Bull. Org. mond. Santé
Bull. Wld Hlth Org. } 1968, **38**, 447-457

Dates of Onset of Relapses and the Duration of Infection in Induced Tertian Malaria with Short and Long Incubation Periods *

N. A. TIBURSKAJA, P. G. SERGIEV & O. S. VRUBLEVSKAJA

The course of induced tertian malaria has been studied in patients in psychoneurological hospitals in Moscow over a long period. Various strains of P. vivax *were used to infect patients; the sporozoites were transmitted by* Anopheles maculipennis atroparvus *bred under laboratory conditions. There are marked differences between the dates of onset of relapses, reckoned from the primary manifestations of the disease, in patients developing malaria after long and short incubation periods.* P. vivax *strains which have a short incubation period are characterized by producing in patients a series of relapses following a long latent period; strains with a long incubation period are characterized by the occurrence of relapses during the first 3 months after the end of the primary series of attacks. However, some* P. vivax *strains give rise to both types of relapse, depending on the incubation period. In any event, the duration of the disease does not, as a rule, exceed 2 years, including the incubation period. The number of mosquitos (and hence the number of sporozoites) used to infect a patient does not have any noticeable effect on the number and frequency of relapses. In short-incubation tertian malaria, the use of quinocide during the period of treatment of the primary manifestations greatly reduced the number of relapses; in long-incubation tertian malaria similarly treated with quinocide, no relapses occurred.*

There has been a large number of epidemiological observations and experimental investigations on relapses and the duration of infection in induced tertian malaria. The most reliable findings in this respect are the data from experimental research carried out in conditions precluding reinfection (James, 1926, 1926-27, 1931; Korteweg, 1933; Nikolaev, 1935, 1939, 1951a, 1951b; Boyd & Kitchen, 1937; Sergiev & Tiburskaja, 1944; Whorton et al., 1947; Coatney & Cooper, 1948; Coatney, Cooper & Young, 1950; Coatney et al., 1950; Young, 1953; Shute & Maryon, 1954; Arnold et al., 1954; Jeffery, 1956; Tiburskaja, 1964a, 1964b, 1965). Nevertheless, the duration of malaria infection and the dates and frequency of onset of relapses have remained a problem of topical interest to this day.

The tenth report of the WHO Expert Committee on Malaria (1964) stresses the need for obtaining additional data on the duration of infection caused by the four species of causal agents of malaria since such data are of great theoretical and practical importance, both for the planning of malaria-control measures and for confirming that eradication has been achieved. To work out criteria for confirmation of malaria eradication it is necessary to possess data on the course of the disease in conditions which preclude reinfection.

In the Therapeutic Malaria Laboratory of the Marcinovskij Institute of Medical Parasitology and Tropical Medicine, Tiburskaja has been studying the features of the course of tertian malaria for over 25 years. The present paper summarizes the data on the duration of infection, and on the dates and frequency of onset of relapses, in cases of malaria caused by different strains of *Plasmodium vivax*.

MATERIAL AND METHODS

Patients in psychoneurological hospitals in Moscow who required malariotherapy were the subject of our observations. In all cases the patient's history in respect of malaria was carefully investigated.

* From the Marcinovskij Institute of Medical Parasitology and Tropical Medicine, Moscow, USSR.

TABLE 1
CHARACTERISTICS OF *P. VIVAX* STRAINS

Group	Name of strain	Where and when isolated	Climatic zone	Length of incubation period (days)	
				Short	Long
1. Strains invariably producing short incubation	Volgograd	Volgograd, 1945	Temperate	11-24	—
	Nahičevan'	Nahičevan' (Azerbaidzhan SSR), 1937	Subtropical	12-19	—
	Viet-Nam	North Viet-Nam, 1954	Subequatorial	14-25	—
2. Strains invariably producing long incubation	Naro-Fominsk	Moscow Oblast, 1946	Temperate	—	250-401
	Kolomna	Moscow Oblast, 1937	Temperate	—	273-337
	Hlebnikovo	Moscow Oblast, 1948	Temperate	—	195-430
3. Strains producing both types of incubation, the short predominating	Moscow	Moscow Oblast, 1953	Temperate	9-20	216-308
	Leninabad	Leninabad (Tadshik SSR), 1950	Subtropical	10-24	257-355
4. Strains producing both types of incubation, the long predominating	Korea	North Korea, 1953	Temperate	17-22	274-390
	Rjazan'	Rjazan', 1945	Temperate	10-37	282-403

People who had had malaria in the past were omitted when the data were being processed.

