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Relapses Following Delayed Treatment of Naturally Induced *Vivax* Malaria of Pacific Origin

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A most difficult problem in the treatment of *vivax* malaria of South and Southwest Pacific origin is the stubborn tendency of the disease to relapse. The exact mechanism of relapse is not known (*9*), but the suggestion has been made that drug therapy which promptly and completely aborts the primary clinical attack may inhibit the development of acquired immunity (*8*). This, in turn, may be partially responsible for the relapse (*9*). Accordingly, it seemed reasonable to consider that prompt therapy of acute attacks such as soldiers obtain might be responsible for the large number of relapses, and to suggest the desirability of investigating the effect of withholding treatment if an opportunity arose (*6*). The establishment by the Surgeon General of a center for the treatment of neurosyphilis at an Army hospital, to which large numbers of soldiers with relapsing *vivax* malaria had been admitted, has given an opportunity to study various facets of the primary attack of malaria. This report presents data on the effect of delay of institution of quinacrine therapy on the tendency to relapse.

Ten white soldiers with malaria, acquired in the South or Southwest Pacific, volunteered as the original sources for the infection of the American anopheline mosquitoes (*10*) used for natural induction of the disease in 69 white soldiers who required malaria therapy because of neurosyphilis. The administration of quinacrine dihydrochloride (2.8 grams in 6 days) was delayed until the patients had had from 8 to 15 paroxysms with an average of approximately 40 hours of fever over 104° F. This level was reached on the average in approximately 20 days, during which blood smears were positive for malaria parasites. The patients were then followed either until a relapse occurred or for at least 60 days without a relapse. Thick smears of the blood were examined twice weekly for parasites during the period of observation, except during an interval of three weeks of furlough immediately after completion of quinacrine therapy. None of the patients received antiluetic therapy with heavy metals during the period of observation for relapse.

It is seen in Table 1 that 45 patients (65 per cent) have had a relapse. There were no significant differences between the mean hours of fever above 104° or between the mean days of parasitemia in those patients who relapsed and those who did not. Of 16 patients observed following quinacrine therapy of the first relapse, 11 (69 per cent) have had a second relapse. In a group of 124 patients who contracted *vivax* malaria in the same overseas areas and whose relapses at Harmon General Hospital were treated promptly with quinacrine, 92 (74 per cent) relapsed. Relapse rates of 70, 76, and 77 per cent following prompt treatment of initial attacks have been reported by Dieuaide (*3*) for three organizations serving overseas. The differences between the rates of relapse following prompt and delayed treatment can hardly be considered of practical significance. Such a result was to be expected from the findings of Boyd and Kitchen (*1*) that there was no relationship between the duration of illness prior to therapeutic termination of the primary attack and the rate of relapse.

TABLE 1

RELAPSES FOLLOWING QUINACRINE TREATMENT OF *Vivax* MALARIA OF SOUTH OR SOUTHWEST PACIFIC ORIGIN

	Delayed treatment of first attack of mosquito-induced therapeutic malaria		Prompt treatment of relapses of naturally acquired malaria	
No. of cases	69		124	
No. of relapses	45*		92†	
Per cent relapse	65		74	
Time to relapse in days‡	Relapses		Relapses	
	Number	Per cent (Cumulative)	Number	Per cent (Cumulative)
Less than 29	2	4	6	7
30– 59	32	76	45	55
60– 89	8	93	21	78
90–119	2	98	12	91
120–149	0	..	3	95
150–179	0	..	5	100
188	1	100	..	..
Total	45	100	92	100

* Average period of observation of nonrelapsers in days: 109 (range, 66–185).
† Average period of observation of nonrelapsers in days: 143 (range, 62–353).
‡ Calculated from time of completion of treatment.

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Seventy-six per cent of the relapses which developed within the period of observation following delayed treatment of the patients with mosquito-induced

therapeutic malaria occurred within 59 days, and 93 per cent within 89 days following completion of quinacrine treatment. In the patients with naturally acquired malaria, 55 per cent of the observed relapses occurred within 59 days and 78 per cent within 89 days. This apparently longer period to relapse in the group with the naturally acquired disease may be due to the fact that the latter patients had had an average of eight relapses before inclusion in the study. For 9 of the 11 patients with induced malaria who had a second relapse following prompt treatment of the first relapse, the interval to the second relapse was from 6 to 52 days longer than the interval from treatment of the primary attack to the first relapse. For 1 patient, the interval was only 2 days longer, and for 1 patient 11 days shorter. The interval between first and second relapses averaged 22 days more than the interval between the primary attack and the first relapse for these 11 patients.

Relapses occurred in men infected with 7 of the 10 "strains" used. With 3 of the strains no relapses occurred, but only 7 men had been infected by these strains. Thirty-three of the neurosyphilitic soldiers were infected with the "Chesson strain" (Ehrman, *et al., 10*), and 25 (76 per cent) had relapses. Although these strains yielded so many relapses after induction of the disease by the bites of mosquitoes, it is noteworthy that in 28 men inoculated intravenously with 5 to 7 cc. of blood containing trophozoites of the same strains of malaria, none have relapsed during a period of observation averaging 106 days and ranging from 66 to 165 days. The importance of the route of inoculation in deciding whether the disease produced is of a relapsing type has previously been noted by James (*5*), and its relation to the production of exoerythrocytic schizonts has been discussed by Porter and Huff (*7*). Evidence that the source of the malaria is also important in determining the rates of relapse (*4*) is suggested by the fact that in 16 soldiers in whom *vivax* malaria of Mediterranean origin was induced by mosquito bites, only 2 (13 per cent) have relapsed to date. These relapses occurred at 111 and 189 days after completion of quinacrine therapy. The period of observation of the 14 patients who did not relapse ranged from 61 to 162 and averaged 113 days.

Although prolonged activity of the infection undoubtedly influences mechanisms of both cellular and humoral immunity (*2*), there is no evidence in this study to support the suggestion that early treatment may delay the development of "immunity" to malaria as measured solely by the incidence of initial relapses. A further delay in administration of quinacrine, perhaps until spontaneous remission, may be associated with a lower rate of relapse. Such rigorous management does not, however, seem justified, since the natural course of the disease is toward eventual cure even with prompt therapy of acute attacks (*3*).

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U. S. News and Notes

Dr. Joseph Hughes will succeed the late Dr. Harold D. Palmer as professor of psychiatry at the Woman's Medical College of Pennsylvania. Since 1943 Dr. Hughes has served with the U. S. Navy. At present he holds the rank of Commander and is chief of the neuropsychiatric service at the Philadelphia Naval Hospital.

Frederick L. Knowles, senior biophysicist, National Institute of Health, has been named editor of the *Journal of the National Malaria Society,* succeeding Dr. R. B. Watson, formerly with the Tennessee Valley Authority, who has joined the staff of the International Health Division of the Rockefeller Foundation. The *Journal* is a quarterly devoted exclusively to malaria and its associated problems. Subscriptions are $3.00 per year and may be obtained through Dr. Martin D. Young, P. O. Box 1344, Columbia, South Carolina.

Dr. Frithjof Setter, until recently immunologist and biochemist in the Michigan State Department of Health Laboratories, has joined the Technical Staff of Parke, Davis and Company, Detroit, as assistant to the director of the Biological Manufacturing Department.