

## *Plasmodium schwetzi* Brumpt, 1939

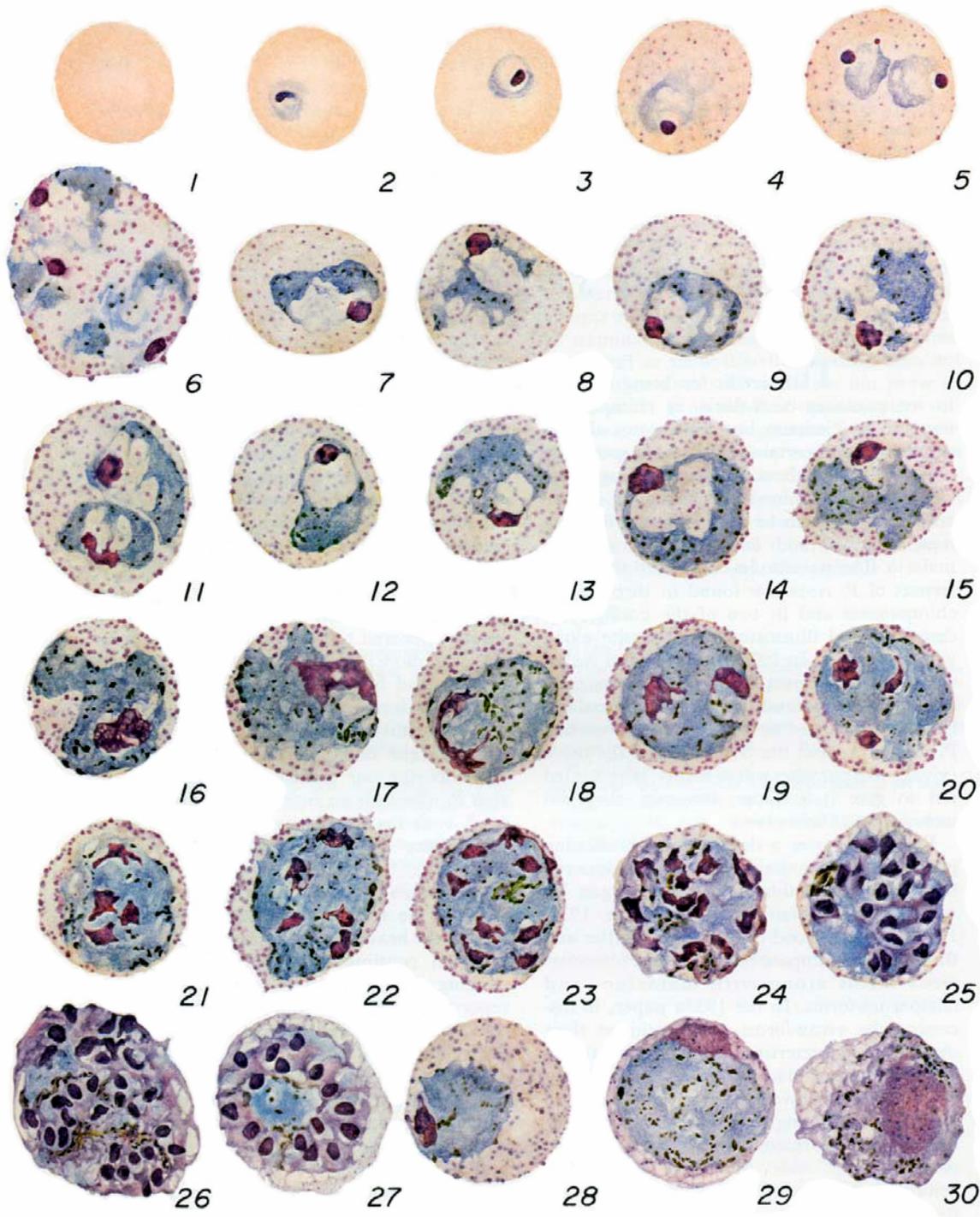
THE credit for being the first to see parasites of malaria in chimpanzees must go to Ziemann but we are not able to determine with certainty just which species he saw. In 1920 Reichenow, while working in the Cameroons, examined the blood of sixteen apes among which he found human-like tertian, quartan, and falciparum parasites of malaria. The parasite he considered the counterpart of *P. vivax* was found in three of the chimpanzees and in two of the gorillas. He described and illustrated that parasite along with the others. In 1922 Blacklock and Adler, working in Freetown, Sierra Leone, saw each of the three human-like parasites of malaria in the chimpanzee as had Reichenow earlier. Probably because the population of the ovale (vivax)-like parasites was so scanty, they elected not to give it a name; however, they did include it in their plate.

For a little over a decade these interesting parasites appear to have been virtually ignored but in the early thirties, Schwetz began his work in the Belgian Congo (Schwetz, 1933, 1933a). In the blood of two adult gorillas and three young chimpanzees he found *Plasmodium vivax*-forms along with malariae- and falciparum-forms. In the 1933a paper, in discussing the vivax-forms, he mentioned their ovale-like characteristics and his beautifully executed colored plate makes this point doubly clear. In 1934 Schwetz, in describing a double infection in a young chimpanzee, again mentioned the close resemblance of the vivax-like parasites to *P. ovale*. And, here again, in a beautifully painted plate, which emphasizes the heavy stippling so characteristic of *P. ovale*, he figured fourteen of the peripheral blood stages. Because of the close

resemblance of these parasites to the human ones, investigators were prompted to attempt cross-infection experiments. The initial results were not altogether convincing which prompted Brumpt (1939), to propose the name *Plasmodium schwetzi* for the ovale-vivax parasite of the chimpanzee under the firm belief that it was enough different, morphologically and biologically, from *P. vivax* or *P. ovale*, to justify the name.

