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Plasmodium ovale Stephens, 1922

BECAUSE of the close resemblance of *Plasmodium ovale* to *P. vivax* it is impossible to tell when *P. ovale* was first seen. Macfie and Ingram (1917) described a parasite in a mixed infection which they found in the blood of a child in the Gold Coast which may well have been *P. ovale.* They mentioned the pronounced Schüffner's stippling in the parasites and at the same time stressed the fact that the organism resembled the quartan parasite, *P. malariae,* which it does. Earlier, Emin (1914) had found a parasite in pilgrims at Camaran, on the Red Sea, which he named *Plasmodium vivax* var. *minuta.* Ziemann (1915) examined some of Emin's material and because his observations were at variance with Emin's, he suggested the name *P. camaranense* Emin which, of course, is zoologically unacceptable irrespective of the worth of his observations. To further complicate the picture, Craig (1900) described a malaria parasite which he found in the blood of American soldiers, returned from the Philippines, and noted especially its tertian fever pattern plus certain peculiar morphological characteristics not found in *P. vivax.* In 1918, Stephens had an East African patient with malaria at the Liverpool School of Tropical Medicine. In examining blood films from the patient, he was struck by the fact that among the parasitized red cells some were oval and with fimbriated edges. In 1922, he published a full description of the blood forms and illustrated the sequence of development in a well executed plate with 22 figures. A fourth species of human malaria, difficult to separate from *P. vivax,* was not readily accepted; but, as evidence accumulated through the work of Stephens and Owen (1927), Yorke and Owen (1930) James, Nicol, and Shute (1932, 1933, 1935) plus the critical comparative study of the sporogonic cycles by Shute and Maryon (1952), acceptance was inevitable, although as late as 1935 Giovannola held that *P. ovale* was a modification of *P. vivax* in chronic infections.

As mentioned earlier, Craig (loc. cit.) had described a vivax-like parasite from the Philippines. In 1914 he accepted it to be *P. vivax* var. *minuta* Emin. In 1933, he reversed his 1914 opinion after he received stained preparations of *P. ovale* from Professor Yorke in Liverpool, stating that the parasite seen by him in 1900 agreed perfectly with *P. ovale.* The importance of this announcement lies in the fact that, for the first time, *P. ovale* had been found outside of Africa.

In 1941, Coatney and Young reviewed all the papers dealing with the nomenclature of the ovale parasite and concluded that none of the names attributed to it could be placed in synonomy. The present authors hold the same opinion, and, that the correct name for the parasite is *Plasmodium ovale* Stephens, 1922.

The ancestral home of *P. ovale* is undoubtedly tropical Africa although it has been reported from time to time from each of the other continents. *Plasmodium ovale* is a rare parasite. In fact, as late as 1949, Brumpt was able to record only 105 cases for the world; only 14 were outside of Africa. In 1966, Lysenko and Beljaev made a careful appraisal of the areas of distribution of *P. ovale,* and, after considering all the reports, many of which are of doubtful validity for reasons readily apparent to malariologists, their conclusion was that, outside of Africa, there are only two areas where *P. ovale* is endemic: the Philippines and New Guinea.

Many hypotheses have been advanced to explain the lack of ovale malaria outside of Africa among which are: 1) climate and vegetation, 2) relation between host and vector, 3) host susceptibility, and 4) relation with simian malaria. It is generally recognized that he highest prevalence of *P. ovale* is in equatorial forests and savannah woodland but, as in northern Senegal, it may occur almost to the borders of the desert. In the area of West Africa, prevalence decreases from south to north in line with the decrease in rainfall. Hence, prevalence is due, in part at least, to a combination of both vegetation and climatic conditions. Yet, in other areas of the world where there are almost identical climatic conditions, there are only sporadic cases, as in the Western Pacific, or none, as in South and Central America.

We will present a full discussion of the vectors as they relate to this problem in a later section but suffice it to say here that several vectors *(A. freeborni, A. maculatus,* etc.) other than *A. gambiae* will transmit *P. ovale* readily so that sporadic area distribution can hardly be linked to a lack of suitable vectors. In the realm of host susceptibility, it would appear from the work of Jeffery *et al* (1954, 1955) and Chin *et al* (1966) that Negroes and Caucasians are equally susceptible to *P. ovale*; and, since natural infections appear in New Guinea populated by Melanesians, and in the Philippines where the people are mainly of Mongoloid stock, it would appear that all people are susceptible to *P. ovale*.

Prior to 1960, when the natural transmission of a simian malaria to man was established by Eyles *et al,* no one had given serious consideration to the possible zoonotic nature of the simian malarias although many early observers, namely Reichenow and Rodhain, mentioned that the forms they saw in apes were like those in man. The latter author (1940) after transferring *P. rodhaini,* and incidentally, *P. schwetzi,* too, from the chimpanzee to man, was convinced that *P. rodhaini* was actually *P. malariae* but he gave no indication whether he considered the infection a zoonosis or an anthroponosis. Brumpt (loc. cit.), in calling attention to the extreme rarity of *P. ovale,* mentioned that perhaps it was "a plasmodium of a cosmopolitan vertebrate wandering in man." Languillon (1957) was more specific. In commenting on his finding *P. schwetzi* in a child, he suggested that *P. ovale* may be an adaptation of the ape parasite. In 1967, Contacos *et al* infected a series of volunteers with *P. schwetzi* via mosquito bite (Contacos *et al,* 1970) and the close resemblance of that parasite to *P. ovale* in man lead Coatney (1968) to suggest that *P. schwetzi* was probably a zoonosis and, if that is the case, the infection is now diagnosed as *P. ovale.* The present authors hold the same view.

If one examines the prevalence figures for Africa, one finds that it is relatively common in the West Coast with, according to Garnham (1966), 10 percent of the young children harboring the parasite in Nigeria, Ghana, Sierra Leone, Liberia, and the Gambia. From these areas, it spreads through Central Africa east to the coast but with greatly reduced incidence except at the southern tip of its range in Mozambique. Lacan (1962), in reporting on 105 cases of *P. ovale* from the French-speaking countries of Africa, noted that practically all were from savannah areas; only 19 were from the forest region. Furthermore, all were children under 8 years of age with maximum incidence in children 2 to 4 years old. Onori (1967) carried out an in depth survey in Uganda where, among 251 ovale infections, he found the parasite more often in infants and adolescents than in older people. The highest prevalence rate (2.6) was in the 1 to 4 year age group and only 0.7 in those individuals 20 years or older. We think it safe to point out that such figures could be misleading as far as the general population is concerned because surveys are more or less limited to children for obvious reasons. A true prevalence figure for the population in any area probably cannot be had because of the evasive nature of the parasite, its easy masking by any one of the other human malarias, and the rapidity with which chronicity, with very low parasitemias, develops.

