Synonyms. The synonyms of malaria in general are ague, jungle fever, paludism. Synonyms of malaria due to *Plasmodium vivax*: benign tertian, vivax malaria. Synonyms of malaria due to *Plasmodium falciparum*: malignant tertian, subtertian, estivo-autumnal, E-A. falciparum malaria. Malaria due to *Plasmodium malariae* is designated quartan malaria or malariae malaria. Malaria due to *Plasmodium ovale* is designated ovale malaria.

Definition. Malaria is an acute and chronic infection characterized by fever, anemia, splenomegaly and often serious or fatal complications. It is caused by protozoa of the genus *Plasmodium*. Four species occur naturally in man, namely: *P. vivax* (Grassi and Feletti, 1890), Labbé, 1899; *P. falciparum* (Welch, 1897) Schaudinn, 1902; *P. malariae* (Laveran, 1881) Grassi and Feletti, 1890; and *P. ovale* Stephens, 1922. There are many strains in these four species.

Distribution. The normal range of malarial infections is between 45° north and 40° south latitude. In certain areas these limits are wider (Fig. 38-1). Malaria due to *P. vivax* is more widely distributed than the other types. It is the prevalent infection in most areas within the temperate zones but is widespread throughout the tropics as well. *Plasmodium malariae* is comparatively rare; it is observed most commonly in temperate areas and in the subtropics. *Plasmodium falciparum* tends to predominate throughout all tropical regions. *Plasmodium ovale* is relatively uncommon; the majority of cases have been reported from Africa, although some have been found in Asia, Europe and South America.

Etiology. The life cycle of the parasites causing malaria in man consists of an exogenous sexual phase, termed sporogony, with multiplication in certain anopheline mosquitoes, and an endogenous asexual phase, termed schizogony, with multiplication in man.

The exogenous, or anopheline, phase of the cycle begins when a suitable anopheline mosquito ingests blood containing the mature sexual forms, the gametocytes. Within a few minutes after reaching the insect’s stomach, the male cell or microgametocyte extends actively motile flagellum-like structures, each of which contains a portion of the nuclear chromatin of the parent cell (Fig. 38-2). These flagella shortly become detached to form microgametes, which migrate to the female cell or macrogametocyte. Meanwhile the latter has undergone maturation in preparation for fertilization. Completion of these changes marks the end of gametogony; subsequent fertilization of the macrogamete by a microgamete initiates the processes of sporogony.

When a microgamete enters the female cell, fusion of the nuclear chromatin from each parent occurs, and shortly thereafter the fertilized cell elongates and becomes motile, forming the ookinetes or traveling vermicle. This penetrates the wall of the mosquito’s stomach, finally lodging beneath the outer layer.

It then undergoes progressive vacuolization to form a growing oocyst (Fig. 38-3). The nuclear chromatin subdivides repeatedly, its particles becoming arranged along cytoplasmic strands bordering the vacuoles. From each particle of chromatin in the protoplasmic mesh a filamentous structure extends into the lumen of a vacuole. The chromatin particles become incorporated in these filaments to form sporozoites. At maturity the oocyst consists of a sponglike spherical body that projects into the body cavity of the insect. In a suitable infected vector several hundred oocysts may be found on
the stomach wall, although as a rule they are scarce (Figs. 38-3, 38-4).

Spontaneous rupture of the oocyst finally occurs. Liberated motile sporozoites, which may number several hundred to several hundred thousand, migrate throughout the body cavity of the mosquito, certain ones reaching and entering the salivary glands. Here they remain dormant until injected into man (Figs. 38-5, 38-6).

The duration of the exogenous phase of the cycle, termed the extrinsic incubation period, varies with the species of *Plasmodium*, with the vectors, and with conditions of temperature and humidity. Under favorable conditions, *P. vivax* and *P. falciparum* complete their development in the mosquito within 7 to 14 days; *P. ovale* requires several

Figure 38-2. Exflagellation of male gametocyte.

Figure 38-3. Fresh unstained preparation showing oocysts on wall of mosquito's stomach.

Figure 38-4. Various stages in development of oocysts—showing sporozoite formation and pigment masses. (Courtesy of Mr. P. G. Shute, F.R.E.S., Ministry of Health, Epsom, England.)
CYCLE IN MAN

Figure 38-5. Life cycle of Plasmodium. (Modified from Bruce-Chwatt and Alvarado. Courtesy of the University of Florida College of Medicine, Gainesville.)
days longer and *P. malariae*, the slowest, may require 3 weeks or more.

The *endogenous* or *human phase* of the cycle begins with the injection of sporozoites by an infected anopheline mosquito. The sporozoites disappear from the peripheral blood after about a half hour, initiating the exo-erythrocytic stage. The parasites next appear in the parenchymal cells of the liver.

The *P. falciparum* parasites in the liver are 15 μm in diameter by the third day after inoculation, contain 40 or more nuclei, and small vacuoles may be present (Fig. 38–7A). As the parasite grows, there is a gradual increase in the number of nuclei; cords or islands of cytoplasm appear from which the merozoites are formed. After about 6 days the parasite is mature, is irregular in shape with lobes or projections, is about 60 μm in longest diameter and produces about 40,000 merozoites. The release of the merozoites from the mature schizont coincides with the appearance of ring stages in the erythrocytes of the peripheral blood (Fig. 38–7B). This primary development constitutes the pre-erythrocytic stage of the endogenous cycle.

The rate of development and some of the morphologic characteristics of the parasite in the liver vary with the species of parasites: *P. vivax* has a cycle length of 8 days, with a mature schizont that is round, 45 μm in size, and which contains 10,000 merozoites; *P. ovale* requires 9 days for development, has an irregular multilobular mature schizont about 80 × 50 μm, and produces 15,000 merozoites; *P. malariae* requires 15 days, with a mature schizont that is oval, mean diameter of 51 μm, and produces 7,500 to 18,600 merozoites.

The pre-erythrocytic parasites do not contain pigment. Except for the destruction of the parasitized parenchymal cells, there is little evidence of injury to the liver.

In relapsing malaria, such as *P. vivax*, the evidence indicates that the exo-erythrocytic parasites persist in the liver parenchymal cells. After a latent period, merozoites are produced which invade the erythrocytes (Fig. 38–7B), producing a parasite relapse and, if in sufficient quantities to produce symptoms, a clinical relapse (Fig. 38–5).

**MORPHOLOGY.** All forms that occur in the blood stain well with Romanowsky stains; the cytoplasm is blue and the chromatin or nuclear substance is bright red. Pigment produced by the parasite in its growth appears as brownish or blackish granules. The earliest form seen in erythrocytes consists of a small ring of blue-stained cytoplasm with one or two dots of chromatin, giving rise to
Figure 38-7. 1. Exo-erythrocytic stages of *Plasmodium falciparum* in liver. 1, This is one of the smallest parasites seen. Diameter 15 μm. Probably 3 days old. 2, A larger parasite than that shown in 1. Sections cut at 2 μm and stained with Delafield's hematoxylin. 3, A larger stage than that in preceding figures. 4, A still larger stage with nuclei and cytoplasm more condensed on the left side. Note that although sinusoids may be seen clearly on each side of the parasite, the parasite is not in contact with these spaces. 5, A parasite approaching maturity with vacuolization cutting the cytoplasm into cords and islands (Shortt's "pseudocytomeres"). Note the growth of the parasite around the unchanged nucleus of the hepatic epithelium. 6, A mature schizont. Note the cords and islands in the parasite and the formation of merozoites, especially at the top of the parasite. Diameter about 60 μm. (Courtesy of Jeffery, Wolcott, Young, and Williams: Am. J. Trop. Med. Hyg. 7:917, 1952.)
the descriptive term "signet ring." In the course of a few hours the ring develops into an actively motile ameboeid form, the trophozoite. This term is applied to all the more mature intermediate stages in which the chromatin still appears as a single mass. Later in development the chromatin undergoes repeated division. Stages that exhibit cleavage of the chromatin without segmentation of the cytoplasm are referred to as presegmenting schizonts. When division of both the chromatin and cytoplasm has been completed, the form is termed a mature schizont, each member of the resulting new generation of parasites being called a merozoite.

Gametocytes are less numerous than asexual forms and therefore do not become readily apparent during the first schizogonic generations of vivax, ovale and malariae infections. In falciparum infections, gametocytes appear about the tenth day of parasite patency. In vivax, ovale and malariae infections, all forms from the early ring to the mature schizont and gametocyte are found in the peripheral blood. In falciparum infections, on the other hand, only rings and gametocytes are usually demonstrable. The intermediate development of this species occurs in the capillaries of the viscera, and the intermediate stages are seen in the peripheral blood only infrequently and are usually associated with heavy infections.

*Plasmodium vivax.* The young plasmodia appear in Giemsa-stained blood films as delicate rings of blue cytoplasm, each with a red bead of chromatin, the so-called "signet ring." They are approximately one-third the diameter of a normal red blood cell. The chromatin dots are usually but not invariably single, and ordinarily not more than one parasite is observed within a single red cell. The ring undergoes rapid growth and development, the cytoplasm becomes heavier and thicker, and the chromatin mass enlarges. Within 5 or 6 hours yellowish brown pigment granules appear within the substance of the parasite, which now develops into an actively motile trophozoite with bizarre outlines in the stained film. The infected red cell is enlarged; it stains less deeply and may present a diffuse, bright red stippling, the Schüffner's dots; this stippling is not present in all cases. When the parasite fills or nearly fills a considerably enlarged and pale red cell, motility ceases, and the chromatin undergoes successive divisions into 12 to 24 fragments, with an average of 16. The cy-

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**Figure 38-7 Continued.**

B. This inverted microscope sequence shows (from upper left to lower right) the invasion of a red blood cell by a malaria parasite (arrow). Following attachment of the parasite to the red blood cell, there is a marked distortion of the red blood cell followed by the relatively slow invasion of the red blood cell by the parasite. (Courtesy of B. Plochinik; The NIH Record, March 23, 1975.)
Figure 38-8. *Plasmodium vivax*. 1. Normal sized red cell with marginal ring form trophozoite. 2. Young signet ring form trophozoite in a macrocyte. 3. Slightly older ring form trophozoite in red cell showing basophile stippling. 4. Polychromatophilic red cell containing young tertian parasite with pseudopodia. 5. Ring form trophozoite showing pigment in cytoplasm, in an enlarged cell containing Schüffner's stippling. (Schüffner's stippling does not appear in all cells containing the growing and older forms of *P. vivax* as would be indicated by these pictures, but it can be found with any stage from the fairly young ring form onward.) 6. 7. Very tenuous medium trophozoite forms. 8. Three ameboid trophozoites with fused cytoplasm. 9, 11, 12, 13. Older ameboid trophozoites in process of development. 10. Two ameboid trophozoites in one cell. 14. Mature trophozoite. 15. Mature trophozoite with chromatin apparently in process of division. 16, 17, 18, 19. Schizonts showing progressive steps in division (presegmenting schizonts). 20. Mature schizont. 21, 22. Developing gametocytes. 23. Mature microgametocyte. 24. Mature macrogametocyte. (Courtesy of the National Institutes of Health, U.S.P.H.S.)
The length of the asexual cycle varies from 42 to 47 hours, depending upon the strain of *P. vivax*.

The mature male gametocyte is often about the size of a normal red cell and lies within an enlarged decolorized erythrocyte; its cytoplasm stains a light grayish or pinkish

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**Figure 38-9.** *Plasmodium vivax* in thick smear. (Courtesy of the National Institutes of Health, U.S.P.H.S.)

1. Ameboid trophozoites.
2. Schizont–2 divisions of chromatin.
5. Blood platelets.
7. Eosinophil.
blue, and the chromatin appears as granules loosely aggregated in the center or distributed as a transverse band. The pigment is darker than in the schizont and is uniformly distributed. The female gametocyte may be almost twice the size of a normal erythrocyte: its cytoplasm takes a deep blue stain, and the chromatin is compact, usually situated near the periphery.

*Plasmodium falciparum.* The young rings are smaller and more delicate than those of *P. vivax*; they are often hairlike and may show single or double chromatin dots. Multiple infection of erythrocytes is com-

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Figure 38-11. *Plasmodium falciparum*—thick film. (Courtesy of the National Institutes of Health, U.S.P.H.S.)

1. Small trophozoites.
2. Gametocytes—normal.
3. Slightly distorted gametocyte.
4. "Rounded-up" gametocyte.
5. Disintegrated gametocyte.
8. Cellular remains of young erythrocyte.
Plasmodium falciparum. The ring forms appear as a fine blue line with a delicate chromatin dot, apparently applied to the margin of a red cell. Plasmodium falciparum remains in the ring stage longer than most species of Plasmodium. The rings increase only slightly in size and remain smaller and more delicate. After a few hours, ring forms disappear from the peripheral circulation to undergo further development in the capillaries of the viscera. There, immature and mature forms appear as small masses of light-stained cytoplasm containing a chromatin granule, which is only slightly larger than that of the ring, and a small round mass or block of black pigment. Unlike P. vivax and P. malariae, which have diffuse pigment that forms an aggregate late in schizogony, the pigment of P. falciparum appears as a solid block in the young trophozoite shortly after the ring stage. The mature stages of the parasite are only about two-thirds the size of a normal red blood cell (Figs. 38-10, 38-11).