The patients were infected by mosquito bites of the subspecies *Anopheles maculipennis atroparvus* bred in laboratory conditions. The mosquitos were allowed to feed on patients with gametocytes in their blood and were then kept in an incubator at a temperature of 23°C–25°C until the end of sporogony; 3 or 4 days after the end of sporogony they were used to infect patients. Various numbers of mosquitos (from 1 to 12) were employed for the purpose.

To detect plasmodia, the blood was examined, by the thick drop method, from the tenth day after infection onwards. From then on, the patients'

TAB

TIME OF ONSET AND NUMBER OF RELAPSES IN CASES IN WHI

Group of *P. vivax* strains	Individual strain	No. of patients	No. of patients with relapses	Relapses		No. of patients in whom the following No. of relapses occurred				
				Short-term	Long-term	1	2	3	4	5
Strains regularly producing short incubation	Volgograd	29	24	5	35	14	6	3		1
	Nahičevan	6	5	1	6	3	2			
	Viet-Nam	4	3	1	6	1	1	1		
Strains regularly producing both types of incubation, the short predominating	Moscow	64	55	4	107	24	14	10	6	1
	Leninabad	27	21	2	32	11	7	3		
Strains regularly producing both types of incubation, the long predominating	Korea	3	3	1	4	1	2			
	Rjazan'	8	6	3	8	4		1	1	
Totals for all 7 strains		141	117	17	197	58	32	18	7	2

temperatures were taken 4 times a day. Blood examination and temperature readings continued until the parasites had disappeared from the peripheral blood. After that, the blood was examined once a week throughout the entire period of observation. The patients were kept under observation for from 8 to 36 months.

To ascertain the duration of infection and the dates of onset of relapses, the case-histories of 390 people with induced tertian malaria (sporozoite infection) were analysed. A total of 236 of the patients received schizontocidal preparations, 135 schizontocides plus quinocide, and 19 received quinocide by itself. The patients were infected with strains of *P. vivax* isolated in different geographical zones. Brief particulars of the strains are given in Table 1. The strains belong to four groups which differ with regard to their incubation periods (Tiburskaja, 1964); this is also shown in Table 1.

Infection of patients requiring pyretotherapy was carried out in every month of the year. The tables given below show dates from the time of infection. The processed material is presented separately for two groups of cases of malaria: those caused by strains producing short incubation, and cases due to strains producing long incubation.

RESULTS OF OBSERVATIONS

During the primary series of attacks patients were treated, regardless of the type of incubation, with quinine, mepacrine (acrichin), proguanil (bigumal), chloroquine, and with pyrimethamine (chloridin) in combination with cycloquine (halochin) or proguanil. The drugs were usually administered for 5 days to 7 days. Treatment with cycloquine in combination with pyrimethamine was an exception, lasting 1 day. Before treatment began the patients, in most cases, had had from 6 to 10 attacks.

Duration of infection and dates and frequency of onset of relapses in short-incubation malaria

On the patients in whom the disease developed after a short incubation period, 39 had been infected with strains that produce manifestations of infection only after a short incubation period (Nahičevan, Volgograd and Viet-Nam strains) and 102 with strains that regularly produce both types of incubation period (Moscow, Leninabad, Korea and Rjazan' strains) (Table 2).

After the end of the primary attacks, relapses were observed in 117 out of 141 patients, or in about 83% of cases. Only in 24 cases were manifestations of infection confined to the primary series of attacks. The number of relapses varied widely in individual patients. A total of 58 patients had 1 relapse, 32 had 2, 18 had 3, 7 had 4, and 2 had 5 relapses. Relapses were found to occur from the second month onwards but the bulk of them (159) occurred in the eighth to twelfth months. After that their numbers substantially decreased. Isolated relapses were observed, however, as late as the twenty-fourth month after infection. Of the 214 relapses, 17 were in the first 3 months (short-term relapses), and 197 after longer intervals.