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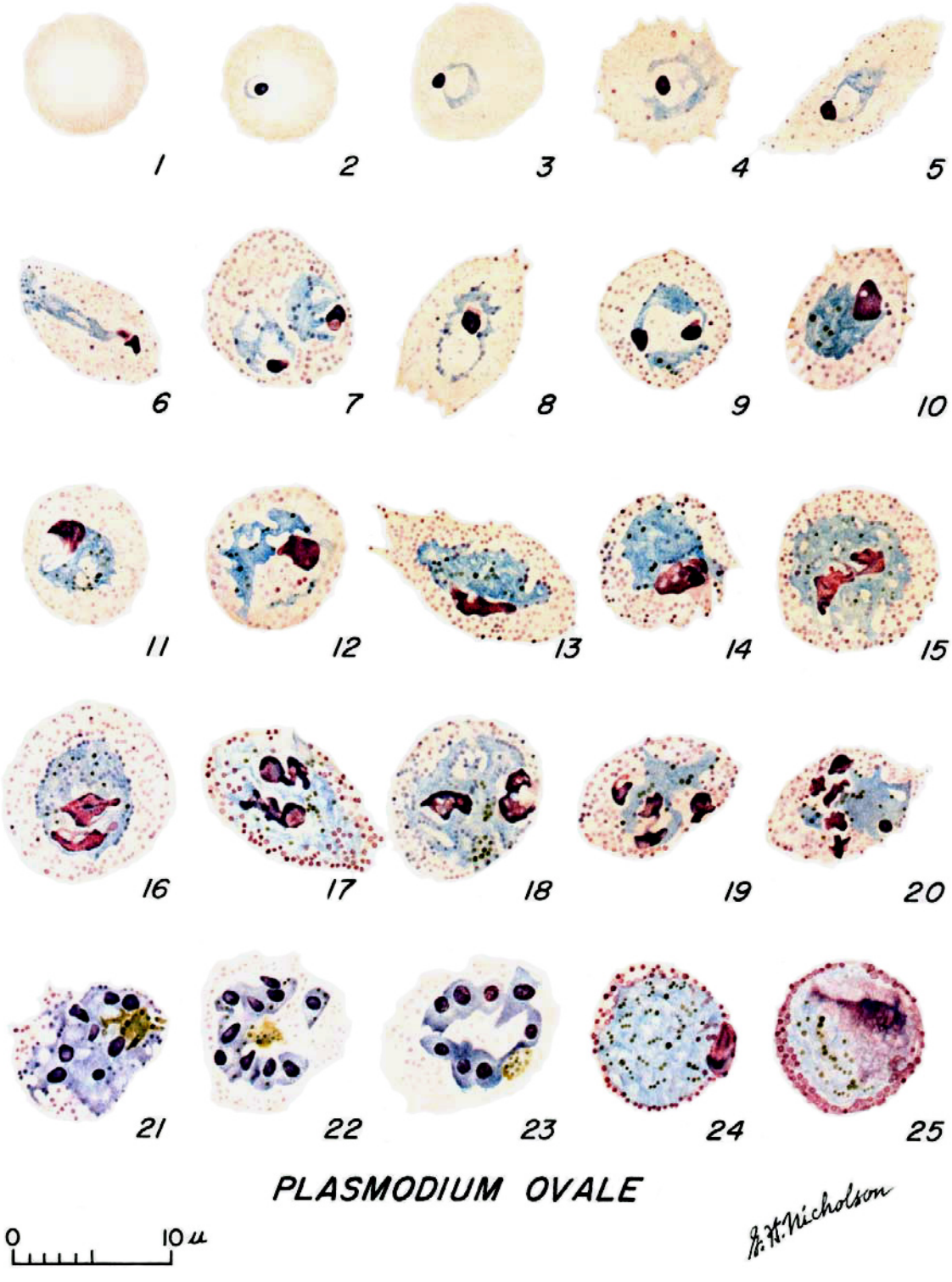
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PLASMODIUM OVALE
R. H. Nicholson
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Cycle in Blood

PLATE XXV

The young ring forms have a prominent circular nucleus eccentrically placed with a wisp of cytoplasm surrounding a vacuole (Fig. 2). As the parasite grows, the erythrocyte becomes enlarged, the cytoplasm increases in amount, and the vacuole disappears (Fig. 10); older trophozoites come to occupy about half the host erythrocyte (Figs. 10, 11). The cytoplasm may appear pulled out and ragged (Figs. 5, 8) or assume a band-like form, reminiscent of *P. malariae,* (Fig. 6); double infections are not uncommon (Fig. 7). The host cell may appear oval with fimbriated edges (Figs. 8, 13) when the smear is dried in an atmosphere of low humidity; the same feature does not occur in *P. vivax* preparations made under the same conditions. The pigment first appears as fine dust-like grains which later come together to form small greenish-brown beads (Fig. 18) and later mass together in yellowish-brown patches (Fig. 21). The most distinctive characteristic of the circulating ovale parasite is the stippling or Schüffnerization, an apt term probably first applied by Hauer (1937). This stippling appears early in the growth of the parasite (Fig. 4) and becomes intense as the parasite grows (Figs. 15, 17). The host cell cytoplasm becomes pale and transparent and appears as a mass of stippling (Figs. 17, 19). Schüffnerization in *P. ovale* is intense, more pronounced than in *P. vivax* and not too different from *P. schwetzi.*

The cytoplasm of the parasite takes a decided blue stain which fades somewhat during early schizogony (Figs. 16-18) only to appear as purplish-blue during the late stages (Figs. 21-23). The large deep red-staining nuclei of the young forms become larger with deeper red patches as growth proceeds so that just preceding division it is 2 to 4 times its original size (Fig. 14) or about double the size of the same stage nucleus in *P. vivax* but only slightly larger than *P. schwetzi.*

Through the early divisions the nuclei remain large (Figs. 16-19) and at maturity there are ordinarily 8 merozoites although during relapse or following continued passage, the number may be 12 to 16 and located in a much enlarged host cell.

The immature gametocyte is difficult to separate from the compact late trophozoite; but, as growth proceeds, these forms grow to fill the enlarged host erythrocyte.

The cytoplasm of the mature macrogametocyte (Fig. 24) stains a medium blue with an eccentrically placed red-staining prominent nucleus with darker staining areas. The pigment is in granules arranged like a string of beads and these short strands lie scattered in the cytoplasm. The stippling is prominent, takes a red stain, and is arranged in a ring around the parasite.

The mature microgametocyte takes a lighter and more delicate blue stain. The large nucleus occupies about half the parasite. It has a dark red-staining area from which the color fades to a light pink toward the edge. The pigment is in large to medium sized granules scattered throughout the cytoplasm. The parasite is completely enclosed by a prominent circle of eosinophilic stippling (Fig. 25).

The asexual cycle occupies 48 hours.