As work continued on these forms the concensus appeared to be that the schwetzi parasite was more like *P. vivax* than it was like *P. ovale* and hence Bray (1958) felt justified in making it a subspecies of *P. vivax*. We are not sympathetic toward subspecies designations, except under very special conditions, and, because our studies have convinced us that *P. schwetzi* is an entity, more closely allied to *P. ovale* than to *P. vivax*, we have elected to consider the parasite *Plasmodium schwetzi* Brumpt.

*Plasmodium schwetzi* is an African-based parasite with the apes in Sierra Leone and Liberia having the heaviest incidence of infection. The infection continues east and south, almost running out in the eastern Congo. It has been reported as absent in the Lake Kivu area of the Democratic Republic of the Congo by Schwetz and by van den Berghe and, so far, it has not been reported in Uganda. However, we isolated the parasite recently from a chimpanzee taken in the vicinity of Lake Edward, north of Lake Kivu, which places its distribution east to about 29°. *Plasmodium schwetzi* can therefore be said to occur in an area from the Cameroons to 29° E in the lower Congo and thence west into Liberia and Sierra Leone.



0 10μ

PLASMODIUM SCHWETZI

*G.A. Nicholson*

## Cycle in the Blood

### PLATE XVIII

The earliest parasites are relatively compact rings with a round to oval nucleus which stains dark reddish-black with Giemsa. There is practically no cell enlargement, no stippling, and no visible pigment in these early developmental stages (Figs. 2, 3). The first evidence of the parasite's growth is seen in the older ring forms with the expansion of the cytoplasm; the nucleus remains circular to oval, compact, and deep staining. Some enlargement of the invaded red blood cell is seen by the time the parasite occupies one quarter of the host cell (Figs. 4, 5). Light, granular stippling also appears at this time. Multiple infections are not uncommon (Fig. 5). The trophozoite grows with some increase in amoeboidity; the cytoplasm takes a more intense stain indicating that the cytoplasmic density increases as the parasite matures (Figs. 7-10). The host cell is definitely enlarged, the size is stabilized and does not change markedly with the development of the schizonts so long as only one parasite is involved in a single blood cell. The stippling is abundant, evenly distributed, and uniformly coarse. The amount of pigment increases as the parasite matures and appears as greenish-black moderately coarse granules scattered through the cytoplasm. At times this pigment seems to appear in clusters (Fig. 10). The nucleus increases in size as the parasite grows and generally maintains its oval to circular outline although the specific border may be somewhat irregular. With the increase in size the staining of the nucleus lightens considerably from very deep purple to a wine-red with darker inclusions. In the mature trophozoite, the cytoplasm increases in amount but the intensity of the staining is much the same as that found in the

growing trophozoites (Figs. 12-15). The cytoplasmic vacuole, which is quite common in the younger stages, gradually disappears as the parasite matures. Pigment increases in amount and the size of the individual granules seems to become larger and more prominent. There is an increase in the size *or* the nucleus which is irregular in shape and now displays a lighter staining reaction than that seen in the younger stages (Fig. 15).

During the early stages of nuclear division there is little or no change in the parasite or the host cell except that with continued nuclear division there may be some host cell distortion, reminiscent of *P. ovale*, (Figs. 22, 23) which proceeds as the schizont continues to grow (Figs. 23-25). Following the 6 to 8 nucleate stage, the cytoplasm appears more purple than blue. It is frequently fragmented and irregular in shape although, in some instances, a large segment of the cytoplasm is free of nuclei and these segments retain their initial blue color (Fig. 25). The pigment organizes into one or more distinct masses and these masses take on a yellowish cast (Fig. 25). The stippling becomes difficult to differentiate as the parasite frequently fills most of the red blood cell leaving only a pale eosinophilic web around the border of the parasite (Figs. 25, 27).

The mature schizont usually has from 12 to 16 distinct nuclear masses not infrequently discretely organized around a combination of a blue staining cytoplasmic residual and clusters of pigment (Fig. 27). Mature schizonts are frequently in distinctly oval red blood cells. As the number of nuclei increases, the individual nuclei decrease in size, lose their wine-red color, and assume the dark purple color seen in the young ring stages.

The macrogametocyte is regular in shape.

#### PLATE XVIII.—*Plasmodium schwetzi*.

Fig. 1. Normal red cell.

Figs. 2, 3. Young trophozoites.

Figs. 4-14. Growing trophozoites, showing double and triple host cell infections.

Figs. 15-18. Older and mature trophozoites.

Figs. 19-24. Developing schizonts.

Figs. 25-27. Nearly mature and mature schizonts.

Figs. 28, 29. Half-grown and mature macrogametocytes.

Fig. 30. Mature microgametocyte.

