Chapter 35

MALARIA

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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.[1]

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, viz., *P. vivax, P. falciparum, P. malariae* and *P. ovale*.

Distribution. The nomal range of malarial infections is between 45° north and 40° south latitude. In certain areas these limits are wider (Fig. VI.26). 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 topics 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.

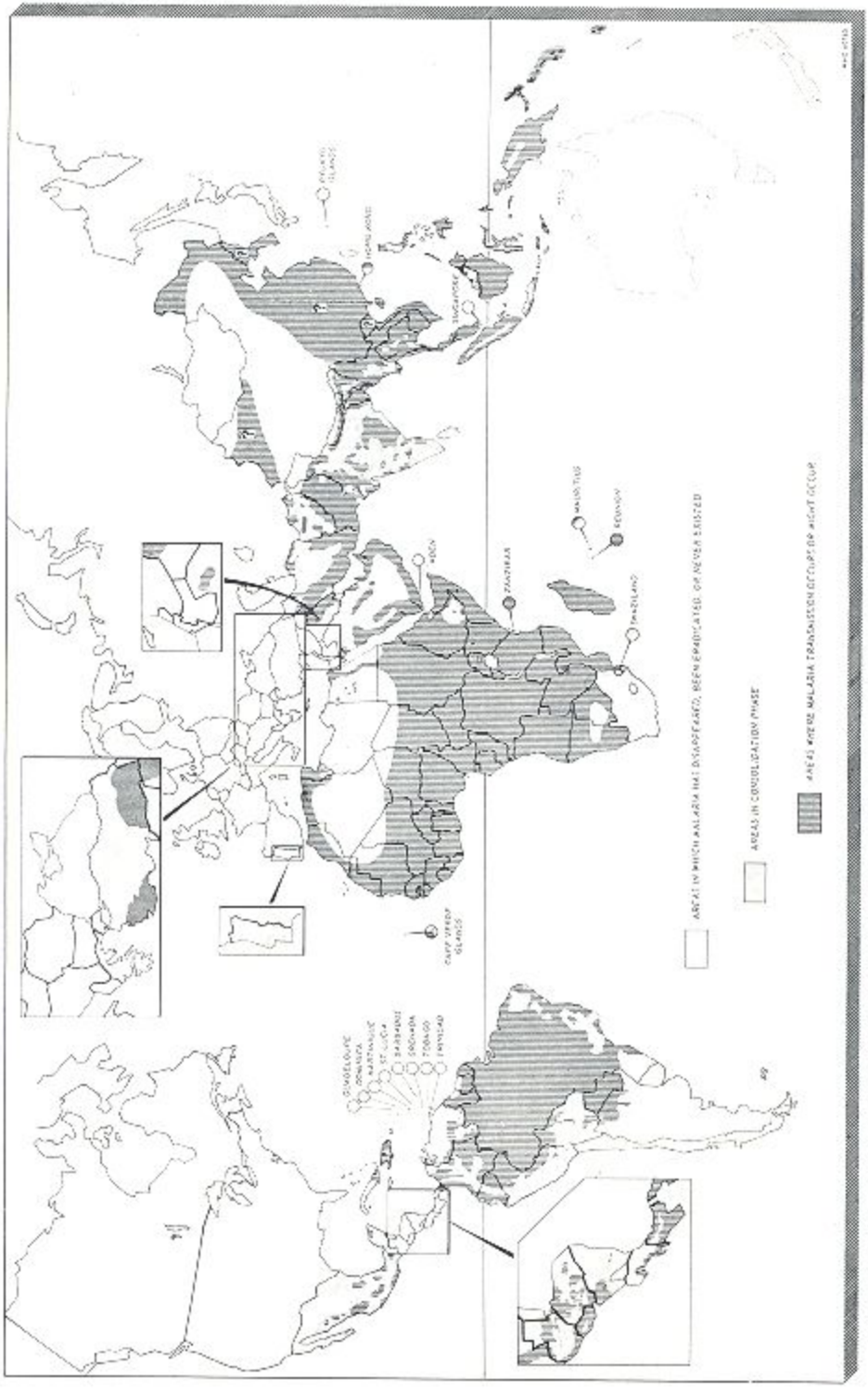

FIGURE VI.26. Malarious areas of the world showing the progress of eradication. From WHO Chronicle, Vol. 19, No. 9, September, 1965. (Courtesy of the World Health Organization.)

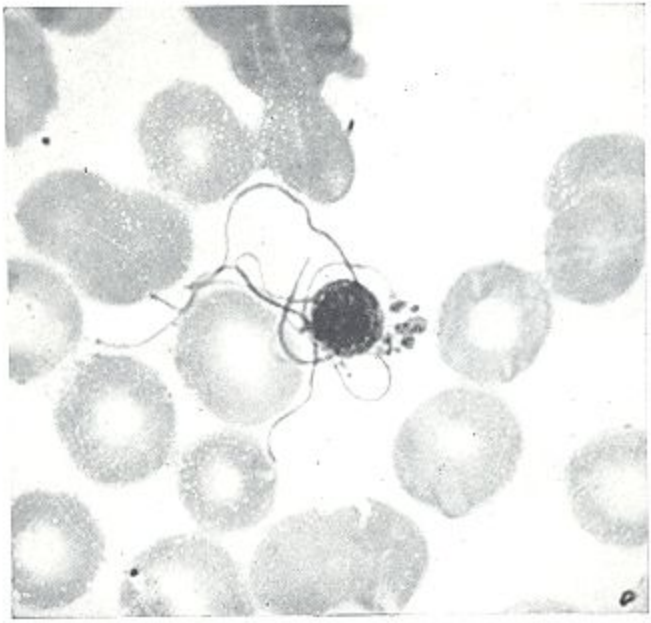

FIGURE VI.27. Exflagellation of male gametocyte.

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. VI.27). 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 ookinete or traveling vermicule. 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. VI.28). 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 spongelike 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 (Fig. VI.29).

Spontaneous rupture of the oocyst finally occurs (Fig. VI.31). 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. VI.30, VI.32).

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 days longer and *P. malariae* may require three 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 15μ in diameter by the third day after inoculation, contain 40 or more nuclei, and small vacuoles may be present (Fig. VI.40). As the parasite grows, there is a gradual increase in the number of

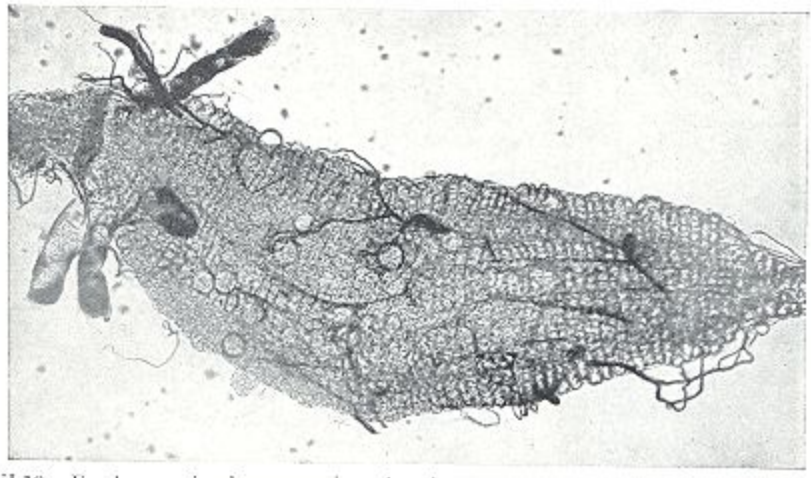

FIGURE VI.28. Fresh unstained preparation showing oocysts on wall of mosquito's stomach.

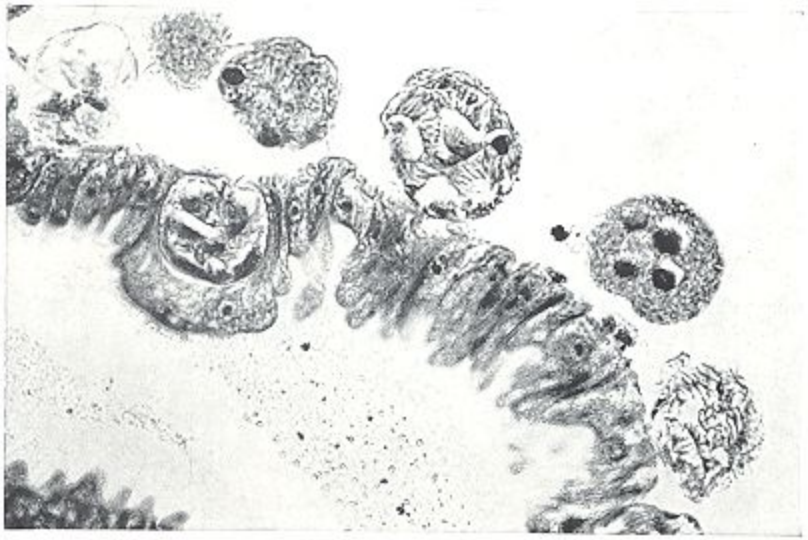

FIGURE VI.29. Various stages in development of oocysts—showing sporozoite formation and pigment masses. (Courtesy Mr. P. G. Shute, F.R.E.S., Ministry of Health, Epsom, England.)

