species (table 1). Serum (rose bengal–positive, Wright 1:160, immunofluorescence 1:160) and CSF (rose bengal–positive, immunofluorescence 1:64) *Brucella* serology were positive and the patient was treated with daily rifampin, 900 mg, plus doxycycline, 200 mg, for 8 weeks with complete recovery.

Brucellosis and tuberculosis are still endemic in our country. When the central nervous system is involved, the clinical picture and CSF analysis (elevation of protein, decreased glucose, and lymphocytic pleocytosis) may appear similar [6]. Fortunately, CSF and blood serology in neurobrucellosis are rarely negative, especially when a complete battery of tests is available, such as rose bengal and Wright agglutination, Coombs' test, and indirect immunofluorescence (as is the case in our hospital) or ELISA [7]. However, in the absence of these examinations, a correct diagnosis may be difficult [8].

Increased (>9 units/l) ADA in CSF has been reported to have a sensitivity of 1 and specificity of 0.99 in the diagnosis of tuberculous meningitis [9]. However, patients with neurobrucellosis were not included in the control groups. False-positive results have been reported in cases of purulent meningitis [9, 10], but that condition could hardly be confused with tuberculous meningitis. However, neurobrucellosis can easily be mistaken for tuberculous meningitis.

On the basis of our data, we think that physicians in countries where brucellosis and tuberculosis are endemic should take care when interpreting increased ADA in CSF, at least until neurobrucellosis can be definitively excluded.

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The Hyperreactive Malarial Splenomegaly Syndrome in a European: Has the Treatment a Modulatory Effect on the Immune System?

COLLEAGUES—The hyperreactive malarial splenomegaly (HMS) syndrome, also known as tropical splenomegaly syndrome, is believed to represent an aberrant immunologic response to repeated malarial infections and occurs in adult long-term residents of malarious areas. The syndrome is characterized by a gross splenomegaly with hypersplenism, high titers of malarial IgM antibodies, a high polyclonal IgM level, hepatic and medullary lymphocytic proliferation, and normal phytohemagglutination response of lymphocytes [1]. We report a case of HMS syndrome in a white male patient once a resident of Madagascar.

A 60-year-old Swiss man had lived for 30 years in Madagascar. He had taken antimalarial prophylaxis (chloroquine) irregularly. In 1983 he gave a history of malaria which was treated by Fansidar (Roche, Basel, Switzerland). At this time the spleen was not enlarged. At the end of 1986 the complaints were tiredness, anorexia (loss of 5 kg/year), fever, and malaise. There was no history of alcoholism or jaundice. In 1987 he returned to Switzerland; 2 months later he did not feel any improvement and therefore was hospitalized. On examination he looked pale, his weight was 73 kg, and his height 173 cm. During the hospitalization he was never febrile. The liver was not enlarged, but the spleen was tender and the lower edge reached the umbilicus. There were no stigmata of liver disease or other abnormal physical signs.

Laboratory findings included a hemoglobin concentration of 78 g/l (mean corpuscular volume, 85 fl; mean corpuscular hemoglobin, 31 pg), white blood cell count of 2.8×10^9/l (neutrophils 49%, lymphocytes 45%, monocytes 3.5%, eosinophils 1%), and thrombocytes diminished to 113×10^9/l. Erythrocyte sedimentation rate (ESR) was 130 mm/h. Plasma urea, creatinine, electrolytes, and liver function tests were all in the normal range. The proteins were 91 g/l. Electrophoresis showed raised immunoglobulins without monoclonal spike: serum IgG, 31 (normal, 8–18) g/l; IgA, 1.1 (0.7–4) g/l; and IgM, 14.7 (0.7–2.8) g/l.

Blood smears for malarial parasites were negative several times. No abnormalities or parasites were found in the stool or urine. Anti-

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body tests for cytomegalovirus, chlamydia, Epstein-Barr virus, toxoplasma, schistosoma, and brucella were negative. The malarial antibody titers (IFI, Tropical Institute, Basel, Switzerland) for plasmodium falciparum and vivax were 1:5120. Sonography and computed tomography of the abdomen confirmed the splenomegaly (24 × 11 cm, 2400 cm^3). A liver biopsy showed marked sinusoidal infiltration with lymphocytes but no malarial pigment. Bone marrow examination showed a hyperplasia of the erythroid cells and an excess of lymphocytes. No evidence of any malignant cells or pigments was seen.

Thus, the patient presented a typical picture of HMS syndrome. No improvement could be seen during the first 2 months after his return from Madagascar to Switzerland, so we introduced antimalarial treatment at a prophylactic dose (chloroquine, 300 mg/week). The patient soon began to feel well and had no further complaints. The spleen diminished progressively, the ESR fell almost to the normal range, and the pancytopenia disappeared (figure 1).

This is the first case, to our knowledge, of a white male patient meeting the accepted criteria of HMS syndrome. It was previously not known if this illness would strike only the population of tropical countries. Different factors play an important part in the pathogenesis of this syndrome: a long period of exposure to malaria, the antimalarial drug prophylaxis [2], and a genetic or environmental predisposition [3, 4]. The association of antigens and haplotypes of HLA-DR2 was found to be more frequent in patients suffering from gross splenomegaly than in those with moderate splenic enlargement [5]. It is still not known whether a European would have the same aberrant immunologic response.