Parasitized cells of the peripheral blood may show cell-like or comma-like red markings, Maurer’s dots. These are larger and less numerous than the Schüffner’s dots. The infected red blood cells are not enlarged or decolorized. The time required by P. falciparum for completion of one generation of schizogony is about 48 hours. From 8 to 24 merozoites are formed.

The gametocytes are elongated, usually curved, sausage-shaped bodies. The male, or microgametocyte, stains lightly. Its chromatin is loose and scattered, and abundant granular brownish pigment is dispersed through the cytoplasm. The female, or macrogametocyte, is often more slender, longer, and stains more deeply blue. Its chromatin tends to appear as a compact mass in or near the center, and the pigment is usually closely approximated to the chromatin. The gametocytes or “crescents” first appear after several generations of schizogony and subsequently recur in successive waves, usually following waves of trophozoites.

Plasmodium malariae. The ring forms of P. malariae are about the size of those of P. vivax. Trophozoites are more compact, less ameboid and tend to assume round or ovoid shapes. Band forms are common. The parasite extending as a band across the infected cell. The pigment is darker brown, coarser, and appears in greater quantity and earlier than with P. vivax. The mature schizont fills or nearly fills an unenlarged and normally stained red cell. Six to 12 merozoites are formed; the usual number is eight. These are arranged about the centrally collected pigment mass, giving rise to a “daisy head” or rosette appearance. The asexual cycle requires 72 hours. Gametocytes present the same differences between the sexes with respect to staining qualities and arrangement of chromatin granules as in P. vivax (Figs. 38-12, 38-13).

Plasmodium ovale. This relatively uncommon species resembles P. vivax in many respects. Infected cells very early may show large numbers of coarse Schüffner’s dots. The growing trophozoites exhibit relatively little ameboid activity and consequently are more compact and more regular in outline than P. vivax. Band forms are noted frequently. The mature schizonts form six to 12 merozoites, with an average of eight. The gametocytes resemble those of P. vivax and are difficult to distinguish from them. The infected red cells are less enlarged than in P. vivax infections but are decolorized. The margin of the infected cell is often crenated or fimbriated and the cell tends to be oval in shape (Fig. 38-14). The asexual cycle lasts about 56 hours.

Host-Parasite Relationship. Following injection of sporozoites by infected mosquitoes at the end of the extrinsic incubation period, the parasites develop in the liver parenchymal cells. Upon the maturation of these pre-erythrocytic stages, merozoites are released which invade erythrocytes, marking the end of the prepatent period. For the detection of the parasites by ordinary microscopic examination of the thick blood smear, a minimum of ten parasites per cubic millimeter of blood is normally required.

The prepatent periods vary according to species, the usual lengths being: P. vivax, 12 to 14 days; P. falciparum, 10 to 13; P. ovale.
12 to 20, and P. malariae, 27 to 37. These periods may be shortened, but not to less than 5 days, by inoculations of larger numbers of sporozones, or lengthened by the injections of fewer sporozones.

The interval between the infective bite and the first elevation of temperature to 37.8° C (100° F) is termed the intrinsic incubation period. It may coincide with the prepatent period; rarely is shorter, and more often is 1 or 2 days longer. Some P. knowlesi infections may have protracted incubation periods of 9

Figure 38-13. Plasmodium malariae in thick smear. (Courtesy of the National Institutes of Health, U.S.P.H.S.)

1. Small trophozoites.
2. Growing trophozoites.
4. 5. 6. Schizonts (presegmenting) with varying numbers of divisions of the chromatin.
7. Mature schizonts.
8. Nucleus of leukocyte.
10. Cellular remains of young erythrocytes.

Free translation of legend accompanying original plate in "Guide pratique d'examen microscopique du sang appliqué au diagnostic du paludisme" by Georges Villain. Reproduced with permission from "Biologic Medicale" supplement, 1935.

(Courtesy of Aimée Wilcox, National Institutes of Health Bulletin No. 180, U.S.P.H.S.)
months or more, and *P. ovale* of several years. The febrile reaction is related to the sporulation of parasites. The densities of the parasites at the first fever in a nonimmune person usually are between 10 and 100 per cu mm, but they may be below densities (10 per cu mm) detectable by ordinary microscopic examination or, especially in persons with high immunity, may be in the thousands per cu mm. In general, *P. falciparum* has greater densities in all stages of the asexual cycle than do the other species.

There are fundamental differences in the invasive characteristics of these three species of *Plasmodium*. These differences are to a considerable extent responsible for the marked variations in severity of the disease produced by them.

*Plasmodium vivax* attacks the reticulocytes almost exclusively and appears incapable of invading mature erythrocytes. This imposes a limit on the magnitude of the parasitemia, which usually ranges from 8000 to 20,000 per cu mm and only rarely exceeds 50,000 per cu mm.

*Plasmodium falciparum*, however, invades all the red cells irrespective of age. There is consequently no limiting factor to prevent progressively increasing parasitemia. Very high densities may therefore be encountered in *falciparum* infections. A parasitemia of 500,000 parasites per cu mm carries a grave prognosis, and even low parasite densities should be considered dangerous. Unlike *P. vivax* and *P. malariae*, *P. falciparum* induces physical changes in the infected red blood cells which contribute importantly to the pathology of the infection. The infected cells agglutinate and adhere to the capillary endothelium. These effects produce capillary obstruction and ischemia in many tissues of the body.

*Plasmodium malariae* attacks predominantly the mature erythrocytes. Parasitemias exceeding 20,000 per cu mm are uncommon. After the acute primary attack, the infection tends to become chronic, often persisting for years in a patent or subpatent condition.

**Characteristics of *P. vivax* Infections.** In the early stages of infection by *P. vivax*, usually two groups of parasites undergo schizogony concurrently, maturing on alternate days. This results in the release of a new generation of merozoites each day and a corresponding quotidian febrile reaction. Gradually or suddenly one group may drop out. Maturation of the single group or brood of parasites then occurs in 42 to 47 hours, and the accompanying febrile curve becomes characteristically tertian, appearing progressively earlier every other day. In an untreated case a second group ultimately may reappear, its members gradually increasing in numbers as the others decrease, and the fever again becomes quotidian. The naturally evolving *vivax* infection, therefore, consists of a series of such alternating and overlapping groups with corresponding periods of tertian and quotidian fever. The latter type of curve depends upon this phenomenon and not, as has been said in the past, upon double infection acquired on different days. Gametocytes infective to mosquitoes appear in the peripheral blood within a few days after the end of the prepatent period.

**Characteristics of *P. falciparum* Infections.** Infections by *P. falciparum* differ in certain important respects from those by *P. vivax*. The period required for maturation of the parasites is approximately 48 hours, and schizogony is less synchronized. Release of the new generation of parasites is continued over a longer period. As a result, the febrile episodes are less regular and more prolonged in duration. In severe infections the fever frequently is continuous.

Gametocytes do not appear in the peripheral blood until about 10 days after the onset of the primary parasitemia. They become infective for mosquitoes about 4 days later. In naturally evolving infections, as the gametocyte count rises, the trophozoite count diminishes, and clinical improvement or remission of symptoms frequently occurs. The primary parasitemia is characterized by such a series of successive trophozoite-gametocyte waves. Parasite counts in *falciparum* malaria characteristically fluctuate much more markedly than do those of *vivax*, often showing alternating high and low densities on successive days.
Characteristics of P. malariae Infections. In the early stages of infections by P. malariae, there is usually only one group of parasites undergoing schizogony. The febrile episodes, therefore, recur at intervals of approximately 72 hours. Subsequently one or two additional groups may appear, producing a double quartan fever or even quotidian fever. Gametocytes usually are scanty.

Characteristics of Mixed Infections. When two species of malaria are present in the human host simultaneously, there appears to be an antagonism between them. If P. falciparum and P. vivax are both present, the former predominates initially, after which the vivax runs its course. When P. vivax and P. malariae are together, the P. vivax is the dominant species initially, sometimes to the complete expulsion of the P. malariae. Plasmodium vivax is even more dominant over P. ovale when the two are together than over P. malariae.

The Primary Attack and Relapses. Study of naturally induced mosquito-transmitted vivax infection indicates that in wholly susceptible persons the patent primary parasitemia may persist for as long as 3 months. In the course of this period, however, there may be transitory intervals when the parasite densities are depressed. Such depressions are accompanied frequently by clinical remissions. The duration of clinical symptoms is considerably shorter than the total period of primary parasitemia, and it may be continuous or interrupted by one or more remissions. Any clinical activity occurring within this period is considered part of the primary attack of malaria.

Disappearance of the asexual parasites for several weeks, either naturally or because of treatment, marks the end of the primary attack. The exo-erythrocytic parasites persist in the parenchymal cells of the liver; and it is believed that, after a latent period, these produce parasites which again invade the erythrocytes, causing relapses. The intervals to relapse after noncurative treatment vary. In some vivax strains, this interval may be 9 to 10 months, in others several weeks. In contrast to vivax infections, the exo-erythrocytic forms of falciparum are short-lived and do not persist in the liver.

The natural duration of malaria infections varies. Experimentally induced infections of a single vivax strain may persist for 12 or 18 months. Some of the vivax strains acquired in the Pacific during World War II persisted for as long as 4 years. Plasmodium falciparum experimental infections endure an average of 7 to 9 months, with a small proportion lasting 17 months. Plasmodium malariae may persist for many years, most of the time without a demonstrable parasitemia or clinical symptoms. Plasmodium ovale apparently relapses only infrequently and only rarely persists longer than 1 year.

Immunity. Experimental studies have indicated that infections by P. vivax and P. falciparum produce a partial homologous immunity. This is strictly strain-specific, the individual becoming partially or totally refractory to subsequent reinfection by the strain previously used. He is not immune, however, to other strains of the same species, although the severity of the infection produced by them may be modified. There is no cross-immunity between species; thus, infection by P. vivax confers no immunity against P. falciparum, and the clinical disease produced by the latter is unmitigated in severity. The Negro race has an immunity against P. vivax.

The development of immunity is characterized initially by the acquisition of tolerance to the infection. This is expressed by cessation of clinical phenomena despite persistence of a parasitemia considerably in excess of that which accompanied the onset of the initial clinical activity. It apparently represents a form of immunity depending upon a persisting latent infection. The defense mechanism, however, is probably largely cellular in nature. This immunity, expressed as tolerance and premunition, is of great importance in the epidemiology of malaria. Agglutinins, precipitins, complement-fixing and fluorescent antibodies are produced. There is a marked increase in immunoglobulins IgM, IgA and IgG shortly after parasite patency with a decrease in the albumin-globulin ratio. The rise in titers of
the immunoglobulins generally parallels the increase in parasite density until the parasitemia peak. At that time IgM and IgA decline; IgG may remain elevated for long periods.

Fluorescent antibodies contribute to the increase of total immunoglobulins but tend to persist long after the percentages of the latter have returned to preinfection levels. The IgG fluorescent antibodies persist longer than the IgM or IgA so that the former may be used epidemiologically to measure past infections. Since IgM disappears more rapidly, a high response to it and to IgG indicates a current infection or an infection within the past 1 to 3 months.

Persons with elevated immunoglobulin levels may develop parasitemias owing to relapses or reinfections.

A small fraction of the IgG and IgM antibodies may exert a protective effect against infections. When given to malarious children, parasitemias were suppressed and symptoms were alleviated temporarily.

Attempts to produce vaccines in the past met with little success. Recently, however, a merozoite vaccine of *P. knoedleri*, a monkey malaria, gave partial or complete protection against challenges of the same or variant strains in rhesus monkeys. Also, the first active immunization of man against sporozoites has been achieved. Several volunteers who received large numbers of X-irradiated *P. falciparum* or *P. vivax* sporozoites were protected against later exposure to homologous and heterologous strain sporozoites of the same species. The duration of this immunity does not appear to exceed 6 months and it was ineffective against blood-induced infections.

Congenital malaria appears to be relatively common in babies born to nonimmune but infected mothers. However, congenital malaria is very rare in African babies of immune mothers, although the placentas are frequently infected, sometimes heavily, with *P. falciparum* (Fig. 38-15). The birth weight of these babies is often subnormal. The reason for the rare occurrence of congenital malaria in highly endemic areas is not known.

It has been suggested that sickle-cell trait or glucose-6-phosphate dehydrogenase deficiency confers some protection against malaria. This would be mainly by increasing survival rates.