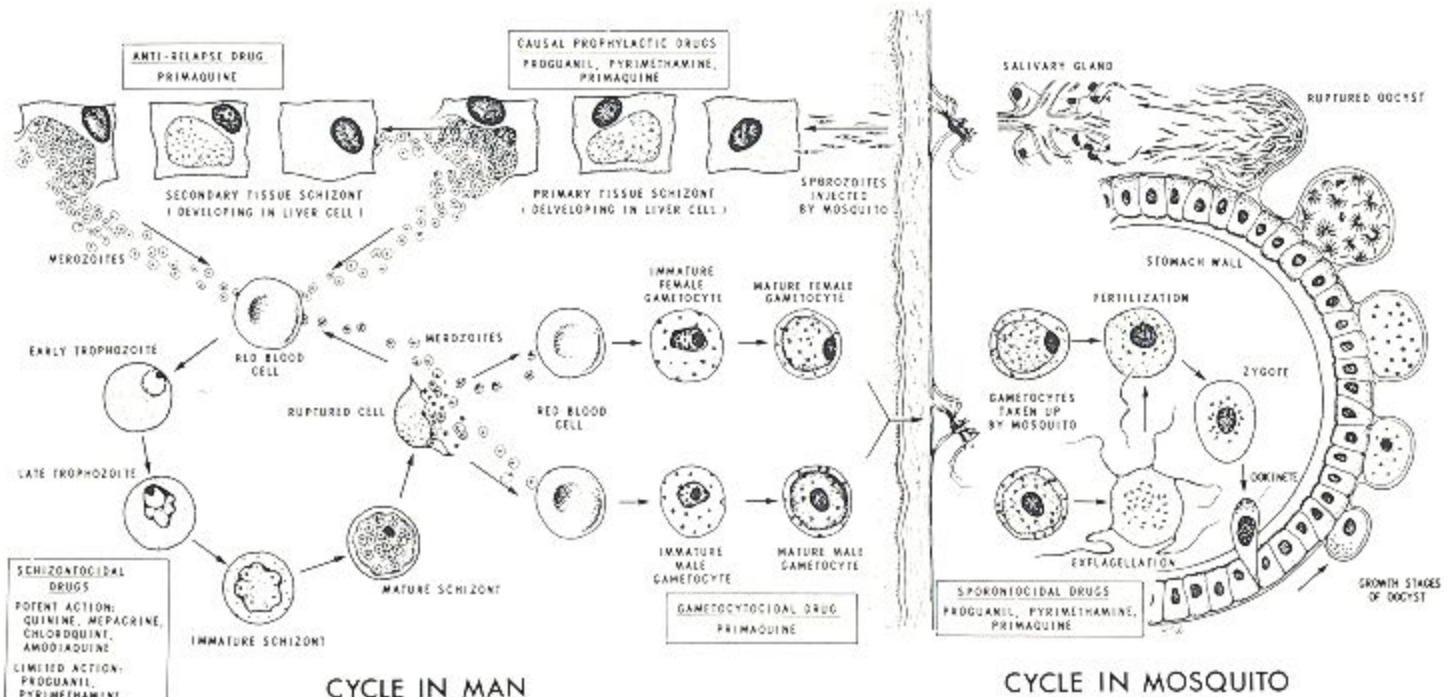

FIGURE VI.30. Life cycle of *Plasmodium*. (Modified from Bruce-Chwatt and Alvarado. Courtesy of University of Florida College of Medicine.)

nuclei; cords or islands of cytoplasm appear from which the merozoites are formed. After about six days the parasite is mature, is irregular in shape with lobes or projections, is about 60μ 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. 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 eight days, with a mature schizont that is round, 45μ in size, and which contains 10,000 merozoites; *P. ovale* requires nine days for development, has an irregular multilobular mature schizont about 80μ x 50μ, and produces 15,000 merozoites;

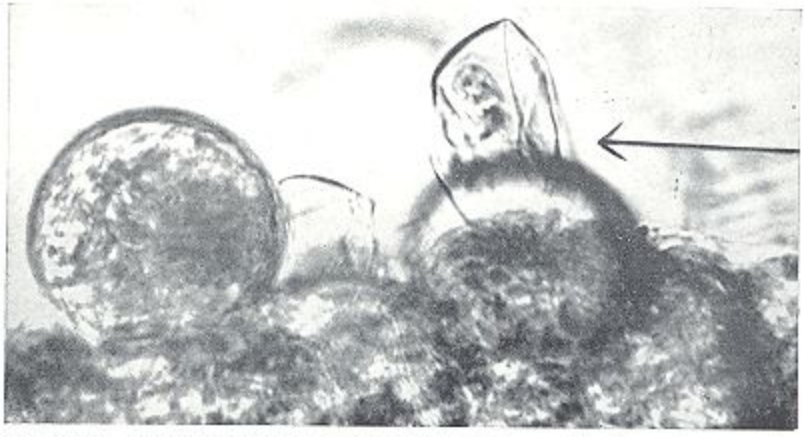

FIGURE VI.31. Empty capsule of oocyst after rupture and release of sporozoites.

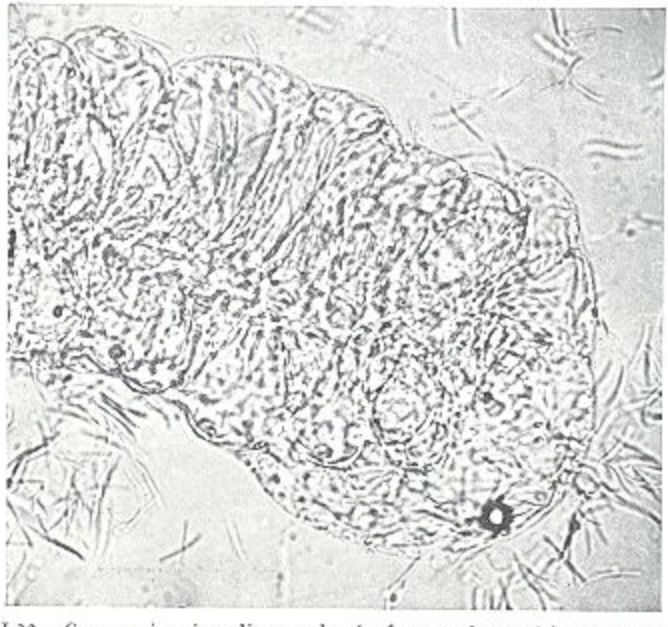

FIGURE VI.32. Sporozoites in salivary gland of mosquito and in surrounding fluid.

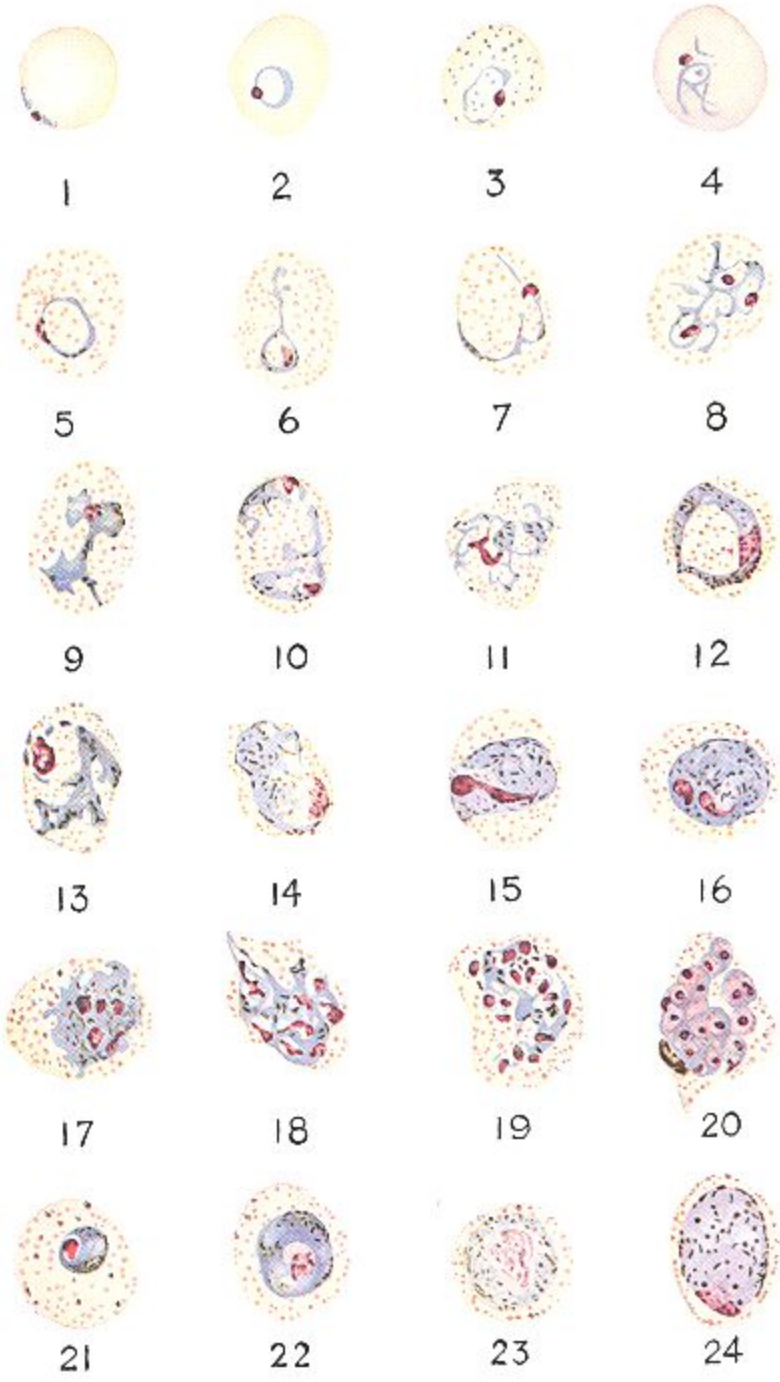

FIGURE VI.33. *See opposite page for legend.*

P. malariae requires over 11 days for the cycle and so far only the intermediate stages of the schizont have been described.

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 malarias, such as *P. vivax* and *P. malariae*, 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, producing a parasite relapse and, if in sufficient quantities to produce symptoms, a clinical relapse (Fig. VI.30).

Morphology. All forms which 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 the descriptive term, "signet ring." In the course of a few hours the ring develops into an actively motile ameboid 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 which 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

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Figure VI.33. *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 basophilic 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 National Institutes of Health, U.S.P.H.S.).

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 five or six 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 cytoplasm then undergoes similar subdivision, each portion including one of the chromatin masses. This mature schizont contains the new generation of asexual parasites, called merozoites, and also the pigment formed during the period of growth clumped into one or two loose masses (Figs. VI.33, VI.34). 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 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 common. The frequently seen accolé or appliqué form appears 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, intermediate 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. VI.35, VI.36).

Parasitized cells of the peripheral blood may show cleftlike or commalike 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 considered to be 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.

