and pulse rate 124. Procaine amide, 1 g., was injected intravenously. Within five minutes the blood pressure became 65 and pulse fell to 90. The bleeding stopped. The operation was continued uneventfully, there being only three swabs used, and the sucker was discontinued completely once the blood pressure had fallen to 65 mm. The blood pressure gradually rose to 75 mm. after 70 minutes, but no further bleeding occurred. The pulse was 92. On levelling, the blood pressure rose to 100 mm. Hg. Recovery was uneventful.

Discussion

Cases B and C show an interesting relationship between pulse rate and blood pressure. On the administration of hexamethonium bromide the pulse rate is seen to rise, and the fall in blood pressure is only slight. The injection of procaine amide causes both the blood pressure and the pulse rate to fall. It seems highly probable that the main action of the procaine amide is on the pulse rate, and that the fall in blood pressure is secondary and due to the prevention of this tachycardia.

It would seem reasonable to suppose that the rise in pulse rate following hexamethonium bromide is an effort by the body to compensate for the fall in blood pressure, and occurs possibly through the secretion of adrenaline. The prevention of this compensatory tachycardia seems to be a necessary concomitant of a successful hypotensive anaesthetic, for it has long been observed that almost all the unsuccessful cases have an elevated pulse rate.

It may well be that the omission of gallamine triethiodide, with its tendency to produce tachycardia, will further increase the success rate. This substance was used in our first hexamethonium bromide/procaine amide series so as to make it strictly comparable with the 50 control cases using hexamethonium bromide alone. Enderby has omitted the use of gallamine triethiodide recently, but continues to get a percentage of cases in which a compensatory tachycardia detracts from a good ischaemic result.

Another point of interest is the age group of the 17 cases in which the addition of procaine amide was deemed advisable. Thirteen of the total were under 30 years of age, and this strengthens our previous view that the failures were mostly in the younger age group of patients. Thus the anaesthetist who deals more with the older age group will have greater success with hexamethonium bromide alone and less need for an adjuvant in order to achieve hypotension.

Conclusions

If it is deemed advisable to use hexamethonium bromide and procaine amide together—for example, with ventricular arrhythmias and maxillo-facial operations—no toxic effects occur. The blood pressure, however, does fall more than with either one of these used separately, and also with smaller doses. The drugs show a true potentiation of each other's hypotensive effects. The anaesthetist must use supreme caution and vigilance when using them together.

If hexamethonium bromide fails to bring the blood pressure down to a level in which bleeding is negligible the result will almost always be safely and quickly achieved by the subsequent addition of 1 g. of procaine amide intravenously.

Failure of hexamethonium bromide alone seems to occur with the greatest frequency in patients under the age of 30, and it may be anticipated that procaine will be required most often in this age group.

Summary

A series of 50 cases is reported in which procaine amide was used before the administration of hexamethonium bromide, and the results are compared with a control series.

A further series of 17 cases is reported in which hexamethonium bromide failed to produce a sufficient fall in blood pressure, and which responded after the administration of procaine amide.

The effect on the pulse rate and its relationship to the hypotensive effect of these two drugs are clearly demonstrated.

We wish to thank our colleagues for their encouragement and assistance with these investigations and their permission to use some of their records, and Messrs. Squibb for generously supplying procaine amide ("pronestyl"). We are also indebted to Dr. D. A. Robertson, cardiologist at this unit, for his help and advice.

[ADDENDUM.—Since completing the foregoing article in February, 1952, work has gone forward with procaine amide, and 150 additional cases have received this drug. Careful observations have been made and records kept. So far no cases of allergy or untoward side-effects have been noticed. The pulse rate has almost invariably been reduced, with resulting benefit. The drug is being used by us in doses of 0.5 to 1 g. in those cases in which the pulse rate remains higher than 110. An additional paper is being produced on this series.

We are indebted to Messrs. May and Baker Ltd. for supplying the entire requirements of this later series of cases.]

REFERENCES

- Brodie, B. B., Lief, P. A., and Poet, R. (1948). *J. Pharmacol.*, **94**, 359.
 Burstein, C. L. (1949). *Anesthesiology*, **10**, 133.
 Enderby, G. E. H. (1950). *Lancet*, **1**, 1145.
 — and Peimere, J. F. (1951). *Ibid.*, **1**, 663.
 Joseph, S. I., Helrich, M., Kayden, H. J., Orkin, L. R., and Rovenstine, E. A. (1951). *Surg. Gynec. Obstet.*, **93**, 75.
 — and Rovenstine, E. A. (1951). *J. Pharmacol.*, **101**, 19.
 Kayden, H. J., Brodie, B. B., and Steele, J. M. (1951). *Mod. Conc. cardiovas. Dis.*, **20**, 100.
 — Steele, J. M., Mark, L. C., and Brodie, B. B. (1951). *Circulation*, **4**, 13.
 Mark, L. C., et al. (1951). *J. Pharmacol.*, **102**, 5.
 Newman, P. J., and Clark, B. B. (1950). *Fed. Proc.*, **9**, 304.
 Schaffer, A. I., Blumenfeld, S., Pitman, E. R., and Dix, J. H. (1951). *Amer. Heart J.*, **42**, 115.

