Malaria is an Italian word composed of “mala” and “aria,” derived from malus (bud), and aeris (air). It was first used to describe a fever (miasma), which was wrongly attributed to exposure to poisonous air rising from marshes. Although the disease had been described in the Hippocratic Collection (460 to 377 BC) and its relation to mosquitoes suggested in the 5th century AD, by the Indian physician Susruta, it was only in 1880 that Charles Laveran, a French physician working in Algeria, discovered the true causative agent as being a sporozoan of the genus *Plasmodium*. More than a century later, we got to map the malaria genome, identifying a huge number of genes located on 14 chromosomes.

Malaria is acquired through the sting of an infected *Anopheles* mosquito, which injects the sporozoites into the host’s dermis. These are carried with the blood stream to the liver, where they mature in the hepatocytes (extra-erythrocytic cycle) to tissue schizonts that release their merozoites into the hepatic sinusoids. The latter invade the red cells, starting the erythrocytic cycle, which comprises ring forms, trophozoites, and, subsequently, schizonts that contain a new generation of merozoites. The parasitized cells are induced by plasmodial DNA to develop a microtubular system that conveys nutrients to the parasite. They eventually rupture and release the merozoites, which repeat the same cycle. A few merozoites are sexually differentiated into male and female gametocytes, which are essential for the completion of the sexual cycle in the vector.

**Epidemiology**

Malaria is widely spread throughout the world and affects close to 400 million people, most of whom live in Africa, India, Southeast Asia, and Latin America. With the increasing immigration of natives from those regions to Europe and North America, “imported malaria” imposed itself on the list of differential diagnosis of many medical conditions in the West as recurrent fever, jaundice, hemolytic anemia, acute renal failure (ARF), systemic inflammatory response (SIR) syndrome, and posttransplantation pyrexia (1).

An increasing number of Caucasians acquire the disease through traveling or living in endemic areas. This risk has been known for many centuries. Celebrities known to have contracted the disease while traveling to Africa or Asia include the Italian poet Guido Cavalcanti in 1300, the British explorer Sir Richard Burton in 1858, and the American president John F. Kennedy while serving in the Pacific during World War II. Malaria in nonimmune Caucasians is notoriously severe, with cerebral and renal complications often supervening with a fatal outcome.

Infected mosquitoes can also travel with passengers or cargo and have been reported to transmit the disease to visitors of major European airports (“airport malaria”). They could even establish endemic foci in the West as reported from Belgium and the United States.

**Pathogenicity**

Several species affect humans, leading to different patterns of the disease. The most important are *Plasmodium falciparum*, which causes falciparum malaria, *P. malariae*, which causes Quartan malaria, and *P. vivax* and *P. ovale*, which cause tertian malaria. Genetic interspecies differences explain the variance in the clinical syndromes caused by these sporozoans. These include the rate of multiplication, expression of different antigenic and ligand proteins on the host’s parasitized cells, influence of host factors on the parasite’s antigenic variability, and others. A striking expression of this divergence is the ability of different strains to invade human red cells of different ages. Thus, *P. vivax* and *P. ovale* infect only young red cells, whereas *P. malariae* infects only aging cells. *P. falciparum* invades erythrocytes at any age, which explains the heavy parasitemia associated with this species. In contrast, erythrocytes with hemoglobin S typically are resistant to this species.

Parasitized erythrocytes initiate the three principal pathogenic features in plasmodium infections: hemodynamic, immunologic, and metabolic perturbations. The complex malarial syndrome represents the ultimate interaction among these lines (Figure 1).

**Hemodynamic Derangement**

Parasitized red cells are sticky. They tend to adhere to adjacent healthy erythrocytes (2), blood platelets (3), and the capillary endothelium (4). This results in the formation of intravascular rosettes and clumps, which can impede the microcirculation. Although this feature is observed with all plasmodial infections, its major clinical impact is in falciparum malaria, where it has been long associated with serious sequelae, particularly in the nervous system (5).
The adhesive ligands on parasitized red cell membranes have long been identified as “knobs” composed of abnormal proteins encoded by the parasite’s genome. The major family of adhesive proteins is called plasmodium falciparum erythrocyte membrane proteins (PfEMP) (6), which includes several members identified by sequential numbers. PfEMP-1 seems to be the major determinant of erythrocyte adhesiveness and subsequent malarial morbidity. A striking feature of this protein is variability, being structurally and antigenically different in consecutive generations of parasitized red cells. This is attributed to switching between alleles in the “major var gene” in successive merozoite generations. Switching is largely a spontaneous process (7) but is also influenced by host factors, as shown by the effect of splenectomy in experimental models (8). This “cross talk” between the parasite and the host keeps the balance, which permits both to survive.