Figure 38-15. Section of placenta from a patient with *P. falciparum* infection. Numerous red blood corpuscles in the intervillous space (maternal side) are parasitized (arrows); the corpuscles in the chorionic villus (fetal side) are not parasitized. (Courtesy of the Louisiana State University School of Medicine, New Orleans.)
Epidemiology. Malaria has a high morbidity rate and until recently was responsible for more deaths per year than any other transmissible disease. As recently as 1955, it was estimated that there were 250 million cases of malaria with 2.5 million deaths annually. Eradication programs in many parts of the world have greatly reduced the prevalence of malaria. At the end of 1972, it was estimated that of the 1840 million people then living in the originally malarious areas of the world for which information is available, 73 per cent were in areas where malaria has been eradicated or where eradication programs were in progress. The remainder, approximately 494 million, were in areas where eradication programs were not yet in operation, although control measures were in effect in some places. Malaria is the major health problem in many countries.

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<table>
<thead>
<tr>
<th>Region</th>
<th>Area</th>
<th>Species</th>
<th>Light Requirements</th>
<th>Water, Vegetation, Etc.</th>
<th>Adult Behavior</th>
<th>Efficiency as a Vector</th>
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<tbody>
<tr>
<td>Neotropical</td>
<td>United States (and bordering areas):</td>
<td>Anopheles freeborni</td>
<td>Sun</td>
<td>Fresh, clear seepage from ditches, rice fields, edges of slow streams; irrigation water</td>
<td>Enters houses, feeds readily on man</td>
<td>Was dangerous in interior valleys of western U.S.</td>
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<td>Dixie portions of Rocky Mountain and Pacific area and N.W. Mexico</td>
<td></td>
<td>Sea usually, sometimes in partial shade</td>
<td>Fresh, pools, ponds, lakes, bogs, swamp, slow flowing rivers, dense aquatic vegetation</td>
<td>Active at night; feeds on human or animal blood; may remain in houses all day</td>
<td>Was most important carrier in the eastern U.S.</td>
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<td>Coastal Mexico to New Hampshire and Ontario west to Minnesota</td>
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<tr>
<td>Neotropical</td>
<td>Mexico, Central America (and bordering areas):</td>
<td>A. albimanus</td>
<td>Sun or partial shade</td>
<td>Fresh or brackish, fairly pure, stagnant water; rooted vegetation favorable in large lakes, swamps; lagoons, flood plains</td>
<td>Nocturnal; prefers man, but does bite animals; enters houses, usually leaves at dusk after feeding</td>
<td>Most important vector in Central America and Caribbean, especially in rainy season</td>
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<td>S.E. Texas, through Mexico and West Indies, south to Colombia and Ecuador; east through northern Venezuela</td>
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<td>Mexico</td>
<td>A. atroparvus</td>
<td>Sun</td>
<td>Clear pools, streams and springs rich in algae, in dry season</td>
<td>Enters and rests in houses</td>
<td>Most important vector in some areas</td>
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<td>See South America, etc. for:</td>
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<td></td>
<td>South Central U.S., south to Chile and Argentina; Grenada</td>
<td>A. darlingi</td>
<td>Sun</td>
<td>Clear pools, streams and springs rich in algae, in dry season</td>
<td>Enters and rests in houses</td>
<td>Most important vector in some areas</td>
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<td>Mexico, through Central America and Trinidad to Peru, Brazil</td>
<td>A. pseudopunctipennis</td>
<td>Shade-preferring</td>
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<td>Caribbean area:</td>
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<td></td>
<td>Trinidad and Brazil</td>
<td>A. albimanus</td>
<td>Sun or shade</td>
<td>Backlands, tidal swamps, rainwater; rice fields; ponded swamps; swamps; marshland; swamps; floods; flooded lands; swamps; swamps</td>
<td>May fly 3 miles; enters houses; feeds on man (first 3 miles in Panama)</td>
<td>Important in mountain valleys of South America, Central America and Mexico</td>
</tr>
<tr>
<td></td>
<td>South America (and bordering areas):</td>
<td>A. aegypti</td>
<td>Shade-preferring</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>See Mexico, C.A. for:</td>
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<tr>
<td></td>
<td>S. Brazil</td>
<td>A. albimanae</td>
<td>Sun or shade</td>
<td>Backlands, tidal swamps, rainwater; rice fields; ponded swamps; swamps; marshland; swamps; floods; flooded lands; swamps; swamps</td>
<td>May fly 3 miles; enters houses; feeds on man (first 3 miles in Panama)</td>
<td>Important in mountain valleys of South America, Central America and Mexico</td>
</tr>
<tr>
<td></td>
<td>Guatemala to N.E. Argentina and Paraguay; Trinidad</td>
<td>A. albimanus</td>
<td>Sun or shade</td>
<td>Leaf bases of bromeliads (epiphytes on Euphorbia and other trees)</td>
<td></td>
<td>Important in mountain valleys of South America, Central America and Mexico</td>
</tr>
<tr>
<td></td>
<td>Colombia, Venezuela</td>
<td>A. morsitans</td>
<td>Partial shade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Central America (below and Greater) South America (Venezuela to Argentina)</td>
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<tr>
<td></td>
<td>Colombia, Venezuela</td>
<td>A. morsitans</td>
<td>Sun or partial shade</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Central America (below and Greater) South America (Venezuela to Argentina)</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td>Colombia, Venezuela</td>
<td>A. pseudopunctipennis</td>
<td>Shade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Central America (below and Greater) South America (Venezuela to Argentina)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Region</td>
<td>Species</td>
<td>Type</td>
<td>Habitat</td>
<td>Behavior</td>
<td>Vector Information</td>
<td></td>
</tr>
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<td>------------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Europe</td>
<td>A. leucocytozoon felis</td>
<td>Sun</td>
<td>Brackish water along coast; fresh water inland</td>
<td>Frequent in houses; feeds primarily on human blood</td>
<td>Important vector</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sun to partial shade</td>
<td>Blackish coastal marshes; fresh water of rice fields, upland streams; tidal flats</td>
<td>Prefers human blood; enters houses in large numbers</td>
<td>Important vector</td>
<td></td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Vector in Hungary and Albania</td>
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</tr>
<tr>
<td></td>
<td>A. superpictus</td>
<td>Sun or shade</td>
<td>Marshes, rock pools, wells, chieftains</td>
<td>Domestic in Palestine; enters houses freely (especially in some regions)</td>
<td>Important in urban areas</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Vector in Egypt and Israel</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A. stephanhirs antilleanus</td>
<td>Sun</td>
<td>Freshwater pools, streams, drains, seaports, especially in fall districts</td>
<td>Essential hosts readily; lines mostly after dark; may migrate 2 miles</td>
<td>Important in urban areas</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Important in Europe, Middle East, Pakistan</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A. solani</td>
<td>Sun</td>
<td>Among algae along stream margins; rain pools, small pools of stream beds in hills</td>
<td>Bites man</td>
<td>Important vector</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A. falciparum</td>
<td>Partial shade</td>
<td>Clear water of swamps, weedy banks of streams, rivers, ditches; mangroves of lakes, ponds, under-ground seepages</td>
<td>Enters houses in large numbers; feeds freely on human blood; few migrates up to 400 miles</td>
<td>Always important (also carries malaria)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sun or light shade</td>
<td>Paddies, shallow ponds, borrow pits, hard plains, ditches, over-flowing; rarely rain barrels, cisterns</td>
<td>Prefers human blood, abundant in homes and houses; few migrates up to 400 miles</td>
<td>Always important (also carries malaria)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A. quartana</td>
<td>Sun to slight shade</td>
<td>Clear water in grassy holes, native wells, streams, swamps</td>
<td>Found commonly in human dwellings</td>
<td>Important where prevalent</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Among Pyons in open palm; swamps; stream margins (vegetation)</td>
<td>Abundant in houses in Nigeria; bites at night or at dawn</td>
<td>Important where common</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A. brumpti</td>
<td>Sun to slight shade</td>
<td>Among vegetation on margins of pools, streams, permanent swamps</td>
<td>Often found indoors</td>
<td>Rather important where common</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Clear water, in swamps (Pyons and other vegetation)</td>
<td>Found in native lands</td>
<td>Rather important where common</td>
<td></td>
</tr>
</tbody>
</table>

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*Table continued on the following page*
<table>
<thead>
<tr>
<th>Region</th>
<th>Area</th>
<th>Species</th>
<th>Light Requirements</th>
<th>Water, Vegetation, etc.</th>
<th>Adult Behavior</th>
<th>Efficiency as Vector</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sierra Leone, Liberia, Ghana, Nigeria, Cameroon—eastward to Mozambique</td>
<td><em>A. mali</em></td>
<td>Heavy shade</td>
<td>Among vegetation along sides of running streams</td>
<td>Common in huts and camps, hot rate in houses</td>
<td>Possibly important where prevalent</td>
<td></td>
</tr>
<tr>
<td>Coastal West Africa</td>
<td><em>A. messeae</em></td>
<td>Shade</td>
<td>Breeding associated with black mangrove trees (<em>Avicennia sp.</em>) or brackish water; coastal streams and tidal swamps</td>
<td>Feeds more on dark nights; most remain in huts after feeding</td>
<td>Important in some coastal areas of West Africa</td>
<td></td>
</tr>
<tr>
<td>Many parts of Africa: Malagasy Rep., Israel, E. Central and S. Africa: Zambia, Rhodesia, Sudan</td>
<td><em>A. pharoensis</em></td>
<td>Sun to partial shade</td>
<td>Swamps and rice fields; vegetation essential</td>
<td>Enters houses in large numbers; bites man readily but prefers animal blood</td>
<td>Important in upper Nile Province, Sudan, Mali</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>A. mygalus</em></td>
<td>Sun</td>
<td>Pools, marshes, hovens, artificial containers</td>
<td>Rests in crevices and outdoor basins near breeding places; occasionally found in large numbers indoors</td>
<td>Rhodesia Former Fr. W. Africa, Sudan, Angola of secondary importance</td>
<td></td>
</tr>
</tbody>
</table>

**Oriental**
- Afghanistan, Pakistan, India, Burma, Ceylon, whole Malay region and Philippines
- W. Pakistan to Burma; Sri Lanka, Thailand, Tonkin Prov., S. Arabia
- Indonesia, Sumatra, Java, Borneo, Lesser Sunda Islands, S. Celebes
- Philippine Islands
- Indochina, Malaya, Thailand, Vietnam
- India, Burma, Ceylon, China, Korea, Japan, Taiwan, Okinawa, Indonesia

<table>
<thead>
<tr>
<th>Species</th>
<th>Light Requirements</th>
<th>Water, Vegetation, etc.</th>
<th>Adult Behavior</th>
<th>Efficiency as Vector</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>A. serpens</em></td>
<td>Sun</td>
<td>Stagnant water of pools, ditches, wells, slow streams, irrigation ditches</td>
<td>Prefers cattle to man; flies great distances; occurs up to 2100 m.</td>
<td>Of secondary importance</td>
</tr>
<tr>
<td><em>A. stephensi</em></td>
<td>Sun</td>
<td>Stagnant water in rice fields, ponds, pools, ditches, backwater drainages</td>
<td>Prefers cattle but bites man freely; rests in cow sheds and houses during day</td>
<td>Most important vector in India; only vector in Sri Lanka</td>
</tr>
<tr>
<td><em>A. maculatum</em></td>
<td>Sun</td>
<td>Stagnant water in rice fields, ponds, pools, ditches, backwater drainages</td>
<td>Prefers human blood (14) found in large numbers in cow sheds, horse, and flocks</td>
<td>Important vector in rural flood plains (500-1000 meters)</td>
</tr>
<tr>
<td><em>A. trivittatus</em></td>
<td>Sun</td>
<td>Stagnant water in rice fields, ponds, pools, ditches, backwater drainages</td>
<td>Feeds readily on man; found in houses, cow sheds (500 to 750 m), strong flocks</td>
<td>Important in Bengal, Malaya, Vietnam, Indonesia</td>
</tr>
<tr>
<td><em>A. aegypti</em></td>
<td>Sun</td>
<td>Stagnant water in rice fields, ponds, pools, ditches, backwater drainages</td>
<td>Not recorded as domestic</td>
<td>Proved vector in some localities</td>
</tr>
<tr>
<td><em>A. albopictus</em></td>
<td>Sun</td>
<td>Stagnant water in rice fields, ponds, pools, ditches, backwater drainages</td>
<td>Not recorded as domestic</td>
<td>Important in Vietnam</td>
</tr>
<tr>
<td><em>A. gambiae</em></td>
<td>Sun</td>
<td>Stagnant water in rice fields, ponds, pools, ditches, backwater drainages</td>
<td>Not recorded as domestic</td>
<td>Vector in S. Japan, Korea, Okinawa, Indonesia and in China</td>
</tr>
</tbody>
</table>