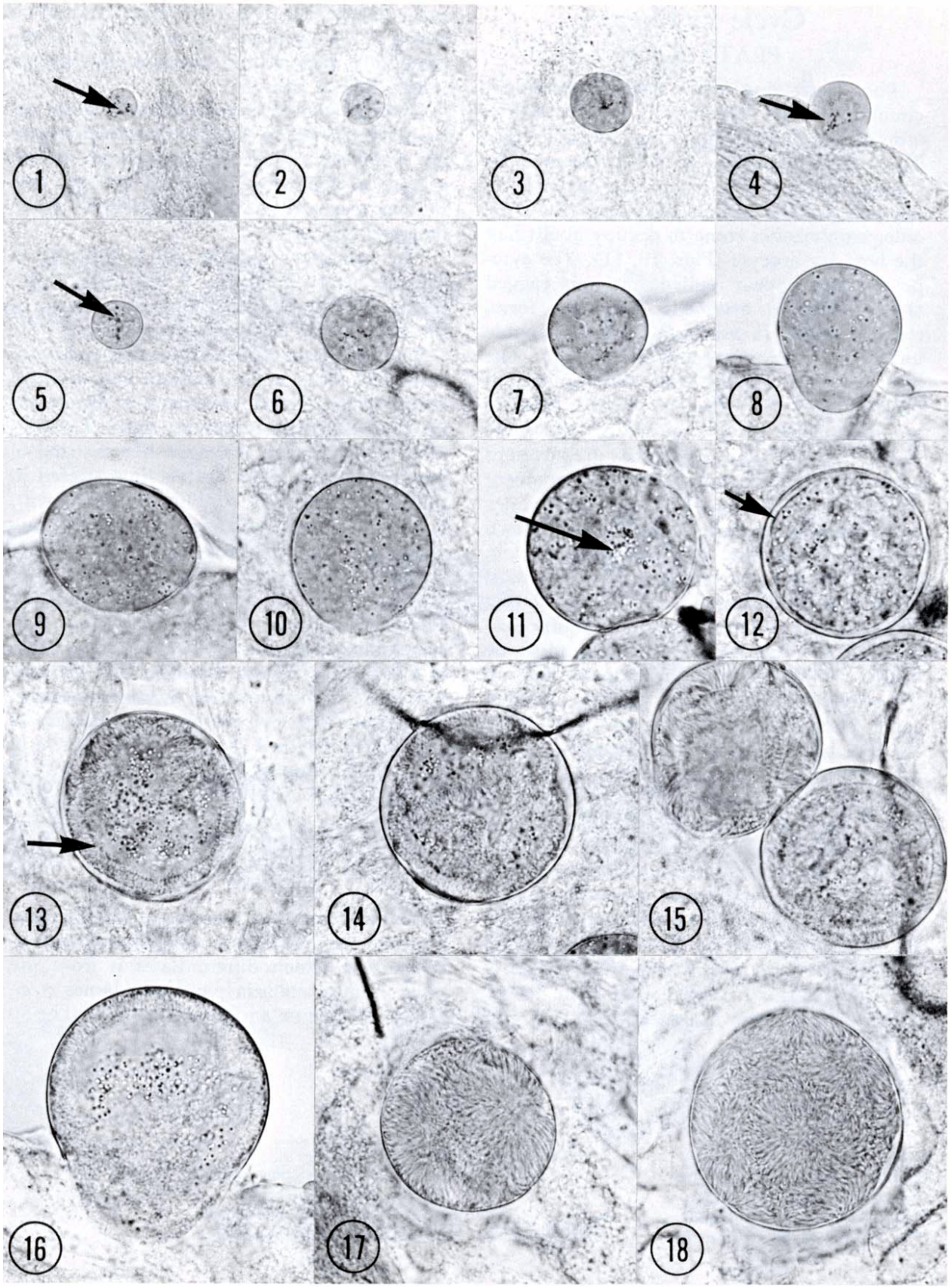
Sporogonic Cycle

PLATE XXVI

Within the oocyst of *P. ovale,* the pigment granules are arranged in a highly characteristic pattern which differentiates it from the other human malaria parasites (James *et al,* 1932, 1933; Shute and Maryon, 1952). The 50 to 60

PLATE XXV.—*Plasmodium ovale.*

Fig. Normal red cell.
Figs. 2-5. Young trophozoites.
Figs. 6-12. Growing trophozoites.
Figs. 13-15. Mature trophozoites.
Figs. 16-22. Developing schizonts.
Fig. 23. Mature schizont.
Fig. 24. Adult macrogametocyte.
Fig. 25. Adult microgametocyte.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grains of dark brown pigment granules are arranged in several patterns, but the most common is two rows or chains which cross each other at right angles in the center of the oocyst. This pattern is first seen on the 4th day of growth, but is more plainly visible on the 6th to 8th days. Jeffery (1954) reported that this pattern of the pigment was present in 38.2 percent of the oocysts of the Donaldson strain. In contrast, such a pattern was found in two strains of *P. vivax* in only 8.0 and 7.2 percent of the oocysts.

The oocysts, in *A. atroparvus* mosquitoes, according to Shute and Maryon (loc. cit.), grew at a daily rate of about 2 μ from the 3rd to the 6th day at an incubation temperature of 25° C. There was a sharp increase in size between the 7th and 8th days of about 5 μ; this daily increase of 5 μ continued until the 12th day. Completion of the cycle required 15 days. Oocysts ranged from a minimum of 9 μ to a maximum of 37 μ in diameter.

James *et al* (1932) found that a strain of *P. ovale* from the Congo required 16 days to complete its development whereas Sinton *et al* (1939), using strains from the Congo and the Gold Coast (Ghana), reported completion of development in *A. atroparvus* in 15 days. Using the Donaldson strain from the West Pacific and *A. quadrimaculatus* and *A. albimanus* mosquitoes, Jeffery (1954) found sporozoites in the salivary glands as early as day 14 although they usually appeared on day 15.

Collins *et al* (1969), using a strain of *P. ovale* from West Africa, studied the oocyst growth rate in 5 species of anophelines *(A. freeborni, A. b. balabacensis, A. maculatus, A. stephensi,* and *A. quadrimaculatus)*. The results (Table 20) show a fairly close agreement with those of previous workers concerning the length of time required for completion of the cycle (14 to 15 days). However, they found a much greater range in oocyst diameters with maximum sizes of up to 96 μ. There was little difference in the size of the oocysts in the different species until day 14, at which time, those in *A. maculatus* were noticeably smaller. The larger oocysts were found in the *A. freeborni* mosquitoes.

A comparison of the oocyst growth curve of *P. ovale* with that of *P. cynomolgi* (Fig. 37), indicates that the former is a much slower growing parasite. There was approximately a 30 μ difference in oocyst diameters after 10 days of extrinsic incubation. Whereas the *P. cynomolgi* parasites in *A. freeborni* mosquitoes completed their development in 11 days, the *P. ovale* parasites required 14 days. A comparison of the growth rate of *P. ovale* with *P. vivax* and *P. falciparum* (see Chapter 5) indicates that it is the slowest growing of the human tertian malarias although it eventually becomes the largest by day 14. However, *P. ovale* completes its sporogonic cycle 3 days sooner than does *P. malariae* (see Chapter 18).