2

TERTIAN MALARIA DEVELOPED AFTER A SHORT INCUBATION PERIOD

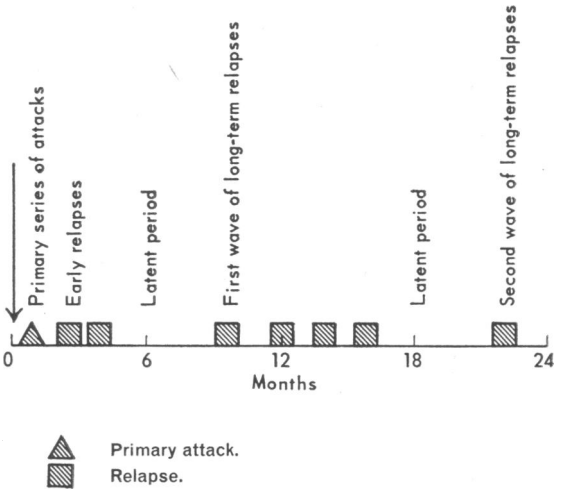
Time of onset of relapses (months after infection)																				Duration of infection (days)
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	18	20	21	24	
	3		2	1		1		5	8	8	4	2	1	3	2					468
	1					1	2	1	1	1										321
			1				1				1	1			1				1	710
	3		1	3		3	18	28	25	15	8	3	3			1				511
	1		1			2	2	7	6	5	5	1	2				1	1		623
		1			1		1			1	1									350
	1	1	1	1					2	2	1	2								381
—	9	2	6	5	1	7	24	41	42	32	20	9	6	3	3	1	1	1	1	

The duration of the infection caused by the *P. vivax* strains studied, when treatment was carried out without recourse to 8-aminoquinoline derivatives, was not more than 16 to 18 months in the majority of patients, but in individual cases the infection lasted longer (up to 20 to 21 months in cases infected with the Leninabad strain, and up to 24 months in cases infected with the Viet-Nam strain). In the light of these data it may be assumed that in tertian malaria with short incubation the duration of infection does not exceed 2 years.

To summarize, the course of the disease in short-incubation malaria is represented diagrammatically in Fig. 1.

FIG. 1

THE COURSE OF THE DISEASE IN SHORT-INCUBATION TERTIAN MALARIA



After the end of the primary series of attacks a small number of short-term relapses are observed. A long latent period follows, after which comes a wave of long-term relapses succeeding one another at short intervals. This wave of long-term relapses may be immediately followed by a further latent period of some months and then by a further wave of long-term relapses. In this case, the patient can be a source of infection during the 2 transmission seasons which follow the primary infection.

To ascertain the influence of the season of infection upon the number of relapses, the patients were classified into groups according to the month of the year in which the primary manifestations of malaria had been observed. For each group both the total number of relapses and the number of short-term and long-term relapses separately were calculated (Table 3). The table shows that the time of year does not have

TABLE 3

RELATIONSHIP OF THE NUMBER OF RELAPSES TO THE MONTH OF THE YEAR IN WHICH PRIMARY MANIFESTATIONS WERE OBSERVED IN CASES IN WHICH TERTIAN MALARIA DEVELOPED AFTER A SHORT INCUBATION PERIOD

Month	No. of patients with primary manifestations of malaria	No. of patients with relapses	Total No. of relapses	Relapses	
				Short-term	Long-term
January	12	11	18	1	17
February	10	8	18	1	17
March	11	8	12	2	10
April	15	11	19	3	16
May	8	8	11	3	8
June	9	4	9	1	8
July	17	17	27		27
August	20	18	33	1	32
September	15	12	23	2	21
October	5	3	10	1	9
November	12	11	23		23
December	7	6	11	2	9

any appreciable effect either on the number of relapses or on their nature. The correlation between short- and long-term relapses characteristic of short-incubation malaria persists irrespective of the season of infection.

As has already been mentioned, malaria was induced in the patients by bites of different numbers of mosquitos (1 to 12). Data on the number of relapses in patients bitten by different numbers of mosquitos are given in Table 4. From the material shown in the table it has not been possible to establish any clear-cut relation between the number of relapses a patient has and the number of mosquitos employed to infect him. Thus, in a substantial number of patients infected by the bite of a single mosquito, 2, 3 and 4 relapses were observed. On the other hand, in some of the cases in which patients were infected by bites of 5, 6, 7 and 9 mosquitos, no relapses occurred.