Vector in Tonkin Prov.
<table>
<thead>
<tr>
<th>Country/Region</th>
<th>Species</th>
<th>Climate/Environment</th>
<th>Behavior/Feeding Habits</th>
<th>Important Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>India, Sri Lanka, Burma, S. China, Thailand, Malaya, Indonesia, Vietnam, Taiwan, Philippines</td>
<td><em>A. marshalli</em></td>
<td>Sun to very slight shade</td>
<td>Stagnant jungle pools and marshes; brackish water in mangrove swamps</td>
<td>Important in Malaya and Indonesia</td>
</tr>
<tr>
<td>Indonesia, Burma, etc. for</td>
<td><em>A. minimus</em></td>
<td>Shade</td>
<td>Stagnant pools, rice fields</td>
<td>Important in some areas</td>
</tr>
<tr>
<td>Indonesia, Burma, etc. for</td>
<td><em>A. marshalli</em></td>
<td>Shade</td>
<td>Stagnant pools, rice fields</td>
<td>Important in some areas</td>
</tr>
<tr>
<td>India, Sri Lanka, Burma, Thailand, Vietnam, China, Malaya, Sumatra, Java, Borneo, Celebes</td>
<td><em>A. minax</em></td>
<td>Sun and shade</td>
<td>Clear water of shaded streams, rivers, vegetated ponds, pools, floating insect</td>
<td>Of little importance (found infected in Malaya, Indonesia)</td>
</tr>
<tr>
<td>India, Sri Lanka, Burma, Thailand, Vietnam, China, Malaya, Sumatra, Java, Borneo, Celebes</td>
<td><em>A. triseriatus</em></td>
<td>Sun, largely</td>
<td>Clear water of shaded streams, rivers, vegetated ponds, pools, floating insect</td>
<td>Of some importance in Malaya and Indonesia</td>
</tr>
<tr>
<td>India, Sri Lanka, Burma, Vietnam, Malaya, Sumatra, Java, Borneo, Philippines</td>
<td><em>A. leucospis</em></td>
<td>Heavy shade required</td>
<td>Clear water of shaded streams, rivers, vegetated ponds, pools, floating insect</td>
<td>Found infected in Indonesia</td>
</tr>
<tr>
<td>India, Sri Lanka, Burma, Vietnam, Malaya, Sumatra, Java, Borneo, Philippines</td>
<td><em>A. minax</em></td>
<td>Sun or shade</td>
<td>Clear water of shaded streams, rivers, vegetated ponds, pools, floating insect</td>
<td>Believed important in Celebes</td>
</tr>
<tr>
<td>See Afghanistan, etc. for</td>
<td><em>A. albo-toxalbus</em></td>
<td>Shade</td>
<td>Fresh, brackish, or contaminated pools, borrow pits, swallows, roof gutters, containers</td>
<td>Important in New Guinea and in Solomon Islands</td>
</tr>
<tr>
<td>See Afghanistan, etc. for</td>
<td><em>A. solomonensis</em></td>
<td>Shade</td>
<td>Fresh, brackish, or contaminated pools, borrow pits, swallows, roof gutters, containers</td>
<td>Important in New Guinea and in Solomon Islands</td>
</tr>
<tr>
<td>See Australia, etc. for</td>
<td><em>A. solomonensis</em></td>
<td>Shade</td>
<td>Fresh, brackish, or contaminated pools, borrow pits, swallows, roof gutters, containers</td>
<td>Important in New Guinea and in Solomon Islands</td>
</tr>
<tr>
<td>Australia, New Guinea</td>
<td><em>A. solomonensis</em></td>
<td>Shade</td>
<td>Fresh, brackish, or contaminated pools, borrow pits, swallows, roof gutters, containers</td>
<td>Important in New Guinea and in Solomon Islands</td>
</tr>
</tbody>
</table>

*Some secondary and suspected vectors are not included.*
especially in the African region. The great importance of malaria as a military problem was demonstrated in World War I when, in the course of campaigns in Macedonia, the British, French and German armies were immobilized by this disease. In World War II it constituted the major problem of military medicine throughout the tropical and subtropical theaters, particularly in the Mediterranean, India, Burma, China, the Philippines and the south and southwest Pacific. In the latter area malaria had a profound effect upon the development and progress of military operations. In this region also a peculiarly resistant strain of *P. vivax* was encountered which was characterized by repeated relapses over an unusually long period. Experience in Korea demonstrated that malaria may be a problem for armies in the field even in the temperate zone. In the recent Vietnam conflict, malaria was a leading cause of casualties, a problem which was compounded by the presence of drug-resistant strains of *P. falciparum*.

The degree of endemicity or the level of transmission of malaria in any region is determined by a variety of interrelated factors. The most important of these are:

1. The prevalence of infection in man—the reservoir.
2. The species of indigenous anopheline mosquitoes, their relative abundance, their feeding and resting behaviors and their individual suitability as hosts for plasmodia—the vector.
3. The presence of a susceptible human population—the new host.
4. Local climatic conditions.
5. Local geographic and hydrographic conditions which determine anopheline breeding areas (Fig. 38-16, Table 38-1).

It is apparent, however, that there must be other controlling influences, for in areas in which the disease is endemic the prevalence of malaria over long periods exhibits cyclic increases and recessions, the causes of which are not understood.

In many parts of the world there is a definite annual fluctuation and a usual sequence in the times of appearance of the different types of the disease. These are probably dependent upon seasonal variations of temperature, humidity and rainfall affecting both the breeding of anopheline vectors and the development of the exogenous phase of the parasites in them.

The average climatic conditions in the temperate zone permit development and transmission of *P. vivax* and *P. malariae* but are less favorable to *P. falciparum*. These factors, together with relapse characteristics, undoubtedly are important in the seasonal incidence of the types of malaria in cooler parts of the endemic areas. In such regions *P. vivax* infections are the earliest to appear in the spring, whereas *P. falciparum* and *P. malariae* do not reach their peak until late summer and early autumn.

In the true tropics rainfall is the determining factor controlling anopheline breeding. In areas where there are wet and dry seasons each year there are commonly two peaks of incidence. The first follows shortly after the beginning of the rains. The second, and frequently the more important, appears at the end of the rainy season when ample anopheline breeding areas are present and when the destructive action of heavy rainfall upon the larvae is diminished.

In mountainous tropical countries both *P. vivax* and *P. falciparum* are prevalent in the hot, moist lowlands. At higher altitudes as the average temperatures more nearly approach those of temperate zones, *P. falciparum* gradually disappears. *Plasmodium vivax*, however, may be heavily endemic in certain regions at altitudes even in excess of 2400 m.

Evaluation of the malaria problem in any area entails study of all the known factors that contribute to the endemicity and the transmission of the disease.

*Malaria reconnaissance* provides a rapid, superficial and statistically inexact estimate of the situation. The data provided by such an investigation are insufficient for the preparation of a detailed control program.

A *malaria survey*, on the other hand, is an intensive, detailed, often time-consuming study of all relevant local factors. It should
be carried on throughout a year to secure accurate information adequate for planning a control program.

**EVALUATION OF INFECTION OF THE HUMAN RESERVOIR.** Evaluation of the degree of infection of the human reservoir is based upon the following findings:

**Spleen Rate.** This is the per cent prevalence of splenomegaly in children of the indigenous population 2 to 9 years of age inclusive. The age group may be varied in certain regions.

**Adult Spleen Rate.** When the number of children is insufficient, adults may be included in the figures. The prevalence of splenomegaly in the adult population is lower, however, and consequently the qualifying term “adult” must be included to avoid misinterpretation of the data.

**Parasite Rate.** This is the per cent prevalence of blood films showing malarial parasites. Children of the indigenous population 2 to 9 years of age inclusive are often used for this measurement.

**Transmission Index.** This is the per cent incidence of blood films showing malarial parasites in infants of the indigenous population under 1 year of age. It provides important information concerning variations in the seasonal transmission rate of malaria in the particular area and is the best indication of the effectiveness of control measures.

Certain arbitrary terms have been accepted to express the intensity of infection in a given area. These are rates in children 2 to 9 years of age and are as follows:

- **Hypoendemic:** spleen, 0 to 10 per cent; or parasite, 0 to 10 per cent (may be higher during part of the year).
- **Mesoendemic:** spleen, 11 to 50 per cent; or parasite, 11 to 50 per cent (may be higher during part of the year).
- **Hyperendemic:** spleen, over 50 per cent, adult spleen rate also high; or parasite, constantly over 50 per cent.
- **Holoendemic:** spleen, constantly over 75 per cent; adult spleen rate low, adult tolerance high; or parasite rate in infants (1 year age group) constantly over 75 per cent.

**THE INSECT VECTOR.** The definitive host of the plasmodia is the anopheline mosquito. There are over 200 known species of anophelines, of which over 60 have been incriminated as vectors of malaria.

Determination of the particular species which are or may be efficient vectors and estimation of their relative abundance in an area are essential functions of the malaria survey. The marked variation in the capacity among different species to transmit the disease depends upon certain fundamental biologic differences. Certain individuals within each species are physiologically unsuitable hosts, and the plasmodia cannot complete their development in them. Some anophelines are domestic, breeding and remaining in the vicinity of human habitations; others are forest dwellers, breeding in and rarely leaving the jungle. Many anophelines feed almost exclusively on animal rather than human blood, whereas others feed with equal frequency on blood from man or animals. Some remain in or close to dwellings after obtaining a blood meal; others immediately leave the human environment. Similarly, there are great variations in flight range. Some anophelines are weak fliers and travel only short distances, but the normal flight range of others may be several miles.

Malaria tends to be a “place” disease, with highest incidence close to important mosquito-breeding areas, and the location and description of such areas are therefore essential functions of the survey. In general, anopheline larvae require clear water, with an adequate content of algae for optimal growth. The typical habitats of different species vary greatly. Some species seek only sunlit water; others flourish in shade. Certain ones cannot utilize water containing even small amounts of salt; others thrive in brackish water containing 40 to 60 per cent sea water. Some species utilize streams or seepage areas, others only swamps and marshes. Such variations in specific habitats form the basis for so-called naturalistic control methods which are designed to alter the natural characteristics of a breeding area, rendering it unsuitable for larval development.

The final evaluation of the importance of a particular anopheline species as a vector of malaria is based upon certain specific procedures.

**Epidemiologic Index.** This expression
represents the attempt to establish a significant correlation between the prevalence of a particular species of anopheline and the transmission of the disease. It is seldom a practicable procedure and rarely affords dependable evidence.

Experimental Index of Infection. Laboratory-raised female anophelines of a given species are fed upon a human gametocyte carrier. They are subsequently dissected, and the percentage showing oocysts on the stomach wall and sporozoites in the salivary glands is noted. This procedure may give accurate information of the biologic suitability of the particular anopheline to serve as a definitive host for the Plasmodium. It does not provide information as to the importance of the species as a natural vector. A number of species, of no practical importance in the transmission of malaria, may nevertheless yield a high index of experimental infection.

Natural Index of Infection. Large numbers of captured female anopheline mosquitoes are dissected, and the per cent prevalence of oocyst formation on the stomach wall and of sporozoite infection in the salivary glands is noted. The prevalence of salivary gland infection provides the more important information. A salivary gland index as low as 0.1 per cent or even lower nevertheless indicates an important transmitter when the species is very abundant. Much higher rates may be encountered exceptionally. In the course of epidemic malaria in northeastern Brazil the salivary gland infection rate of Anopheles gambiae reached 30.2 per cent. (See p. 788.)

The Precipitin Test. The precipitin test applied to the gut contents of engorged mosquitoes provides a means of distinguishing between anthropophilic and zoophilic species (p. 837).

Pathology. Malaria is accompanied by

Figure 38-17. An ultrastructural view of the red pulp of the spleen in malaria. Severed (long arrow) red cell (R), one part having passed into sinus (S), with the parasitized (P) part remaining trapped in cord (C). Break has occurred in thin stalk that lies in the fenestration of basement membrane (Bm) and between two endothelial cells (En). Within the cord are two other parasite-containing pitted red cells, one showing a broken red cell stalk (short arrow). X 11,700. (Courtesy of Schmitzer, B., Sodeman, T. M., Mead, M. L., and Contacos, P. G. 1973. Blood 41: 207-218. Used by permission.)
the destruction of enormous numbers of red blood cells, both parasitized and non-parasitized, and by a consequent increase in the bilirubin content of the blood. The hemolysis may be so intense in *P. falciparum* infections as to cause hemoglobinuria and blackwater fever. Sequestration of red cells by the reticuloendothelial system is a major factor in the reduction of erythrocytes. In the spleen, malaria-parasitized erythrocytes are phagocytosed in toto by cordal macrophages, some are pitted of parasites, and others are hemolyzed by splenic microvasculature (Fig. 38–17). Severe grades of anemia may be produced and reticulocyte crisis may follow upon effective therapy. In chronic cases, however, the anemia may be refractory. At least three factors appear to contribute to this: the continued destruction of erythrocytes, the failure of the liver to reincert liberated iron and, in *P. vivax* infections, the selective parasitization of reticulocytes. Thrombocytopenia accompanies malaria, being most pronounced just preceding the maximum parasitemia. Platelet destruction appears to be caused by sequestration primarily in the spleen.

In chronic malaria there is characteristically a moderate leukopenia with an absolute increase in the number of monocytes.

Malarial pigment (hemozoin) is taken up by circulating polymorphonuclear leukocytes and monocytes and especially by the reticuloendothelial cells of the viscera. One of the striking features of the gross pathologic picture in patients who have died after prolonged infection is a slaty or blackish pigmentation of the organs, especially the spleen, liver and brain (Fig. 38–18).

