identified on the island of Borneo and, to a lesser extent, elsewhere in Southeast Asia, where the main hosts, long-tailed and pig-tailed macaques, are found.

The epidemiology of malaria is complex and may vary considerably even within relatively small geographic areas. Endemicity traditionally has been defined in terms of parasitemia rates or palpable-spleen rates in children 2–9 years of age and classified as hypoendemic (<10%), mesoendemic (11–50%), hyperendemic (51–75%), and holoendemic (>75%). Until recently, it was uncommon to use these indices for planning control programs; however, many countries are now conducting national surveys to assess program progress. In holo- and hyperendemic areas (e.g., certain regions of tropical Africa or coastal New Guinea) where there is intense *P. falciparum* transmission, people may sustain more than one infectious mosquito bite per day and are infected repeatedly throughout their lives. In such settings, rates of morbidity and mortality due to malaria are considerable during early childhood. Immunity against disease is hard won in these areas, and the burden of disease in young children is high; by adulthood, however, most malarial infections are asymptomatic. As control measures progress and urbanization expands, environmental conditions become less conducive to transmission, and all age groups may lose protective immunity and become susceptible to illness. Constant, frequent, year-round infection is termed *stable transmission*. In areas where transmission is low, erratic, or focal, full protective immunity is not acquired, and symptomatic disease may occur at all ages. This situation usually exists in hypoendemic areas and is termed *unstable transmission*. Even in stable-transmission areas, there is often an increased incidence of symptomatic malaria coinciding with increased mosquito breeding and transmission during the rainy season. Malaria can behave like an epidemic disease in some areas, particularly those with unstable malaria, such as northern India (the Punjab region), the horn of Africa, Rwanda, Burundi, southern Africa, and Madagascar. An epidemic can develop when there are changes in environmental, economic, or social conditions, such as heavy rains following drought or migrations (usually of refugees or workers) from a nonmalarious region to an area of high transmission, along with failure to invest in national programs; a breakdown in malaria control and prevention services caused by war or civil disorder can intensify epidemic conditions. This situation usually results in considerable mortality among all age groups.

The principal determinants of the epidemiology of malaria are the number (density), the human-biting habits, and the longevity of the anopheline mosquito vectors. More than 100 of the >400 anopheline species can transmit malaria, but the ~40 species that do so commonly vary considerably in their efficiency as malaria vectors. More specifically, the transmission of malaria is directly proportional to the density of the vector, the square of the number of human bites per day per mosquito, and the tenth power of the probability of the mosquito's surviving for 1 day. Mosquito longevity is particularly important because the portion of the parasite's life cycle that takes place within the mosquito—from gametocyte ingestion to subsequent inoculation (*sporogony*)—lasts 8–30 days, depending on ambient temperature; thus, to transmit malaria, the mosquito must survive for >7 days. Sporogony is not completed at cooler temperatures—i.e., <16°C (60.8°F) for *P. vivax* and <21°C (69.8°F) for *P. falciparum*; thus transmission does not occur below these temperatures or at high altitudes, although malaria outbreaks and transmission have occurred in the highlands (>1500 m) of eastern Africa, which were previously free of vectors. The most effective mosquito vectors of malaria are those, such as *Anopheles gambiae* in Africa, that are long-lived, occur in high densities in tropical climates, breed readily, and bite humans in preference to other animals. The entomologic inoculation rate (i.e., the number of sporozoite-positive mosquito bites per person per year) is the most common measure of malaria transmission and varies from <1 in some parts of Latin America and Southeast Asia to >300 in parts of tropical Africa.

ERYTHROCYTE CHANGES IN MALARIA

After invading an erythrocyte, the growing malarial parasite progressively consumes and degrades intracellular proteins, principally hemoglobin. The potentially toxic heme is detoxified by lipid-mediated crystallization to biologically inert hemozoin (malaria pigment). The parasite also alters the RBC membrane by changing its transport properties, exposing cryptic surface antigens, and inserting new parasite-derived proteins. The RBC becomes more irregular in shape, more antigenic, and less deformable.

In *P. falciparum* infections, membrane protuberances appear on the erythrocyte's surface 12–15 h after the cell's invasion. These "knobs" extrude a high-molecular-weight, antigenically variant, strain-specific erythrocyte membrane adhesive protein (PfEMP1) that mediates attachment to receptors on venular and capillary endothelium—an event termed *cytoadherence*. Several vascular receptors have been identified, of which intercellular adhesion molecule 1 is probably the most important in the brain, chondroitin sulfate B in the placenta, and CD36 in most other organs. Thus, the infected erythrocytes stick inside and eventually block capillaries and venules. At the same stage, these *P. falciparum*–infected RBCs may also adhere to uninfected RBCs (to form rosettes) and to other parasitized erythrocytes (agglutination). The processes of cytoadherence, rosetting, and agglutination are central to the pathogenesis of falciparum malaria. They result in the sequestration of RBCs containing mature forms of the parasite in vital organs (particularly the brain), where they interfere with microcirculatory flow and metabolism. Sequestered parasites continue to develop out of reach of the principal host defense mechanism: splenic processing and filtration. As a consequence, only the younger ring forms of the asexual parasites are seen circulating in the peripheral blood in falciparum malaria, and the level of peripheral parasitemia underestimates the true number of parasites within the body. Severe malaria is also associated with reduced deformability of the uninfected erythrocytes, which compromises their passage through the partially obstructed capillaries and venules and shortens RBC survival.

In the other human malarias, sequestration does not occur, and all stages of the parasite's development are evident on peripheral-blood smears. Whereas *P. vivax*, *P. ovale*, and *P. malariae* show a marked predilection for either young RBCs (*P. vivax*, *P. ovale*) or old cells (*P. malariae*) and produce a level of parasitemia that is seldom >2%, *P. falciparum* can invade erythrocytes of all ages and may be associated with very high levels of parasitemia.

HOST RESPONSE

Initially, the host responds to plasmodial infection by activating nonspecific defense mechanisms. Splenic immunologic and filtrative clearance functions are augmented in malaria, and the removal of both parasitized and uninfected erythrocytes is accelerated. The spleen is able to remove damaged ring-form parasites and return the once-infected erythrocytes to the circulation, where their survival period is shortened. The parasitized cells escaping splenic removal are destroyed when the schizont ruptures. The material released induces the activation of macrophages and the release of proinflammatory cytokines, which cause fever and exert other pathologic effects. Temperatures of ≥40°C (104°F) damage mature parasites; in untreated infections, the effect of such temperatures is to further synchronize the parasitic cycle, with eventual production of the regular fever spikes and rigors that originally served to characterize the different malarias. These regular fever patterns (quotidian, daily; tertian, every 2 days; quartan, every 3 days) are seldom seen today in patients who receive prompt and effective antimalarial treatment.

The geographic distributions of sickle cell disease, hemoglobins C and E, hereditary ovalocytosis, the thalassemias, and glucose-6-phosphate dehydrogenase (G6PD) deficiency closely resemble that of falciparum malaria before the introduction of control measures. This similarity suggests that these genetic disorders confer protection against death from falciparum malaria. For example, HbA/S heterozygotes (sickle cell trait) have a sixfold reduction in the risk of dying from severe falciparum malaria. Hemoglobin S–containing RBCs impair parasite growth at low oxygen tensions, and *P. falciparum*–infected RBCs containing hemoglobins S and C exhibit reduced cytoadherence because of reduced surface presentation of the adhesin PfEMP1. Parasite multiplication in HbA/E heterozygotes is reduced at high