TABLE 4

RELATIONSHIP OF THE NUMBER OF RELAPSES IN CASES OF TERTIAN MALARIA WITH A SHORT INCUBATION WITH THE NUMBER OF MOSQUITOS EMPLOYED FOR INFECTION

No. of mosquitos employed to infect a patient	Total No. of patients	No. of patients in whom the following No. of relapses occurred:				
		1	2	3	4	5
1	78	35	18	9	3	—
2	22	13	2	3	1	1
3	14	7	1	3	—	—
4	3		2	—	1	
5	9	1	4		1	1
6	6		4			
7	3		1	1		
8	3	2		1		
9	1					
10	1				1	
12	1			1		

The number of sporozoites introduced into a patient does not have a decisive effect on the number of relapses suffered by the patient. In one case, a patient infected by 1 mosquito with scanty sporozoites in its salivary glands had 4 long-term relapses. In another, a patient infected by 8 mosquitos whose salivary glands contained large numbers of sporozoites, had only 1 long-term relapse.

In evaluating these data it must be remembered, however, that the number of patients infected by bites of 5 to 12 mosquitos was small. In addition, in the conditions of the experiment the individual patients were infected by bites at the same time by several mosquitos infected with the same strain.

Duration of infection, and dates and frequency of onset of relapses, in cases of malaria following a long incubation period

Of the patients in whom the disease developed after a long incubation period, 40 had been infected with strains that will produce manifestations of infection only after a long incubation period (Naro-Fominsk, Kolomna and Hlebnikovoj strains) and 55 with strains invariably producing both types of incubation (Moscow, Leninabad, Korea and Rjazan' strains) (Table 5).

In 58 of these 95 patients, manifestations of infection were confined to the primary attacks. Relapses were observed in 37 patients, the number of relapses being small; the total number of relapses was 48. The frequency of relapses was approximately the same in patients infected with different long-incubation strains. The number of relapses observed in any one patient did not exceed 2; 26 patients had 1 relapse, 11 had 2. The largest number of relapses occurred during the first 3 months after the end of the primary attack. In all, 38 of the 48 relapses were observed during those months, and only 9 later.

The duration of incubation did not exceed 16 months in the majority of patients. The maximum duration was observed in patients infected with the Korea strain (19 months) and the Hlebnikovoj strain (20 months). It may be assumed, therefore, that in long-incubation malaria the duration of infection does not exceed 2 years.

It should be noted that the primary manifestations of infection and short-term relapses in long-incubation malaria coincide in time with the period of long-term relapses in short-incubation malaria. Consequently, in this period there are highly favourable conditions for the transmission of malaria even during the short period when climatic conditions permit the completion of sporogony.

The course of the disease in malaria with a long-incubation period is represented diagrammatically in Fig. 2.

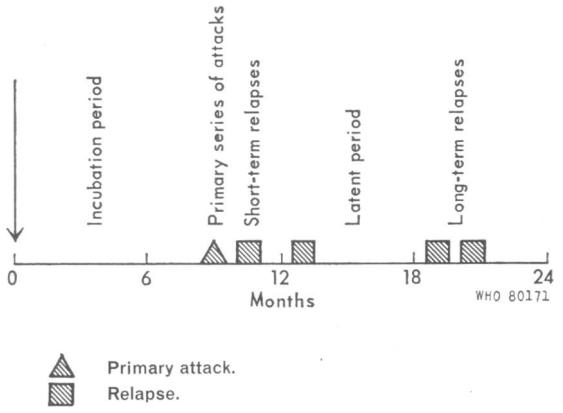
TABLE 5

TIME OF ONSET AND NUMBER OF RELAPSES IN CASES OF TERTIAN MALARIA WITH A LONG INCUBATION PERIOD

Group of strains	Individual strains	No. of patients	No. of patients with relapses	Relapses		No. of patients in whom the following numbers of relapses occurred:		Time of onset of relapses (months after infection)										Duration of infection (days)
				Short-term	Long-term	1	2	9	10	11	12	13	14	15	16	19	20	
Strains invariably producing long incubation	Naro-Fominsk	17	7	5	3	6	1			1	1	2	1	2	1			480
	Kolomna	4	1	—	1	1							1					423
	Hlebnikovo	19	8	7	2	7	1				2	1		3	1	1	1	580
Strains regularly producing both types of incubation, the short predominating	Moscow	13	6	7	—	5	1	1	1	3	1	1						364
	Leninabad	10	3	6	—	—	3		1	1	3	1						394
Strains regularly producing both types of incubation, the long predominating	Korea	18	9	10	3	5	4			1	3	2	4	1		2		548
	Rjazan'	14	3	4	—	2	1			1		2	1					401
Totals for all 7 strains		95	37	39	9	26	11	1	2	7	10	9	7	6	2	3	1	—

FIG. 2

THE COURSE OF THE DISEASE IN LONG-INCUBATION TERTIAN MALARIA



A long incubation period, which in the majority of patients lasts 9 to 14 months, is followed by the primary series of attacks. After the end of the first series of attacks short-term relapses are observed in a certain proportion of the patients. In a small number of cases there is then a latent period of some months, followed by long-term relapses. When the disease follows this pattern, as in the case of short-incubation malaria, manifestations of malaria are possible during the 2 transmission seasons which follow the patient's infection.