The first experimental transmission of *P. ovale* was via the bites of *A. atroparvus* mosquitoes (James *et al,* 1932, 1933). During the course of their studies, James and his co-workers (1949) obtained 36 transmissions of this parasite via *A. atroparvus.* With the Donaldson strain, infections were transmitted to 37 patients using *A. quadrimaculatus* and *A. albimanus*

PLATE XXVI.—Developing oocysts of *Plasmodium ovale* (West African strain) in *Anopheles b. balabacensis* and *A. freeborni* mosquitoes. X 580.

Fig. 1. 4-day oocyst showing scattered pigment.
Fig. 2. 5-day oocyst.
Fig. 3. 6-day oocyst.
Fig. 4. 6-day oocyst showing "Prince of Wales Feathers" arrangement of pigment.
Fig. 5. 7-day oocyst showing crossing of pigment.
Fig. 6. 8-day oocyst.
Fig. 7. 9-day oocyst showing scattered pigment and small vacuaoles.
Fig. 8. 10-day oocyst.
Fig. 9. 10-day oocyst.
Fig. 10. 10-day oocyst.
Fig. 11. 11-day oocyst showing many small vacuoles.
Fig. 12. 12-day oocyst showing first signs of differentiation.
Fig. 13. 13-day oocyst showing differentiation.
Fig. 14. 13-day oocyst.
Fig. 15. 13-day oocysts.
Fig. 16. 14-day oocyst showing concentration of sporozoites near periphery and small vacuoles in center.
Fig. 17. 14-day fully differentiated oocyst.
Fig. 18. 14-day fully differentiated oocyst.

mosquitoes (Jeffery *et al,* 1954). Later, Jeffery *et al* (1955) reported 4 transmissions of a Liberian strain of *P. ovale* via the bites of *A. quadrimaculatus* and *A. albimanus* mosquitoes. Bray (1957) using *A. gambiae* mosquitoes, transmitted a local strain of *P. ovale* to a Liberian child and to a chimpanzee. Chin *et al* (1966) reported transmission of a West African strain of this parasite to 5 volunteers using *A. freeborni* and *A. maculatus* mosquitoes.

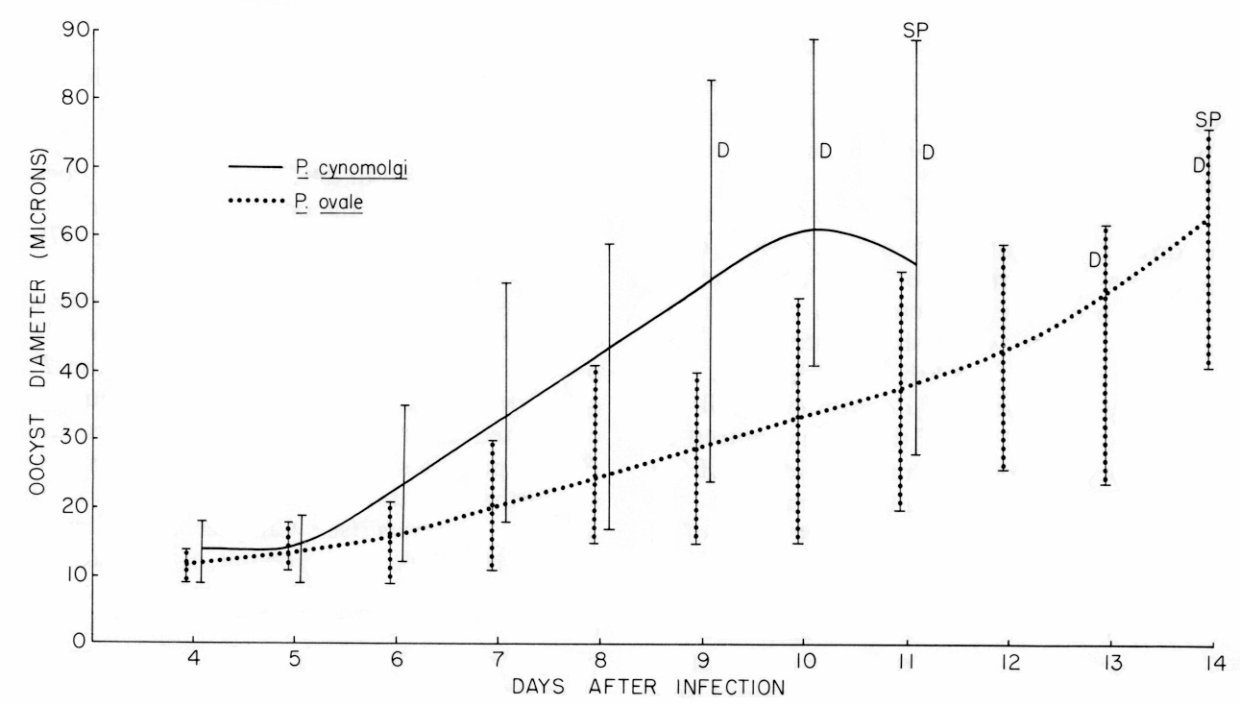

FIGURE 37.—Range in oocyst diamters and the mean oocyst diameter curves of *Plasmodium ovale* and *P. cynomolgi* in *Anopheles freeborni* mosquitoes. (D = oocyst differentiation; SP = sporozoites present in the salivary glands).

TABLE 20.—Oocyst diameters of *Plasmodium ovale* in *Anopheles freeborni, A. b. balabacensis, A. maculatus, A. stephensi,* and *A. quadrimaculatus.*

Days after Infection	*A. freeborni*			*A. b. balabacensis*			*A. maculatus*			*A. stephensi*			*A. quadrimaculatus*		
	No.	Range	Mean*	No.	Range	Mean	No.	Range	Mean	No.	Range	Mean	No.	Range	Mean
4	52	9-14	12	38	8-12	11	50	9-14	12	50	8-15	11	53	8-15	12
5	103	11-18	14	100	10-21	14	100	8-19	14	100	10-20	15	100	8-20	15
6	126	9-21	16	100	10-20	16	100	11-24	17	100	10-21	16	100	12-25	19
7	100	11-26	20	98	12-28	20	100	13-34	20	100	13-27	20	100	14-30	24
8	100	15-41	28	100	17-35	26	100	17-35	26	100	15-35	27	100	15-35	30
9	136	15-40	28	109	18-39	29	101	14-35	24	100	15-39	30	100	20-38	35
10	102	15-51	38	100	19-41	32	100	17-43	30	100	14-41	30	100	15-41	29
11	100	20-55	39	55	25-51	36	104	14-50	32	60	25-51	42	108	18-54	39
12	96	24-59	43	89	27-55	40	100	27-53	39	100	12-60	42t	100	19-59	42
13	108	24-65	46†	96	25-65	42	100	20-61	41	100	22-61	45t	30	22-66	44
14	20	41-76	64†**	100	35-71	52†	100	38-71	51†**				108	25-84	54†**
15	50	43-96	68†**	50	35-80	59†**	39	25-55	48†**	8	43-54	48†			
Totals	1093	9-96		1035	8-80		1094	8-71		918	8-61		999	8-84	

* Measurements expressed in microns; incubation temperature 25° C.
† Oocyst differentiation.
** Sporozoites present in the salivary glands.

