PYRIMETHAMINE IN TREATMENT OF VIVAX MALARIA

PRELIMINARY REPORT

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Pyrimethamine ("daraprim"), a 2:4-diaminopyrimidine compound, has been shown to be highly effective against blood-induced infection of *Plasmodium gallinaceum* and *P. berghei* (Falco *et al.*, 1951). Jaswant Singh, Misra, *et al.* (1951) recently observed that the drug is four times as active as proguanil against *P. knowlesi* in rhesus monkeys, and that it has causal prophylactic action against *P. gallinaceum* in fowls (Jaswant Singh, Basu, and Ray, 1952). Jaswant Singh, Krishnaswamy, *et al.* (1952) have also reported that *P. berghei* in albino mice showed phenomenal sensitiveness to pyrimethamine.

In *P. falciparum* and *P. malariae* infections, McGregor and Smith (1952) have demonstrated that the compound has powerful action on dividing schizonts, but less so against trophozoites. But so far, to our knowledge, very little has appeared in the literature on the effect of the drug against *P. vivax* infections.

Present Investigation

The present report records findings on the effects of this compound on the clinical symptoms and also on the parasites in the first 30 cases of vivax malaria attending hospitals in Delhi State. Seventeen patients gave a previous history of malaria during the past year or so, and in these the spleen was palpable in five cases. On the first examination of blood smears, besides other forms, gametocytes were detected in 11 cases. In 13 other cases there was no previous history of malaria, the spleen was not palpable, and gametocytes were detectable in 9.

Pyrimethamine was administered orally, and each patient received a single dose of 25 mg. (2½ tablets, each containing 10 mg.) of the base. The results are tabulated. The overall

Clearance of Clinical Symptoms, Asexual Parasites, and Gametocytes in Hours

Clearance of	In Hours						Total Cases
	24	48	72	96	120	144	
Clinical symptoms:							
Group I	9	3	5	—	—	—	17*
Group II	5	2	6	—	—	—	13
Total	14	5	11	—	—	—	30
Asexual parasites:							
Group I	6	8	3	—	—	—	17
Group II	5	5	2	1	—	—	13
Total	11	13	5	1	—	—	30
Gametocytes:							
Group I	1	1	4	5	2	1	14
Group II	—	—	3	2	1	3	9
Total	1	1	7	7	3	4	23

Group I = with previous history of malaria.

Group II = No history of previous attacks.

* Five out of 17 cases had enlarged spleen.

picture appears to be that 46.6% (14 out of 30) of the patients became afebrile within 24 hours, 63.3% within 48 hours, and 100% within 72 hours. In 36.6% of the cases clearance of asexual parasites was attained within 24 hours, in 80% within 48 hours, and in 96.6% within 72 hours.

Out of 14 patients who became afebrile within 24 hours, 9 (64.3%) were from Group I—that is, they had had previous attacks of malaria during the course of a year or so—as compared with 35.7% in Group II, without any previous history. Further, it was observed that 6 out of 13 cases (46.1%) in Group II had the second paroxysms 48 hours after the treatment, as against 5 out of 17 (29.4%) in Group I.

The rate of asexual parasite clearance within 24 hours was 54.5% (6 out of 11) in Group I, and 45.5% (5 out of 11) in Group II. Moreover, parasite clearance in all cases in Group I occurred within 72 hours, against 96 hours in Group II.

Thus it would seem that clearance of symptoms and asexual parasites was more rapid in those who had a previous history of malaria than in those who had not. McGregor and Smith (1952) observed that in *P. falciparum* and *P. malariae* malaria the drug acts "just as swiftly in non-immunes as in subjects who possess considerable immunity." But in view of the present observations we are unable to lend support to this view so far as vivax malaria in India is concerned. Therefore the question of repeating the dose may have to be considered, particularly in cases without any previous history of malaria.

The action of pyrimethamine on gametocytes was found to be much slower, and in only 39.1% of the cases did the gametocytes disappear within 72 hours; in 4 out of 23 cases (17.3%) they persisted for 120 hours or more.

The redeeming feature of pyrimethamine seems to be its remarkable effectiveness against *P. vivax* in so small a dose (25 mg.). It would appear that the drug has a future, and further work is indicated.

In view of the high degree of cross-resistance between proguanil and pyrimethamine, recently demonstrated in simian malaria by Jaswant Singh, Ray, *et al.* (1952), one must withhold final judgment until reports on large-scale and continued observations are available, particularly from areas where some strains of plasmodia have been reported to be refractory to proguanil (Field and Edeson, 1949; Gilroy, 1950, personal communication; Chaudhuri, 1951; Wilson *et al.*, 1952).

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REFERENCES

- Chaudhuri, R. N. (1951). *Rep. Sci. Advisory Board, 1951, Indian Council of Med. Res.*, p. 18.
 Falco, E. A., Goodwin, L. G., Hitchings, G. H., Rollo, I. M., and Russell, P. B. (1951). *Brit. J. Pharmacol.*, 6, 185.
 Field, J. W., and Edeson, J. F. B. (1949). *Trans. roy. Soc. trop. Med. Hyg.*, 43, 233.
 Jaswant Singh, Basu, P. C., and Ray, A. P. (1952). *Indian J. Malar.*, 6, 123.
 —, Krishnaswamy, A. K., Satya Prakash, Ray, A. P., and Ramakrishnan, S. P. (1952). *Ibid.*, 6, 183.
 —, Misra, B. G., Ray, A. P., Basu, P. C., and Bami, H. L. (1951). *Ibid.*, 5, 531.
 —, Ray, A. P., Basu, P. C., and Nair, C. P. (1952). *Trans. roy. Soc. trop. Med.*, 46, 639.
 McGregor, I. A., and Smith, D. A. (1952). *British Medical Journal*, 1, 730.
 Wilson, T., Munro, D. S., and Richard, D. R. (1952). *Ibid.*, 1, 564.

A new edition of the *Alphabetical and Local List of Old Students* has just been issued from St. Thomas's Hospital Medical School. The list, which is revised to March 30, 1953, and supersedes the 1948 issue, gives brief details of nearly 3,000 alumni of the Medical School. It may be obtained from the Beadle of the Medical School, Albert Embankment, London, S.E.1, price 5s. 3d., including postage.