Other adhesive protein families have been identified in the erythrocyte knobs, including the histidine-rich proteins (9), rifins (10), rosettins (11), and others. Most of these are also variable proteins of importance in the host–parasite relationship, but their relative pathogenetic significance seems to be less prominent than that of the PfEMP-1.

The main red cell receptors for PfEMP-1 are the CR1 and glycosaminoglycans (12). There are many platelet and endothelial receptors. Although some are constitutively expressed, as CD36, PECAM-1/CD31, thrombomodulin, and chondroitin-4-sulfate, many are induced by the host’s immune response as a part of widespread endothelial activation, including E-selectin, P-selectin, ICAM-1, and VCAM-1 (13).

The hemodynamic element in the pathogenesis of malaria is not limited to capillary lumen obstruction by sticky cell aggregates. The associated endothelial activation leads to the release of several vasoactive cytokines. Specifically reported are thromboxane, catecholamines, and endothelin, but there is no doubt that other local mediators are involved in the ultimate response of the peripheral capillaries to the complex scenario of falciparum malarial infection (14).

**Immune Perturbation**

Antigenic proteins are expressed on the cell membranes of both the parasite and the parasitized host cells. However, owing to the intracellular residence of the sporozoan during most of its life cycle in man, it is the novel polypeptide expression on the parasitized red cells that constitutes the major part of the antigen load. In addition to the adhesive proteins described earlier, other antigenic proteins have been identified on parasitized red cells, monocytes, and hepatocytes. These include “var” gene products other than the PfEMP-1 (15), the ring-infected erythrocyte surface antigen (16), Pf332 (17), 70-kD and 78-kD heat shock proteins (18), and others.

Although all of these antigens are able to activate the peripheral blood mononuclear cells, there is evidence that they provoke a differential immune response. For example, glycosylphosphatidylinositol moieties covalently linked to the surface antigens of falciparum malarial parasites seem to act like endotoxin that interacts with upregulated monocyte CD14 receptors (19), thereby provoking a Th1 proinflammatory response. Conversely, the Pf332 antigen seems to interact with a
different monocyte receptor that favors Th2 proliferation (17), which is associated with immunity to reinfection.

The hallmark of proinflammatory monocyte activation is the release of tumor necrosis factor-α (TNF-α), which has a pivotal role in the pathogenesis of acute malarial morbidity (14). Of equal significance is the release of IL-6, which is the main proliferative signal for Th1 cells. The latter secrete interferon-γ, which amplifies the monocyte response by a positive feedback mechanism (20). The observed increase in neopterin serum levels in malignant malaria is the consequence of this augmented release of interferon-γ.

Th1 activation also leads to B-lymphocyte proliferation, with IL-2–induced switching to IgG4 synthesis. This often leads to autoantibody formation that is usually associated with *P. falciparum* and *P. vivax* infections. Anticardiolipin, antiphospholipid (21), and antineutrophil cytoplasmatic (22) antibodies have been suggested to have a role in the pathogenesis of microvascular complications. Antibodies to triosephosphate isomerase (23) have been associated with prolonged complement-dependent hemolytic anemia after acute malaria.

Th2 activation has an immune modulatory function and is associated with immunity to reinfection. The release of IL-4 induces B-lymphocyte proliferation, favoring IgE and IgG4 synthesis (24). Together with IL-10, IL-4 downregulates the monocytes and inhibits the release of IL-8. In addition, Th2 lymphocytes have been recently shown to behave as proinflammatory cells. This is particularly manifest in cerebral malaria, where IgE antibody levels are considerably elevated (25). Malarial antigen-IgE antibody complexes are identified by CD23 monocyte receptors, leading to increased TNF-α generation through a nitric oxide–transduction mechanism. The interaction of TNF-α and IL-5 leads to eosinophil activation, which seems to be crucial in cerebral malaria (26).

Peripherally γ-δ T lymphocytes are strongly upregulated in malaria (27). They seem to have a mandatory role in the regulation of the early immune response and the elimination of chronic infection. However, their exact role in this respect is not yet understood.

*P. falciparum* directly activates C3 through the alternative pathway. This may be responsible for some of the immune-mediated phenomena that cannot be explained by the paucity of circulating immune complexes in this infection. It also activates the intrinsic coagulation cascade, which participates in the pathogenesis of thrombotic complications (14).