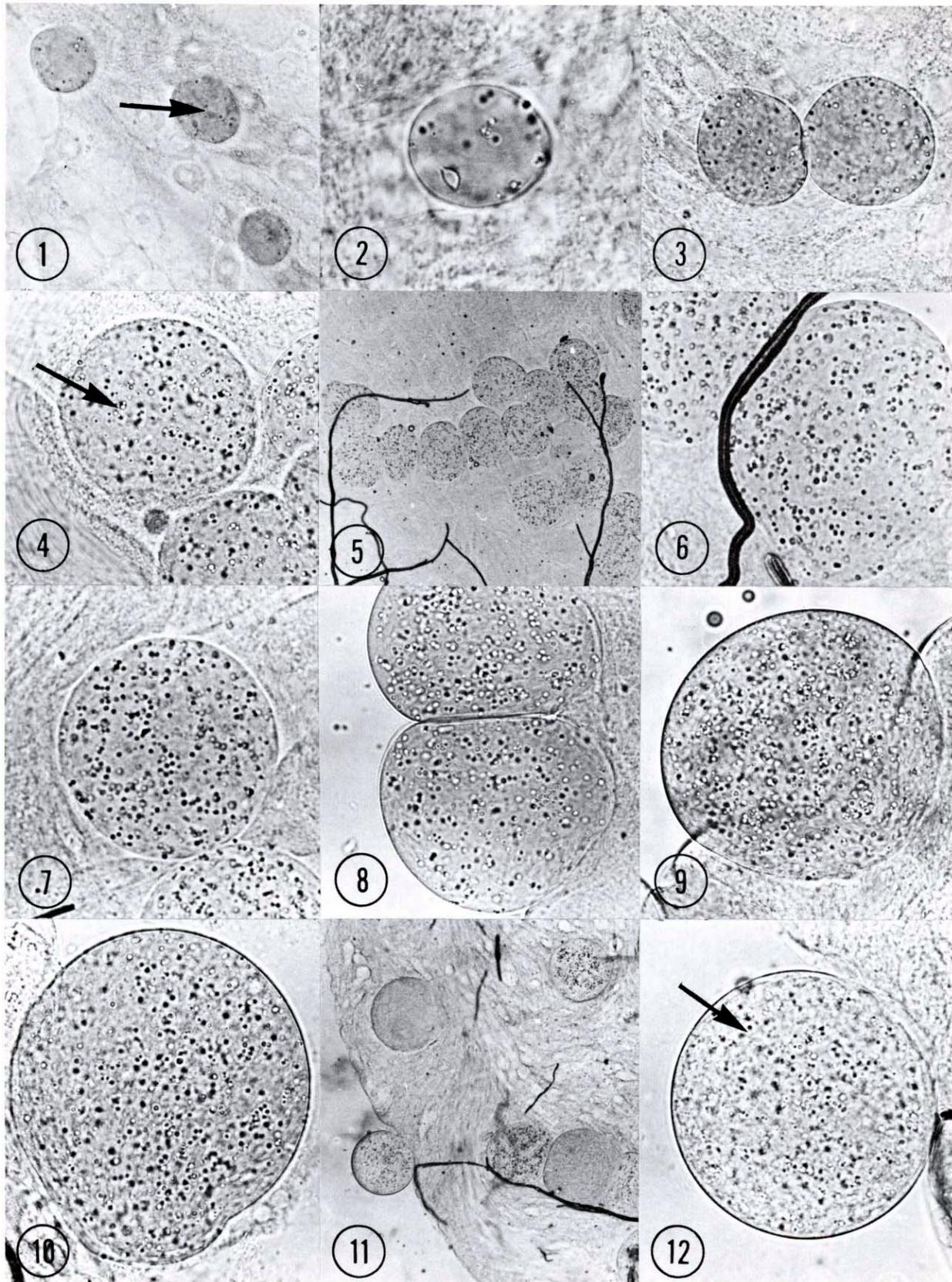


PLATE XIX.—Developing oocysts of *Plasmodium schwetzi* in *Anopheles b. balabacensis* mosquitoes. X 580 (except where indicated).

Fig. 1. 4.5-day oocyst showing scattered pigment.

Fig. 2. 5.5-day oocyst. X 928

Fig. 3. 6.5-day oocysts showing small vacuoles and pigment.

Fig. 4. 7.5-day oocysts showing numerous small vacuoles.

Fig. 5. 8.5-day oocysts showing prominent vacuolation. X 145.

Fig. 6. 8.5-day oocysts.

Fig. 7. 8.5-day oocysts.

Fig. 8. 9.5-day oocysts showing less prominent vacuolation.

Fig. 9. 10.5-day oocyst.

Fig. 10. 11.5-day oocyst.

Fig. 11. 12.5-day oocysts. X145

Fig. 12. 12.5-day oocyst showing first signs of differentiation.

