We describe 2 patients with autoimmune thrombocytopenic disease who developed classic dengue fever associated with serious bleeding and extremely low platelet counts (1000 cells/mm$^3$ and 3000 cells/mm$^3$, respectively). Such patients should be properly advised as to the possibility that common dengue fever may substantially enhance their risk for hemorrhagic complications.

Dengue fever (DF) is the most prevalent and expanding arboviral disease in humans, and its incidence is increasing. Transmitted by *Aedes* mosquitoes and epidemic in most tropical areas, the disease may have a high attack rate among people of any age, regardless of whether they are residents of or travelers to areas of endemicity. Neither a specific treatment nor a vaccine is presently available [1, 2]. The most common presentation (in >90% of cases) is that of “classic” DF, an acute self-limited disease that causes a high fever, musculoskeletal pain, and rash. On occasion, DF with severe bleeding or shock, known as “dengue hemorrhagic fever” (DHF), may occur, especially in children, and it can be fatal [2]. DF is caused by 4 distinct viruses that belong to the *Flaviviridae* family (dengue virus serotypes [DEN] 1–4), all of which cause a clinically identical disease. Because these viruses induce only partial cross-immunity, a first episode of the disease, or “primary DF,” may be followed by “secondary DF,” a sequence considered to enhance clinical severity and favor DHF [1]. Thrombocytopenia (TCP) of moderate degree is a usual finding associated with both forms of the disease [3]. We describe 2 adults from an area of endemicity who developed DF while they had chronic underlying autoimmune TCP.

**Patient 1.** A 32-year-old West Indian man had idiopathic thrombocytopenic purpura diagnosed in 1994. His platelet count ranged from 14,000 cells/mm$^3$ to 50,000 cells/mm$^3$, and the disease proved to be refractory to steroids, dapsone, danazol, and iv immunoglobulins (IVIG) and, finally, to splenectomy. The patient however, had remained asymptomatic for years, and had stopped taking all medications in 1995.

In late 1996, in the context of an epidemic of DF due to the DEN-2 virus, the patient developed an acute, febrile (temperature, 40.5°C), and painful illness with extensive superficial bleeding, nuchal rigidity, and a state of confusion. *The patient had not taken aspirin*. On day 2 after the onset of DF, despite the patient’s negative blood culture results and a platelet count of 12,000 cells/mm$^3$, lumbar puncture was performed, and bacterial meningitis was ruled out as a diagnosis. Within 4 days of the onset of DF, bleeding worsened, and the platelet count decreased to 1000 cells/mm$^3$. The patient had low back pain with anesthesis of the sacral dermatomes and impotence. In addition, sphyncteric disturbances appeared that suggested intradural hematoma of the conus medullaris. At this time, a diagnosis of DHF was considered. The hematocrit value, however, remained within normal limits. Neither IVIG nor megadoses of steroids had any effect. Only transfusion of platelets produced a transient increase of up to 40,000 cells/mm$^3$ and stopped the bleeding.

A clinical diagnosis of DF was made and later was confirmed by positive results of an IgM antibody capture assay (MAC-ELISA; performed on day 6) and by virus culture that yielded a DEN-2 strain. A bone marrow aspirate obtained on day 4 was hypocellular, with very scant megakaryocytes and hemophagocytic macrophages that contained erythrocytes and platelets. Ten days later (on day 14), the marrow picture had changed to a regenerative pattern with numerous megakaryocytes, and the life span of the platelets had been shortened to 50 h (normal life span, 72–96 h). The patient recovered from DF within 6 days and from neurologic impairment within 1 month (MRI of the spine performed on day 15 did not show evidence of compressive hematoma). At the final follow-up in June 2000, no other episodes of bleeding had occurred, despite persistently low platelet counts (10,000 to 20,000 cells/mm$^3$).