### Metabolic Disturbance

The metabolic abnormalities associated with plasmodial infection are the consequence of (1) perturbation of the host’s red cell membranes, (2) the parasite’s consumption of nutrients and cofactors, (3) repercussions of the described hemodynamic and immunologic disturbances, and (4) side effects of treatment.

#### Cell Membrane Abnormalities

In addition to the *de novo* synthesis of antigenic and adhesive polypeptides encoded by the parasite’s DNA, changes in the constitutive parasitized cell membrane structure may lead to important functional abnormalities. Most notorious in falciparum malaria is the inhibition of the erythrocyte magnesium-activated ATPase (28). This impairs the sodium pump in a “sick-cell syndrome” fashion, leading to internal dilution hyponatremia. Secondary calcium influx alters the calmodulin-dependent erythrocyte kinetics, reduces hemoglobin–cell wall interaction, and curtails red cell deformability. This further augments the peripheral hemodynamic derangement and increases the erythrocyte mechanical fragility. Shortened red-cell survival is, therefore, almost invariable in malaria.

Even nonparasitized red cells suffer membrane changes that lead to rosette formation. Many factors have been incriminated in this phenomenon, including parasite-derived rosettins (11), Ig-, and other plasma protein abnormalities. As mentioned earlier, rosette formation is an important contributor to the disturbed peripheral blood rheology in malaria.

It is not clear whether the same or other factors or the abnormal cytokine profile that supervenes in malaria is responsible for the hepatocyte membrane abnormality that leads to cholestatic jaundice in the majority of cases. The same question applies to leaky muscle membranes associated with malarial rhabdomyolysis (29).

#### Parasite’s Energy Consumption

Plasmodia consume large quantities of glucose for their own energy requirements. This seems to overwhelm the host’s compensatory mechanisms, often leading to clinically overt hypoglycemia. Quinine therapy may lead to further lowering of the blood sugar level owing to the stimulatory effect of the drug on the pancreatic β cells (29). Kinetic studies are awaited to confirm this hypothetical conflict between the energy needs of the host and the parasite.

A recent study also showed an increase of the serum transketolase activity in patients with falciparum malaria. This indicates thiamine depletion, which is attributed to the increased demand for the parasite’s glycolytic pathway (30). Because thiamine pyrophosphate is an essential coenzyme for several metabolic key reactions, its depletion may be an additional factor in depressing the host’s aerobic glycolysis, increased anaerobic glycolysis (Pasteur effect), and lactic acid accumulation. However, none of the clinical manifestations of severe malaria, particularly the neurologic, could be statistically correlated to measurable biochemical parameters of thiamine deficiency.

#### Tissue Hypoxia

The disturbed peripheral blood rheology induced by rosetting, clumping, and endothelial adhesion of parasitized red cells; the release of local cytokines; and the immune-mediated systemic inflammatory response all contribute to peripheral pooling and impeded tissue oxygenation.

The metabolic consequences of tissue hypoxia and potential impairment of glucose availability include increased lactic acid production with increased lactate/pyruvate ratio (29), depressed mitochondrial respiration (31), and increased generation of reactive oxygen molecules. Inducible nitric oxide generation and abnormal lipid peroxidation are documented consequences of the increased oxidative stress in falciparum malaria (32).
Clinical Profile

Malaria is a pyrexial illness that typically begins with a chill, followed by rapid increase in temperature that lasts for a few hours before resolving by crisis associated with excessive sweating. This cycle, which corresponds to the completion of one of the parasite’s erythrocytic cycles and subsequent lysis of infected red cells, may be repeated several times during the first day or two of clinical illness, then it occurs less frequently with a tendency to periodicity. Constitutional manifestations such as headache, malaise, and muscle and joint aches are usually encountered, more often in ex-patriots and during the first infection episode in natives. The spleen may be enlarged, particularly with relapsing disease. Anemia and neutrophil leukocytosis are prominent laboratory findings. The diagnosis is confirmed by direct visualization of the parasite in Giemsa-stained peripheral blood smears. Fluorescence staining with acridine-orange enhances the diagnostic accuracy of peripheral blood examination. DNA probes have been introduced but are not yet widely applicable. Serology is of limited diagnostic value, particularly in endemic areas.

The disease may become chronic if the sporozoan manages to establish a persistent extra-erythrocytic reservoir cycle in the liver, which may occur with non-falciparum infections. The latter notoriously progress to serious acute complications (Table 1).