In the cases of malaria with a long incubation period, as in the cases of the other type, it was not possible to detect any connexion between the number of relapses and the number of mosquitos employed for infecting the patient. Irrespective of the number of mosquitos employed to induce malaria, there were not more than 2 relapses. Two relapses occurred in patients infected by 1, 2, 3, 4, 5 or 9 mosquitos (Table 6).

Similarly, the season in which the initial manifestations of malaria were observed does not have any appreciable effect either upon the number of relapses or upon their nature (Table 7).

Nature of relapses after quinocide treatment

A total of 116 patients infected with the Moscow, Korea and Viet-Nam strains were treated with quinocide alone or in combination with a schizontocidal drug (proguanil, cycloquine or chloroquine, or cycloquine in combination with pyrimethamine). The quinocide treatment was given either during the period of the primary manifestations of malaria (107 patients) or during the period between attacks with a view to preventing relapses (9 patients).

TABLE 6

RELATIONSHIP BETWEEN THE NUMBER OF RELAPSES AND THE NUMBER OF MOSQUITOS USED FOR INFECTION IN CASES IN WHICH TERTIAN MALARIA DEVELOPED AFTER A LONG INCUBATION PERIOD

No. of mosquitos employed to infect a patient	Total No. of patients infected	No. of patients in whom the following No. of relapses occurred:	
		1	2
1	52	13	3
2	25	7	2
3	6	2	2
4	4	2	1
5	4	—	2
6	1	—	—
9	2	1	1
10	1	1	

If the results of the treatment are compared it will be seen that in the groups of patients who received an insufficient dose of quinocide during treatment (117 mg–163.8 mg of base) a considerable number of relapses occurred: 12 patients out of 31 had relapses, and the total number of relapses was 16 (2 short-term and 14 long-term). The long-term relapses occurred in the seventh to tenth months after the time of infection. The duration of infection in these cases did not exceed 12 months. However, where the full dose of quinocide for the course (calculated to be 218.4 mg or 234 mg of base) was given in combination with schizontocidal drugs alone during the period of treatment of the primary manifestations of malaria, the number of individuals who suffered from relapses was very much smaller than in the case of the patients treated with schizontocidal drugs alone (5% as against 83%). During the 10–12 months after infection relapses were observed in 4 patients out of 76.

When the full dose for the treatment (234 mg of base) was administered during the period between attacks, relapses occurred in 3 patients out of 9. There were 5 relapses in all, occurring between the ninth and twelfth months after infection. In these groups of patients, as in the other groups, the duration of infection did not exceed 12 months. Thus, where relapses occurred after quinocide treatment they took place from 7 to 12 months after infection,

TABLE 7
RELATIONSHIP BETWEEN THE NUMBER OF RELAPSES AND THE MONTH IN WHICH THE PRIMARY MANIFESTATIONS OF MALARIA OCCURRED IN CASES IN WHICH TERTIAN MALARIA DEVELOPED AFTER A LONG INCUBATION PERIOD

Month in which primary manifestations of malaria occurred	No. of patients	No. of patients with relapses	Total No. of relapses	Relapses	
				Short-term	Long-term
January	7	3	4	4	
February	10	2	3	2	1
March	7	5	8	7	1
April	8	3	6	6	
May	10	1	1	1	
June	2				
July	7	5	5	4	1
August	7	5	6	6	
September	11	6	7	2	5
October	8	1	1	1	
November	12	4	5	4	1
December	6	2	2	2	

i.e., during the same period as the relapses occurring after treatment with schizotropic preparations.

Treatment with quinocide in combination with schizontocidal drugs was given during the period of the primary manifestations of infection to 38 patients, who had been infected with the Moscow, Korea and Leninabad strains of *P. vivax* and had shown signs of the disease after a long incubation period. Long-term relapse was observed only in 1 patient, who had received an insufficient total dose of quinocide (163.8 mg of base). In the groups of patients who received 218.4 mg and 234 mg of base there were no relapses. Though the amount of material is not large, some conclusions may nevertheless be drawn from it.