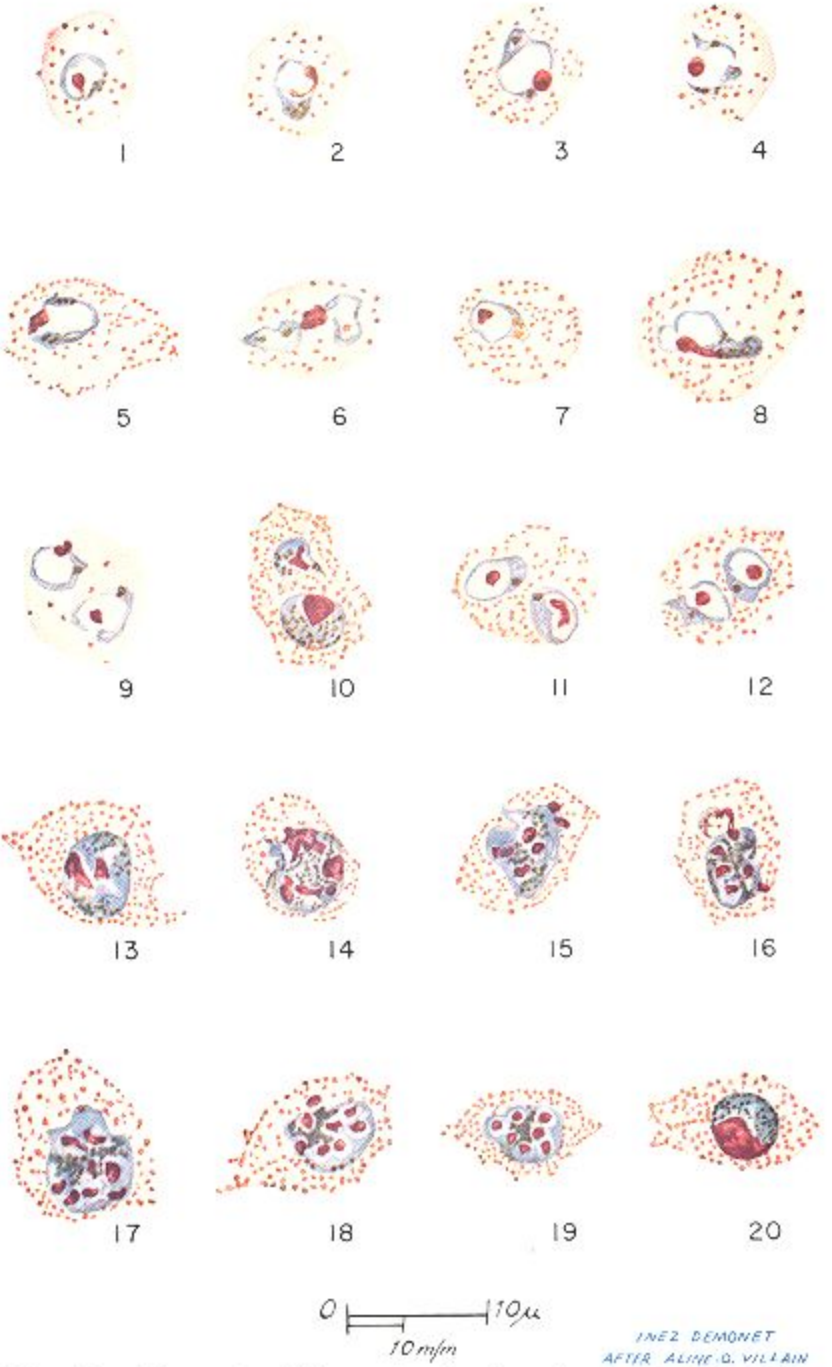


FIGURE VI.39. *Plasmodium ovale*. *1*, Young ring-shaped trophozoite. *2*, *3*, *4*, *5*, Older ring-shaped trophozoites. *6*, *7*, *8*, Older ameboid trophozoites. *9*, *11*, *12*, Doubly infected cells, trophozoites. *10*, Doubly infected cell, young gametocytes. *13*, First stage of the schizont. *14*, *15*, *16*, *17*, *18*, *19*, Schizonts, progressive stages. *20*, Mature gametocyte.

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 "Biologie Medicale" supplement, 1935.

(Courtesy of Aimee Wilcox, National Institutes of Health Bulletin No. 180, U.S.P.H.S.)

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 cubic millimeter 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 from 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 ten days after the onset of the primary parasitemia. They become infective for mosquitoes about four 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

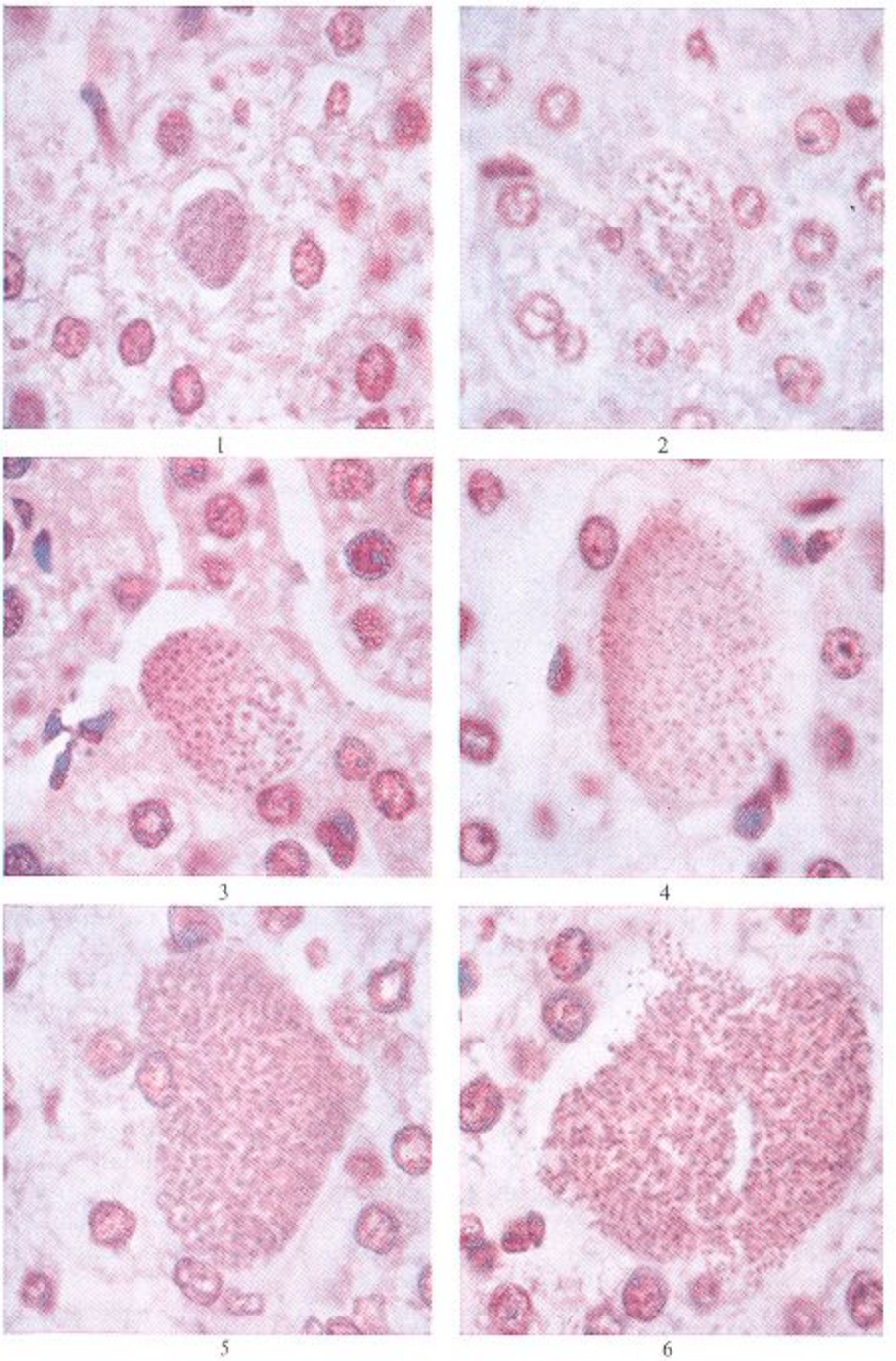


FIGURE VI.40. Exo-erythrocytic stages of *Plasmodium falciparum* in liver. *1*, This is one of the smallest parasites seen. Diameter 15μ. Probably three days old. *2*, A larger parasite than that shown in *1*. Sections cut at 2 μ and stained with Delafield's hematoxylin. *3*, A larger stage than that 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 60μ. (Courtesy Jeffery, Wolcott, Young, and Williams: Am. J. Trop. Med. Hyg. *1*:917, 1952.)

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 three 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 nine to ten 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 four years. *Plasmodium falciparum* experimental infections endure an average of seven to nine 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 one year.

Immunity. The Negro race has a relative racial immunity against *P. vivax*.[2] 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 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 is frequently 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 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 represents apparently a form of immunity depending upon a persisting latent infection. Agglutinins, precipitins and complement-fixing antibodies are produced. 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.

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, but at the end of 1964 it was estimated that 393 million people lived in areas where such programs have not yet been started. 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 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. More recently, experience in Korea has demonstrated that malaria may be a problem for armies in the field even in the temperate zone.

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. VI.41, Table VI.7).