Renal Involvement in Malaria

There are two major renal syndromes associated with Malaria (1): (1) a chronic and progressive glomerulopathy that mainly affects African children, classically complicating quaran malaria, and (2) ARF associated with falciparum malaria in Southeast Asia, India, and sub-Saharan Africa (Figure 2).

Chronic Malarial Nephropathy

*P. malariae* is the established cause of chronic malarial nephropathy (29), although a few cases have been recently associated with *P. vivax*. The disease affects children, usually 4 to 8 yr old. It presents as a steroid-resistant nephrotic syndrome. The characteristic histopathologic lesion is mesangio-
capillary glomerulonephritis, with subendothelial immune complex deposits containing IgG, C3, and malarial antigens. These deposits typically are seen as small lacunae in silver-stained biopsy sections. The disease proceeds to renal failure even after successful eradication of the infection.

Acute Malarial Nephropathy

ARF complicates falciparum malaria in fewer than 1 to 4.8% of native patients in endemic areas, yet it is much more frequent in nonimmune Europeans; reported figures usually are 25 to 30%. The contribution of malaria to the overall hospital admissions for ARF varies from 2 to 39% (29,33) according to the local prevalence of the disease, the relative preponderance of other causes, patient referral policy, and other factors.

*P. falciparum* is the causative species in the overwhelming majority of cases. *P. vivax* occasionally is incriminated. Most cases are oliguric, hypercatabolic, and associated with other malarial complications, probably depending on the relative impact of different pathogenetic mechanisms.

Jaundice is the most common association with malarial ARF, occurring in more than 75% of cases (34). It typically is “biphasic,” with an unconjugated component resulting from the excessive hemolysis and a conjugated element resulting from cholestasis. True malarial hepatitis also occurs in approximately 20% of cases, which is hallmarked by elevated serum transaminases, particularly alanine aminotransferase. Postmortem liver biopsy in such cases shows Kupffer cell hyperplasia, pigment deposition, foci of steatosis, and necrosis.

Anemia occurs in at least 70% of patients and is reported as being severe in 40%. It typically is hemolytic, although blood loss may also contribute. A recent report suggests the hemophagocytic syndrome as the cause of severe anemia in a Japanese patient who acquired falciparum infection during a visit to the tropics (35).

Thrombocytopenia occurs in 70% of cases, half of which develop an overt bleeding tendency. In the majority of cases, this is part of a disseminated intravascular coagulation initiated by the gross rheologic abnormality in severe malaria (29).

Peripheral blood pooling as a result of dramatic reduction of the peripheral vascular resistance occurs in two thirds of cases.
The effective arterial blood volume is reduced, and hypotension occurs on presentation in 20% of cases. A frank SIR syndrome occurs in approximately 5%. Occasionally, a patient may progress to acute respiratory distress (1).

Cerebral malaria is rarely associated with MARF. Unlike the latter, its incidence and severity correlate with intensity of infection (30), reflecting the importance of excessive erythrocyte rosetting as the most important single factor in the pathogenesis of cerebral malaria.

Proteinuria, usually less than 1 g/24 h, occurs in 60% of cases (29). It usually resolves completely with recovery from MARF. However, persistent proteinuria may be noticed in those who have significant interstitial or glomerular involvement (vide infra). There are no specific findings in the urinary sediment.

Hyponatremia is a typical biochemical finding in MARF, being reported in up to 55% of cases. Although internal dilution is the usual mechanism (vide supra), true sodium wastage that occurs before the onset of oliguria has been reported (1). The observed elevation of serum antidiuretic hormone (29) does not seem to play a significant role in the pathogenesis of hyponatremia in MARF (1).

Hyperkalemia is striking and often fatal. It is attributed to hemolysis, rhabdomyolysis, and acidosis, particularly in the presence of impaired renal function. Lactic acidosis is common, reflecting the degree of tissue hypoxia. Serum calcium is often reduced out of proportion of the phosphate retention, which may be due to hypoparathyroidism of unknown cause (36).

The histologic picture in MARF shows a variable mixture of acute tubular necrosis (ATN), interstitial nephritis, and glomerulonephritis (1) (Figure 3), thereby displaying the three major pathogenetic mechanisms described earlier (vide supra) (Figure 4). ATN is the most consistent histologic finding. Tubular changes include cloudy swelling, hemosiderin granular deposits, and variable degrees of cell necrosis. The tubular lumen often contain hemoglobin casts. The interstitium is edematous with a moderate to dense mononuclear cellular infiltration, and the venules may show clumps of parasitized erythrocytes.