Cycle in the Tissue

The tissue stages of *P. ovale* were first described in liver biopsy material from a human volunteer by Garnham *et al* (1955). The youngest stages described by these authors were considered to be 5-day stages and measured from 28 to 60 μ in length. The smallest of these forms were oval with regular or smooth edges. The larger of these 5-day forms showed small convolutions on the surface. The most striking feature observed in these immature forms was the "relatively" enormous size of the nuclei-approximately 2 μ. The 9-day tissue stage of ovale measured from 70 to 80 μ by 50 μ. The surface was lobated and the nuclei were about half the size found in the 5-day stage, in other words, roughly 1 μ.

The nuclei of the tissue stages had an uneven margin and the cytoplasm was granular. Sometimes the cytoplasm was clumped around each nucleus so that the tissue stage appeared to contain clefts or to be vacuolated. A definite limiting membrane was described for many of the schizonts.

As the EE body of *P. ovale* approaches maturity (on or about the 9th day), it goes through what is described as 3 stages: 1) nuclear multiplication progresses rapidly with no evident merozoite formation; 2) the appearance of merozoites at the edges of the EE bodies, with active nuclear division continuing elsewhere within the parasite; and 3) complete maturation of the schizont with rupture.

The merozoite of the *P. ovale* tissue schizont is described as a remarkable structure. It is large (1.8 μ in diameter), spherical, and consists of 2 portions; a larger portion of cytoplasm and a smaller portion which is the nucleus situated at one side of the parasite. The number of merozoites in one schizont of *P. ovale* has been reported to be as high as 15,000±.

In the paper describing the tissue stages of *P. ovale,* the authors noted that *P. ovale* tissue stages differ markedly from those of *P. vivax* and *P. inui.* They were of the opinion, however, that there was a superficial resemblance to those of *P. falciparum,* at least in regard to size and form. Bray (1957) described the development of *P. ovale* tissue stages in the chimpanzee. He reported 7-day stages measured an average of 36.6 x 30.3 μ (range of 45 to 28 μ. x 39 to 23 μ. He described 4 different forms of schizonts which occurred regularly in the chimpanzee material. Eighteen day schizonts measured from 91 to 40 μ x 50 to 31 μ. One schizont, found in a 39-day biopsy, measured 31 x 33 μ.

In his paper, Bray (1957) points out that the EE bodies of *P. ovale* display at least 3 characteristics that have not been noted in the tissue stages of *P. vivax* or *P. falciparum;* namely, 1) a definite limiting membrane or periplast; 2) peripheral nuclear bars tangential rather than radial; and 3) a minor but distinct hypertrophy of the host cell nucleus.

Rupture of the mature schizonts of the pre-erythrocytic cycle is believed to occur chiefly on the 9th day after exposure to infection. The positive biopsies of 18 and 39 days suggest the apparent existence of second-generation forms. Bray *et al* (1963) attempted to demonstrate the existence of one or more exoerythrocytic cycles after the initial EE cycle, in the chimpanzee. Biopsy on the 19th day revealed bursting and mature schizonts as had been observed on the 9th day, suggesting the existence of at least a second generation.

Course of Infection

Sinton *et al* (1939) alluded to a mean prepatent period for several strains of *P. ovale* of about 15 days. James *et al* (1949) reported incubation periods (which may, on occasion, be the same as the prepatent period) of 11 to 16 days with a mean of 13.6 days in sporozoite induced infections with 6 different strains of *P. ovale.* They reported one case with a delayed incubation period of 85 days. The Donaldson strain (Jeffery *et al,* 1954) exhibited prepatent periods of 12 to 20 days with a mean of 15.3 days. Employing a Liberian strain, Garnham *et al* (1955), Jeffery *et al* (1955), and Bray (1957) reported prepatent periods of 13.5, 14 to 15 (mean 14.5), and 14 days, respectively. Chin *et al* (1966) working with a West African strain obtained prepatent periods of 14 to 18 days with a mean of 16.8 days.

Generally, *P. ovale* infections are considered to be the least severe of the 4 species

of human malaria and are characterized by a mild clinical course. In the mosquito induced infections reported by James *et al* (1949) the onset of the typical primary attack was definitely less severe than that observed with vivax malaria. The characteristic rigor of vivax malaria was a rarity with ovale malaria; only one or two characteristic rigors occurring during the early stages (10 days or so) of the primary attack. Even though the patient may feel chilly, chattering of teeth and the classical shaking with a sensation of being cold from head to foot are seldom or never seen. However, they found the duration of the entire paroxysm to be the same for ovale as it is in vivax malaria (6 to 10 hours). Garnham *et al* (1955) took exception in that the paroxysms in their cases were usually accompanied by chills as well as severe and persistent headache. Temperatures of up to 105° F in one volunteer persisted for 3 weeks. The spleen became palpable after about 10 days.

James *et al* (1949) observed another obvious difference between ovale and vivax malaria; namely, the degree of fever at the peaks of the paroxysms. They reported that only 30 out of 197 patients (15 percent) had 10 or more febrile paroxysms with peak temperatures exceeding 103° F. With the Donaldson strain (Jeffery *et al,* 1954), only 10 percent of the subjects had 10 paroxysms with peak temperatures exceeding 103° F. The first fevers were seen from 14 to 26 days after exposure to infection, with a mean of 17.7 days or a median of 17 days; maximum mean fever was 105.2° F. The number of paroxysms observed in infections (103 cases) with this strain ranged from 1 to 22 with a mean or median of 8. With the West African strain of ovale malaria, we observed a temperature of only 103.6° F when the parasite count was as high as 32, 450 per mm^3.

Using the interval between tertian fever peaks as reference points, the periodicity of Donaldson strain infections was found to range from 34 to 61 hours with a median of 49 hours.

Maximum parasitemia is considered to be generally lower than that observed with vivax malaria. Sinton *et al* (1939) reported variations in maximum parasitemias ranging from 125 to 20,000 per mm^3 while James *et al* (1949) reported maximum parasite densities ranging from 500 to 100,000 per mm^3. Jeffery *et al,* in studies with the Donaldson strain, reported ranges of maximum counts from 464 to 25,940 parasites per mm^3 with a mean of 8,376. With the West African strain of *P. ovale,* we have observed maximum counts ranging up to 32,450 parasites per mm^3 in blood-induced infections.