The spleen varies in size, color and consistency, depending upon the duration and severity of the infection. Usually it is enlarged and dark or slate-colored. After long continued infections it may weigh 1000 gm or more. In acute malaria the spleen is congested and soft; the capsule is distended, and occasionally spontaneous or traumatic rupture may occur. In fatal cases there may be hemorrhagic areas of the pulp, thrombi in the arterioles, and areas of infarction. The majority of cases show distinct diminution in the size of the splenic follicles. In chronic cases fibrosis of the trabeculae is prominent. There is marked hyperplasia of the reticuloendothelial elements.

The presence of malarial pigment in these phagocytic cells is a salient microscopic feature. Both phagocytosed and free pigment are concentrated in the red pulp; however, it is unusual to find phagocytosed pigment in any part of the follicle. From 1 to 50 or more granules of pigment may be present in the cytoplasm of a single cell. The pigment usually appears as single, round, dark

![Figure 38–18. Phagocytosed and free malarial pigment in the spleen; numerous individual granules and aggregates of pigment in a single phagocyte. (Courtesy of the Louisiana State University School of Medicine, New Orleans.)](image-url)
brown blocks (characteristic of *P. falciparum*) or as small, black conglomerate masses in the phagocyte (Fig. 38-18). Hemozoin must be distinguished from iron pigment, which may be present in the same cell, by the lighter color of the iron, and from formalin pigment by the irregular crystalline shape of the formalin. Dark yellow hemosiderin may be seen in the spleen pulp but not in the malpighian corpuscles.

The liver is usually somewhat enlarged and dark in color. On microscopic examination the endothelial and Kupffer cells are seen to be packed with black pigment (Fig. 38-19). The cells of the parenchyma may contain considerable amounts of hemosiderin and show cloudy swelling and vacuolization. Malarial pigment is not present in the hepatic parenchymal cells. Occasionally, necrotic foci are seen in the portal areas and in the central zones of the liver lobules.

The brain is frequently lead-colored because of the malaria pigment. Engorgement of the cerebral capillaries is a prominent feature; the capillary network of the brain is distended with erythrocytes. There may be extensive capillary plugging by masses of parasitized red cells (Fig. 38-20). In vessels of larger caliber, erythrocytes containing older forms of *P. falciparum*, owing to their adhesive nature, may be seen in contact with the endothelial lining, while the noninfected red cells occupy the lumen. This arrangement of the parasitized corpuscles is referred to as margination (Fig. 38-21A, B). In fatal cases hemorrhages are found in the subcortical white matter but not in the gray matter. They are also seen commonly in the pons, medulla and cerebellum. These take the form of ring hemorrhages encircling an area of necrosis in which a central plugged vessel may be discerned. In addition, malarial granulomas (Dürck's nodules) frequently are present. These noninflammatory granulomas resemble the areas of simple hemorrhage, except that with the initiation of a reparative process, a single or multiple layered ring of neuroglial cells is interposed between or mixed with the hemorrhagic belt and the necrotic zone which surrounds the remains of the small, central vessel (Fig. 38-21C).

Toxic acute focal or interstitial myocarditis with capillary obstruction in the myocardium also may be present in fatal cases. In the presence of prominent gastrointestinal symptoms, lesions in the stomach and intestines are not uncommon. These are punctate hemorrhages, capillary obstruction by parasitized erythrocytes, necrosis of epithelium and, occasionally, hemorrhage into the lumen. The bone marrow may reveal large numbers of parasitized cells and considerable amounts of malarial pigment.
Figure 38-20. Agglutinated parasitized erythrocytes in capillaries of brain—*falciparum* malaria.

Acute malaria may be associated with profound disturbances of body chemistry. There is reduction of the total plasma proteins with reversal of the albumin-globulin ratio but usually not above unity. The serum euglobulin is increased. Cholesterol, lecithin and glucose rise during the chill but usually are slightly decreased during the afebrile period. Plasma potassium is greatly increased by the rupture of erythrocytes. There is a decrease in lewulose and galactose tolerance, indicating disturbance of the glycogenetic function of the liver. In heavy infections, bilirubin may be discharged into the blood plasma in considerable quantities, producing an indirect van den Bergh reaction. The blood urea ordinarily does not undergo significant change in malaria; howev-

Figure 38-21. A. Vessel of brain with parasitized erythrocytes in contact with the endothelial lining (margination) and noninfected red cells occupying the center of the lumen. A pigment granule of *P. falciparum* is prominent in each of the parasitized cells. B. Margination with double or multiple rows of adhesive parasitized red corpuscles partially occluding the lumen of the vessel. C. Malarial granuloma composed of a central thrombosed vessel, necrotic intermediate zone and peripheral rows of neuroglial cells mixed with erythrocytes (Durek's nodule). (Courtesy of the Louisiana State University School of Medicine, New Orleans.)
er, when there is sufficient damage to the kidneys in malignant \textit{falciparum} or black-water fever to interfere with renal function, varying degrees of nitrogen retention and uremia may occur.

**Clinical Characteristics.** Salient features of malaria are periodic fever, splenomegaly, anemia and leukopenia. The characteristic periodicity of the fever (in \textit{vivax} and quartan infections) is associated with the rhythmic maturation of the sporulating forms in the blood and their massive release by rupture of the erythrocytes. The enlargement of the spleen, and to a lesser degree of the liver, is correlated with an increase in reticuloendothelial cells which, as one mechanism of immunity in malaria, phagocytose not only merozoites upon their release but also pigment, parasitized and nonparasitized red corpuscles. Since the malarial organisms live in and at the expense of the erythrocytes, destroying all those attacked, the primary effect of their presence is manifested usually by a normocytic normochromic anemia. Some patients with acute malaria have herpes labialis; others with chronic malaria may have urticaria.

The clinical phenomena accompanying infection by \textit{P. falciparum} differ greatly in their evolution and in the hazard to the infected individual from those accompanying infection by \textit{P. vivax}, \textit{P. malariae} or \textit{P. ovale}. \textit{Falciparum} malaria is always dangerous and may be fatal. The other types, although capable of producing severe illness, commonly are free from dangerous complications and grave menace to life. The capacity of \textit{P. falciparum} to invade both mature erythrocytes and reticulocytes is probably directly related to the intense and rapidly increasing parasitemia that accompanies this infection. Furthermore, the infected red blood cells tend to agglutinate and to adhere to capillary endothelium. Large numbers of parasitized red cells distend the visceral capillaries and slow the circulation. This may lead to thrombosis, which produces areas of local anoxemia and ischemia (Fig. 38–21).

The usual intrinsic incubation period for \textit{vivax} malaria is 11 to 15 days; \textit{falciparum}, 11 to 14 days; \textit{ovale}, 14 to 26 days; and quartan from 3 to 4 weeks. Prodromes consisting of malaise, muscle pains, headache, anorexia and slight fever may exist for a few days before the onset of the acute phenomena. In many instances, however, the initial attack comes on abruptly without prodromes.

**Vivax and Quartan Malaria.** The classic clinical picture of malaria with its alternation of “good” and “bad” days is much more the exception than the rule. Even in \textit{P. vivax} infections the initial clinical attack seldom exhibits tertian fever at the outset; usually there are two groups of parasites out of phase with one another and these, maturing on alternate days, produce daily, or quotidian, rather than tertian fever. Later, one group may drop out, and the release of a new generation of parasites will then occur on alternate days, at intervals of 42 to 47 hours. Only then does the fever become tertian (Fig. 38–22).

The typical paroxysms of benign tertian and quartan malaria are similar except for the difference in periodicity. The onset is abrupt and frequently initiated by a rigor which may vary from a slight subjective chilliness to a frank chill accompanied by a sensation of extreme cold, although the temperature meanwhile rises rapidly to 40 to 41°C (104 to 106°F). The pulse is rapid and of small volume. Polyuria, nausea and vomiting are common. After 20 to 60 minutes the hot stage begins, accompanied at first by relief from the sense of intense cold, but shortly followed, however, by an increasing and severe headache and a sensation of intense heat. At this stage the face is flushed and the pulse full. Epigastric discomfort, nausea and vomiting are more prominent. Frequently there is mild delirium, and although the temperature does not remain long at the fastigium, the sweating stage, ushered in by the appearance of moisture on the previously dry skin, increases to a profuse diaphoresis of the entire body. With this change the temperature falls rapidly and the pulse returns to normal. This is followed frequently by sleep, after which the individual awakes somewhat exhausted but otherwise feeling well. The sweating stage lasts 2 to 3 hours and the entire paroxysm averages 10 hours.
During the paroxysm there is a moderate leukocytosis, whereas in the afebrile period leukopenia with an increase in the number of large mononuclears is usual.

In quartan malaria the attacks occur every 72 hours, if only a single brood of parasites is present. The rise of temperature is less abrupt, and the total duration of the paroxysm averages 11 hours.

Anemia is a common complication of any type of malaria. In addition, rupture of the spleen may occur in *vivax* malaria but is not common. Nephrosis, with large amounts of albumin in the urine, occurs in chronic malaria, chiefly in *P. malariae* infections.

**Ovale Malaria.** Infections with this species resemble those due to *P. vivax* but tend to be milder. The untreated primary course is shorter than *P. vivax* and the parasitemia is lower. With a single brood of parasites, the time between clinical attacks averages 49 or 50 hours. Multiple broods cause daily fevers.

**Falciparum Malaria.** The onset of malignant tertian malaria is frequently insidious. The individual complains of gradually increasing headache, of gastrointestinal symptoms, or of a clinical complex that is suggestive of influenza and frequently misdiagnosed unless examination of the blood is carried out. In other instances onset is abrupt and dramatic. Characteristically there are: a sensation of chilliness rather than a frank chill; a prolonged and intensified hot stage; and lack of the marked terminal sweating, with its accompanying drop in temperature, characteristically observed in *P. vivax* infections. The fever curve frequently shows prolongation of the fastigium, often with primary fall and secondary rise, before returning to or toward normal. This double-peaked elevation is characteristic when it is observed. Frequently, however, the fever is continuous or remittent instead of intermittent. During the periods of remission there is little or no return of the sense of well-being. Commonly, the tertian periodicity of the infection is indicated by exacerbation of a continuous fever. Defervescence in *falciparum* malaria frequently occurs by lysis rather than by crisis. In those instances in which the fever curve is remittent, the paroxysm often lasts 20 to 36 hours. These variations in the fever curve are to be explained by the phenomena of anticipation and retardation of the events of schizogony as a result of which the new generation of parasites is released over a prolonged period.

Prostration is more marked and the tendency to delirium greater than in *P. vivax*
and *P. malariae* infections. Nausea and vomiting frequently occur, and the spleen is generally palpable and tender. The parasite density in the peripheral blood can vary widely in a few hours, and it may be necessary to make repeated smears at intervals of several hours to determine the maximum number of parasites.

**Pernicious Types.** *Falciparum* malaria is notorious for its tendency to produce, suddenly and without warning, severe and dangerous types of disease to which the terms pernicious or malignant malaria have been applied. These may be rapidly fatal if not recognized promptly and treated adequately. Several clinical types are known. The various types may exist simultaneously, differing only in degree. The tendency of falciparum-infected erythrocytes to clump the small capillaries of the viscera and thus interfere with the blood supply is related to many of the complications associated with this malaria species.

**Bilious Remittent Fever.** The onset is characterized by marked nausea and profuse, continuous vomiting. Jaundice customarily appears about the second day, earlier than in yellow fever and later than in blackwater fever. The urine frequently contains bile pigment and yields a yellow foam test. Epigastric distress and liver tenderness are marked, and hemorrhage from the stomach may occur, producing coffee-ground vomitus. The temperature tends to be high, and the fever curve is usually remittent rather than continuous. Dehydration and disturbance of the alkaline reserve and of mineral balance may develop rapidly.

**Cerebral Malaria.** The onset of cerebral malaria may be sudden or gradual, and the clinical picture may be varied. The patient may complain of progressively increasing headache with little or no fever and then gradually lapse into coma; or a clinical picture in which there appears little cause for immediate concern may be superseded without warning by a progressive and uncontrollable rise of temperature to levels in excess of 42.2°C (108°F). In addition to hyperpyrexia, convulsive seizures are common. Involvement of the cranial nerves may be evident; delirium may occur. These clinical phenomena may occur within a few hours and rapidly may become fatal. In some instances, the onset may be sudden and characterized by mania or other acute psychotic manifestations. The initial stages of cerebral malaria not infrequently have been mistaken for acute alcoholism. The results of such a diagnostic error are usually disastrous.

Cerebral edema occurs. The viscosity of the blood increases which, combined with the large numbers of infected erythrocytes clogging the capillaries, contributes to the slowing of the circulation and finally to capillary obstruction. This leads to local ischemia and anoxia. The extensive interference with the vascular supply to the central nervous system in cerebral malaria may produce any combination of symptoms and signs indicative of severe and extensive involvement of the brain. In children, convulsions are a frequent presenting symptom. There are no constant or significant changes in the spinal fluid. The spinal fluid pressure, however, may be elevated considerably above normal. In such instances, repeated lumbar drainage is an important therapeutic procedure.

