effectually sterilizes gametocytes, this course, reinforced with mepacrine in massive dosage on the first day of treatment, seems more likely to fulfil all the requirements listed above than any other form of treatment available. We would advise, however, that such a course be followed up by a maintenance dose of 100 mg. of paludrine daily for the ensuing six weeks, in order to cover the period during which *P. falciparum* relapses are most likely to occur. In endemic areas where strict paludrine prophylaxis is in force the patient would come under this regime automatically.

Summary

An account is given of a series of prophylactic and therapeutic trials with paludrine carried out at Horton Hospital, Epsom, against a strain of *P. falciparum* obtained from a native child resident in Lagos, Nigeria.

Paludrine was found to act as a true causal prophylactic of infections with this strain of parasite. The prophylactic dosage recommended for non-immune adults exposed to malarial infection in West Africa is 100 mg. daily.

Paludrine controlled the clinical attack caused by infections with this strain, but its action in this respect and in clearance of asexual parasites from the peripheral blood was somewhat less rapid than that of mepacrine or quinine.

Paludrine unaided failed to effect radical cure of infections with this strain, a finding in marked contrast with the results achieved by Fairley *et al.* (1946) in their researches on New Guinea strains of *P. falciparum*.

Radical cure of the Lagos strain of *P. falciparum* has apparently been effected with (a) 300 mg. of paludrine twice daily for 10 days, reinforced with 900 mg. of mepacrine given in three doses on the first day of treatment (6 cases); (b) 300 mg. of paludrine twice daily for 10 days, reinforced with 30 gr. (2 g.) of quinine hydrochloride given in three doses on the first day of treatment (5 cases); and (c) 10 gr. (650 mg.) of quinine hydrochloride twice daily for 10 days (5 cases).

Following a course of 300 mg. of paludrine twice daily for 10 days gametocytes were rendered non-infective to mosquitoes for as long as they continued to be present in the peripheral blood in sufficient numbers for infection to occur.

Reinforcement of a course of 300 mg. of paludrine twice daily for 10 days with 900 mg. of mepacrine administered in three doses on the first day of treatment shortened the average duration of pyrexia and clinical symptoms by approximately twenty-four hours.

It is considered that such a course, followed by a maintenance dose of 100 mg. of paludrine daily for the ensuing six weeks, would fulfil the main objectives in the treatment of *P. falciparum* malaria infections—namely, rapid termination of the clinical attack, a high radical cure rate, sterilization of gametocytes, and minimum risk of injurious side-effects.

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The Secretary of State for Scotland has appointed Mr. T. D. Haddow to be an Under Secretary in the Department of Health for Scotland. Mr. Haddow, who is 35 years of age, was educated at Watson's College and Edinburgh and Cambridge Universities. He had the distinction of taking first place in the 1935 competition for entry into the administrative grade of the Civil Service. He was appointed to the Department of Health for Scotland in October, 1935, as an Assistant Principal, promoted to the rank of Principal in 1940, and to Assistant Secretary in 1943. He was closely associated with the preparatory work in connexion with the National Health Service. Under the auspices of the Commonwealth Fund of New York, Mr. Haddow is at present in the U.S.A. studying the administration of public health in that country, and he will complete these studies before returning to take up his new appointment.

INTRAVENOUS "PALUDRINE" (PROGUANIL)

BY

R. N. CHAUDHURI, M.B.Cal., M.R.C.P.Ed.,
T.D.D.Wales

Professor of Tropical Medicine

AND

H. CHAKRAVARTI, M.B.Cal.

Assistant Research Officer

School of Tropical Medicine, Calcutta

In the spring of 1947 we received a supply of paludrine acetate (soluble proguanil) for intravenous use in the treatment of malaria. This preliminary report is a record of its employment in 11 patients admitted to the hospital attached to this institution, one of them being transferred from another hospital. All were Indians, nine males and two females, ranging in age from 9 to 60 years. The duration of illness was four days or less in nine cases and about a week in two, but in none had any antimalarial treatment been given before admission. *Plasmodium falciparum* infection was predominant, being present in 8 cases, while two had *P. vivax* and one had mixed infection. Four patients were gravely ill with pernicious symptoms, four had heavy parasitic infection with frequent vomiting, while three had what may be called ordinary malaria without any complication.

