

Plasmodium falciparum (Welch, 1897)

SYNONYMS: *Oscillaria malariae* Laveran, 1881; *Plasmodium malariae* Marchiafava and Celli, 1885; *Laverania malariae* Feletti and Grassi, 1890; *Haemamoeba praecox* Grassi and Feletti, 1890, *partim*; *Ematozoo falciforme* Antolisei and Angelini, 1890; *Haemamoeba immaculata* Grassi, 1891; *Haemamoeba laverani* Labbe, 1894; *Haematozoon falciforme* Thayer and Hewetson, 1895; *Haematozoon falciparum* Welch, 1897; *Haemosporidium sedecimanae* Lewkowicz, 1897; *Haemosporidium undecimanae* Lewkowicz, 1897; *Haemosporidium vigesimotertiana* Lewkowicz, 1897.

As mentioned in an earlier chapter, Laveran in his early studies (1880,1881) of the parasites of human malaria saw each of the principal species and in 1881 used the name *Oscillaria malariae* for these parasites, including the crescent-shaped bodies; then, and later, he steadfastly held to the belief that only one species was involved. Garnham (1966) gives an interesting account of Laveran's first observations of the falciparum parasite in 1880 in the blood of a young soldier who had been in Algeria for about a year. In 1892, Grassi and Feletti, as an honor to Laveran, proposed the genus name *Laverania* which was zoologically correct, providing two genera are recognized. However, since most authors recognize only the genus *Plasmodium* Marchiafava and Celli, 1885, the latter took precedence under Opinion No.104 of the International Commission on Zoological Nomenclature, 1928.

The confusion which surrounded the naming of this parasite was linked to its masked periodicity and to the presence of crescent-shaped bodies. Marchiafava and Bignami (1892)

resolved some of the mysteries of the parasite, as seen in the peripheral blood, by setting forth its 48-hour cycle, and showing that the small parasites and the crescents were parts of the same cycle. On clinical grounds, they pointed out its perniciousness. Mannaberg (1893), in his concisely written little book, pointed out the error of ascribing triple etiology, as Feletti and Grassi (1890) had done, to the malignant tertian parasite and his illustrations, colored Plate IV, leave little doubt that he was familiar with the circulating blood forms of the parasite.

Several different names were proposed for the parasite between 1885 and Welch's *Haematozoon falciparum* of 1897. The latter name called attention to the sickle-shaped parasites and, probably for that reason, was widely accepted by the scientific community, even though taxonomically incorrect. Such a situation is intolerable because of the priority rule and a long struggle began among taxonomists to resolve the dilemma.

In 1929, Sergent *et al* made an exhaustive study of the situation and came to the conclusion that the correct name for the malignant tertian parasite should be *Plasmodium praecox* Grassi and Feletti, 1890. In 1935, Giovannola reexamined the problem and decided that the correct name should be *Plasmodium immaculatum* (Grassi and Feletti, 1892); but, in 1938, Christophers and Sinton pointed out that if that name were accepted, it must be credited to Grassi, 1891. The latter authors went on to point out that *malariae* was the name applied originally by Laveran and is, therefore, the *de jure* name.

It was abundantly clear that strict adherence to the rules of zoological nomenclature would create intolerable confusion and when Sergent *et*

al (1939) withdrew their proposal of 1929, there appeared a united front, joined by Coatney and Young in 1941, for the general adoption of the commonly used *de facto* name. However, a ruling was necessary to give status to the consensus. At the 1954 meeting of the International Commission on Zoological Nomenclature, the trivial name *falciparum* of Welch (1897) was validated but privilege was given for its use with either the genus *Plasmodium* or with *Laverania* (see Hemming, 1954). The ruling settled the specific name, and, it was hoped, at least in some quarters, that in spite of privilege, *Plasmodium* would be the accepted name for the genus. However, Bray (1958) redefined the genus *Laverania* and consigned two species to it: *falciparum* and *reichenowi*. Although he, and certain others, felt strongly about the designation, he was willing to concede "the use of the genus is not obligatory." There was a great deal of heated discussion regarding Bray's proposal, most of it without the benefit of printers ink, with the result that, in 1963, he relegated *Laverania* to subgeneric rank. During the years since 1963, the use of *Laverania* as a genus name has continued to lose favor. In fact, Garnham (1966), although he supported Bray's proposal in 1958, fails to mention its revival after the 1954 decision. We feel, that in the interest of uniformity and convenience, the name of the malignant tertian parasite should be *Plasmodium falciparum* (Welch, 1897).

