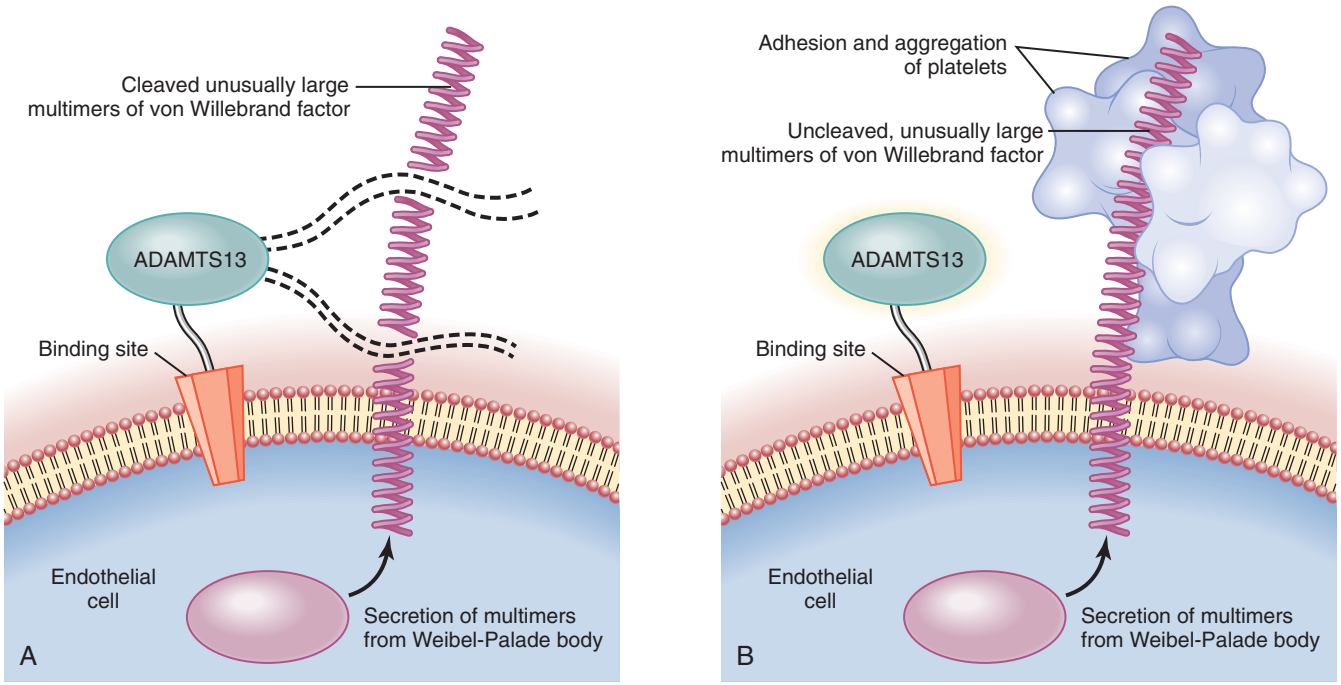

FIGURE 30-4 Relation between ADAMTS13 activity, excessive adhesion and activation of platelets, and thrombotic thrombocytopenic purpura. **A,** In normal subjects, ADAMTS13 (i.e., von Willebrand factor–cleaving metalloprotease) molecules attach to binding sites on endothelial cell surfaces and cleave unusually large multimers of von Willebrand factor as they are secreted by stimulated endothelial cells. The smaller von Willebrand factor forms that circulate after cleavage do not induce the adhesion and aggregation of platelets during normal blood flow. **B,** Absent or severely reduced activity of ADAMTS13 in patients with thrombotic thrombocytopenic purpura prevents timely cleavage of unusually large multimers of von Willebrand factor as they are secreted by endothelial cells. The uncleaved multimers induce the adhesion and aggregation of platelets in flowing blood. (From Moake JL: Thrombotic microangiopathies, N Engl J Med 347:589–600, 2002.)

anti-ADAMTS13 autoantibodies (mostly immunoglobulin G [IgG]), or, much less commonly, genetic.

Other laboratory abnormalities are manifestations of the MAHA and include thrombocytopenia; an elevated LDH concentration, indirect bilirubin concentration, and reticulocyte count; and a low haptoglobin concentration. Coagulation laboratory test results (e.g., prothrombin time, activated partial thromboplastin time, fibrinogen level) are typically normal, although levels of fibrin split products may be elevated. AKI, microscopic hematuria, and low-grade proteinuria are frequently detected.

Without treatment, TTP has a mortality rate of about 90%, with most deaths occurring within 3 months of the onset of symptoms. Treatment with plasma infusion can normalize ADAMTS13 levels, reducing intravascular hemolysis and mortality rates. Plasmapheresis and replacement with fresh-frozen plasma has the advantage of removing inhibitory autoantibodies in addition to normalizing ADAMTS13 levels because of the large volume of plasma that can be infused.

ADAMTS13 activity must be assayed before therapy is initiated to obtain accurate results, but treatment should not be delayed for the results to return. The severity of ADAMTS13 deficiency (<5%) predicts future relapse, although those with severe deficiency are just as likely to respond initially to plasmapheresis as those with a mild deficiency. Patients with MAHA due to other causes not associated with ADAMTS13 deficiency usually do not respond to plasmapheresis or plasma infusion. Patients with HUS do not have abnormalities in ADAMTS13 levels or function.

Hemolytic-Uremic Syndrome

Gastrointestinal tract infection with the Shiga-toxigenic *Escherichia coli* strain O157:H7 produces a diarrheal illness that is complicated in about 15% of cases by a MAHA with intraglomerular thrombosis and AKI, a condition referred to as diarrheal (D+) HUS. *Shigella dysenteriae* serotype 1 or other Shiga toxin–producing strains of *E. coli* may also cause D+ HUS. D+ HUS most commonly affects infants and children, although adults may also be affected. Cases of D+ HUS often cluster because of outbreaks of *E. coli* O157:H7, with peaks occurring in summer and autumn. *E. coli* is endemic in the gastrointestinal tract of cattle, and cases are often tracked to undercooked meat, exposure to bovine fecal matter, animal exposure, or other contaminated food products.

Shiga-toxigenic bacterial strains commonly produce a prodrome of painful, bloody diarrhea, which precedes the development of HUS by 2 to 12 days (median, 3 days). Shiga toxin is directly thrombogenic in the renal vasculature. Although intravascular coagulation in D+ HUS is usually limited to the kidney, the heart, gastrointestinal tract, and central nervous system may also be affected.

Laboratory abnormalities in HUS include elevated creatinine levels, anemia, schistocytes on the peripheral smear, elevated reticulocyte count, and thrombocytopenia. In contrast to disseminated intravascular coagulation, fibrinogen levels are normal or high, and the prothrombin time is normal or only slightly prolonged. Fresh stool should be sent for culture of *E. coli* O157:H7, which can aid in tracing the source of an outbreak.