**Aldig Malaria.** The aldig forms of *falciparum* malaria accompany extensive vascular involvement of the gastrointestinal tract and other abdominal viscera. Profound prostration, with a tendency to fatal syncope, marked coldness of the skin, subnormal temperature and circulatory collapse occur. Jaundice may be present. Severe grades of anemia may develop rapidly. Acute diarrhea unaccompanied by fever and often ending fatally has long been recognized as an aldig form of pernicious malaria.

Other recognized types of pernicious malaria are the gastric, which is characterized by persistent vomiting, and the dysenteric, in which there is a bloody diarrhea due to extensive capillary thrombosis in the intestinal walls. The blood in the stools frequently contains immense numbers of parasites.

Orthostatic hypotension is a prominent clinical feature. Acute renal insufficiency characterized by progressive oliguria may occur in the absence of the rapid hemolysis associated with blackwater fever. Shock, pul-
monary edema, and secondary bronchopneumonia are seen in severe *falciparum* malaria.

The general mortality for the pernicious forms of *falciparum* malaria may be as high as 50 per cent.

Diagnosis. The clinical diagnosis of malaria frequently is difficult. It may be confused with many diseases, both cosmopolitan and tropical. This situation is inevitable in view of the pathologic changes, which consist mainly of mechanical interference with the vascular supply in many organs of the body. Among the tropical diseases it may be confused with kala-azar, amebic liver abscess, relapsing fever and yellow fever. Among the cosmopolitan diseases it may frequently simulate typhoid fever, tuberculosis, brucellosis, influenza, pyelitis and other septic conditions, including malignant endocarditis as well as acute or chronic organic disease of the central nervous system. Malaria commonly is associated with positive Wassermann and Kahn reactions.

Definitive diagnosis depends upon demonstration of the parasites. For this purpose the thick blood film is far superior to the thin film technique, since in light infections it may be impossible to find plasmodia in the thin film. The thick film will yield three to four times as many positive findings and will reveal the plasmodia in virtually all active clinical cases. (See Diagnostic Methods, p. 809.) It may be necessary to examine stained thin blood films for positive identification of the particular species present.

Other characteristics of the stained thin blood films may be suggestive. Leukocytes containing ingested malarial pigment may be seen. There is often a leukopenia with a relative increase of monocytes. In chronic cases a sustained submaximal reticulocyte crisis beginning 4 to 7 days after the institution of specific therapy is suggestive.

A history of having been in a malarious area, periodicity of the febrile curve and splenomegaly should arouse suspicion of malaria. In chronic cases, however, there may be little if any significant splenic enlargement. Sternal puncture and examination of the stained marrow smear may be useful in the rare case where parasites cannot be found on a thick blood film.

In view of the marked differences in severity and prognosis between *falciparum* malaria and the other forms of the disease, accurate identification of the species of *Plasmodium* is essential. Table 38–2 presents the significant differential characteristics that may be seen in the stained thin blood film.

Because of the importance of the thick film in the differential diagnosis of human malaria, the characteristics of the three principal species are summarized in Table 38–3. *Plasmodium ovale* usually cannot be identified with certainty in the thick film.

Although immunodiagnosis of malaria has advanced greatly in recent years, the

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>P. falciparum</th>
<th>P. vivax</th>
<th>P. ovale</th>
<th>P. malaris</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infected erythrocyte enlarged</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Infected erythrocyte, fimbriated and/or oval</td>
<td>Rare</td>
<td>Rare</td>
<td>Frequent</td>
<td>Rare</td>
</tr>
<tr>
<td>Infected erythrocyte decolorized</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Infected erythrocyte, Schüffner's dots*</td>
<td>Rare</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Infected erythrocyte, Maurer's dots*</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Multiple infections in erythrocytes*</td>
<td>+</td>
<td>Rare</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Parasite, all forms in peripheral blood</td>
<td>Rare</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Parasite, large coarse rings</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Parasite, double chromatin dots*</td>
<td>+</td>
<td>Rare</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Parasite, accolé forms*</td>
<td>+</td>
<td>Rare</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Parasite, band forms*</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Parasite, sausage-shaped gametocytes</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Number of merozoites</td>
<td>8–24</td>
<td>12–24</td>
<td>8–12</td>
<td>6–12</td>
</tr>
</tbody>
</table>

*Not invariably but suggestive when seen.
<table>
<thead>
<tr>
<th>Stage of parasite</th>
<th>Plasmodium falciparum</th>
<th>Plasmodium vivax</th>
<th>Plasmodium malariae</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small trophozoite (early ring)</td>
<td>Small size rings, with small chromatin dots and delicate, wavy cytoplasm. Frequently rings have double chromatin dots. Tend to move in large number of rings. Many rings form with no older stages—practically certain to be <em>falciparum</em> infection. Diagnosis on small number of rings may often be assisted by finding distinguishing gametocytes, though this stage is not necessarily present.</td>
<td>Larger, heavier, ring form than in <em>falciparum</em>, often with variety of cytoplasmic patterns and irregularities in shape. Usually older stages of parasite can be found also.</td>
<td>Ring is likely to be heavy, with large dot of chromatin and small amount of cytoplasm, which is often darkly stained, without a nucleus. Pigment forms early and may appear as haze in cytoplasm of this stage. Rungs practically always associated with older forms. The ring phase is brief, so this stage is not found as often as older stages.</td>
<td>Ring forms often not complete circle—may be &quot;swollen&quot; forms, &quot;clawing&quot; forms, or &quot;intercepted rings.&quot; When rings only are present and number is small, it is practically impossible to differentiate species.</td>
</tr>
<tr>
<td>Growing trophozoite</td>
<td>Heavy large rings form—resemble strong rings of white. Sometimes these pigment granules or have rather clear in cytoplasm.</td>
<td>Stage usually anucleate in appearance, with large variety of shapes. Cytoplasm freedom fragmented and arranged irregularly in clusters of varying size pieces or streaks about or close to a large chromatin mass. Small yellowish brown pigment granules scattered throughout parts of the cytoplasm. This is the most characteristic stage of <em>vivax</em>. Frequently other younger or older stages accompany this one.</td>
<td>Small, usually rounded compact forms. &quot;Like marbles in a ring.&quot; Pyriform, heavy, dark, large-grained pigment. Forms frequently so solid that chromatin seems buried in the mass. This stage and the one that follows are the commonest forms of this parasitic realm.</td>
<td>In heavily stained films and in films which have been kept for several days before staining, the &quot;ghost&quot; of the enlarged host cell and persistence of Schüffner's stippling or a pinkness remains from the stippling may assist in diagnosis of rings.</td>
</tr>
<tr>
<td>Large trophozoite</td>
<td>Ring canal seen or almost lost. Parasite quite small and compact, cytoplasm often quite pale, irregularly scattered or small. Five- to sixfold variations in mass size, very dark choms or chom. Stage is usually found only when the infection is acute and usually accompanied by numbers of ring-form trophozoites.</td>
<td>Frequently quite solid and dark staining. More or less irregular in outline, possibly with one or more variates. Fine brown or pigment scattered throughout cytoplasm. May be confused with macrogametocyte.</td>
<td>Compact, dark, larger than &quot;growing&quot; stages. Sometimes in thinner portion of the smear, spreading in normal size. Prefere to coarse, dark brown pigment—often making the chromatin. May be confused with &quot;rounded up&quot; <em>falciparum</em> gametocyte or with gametocyte of <em>malariae</em>.</td>
<td>On rare occasions Manton's dots have been observed in thick films of <em>falciparum</em>. The invariably found stages of <em>falciparum</em> are, of course, some nearly found in thick films. Band forms have tendency to become rounded in thick films of <em>malariae</em>—except perhaps in very thin edge of smear.</td>
</tr>
<tr>
<td>Schizont (presegmenting)</td>
<td>Stage not often seen and is usually accompanied by large numbers of growing trophozoites when present. Parasite is very small. Contains 2 or more divisions of chromatin and very little cytoplasm. Usually associated with red blood cells. May be confused with same stage of <em>malariae</em>.</td>
<td>Irregular or compact clusters of chromatin divisions, often dense reddish purple in color. Cytoplasm in irregular broken masses and strips, containing light brown pigment granules which are clumped in spots. Usually accompanied by other stages. May be confused with same stage of <em>malariae</em>.</td>
<td>Much like vivax of the same stage except that parasites are often smaller with darker, larger pigment granules. Often so compact that internal structure is difficult to define. Usually accompanied by other stages. May be confused with presegmenting schizonts of <em>malariae</em>.</td>
<td>Schizonts are much like thick forms of same stages—more compact, smaller in thicker portions of smear. This is the most difficult stage to get in a normal film on which to diagnose species.</td>
</tr>
</tbody>
</table>
**Mature schizont**

Seldom seen except in severe cases. Always associated with many small trophozoites. Usually contains around 20 or more tiny merozoites clustered around a small, very dark, pigment mass.

**Young gametocyte**

Sometimes long, slender and pointed, with pigment scattered in the ends. Usually associated with many trophozoites.

**Mature gametocyte**

Differentiation of sex is difficult or impossible. At " crescent" or "smog" shapes, may be quite diagnostic of species. In thicker portion of smear may take on oval or rounded, somewhat edematous appearance, which may be confused with male trophozoites or gametocyte. Often may be distinguished by difference in amount and appearance of pigment or by pink or red "flag" protruding from edge of the pigment. May be accompanied by ring form trophozoites or appear alone and in frequency. Often appears in "clusters."

**Macro gametocyte**

Macrogametocyte is larger, as a rule, than in other species; pigment is light, delicate, well dispersed through undifferentiated cytoplasm. Except in thin edge of film cannot be differentiated from some mature trophozoites of same species. Microgametocyte often distinguishable as large bands of chromatin (from pink or purple) well defined by bands of pale or colorless cytoplasm in which pigment granules are more or less evenly dispersed. Other stages of the parasite can usually be found.

Most distinctive stage of malaria in thick film. Often found in large numbers—usually with trophozoites or presegmented forms or both. About 8 merozoites each with large chromatin mass and small amount of cytoplasm—may be compact or clearly separated. Frequently the chromatin and pigment only are seen, the chromatin being more and well separated. The dark heavy pigment is more often concentrated, though sometimes dispersed.

At a rule, few in number, somewhat smaller than rings, otherwise have the same distinguishing features except that pigment is coarser and darker. May resemble rounded falciparum gametocytes.

serologic tests must be interpreted with care, since positive reactions may indicate active infection, or a previous infection, or even only the presence of antibodies against substances antigenically related to plasmodia. Cross-reactions may occur among the various species. The tests used most successfully as an aid to diagnosis, or to establish the prevalence of malaria in a population, or to screen potential blood donors are the complement-fixation, the agglutination and the indirect immunofluorescence. Of these, the indirect hemagglutination (IHA) test and the indirect fluorescent antibody (IFA) test are particularly well suited for epidemiologic surveys.

**Prognosis.** The prognosis for recovery from the primary attack of malaria due to *P. vivax, P. malariae* or *P. ovale* is excellent. *Falciparum* malaria carries a good prognosis if treated adequately; untreated, its mortality is sometimes very high. Radical cure of malaria in the great majority of cases is possible with proper use of the new antimalarial drugs.

**Treatment.** Drugs have several functions in malaria: treatment of clinical attack; curative therapy to prevent relapses; suppressive and prophylactic action to prevent the acquiring or the clinical manifestations of the disease; and sporontocidal effect, which prevents transmission by mosquito vectors. There are several drugs exerting some of these effects but none exerts all. The chemical groupings of the drugs are: cinchona alkaloids—quinine; 4-aminoquinolines—chloroquine, amodiaquine; 8-aminoquinolines—primquine, pamaquine; 9-aminoacridines—mepacrine; biguanides—proguanil; diamino pyrimidines—pyrimethamine, trimethoprim; sulfone—dapsone, sulfonamides—sulfadiazine, sulfadimethoxine, sulfisoxazole, sulfadoxine, sulfalcene; antibiotics—tetracycline, doxycycline, minocycline.

The 4-aminoquinoline drugs, amodiaquine and chloroquine, are the drugs of choice for the treatment of acute malaria except where the malaria originates in areas of known resistance to these compounds. In the majority of cases, fever is controlled within 24 hours and thick blood films usually become negative for parasites in 48 to 72 hours. *Plasmodium malaria* responds more slowly than the other species. These drugs will terminate infections by sensitive strains of *P. falciparum*. The gametocytes of *P. falciparum* are not removed or sterilized. For the malaria that have prevailing stages, such as *P. vivax*, the addition of primaquine to the regimen generally will prevent relapses, but this varies according to the strain of parasite. Amodiaquine and chloroquine are useful as suppressive agents, in the absence of drug resistance. Some strains of *P. falciparum*, probably relatively few, are resistant to these drugs. Amodiaquine has been reported to be more effective than chloroquine against some resistant strains.