TREATMENT OF ACUTE MALARIA WITH PYRIMETHAMINE

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Pyrimethamine, which is 2:4-diamino-5-*p*-chlorophenyl-6-ethylpyrimidine, is the latest of the new synthetic anti-malarial drugs to be tested by us in the Malaria Research Division of this institute. This compound is produced by Burroughs Wellcome & Co. under the trade name "daraprim," and was formerly known by the experimental number B.W. 50-63.

Falco *et al.* (1951) found that pyrimethamine was active in very small doses against *Plasmodium gallinaceum*, *P. berghei*, and *P. cynomolgi*, and its toxicity was slight. Rollo (1951) reported that proguanil-resistant strains of *P. gallinaceum* and *P. berghei* were susceptible to pyrimethamine, and found that *P. gallinaceum* could not readily be made resistant to pyrimethamine by the usual methods. Archibald (1951) gave the first account of the effect of pyrimethamine in human malaria. Single doses of as little as 5 mg. cleared *P. falciparum* trophozoites from the blood of Nigerian schoolchildren; his patients, however, seem to have been parasite carriers rather than sufferers from acute malaria.

Through the kindness of Brigadier J. S. K. Boyd, Director of the Wellcome Laboratories of Tropical

Medicine, we obtained a supply of pyrimethamine, and have used it to treat 126 patients with acute malaria. This paper includes the results up to June, 1952.

Experimental Methods and Standards

Our patients were drawn from the Asian population of the Kuala Lumpur and Tampin districts of the Federation of Malaya. They may be regarded as semi-immunes; but they came to hospital seeking treatment for fever, and were admitted to the General Hospital, Kuala Lumpur, or the District Hospital, Tampin, where they were under the personal supervision of one or other of us. The cases here recorded were previously untreated and uncomplicated infections due to a single species of malaria parasite, and usually with fever and other symptoms of acute malaria.

Parasite counts were made daily on all patients, using the Dreyer-Sinton fowl-cell technique, and thick blood films stained by Field's rapid method were also examined once or twice daily to check progress. A film was reported negative if no parasites were seen in 100 thick film fields. Pulse rates and temperatures were charted four-hourly.

The doses of pyrimethamine were given to each patient by one or other of us, and were seen to be swallowed along with a drink of water. The drug was supplied in tablets of two sizes, containing respectively 10 and 25 mg. of pyrimethamine base, and all doses are stated in terms of base.

At the start of our trial little was known about the effectiveness of pyrimethamine in the treatment of acute malaria or what the optimum dose should be. Treatment was therefore restricted to patients in good physical condition whose parasite counts were relatively low. After a single dose of 20 mg. had proved ineffective in one falciparum and one vivax infection, we decided to begin with single doses of 50 mg.

Results

(1) *Acute Falciparum Malaria*.—Fifteen patients were treated with a single dose of 50 mg. of pyrimethamine; 39 received 100 mg., in divided doses of 50 mg. each at intervals of 4 to 12 hours, and 26 received a total dose of 300 mg. in five days—100 mg. on the first day, followed by 50 mg. daily for the next four days. The results are summarized in Table I. They were disappointing. The

TABLE I.—Average Duration of Asexual Parasitaemia and Fever after Treatment of Acute Falciparum Malaria with Pyrimethamine

Dose of Pyrimethamine Base	No. of Cases	No. of Failures*	Average Duration of Parasitaemia and Fever in Days (Excluding Failures*)		Average Asexual Parasite Count per c.mm. Before Treatment	Range of Parasite Counts
			Parasitaemia	Fever		
50 mg. × 1	15	2	1.9	2.0	16,400	1,000–92,600
100 mg. in 12 hours	39	4	2.4	2.1	9,200	600–27,400
100 mg. × 1 50 mg. × 4	26	7	2.6	2.3	12,600	2,100–46,400

* Failure means that asexual parasites were still present on the seventh day, or that therapeutic intervention with another drug was necessary before the seventh day.

most disturbing feature was the failure to cure so many of the patients. But, apart from these failures, the clinical action of the drug was slow, and more than one-third of the successfully treated patients had persistence of fever and symptoms for a day or two after trophozoites had disappeared from thick blood films. A similar delayed action on fever is often seen when treating falciparum malaria with proguanil, but is rare with other synthetic drugs. In a comparable series of 25 patients treated with single doses of 300 mg. of chloroquine base there were no failures; the average duration of parasitaemia was 2.3 days, but the average duration of fever was only 1.2 days.

