toxin also inhibits the endothelial production of ADAMTS13. In familial cases of adult TTP/HUS, there is a genetic deficiency of the ADAMTS13 metalloprotease that cleaves large multimers of von Willebrand's factor. Absent ADAMTS13, these large multimers cause platelet clumping and intravascular hemolysis. An antibody to ADAMTS13 is found in many sporadic cases of adult TTP/HUS, but not all; many patients also have antibodies to the thrombospondin receptor on selected endothelial cells in small vessels or increased levels of plasminogen-activator inhibitor 1 (PAI-1). Some children with complement protein deficiencies express atypical HUS (aHUS), which can be treated with liver transplant. The treatment of adult TTP/HUS is daily plasmapheresis, which can be lifesaving. Plasmapheresis is given until the platelet count rises, but in relapsing patients it normally is continued well after the platelet count improves, and in resistant patients twice-daily exchange may be helpful. Most patients respond within 2 weeks of daily plasmapheresis. Since TTP/HUS often has an autoimmune basis, there is an anecdotal role in relapsing patients for using splenectomy, steroids, immunosuppressive drugs, bortezomib, or rituximab, an anti-CD20 antibody. Patients with childhood HUS from infectious diarrhea are not given antibiotics, because antibiotics are thought to accelerate the release of the toxin and the diarrhea is usually self-limited. No intervention appears superior to supportive therapy in children with postdiarrheal HUS.

#### ANTIPHOSPHOLIPID ANTIBODY SYNDROME (SEE CHAP. 379)

#### GLOBAL CONSIDERATIONS

##### INFECTIOUS DISEASE-ASSOCIATED SYNDROMES



A number of infectious diseases will injure the glomerular capillaries as part of a systemic reaction producing an immune response or from direct infection of renal tissue. Evidence of this immune response is collected by glomeruli in the form of immune deposits that damage the kidney, producing moderate proteinuria and