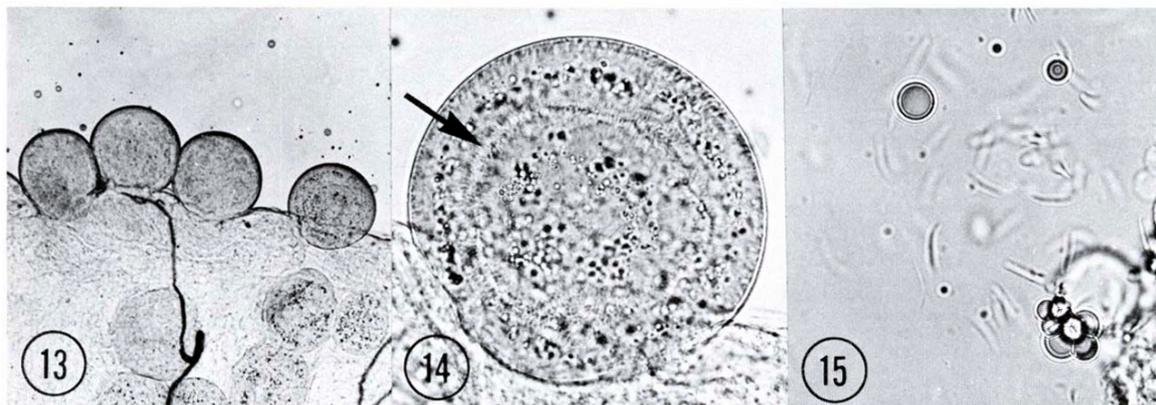


PLATE XX.—Developing oocysts and sporozoites of *Plasmodium schwetzi* in *Anopheles b. balabacensis* mosquitoes. X 580 (except where indicated).

Fig. 13. 13.5-day oocysts. X 145.

Fig. 14. 13.5-day oocyst showing more advanced stage of differentiation.

Fig. 15. Sporozoites present near salivary gland tissue 15.5 days after feeding.

and stains uniformly blue. The pigment is coarse, black to greenish-black and evenly distributed. The nucleus, usually oval and peripheral, stains a deep wine-red. The mature parasite almost fills the enlarged erythrocyte and is surrounded generally by the eosinophilic web-like border of the host cell (Figs. 28, 29).

The microgametocyte is usually brightly colored with reddish-purple cytoplasm and a large, diffuse wine-red nucleus. The cytoplasmic edge of the parasite is frequently crenated or lace-like and tends to merge with the eosinophilic web of the enlarged host cell. The pigment is coarse, black to greenish-black and evenly distributed (Fig. 30).

The parasite has a 48-hour cycle in the chimpanzee. According to Bray (1963) the cycle may lengthen to a 50- to a 52-hour cycle as the infection progresses; we did not observe this phenomenon.

## Sporogonic Cycle

### PLATE XIX, XX

The natural vector of this parasite is unknown. The earliest attempt to find a vector was that of Blacklock and Adler (1922) who obtained negative results after feeding 40 *A. costalis* (= *A. gambiae*) on a chimpanzee infected with *P. reichenowi* and *P. schwetzi*. Rodhain and Lassman (1940) successfully infected *Anopheles maculipennis* var. *atroparvus* with *P. schwetzi*. The oocysts were large, measuring up to 88.8  $\mu$ ; *P. vivax*, in their experience, measured up to 66  $\mu$ . Rodhain (1955) obtained a 66 percent infection rate in *A. m. atroparvus*. The oocysts matured in 13 to 14 days; the dimensions were 70 to 74  $\mu$ . The sporozoites were in the glands by day 14 to day 15; their chromatin was centrally located.

Bray (1958) was able to study the sexual

development in *A. gambiae*. In that host, the cycle required 10 days at 75-80° F. He did not feel that *A. gambiae* constituted a good vector because the salivary glands were scantily infected. The mature oocysts had an average diameter of 60.6  $\mu$  on the 10th day which is larger than *P. vivax* (45 to 55  $\mu$ ). At the 4- and 5-day level Bray found the *P. schwetzi* oocysts resembled exactly those of *P. vivax*.

Garnham (1966) reported that *P. schwetzi* developed readily in *A. aztecus* at a temperature of 22° C. The oocysts had grown to 18  $\mu$  at day 6 and to 68  $\mu$  after day 13. In the young oocysts the pigment was found in straight or curved lines. We have been able to infect the Asian anophelines, *A. b. balabacensis* and *A. maculatus*, as well as the California-based anopheline, *A. freeborni* (Collins *et al.*, 1969). The mosquitoes were incubated at 25° C beginning 30 hours after exposure. The oocyst diameters are presented in Table 16. In *A. b. balabacensis*, at day 3.5, the mean oocyst diameter was 16  $\mu$  with a range of 12 to 21  $\mu$ . The oocysts continued to grow so that by day

14.5, the mean diameter was 81  $\mu$ , with a range of 47 to 103  $\mu$ . The most obvious morphological feature of the oocysts was the presence of numerous small, spherical inclusions which appeared to be vacuoles (Plate XIX). Although such inclusions are found in the oocysts of most of the plasmodia, they are more abundant in *P. schwetzi*. Inclusions were also found abundant in *P. gonderi* and *P. simium* but to a lesser extent. The oocysts are larger than those of most species; their size was comparable to those measured by Rodhain in *A. m. atroparvus*. Sporozoites were present in the salivary glands on day 14.5 and were viable in that *P. schwetzi* infection was transmitted to human volunteers as discussed below.