Plasmodium falciparum has a worldwide distribution and is concentrated in the tropics and subtropics. It invades the temperate zone and, as a consequence, it used to be common in southeastern United States, the littoral areas of the Mediterranean, and in the Balkans. It has since disappeared from those areas generally as a result of better economic conditions, good control, and/or eradication programs.

Altitude has an important bearing on the transmission of *P. falciparum*, and other species, too, but the height at which it disappears is variable depending on the temperature at which the vector can maintain itself. Under ordinary circumstances, transmission fails above 1500 meters. Exceptions are not uncommon, however.

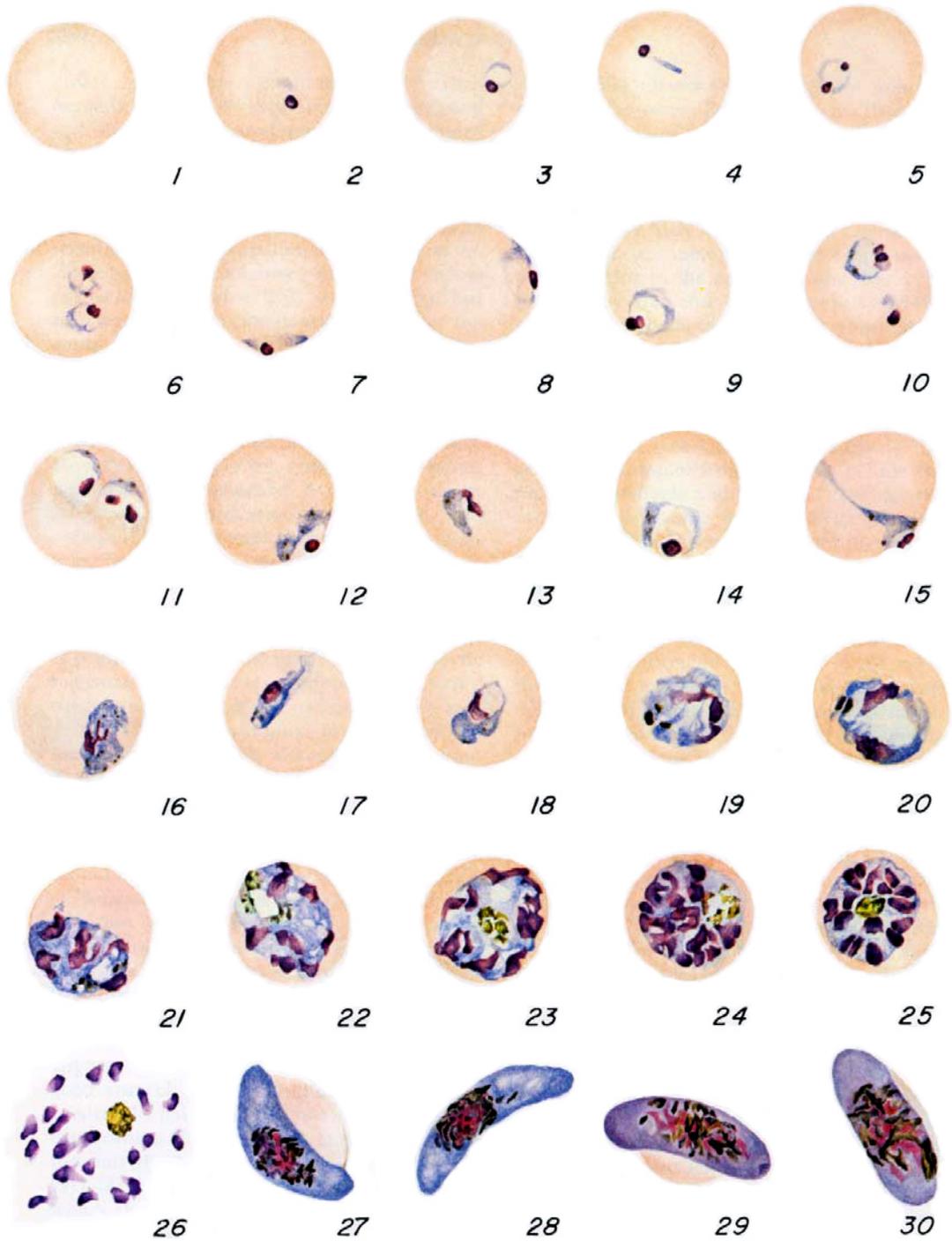
Polumordvinov (1945) reported infections in southern Tadjikistan at 2750 and 2850 meters which is the limit of human settlements in that region. Garnham (1948) described an epidemic in the highlands of Kenya, as high as 2600 meters, where at Kericho, for example, the parasite rate was 8 percent prior to the epidemic, but rose to 36 percent by the end of it. Hackett (1945), working in Bolivia, demonstrated transmission at 2600 meters.