Figure 38 shows the minimum and maximum parasitemia curves for 24 blood-induced infections with the Donaldson strain of *P. ovale*, (17 Negro and 7 Caucasian) as well as

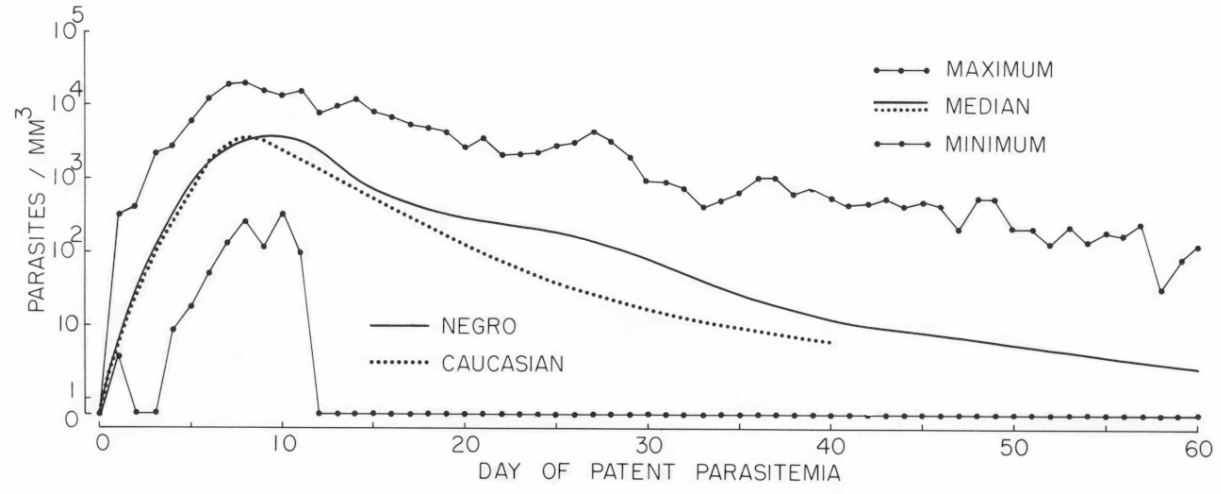

FIGURE 38.—Maximum and minimum parasite counts and median parasitemia curves of 24 blood-induced infections of *Plasmodium ovale* in man (17 Negro and 7 Caucasian).

the median parasitemia curves for the two groups. It can be seen that peak parasitemia was reached in the Caucasian and Negro patients on the 8th and 10th days of patent parasitemia with maximum median counts of 4,576 and 3,645 parasites per mm^3, respectively, followed by a steady and slow decline to rather low level parasitemia by day 40. There is no apparent difference between the median parasitemias for the two groups of patients. This is in great contrast with what is generally observed with vivax malaria infections in Negro and Caucasian patients. The differences between the minimum and maximum parasitemia curves on a day to day basis point out the great variability one can observe in infections with most human malarias.

Duration of parasitemia in sporozoite induced infections with the Donaldson strain ranged from 29 to 91 days with a mean of 53.2 days or a median of 51 days. During this period, clinical manifestations lasted for 8 to 26 days with an average of 16.9 days. Primary attacks of ovale malaria characteristically terminate spontaneously without the use of antimalarial drugs even though low level asymptomatic parasitemia may continue intermittently for a time. After cessation of symptoms, in cases of Donaldson strain ovale malaria, parasites continued to be present in the peripheral blood for 11 to 89 days with an average duration of 37.5 days. No more than 2 percent required partial suppression or early termination of the infection as compared to 61 to 87 percent for some strains of vivax malaria.

Ovale malaria, in contrast to most strains of vivax malaria, is equally infective to Negroes and Caucasians. Sinton *et al* (1939) noted the susceptibility of a Negro patient who had been previously resistant to other human malarias and suggested that the Negro may show lower racial immunity to ovale malaria than to other malarias. Jeffery *et al* (1954, 1955) found that Negro and Caucasian patients inoculated either with Donaldson strain or the Liberian strain of ovale malaria were equally susceptible to infection. In fact, they observed no obvious differences in prepatent period, incubation period, or clinical activity.

There can be no doubt that ovale malaria is a true relapsing infection; i.e., sporulation from tissue stages in the liver subsequent to the primary attack. James *et al* (1949) reported that, in their experience with 36 patients infected by the bites of mosquitoes, no relapses were observed. It is not unlikely that asymptomatic relapses were missed if patients were followed up on a strict clinical basis. Sinton (1939) encountered one relapse in a series of sporozoite induced cases of ovale malaria. Jeffery *et al* (1954) found that relapses were observed frequently in 38 mosquito induced infections of Donaldson strain ovale malaria. Most of them were asymptomatic relapses. Only 2 of the 38 patients showed symptomatic relapse at 148 and 235 days after termination of the primary attacks with chloroquine. One of these patients subsequently experienced an asymptomatic relapse with low grade parasitemia 152 days later.

Garnham *et al* (1955) observed relapses in two cases; one relapsed 103 days after chloroquine and again 68 days later and the other relapsed after 98 days, and, again, 101 days later. Chin and Coatney (1971) found that infections with a West African strain of ovale malaria relapsed from 1 to 3 times during a one year period. Relapses occurred as early as 17 days after treatment of the primary attack in one case and as late as 255 days in another case. All of the relapses were symptomatic, except one.

Earlier authors spoke of latent infections (which we recognize as delayed primary attacks), a phenomenon not too uncommon with vivax malaria. As mentioned earlier, James *et al* (1949) reported such a period of 85 days in one of their mosquito induced infections. Jeffery *et al* (1954), Trager and Most (1963), and Chin and Contacos (1966) reported delayed primary attacks of 4, 1.8 and 3.5, and 1.3 years, respectively. These delayed primary infections were probably not true latent infections in the classical sense. Rather, they represent late tissue parasite (relapse) activity.

Bray (1957) reported that infection of chimpanzees with ovale malaria, can be obtained either by the inoculation of sporozoites or parasitized blood. In the intact animal, there was evidence of some natural resistance with spontaneous termination of patent parasitemia after 8 days. On the other hand, splenectomized chimpanzees allowed parasitemia to increase for 10 days with a total duration of patent

parasitemia of 21 days. In addition, the infection in the chimpanzee differs from that in man by its tendency to produce blood schizonts with more than the usual number of merozoites.

Host Specificity

Man is the natural host of this parasite. Infections have been obtained in intact and splenectomized chimpanzees *(Pan troglodytes versus)* by the inoculation of sporozoites from *A. gambiae* mosquitoes (Bray, 1957). Attempts to infect rhesus monkeys *(M. mulatta)* by the inoculation of parasitized blood have been unsuccessful (Christophers, 1934; Jeffery, 1961). We have made 6 unsuccessful attempts to infect *A. trivirgatus* monkeys with *P. ovale.* However, in view of the ease with which infections with the other human malarias have been adapted to this host, its eventual adaptation is thought likely.