Drugs, especially chloroquine and amodiaquine, should be taken after meals with fluid. This reduces the possibility of occasional nausea, vomiting or mild gastrointestinal disturbances.

**Chloroquine.** Synonyms: Aralen, Nivaquine. The drug is a white crystalline powder with a bitter taste and is freely soluble in water. It is available in tablets for oral administration, each 0.25 gm equivalent to 0.15 gm of base, and in ampules containing 50 mg per ml equivalent to 40 mg of base for intramuscular and intravenous use.

Absorption is relatively complete and rapid when the drug is taken by mouth. It is stored in the tissues, excreted slowly and does not discolor the skin. Chloroquine usually is well tolerated in the dosages employed clinically. In certain individuals it may cause mild transient headache, visual disturbances, pruritus, trivial gastrointestinal complaints, psychic stimulation and, rarely, a lichen planus-like eruption. When given intravenously undiluted, there is a fall of systolic blood pressure with little or no change in the diastolic pressure. When well diluted and given slowly no significant change occurs. Excretion is accelerated by acidification of the urine.

**Amodiaquine.** Synonyms: Camoquin, Cam-aoi, Bacoquin. Most formulations are prepared as the hydrochloride and distributed in tablets containing 200 mg base. Bacoquin is prepared as the base, is tasteless.
and is distributed as tablets with 150 mg base or as a syrup, each ml containing 30 mg of base.

Amodiaquine is a yellow crystalline powder and has a bitter taste. It forms a 5 per cent solution in water at room temperature and is rapidly absorbed from the gastrointestinal tract. It is virtually free of toxic effects at normal dosages, although long continued administration in amounts considerably above the recommended therapeutic dosage may be accompanied by loss of energy, insomnia, epigastric discomfort and anorexia.

Quinine. Quinine is rapidly absorbed from the gastrointestinal tract; 60 to 70 per cent is oxidized in the body and the remainder rapidly excreted in the urine. Indications of poisoning appear when the blood level rises to about 10 mg per 100 ml.

Quinine destroys the parasites in the red cells less rapidly than the 4-aminoquinolines. For many years it was the standard drug for treating malaria, and it is still used in some countries where the higher costs of the other drugs are a factor or where the quinine industry exists. There is a wide variation in the responses of different strains of *P. falciparum* to quinine. Some strains require larger total amounts of quinine than others.

Quinine, alone or in combination with another compound, is the drug of choice for treating patients with 4-aminoquinoline-resistant strains of malaria. It is advisable to use quinine initially for acute cases of *P. falciparum* from South America or Southeast Asia.

In therapeutic doses it has little effect on the circulatory system. In excessive dosage it produces an initial rise in pulse rate and blood pressure followed by a depression of both. When given intravenously in too large a dose or too quickly, rapid progressive fall of blood pressure occurs, with the appearance of circulatory collapse due to cardiac depression and vasodilatation.

Cinchonism is the expression of the toxic action of quinine upon the central nervous system. It is characterized by mental depression, giddiness, headache, sense of fullness in the head, tinnitus, deafness, amblyopia and occasional blindness. There may be mental confusion and somnolence as well. True idiosyncrasy to quinine results in the symptoms of cinchonism after small doses that are well within the normal therapeutic range.

Primaquine Diposphate. This drug is chemically related to pamaquine but is less toxic. It is an orange crystalline solid with a bitter taste and is slightly soluble in water. It is supplied in tablets, 26.5 mg of the salt being equivalent to 15 mg of the base.

The drug may cause severe hemolytic reactions. Dark-skinned races and certain Caucasian groups in the Mediterranean area are particularly susceptible. This reaction is linked with a defect of the glucose-6-phosphate dehydrogenase in the erythrocytes of susceptible persons. Acute intravascular hemolysis may occur in such people after the single administration of 60 mg or the daily administration of 30 mg of the drug. As only the older red blood cells are destroyed, the hemolysis is self-limited. If the usual adult dose of 15 mg base is not exceeded, hemolysis is not of clinical significance. Primaquine administration should be discontinued if severe cyanosis or passage of dark urine occurs.

Primaquine should not be given to subjects receiving at the same time drugs capable of depressing the myeloid elements of the marrow. Quinacrine enhances the toxic effects of primaquine by preventing its metabolic degradation.

Primaquine is relatively ineffective against the erythrocytic forms of malaria. It quickly sterilizes the gametocytes. It is active against the exo-erythrocytic forms and therefore is useful in preventing relapses.

Pamaquine is more toxic than primaquine and has been displaced by the latter.

Dihydropybral Reductase Inhibitors. This group includes proguanil, pyrimethamine and trimethoprim. They are slow-acting schizontocides and are not drugs of choice to be used alone for the treatment of the clinical attacks. They are normally used in combination with other drugs. The principal use of the first two is for prophylaxis. They are
sporontocidal and thus prevent the development of the infection in mosquitoes. Resistance is easily acquired by both the asexual and sexual parasites. Cross-resistance occurs among these drugs.

*Proguanil.* Synonyms: Chlorguanide, Guanaturon, Paludrine. Proguanil hydrochloride is a colorless, bitter pyrimidine compound that is rapidly absorbed from the gastrointestinal tract and is excreted in the feces and urine. There are no significant toxic effects at therapeutic dosage levels.

*Pyrimethamine.* Synonyms: Daraprim, Malocide. Pyrimethamine is chemically related to chlorguanide. It is a tasteless, odorless, freely soluble white powder. The drug is concentrated in the liver, spleen, brain and bone marrow. It is free from toxic or unpleasant side effects at recommended dosage levels. When administered in amounts far exceeding therapeutic levels it produces megaloblastic changes in the marrow, inhibition of leukopoiesis, marked reduction of erythrocyte, leukocyte and platelet counts, atrophy of lymphatic tissue and degenerative changes in the intestinal epithelium.

*Trimethoprim.* This diaminopyrimidine is closely related to pyrimethamine. Its principal use has been in the treatment of clinical attacks in combination with other drugs, especially the sulfonamides, with which it has a synergistic effect.

*Sulfonamides and Sulfones.* Several of the sulfonamides in combination with other drugs have been used to treat clinical attacks, e.g., sulfadiazine, sulfaflurazone, sulfadimethoxine, sulfadoxine, and sulphalene. The last two are long-acting. These drugs are often combined with pyrimethamine or trimethoprim.

The sulfones diphenylsulfone (dapsone) and sulfadiamine (DADDS) are useful as suppressive agents mainly after treatment with some of the more active schizontocidal compounds, such as the 4-aminoquinolines. They are not recommended alone for the treatment of clinical malaria. Resistance occurs easily.

*Tetracyclines.* Tetracycline hydrochloride, minocycline and doxycycline tend to be curative, but their action is so slow that it is necessary to add a faster acting drug, such as quinine, during the first several days of treatment.

The following 7-day regimens gave good results in limited trials: tetracycline hydrochloride, 1 or 2 gm daily; or doxycycline, 0.2 gm daily; or minocycline, 0.1 to 0.4 gm daily.

The World Health Organization warns against the widespread use of the tetracyclines, sulfonamides, sulfones and trimethoprim because of the danger of inducing concomitant resistance in bacteria. The Organization recommends that the use of the latter three compounds be restricted to drug prophylaxis in areas with chloroquine-resistant *P. falciparum.*

*Mepacrine Hydrochloride.* Synonyms: Atabrine, quinacrine. Mepacrine is a yellow acridine dye with a bitter taste. It is soluble in water; it is absorbed rapidly, deposited in the tissues, especially the liver and gallbladder, and causes a yellow discoloration of the skin. Excretion is slow. The drug is present in the breast milk of nursing mothers.

Mepacrine (quinacrine) usually is well tolerated, although in certain individuals it acts as a gastrointestinal irritant, causing epigastric pain, nausea, vomiting and diarrhea. These symptoms usually are transient phenomena that may be controlled by giving the drug with food or sweetened fluids. With rare exceptions mepacrine may be taken over long periods without ill effect. Rarely, dermatitis occurs. This may take the form of atypical lichen planus, eczematoid or exfoliative lesions. There may be leukoplakia or pigmentation of the mucous membrane of the mouth. Mepacrine should not be administered in conjunction with pamaquine or primaquine because of the danger of acute hemolytic crises.

The drug is active against the erythrocytic forms of the plasmodia. Although a single course of therapy commonly will terminate infections by *P. falciparum,* it is not so effective as the 4-aminoquinolines. It does not affect the relapse rate of *vivax* or *malariae* malaria. When taken as a suppressive, it will prevent falciparum malaria.
Table 38-4. Chemotherapy of Malaria

Treatment Schedules
The doses suggested in this summary are for adults of approximately 70 kg (154 lb) body weight. In general they should be adjusted according to the usual rules for weight and age. The doses recommended for prophylaxis and suppression in children are reduced according to weight.

Treatment of the Uncomplicated Attack in Nonimmune Subjects
1. Amodiaquine dihydrochloride or chloroquine phosphate or sulfate: 600 mg of base; 300 mg 6 hours later; 300 mg daily for the next 2 days.
   OR
2. Amodiaquine dihydrochloride: 600 mg of base first day; 400 mg daily for next 2 days.
   OR
3. Quinine sulfate: 650 mg of the salt (10 grains) 3 times daily for 7, 10, or 14 days.

Emergency Treatment
4. Chloroquine dihydrochloride: 200 mg of base intramuscularly repeated in 6 hours if necessary. Transfer to oral therapy as soon as possible. Do not use for P. falciparum infections originating from areas where 4-aminoquinoline resistance is present.
   OR
5. Quinine dihydrochloride: 650 mg of salt in normal saline, glucose saline, or plasma injected very slowly, repeated in 6 hours if necessary; not more than 3 injections in 24 hours. Or the drug may be administered by intravenous drip at the rate of 2 gm (30 grains) in 24 hours. Transfer to oral therapy as soon as possible. (See text.)

Treatment of Drug-Resistant P. Falciparum
6. Quinine as No. 3 above, if strains do not originate from Southeast Asia.
7. If strains are from Southeast Asia:
   Quinine 650 mg 3 times daily for 10 to 14 days
   PLUS
   Pyrimethamine 25 mg twice daily for 3 days.
To reduce the rate of relapses, the following may be added:
   Sulfadiazine 500 mg 4 times daily for 5 days.
   OR
   Dapsone 25 mg daily for 28 days, beginning on treatment day 7 or 11.
In the rare event that quinine resistance is suspected, regimens combining a sulfonamide and an antifol, such as pyrimethamine or trimethoprim, are often effective against the clinical attacks (one example follows). Relapses may occur.
   8. 50 mg pyrimethamine as single or divided dose
   PLUS EITHER
   1.0 gm sulfadoxine, single dose.
   OR
   1.0 gm sulfadimethoxine, single dose.

Treatment of Clinical Attack in Semi-Immune Subjects
9. Chloroquine diphosphate or sulfate: 600 mg of base, single dose.
   OR
10. Amodiaquine dihydrochloride: 600 mg of base, single dose.
   OR
11. Quinine sulfate: 1.0 to 1.5 gm salt (15 to 23 grains) daily for 2 to 5 days.

Radical Cure of Vivax, Ovale and Malariae Infections
12. Primaquine diphosphate: 15 mg of base daily, in single or divided doses, for 14 days; reinforced by standard treatment with a schizontocidal drug if given during an acute attack.

Prophylaxis and Suppression
13. Chloroquine diphosphate or sulfate*: 300 mg of base plus 30 to 45 mg primaquine once weekly.
   OR
14. Amodiaquine dihydrochloride*: 300 mg of base plus 30 to 45 mg primaquine once weekly; for partially immune, 400 to 600 mg every 2 weeks.
   OR
15. Pyrimethamine: 50 mg and primaquine 40 mg weekly.
   OR
16. Proguanil: 100 to 200 mg daily.

*Begin taking drugs 1 week before entering and 4 to 8, preferably 8, weeks after leaving malarious area. These regimens may not be completely effective against some strains of P. falciparum, especially if resistance is present. Despite prophylaxis, infections of clinical attacks of P. vivax and P. malariae, and even the rare P. ovale, may occur several months or years after leaving the malarious area.
efficient suppressive agent when taken in dosage of 0.1 gm daily. Clinical attacks begin to appear about 2 weeks after discontinuing the medication.

Mepacrine is not used widely.

Treatment of Clinical Malaria. Most simple acute cases respond rapidly to the standard regimens of 1.5 gm of amodiaquine or chloroquine base or 1.4 gm amodiaquine base. *Falciparum* malaria in the nonimmune individual is a highly dangerous infection that requires immediate and effective therapy. The grave complications presented by the pernicious forms of the disease may develop with great rapidity and commonly are accompanied by high mortality rates. Acute *falciparum* malaria and the paroxysms of *vivax* malaria frequently are accompanied by profuse nausea and vomiting. Particularly in the former, it may be necessary to initiate treatment by parenteral therapy. This, however, should be superseded as early as is practicable by oral medication. The drug regimens are shown in Table 38-4. New drugs and combinations are being tested. One of the most effective both curatively and prophylactically is the 4-quinolinemethanol compound WR 142,490 (proposed generic name, melfloquine).