**Patient 2.** A 27-year-old West Indian woman had systemic lupus erythematosus diagnosed in early 1993. She also had minor purpura and a platelet count of 5000 cells/mm$^3$. Antiphospholipid antibodies were absent. All clinical and biological parameters showed marked improvement when the patient received steroids. In late 1997, during an epidemic of disease due to DEN-2 and DEN-4, the patient—who was still receiving prednisone, 20 mg/day—had acute fever (temperature, 40.2°C) and rash with diffuse
pain. No aspirin, only paracetamol, had been given. On day 5, the patient’s platelet count decreased from an initial count of 30,000 cells/mm² to 3000 cells/mm², and extensive purpura developed. A diagnosis of DHF was considered. Hemoglobin and hematocrit levels, however, remained within normal ranges. A high dosage of iv methylprednisolone, 500 mg/day for 3 days, was given. Within 1 week, the patient had a complete clinical recovery and a platelet count of 32,000 cells/mm². Results of IgM serologic tests confirmed the presence of DF infection. Virus culture was not performed. No other episodes of acute TCP occurred during the following 3 years.

Discussion. These cases illustrate the large, harmful, and misleading decrease in the platelet count that may be a result of common DF occurring in individuals who coincidentally have underlying TCP. This situation is not unique, because there are other examples of viral infections that may seriously destabilize chronic cytopenic conditions, such as parvovirus B19 infection in humans, that cause severe erythoblastopenic anemia in patients with hemolytic anemia [4]. Because both patients were adults who used to live in an area of endemicity, they presumably had secondary DF.

The pathophysiological findings associated with DF, either the primary or secondary form, appear to be complex and are not fully understood. The following processes, acting successively or in combination, have been demonstrated to interfere with the platelet cell: early transient marrow suppression with damage to megakaryocytes [5]; platelet aggregation to endothelial cells targeted by DF viruses [6]; hemophagocytosis [7, 8]; and finally, immune destruction of platelets, with dengue antibody complexes being found on their membrane [9]. Most of these features were documented in patient 1.

From a clinical and diagnostic perspective, 3 points will be discussed in brief. First, classic DF, not only DHF, may induce marked thrombocytopenia in up to 50% of healthy subjects [10], with a platelet count that is sometimes as low as 10,000 platelets/mm²; this feature should not lead to misclassification. Actually, according to the World Health Organization, the diagnostic criteria for DHF are as follows: an acute febrile illness of 2–7 days' duration, minor or major bleeding, TCP (<10⁵ cells/µL), and also evidence of plasma leakage (documented by at least a one-fifth increase in the hematocrit level, serous effusions, hypoalbuminemia, or hypoproteinemia) [11]. Because none of the latter criteria were present in our patients, the disease was therefore classified, sensu stricto, as classic DF.

Second, the occurrence of a sudden fever with severe headache, hemorrhage, and a large decrease in the platelet count in a patient who has undergone splenectomy or immunosuppression, may suggest bacterial meningitis and/or sepsis coagulopathy. In this context, performance of lumbar puncture may be tempting but harmful (patient 1), and it is actually contraindicated.

Third, there is no rapid diagnostic test for DF, with the exception of PCR, which is not routinely available. For all other procedures, results are not yielded until a minimum duration of 5–7 days after clinical onset of the disease. The IgM diagnostic test, which is the most widely used test and is usually sufficient for diagnosis in the context of an epidemic, is only presumptive, despite having sensitivity and specificity rates of 90%–97% and 98%, respectively, with use of the MAC-ELISA [12]. Definitive diagnosis requires positive results of virus culture (of much lower sensitivity) or PCR, antigen detection in tissue samples, or detection of a 4-fold increase in IgG antibody titers in 2 separate serum samples [12].

In conclusion, because air travel and cruises to the tropics are becoming more popular, emerging DF should not be overlooked [1, 8]. Although DF is benign in a large majority of healthy subjects, presence of the disease may be of concern in subjects with chronic TCP, a relatively common condition. In such subjects, it may possibly enhance the risk of hemorrhage, although this is a poorly documented point that will require more information.

References