The natural vector of *P. ovale* is unknown. However, since Bray (loc. cit.) was able to obtain infections in *A. gambiae* mosquitoes after they fed on man and on the chimpanzee, this is strongly indicative that it is a vector in Africa. Vectors of this parasite found in the west Pacific have not been determined. Other mosquitoes which have been experimentally infected are shown in the table below:

SPECIES	REFERENCES
Anopheles albimanus	Jeffery, 1954; Jeffery *et al,* 1954,1955
A. atroparvus	James *et al,* 1932, 1933; Sinton *et al,* 1939; Shute and Maryon, 1952; Garnham *et al,* 1955
A. freeborni	Chin *et al,* 1966
A. maculatus	Chin *et al,* 1966
A. quadrimaculatus	Jeffery, 1954; *Jeffery et al,* 1954
A. superpictus	Garnham, 1966

In addition, we have infected *A. stephensi* and *A. b. balabacensis* mosquitoes with a West African strain of *P. ovale.* In a comparative study, Jeffery (1954) showed that *A. quadrimaculatus* mosquitoes were more susceptible than strains of *A. albimanus* from Panama and the Florida Keys, to the Donaldson strain of *P. ovale.* The relative susceptibility was *A. quadrimaculatus,* 100; *A. albimanus* (Florida Keys), 77; *A. albimanus* (Panama), 46. In a comparative study with the West African strain, (Table 22), we found that *A. stephensi* mosquitoes were the most susceptible, followed by *A. freeborni, A. b. balabacensis, A. quadrimaculatus, A. maculatus,* and finally, *A. albimanus.* There was a lesser variation in susceptibility to infection than has been found in studies with the other primate malarias.

Immunity and Antigenic Relationships

Sinton *et al* (1939a) showed that a high and almost equal degree of resistance to reinfection

TABLE 22.—Comparative infectivity of *Plasmodium ovale* to *Anopheles freeborni, A. stephensi, A. b. balabacensis, A. quadrimaculatus, A. maculatus,* and *A. albimanus.*

Mosq. species comparison*	Number tests	Number of mosquitoes		Percent infection		GII** ratios
		Standard	Other	Standard	Other	
F-1	6	169	153	59.8	58.2	100
F-1 : St-1	8	206	96	73.8	78.1	121.3
F-1 : Bal	14	253	452	69.6	41.2	83.4
F-1 : Q-1	16	238	302	76.9	61.6	43.7
F-1 : Mac	5	23	23	78.3	30.4	43.4
F-1 : Alb						30.7

* F-1 = *Anopheles freeborni;* St-1 = *A. stephensi;* Hal = *A. b. balabacensis;* Q-1 = *A. quadrimaculatus;* Mac = *A. maculatus;* Alb = *A. albimanus.*

**GII = Gut Infection Index = average number of oocysts per 100 guts; the GII ratio is the relationship of the GII of *A.freeborni* to another species where the GII of *A. freeborni* = 100.

developed to homologous and to heterologous strains following a primary infection with *P. ovale.* On the other hand, these investigators found that ovale malaria could be successfully established in persons who were apparently immune to the other species of human malaria.

Jeffery *et al* (1954, 1955) studied the immunologic relationships of several strains of ovale malaria. They observed that one infection with the Donaldson strain of ovale malaria conferred immunity to reinfection with the same strain. Moreover, in comparing a Pacific strain (Donaldson) and a West African strain (Liberian) of *P. ovale,* they found considerable cross-immunity between them, but in no way was the immunity complete. However, the degree of cross-immunity was greater than expected; not only in view of the wide geographic separation in the origin of the two isolates, but also on the basis of their experience with various strains of vivax and falciparum malaria.

These investigators further reported that ovale malaria (Donaldson strain) conferred no effective immunity against the other 3 species of human malaria. The converse was also observed; namely, that previous experience with other species of human malaria did not appreciably effect subsequent susceptibility to infection with the Donaldson strain of *P. ovale.* For example, a previous Chesson vivax infection did not seem to confer appreciable immunity against a subsequent Donaldson strain infection.

Sinton (1940), on the basis of his studies on the immunity acquired as a result of sporozoite induced infections as compared to the immunity acquired by those infections induced by erythrocytic asexual stages, suggested that immunity in malaria is more complete if the initial infection is induced by sporozoites.

Garnham (1966) stated that the antigenic structure of different strains of *P. ovale* seems to be remarkably homogenous. Sinton (1940), in studying heterologous strain immunity of ovale malaria concluded that the heterologous antigenic element seemed to be so small in the strains studied by him "as to make them almost identical immunologically."

It seems safe to say, that at this writing, no clear-cut statement can be put forth regarding immunity involving *P. ovale.*

Meuwissen (1966) found a high degree of cross-reactivity with *P. fieldi* antigen in sera of patients with *P. ovale* infections using the indirect fluorescent antibody test. In a later study (1968), he found that *P. ovale* antisera would cross-react to the *P. cynomolgi bastianellii* antigen but at a lower level than to the homologous antigen or to the *P. fieldi* antigen.

REFERENCES

BRAY, R. S., 1957. Studies on malaria in chimpanzees. IV. *Plasmodium ovale.* Am. J. Trop. Med. & Hyg. *6* : 638-645.

BRAY, R. S., BURGESS, R. W., and BAKER, J. R., 1963. Studies on malaria in chimpanzees. X. The presumed second generation of the tissue phase of *Plasmodium ovale.* Am. J. Trop. Med. & Hyg. *12* : 1-12.

BRUMPT, E., 1949. The human parasites of the genus *Plasmodium.* In Malariology, Vol. I by Boyd. W. B. Saunders, Philadelphia, Pa. pp. 787.

CHIN, W., CONTACOS, P. G., and BUXBAUM, J. N., 1966. The transmission of a West African strain of *Plasmodium ovale* by *Anopheles freeborni* and *Anopheles maculatus.* Am. J . Trop. Med. & Hyg. *15* : 690-693.

CHIN, W. and CONTACOS, P. G., 1966. A recently isolated West African strain of *Plasmodium ovale.* Am. J. Trop. Med. & Hyg. *15* : 1-2.

CHIN, W. and COATNEY, G. R., 1971. Observations on relapse activity of mosquito-induced infections of *Plasmodium ovale* from West Africa. Am. J. Trop. Med. & Hyg. (in press).

CHRISTOPHERS, R., 1934. Malaria from a zoological point of view. Proc. Royal Soc. Med. *27* : 991-1000.

COATNEY, G. R., 1968. Simian malarias in man: facts, implications, and predictions. Am. J. Trop. Med. & Hyg. *17* : 147-155.

COATNEY, G. R. and YOUNG, M. D., 1941. The taxonomy of the human malaria parasites with notes on the principal American strains. Human malaria. Am. Assoc. Advancement of Science. No.15.

COLLINS, W. E., ORIHEL, T. C., CONTACOS, P. G., JETER, M. H., and GELL, L. S., 1969. Some observations on the sporogonic cycle of *Plasmodium schwetzi, P. vivax* and *P. ovale* in five species of *Anopheles.* J. Protozool. *16* : 589-596.