In patients with *falciparum* malaria who have not responded to the chloroquine or amodiaquine treatment, or who have a parasite relapse after a previous response to these drugs, or who are gravely ill with infections which could be resistant to these drugs, the drugs of choice are quinine. 650 mg 3 times daily for 10 to 14 days accompanied by pyrimethamine, 25 mg twice daily for 3 days.

When the patient is unable to retain quinine because of vomiting, or when coma, presumed due to *falciparum* malaria, is present, the drug may be given intravenously. This treatment carries a serious hazard and should be resorted to only when the patient's condition clearly warrants the risk and no other form of treatment is possible. Quinine is administered intravenously as the dihydrochloride, 600 mg in 200 to 600 ml of normal saline, by very slow intravenous drip over a period of at least 30 minutes with constant monitoring of the blood pressure and of the pulse to detect hypotension or arrhythmia. The same intravenous dose may be repeated at intervals of 6 to 8 hours if the patient's condition requires. Oral therapy, by stomach tube if necessary, should be utilized as soon as possible.

Treatment of Complications of Malaria. Most of the complications are due to high levels of *P. falciparum* parasitemia. The complications must be treated promptly and concurrently with the administration of antimalarial drugs. Dexamethasone, 4 to 6 mg every 4 to 6 hours, has proved useful in the treatment of cerebral and pulmonary symptoms and in blackwater fever. Convulsions should be controlled by a suitable anticonvulsant drug. When the erythrocyte count has fallen to 2 million or fewer cells, transfusion of blood is indicated. Prednisolone phosphate will help control hemolysis. Hemolysis due to primaquine in persons with glucose-6-phosphate dehydrogenase deficiency is self-limited. Shock requires fluid replacement. Corticosteroids may be helpful. In renal failure, careful fluid management is necessary, drug dosage is reduced and either peritoneal or hemodialysis may be required. Hyperpyrexia is reduced by evaporation of water from the body surface, such as by covering with a wet sheet and fanning vigorously. Acute dehydration, dysentery and diarrhea require fluid replacement.

Prevention of Relapses of Vivax Malaria. Relapses of *vivax* malaria may be prevented in the great majority of cases by the standard course of treatment of the acute attack using chloroquine or amodiaquine and concurrent administration of primaquine diphosphate 26.5 mg (15 mg base) daily for 14 consecutive days. An alternate regimen is 600 mg of chloroquine base and 45 mg primaquine base weekly for 8 weeks. Patients receiving this treatment should be under observation for evidence of hemolytic anemia, an indication for discontinuing medication. Particular caution is required in the case of Negro patients (Table 38-4).

Suppressive Treatment. Although prevention of infection is not possible, clinical attacks of *vivax* and *malariae* malaria can be held in abeyance for prolonged periods by the administration of various antimalarial drugs. However, following cessation of med-
ication, clinical attacks due to infection by *P. vivax* and *P. malariae* may begin to occur after 10 or more days. In the case of infections of *P. falciparum*, suppressive regimens with certain of the available drugs will eradicate the infection without the development of clinical malaria. The routines for suppressive treatment are shown in Table 38–4. If pyrimethamine is used for suppression or prophylaxis, it should be used only in combination with other drugs. The British and Australians continue to use proguanil, 100 to 200 mg daily, as prophylaxis.

To be effective, suppressive treatment must be taken regularly. A breakthrough of clinical activity will occur when drug administration is irregular or insufficient. It may occur likewise in the presence of excessive fatigue, acute infections, trauma and hemorrhage or exposure to high altitudes, since these conditions tend to activate latent malaria. Resistance may appear when pyrimethamine and proguanil are used.

**Drug Resistance.** Resistance to proguanil and pyrimethamine has occurred widely. Strains of *P. falciparum* resistant to the 4-aminoquinoline drugs, chloroquine and amodiaquine, occur in Colombia, Brazil, Venezuela, Guyana, Surinam and Panama in the Western Hemisphere, and in Assam, Burma, Malaysia, Cambodia, Laos, Thailand, Vietnam, Sakah, Sarawak, Kalimantan and Philippine Islands in the Eastern Hemisphere. Some of these strains also are resistant to the other synthetic schizontocidal drugs, making it necessary to resort to quinine to control and cure the infections. The manifestations of resistance vary according to the strain, ranging from no apparent response to the drug to a temporary response. Failure to reduce drastically the parasitemia at 48 hours after the initiation of treatment or to eliminate fevers 72 hours thereafter probably signifies resistance and indicates the necessity for use of another drug, preferably quinine.

**Induced Malaria in Man.** For many years, malaria was induced in man for the therapy of neurosyphilis. Many thousands of patients benefited from this treatment. By the study of these controlled infections, much knowledge has been gained in all phases of the biology of malaria, and the development of new drugs has been aided greatly. All four species of the human malarias are transmitted successfully both by infected blood and by sporozoites from the mosquitoes, although a large proportion of the Negro race shows partial or full immunity to *P. vivax*. *Plasmodium knowlesi*, a monkey malaria, also has been used for malaria therapy of neurosyphilis.

**Malaria of Nonhuman Primates.** Species of *Plasmodium* found in nonhuman primates include: in the prosimians (lemurs), *P. girardi* and *P. lemuris*; in the monkeys, *P. brasilianum*, *P. coatneyi*, *P. cynomolgi*, *P. fieldi*, *P. fragile*, *P. simiae*, *P. gonderi*, *P. inui*, *P. knowlesi* and *P. simium*; in the apes, *P. ceyles*, *P. hylobati*, *P. pitheci*, *P. reichenowi*, *P. jefferyi*, *P. silvaticum*, *P. rodbani* *P. schuetzi* and *P. youngi*. Some subspecies of the above have been proposed.

Some of the simian malarias have been induced experimentally in humans by infected blood (*P. knowlesi*, *P. inui*, *P. cynomolgi* and *P. schuetzi*). In general, the infections tend to be much milder and shorter than those caused by the usual malaria parasites of man. Because of these characteristics, *P. knowlesi* was used for many years for the treatment of neurosyphilis. Recent work demonstrating that several of the simian malarias (*P. cynomolgi*, *P. brasilianum*, *P. ceyles*, *P. knowlesi*, *P. schuetzi*) can be experimentally transmitted to man by the bites of infected mosquitoes suggests the possibility of zoonoses. At present, there is no evidence that such transmissions actually occur in nature to any significant degree, although a recent natural infection in man of *P. knowlesi* and of *P. simium* confirms the zoonotic potential of simian malarias.

**Human malaria will grow in splenectomized apes.** Recently it was shown that *P. vivax*, *P. falciparum* and *P. malariae* of human origin will grow well in certain of the small monkeys of the Western Hemisphere. The *Aotus* monkey is the most receptive host, but after adaptation to this host, *P. vivax* will grow in some other species. These models are useful for the study of the biology of malaria and especially for drug development.
Blackwater Fever

Blackwater fever (hemoglobinuric fever) is one of the most dangerous complications of malaria. It is characterized by prostrating chills, profuse vomiting, early jaundice, the passage of dark red to black urine, and a rapidly developing anemia. It is essentially an acute intravascular hemolysis with hemoglobinemia, hemoglobinuria and renal insufficiency.

Etiology and Epidemiology. Blackwater fever ordinarily occurs only in individuals who live or have lived in malarious regions. It was once common in highly malarious areas, but is now greatly reduced and at a low level. Plasmodia may be found in the peripheral blood, and the history generally reveals a succession of malarial attacks. *Plasmodium falciparum* usually is the species involved.

The pathogenesis of the hemolysis in blackwater fever is obscure. Drugs, especially quinine, have been suggested as important factors, as have immune reactions and sensitization to the malaria parasite.

Pathology. Sudden destruction of red blood cells occurs and large amounts of hemoglobin are released. The mechanism for the disposal of blood pigment is overloaded. Hemoglobin, methemalbumin and hemoglobinuric uric acid accumulate in the plasma. When the renal threshold is reached, hemoglobinuria appears and methemoglobin and bile pigments are present in the urine. Renal anoxia and ischemia are probably of great importance in reducing glomerular filtration and tubular reabsorption. Dehydration increases the hazard of renal failure.

The pathologic changes in the viscera are predominantly those of chronic malaria. In addition, the liver may show either cloudy swelling or necrosis of parenchymal cells, particularly in the regions of the central veins. It is yellowish brown due to hemosiderin.

The kidneys are large and black. Renal tubules are blocked with debris and hemoglobin casts. Cloudy swelling and degeneration of the tubular epithelium and hemoglobin casts, indicative of hemoglobinuric nephrosis, may be present. Glomerular alteration, consisting principally of generalized ischemia, enlargement and increased cellularity of the glomeruli, and hyperchromatism and swelling of the endothelium have been reported in patients with clinical evidence of azotemia. Granular eosinophilic

Figure 38-23. Kidney in blackwater fever, showing hemoglobin casts in distal convoluted tubules and degeneration and regeneration of tubular epithelium.
material may be observed within the collecting tubules (Fig. 38-25). Coarse pigmented casts frequently are present in the distal convoluted tubules.

**Symptomatology.** Blackwater fever presents three cardinal symptoms—hemoglobinuria, fever and jaundice. The onset is usually sudden, with very severe chill, marked prostration, pain over the region of the kidneys and a rapid rise of temperature to 40 or 40.6°C (104 or 105°F). The fever may be continuous or remittent, and rather profuse sweating is apt to accompany drops of temperature. Severe nausea and vomiting accompanied by epigastric distress usually appear early and may be continuous and serious. Jaundice appears within a few hours after the onset and may become intense if the hemolysis is extensive or long continued. Not infrequently the onset of symptoms is accompanied by the desire to void, and the urine specimen presents the color characteristic of the disease. The pulse is usually rapid, feeble and of low tension. Pallor proportionate to the degree of anemia rapidly becomes apparent. The red blood count may fall by as much as 2 million within a period of 24 hours.

The clinical course may terminate after one such abbreviated episode, there may be recurring hemolytic crises, or the process may be continuous, extending over several days in the course of which the fever, hemolysis and hemoglobinuria continue.

**Prognosis.** The general mortality rate is 25 to 50 per cent. In approximately half the fatal cases death results from renal failure. Marked and persistent vomiting and hiccup are unfavorable signs, as are a rising curve of the blood urea and a falling urinary output. One attack of blackwater fever seems to predispose to subsequent attacks.

**Diagnosis.** The occurrence of hemoglobinuria, fever and jaundice in an individual known to have had malaria is strong presumptive evidence of blackwater fever. Other causes of hemoglobinuria, however, must be considered.

Parasites are found in only 50 to 70 per cent of cases. When present they may be difficult to find after the first 24 hours.

In addition to the characteristic color of the urine, microscopic examination reveals the presence of much amorphous sediment, occasional red blood cells and casts of various types. Albumin is present in considerable amounts.

**Treatment.** The principles governing the treatment are essentially those for acute hemolytic transfusion reactions: Mannitol and hydration to institute and maintain diuresis, alkalinization to minimize the formation of hemoglobin casts in the kidney, and the use of peritoneal or hemodialysis if renal failure occurs. An intravenous infusion should be administered and 20 gm of mannitol (110 ml of a 20 per cent solution) given over 5 to 10 minutes after the patient has been sufficiently hydrated. If urine flow in the next 2 hours is under 60 ml per hour, fluids should be restricted and the patient treated as for acute renal failure. If urine flow exceeds 60 ml per hour, then hydration should be continued and 100 ml of 20 per cent mannitol administered often enough to maintain a urine flow of 100 ml or more per hour. The patient must be carefully monitored during prolonged mannitol therapy for sodium loss and possible resultant hypokalemia. Packed red blood cells should be given, if necessary, to combat severe anemia. Corticosteroids are recommended as in other lytic anemias.

**Antimalarial Therapy.** When malarial parasites are present in the peripheral blood, immediate intensive treatment with a rapidly acting plasmodicidal drug is essential. The drugs of choice are chloroquine and amodiaquine, in the absence of resistance. Otherwise a combination of pyrimethamine and one of the sulfonamides may be tried. Mepacrine and the 8-aminoquinolines are contraindicated. Opinion is divided on the use of quinine and it is not indicated if there is a history of repeated attacks treated with quinine. In the presence of disturbed renal function and fluid and electrolyte imbalance, the administration of quinine entails a serious hazard and requires alert and constant supervision of the patient.

**Prophylaxis.** In the prevention of blackwater fever, malaria prophylaxis and adequate treatment of clinical malaria, espe-
cially when due to *P. falciparum*, are essential. Recognition of the so-called *preblackwater state* is important. This is characterized by toxemia, slight jaundice, enlargement and tenderness of the liver and abnormally dark-colored urine. In the presence of this condition, hospitalization and careful antimalarial therapy are essential. The prevention and control of malaria form the basis of prophylaxis.

**REFERENCES**