Paludrine acetate* was supplied in 5-ml. ampoules, each containing 100 mg. of the drug. As it was sent to us for experimental trial there were no instructions regarding dosage, and so we had to proceed cautiously, starting with 25 mg. and increasing to 400 mg. in a single injection. In four cases paludrine was given both orally and intravenously.

Case Reports

Case 1.—A boy aged 14, weight 70 lb. (31.75 kg.), was admitted on April 16, 1947, for remittent fever of four days' duration with severe headache. On admission his temperature was 100.2° F. (37.9° C.). Liver and spleen were not palpable; blood showed *P. falciparum* rings. On the following day, while the temperature was 105° F. (40.6° C.), 25 mg. of paludrine was given intravenously. The blood pressure was 102/45 mm. Hg before and 104/50 five minutes after the injection. On the second day of the injection the temperature was almost normal, but next day it shot up to 104.5° F. (40.25° C.), and remained at about this level for five days and thereafter was of intermittent type. The blood was negative on the third day and

FIG. 1.—Temperature chart of Case 1

crescents appeared on the sixth day. On the ninth day, when the temperature was still high, *P. falciparum* rings reappeared in the blood and the spleen became palpable when 50 mg. of paludrine was given intravenously twice daily for two days. This controlled the fever in 60 hours and cleared the blood of asexual parasites in 48 hours (Fig. 1). The blood pressure

*Paludrine acetate has now been replaced by paludrine lactate, which is more soluble and less irritant. An ampoule of 2 ml. contains 100 mg. of the drug. We have used it intramuscularly with satisfactory results, which will be published later.

before and after the injections showed little or no variation. The patient was subsequently under observation for eight months, during which period he had no recurrence of fever.

Case 2.—A man aged 50, weight 90 lb. (40.8 kg.), was admitted on April 22, 1947, with a history of relapsing *P. vivax* malaria, the duration of the present attack of fever being two days. Blood showed *P. vivax* rings, schizonts, and gametocytes in large numbers. The temperature on admission at 10 a.m. was 99.4° F. (37.4° C.), but it shot up to 106° F. (41.1° C.) at 2 p.m., when 50 mg. of paludrine was given intravenously followed by one tablet (100 mg.) thrice daily for five days. The blood pressure was 170/85 mm. Hg before and 150/80 after the injection. The temperature was slightly raised on the following day and became normal on the day after, while the blood was clear of asexual parasites in 48 hours.

Case 3.—A man aged 34, weight 100 lb. (45.35 kg.), was admitted on May 2, 1947, with a history of fever on alternate days. The spleen was palpable and blood showed *P. vivax* parasites in large numbers. On the 6th he was given three injections of paludrine, 100 mg. each, at intervals of four hours, with a satisfactory clinical response, the temperature becoming normal in 24 hours and the blood parasite-free in 72 hours.

Case 4.—A man aged 60, weight 88 lb. (39.92 kg.), was admitted on July 23, 1947, as a case of enteric fever of about ten days' duration. He was looking toxic and dehydrated, and his general condition was low. As he was also semiconscious it was difficult to feed him. The spleen was palpable and the blood showed *P. falciparum* rings +++ and scanty crescents. Paludrine 100 mg. was given intravenously at 2, 6, and 10 p.m. and 2 a.m., and was well tolerated. The blood pressure before and after each injection was as follows:

		Before		After
1st injection	.. ..	78/55 Hg	.. ..	80/58 Hg
2nd ..	.. ..	70/50 Hg	.. ..	75/55 Hg
3rd ..	.. ..	80/55 Hg	.. ..	80/60 Hg
4th ..	.. ..	80/55 Hg	.. ..	80/58 Hg

The patient became fully conscious on the following day and took food much better. The temperature became normal after 32 hours and no asexual parasites were seen after 48 hours, while crescents persisted. There was slow but steady improvement in the general condition, but after about three weeks, while still in the hospital, he had a relapse, for which paludrine was given in doses of one tablet thrice daily for ten days with good response. He was followed up for the next six months, during which period he had no fever.