There are many accounts of havoc among early civilizations which is attributed to malignant malaria, but proof that malaria was the actual culprit was lacking until early in this century. Examples from this era include the report by Raffaele and Coluzzi (1949) for the area around Cassino in Italy. Prior to 1943, malaria, although present, was of little importance. In 1945, following the bloody fighting between the German and the Allied Armies, with destruction of dykes and other control measures in 1943-44, about 100 percent of the people were infected; 43 percent of the infections were *P. falciparum*. The mortality in some villages of the area was 10 percent. In this hemisphere, the classic example of introducing an efficient vector into a susceptible *P. falciparum* population is that of *Anopheles gambiae* in northeast Brazil as recounted by Soper and Wilson (1943). The first *A. gambiae* probably arrived in the area from Africa in 1929; its transmission potential was recognized in 1930, but scant attention was paid to it until it reached the Assu and Apode valleys in Rio Grande do Norte in 1938. It spread over some 12,000 square miles leaving illness, death, and desolation until finally eradicated in 1940 by an encircling technique which, at its inception, many malariologists called an "audacious experiment."

Among the human malarialias, *P. falciparum* is considered the youngest evolutionarily and the least efficient as a parasite because its malignant nature tends to eliminate its host.

We have studied many different strains of *P. falciparum*, some of which will be discussed later in this chapter.

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PLASMODIUM FALCIPARUM

J.H. Nicholson

Cycle in the Blood

PLATE XLII

The youngest ring forms of *Plasmodium falciparum* are smaller than those of other human malarias and are commonly referred to as tiny, hair-like rings, with a vacuole, and a prominent nucleus. Sometimes, there is an accessory chromatin dot (Fig. 2-5). Multiple invasion of the host cell by equal-aged parasites is more common in this species than in the other human malarias (Figs. 6, 10, 11). Field and Shute (1956) illustrate 7 ring-stage parasites in a single cell and state that "eight rings in a cell has been recorded." Appliqué or accollé forms are common and, hence, have some diagnostic value. As development proceeds, the overall size of the parasite is increased, the vacuole and the nucleus of the parasite become more prominent (Fig. 14), and tenue forms (Fig. 15) may appear; aside from these abnormal forms (see Field and Shute, 1956), there is no appreciable amoeboidity. The parasite now becomes smaller and more compact, the cytoplasm stains a deep blue, it loses its vacuole, the nucleus ceases to be circular, and dark pigment grains appear in the cytoplasm (Figs. 16-19).

At this juncture, the number of parasites in the peripheral blood decreases due to their penchant for retreating into the deeper circulation—a practice common to *P. coatneyi*, too—so that in cases of high synchronicity, it is sometimes difficult to find late developing forms. In general, however, the phenomenon of asynchronicity produces enough tardy forms to permit following the remainder of the cycle. As a rule, the presence of appreciable numbers of segmenters in the peripheral blood is an indicator of grave consequences, but this is not always the case. In our own experience, we have seen a case in which the patient was not particularly ill, was ambulatory, and had a

parasite count of about 5,000 per mm³, yet he continued to show a high proportion of segmenters for several days.