Many of our patients came from areas where proguanil-resistant strains of *P. falciparum* were known to exist. It was possible that such strains were also resistant to pyrimethamine, and that this would explain the failures and indeed the persistence of symptoms in so high a proportion of our patients. We tested this hypothesis by giving pyrimethamine to patients whom proguanil had failed to cure.

(2) *Treatment of Proguanil-resistant Falciparum Infections with Pyrimethamine*.—Twenty-four patients with acute falciparum malaria had responded little or not at all to doses of 300 mg. of proguanil daily for an average of 3.7 days; they were then given 100 mg. of pyrimethamine in two doses of 50 mg. each. The results are summarized in Table II. Apart from the two immediate failures, one

TABLE II.—Average Duration of Parasitaemia and Fever in Proguanil-resistant Falciparum Infections Treated with 100 mg. Pyrimethamine

No. of Cases	No. of Failures*	Average Duration of Parasitaemia and Fever in Days (Excluding Failures*)		Average Asexual Parasite Count per c.mm. on Day Pyrimethamine was Given	Range of Parasite Counts
		Parasitaemia	Fever		
24	2	1.9	1.8	7,814	200–54,700

* Failure means that asexual parasites were still present on the seventh day, or that therapeutic intervention with another drug was necessary before the seventh day.

TABLE III.—Average Duration of Parasitaemia and Fever after Treatment of Acute Vivax Malaria with Pyrimethamine

Dose of Pyrimethamine Base	No. of Cases	Average Duration of Parasitaemia and Fever in Days		Average Asexual Parasite Count per c.mm. Before Treatment	Range of Parasite Counts
		Parasitaemia	Fever		
50 mg. × 1	11	3.1	2.0	5,470	600–14,600
100 mg. in 12 hours	11	3.4	1.9	5,640	400–18,600

patient treated with pyrimethamine on day 4—that is, after three full days' treatment with proguanil—and discharged from hospital apparently cured on day 12, returned six days later with a temperature of 102° F. (38.9° C.) and falciparum trophozoites in his blood. Excluding the two failures and two afebrile patients, only 2 patients out of 20 had persistence of fever and symptoms after trophozoites had disappeared from their peripheral blood. These results are so similar to those in Table I as to suggest that resistance to proguanil plays little part in determining how falciparum malaria will respond to treatment with pyrimethamine.

(3) *Acute Vivax Malaria*.—Eleven patients with acute vivax malaria were treated with the 50-mg. single dose, and 11 with the 100-mg. dose. The results are summarized in Table III. Parasite clearance was slow, but there were no failures; fever and symptoms did not persist after trophozoites had disappeared from the peripheral blood.

Discussion

Comparison with Results from Elsewhere.—During the progress of this work accounts of therapeutic trials of pyrimethamine in other countries became available. One, by Schneider *et al.* (1952), was from Tunisia and Indo-China; another, by McGregor and Smith (1952), was from the Gambia. More recently still, Goodwin (1952) has reviewed these results, and has also given details of other clinical trials in Assam. The general tenor of these reports is favourable, yet occasional failures appear in the records, and Schneider *et al.* make special mention of the slow clinical response, and of the fact that results were not improved by using more than a 50-mg. single dose. More

work is needed before the value of pyrimethamine in the treatment of malaria can be assessed. Our own results indicate that it is unsuitable for the treatment of acute malaria caused by Malayan strains of *P. falciparum*; its effect on parasitaemia is so uncertain that it could not be relied upon in a heavy infection.

Drug-resistance.—In recent years, and particularly since the advent of proguanil, the problem of drug-resistance in malaria parasites has assumed a new importance. Not only must the ability of parasites to develop resistance against a drug be investigated, but also the possibility of cross-resistance between different drugs. Schmidt (1953) found that *P. cynomolgi* in monkeys could quickly be made resistant to pyrimethamine, that the resistant quality was transmissible through the mosquito, and that resistant trophozoites were also refractory to treatment with proguanil. Rollo (1952) produced resistance to pyrimethamine in *P. gallinaceum* and *P. berghei*, but found that the drug was almost as active against proguanil-resistant strains in the laboratory as against normal strains. We are still uncertain whether falciparum infections which fail to respond to pyrimethamine are also resistant to proguanil; but the figures in Table II suggest that proguanil-resistant strains of *P. falciparum* behave similarly to unselected Malayan strains of falciparum when treated with pyrimethamine.