This was a serious case of *P. falciparum* malaria in an old man with symptoms simulating typhoid fever. Four intravenous injections of paludrine, 100 mg. each at intervals of four hours, had an immediate response.

Case 5.—A man aged 20, weight 90 lb. (40.8 kg.), was admitted to the Medical College Hospital under Dr. J. C. Banerjee on Aug. 23, 1947. The history was that he had a sudden attack of fever on the 20th but carried on with his work until the 22nd. On the following day his fever was high, and he had seven or eight bilious vomits and five or six loose stools with mucus. His condition rapidly deteriorated; he became unconscious at 3 p.m. and was brought to the hospital at about midnight. Blood examination showed *P. vivax* rings. He was given an intravenous injection of paludrine, 100 mg., followed by two tablets of the drug by nasal tube thrice daily for five days. After two more paludrine injections on Aug. 27 and 28 the temperature became normal, but he still remained almost unconscious. On the 30th he was transferred to this hospital along with other patients to make room for casualties due to communal riots in the city. On examination the patient was in a lethargic state, being unable to hear, talk, eat, or even recognize his own mother. At times he was restless, but there was no rigidity or paralysis. Reflexes were normal, pupils equal and reacting, and fundus oculi healthy. The spleen was palpable and the blood pressure 85/55 mm. Hg. Stools passed involuntarily. Blood showed crescents daily from Sept. 5 to 17, and also scanty *P. falciparum* rings on the 8th and 9th, but with no rise of temperature. No antimalarial drug was given and he was fed by nasal tube. After ten days of vegetative existence he began to improve mentally and physically and gradually regained consciousness. He could then sit up and take his food himself and speak, though indistinctly, but developed volitional tremors. At this stage he was taken back

to the Medical College Hospital, where he made good progress except for an attack of *P. vivax* malaria. He visits us periodically, and up to now has been normal.

This patient was desperately ill with cerebral malaria and had apparently both *P. falciparum* and *P. vivax* infections, which responded well to paludrine given intravenously and by the nasal route; but symptoms suggestive of encephalitis developed and he remained in that stage for several weeks. These symptoms appeared to be a sequel of cerebral malaria and not due to large doses of paludrine. It is of interest, however, to note that, despite this dosage, the patient had an early *P. falciparum* relapse without fever and later *P. vivax* relapse with fever while in hospital.

Case 6.—A man aged 40, weight 120 lb. (50.43 kg.), was admitted on Sept. 30, 1947, with a history of high continuous fever for three days, with intense headache and frequent vomiting. His general condition was low, temperature 102.4° F. (39.1° C.), spleen just palpable, and tongue coated and dry. The blood showed *P. falciparum* rings +++. An intravenous injection of 200 mg. of paludrine was given immediately, followed by two more injections of 100 mg. each at intervals of four hours. The temperature became normal three days after the injections, although the blood was negative on the second day.

Case 7.—A man aged 30, weight 75 lb. (34 kg.), was admitted on Oct. 3, 1947, for remittent fever and repeated vomiting of about a week's duration. The spleen was palpable and the blood showed *P. falciparum* rings +. Soon after admission he had a severe rigor, which was considerably relieved by an intravenous injection of 5 ml. of 10% calcium gluconate. As he was unable to retain anything by mouth he was given an intravenous injection of 300 mg. of paludrine. On the third day he became afebrile and the blood was free of rings.

Case 8.—A man aged 20 was admitted on Oct. 9, 1947, with fever and frequent vomiting that started the same morning. He had had *P. vivax* malaria three weeks previously and been treated with "chloroquin." The spleen was just palpable and blood showed *P. falciparum* rings +. Next day, when the temperature was 105° F. (40.6° C.), he was given an injection of 400 mg. of paludrine, followed orally by 100 mg. thrice daily for three days. On the 13th he was afebrile and the asexual parasites had disappeared. No untoward effect was observed, and the blood pressure before and after the injection was 102/65 and 105/65 mm. Hg.