A comparison of the growth rate of *P. schwetzi* with that of *P. cynomolgi* in *A. b. balabacensis* mosquitoes (Fig. 32) shows that they are approximately of the same size through 10.5 days. However, the oocysts of *P. cynomolgi* have differentiated by that time and sporozoites are present in the salivary glands. In contrast, the oocysts of *P. schwetzi* continue to grow and do

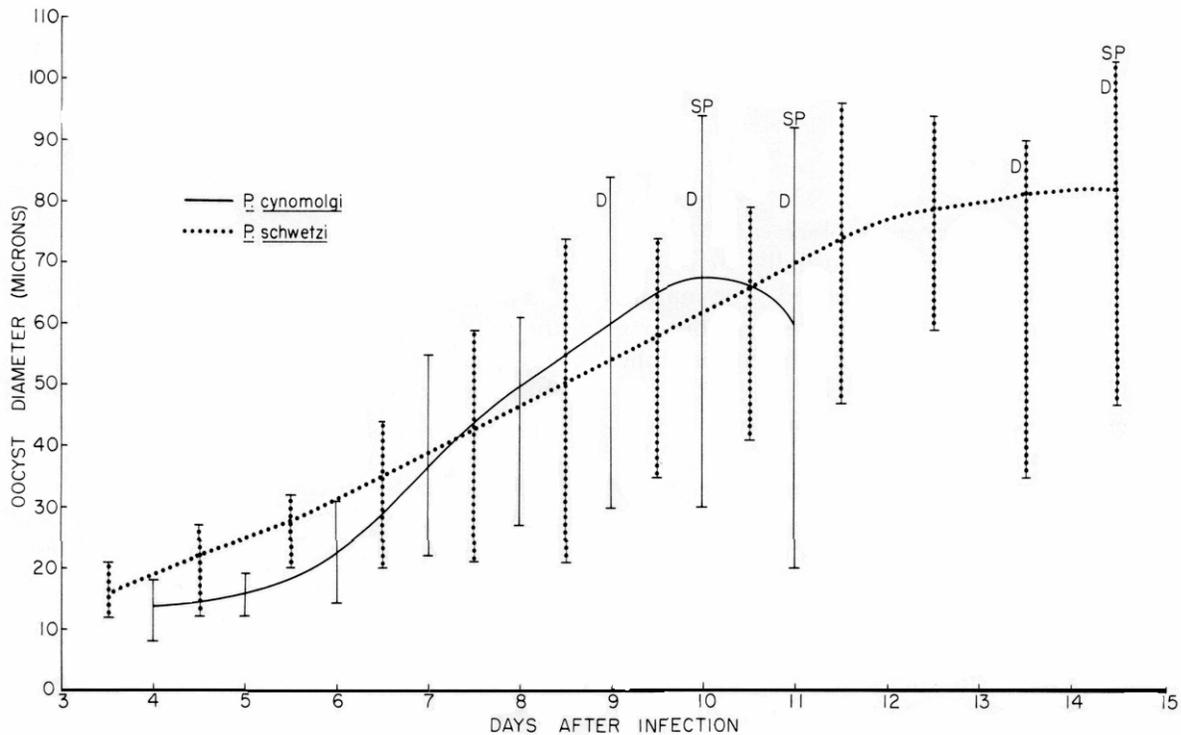


FIGURE 32.—Range in oocyst diameters and the mean oocyst diameter curves of *Plasmodium schwetzi* and *P. cynomolgi* in *Anopheles b. balabacensis* mosquitoes. (D = oocyst differentiation; SP = sporozoites present in the salivary glands).

not differentiate until day 13.5 with sporozoites in the glands on day 14.5. In other words, *P. schwetzi* requires approximately 4.5 days longer to complete the sporogonic cycle than does *P. cynomolgi*.

## Cycle in the Tissue

We regret to say there are no data on the exoerythrocytic cycle of *P. schwetzi*. We were fortunate in obtaining good infections in mosquitoes, discussed above, but unfortunately no chimpanzees were available to us at that time and therefore the opportunity for finding these forms was lost.

## Course of Infection

The natural hosts of *Plasmodium schwetzi* are the chimpanzee and the gorilla. It was from these hosts that Reichenow described the parasite originally, having found it in three of eight chimpanzees and in two of eight gorillas. One of the young chimpanzees showed a moderate infection but in the other animals the parasitemia was low. It does not appear to evoke clinical symptoms even in young chimpanzees and we observed no clinical evidence of infection in splenectomized older chimpanzees even though they exhibited high parasitemias.

*Plasmodium schwetzi* generally occurs as a mixed infection with *P. reichenowi* and *P. rodhaini* and, prior to our studies, begun in 1967, it was assumed that initially one or both of the latter parasites dominated or suppressed the *P. schwetzi* infection. This may be true for intact animals in nature; however, when *P. reichenowi* and *P. schwetzi* are introduced together into a splenectomized and an intact chimpanzee the *schwetzi* malaria assumes almost complete dominance over *P. reichenowi*.

So far all attempts to infect any of the monkeys with this parasite have failed.

The parasite will grow and produce disease in man as will be detailed below. The early attempts to infect man with *P. schwetzi* resulted in failure. The first was that of Blacklock and Adler (1922) who transferred blood from a chimpanzee infected with *P. schwetzi*, *P. reichenowi*, and *P. rodhaini* to two people. One person received the blood both intravenously and intramuscularly and the other received it subcutaneously. Neither one exhibited evidence of a malarial infection after an observation period of 28 and 17 days, respectively. Rodhain and Muylle (1938) tried to infect three patients requiring malaria therapy. The first patient received the parasitized chimpanzee blood by intramuscular injection, the second and third by the intravenous route. None of the patients

TABLE 16.—Oocyst diameters of *Plasmodium schwetzi* in *Anopheles b. balabacensis*, *A. maculatus*, and *A. freeborni*.