CONTACOS, P. G., COATNEY, G. R., ORIHEL, T. C., COLLINS, W. E., CHIN, W., and JETER, M. H., 1970. Transmission of *Plasmodium schwetzi*

REFERENCES—Continued

from the chimpanzee to man by mosquito bite. Am. J. Trop. Med. & Hyg. *19* : 190-196;

CRAIG, C. F., 1900. Report bacteriological Lab., U.S. Army General Hospital, Presidio of San Francisco, Calif. for 1899-1900. Surgeon-General's Rept., U.S. Army.

CRAIG, C. F., 1914. New varieties and species of malaria plasmodia. J. Parasit. *1* : 85-94.

CRAIG, C. F., 1933. The nomenclature of *Plasmodium ovale* Stephens 1922. Am. J. Trop. Med. *13* : 539-542.

EMIN, A., 1914. Une variete nouvelle du parasite de Laveran. Séance *7*: 385-387.

EYLES, D. E., COATNEY, G. R., and GETZ, M. E., 1960. Vivax-type malaria parasite of macaques transmissible to man. Science *131* : 1812-1813.

GARNHAM, P. C. C., 1966. Malaria parasites and other haemosporidia. Blackwell Scientific Publications. Oxford. pp.1114.

GARNHAM, P. C. C., BRAY, R. S., COOPER, W., LAINSON, R., AWAD, F. I., and WILLIAMSON, J., 1955. The pre-erythrocytic stage of *Plasmodium ovale.* Trans. Roy. Soc. Trop. Med. & Hyg. *49* : 158-167.

GIOVANNOLA, A., 1935. *Plasmodium ovale* considered as a modification of *Plasmodium vivax* after a long residence in the human host. Am. J. Trop. Med. *15* : 175-186.

HAUER, A., 1937. Ueber neue Beobachtungen an einem *Plasmodium ovale* -Stamm. Arch. f. Schiffs- u. Trop.-Hyg. *41* : 153-157.

JAMES, S. P., NIGOL, W. D., and SHUTE, P. G., 1932. *Plasmodium ovale* Stephens: passage of the parasite through mosquitoes and successful transmission by their bites. Ann. Trop. Med. Parasit. *26* : 139-145.

JAMES, S. P., NIGOL, W. D., and SHUTE, P. G., 1933. *Plasmodium ovale* Stephens 1922. Parasitology *25* : 87-95.

JAMES, S. P. NIGOL, W. D., and SHUTE, P. G., 1935. The specific status of *Plasmodium ovale* Stephens. Am. J. Trop. Med. *15* : 187-188.

JAMES, S. P., NIGOL, W. D., and SHUTE, P. G., 1949. Ovale malaria. In Malariology, Vol. II by Boyd. W. B. Saunders Co. Philadelphia, Pa.

.JEFFERY, G. M., 1954. The Donaldson strain of malaria. 3. The infection in the mosquito. Am. J. Trop. Med. & Hyg. *3* : 651-659.

JEFFERY, G. M., 1961. Inoculation of human malaria into a simian host, *Macaca mulatta.* J. Parasit. *47* : 90.

JEFFERY, G. M., YOUNG, M. D., and WILCOX, A., 1954. The Donaldson strain of malaria. 1. History and characteristics of the infection in man. Am. J. Trop. Med. & Hyg. *3* : 628-637.

JEFFERY, G. M., WILCOX, A., and YOUNG, M. D., 1955. A comparison of West African and West Pacific strains of *Plasmodium ovale.* Trans. Roy. Soc. Trop. Med. & Hyg. *49* : 168-175.

LAGAN, A., 1962. *Plasmodium ovale* in French-speaking countries of Africa. Mimeographed document: Wid. Hlth. Org. WHO/Mal/363.

LANGUILLON, J., 1957. Carte epidemiologique du paludisme au Cameroun. Bull. Soc. Path. Exot. *50* : 585-600.

LYSENKO, A. JA. and BELJAEV, A. E., 1966. Mimeographed document: WId. Hlth. Org. WHO/Mal/66.577.

MACFIE, J. W. S. and INGRAM, A., 1917. Observations on malaria in the Gold Coast colony, West Africa. Ann. Trop. Med. Parasit. *11* : 1-23.

MEUWISSEN, J. H. E., TH., 1966. Fluorescent antibodies in human malaria, especially in *Plasmodium ovale.* Trop. geogr. Med. *18* : 250-259.

MEUWISSEN, J. H. E. TH., 1968. Antibody responses of patients with natural malaria to human and simian Plasmodium antigens measured by the fluorescent antibody test. Trop. geogr. Med. *20* : 137-140.

ONORI, E., 1967. Distribution of *Plasmodium ovale* in the eastern, western and northern regions of U gand.a. Bull. WId. Hlth. Org. *37* : 665-668.

RODHAIN, J., 1940. Les plasmodiums des anthropoides de I'Afrique centrale et leurs relations avec les plasmodiums humains. Ann. Soc. BeIge de Med. Trop. *20* : 489-505.

SHUTE, P. G. and MARYON, M., 1952. A study of human malaria oocysts as an aid to species diagnosis. Trans. Roy. Soc. Trop. Med. & Hyg. *46* : 275-292.

SINTON, J. A., HUTTON, E. L., and SHUTE, P. G., 1939. Studies of infections with *Plasmodium ovale.* I. Natural resistance to ovale infections. Trans. Roy. Soc. Trop. Med. & Hyg. *32* : 751-762.

SINTON, J. A., HUTTON, E. L., and SHUTE, P. G., 1939a. Studies of infections with *Plasmodium ovale.* II. Acquired resistance to *ovale* infections. Trans. Roy. Soc. Trop. Med. & Hyg. *33* : 47-68.

SINTON, J. A., 1940. Studies of infections with *Plasmodium ovale.* IV. The efficacy and nature of the immunity acquired as a result of infections induced by sporozoite inoculations as compared with those by trophozoite injections. Trans. Roy. Soc. Trop. Med. & Hyg. *33* : 439-446.

STEPHENS, J. W. W., 1918. (See Stephens, 1922.) STEPHENS, J. W. W ., 1922. A new malaria parasite of man. Ann. Trop. Med. Parasit. *16* : 383-388.

STEPHENS, J. W. W. and OWEN, D. U., 1927. *Plasmodium ovale.* Ann. Trop. Med. Parasit. *21* : 293-302.

TRAGER, W. and MOST, H., 1963. A long-delayed primary attack of *ovale* malaria. Am. J. Trop. Med. & Hyg. *12* : 837-839.

YORKE, W. and OWEN, D. U., 1930. *Plasmodium ovale.* Ann. Trop. Med. Parasit. *24* : 593-600.

ZIEMANN, H., 1915. Ueber eigenartige malariaparasiten- formen. Zentralbl. Bakt. I. Abt. Orig. *76*: 384-391.