It is apparent, however, that there must be other controlling influences, for in areas in which the disease is endemic the incidence 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 com-

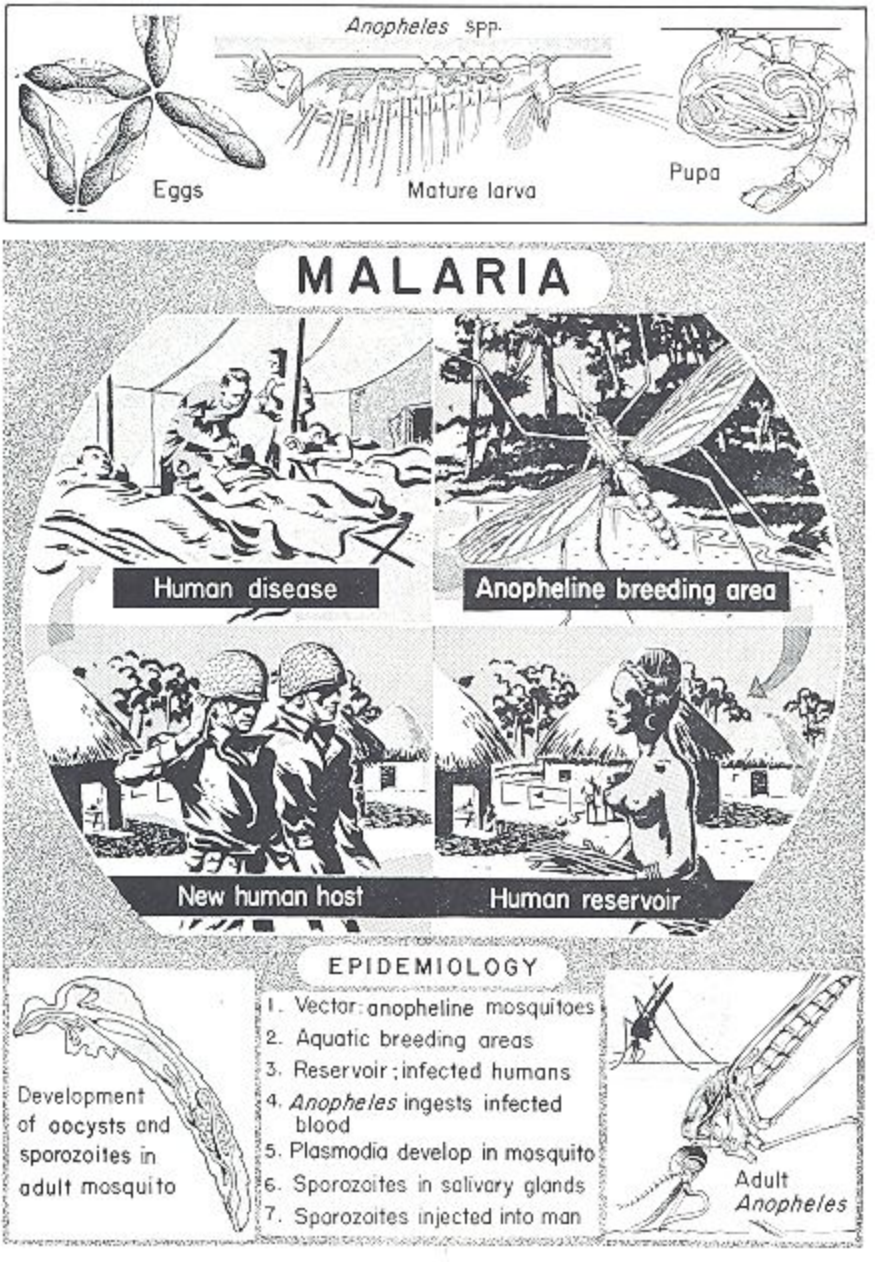


FIGURE VI.41. Epidemiology of malaria.

monly 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 dis-

appears. *Plasmodium vivax*, however, may be heavily endemic in certain regions at altitudes even in excess of 8000 feet.

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 incidence 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 incidence 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 incidence 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 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

(*Text continues on page 343.*)

Table VI.7. Principal Vectors of Human Malaria*

Region	Area	Species	Type of breeding place: Light requirements	Type of breeding place: Water, vegetation, etc.	Adult behavior	Efficiency as vector
Nearctic	United States (and bordering areas):					
	Drier portions of Rocky Mountain and Pacific area and N.W. Mexico	*Anopheles freeborni*	Sun	Fresh, clear seepage from ditches, rice fields, ridges of slow streams; irrigation water	Enters houses; feeds readily on man	Dangerous in interior valleys of west coast of U. S.
	Coastal Mexico to New Hampshire and Ontario west to Minnesota	*A. quadrimaculatus*	Sun usually, sometimes in partial shade	Fresh pools, ponds, lakes, lagoons, swamps, slow flowing rivers, in dense aquatic vegetation	Active at night; feeds on human or animal blood; may remain in houses all day	Most important carrier in the eastern U. S.
Neotropical (Largely)	Mexico, Central America (and bordering areas):					
	S.E. Texas, through Mexico and West Indies, south to Colombia and Ecuador; east through northern Venezuela	*A. albimanus*	Sun or partial shade	Fresh or brackish fairly pure, stagnant water; matted vegetation favorable in large lakes; swamps; lagoons; hoof prints	Nocturnal; prefers man, but also bites animals; enters houses, usually leaves at dawn after feeding	Most important vector in Central America and Caribbean, especially in rainy season
	Mexico	*A. aztecus*	Sun	Ground water, canals and pools of clear water with emergent or submerged vegetation	Enters and rests in houses	Sole important vector in some areas
	See South America, etc., for:	*A. darlingi*				
	South Central U.S., south to Chile and Argentina; Grenada	*A. pseudopunctipennis pseudopunctipennis*	Sun	Clear pools, streams and springs rich in algae, in dry season	Enters houses and feeds readily on man in certain areas only	Important in mountain valleys of South America, Central America and Mexico
	Mexico, through Central America and Trinidad to Peru, Brazil	*A. punctimaculata*	Shade preferred	Shaded pools, swamps, sluggish streams	Abundant in undrained jungle; strong flier; enters dwellings; feeds on man	Vector in parts of Panama; proved vector in parts of W. Colombia
	Caribbean area:					
	See Mexico, Central America for:	*A. albimanus*				
	Panama, Trinidad, Lesser Antilles, south to Brazil	*A. aquasalis* (*tarsimaculatus* of certain authors)	Sun or shade	Brackish tidal swamps; rarely in fresh water of rice fields (inland Trinidad)	May fly three miles; enters houses, feeds on man (less true in Panama?)	Important in many localities: Trinidad, coastal Brazil
	Trinidad and Venezuela to Brazil	*A. bellator*	Partial shade	Leaf bases of bromeliads (epiphytic on *Erythrina* and other trees)	Prefers man; bites at night or in shade (day time); enters dwellings occasionally, returns to forest	Important in cocoa-growing areas of Trinidad, and in coastal states of Brazil

Neotropical	South America (and bordering areas):	*A. albimanus*				
	See Mexico, C.A. for:	*A. cruzii*	Partial shade	Leaf bases of bromeliads	Bites man readily; enters houses	Important in coastal states of So. Brazil
	So. Brazil	*A. albitarsis*	Some shade (not extreme)	Among mats of aquatic vegetation in large ponds, marshes, overflows near rivers; hoof prints; artificial containers	Enters houses and shows preference for human blood in some areas	Important in Brazil and probably N.E. Argentina
	Guatemala to N.E. Argentina and Paraguay; Trinidad					
	Colombia, Venezuela	*A. nuneztovari*	Sun to partial shade	Muddy pools and lagoons	Bites and rests outdoors	Important in some areas
	Central America (British Honduras and Guatamala); South America (Venezuela to Argentina)	*A. darlingi*	Shade	Clear, fresh lagoons, overflows, etc., among debris, surface vegetation; avoids brackish water	Invades houses; prefers human blood. A domestic species	Most dangerous vector in tropical S. America from Venezuela, the Guianas to S. Brazil
	See Mexico, C.A. for:	*A. pseudopunctipennis pseudopunctipennis*				
Palaearctic	Europe:					
	S. Palaearctic North of Mediterranean; from England to Japan; from Sweden and Siberia to Portugal, Spain, Italy, Mongolia	*A. labranchiae atroparvus*	Sun	Brackish water along coast; fresh water inland	Frequents houses; feeds readily on man, also stabled animals	Carries "house malaria" of winter months, especially in Netherlands
	N.W. Africa, Spain, Sicily, Sardinia, Corsica, Italy, Dalmatian Coast, islands of central Mediterranean	*A. labranchiae labranchiae*	Sun to partial shade	Brackish, coastal marshes; fresh water of rice fields, upland streams; other situations	Prefers human blood; enters houses in large numbers	Important vector
	Norway and Sweden to Italy; England to Black Sea; eastern Mediterranean	*A. messeae*	Sun	Cool, fresh standing water; lakes, marshes	Prefers animal to human blood; hibernates in barns, houses	Vector in Hungary and Albania
	N.E. and central Italy, Sardinia, Balkans; U.S.S.R. to W. China	*A. sacharovi (= elutus)*	Sun	Open inland marshes and coastal marshes even if brackish	Feeds without preference on man, animals, enters houses (bedrooms); hibernates in cold weather, but feeds on cattle in lowlands during winter	Important in Balkans, Israel; preference for cattle reduces its importance as vector in other areas
	See Persian Gulf, etc. for:	*A. superpictus*				
	North Africa, Middle East:					
	Europe, N. Africa, Asia Minor, Turkestan	*A. claviger (= bifurcatus)*	Sun or shade	Marshes, rock pools, wells, cisterns	Domestic in Palestine; enters houses, bites man freely (wild in some regions)	Most important urban vector in Israel, Syria and Lebanon
	See Central and South Africa for:	*A. pharoensis*				
	See Europe for:	*A. sacharovi*				
	Canaries, Algeria, Tunisia, Egypt, Israel, Syria, N. W. India	*A. sergenti*	Sun to partial shade	Rice fields, borrow pits, slow irrigation flows (dense vegetation); seepage, neglected drains	Enters houses readily; bites mostly after dark; may migrate 2 miles	Vector in Egypt and Israel
	Persian Gulf and Caucasian area					
	See Europe for:	*A. sacharovi*				
	E. Arabia, S. Iraq; Iran, India, Burma	*A. stephensi stephensi*	Relative shade	Wells, cisterns, flower pots, cans, roof-gutters	Feeds readily on man; rests in barracks, houses, cowsheds	Important in urban areas

* Some secondary and suspected vectors are not included.