During schizogony, the nucleus divides repeatedly, the parasite increases in size until it may occupy a large part of the host cell. At first the pigment comes together in small aggregates, but, as the parasite nears maturity, it collects in a single yellowish-brown mass. The mature schizont is less symmetrical than those of other human malarias and its merozoites number 8 to 20; the usual number is about 16 (Figs. 20-25).

One of the striking features of erythrocytes infected with the asexual parasites is the early development of Maurer's dots, or clefts, which make their appearance shortly after the hair-like ring stage. As the development of the parasite proceeds, these abnormalities become more pronounced. They are demonstrable in the parasitized red cells only under certain staining procedures, not ordinarily applied, and therefore are not shown in our plate.

The mature gametocytes are unique among human malarias because of their sickle or crescent shape, a feature well appreciated by Laveran. In most malarias, the gametocytes appear about the same time as the asexual forms, but in falciparum malaria, it is about 10 days after the first appearance of the asexual forms that they appear as a wave of full grown parasites. Preceding their appearance, the young gametocytes have been growing in the blood spaces of the spleen and bone marrow.

The macrogametocyte is relatively slender, has pointed ends, and is generally longer than the microgametocyte. The cytoplasm stains a decided blue. The nucleus is compact and may be masked by pigment granules which appear to cover it. The red cell may be seen as stretching across the curvature of the gametocyte (Figs. 27,

PLATE XLII.—*Plasmodium falciparum*.

Fig. 1. Normal red cell.

Figs. 2-11. Young trophozoites.

Figs. 12-15. Growing trophozoites.

Figs. 16-18. Mature trophozoites.

Figs. 19-22. Developing schizonts.

Figs. 23-26. Nearly mature and mature schizonts.

Figs. 27, 28. Mature macrogametocytes.

Figs. 29, 30. Mature microgametocytes.

28). The microgametocyte is sausage-shaped with blunt-rounded ends. The cytoplasm stains light blue to purplish-blue. The nucleus occupies about half the total length of the parasite. It is diffuse, and generally shows some dark red dots scattered in a pale pink area. Lying well within the periphery of the nuclear area are clustered dark brown to black pigment granules. The host cell generally hugs the body of the parasite, but may show as a bulb-like area in the slight curvature of the gametocyte (Figs. 29, 30).

The asexual cycle is 48 hours.

Sporogonic Cycle

PLATE XLIII

There have been many studies on the sporogonic cycle of *P. falciparum* since Ross (1897) described finding oocysts on the gut of a mosquito which had fed on a gametocyte carrier. Bastianelli *et al* (1898) observed pigmented oocysts in anopheline mosquitoes which had fed on an individual infected with *P. falciparum*,

and, in the same year, Grassi *et al* (1898) observed complete development of *P. falciparum* in *Anopheles claviger* (= *A. maculipennis*). In 1899, Bastianelli and Bignami not only described the development of the parasite in mosquitoes, but, also, demonstrated its transmission to man.

Shute and Maryon (1952) observed the development of oocysts of *P. falciparum* in *A. atroparvus* mosquitoes incubated at a temperature of 25° C. The black pigment granules (between 10 and 20 in number) were usually arranged (between days 3 and 7) in a double semicircle around the periphery of the oocyst. By the 8th day, the pigment was obscure; the oocysts measured from 8 to 60 μ in diameter. The sporogonic cycle was completed in 11 to 12 days. From the 3rd to the 5th day, the daily increase in oocyst diameter was approximately 4 μ . From the 6th to the 10th day, the daily increase was about 10 μ .