Days after Infection	<i>A. b. balabacensis</i>			<i>A. maculatus</i>			<i>A. freeborni</i>		
	No.	Range	Mean*	No.	Range	Mean	No.	Range	Mean
3.5	100	12-21	16	16	13-15	14	41	9-14	12
4.5	81	12-27	23	12	15-22	19	45	15-21	18
5.5	20	20-32	27	34	13-22	19	75	9-25	20
6.5	65	20-44	35	26	17-26	21	64	19-35	27
7.5	75	21-59	45	64	20-45	32	40	27-53	41
8.5	56	21-74	58	52	26-60	42	60	32-71	55
9.5	60	35-74	53	52	28-59	43	9	51-64	56
10.5	60	41-79	62	60	31-84	55			
11.5	60	47-96	77	15	39-80	63‡			
12.5	15	59-94	79	63	35-83	57‡			
13.5	54	35-90	74†	13	39-76	51†‡			
14.5	41	37-103	81†**	40	28-83	58†‡			

\* Measurements expressed in microns; incubation temperature 25° C.

† Oocyst differentiation.

‡ Oocyst degeneration.

\*\* Sporozoites present in the salivary glands.

contracted the infection. In the same year (1938) Rodhain, van Hoof and Muylle reported their failures in trying to infect man with the vivax parasite (= *P. schwetzi*) and in 1939 Rodhain again tried to infect man with *P. schwetzi* by the inoculation of infected blood; it failed. He drew the conclusion that *P. schwetzi* was a true parasite of the chimpanzee and not infective to man.

In 1940 Rodhain, concerned with the possible transfer of *P. rodhaini* to man, passaged blood from a chimpanzee infected with *P. rodhaini* and with *P. schwetzi* to two people. The quartan infection appeared in each of the inoculated individuals and with it there appeared a vivax-like parasite too; i.e., *P. schwetzi*. Rodhain expressed some doubt about the latter being *P. schwetzi*, probably because of his previous failures to infect man, and, because the chimpanzee had been inoculated with known *P. vivax* some two years before; that infection had persisted for some weeks. The infection then disappeared and was not seen subsequently during the following two years. In the light of what happened later it is more than probable that the vivax-like parasite in the recipients was actually *P. schwetzi*. For the next fifteen years the question of whether *P. schwetzi* would infect man was allowed to lie fallow.

In 1955 and 1955a Rodhain and Dellaert reported that they had been able to infect man with *P. schwetzi*. They detailed the successful infection of a man and from him to other humans, then back to the chimpanzee, and, again, back to man. In each instance the infection was initiated by the inoculation of parasitized blood. In their first paper, in commenting on the parasite in man they mentioned its close resemblance to *P. ovale*, a fact mentioned as early as 1934 by Schwetz and later by Bray (1958). One wonders, in view of their unqualified success in 1955, why they made no mention of Rodhain's transfer of *P. schwetzi* to man in 1940.

Our own studies of this parasite in man came about through a series of fortuitous circumstances (Contacos *et al*, 1970). Several chimpanzees at the Delta Regional Primate Research Center in Covington, Louisiana became available for studies in malaria. Blood parasitized with *P. reichenowi* and *P. schwetzi*,

obtained from a chimpanzee at the National Communicable Disease Center, Atlanta-Chamblee, Georgia, was inoculated into a chimpanzee in Covington, Louisiana. A patent infection of the two malaria parasites developed in this chimpanzee; but, in a rather short period of time, the *P. schwetzi* parasite became the predominant one. When gametocytes of this species were numerous, mosquitoes (*Anopheles freeborni*, *A. maculatus*, and *A. b. balabacensis*) from our laboratories in Chamblee were shipped by air to New Orleans and carried to Covington, Louisiana, for feeding on the chimpanzee. These were returned to the insectary in Chamblee, Georgia, within 30 hours.

When it was observed that there were sporozoite positive glands in the *A. b. balabacensis* mosquitoes on day 15.5, it was decided to expose three volunteers (2 Caucasians and 1 Negro) to infection. Of the three volunteers exposed to infection by bites of 7 to 9 heavily infected mosquitoes, two (both Caucasians) developed patent infections. One volunteer developed a patent infection at 24 days (day zero being the day of exposure). The other volunteer experienced generalized malaise and headache at irregular intervals beginning on day 14, and on two occasions, day 15 and 17, exhibited temperatures of 100.4 and 99.8° F, respectively. However, this volunteer did not develop a patent infection until day 104. The third volunteer, a Negro, exposed to infection by mosquito bite, did not develop a patent infection through 200 days of observation. Ten other volunteers (9 Caucasians and 1 Negro) were exposed to infection by the inoculation of parasitized human blood. Only the 9 Caucasians developed patent infections,

Patency of infection persisted for up to 145 days. Figure 33 shows the pattern of parasitemia for the above-mentioned infections of *P. schwetzi* in man through 75 days. It can be seen that there is an initial peaking of parasitemia during the first three weeks of patent parasitemia (maximum count of 2,750 parasites per mm<sup>3</sup> of blood). However, it should be noted that parasite counts of 1,000 per mm<sup>3</sup> or higher were frequently observed through the first 65 days of parasitemia.