Two cases that could correspond to HMS syndrome in Europeans have been reported. The first, a Caucasian residing in Africa, showed all the criteria except the high IgM level, which was not measured [6]. The high IgM level (at least 2 SD above the local mean) allows differential diagnosis from other splenomegalies [2]. Although enlargement of the spleen (minimal at 10 cm below the costal margin) is a major criterion of this syndrome [2], the second published case in a European [7] reported a barely palpable spleen. Those authors believed that the irregular antimalarial prophylaxis was the cause of the minimal enlargement. However, our case meets all the criteria of HMS syndrome.

Studies explaining the pathogenesis indicate that serum samples from patients with HMS syndrome contain lymphocytotoxic antibodies (IgM) triggered by repeated or persistent exposure to malarial parasites with specificity for $T8^+$ suppressor lymphocytes, thus leaving relatively unopposed the stimulating effect of helper T lymphocytes on B cells [8]. The high level of B cell activity explains the production of protein in high concentrations. The treatment consists in the inhibition of the triggering mechanism of IgM production. Antimalarial therapy (in prophylactic dose) is usually followed by disappearance of the symptoms [2].

As blood smears for malarial parasites were negative several times and as our patient was never febrile, we were interested to see his spontaneous course in the absence of new malarial infection in Switzerland. Because he felt no improvement during the first 2 months, administration of chloroquine, in an antimalarial prophylactic dose, was necessary. This treatment induced a progressive disappearance of the clinical and laboratory signs.

Chloroquine seems to have a modulatory effect on the immune system. In addition to our case, studies recently published [9] show that this drug in doses recommended for malarial prophylaxis reduces the antibody response to primary immunization with intradermal human diploid-cell rabies vaccine. These results are explained by the impaired secretion of a lymphocyte-activating factor, interleukin-1 [10]. However, the precise mechanism of chloroquine activity is not known, and further studies are necessary to understand the effect of this drug on the immune system in HMS syndrome.

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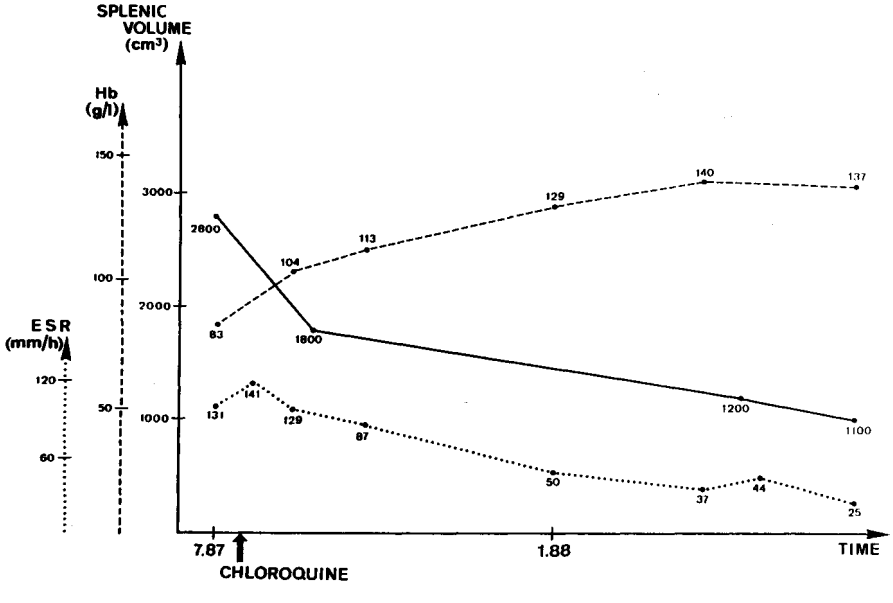

Figure 1. Evolution of splenic volume, hemoglobin (Hb) concentration, and erythrocyte sedimentation rate (ESR) after administration of chloroquine.

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New and Old Drugs for Treating Typhoid Fever

COLLEAGUES—Typhoid fever continues to be a common public health problem and a significant cause of morbidity and mortality in many parts of the world. Despite the excellent in vitro activity of many antibiotic drugs against *Salmonella* species, the clinical efficacy of some is unclear and others are now being evaluated. Thus, the best treatment remains controversial as evidenced by several studies recently published in the Journal [1-3]. These studies demonstrated the clinical efficacy of some third-generation cephalosporins and quinolones in the treatment of typhoid fever. The authors suggested that these new drugs may be a good alternative to chloramphenicol, which is cited in all of these studies as remaining the drug of choice for treatment of typhoid fever. Although most clinicians will agree, we are uncertain that a definitive study of chloramphenicol in the treatment of typhoid fever has been carried out.

The renewed interest in the clinical efficacy of new drugs for treating typhoid is justified mainly by the potentially dangerous side effects of chloramphenicol and the data derived from studies showing that ampicillin is not as active as chloramphenicol. We recently reviewed several studies published many years ago [4-7] and observed that inadequate dosage and route of administration of ampicillin could have been responsible for these less favorable results. In fact, more recent studies have shown that intravenous ampicillin in high doses (150-200 mg/kg/day) is highly effective in treating typhoid fever [8, 9].

During a recent outbreak of typhoid fever in Israel, we compared the clinical efficacy of chloramphenicol with high-dose intravenous ampicillin [10]. Our results not only confirmed the above-mentioned data but also showed a more rapid defervescence and a lower relapse rate with this ampicillin regimen. We think that this less toxic drug, which has all of the advantages of chloramphenicol such as clinical efficacy and oral availability (for continuing treatment after defervescence occurs), should be considered in the treatment of typhoid fever. Certainly it is a less expensive alternative for the public health systems of developing countries.

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