Our studies of the sporogonic cycle of this

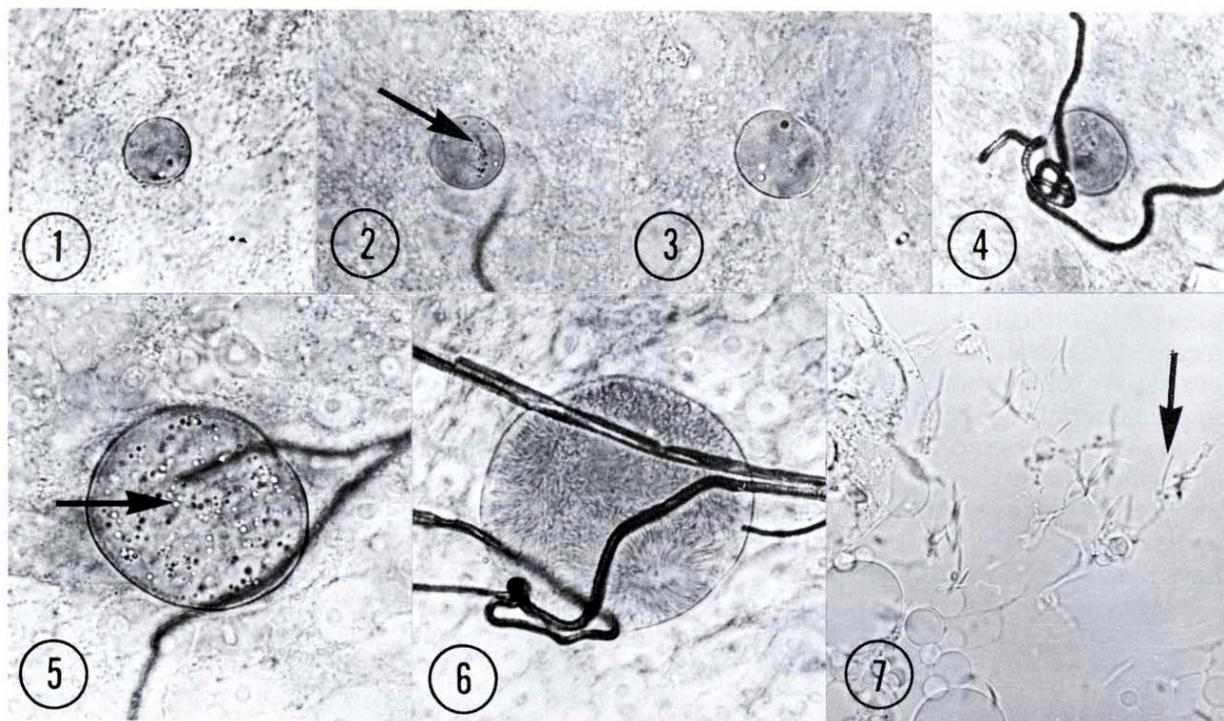


PLATE XLIII.—Developing oocysts and sporozoites of *Plasmodium falciparum* in *Anopheles freeborni* mosquitoes. X 580.

Fig. 1. 7-day oocyst.

Fig. 2. 7-day oocyst showing line of pigment.

Fig. 3. 8-day oocyst.

Fig. 4. 10-day oocyst.

Fig. 5. 14-day oocyst showing numerous small vacuoles.

Fig. 6. 14-day differentiated oocyst.

Fig. 7. Sporozoites present near salivary gland tissue 14 days after feeding.

parasite have been limited, but we have followed its development in *A. freeborni* infected with the Malayan IV and the McLendon strains of *P. falciparum*, and in *A. quadrimaculatus* infected with the McLendon strain only (Table 34). In *A. freeborni*, with the Malayan IV strain, on day 5, oocysts had mean diameters of 12 μ, with a range of 8 to 15 μ; on day 12, the mean size was 50 μ, with a range of 21 to 78 μ. There are some differences in the development of the 2 strains in *A. freeborni*. The Malayan IV had slightly larger mean oocyst diameters, but, more significantly, sporozoites were present in the salivary glands on day 12 whereas the McLendon strain required 14 days. The development in the *A. quadrimaculatus* was similar to that seen in *A. freeborni* infected with the McLendon strain. Sporozoites were present in the salivary glands on day 14.

A comparison of the oocyst growth rate of the Malayan IV strain of *P. falciparum* with that of *P. cynomolgi* (Fig. 57) shows a marked difference between the 2 parasites. The *P. cynomolgi* was much larger both with regard to mean and maximum oocyst diameters. Sporozoites were present in the salivary glands of the mosquitoes infected with *P. cynomolgi* one day sooner than in those infected with *P. falciparum*.