The fever patterns for infections of *P. schwetzi* in man were variable with a tertian

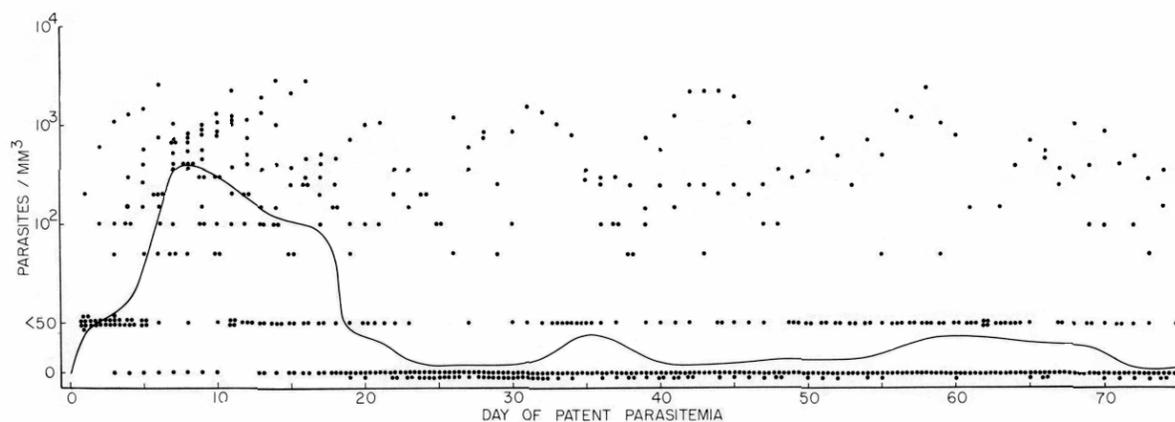


FIGURE 33.—Median parasitemia curve and individual parasite counts in 11 *Plasmodium schwetzi* infections in man (2 sporozoite-induced and 9 blood-induced).

pattern only occasionally evident in most of the volunteers. Paroxysms often occurred daily indicating a two-brood infection. The maximum temperature observed in any volunteer was 105.6° F. Several volunteers had fever free intervals in spite of the presence of patent parasitemia.

Major complaints consisted of headache, generalized malaise, anorexia, and nausea. Vomiting and frank chills were frequently observed. Even though antimalarial therapy was given to several of the volunteers for various reasons, it was not necessary for clinical and/or parasitologic reasons.

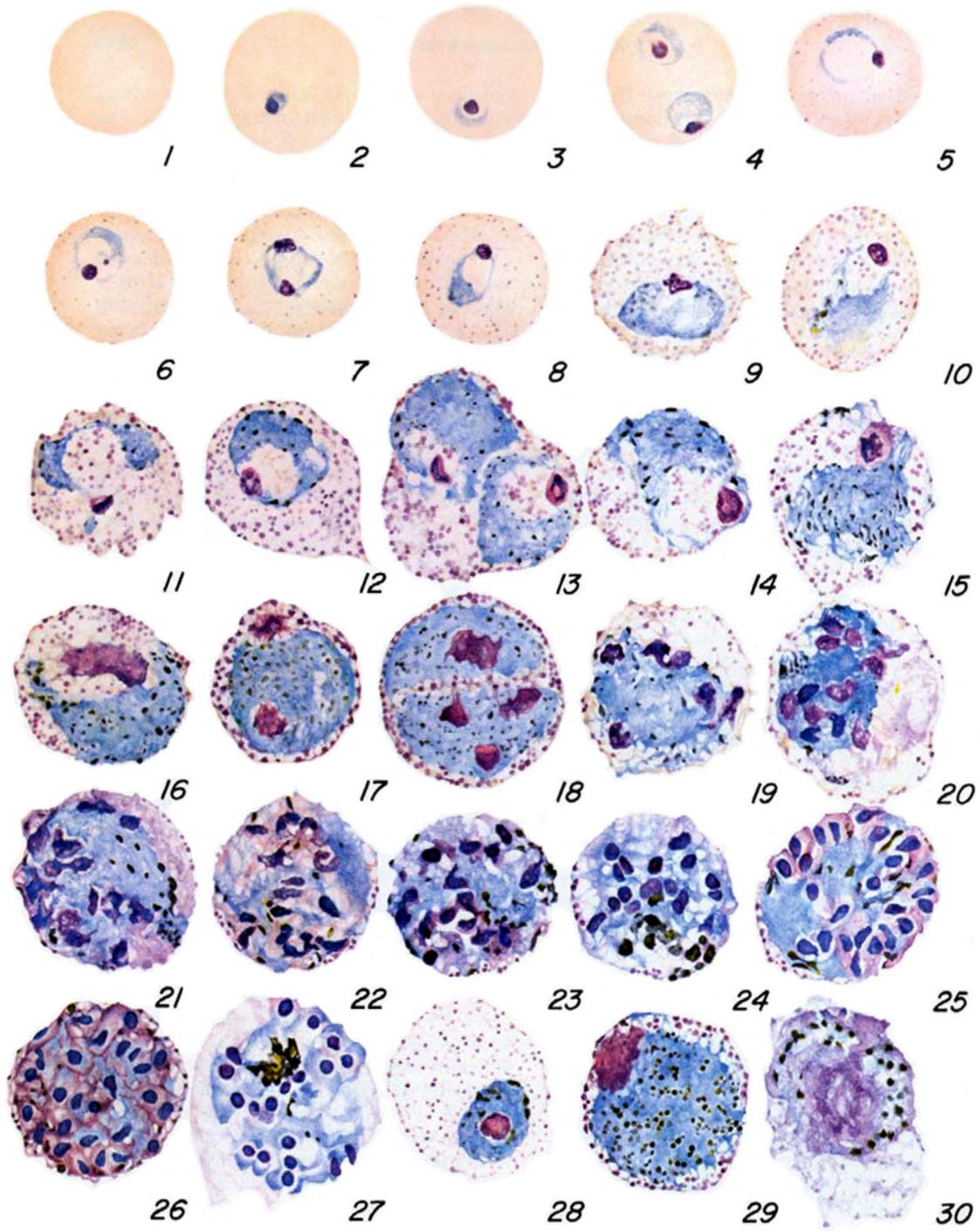
An intriguing facet of our human trials was that the two Negro volunteers failed to develop patent infections. This was totally unexpected, especially, in view of the fact that *P. schwetzi* is an African-based parasite. We would not have been too surprised if the sporozoite-induced case had failed to come down but failure in the blood-induced trial left us entirely "at sea".