Case 9.—A woman aged 25, weight 87 lb. (39.46 kg.), was admitted in the evening of Oct. 9, 1947, with a history of high fever for four days and of unconsciousness the night before. On admission her temperature was 103° F. (39.4° C.). She was conscious but dazed, and complained of intense headache and frequent vomiting. The spleen was palpable and blood showed *P. falciparum* rings +. Paludrine, 400 mg., was given intravenously on the following day. After about 6 ml. had been injected rather rapidly she complained of a hot sensation all over the body and began to sweat. This symptom passed off soon and the injection was completed. The blood pressure before and after the injection was 120/65 and 120/70 mm. Hg respectively. Subsequently she complained of pain along the course of the injected vein up to the axilla, and this persisted for about four days. The temperature became normal in 56 hours and the blood free of parasites in 28 hours.

This patient had vasomotor reactions after part of the injection given rapidly. Probably she also had some local phlebitis.

Case 10.—A boy aged 15, weight 82 lb. (37.19 kg.), was admitted on Oct. 9, 1947, for fever and excessive vomiting for two days. His condition on admission was low; he was very thirsty but was unable to retain anything. The pulse was fast and soft, urine scanty, and temperature 100.4° F. (38° C.). The spleen was palpable, and the blood showed *P. falciparum* rings +. Paludrine, 400 mg., was given intravenously, followed by one 100-mg. tablet thrice daily for four days. There was a striking improvement in the patient's condition; the temperature was normal and the blood became parasite-free after 36 hours.

Case 11.—A girl aged 9 was admitted on Oct. 31, 1947, with a history of high continuous fever for three days, starting with

chill and rigor and persistent vomiting. She had been delirious and restless on the previous night, and on admission was semi-conscious, with a temperature of 104° F. (40° C.), rising to 106° F. (41.1° C.) soon after. The pulse was feeble and very rapid, about 160 (?) a minute, while the respiration was hurried and laboured. A few scattered rales and rhonchi were heard in the lungs. The heart sounds were short and weak; blood pressure 120/60 mm. Hg. The blood showed *P. falciparum* rings. She was immediately given an injection of 100 mg. paludrine; five minutes after the injection the blood pressure was 122/60. Another injection was given after four hours, and the treatment also included sponging and the administration of oxygen, fluids, glucose, and nikethamide injections. The condition steadily deteriorated, and she died 16 hours after admission.

Discussion

Dosage.—Antimalarial drugs are given parenterally only when for any reason, such as loss of consciousness or persistent vomiting, the patient is unable to swallow or retain them, and as soon as these symptoms are controlled the drugs are continued orally. These indications were present in 8 out of 11 cases in this series. Paludrine injections were first tried in two uncomplicated cases of malaria. In one, that of a boy of 14 with *P. falciparum* infection, a dose of 25 mg. had no effect on the temperature, which continued unabated for several days, nor on the parasite, crescents appearing on the sixth day and *P. falciparum* rings reappearing on the ninth day. Both, however, were controlled with 200 mg. of paludrine (50 mg. given twice a day for two days) in about 48 hours after the injection. The other case was heavily infected with *P. vivax* malaria and was treated with 50 mg. intravenously, followed by oral paludrine, one 100-mg. tablet thrice daily for five days. This brought the temperature to normal and cleared the blood of parasites within 48 hours of the injection.

As there were no untoward effects from these injections it was decided to increase the dose in the cases that came afterwards. Most of them happened to be *P. falciparum* infections complicated by cerebral or gastro-intestinal symptoms. At first the dose was 100 to 200 mg. repeated two to three times a day at four-hourly intervals; later it was one of 300 mg. and ultimately 400 mg. These patients therefore received by injection, either in a single dose or in repeated doses, 300 to 600 mg. of paludrine. To be on the safe side, these injections were accompanied in four cases by paludrine orally.