Experimentally, *P. falciparum* has been transmitted to man via the bites of many species of mosquitoes on numerous occasions. In that connection, Garnham (1966) lists 66 species of anophelines which will serve as hosts of *P. falciparum*.

Cycle in the Tissue

The tissue stages of *Plasmodium falciparum* have been demonstrated in experimental infections of man as well as chimpanzees. This species of human malaria differs from *P. vivax* and *P. ovale* in that the exoerythrocytic cycle is restricted to a single generation; in other words, there is no secondary exoerythrocytic or other continuing fixed tissue stage.

The tissue cycle of *Plasmodium falciparum* was first demonstrated by Shortt *et al* (1949, 1951) in liver biopsy material from a human volunteer who had been bitten by 770 Anopheles mosquitoes (93 percent infection rate) over a period of 3 days. The strain of falciparum malaria used by these authors was of Roumanian origin. The liver biopsy was taken 5% days after mosquitoes had first bitten the volunteer. The exoerythrocytic schizonts described by these authors were considered to be 4-, 5-, and 6-day stages. The 4-day schizonts were described as

TABLE 34.—Oocyst diameters of *Plasmodium falciparum* (Malayan IV and McLendon strains) in *Anopheles freeborni* and *A. quadrimaculatus* mosquitoes.

| Days after Infection | Malayan IV strain | | | McLendon strain | | | | | |
|----------------------|---------------------|-------|-------|---------------------|-------|-------|---------------------------|-------|-------|
| | <i>A. freeborni</i> | | | <i>A. freeborni</i> | | | <i>A. quadrimaculatus</i> | | |
| | No. | Range | Mean* | No. | Range | Mean | No. | Range | Mean |
| 4 | | | | 118 | 5-11 | 10 | | | |
| 5 | 106 | 8-15 | 12 | 193 | 7-14 | 10 | 5 | 8-14 | 11 |
| 6 | 122 | 9-21 | 15 | 115 | 11-20 | 15 | 116 | 8-20 | 14 |
| 7 | 163 | 9-28 | 19 | 152 | 8-20 | 15 | 134 | 12-23 | 18 |
| 8 | 255 | 12-38 | 23 | 120 | 11-31 | 20 | 187 | 11-32 | 19 |
| 9 | 199 | 14-45 | 32 | 169 | 12-41 | 24 | 101 | 18-38 | 28 |
| 10 | 111 | 26-64 | 41 | 150 | 17-53 | 35 | 168 | 18-50 | 33 |
| 11 | 112 | 20-73 | 45† | 132 | 19-61 | 40 | 126 | 20-58 | 40 |
| 12 | 154 | 21-78 | 50†** | 150 | 20-72 | 47† | 110 | 18-60 | 42 |
| 13 | 36 | 31-71 | 56†** | 139 | 19-70 | 49† | 132 | 27-68 | 48† |
| 14 | | | | 164 | 20-67 | 45†** | 109 | 30-68 | 54†** |
| Totals | 1258 | 8-78 | | 1602 | 5-72 | | 1188 | 8-68 | |

* Measurements expressed in microns.
 † Oocyst differentiation.
 ** Sporozoites present in the salivary glands.