TABLE VI.7. PRINCIPAL VECTORS OF HUMAN MALARIA (*Cont'd See page 359*)

REGION	AREA	SPECIES	TYPE OF BREEDING PLACE		ADULT BEHAVIOR	EFFICIENCY AS VECTOR
			LIGHT REQUIREMENTS	WATER, VEGETATION, ETC.		
Palaearctic (cont'd)	Spain, Italy, Balkans to southeast Asia	*A. superpictus*	Sun	Fresh-water pools, streams, drains, seepages, especially in hill districts	Prefers human blood; readily enters houses, tents, barracks; strong fliers	Important in Europe, Middle East, W. Pakistan
	Japan, North and Northeast China, Korea, South Ukraine					
	See Burma, etc. for:	*A. sinensis*				
	China (not south of 30° N. lat.)	*A. pattoni*	Sun	Among algae along stream margins; rain pools, small pools of stream beds in hills	Bites man	Important vector
Ethiopian	Central and South Africa:					
	Tropical Africa, north to Ethiopia	*A. funestus funestus*	Partial shade	Clear water of swamps, weedy banks of streams, rivers, ditches; margins of lakes, ponds; underground seepages	Enters houses in large numbers; feeds freely on human blood; a few migrate up to 4½ miles	Always important (also carries filariasis)
	Tropical Africa, Arabia, Malagasy Rep., Reunion, Mauritania, Liberia; other points	*A. gambiae*	Sun or light shade	Puddles, shallow ponds, borrow pits, hoof prints, ditches, overflows; rarely rain barrels, cisterns	Prefers human blood; abundant in huts and houses; a few migrate up to 3½ miles	Always important (also carries filariasis)
	Sierra Leone, Liberia, Cameroon, Uganda, Dem. Rep. of Congo	*A. hancocki*	Sun to slight shade	Clear water in grassy holes, native wells, streams, swamps	Found commonly in human dwellings	Important where prevalent
	Sierra Leone, Liberia, S. Nigeria, Gabon, Dem. Rep. of Congo	*A. hargreavesi*	More or less shade	Among *Pistia* in open jungle; swamps, stream margins (vegetation)	Abundant in huts in Nigeria; bites at midnight or later	Important where common
	Dem. Rep. of Congo, Uganda, Cameroon	*A. moucheti moucheti*	Sun to slight shade	Among vegetation on margins of pools, streams, permanent swamps	Often found indoors	Rather important where common
	Southern Nigeria	*A. moucheti nigeriensis*	Sun, largely	Clear water, in swamps (*Pistia* and other vegetation)	Found in native huts	Rather important where common
	Sierra Leone, Liberia, Ghana, Nigeria, Cameroon—eastward to Mozambique	*A. nili*	Heavy shade	Among vegetation along sides of running streams	Common in huts and camps, but rare in houses	Possibly important where prevalent
	Coastal West Africa	*A. melas*	Shade	Breeding associated with black mangrove trees (*Avicennia* sp. in brackish water, coastal streams and tidal swamps	Feeds more on dark nights; most remain in huts after feeding	Important in some coastal areas of West Africa
	Many parts of Africa; Malagasy Rep., Israel	*A. pharoensis*	Sun to partial shade	Swamps and rice fields; vegetation essential	Enters houses in large numbers; bites man readily but prefers animal blood	Important in upper Nile Province, Sudan, Mali

Ethiopian (cont'd)	E. Central and S. Africa, N. and S. Rhodesia, Sudan	*A. rufipes*	Sun	pools, marshes, roadways, artificial containers	Rests in crevices and outdoor haunts near breeding places; occasionally found in large numbers indoors	S. Rhodesia, Fr. W. Africa, Sudan; usually of secondary importance
Oriental	Afghanistan, Pakistan, India, Burma, Ceylon:					
	India, S. China, Taiwan, entire Malay region and Philippines	*A. annularis* (= *fuliginosus*)	Sun to partial shade	Large tanks or fresh-water ponds, slowly moving streams, lake margins (with aquatic vegetation)	Prefers cattle to man; flies great distances; occurs up to 7000 ft.	Of secondary importance
	W. Pakistan to Burma; Ceylon; Thailand, Tonkin Prov., S. Arabia	*A. culicifacies*	Sun to partial shade	Wide variety of places; prefers fresh, clean water in pools but can survive in brackish	Prefers cattle but bites man freely; rests in cow sheds and houses during day	Most important vector in India; only vector in Ceylon
	In foothills from W. Pakistan to Burma; South India, Turkestan, Thailand, Tonkin Prov.	*A. fluviatilis* (= *listoni*)	Sun	Stream edges, stream pools, springs, irrigation channels; more rarely swamps, lakes	Prefers human to animal blood; found in houses, cow sheds	Important vector in rural foothills (1000–5000 ft.)
	E. and S. India, Burma, Thailand, Vietnam, S. China, Taiwan	*A. minimus*	Sun	Slow-running streams, springs, with grassy margins, irrigation ditches, rice fields, seepage areas	Remains in houses and cow sheds after feeding	Always important; especially so in India, Burma, Thailand, S. China up to 5500 ft.
	India, Burma, Malaya, Thailand, Vietnam, Indonesia, Philippine Islands	*A. philippinensis*	Sun to partial shade	Pools, drains, ditches, tanks, swamps, borrow pits, rice fields; grass covered stagnant waters	Found in houses, stables, cattle sheds	Important in Bengal; probably *not* vector in Philippine Islands
	See Persian Gulf, etc. for:	*A. stephensi*	.....	.....	.....	.....
	India, Burma, Thailand, Malaya, Sumatra, Java, Borneo, Lesser Sunda Islands, S. Celebes	*A. sundaicus*	Sun	Brackish or salt water in lagoons, swamps and behind coastal embankments	Prefers human blood (?); found in large numbers in cow sheds, houses; strong fliers	Important in Bengal, Malaya, Vietnam, Indonesia
	See Persian Gulf, etc. for:	*A. superpictus*	.....	.....	.....	.....
	India, Burma	*A. varuna*	Sun or shade	Stagnant water of pools, ditches, wells, slow streams, irrigation ditches	Feeds readily on man; found in houses, cow sheds	Proved vector in some localities
	India, Ceylon, Burma, Thailand, Cochin-China, Malaya, Sumatra, Java, Borneo, Celebes	*A. aconitus*	Sun to partial shade	Irrigation ditches, swamps, ponds, rice fields, pools in creek beds, storm drains; reservoirs with grassy margins	Feeds readily on man, animals; found in houses, cow sheds (1200 to 2500 ft.); strong fliers	Important in Vietnam
	See Afghanistan, N.E. India, etc., for:	*A. culicifacies*	.....	.....	.....	.....
	Burma, Vietnam, China, Korea, Japan, Taiwan, Okinawa, Indonesia	*A. sinensis*	Sun	Stagnant water in rice fields, pools, ponds, swamps; rarely stream or lake margins	Not recorded as domestic	Vector in S. Japan, Korea, Okinawa, Indonesia and in China
	India, China, Tonkin Prov., Burma, Taiwan	*A. jeyporiensis candidiensis*	Sun to slight shade	Running water in ditches	Not recorded as domestic	Vector in Tonkin Prov.
	India, Ceylon, Burma, S. China, Thailand, Malaya, Indonesia, Vietnam, Taiwan, Philippines	*A. maculatus maculatus*	Sun to very slight shade	Stream and river beds, seepages; also pools, rice fields, lake margins, ditches	Enters houses temporarily; bites humans	Important in Malaya and Indonesia
	See Afghanistan, etc. for:	*A. minimus*	.....	.....	.....	.....
	See Afghanistan, etc. for:	*A. sundaicus*	.....	.....	.....	.....
	India, Burma, Thailand, Malaya, Laos, Cambodia, Vietnam, Indonesia, Borneo	*A. balabacensis*	Shade	Pools	Feeds in forest canopy and on ground on monkeys and man. Enters houses	Important

Table VI.7. Principal Vectors of Human Malaria (Cont'd)

Region	Area	Species	Type of breeding place: Light requirements	Type of breeding place: Water, vegetation, etc.	Adult behavior	Efficiency as vector
Oriental (cont'd)	E. India, Tonkin Prov., Malaya, Cochin-China, Sumatra, Java, Borneo, Celebes	*A. umbrosus*	Shade (can tolerate sunlight)	Stagnant jungle pools and morasses; brackish water in mangrove swamps	Fierce biter, found in dense forests, jungles, also in houses; strong flier	Important in some areas
	Philippine Islands and south to Java	*A. minimus flavirostris*	Sun and shade	Clear water of shaded streams (bamboo roots); rivers, irrigation ditches, pools, wells	Enters houses to attack man; leaves after feeding, rests under overhanging banks	The important vector in the Philippines
	Indonesia:					
	See Burma, etc. for:	*A. aconitus*	.....	.....	.....	.....
	India, Ceylon, Burma, Thailand, Vietnam, China, Malaya, Sumatra, Borneo, Java, Lesser Sundas, Celebes, New Guinea, Philippines	*A. barbirostris barbirostris*	Sun and shade	Clear water of shaded streams, rivers, vegetated ponds, pools, flowing ditches, canals; borrow pits, rice fields, salt water swamps; wells	Flies by day (in shade); enters houses rarely; prefers blood of domestic animals	Of little importance (found infected in Malaya, Indonesia)
	Malaya, Indonesia, Sarawak	*A. letifer*	Sun and shade	Stagnant drains, pools, dark brown water of peaty soils; found with varying amounts of vegetation: fresh water areas of coastal plains	Enters house, rests outside during day	Important in Malaya, probably other areas
	India, Ceylon, Burma, Thailand, Vietnam, China, Malaya, Sumatra, Java, Celebes, Borneo	*A. nigerrimus*	Sun, largely	Rice fields especially; stagnant vegetated canals, borrow pits, lakes, impounded areas; slow streams	A wild species, invades houses rarely; feeds on man or animals	Of some importance in Malaya and Indonesia
	India, Ceylon, Burma, Vietnam, Malaya, Sumatra, Java, Borneo, Philippines	*A. leucosphyrus leucosphyrus*	Heavy shade required	Rock pools; stagnant pools in beds of mountain streams	A wild species; found in dense jungles	Found infected in Indonesia
	See Burma, etc. for:	*A. maculatus*	.....	.....	.....	.....
	See Afghanistan, etc. for:	*A. minimus*	.....	.....	.....	.....
	India, Malaya, Indonesia, New Guinea	*A. subpictus subpictus*	Sun or shade	Fresh, brackish, or contaminated pools, borrow pits, wallows; roof-gutters, containers	Feeds on man, other animals, but prefers cattle; numerous in cow sheds, houses, barracks	Believed important in Celebes
	See Afghanistan, etc. for:	*A. vagus*	.....	.....	.....	.....
	See Burma, etc. for:	*A. umbrosus*	.....	.....	.....	.....
Australasia	New Guinea, New Britain, Solomons, New Hebrides, Admiralties, N. Australia	*A. farauti*	Sun or slight shade	Fresh or brackish water, natural or artificial, clear or polluted	Bites freely both at night and in day time shade; exclusively anthropophilic	Dominant carrier in this area
	New Guinea, Bismarck Archipelago and Solomon Islands	*A. punctulatus*	Sun	Small rain pools, stream margins; rarely in larger bodies of water	Frequents houses; bites throughout night; strong flier	Important in New Guinea, and in Solomons
	New Guinea, Solomons	*A. koliensis*	Sun	Temporary pools in grass lands at edge of jungle	Enters and rests in houses. Active at night	Important in Solomons
	Australia, New Guinea	*A. bancrofti*	Shade	Swampy areas, vegetation	Nocturnal. Enters and rests in houses and sheds	May be important when present in large numbers

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. 868).