If one compares the characteristics of our infections with the blood induced infections reported by Rodhain and Dellaert (1955), one finds little difference in maximum parasite counts, maximum temperatures, and in numbers of paroxysms. They observed parasitemias ranging up to 2,060 whereas in our volunteers the range was up to 2,750 parasites per mm<sup>3</sup>. They reported maximum temperatures of from 104 to 105.8° F and up to 14 paroxysms. In our volunteers, maximum temperatures ranged from 100.2 to 105.8° F and up to 19 paroxysms were

observed. There was, however, one interesting difference. Rodhain and Dellaert made a point of the absence of splenic enlargement in their infections. In our group, 5 of the 11 volunteers had splenic enlargement ranging from tip to 5 centimeters below the left costal margin, with tenderness in 6 of the volunteers.

One of the more interesting observations of the *schwetzi* infections in man was its close resemblance to human ovale malaria as compared to its appearance in the chimpanzee. The *schwetzi* parasites as seen in human blood films are illustrated in Plate XXI. On superficial observation the *P. ovale* parasites (Plate XXV) do not resemble the *P. schwetzi* parasites as they appear in man. However when one examines the compact nature of the parasite, the ovaling tendency of many of the parasitized red blood cells and the coarse red stippling, the similarities become apparent.

In addition to what has been discussed above, it is recognized that during the initial phase of an ovale infection the mature schizonts generally show eight merozoites, the half number for *P. schwetzi*, but during relapse (Garnham *et al*, 1955), or following continuous passage (Hauer, 1937), the merozoite number is doubled--the *schwetzi* number, and the host cell is appreciably enlarged (Garnham *loc. cit.*), also a *schwetzi* characteristic. It is also recognized that *Plasmodium ovale* generally exhibits a low parasitemia. The infections in our volunteers and in those reported by Rodhain and Dellaert followed the same pattern.



0 10 $\mu$

*J. H. Nicholson*

PLASMODIUM SCHWETZI IN MAN

The distribution of *P. ovale* in Africa was mentioned earlier and if a map showing the distribution of the chimpanzee (and gorilla) is superimposed over one of *P. ovale* one finds very close agreement. Apropos of that situation, Languillon (1957) working in a forest area of the Cameroons which supported a large chimpanzee population, encountered in a small native village five infants infected with malaria. He determined four of these to be *P. ovale* and one to be *P. schwetzi*. In his comments he suggested that *P. ovale* in man may be an adaptation of *P. schwetzi*. He and Rodhain had alluded to the same relationship two years earlier.

Rodhain had a continuing interest in the parasite specificity of the ape malaras beginning in 1940 and in a paper published shortly before his death (1956) he included a title, with the notation "in preparation", on "The Paradox of *Plasmodium schwetzi* in Humans". As far as we know the manuscript was never completed and we are left to speculate as to what he might have written. In view of the close resemblance of *P. schwetzi* in man to *P. ovale*, one may well wonder how much of the malaria being diagnosed as *ovale* malaria is truly *schwetzi* malaria, especially in areas where man and the chimpanzee co-exist.

## Host Specificity

*Plasmodium schwetzi* naturally infects chimpanzees and gorillas (Reichenow, 1920; Schwetz, 1933a). Experimentally, infections have been induced in man by the inoculation of parasitized blood (Rodhain and Dellaert, 1955) and by the bites of infected mosquitoes (Contacos *et al*, 1970). The natural vector is unknown and, in fact, very little information is available on the susceptibility of African anophelines to infection with this parasite. Bray (1958) reported the infection of *Anopheles gambiae* but considered it to be an unsuitable host. Other mosquitoes which have been reported as susceptible to infection are *A. atroparvus* (Rodhain, 1955) and *A. aztecus* (Garnham, 1966). In our own studies (Collins *et al*, 1969), we have obtained infection of *A. b. balabacensis*, *A. freeborni*, and *A. maculatus* mosquitoes; the average number of oocysts per mosquito gut was 82.8, 52.7, and 31.7, respectively. The *A. b. balabacensis* readily transmitted the infection. The latter species is not coindigenous with the parasite and, therefore, cannot serve as its natural vector.

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### Plate XXI.—*Plasmodium schwetzi* in man.

Fig. 1. Normal red cell.

Figs. 2, 3. Young trophozoites.

Figs. 4-13. Growing trophozoites.

Figs. 14-16. Nearly mature and mature trophozoites.

Figs. 17-26. Developing schizonts.

Fig. 27. Mature schizont.

Figs. 28, 29. Developing and mature macrogametocytes.

Fig. 30. Mature microgametocyte.

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