After the primary manifestations of malaria have been treated with quinocide in combination with schizontocidal drugs, the short-term relapses characteristic of tertian malaria with a long incubation period are not observed. Occasional long-term relapses may occur where an insufficient total dose of quinocide has been administered.

DISCUSSION

Observations on the course of induced malaria produced by different strains of *P. vivax* show that the course of the disease differs considerably in cases in which malaria develops after a short incubation period and in those in which it develops after a long one.

After the primary attack, short-incubation malaria is characterized by the onset of long-term relapses, mainly occurring 8 to 12 months after the time of infection. Relapses occur in about 83% of patients treated with schizontocidal drugs. In individual patients, during the long-term relapse a group of attacks takes place at 1- or 2-month intervals.

Long-incubation malaria is characterized by the onset of relapses during the first 3 months after the end of the primary attacks (11 to 15 months from the time of infection). Relapses occur in a smaller proportion of patients (about 39%). No one patient has more than 2 relapses.

There is no great difference in the duration of infection observed between patients in whom malaria develops after a short incubation period and patients in whom it develops after a long one. The duration of infection may be reckoned to be, as a rule, not more than 2 years from the time of infection. These data largely confirm the results of epidemiological observations made in the Soviet Union (Gevorkov, 1946; Duhanina & Luppova, 1948; Jakuševa, Sarikjan & Duhanina, 1951; Jakuševa, 1952, 1953; Prokopenko, 1952; El'kina & Cvetkova, 1952; Duhanina, 1956, 1959).

The material on the dates of relapses in cases caused by strains from groups that possess the biological property of being able regularly to produce both types of incubation is particularly interesting. The strains in question have been studied and classified into special groups by Tiburskaja (1961, 1962, 1964). Thus, in the case of group III strains (Moscow and Leninabad), which in the majority cause malaria with a short incubation period, the primary manifestations of the disease occur after a long incubation period in only a small proportion of patients. Where manifestations of the disease occurred after a short incubation period, relapses were chiefly long-term (about 97% of the total number). Where these strains produced malaria with a long incubation period, only short-term relapses occurred, not exceeding 2 in any one patient.

Group 4, to which the Korea and Rjazan' strains belong, is characterized by the ability to produce the disease mainly after a long incubation period. In only a small proportion of patients does the disease develop after a short incubation period. In cases due to these strains, chiefly long-term relapses were observed, and where manifestations of the disease appeared after a long incubation period relapses occurred mainly during the first 3 months after the end of the primary series of attacks.

If the dates of onset of relapses in the groups of strains producing both types of incubation are compared, it will be noted that they also produce both types of relapses, depending on the type of incubation. In cases in which the primary manifestations of the disease occur after a short incubation period, the onset of relapses follows the same pattern as that to be observed in the strains that produce the disease exclusively after a short incubation, i.e., chiefly long-term relapses occur and there is only a small number of short-term ones.

In cases in which malaria develops after a long incubation period, the pattern of relapses is the same as in the strains that produce the disease only after a long incubation period, i.e., relapses occur mainly in the months immediately following manifestation of the disease, and further subsequent relapses are observed only in individual patients. The features of the groups of strains that produce both types of incubation and, depending upon the type of incubation produced, both types of relapse, can be determined only by lengthy experimental study.

In malaria cases exposed to no risk of reinfection, relapses occurred in the nineteenth, twentieth, twenty-first and twenty-fourth months after the time of infection. Epidemiologists have tried to account for some cases of such late occurrence of relapses by suggesting that there has been simultaneous infection by two strains, one with a short and the other with a long incubation period. As our data show, however, such long-term relapses also occurred after the infection by a single strain. Consequently, in working out criteria for confirmation of malaria eradication, it is necessary to bear in mind the possibility of the disease manifesting itself during the 2 subsequent epidemic seasons. This characteristic is a valuable one for preservation of the plasmodial species.

Up to the present there has been no consensus regarding the connexion between the number of sporozoites introduced (the number of infected mosquitos) and the number of relapses the patient has. James (1926) stated that relapses were no more frequent in people infected with a large dose of sporozoites (by bites of large numbers of mosquitos) than in patients infected with a small dose of sporozoites as a result of bites by a single mosquito. A different opinion is advanced by Coatney, Cooper & Young (1950), who hold that in malaria caused by the Chesson strain fewer relapses occur where patients are infected with a small dose of sporozoites (by being bitten by 1 slightly infected mosquito) than where they are infected by bites of 10 mosquitos.