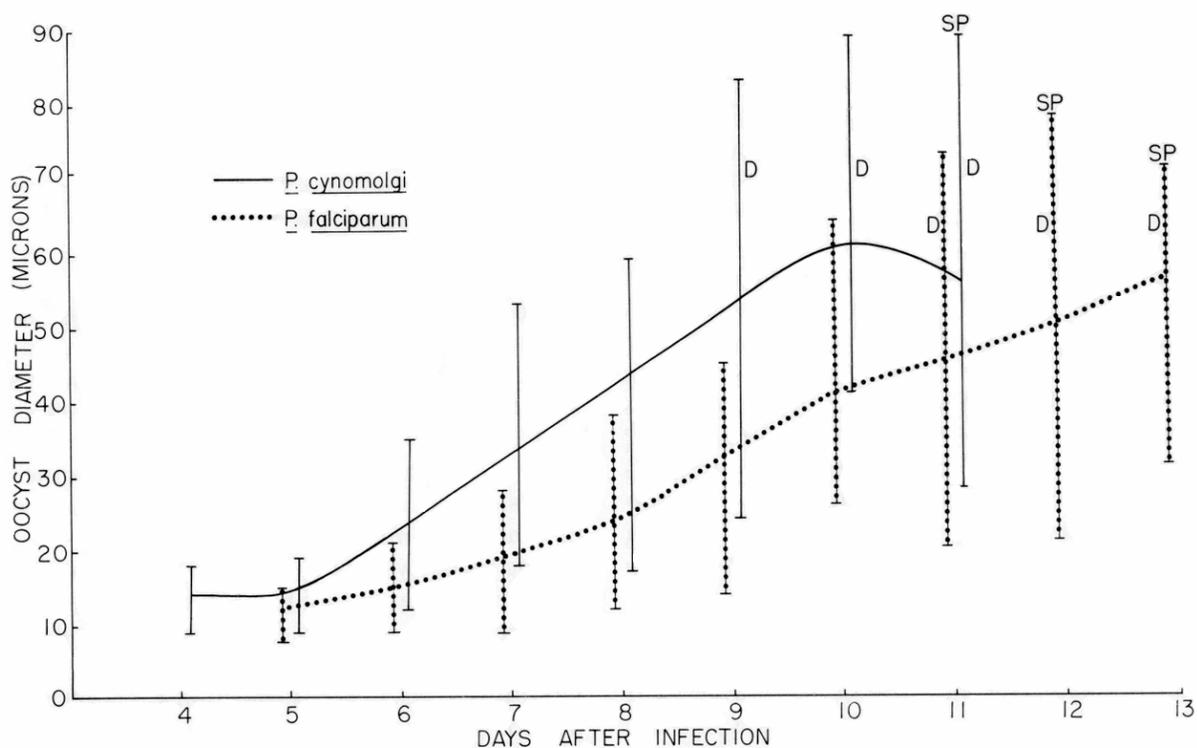


FIGURE 57.—Mean oocyst diameter curves and ranges in oocyst diameter of *Plasmodium cynomolgi* and *P. falciparum* (Malayan IV strain) in *Anopheles freeborni* mosquitoes. (D = oocyst differentiation; SP = sporozoites present in the salivary glands).

ovoid or spherical in shape, with some tendency toward the production of lobose projections. They measured about 30 μ in diameter and were surrounded by a thin membrane. The cytoplasm was fairly dense and there were no vacuoles. Nuclei were rather sparsely distributed, slightly irregular masses measuring approximately 1.5 μ in diameter. Cytoplasm tended to condense around each nucleus; and, according to the authors, this possibly represented the first step in the formation of the so-called pseudocytomeres.

Five-day old schizonts measured roughly 50 μ in their longest dimension. The tendency to produce the lobose character was more pronounced. There was no local tissue reaction. There was a tendency for the cytoplasm to separate into areas resembling cytomeres. These pseudocytomeres varied in shape from spherical to elongate; each contained a large number of nuclei. The size of the individual nuclei, in active division, was roughly 0.8 μ . The membrane surrounding the parasites was less apparent.

The 6-day stages showed the parasite had undergone very rapid growth, expanding in an irregular fashion in many directions. Six-day forms measured 50 to 60 μ in length and were described as being more "misshapen" than *P. vivax* because of the pronounced tendency to lobosity. The number of nuclei had increased tremendously, the cytoplasm being thickly strewn with them. Near maturity, the parasite appeared to break up into small islands of cytoplasm, measuring approximately 2 μ in diameter, each island contained two very small nuclei.

With a final division of the nuclei, one has a mature schizont, measuring 60 μ or more in its greatest dimension, containing an enormous number of merozoites. Each merozoite, about 0.7 μ in diameter, consists of a nucleus with a trace of cytoplasm. The number of merozoites in a large mature schizont was estimated as roughly 40,000.

Jeffery *et al.* (1952) carried out a study, involving 14 patients, designed to demonstrate