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. 865).

Pathology. Malaria is accompanied by the destruction of enormous numbers of red blood cells, both parasitized and nonparasitized, and 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. 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,

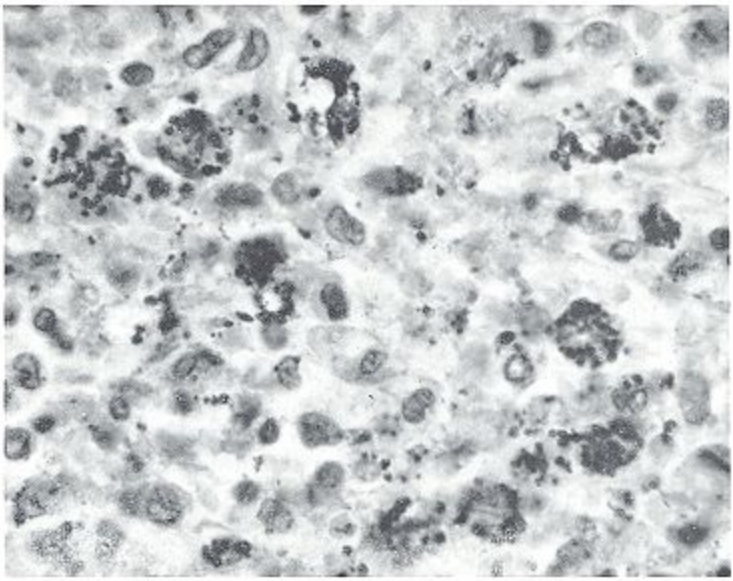


FIGURE VI.42. Phagocytosed and free malarial pigment in the spleen; numerous individual granules and aggregates of pigment in a single phagocyte. (Courtesy of the Louisiana State University School of Medicine.)

the failure of the liver to reconvert liberated iron and, in *P. vivax* infections, the selective parasitization of reticulocytes.

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 is deposited in the reticuloendothelial cells of the viscera. One of the striking features of the gross pathologic process in patients who have died after prolonged infection is a slaty or blackish pigmentation of the organs, especially the spleen, liver and brain (Fig. VI.42).

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 trabeculae and are found also 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 brown blocks (characteristic of *P. falciparum*) or as small, black conglomerate masses in the phagocyte (Fig. VI.42). 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. 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 (Fig. VI.43).

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. VI.44). 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. VI.45 A, 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 (Durck'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. VI.45 C).

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

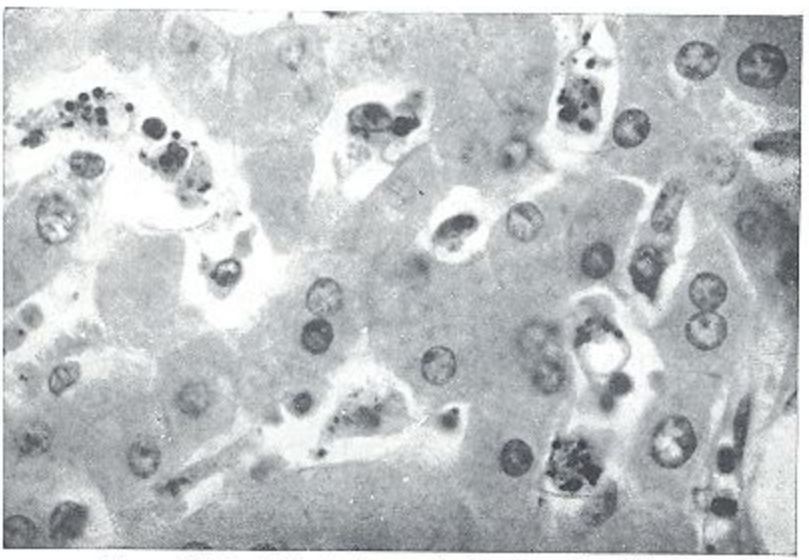


FIGURE VI.43. Malaria pigment in Kupffer cells of liver.

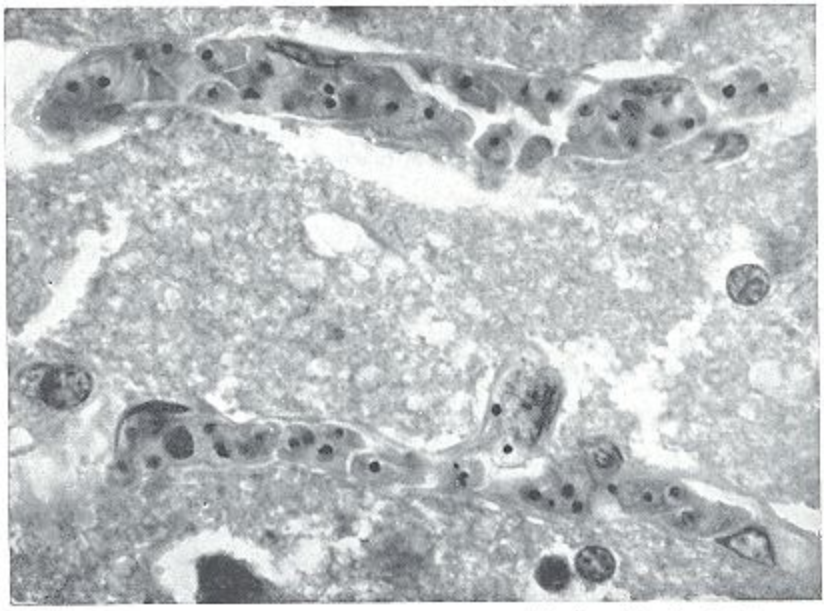


FIGURE VI.44. Agglutinated parasitized erythrocytes in capillaries of brain—*falciparum* malaria.

bone marrow may reveal large numbers of parasitized cells and considerable amounts of malarial pigment.

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 levulose 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; however, when there is sufficient damage to the kidneys in malignant *falciparum*, chronic malaria or blackwater fever to interfere with renal function, varying degrees of nitrogen retention and uremia may occur.

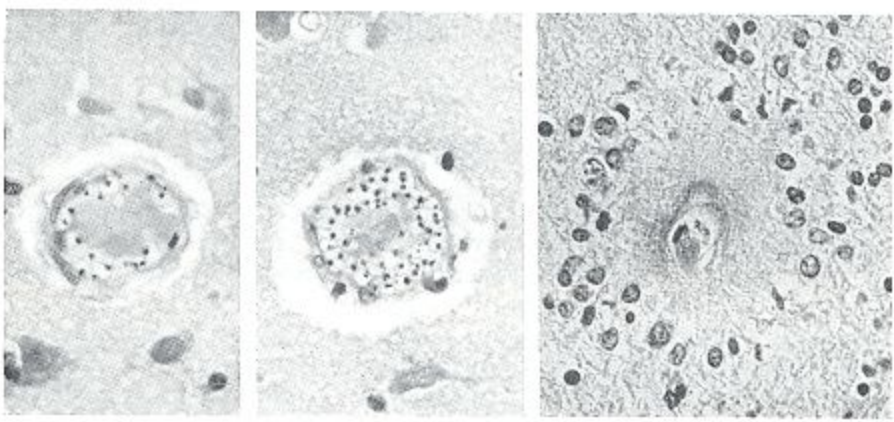
Clinical Characteristics. Salient features of malaria are periodic fever, splenomegaly, anemia and leukopenia. The characteristic periodicity of the fever (in *vivax* and quartan infections) is associated with the rhythmic maturation of the sporulating forms in the blood and their massive release by 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 parasitized and nonparasitized red corpuscles. Malarial pigment, to which the name hemozoin has been applied, occurs as rods and granules, or in *P. falciparum* as small blocks. The pigment is also taken up by the phagocytic reticuloendothelial cells. 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 *P. falciparum* differ greatly in their evolution and in the hazard to the infected individual from those accompanying infection by *P. vivax*, *P. malariae* or *P. ovale*. *Falciparum* malaria, often called malignant tertian, 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 term *benign tertian* is therefore often applied to infections by *P. vivax*. This difference, in part at least, is due to special characteristics of *P. falciparum*. Its capacity to invade both mature erythrocytes and reticulocytes is probably directly related to the intense and rapidly increasing parasitemia which accompanies this infection. Furthermore, the infected red blood cells tend to agglutinate and to adhere to capillary endothelium, forming thrombi which produce areas of local anoxemia and ischemia in the viscera (Fig. VI.45).

The usual intrinsic incubation period for *vivax* malaria is 11 to 15 days, *falciparum* 11 to 14 days, *ovale* 14 to 26 days and quartan about 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 *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. VI.46).

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



A B C

Figure VI.45. *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 (Durck's nodule). (Courtesy of the Louisiana State University School of Medicine.)