Some writers (Nikolaev, 1939, 1951; Duhanina, 1956) suggest that the number of relapses depends on repetition of infection, the massiveness of the infection introduced, and mixed infection with different *P. vivax* strains. Examination of our data shows that, in short-incubation and long-incubation malaria alike, the number of mosquitos employed to infect the patient has no noticeable effect on the number of relapses. In our opinion, the number of relapses depends not on the number of mosquitos employed for infection but on the characteristics of individual *P. vivax* strains.

There is no reason to conclude from this, however, that repeated biting plays no part at all in determining the number of relapses. In natural conditions, the possibility that patients have been bitten by mosquitos infected with different *P. vivax* strains cannot be excluded. This is confirmed by the experimental research of Cooper et al. (1950), who have shown that, when patients are infected simultaneously by *P. vivax* strains markedly different in the nature of the relapses they produce (Chesson and St Elizabeth strains), an infection ensues in which the onset of relapses corresponds to a combination of the types of relapse characteristic of each strain separately.

According to our observations, the time of onset of relapses does not depend on the season of infection; this idea is in conformity with the experimental findings from a number of investigations (Shute, 1939; Boyd & Kitchen, 1944). Relapses occur at the same intervals (from the time of infection) as in natural malaria. This ability of the parasite of tertian malaria to produce relapses after certain intervals corresponding to the season of vector activity in natural conditions is a feature that has developed in the course of evolution.

The use of quinocide during the treatment of the primary manifestations of malaria greatly reduces the number of relapses, and of long-term relapses in particular. Unfortunately, however, radical cure is not always achieved even after a complete course of treatment has been given. In short-incubation malaria, isolated relapses are observed after quinocide treatment at the same dates as those at which relapses occur following treatment with schizontocidal drugs. When patients with long-incubation malaria were treated with quinocide, no relapse s occurred.

RÉSUMÉ

Pour établir des critères d'interruption de la transmission du paludisme, il est nécessaire de disposer d'informations sur l'évolution de la maladie dans des conditions qui rendent impossible toute réinfection. Depuis 25 ans, une étude de l'évolution à long terme du paludisme à *Plasmodium vivax* est effectuée au laboratoire de paludothérapie de l'Institut Marcinovskij de Parasitologie médicale et Médecine tropicale, Moscou. Les données sur la durée de l'infection et sur les dates et la fréquence d'apparition des rechutes ont été recueillies au cours de l'observation de 390 cas de paludisme provoqué à *P. vivax*. L'infection a été réalisée par piqûres d'*Anopheles maculipennis atroparvus* porteurs de diverses souches du parasite. Avant d'être traités, la plupart des malades ont subi six à dix atteintes fébriles.

On constate des différences prononcées entre les délais séparant les manifestations primaires de la maladie et le début des rechutes selon que le paludisme s'est déclaré après une période d'incubation courte ou après une période d'incubation longue. Les souches de *P. vivax* qui déclenchent des symptômes après une période d'incubation courte déterminent chez le patient une série de rechutes après une longue période de latence. En revanche, les souches qui provoquent une atteinte primaire après une longue période d'incubation sont à l'origine de rechutes pendant les trois premiers mois suivant l'atteinte de première invasion. Avec certaines souches cependant, on note l'apparition des deux types de rechute, selon la durée de la période d'incubation.

Lorsque l'incubation du paludisme est de longue durée, les atteintes primaires et les rechutes se produisent à des époques correspondant aux dates des rechutes à long terme observées chez les malades atteints de paludisme à période d'incubation courte. Dans les deux cas, la durée de l'infection ne dépasse pas en règle générale deux années, y compris la période d'incubation.

Selon les auteurs, le nombre des moustiques (ou le nombre des sporozoïtes) utilisés pour infecter le malade n'a pas d'effet notable sur le nombre et la fréquence des rechutes. Quant aux dates d'apparition de ces dernières, elles ne dépendent pas de la saison de l'infection, mais sont déterminées par les caractéristiques propres des souches. L'aptitude des parasites de la fièvre tierce à produire des rechutes à certains intervalles correspondant aux époques d'activité du vecteur dans les conditions naturelles est un caractère acquis au cours de l'évolution.

