HUS appears to cause platelet activation and thrombosis within microvascular beds. There is evidence that reduced endothelial production of prostaglandin I_2 and NO (both inhibitors of platelet aggregation) contributes to thrombosis. The reduction in these two factors and increased production of endothelium-derived endothelin may also promote vasoconstriction, exacerbating the hypoperfusion of tissues.

Platelet aggregation. In contrast to HUS, in TTP the initiating event appears to be platelet aggregation induced by very large multimers of vWF, which accumulate due to a deficiency of ADAMTS13, a plasma protease that cleaves vWF multimers into smaller sizes. The deficiency of ADAMTS13 is most often caused by autoantibodies that inhibit ADAMTS13 function. Less commonly, a chronic relapsing and remitting form of TTP is associated with inherited deficiencies of ADAMTS13. Very large vWF multimers can bind platelet surface glycoproteins and activate platelets spontaneously, providing a pathophysiologic explanation for the microthrombi that are observed in vascular beds.

With this as an introduction, we will now briefly delve into the various subtypes of HUS/TTP and then return to the morphologic features that are common to all.

Typical (epidemic, classic, diarrhea-positive) hemolytic uremic syndrome. This is the best-characterized form of HUS. Most cases occur following intestinal infection with strains of *E. coli* (the most common being O157:H7) that produce Shiga-like toxins, so-called because they resemble those made by *Shigella dysenteriae* (Chapter 17). Epidemics have been traced to various sources, most commonly the ingestion of contaminated ground meat (as in hamburgers), but also drinking water, raw milk, and person-to-person transmission. However, most cases of typical HUS caused by *E. coli* are sporadic. Less commonly, infections by other agents, including *Shigella dysenteriae*, can give rise to a similar clinical picture.

Typical HUS can occur at any age, but children and older adults are at highest risk. Following a prodrome of influenza-like or diarrheal symptoms, there is a sudden onset of bleeding manifestations (especially hematemesis and melena), severe oliguria, and hematuria, associated with microangiopathic hemolytic anemia, thrombocytopenia, and (in some patients) prominent neurologic changes. Hypertension is present in about half the patients.

Precisely how Shiga-like toxin exposure causes HUS is not well understood. According to one model the toxin "activates" endothelial cells, which respond by increasing their expression of leukocyte adhesion molecules and endothelin and decreasing nitric oxide production. In the presence of cytokines such as TNF, Shiga-like toxin may cause endothelial apoptosis. These alterations lead to platelet activation and induce vasoconstriction, resulting in the characteristic microangiopathy. But other possibilities remain. For example, there is some evidence that Shiga-like toxins may bind and activate platelets directly; or alternatively, may bind the regulatory complement protein Factor H and inhibit its activity, causing hyperactivation of complement, an intriguing idea given the clear role of complement activation in some forms of atypical HUS (described below).

In typical HUS, if the renal failure is managed properly with dialysis, most patients recover normal renal function in a matter of weeks. However, due to underlying renal damage the long-term (15 to 25 year) outlook is more guarded. In one study, only 10 of 25 patients with prior typical HUS had normal renal function, and 7 had chronic kidney disease.

Atypical (non-epidemic, diarrhea-negative) hemolytic-uremic syndrome. Atypical HUS occurs mainly in adults in a number of different settings. More than half of those affected have an inherited deficiency of complement-regulatory proteins, most commonly Factor H, which breaks down the alternative pathway C3 convertase and protects cells from damage by uncontrolled complement activation (Chapter 3). A small number of patients have mutations in two other proteins that regulate complement, complement Factor I and CD46 (membrane cofactor protein). Patients with genetic mutations in complement-regulatory proteins may develop HUS at any age. Roughly half of affected individuals have a course marked by multiple relapses and progression to end-stage renal disease. As the deficiencies in complement-regulatory factors are life-long, it is a mystery why the onset of HUS is delayed; additional unknown co-factors that trigger the development of HUS are suspected.

The remaining cases of atypical HUS arise in association with a variety of miscellaneous conditions or exposures. These include:

- The *antiphospholipid syndrome*, either primary or secondary to SLE (lupus anticoagulant). The syndrome is described in detail in Chapter 4. In this setting the microangiopathy tends to follow a chronic course.
- Complications of pregnancy or the postpartum period. So-called *postpartum renal failure* is a form of HUS that usually occurs after an uneventful pregnancy, 1 day to several months after delivery. The condition has a grave prognosis, although recovery can occur in milder cases.
- *Vascular diseases affecting the kidney*, such as systemic sclerosis and malignant hypertension.
- Chemotherapeutic and immunosuppressive drugs, such as mitomycin, cyclosporine, cisplatin, gemcitabine, and antagonists of VEGF.
- Irradiation of the kidney.

Patients with atypical HUS do not fare as well as those with typical HUS, in large part because the underlying conditions may be chronic and difficult to treat. As in typical HUS, some patients have neurologic symptoms; the disease in these patients can be distinguished from TTP by the presence of normal ADAMTS13 levels in the plasma (see later).

Thrombotic Thrombocytopenic Purpura. TTP is classically manifested by the pentad of fever, neurologic symptoms, microangiopathic hemolytic anemia, thrombocytopenia, and renal failure. The most common cause of deficient ADAMTS13 activity is inhibitory autoantibodies, and the majority with such antibodies are women. Regardless of cause, most patients present as adults at ages younger than 40. Less commonly, patients inherit an inactivating mutation in *ADAMTS13*. In those with hereditary ADAMTS13 deficiency, the onset is often delayed until adolescence and the symptoms are episodic. Thus, factors other than ADAMTS13 (e.g., some superimposed vascular injury or