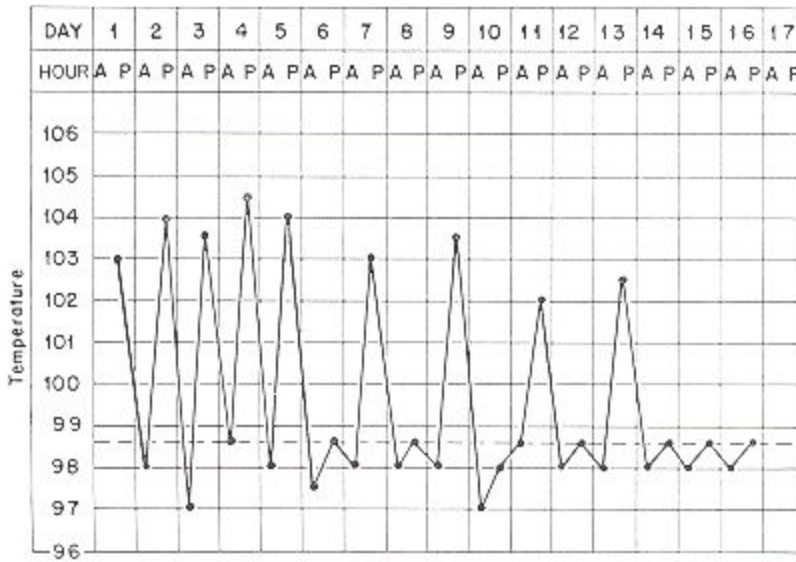


FIGURE VI.46. Fever chart in a *P. vivax* infection showing an initial quotidian tendency becoming tertian. No specific therapy. A = A.M., P = P.M. (Russell, West, Manwell and Macdonald. Practical Malariology. 2nd ed.)

accompanied by a sensation of extreme cold, although the temperature meanwhile rises rapidly to 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 two to three hours and the entire paroxysm averages ten 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 occurs every 72 hours. 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.

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 alkali 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 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.

The extensive interference with the vascular supply to the central nervous system in cerebral malaria, with vascular thrombosis and consequent local ischemia and anoxemia, 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.

Algid Malaria. The algid 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 been long recognized as an algid 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.

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

Diagnosis. The 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 frequently it may 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.[3] 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. 826.) 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 four to seven days after the institution of specific therapy is suggestive.

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 VI.8 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 VI.9. *P. ovale* usually cannot be identified with certainty in the thick film.

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 no one exerts all. The chemical groupings of the drugs are: cinchona alkaloids—quinine; 4-aminoquinolines—chloroquine, amodiaquine; 8-aminoquinolines—primaquine, pamaquine; 9-aminoacridines—mepacrine; biguanides—proguanil; diaminopyrimidines—pyrimethamine.[4, 5]

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 mgm per ml equivalent to 40 mgm 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.

Chloroquine is highly active against the erythrocytic forms of the plasmodia, although *P. malariae* responds more slowly than the other species. *Falciparum* gametocytes are not removed or sterilized.

TABLE VI.8. DIFFERENTIAL CHARACTERISTICS OF THE PLASMODIA OF MAN IN STAINED THIN FILM

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

* Not invariable but suggestive when seen.

TABLE VI.9. DIFFERENTIAL DIAGNOSIS OF MALARIAL PARASITES IN STAINED THICK BLOOD FILMS*

STAGE OF PARASITE	PLASMODIUM FALCIPARUM	PLASMODIUM VIVAX	PLASMODIUM MALARIAE	COMMENTS
Small trophozoite (early ring)	Small size rings, with small chromatin dot and delicate, scanty cytoplasm. Frequently rings have double chromatin dots. Tendency toward large number of rings. Many ring forms with no older stages—practically certain to be *falciparum* infection. Diagnosis on small number of rings may often be assisted by finding distinguishing gametocyte, though this stage is not necessarily present.	Larger, heavier, ring form than in *falciparum*, often with variety of cytoplasmic pattern and irregularities in shape. Usually older stages of parasite can be found also.	Ring is likely to be heavy, with large dot of chromatin and small amount of cytoplasm, which is often "filled in," without a vacuole. Pigment forms early and may appear as haze in cytoplasm of this stage. Rings practically always associated with older forms. The ring phase is brief, so this stage is not found as often as older stages.	Ring forms often not complete circle—may be "swallow" forms, "exclamation mark," "comma" forms, or "interrupted rings." When rings only are present and number is small, it is practically impossible to differentiate species.
Growing trophozoite	Heavy large ring forms—resemble young rings of *vivax*. Sometimes show pigment grains or haze rather clearly in cytoplasm.	Stage usually ameboid in appearance, with large variety of shapes. Cytoplasm frequently fragmented and arranged irregularly in cluster of varying sized pieces or streamers, about or close to a large chromatin mass. Small yellowish brown pigment granules scattered through parts of the cytoplasm. This is the most characteristic stage of *vivax*. Frequently other younger or older stages accompany this one.	Small, usually rounded compact forms, "like marbles in a ring." Profuse, 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 parasite seen.	In heavily stained films and in films which have been kept for several days before staining, the "ghost" of the enlarged host cell and persistence of Schuffner's stippling or a pinkness remaining from the stippling, may assist in diagnosis of *vivax*.
Large trophozoite	Ring vacuole lost or almost lost. Parasite quite small and compact, cytoplasm often quite pale, irregularly circular or oval. One large chromatin dot. Pigment in blurred mass or small, very dark clump or clumps. Stage is usually found only when the infection is intense and usually accompanied by numbers of ring-form trophozoites.	Frequently quite solid and dark staining. More or less irregular in outline, possibly with one or more vacuoles. Fine brown pigment scattered throughout the cytoplasm. May be confused with macrogametocyte.	Compact, dark, larger than "growing" stages. Sometimes in thinner portion of the smear spreads to normal size. Profuse, fairly coarse, dark brown pigment—often masking the chromatin. May be confused with "rounded up" *falciparum* gametocyte or with gametocyte of *malariae*.	On rare occasions Maurer's dots have been observed in thick films of *falciparum*. The infrequently found stages of *falciparum* are, of course, more readily found in thick films. Band forms have tendency to become rounded in thick films of *malariae*—except perhaps in very thin edge of smear.
Schizont (presegmenting)	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 (often pale) in which there is located one or more small, dense blocks of very dark pigment.	Irregular or compact clusters of chromatin divisions, often dark reddish purple in color. Cytoplasm in irregular broken masses and wisps, containing light brown pigment granules which are clumped in spots. Usually accompanied by other stages. May be confused with same stage of *malariae*.	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 *vivax*.	Schizonts are much like thin film forms of same stages—more compact, smaller in thicker portions of smear. This is the most difficult stage (except infrequent ring forms) on which to diagnose species.

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.	Usually contains around 16 merozoites which are individually larger than those of *falciparum*. Usually relatively larger than other species. Nearly always associated with other stages. Not so often found as other stages.	Most distinctive stage of *malariae* in thick film. Often found in large numbers—usually with trophozoites or presegmenting forms or both. About 8 merozoites each with large chromatin dot and small amount of cytoplasm—may be compact or clearly separated. Frequently the chromatin and pigment only are seen, the chromatin dots being bare and well separated. The dark heavy pigment is more often concentrated, though sometimes dispersed	Usually smaller than same stage in thin film.
Young gametocyte	Sometimes long, slender and pointed, with pigment scattered to the ends. Usually associated with many trophozoites.	When found is a small, compact, usually rounded parasite, with one chromatin mass which is often in the center of cytoplasm and frequently has unstained area around chromatin mass. Sex is almost impossible to determine.	Same as *vivax* except that parasite is even less frequently found and resembles compact trophozoite so closely that differentiation is impossible.	
Mature gametocyte	Differentiation of sex is difficult or impossible. As "crescent" or "sausage" shapes, may be quite diagnostic of species. In thicker portion of smear may take on oval or rounded, somewhat eroded appearance, which may be confused with *malariae* trophozoite or gametocyte. Often may be distinguished by difference in amount and appearance of pigment or by pink or red "flag" protruding from the edge of the parasite. May be accompanied by ring form trophozoites or appear alone and infrequently. Often appears in "showers."	Macrogametocyte is larger, as a rule, than in other species; pigment is light, delicate, well dispersed through nonvacuolated cytoplasm. Except in thin edge of film cannot be differentiated from some mature trophozoites of same species. Microgametocyte often distinguishable as large blob of chromatin (varying from pink to purplish red) surrounded by halo of pale or colorless cytoplasm in which pigment granules are more or less evenly dispersed. Other stages of the parasite can usually be found.	As a rule, few in number, somewhat smaller than *vivax*, otherwise have the same distinguishing features except that pigment is coarser and darker. May resemble rounded *falciparum* gametocytes.	

* Courtesy of Aimee Wilcox, Laboratory of Tropical Diseases, NIAID, National Institutes of Health, in "Manual for the Microscopical Diagnosis of Malaria in Man." 3rd ed., 1960; and the American Public Health Association, Standard Methods Committee on Diagnostic Procedures and Reagents: "Diagnostic Procedures and Reagents." 2nd ed., New York, 1945.

Chloroquine and amodiaquine are the drugs of choice for treatment of acute malaria. In the majority of cases fever is controlled within 24 hours, and thick blood films usually become negative in from 48 to 72 hours. Chloroquine will terminate infection by *P. falciparum*. Since *P. vivax* infections have a persisting exo-erythrocytic phase, the use of primaquine in conjunction with chloroquine will prevent relapses of *vivax* malaria in the great majority of cases. Chloroquine is an excellent antimalarial. Strains of *P. falciparum* resistant to chloroquine have appeared. (See pp. 357–359.)[7, 8]

Amodiaquine. Synonyms: Camoquin, CAM-aq1. The drug is prepared as the hydrochloride and is distributed in tablets, each containing 0.2 gm of amodiaquine base.

It 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. Amodiaquine 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. Its action upon the parasite is similar to that of chloroquine. Good results have been reported in the treatment of acute malaria using a single dose of 0.6 to 1.0 gm for adults. The recomended dose for children is 10 mgm per kg of body weight. Amodiaquine has proved to be an efficient suppressive agent. For this purpose a single dose of 0.6 gm taken once every 2 weeks has proved sufficient under most conditions. Strains of *P. falciparum* resistant to amodiaquine have been reported. (See p. 359.)

Quinine. This is a general protoplasmic poison. It 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 mgm 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. It is employed for the treatment of patients with chloroquine-resistant strains of malaria.

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 dosage 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 Diphosphate. 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 mgm of the salt being equivalent to 15 mgm 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 mgm or the daily administration of 30 mgm of the drug. As only the older red blood cells are destroyed, the hemolysis is self-limited. If the usual adult dose of 15 mgm 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.

Proguanil. Synonyms: Chlorguanide, Guanatol, Paludrine. Proguanil hydrochloride is a colorless, bitter pyrimidine compound which 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.