Dans les cas de paludisme à incubation courte, l'emploi de quinocide pendant la période de traitement des atteintes primaires réduit beaucoup le nombre des rechutes. Des rechutes isolées s'observent aux mêmes dates que celles auxquelles se produisent les rechutes après un traitement par les schizontocides. Dans les cas à incubation longue traités par le quinocide, on n'observe aucune rechute.

REFERENCES

Arnold, J. et al. (1954) *J. Lab. clin. Med.*, **44**, 723

Boyd, M. F. & Kitchen, S. F. (1937) *Amer. J. trop. Med.*, **17**, 833

Boyd, M. F. & Kitchen, S. F. (1944) *Amer. J. trop. Med.*, **24**, 221

Coatney, G. & Cooper, W. (1948) *Recrudescence and relapse in vivax malaria.* In: *Proceedings of the Fourth International Congresses on Tropical Medicine and Malaria*, Washington, D.C., vol. 1, p. 629

Coatney, G. R. et al. (1950) *Amer. J. Hyg.*, **51**, 200

Coatney, G. R., Cooper, W. C. & Young, M. D. (1950) *J. nat. Malar. Soc.*, **9**, 381
Cooper, W. C., Coatney, G. R., Culwell, W. B., Eyles, D. E. & Young, M. D., *J. nat. Malar. Soc.*, **9**, 187
Duhanina, N. N. (1956) [*Long-incubation tertian malaria, its distribution in the USSR and its epidemiological features*] Moscow (Thesis)
Duhanina, N. N. (1959) *Trans. Inst. med. Parasit. trop. Med. (Moscow)*, p. 103
Duhanina, N. N. & Luppova, N. N. (1948) *Med. Parazit. (Mosk.)*, **17**, 400
El'kina, E. M. & Cvetkova, E. N. (1952) *Med. Parazit. (Mosk.)*, **21**, 503
Gevorkov, A. A. (1946) *Med. Parazit. (Mosk.)*, **15**, 144
Jakuševa, A. I. (1952) *Sovetsk. Med.*, **4**, 29
Jakuševa, A. I. (1953) *Med. Parazit. (Mosk.)*, **22**, 195
Jakuševa, A. I., Sarikjan, S. J. & Duhanina N. N. (1951) *Med. Parazit. (Mosk.)*, **20**, 321
James, S. P. (1926) *Bull. Off. int. Hyg. publ.* **18**, 1397
James, S. P. (1926-27) *Trans. roy. Soc. trop. Med. Hyg.*, **20**, 143
James, S. P. (1931) *Trans. roy. Soc. trop. Med. Hyg.*, **24**, 477
Jeffery, G. M. (1956) *Amer. J. trop. Med. Hyg.*, **5**, 1
Korteweg, P. C. (1933) *Ned. T. Geneesk.*, **77**, 4547
Nikolaev, B. P. (1935) *Tr. Inst. Ėpidem. (Leningr.)*, **2**, 182
Nikolaev, B. P. (1939) *Med. Parazit. (Mosk.)* **8**, 191
Nikolaev, B. P. (1951a) *Tr. voenno-med. Akad. S. M. Kirova*, **46**, 149
Nikolaev, B. P. (1951b) *Tr. voenno-med. Akad. S. M. Kirova*, **46**, 168
Prokopenko, L. I. (1952) *Med. Parazit. (Mosk.)*, **21**, 496
Sergiev, P. G. & Tiburskaja, N. A. (1944) *Med. Parazit. (Mosk.)*, **13**, 36
Shute, P. G. (1939) *J. trop. Med. Hyg.*, **42**, 201
Shute, P. G. & Maryon, M. (1954) *Riv. Malar.*, **33**, 1
Tiburskaja, N. A. (1961) *Med. Parazit. (Mosk.)*, **30**, 446
Tiburskaja, N. A. (1962) *Med. Parazit. (Mosk.)* **31**, 643
Tiburskaja, N. A. (1964a) *Med. Parazit. (Mosk.)*, **33**, 204
Tiburskaja, N. A. (1964b) [*An account of strains of the causal agent of tertian malaria that produce manifestations of the disease after a long incubation period*] In: [*Problems of Medical Parasitology and Prophylaxis*], Moscow
Tiburskaja, N. A. (1965) *Med. Parazit. (Mosk.)*, **34**, 667
Whorton, C. M. et al. (1947) *J. infect. Dis.*, **80**, 237
WHO Expert Committee on Malaria (1964) *Wld Hlth Org. techn. Rep. Ser.*, **272**
Young, M. D. (1953) *Amer. J. trop. Med. Hyg.*, **2**, 347