Acute interstitial inflammation is a well-recognized pattern of malarial nephritis in rodents and after vaccination with P. falciparum antigens in monkeys. It is attributed to a massive influx of TH1 lymphocytes and is often associated with an acute glomerular lesion. Although isolated interstitial nephritis has not been reported in humans, interstitial inflammation is a common histopathologic associated with ATN and acute glomerulonephritis.

Glomerular lesions are detected in approximately one fifth of autopsies on patients with falciparum malaria. They are characterized by prominent mesangial proliferation with many transit cells. Mesangial matrix expansion is modest, and basement membrane changes are unusual. Deposition of an eosin-
philic granular material has been noticed along the capillary walls, within the mesangium, and in the Bowman’s capsule. The glomerular capillaries often are empty, but they may contain a few parasitized red cells or giant nuclear masses in patients who develop intravascular coagulation. Segmental necrosis may occur when the capillaries are occluded by erythrocyte rosettes. Immunofluorescence shows finely granular IgM and C3 deposits along the capillary walls and in the mesangium. Malarial antigens occasionally are seen, analogous with an animal model, along the glomerular endothelium as well as the medullary capillaries. Electron microscopy shows subendothelial and mesangial electron-dense deposits along with granular, fibrillar, and amorphous material (1,29).

Prognosis

ARF is a serious complication of malaria, with a reported mortality of 15 to 45%. Occasional reports from the West suggest that early treatment in well-equipped medical centers may reduce the mortality to nil. Similarly, a report from India described a reduction of MARF mortality from 75 to 26% when a specialized MARF task force was established in the same institution (37).

Risk factors for high mortality include late referral; short acute illness; high parasitemia; and presentation with oliguria, hypotension, severe anemia, or significant jaundice. Patients with severe diarrhea, multisystem involvement, hepatitis, or acute respiratory distress have a grave prognosis. In children, younger age and the absence of splenomegaly are associated with higher mortality. Opportunistic pulmonary viral or bacterial infections may be encountered in patients with MARF, increasing the risk of mortality by their own right.

Management

Chloroquine used to be the gold standard treatment for malaria. Although it remains effective against \( P. vivax \), \( P. ovale \), and \( P. malariae \), most \( P. falciparum \) strains are chloroquine resistant, with an increasing frequency in endemic areas. Alternative therapies include Fansidar (pyrimethamine + sulfadoxine); the Qinghaosu alkaloids, particularly artemether, artesunate, and atovaquone; and other chemotherapeutics such as mefloquine, benflumetol, and proguanil administered as monotherapy or in combination. Primaquine is still used in \( P. vivax \) and \( P. ovale \) to prevent relapses.

Intravenous quinine remains most widely used in the treatment of cerebral and other serious complications of falciparum malaria. However, it may induce hemolysis in G6PD-deficient patients, leading to fatal “black water fever” in severe cases. Cardiac toxicity is another important complication of quinine treatment, which can be avoided by monitoring the blood level and ECG changes. As mentioned earlier, quinine therapy often leads to hyperinsulinemia, which contributes to the characteristic hypoglycemia of malignant malaria. Quinine and chloroquine are scarcely removed by dialysis or hemofiltration (1), hence the necessity of monitoring their blood level in patients with prolonged oliguria. Both drugs induce hepatic cytochrome P450, hence the necessity to augment cyclosporine doses in kidney-transplanted patients (38).

The treatment of ARF usually poses challenging problems.
owing to the complexity of the syndrome. Large doses of frusemide have been consistently ineffective in altering the course of MARF. However, when used in conjunction with “renal dose” dopamine in early cases, it may obviate the need for dialysis. Other agents reported to be effective in reducing the need for dialysis in MARF include intravenous prostacyclin (1) and direct intrarenal infusion of the calcium channel blocker gallopamid (39).

Fifty to 80% of patients in different series require dialysis. Early dialysis is often needed to deal with the hypercatabolic state. Although peritoneal dialysis is less effective because of the complicating circulatory disturbances, it is often the only available dialysis modality in areas where malaria is endemic. In some cases, continuous arteriovenous hemofiltration or continuous peritoneal dialysis may be indicated. Exchange transfusion is helpful in patients with heavy parasitemia, those with severe jaundice, and those with the SIR syndrome with an overall reduction of mortality by 20% (40). Apheresis has been reported to successfully support anuric patients with cerebral and pulmonary complications (41).

There is no place for corticosteroids in the treatment of malaria. They have been reported as deleterious in cerebral malaria and at least ineffective in the management of other complications.

References