exemplified by aristolochic acid contamination of herbal slimming preparations. Contamination of food sources with toxins, such as the recent outbreak of nephrolithiasis and acute renal failure from melamine contamination of infant milk formula, poses a continuing risk. Large-scale exposure to aristolochic acid remains prevalent in many Asian countries where traditional herbal medicine use is common. Although industrial exposure to lead and cadmium has largely disappeared as a cause of chronic interstitial nephritis in developed nations, it remains a risk for nephrotoxicity in countries where such exposure is less well controlled. New endemic forms of chronic kidney disease continue to be described, such as the nephropathy found among Pacific coastal plantation workers in Central America, which may be related to repetitive heat exposure and fluid losses.

341 Vascular Injury to the Kidney

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The renal circulation is complex and is characterized by a highly perfused arteriolar network, reaching cortical glomerular structures adjacent to lower-flow vasa recta that descend into medullary segments. Disorders of the larger vessels, including renal artery stenosis and atheroembolic disease, are discussed elsewhere (Chap. 354). This chapter examines primary disorders of the renal microvessels, many of which are associated with thrombosis and hemolysis.

THROMBOTIC MICROANGIOPATHY

Thrombotic microangiopathy (TMA) is characterized by injured endothelial cells that are thickened, swollen, or detached mainly from arterioles and capillaries. Platelet and hyaline thrombi causing partial or complete occlusion are integral to the histopathology of TMA. TMA is usually the result of microangiopathic hemolytic anemia (MAHA), with its typical features of thrombocytopenia and schistocytes. In the kidney, TMA is characterized by swollen endocapillary cells (endotheliosis), fibrin thrombi, platelet plugs, arterial intimal fibrosis, and a membranoproliferative pattern. Fibrin thrombi may extend into the arteriolar vascular pole, producing glomerular collapse and at times cortical necrosis. In kidneys that recover from acute TMA, secondary focal segmental glomerulosclerosis may be seen. Diseases associated with this lesion include thrombotic thrombocytopenic purpura (TTP), hemolytic-uremic syndrome (HUS), malignant hypertension, scleroderma renal crisis, antiphospholipid syndrome, preeclampsia/HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome, HIV infection, and radiation nephropathy.

HEMOLYTIC-UREMIC SYNDROME/THROMBOTIC THROMBOCYTOPENIC PURPURA

HUS and TTP are the prototypes for MAHA. Historically, HUS and TTP were distinguished mainly by their clinical and epidemiologic differences. TTP develops more commonly in adults and was thought to include neurologic involvement more often. HUS occurs more commonly in children, particularly when associated with hemorrhagic diarrhea. However, atypical HUS (aHUS) can first appear in adulthood, and better testing has revealed that neurologic involvement is as common in HUS as in TTP. Accordingly, HUS and TTP now should be differentiated and treated according to their specific pathophysiologic features.

Hemolytic-Uremic Syndrome HUS is loosely defined by the presence of MAHA and renal impairment. At least four variants are recognized. The most common is Shiga toxin–producing *Escherichia coli* (STEC) HUS, which is also known as D$^+$HUS or enterohemorrhagic *E. coli* (EHEC) HUS. Most cases involve children <5 years of age, but adults also are susceptible, as evidenced by a 2011 outbreak in northern Europe. Diarrhea, often bloody, precedes MAHA within 1 week in >80% of cases. Abdominal pain, cramping, and vomiting are frequent, whereas fever is typically absent. Neurologic symptoms, including dysphasia, hyperreflexia, blurred vision, memory deficits, encephalopathy, perseveration, and agraphia, often develop, especially in adults. Seizures and cerebral infarction can occur in severe cases. STEC HUS is caused by the Shiga toxins (Stx1 and Stx2), which are also referred to as *verotoxins*. These toxins are produced by certain strains of *E. coli* and *Shigella dysenteriae*. In the United States and Europe, the most common STEC strain is O157:H7, but HUS due to other strains (O157/H$^-$, O111:H$^-$, O26:H11/H$^-$, O145:H28, and O104:H4) has occurred. After entry into the circulation, Shiga toxin binds to the glycolipid surface receptor globotriaosylceramide (Gb3), which is richly expressed on cells of the renal microvasculature. Upon binding, the toxin enters the cells, inducing inflammatory cytokines (interleukin 8 [IL-8], monocyte chemotactic protein 1 [MCP-1], and stromal cell–derived factor 1 [SDF-1]) and chemokine receptors (CXCR4 and CXCR7); this action results in platelet aggregation and the microangiopathic process. *Streptococcus pneumoniae* can also cause HUS. Certain strains produce a neuraminidase that cleaves the N-acetylneuraminic acid moieties covering the Thomsen-Friedenreich antigen on platelets and endothelial cells. Exposure of this normally cryptic antigen to preformed IgM results in severe MAHA.

Atypical HUS is the result of congenital complement dysregulation. The affected patients have the low C3 and normal C4 levels characteristic of alternative pathway activation. Factor H deficiency, the most common defect, has been linked to families with aHUS. Factor H competes with factor B to prevent the formation of C3bBb and acts as a cofactor for factor I, which proteolytically degrades C3b. More than 70 mutations of the factor H gene have been identified. Most are missense mutations that produce abnormalities in the C-terminus region, affecting its binding to C3b but not its concentration. Other mutations result in low levels or the complete absence of the protein. Deficiencies in other complement-regulatory proteins, such as factor I, factor B, membrane cofactor protein (CD46), C3, complement factor H–related protein 1 (CFHR1), CFHR3, CFHR5, and thrombomodulin, have also been reported. Finally, an autoimmune variant of aHUS has been discovered. DEAP (deficient for CFHR protein and positive for factor H autoantibody) HUS occurs when an autoantibody to factor H is formed. DEAP HUS is often associated with a deletion of an 84-kb fragment of the chromosome that encodes for CFHR1 and CFHR3. The autoantibody blocks the binding of factor H to C3b and surface-bound C3 convertase.

Thrombotic Thrombocytopenic Purpura Traditionally, TTP is characterized by the pentad: MAHA, thrombocytopenia, neurologic symptoms, fever, and renal failure. The pathophysiology of TTP involves the accumulation of ultra-large multimers of von Willebrand factor as a result of the absence or markedly decreased activity (<5–10%) of the plasma protease ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13. These ultra-large multimers form clots and shear erythrocytes, resulting in MAHA; however, the absence of ADAMTS13 alone may not itself produce TTP. Often, an additional trigger (such as infection, surgery, pancreatitis, or pregnancy) is required to initiate clinical TTP.

Data from the Oklahoma TTP/HUS Registry suggest an incidence rate of 11.3 cases/10^6 patients in the United States. The median age of onset is 40 years. The incidence is more than nine times higher among blacks than among non-blacks. Like that of systemic lupus erythematosus, the incidence of TTP is nearly three times higher among women than among men. If untreated, TTP has a mortality rate exceeding 90%. Even with modern therapy, 20% of patients die within the first month from complications of microvascular thrombosis.

The classic form of TTP is idiopathic TTP, which is usually the result of a deficiency in ADAMTS13. While TTP had traditionally been associated with infection, malignancy, and intense inflammation (e.g., pancreatitis), ADAMTS13 activity usually is not decreased in these conditions. In idiopathic TTP, the formation of an autoantibody to ADAMTS13 (IgG or IgM) either increases its clearance or inhibits its activity. Upshaw-Schülman syndrome is a hereditary condition characterized by congenital deficiency of ADAMTS13. TTP in these