Summary

Pyrimethamine, a new antimalarial drug of the 2:4-diaminopyrimidine series, has been used in Malaya for the treatment of 126 patients with acute malaria.

Eighty patients had previously untreated acute falciparum malaria. A single dose of 50 mg. of pyrimethamine failed to cure 2 out of 15 patients; a dose of 100 mg. (in two doses of 50 mg. each) failed to cure 4 out of 39; and a total dose of 300 mg. (100 mg. on the first day and 50 mg. daily for the next four days) failed to cure 7 out of 26 patients. Apart from the failures, the action on fever and symptoms was usually slow.

Twenty-four patients whose falciparum infections had proved refractory to treatment with proguanil were given 100 mg. of pyrimethamine. Results were so similar to those described above as to suggest that resistance to proguanil does not affect the response to pyrimethamine, and is therefore unlikely to have been responsible for the failures in the other groups.

Workers in other countries have obtained better results than these, but occasional failures have been encountered, as has also the slow action on fever and symptoms. Whatever the verdict elsewhere, pyrimethamine must be regarded as unsuitable for the treatment of acute malaria due to Malayan strains of *P. falciparum*.

Eleven patients with acute vivax malaria were treated with the 50-mg. single dose, and eleven with the 100-mg. dose. Disappearance of parasites was slow, but there were no failures.

We are greatly indebted to Brigadier J. S. K. Boyd, Director of the Wellcome Laboratories of Tropical Medicine, for the supply of pyrimethamine and for information about its properties.

REFERENCES

- Archibald, H. M. (1951). *British Medical Journal*, 2, 821.
 Falco, E. A., Goodwin, L. G., Hitchings, G. H., Rollo, I. M., and Russell, P. B. (1951). *Brit. J. Pharmacol.*, 6, 185.
 Goodwin, L. G. (1952). *Trans. roy. Soc. trop. Med. Hyg.*, 46, 485.
 McGregor, I. A., and Smith, D. A. (1952). *British Medical Journal*, 1, 730.
 Rollo, I. M. (1951). *Nature, Lond.*, 168, 332.
 — (1952). *Trans. roy. Soc. trop. Med. Hyg.*, 46, 474.
 Schmidt, L. H. (1953). *J. Pharmacol.* In press.
 Schneider, J., Canet, J., and Dupoux, R. (1952). *Bull. Soc. Path. exot.*, 45, 33.

USE OF LOCAL ANALGESIA IN SEPTIC-FINGER SURGERY AT A TEACHING HOSPITAL

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The purpose of this limited survey is to ascertain whether local analgesia is an advantage over general anaesthesia in septic-finger surgery. The operations have been performed by the casualty officers and the casualty dressers; although the latter change once a week, they have operated on two-thirds of the cases. Each new dresser has one or two practical demonstrations of the technique of analgesia and the principles of drainage; he is then allowed to operate single-handed, but with a casualty officer present.

The investigation began in February, 1952, and covers 256 patients operated on between that time and July, 1952. In the final analysis the case records are complete enough in only 209. The youngest patient was 3 years old and the eldest 85.

For the most part we have followed the terminology used in Professor Pilcher's clinic at University College Hospital (Pilcher *et al.*, 1948; Bailey, 1952). We have used local analgesia for the fingers and thumb. The types of infection classified are: (1) Acute paronychia (40.2%). (2) Pulp abscess: this includes the terminal pulp only (24.2%). (3) Apical abscess: the "apex" being that space lying between the true pulp and the end of the finger (9.3%). (4) Subcutaneous abscess, both volar and dorsal (17.9%). (5) Subungual abscess: we use this group to include sepsis following on splinters under the nail (8.2%).

Method of Treatment

Most cases were operated on at their first attendance. When pus has not been obvious on examination we have found that throbbing pain and loss of sleep are the symptoms which are most suggestive of its presence.

Analgesic.—2½% procaine solution without adrenaline was used. For the first two months the injections were given at the sides of the proximal phalanx—but later the nerves were injected as they leave the palm, just distal to the deep transverse metacarpal ligament. After cleansing with tincture of cetrimide, the dorsal skin between

FIG. 1.—Sites for injection of the various fingers.