Chlorguanide is a slowly acting schizonticide which inhibits chromatin division. It inhibits the development of female gametocytes in the mosquito, thus interrupting the exogenous cycle of the plasmodia. Resistant strains of plasmodia have been produced in the laboratory and in the field. It is an effective therapeutic agent against nonresistant strains but slower in action than chloroquine, quinine or quinacrine. The effectiveness, however, varies between different geographic areas. In general, the fever is controlled and trophozoites disappear from the peripheral blood in the course of 48 to 72 hours. In many instances, but not in all, a single course of therapy terminates infection by *P. falciparum.*

It is not the drug of choice for the treatment of acute clinical malaria, especially since the serious complications are brought under control only slowly. Strains of malaria resistant to proquanil have been reported.

An experimental repository preparation of the dihydrotriazine metabolite of chlorguanide, CI-501, exerts long-term protection and is effective therapeutically against *P. vivax* infection. A single intramuscular injection at a dose of 5 mgm of the drug base per kg of body weight provided protection for 9 to 12 months to most volunteers who were exposed to *vivax* malaria by the bites of infected mosquitoes.[6] Resistance has appeared.

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 entirely 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, reduction of erythrocyte and leukocyte counts, atrophy of lymphatic tissue and degenerative changes in the intestinal epithelium.

It is a slowly acting schizonticide. It inhibits the development of female gametocytes of susceptible strains of *P. falciparum* in the mosquito. Resistant strains have appeared in the field and in the laboratory.

Pyrimethamine is not a preferred drug for the treatment of acute malaria. Although a single dose of 0.25 to 0.5 mgm per kg of body weight causes disappearance of nonresistant parasites from the blood, the speed of action in controlling fever and parasitemia is less than that of chloroquine or amodiaquine. Furthermore, in certain areas it has not proved effective against the local strains.

Table VI.10. Chemotherapy of Malaria

TREATMENT SCHEDULES

The doses suggested in this summary are for adults of approximately 150 lb. (70 kg) bodyweight. 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 age.

TREATMENT OF CLINICAL ATTACK IN NONIMMUNE SUBJECTS

1. *Chloroquine diphosphate* or *sulfate:* 600 mgm of base; 300 mgm 6 hours later; 300 mgm daily for next 2 days.

OR

2. *Amodiaquine dihydrochloride dihydrate:* 600 mgm of base first day; 400 mgm daily for next 2 days.

OR

3. *Mepacrine dihydrochloride dihydrate:* 1 gm (5 doses of 200 mgm) first day; 100 mgm thrice daily for next 6 days.

OR

4. *Quinine sulfate* or *dihydrochloride:* 0.65 gm (10 grains) 3 times daily for 7 to 10 days.

EMERGENCY TREATMENT

1. *Chloroquine hydrochloride:* 200 to 300 mgm of base intramuscularly, repeated in 6 hours if necessary. Transfer to oral therapy as soon as possible.

OR

2. *Quinine dihydrochloride:* 600 mgm in normal saline, glucose saline or plasma, injected intravenously *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.)

OR

3. *Mepacrine methane sulfonate:* given intramuscularly in single doses not exceeding 300 mgm; total in first 24 hours, 600 to 900 mgm. Transfer to oral therapy as soon as possible.

TREATMENT OF CLINICAL ATTACK IN SEMI-IMMUNE SUBJECTS

1. *Chloroquine diphosphate* or *sulfate:* 600 mgm of base, single dose.

OR

2. *Amodiaquine dihydrochloride dihydrate:* 600 mgm of base, single dose.

OR

3. *Mepacrine dihydrochloride dihydrate:* 400 mgm; 200 mgm 4 hours later; 300 mgm daily for next 3 days.

4. *Quinine sulfate* or *dihydrochloride:* 1.0 to 1.5 gm (15 to 23 grains) daily for 2 to 5 days.

RADICAL CURE OF VIVAX AND MALARIAE INFECTIONS

1. *Primaquine diphosphate:* 15 mgm 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.

TABLE VI.10. CHEMOTHERAPY OF MALARIA (CONT'D)

PROPHYLAXIS AND SUPPRESSION†

1. *Chloroquine diphosphate* or *sulfate:* 300 mgm of base plus 30 to 45 mgm primaquine once weekly.

OR

2. *Amodiaquine dihydrochloride dihydrate:* 300 mgm of base plus 30 to 45 mgm primaquine once weekly; for partially immunes, 400 to 600 mgm every 2 weeks.

OR

3. *Mepacrine dihydrochloride dihydrate:* 100 mgm daily, *or*, for partially immune subjects, 300 mgm once weekly. Administration *beginning 10 days before exposure to infection.*

OR

4. *Quinine sulfate* or *dihydrochloride:* 650 mgm (10 grains) daily. *Recommended only when none of the above-listed drugs is available, or when resistance to above drugs occurs.*

* Mepacrine should not be given *concurrently* with any of the 8-aminoquinoline drugs.
† The prophylactic regimen should be continued for 8 weeks after leaving an endemic area

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.

It is an efficient suppressive agent when taken in dosage of 0.1 gm daily. Clinical attacks begin to appear about 2 weeks after discontinuing the medication.

TREATMENT OF CLINICAL MALARIA. Most simple acute cases respond rapidly to the standard regimens of 1.4 gm amodiaquine or 1.5 gm chloroquine 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 VI.10.

In patients with *falciparum* malaria who have not responded to the chloro-

quine 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 treatment of choice is quinine (2 gm daily). Because of a variable tendency to develop postural hypotension, patients should be kept at bed rest during quinine administration. The urine output should be measured and if oliguria develops, quinine should be temporarily discontinued. During oliguria, quinine blood levels rise precipitously and acute quinine toxicity ensues. Of major clinical importance is the phenomenon of fluid retention in malaria. Although the exact pathophysiology has not been elucidated, it has been observed that patients with *falciparum* malaria occasionally become hypervolemic as a result of the retention of water and electrolytes and possibly loss of albumin. For these reasons it is imperative that parenteral fluids be used extremely sparingly. Overhydration can lead to cerebral edema, which is easily confused with cerebral malaria. In rare instances, pulmonary edema may result if there is underlying heart disease.

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 mgm 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.

Patients who relapse after quinine therapy should be retreated with quinine. If necessary, the course of quinine may be maintained for 21 days at a dosage of 0.65 gm (10 grains) 3 times daily, as tolerated.

In patients who do not respond clinically or in whom parasitemia persists or recurs after the second course of quinine therapy, combinations of sulfadiazine plus a sulfone (diaminodiphenylsulfone or DDS, the antileprosy drug) may produce a cure. Dose schedules are:

a. 4 gm sulfadiazine daily for 6 days together with 100 mgm DDS daily for 6 days,

or

b. 50 mg of pyrimethamine (Daraprim) daily for 3 days plus 100 mgm of DDS daily for 6 days.

New drugs and other combinations are being investigated.

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 mgm (15 mgm base) daily for 14 consecutive days. 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 VI.10).

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 medication, clinical attacks due to infection by *P. vivax*

and *P. malariae* may begin to occur after ten 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 VI.10.

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 so widely that these drugs are not recommended for use alone in mass administration. If used for suppression or prophylaxis, they should be used only in combination with other drugs.

Strains of *P. falciparum* from Colombia, Brazil, Thailand, Malaya, Cambodia and Vietnam have proved to be resistant to the 4-aminoquinoline drugs, chloroquine and amodiaquine. Some of these strains also were 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.[5, 7, 8] Failure to reduce drastically the parasitemia by 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 has been induced in man for the therapy of neurosyphilis. Many thousands of patients have 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*. *P. 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. giardi, P. lemuris;* in the monkeys, *P. brazilianum, P. coatneyi, P. cynomolgi, P. fieldi, P. girardi, P. gonderi, P. inui, P. osmaniae, P. knowlesi* and *P. simium;* in the apes, *P. eylesi, P. hylobati, P. pithreci, P. reichenowi, P. schwetzi, P. youngi.* Some subspecies of the above have been proposed.

Some of the simian malarias have been induced experimentally into humans by mosquitoes (*P. cynomolgi* [2 subspecies], *P. brazilianum*) and by infected blood (*P. knowlesi, P. inui* and *P. schwetzi*). 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 can be experimentally transmitted to man by the bites of infected mosquitoes suggests the possibility of zoonoses.[9, 10–13] 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* confirms the zoonotic potential of simian malarias.

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 hemobilirubin 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 material may be observed within the collecting tubules (Fig. VI.47). 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 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 two 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 hiccough 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.

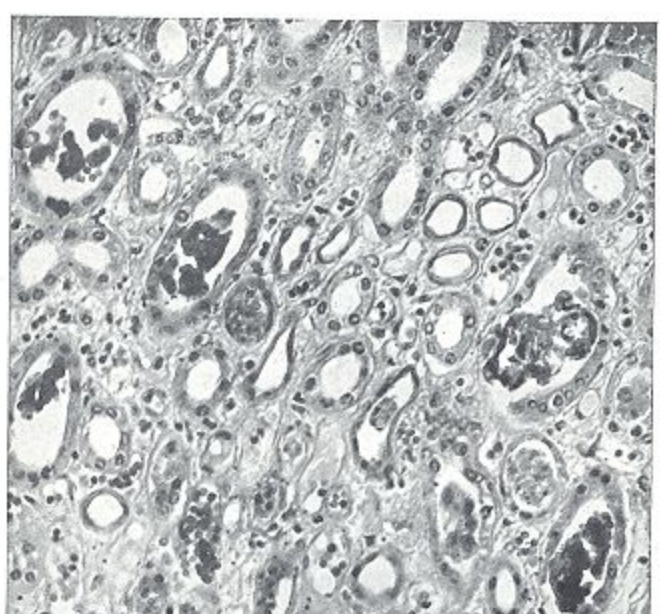


FIGURE VI.47. Kidney in blackwater fever, showing hemoglobin casts in distal convoluted tubules and degeneration and regeneration of tubular epithelium.

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 hyponatremia. Packed red blood cells should be given, if necessary, to combat severe anemia.

ANTIMALARIAL THERAPY. When malaria parasites are present in the peripheral blood, immediate intensive treatment with a rapidly acting plasmocidal drug is essential. The drugs of choice are chloroquine and amodiaquine. Quinine, mepacrine and 8-aminoquinolines are contraindicated. 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, especially 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.

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