Effect on Temperature and Parasites.—The immediate effect of the increased dosage in 7 out of 9 patients was striking. In Cases 3, 4, 6, 7, and 9, which had injections only, the blood became clear of parasites in 24 to 48 hours and the temperature became normal in 32 to 72 hours; there was also improvement in their general condition. This was especially noticeable in Case 4, that of a man of 60, who was semiconscious and in a toxic state on admission. After receiving 400 mg. in twelve hours he soon became fully conscious and began to take his food much better. Cases 8 and 10, which had oral paludrine in addition to injections, showed equally good response even before the drug by mouth could have exerted its full effect.

Paludrine had no such effect in the remaining two cases. One of them (Case 5) had typical cerebral malaria, and, though the mixed *P. falciparum* and *P. vivax* infection was controlled by giving the drug intravenously as well as by the nasal route, he remained unconscious for some time and developed signs indicative of encephalitis; but eventually he recovered fully in spite of subsequent relapses. The other case (No. 11) was that of a girl of 9 with hyperpyrexia and delirium from *P. falciparum* infection who was admitted in a state of failing circulation. Paludrine by injection (two doses of 100 mg.), with stimulants, had no

effect whatsoever, and she died within 16 hours of admission. The patient was brought in in a moribund state, and it is difficult to judge the effect of the drug in such a case.

Other Effects.—Practically all the patients were weak and undernourished before the present attack of malaria. Only one of them weighed above 100 lb. (45.35 kg.). One was below 10 years of age and two were 50 years or over. The blood pressure was low in two cases—viz., 78/55 and 85/55 mm. Hg. Yet paludrine had no adverse effect, and the blood pressure remained remarkably constant even after three or four injections given at four-hourly intervals. One patient (Case 9) complained, while the injection was being given, of a hot sensation all over the body and began to sweat; these symptoms soon passed off, and the blood pressure remained unaffected. Subsequently she complained of pain along the course of the injected vein up to the axilla, which lasted for four days. Later we encountered another patient, not included in this series, who also complained of similar pain, which persisted for five or six days after the injection of 100 mg. The pain was mild but uncomfortable, and was possibly due to some local phlebitis.

Summary

Paludrine acetate (soluble proguanil) was tried intravenously as an experimental measure in a series of 11 cases of malaria, all of which except two had *P. falciparum* infection. The majority of the patients had either cerebral or gastro-intestinal complications and were not suitable for oral medication. Four of them were gravely ill.

Doses varied from 25 to 400 mg., and were repeated in a few cases. The total amount of paludrine injected ranged from 200 to 600 mg. per case.

This series was too small for determination of the optimum dose, but in the majority of cases a dosage of 200 to 400 mg. controlled the temperature and cleared the peripheral blood of asexual parasites in two to three days.

One patient admitted in a moribund state died. Another patient, with typical cerebral malaria, remained unconscious for several days and later developed signs and symptoms of encephalitis, from which, however, he recovered completely.

The injections were well tolerated, but one patient (and another not included in this series) had some phlebitis of the injected vein, which subsided in a few days.

Our thanks are due to Messrs. Imperial Chemical Industries (India), Ltd., for the supply of paludrine acetate; to Dr. J. C. Banerjee, of the Calcutta Medical College, for information about Case 5; and to the Indian Research Fund Association for a grant to carry out clinical trials with recent antimalarials.

In the annual report of the Central Midwives Board for the year 1947-8 reference is made to the changes and improvements which have been brought about in recent years in the midwifery services of the country. Revision of the rules has been considered, and the Board has come to the conclusion that while some of the rules are still necessary they should be phrased in such a way that "they indicate a general standard of professional work which it is desirable to maintain rather than set out in precise detail the methods by which such a standard should be attained." During the year the Board decided to incorporate training in analgesia in the ordinary syllabus of training for a pupil midwife. Up to March 1, 1948, some 11,759 midwives possessed either the Board's certificate of proficiency or a certificate issued by a training institution. The Royal College of Obstetrics and Gynaecology was asked by the Board to report on the suitability of trichlorethylene as an analgesic for use by midwives, but the Council of the Royal College was unable to recommend that this substance should be used by midwives without supervision. The number of midwives who were practising in 1947 was 17,400. This maintains the steady increase recorded since 1942, when the figure was 15,615. The number of pupil midwives who were successful at the first examination was a record—3,832 compared with 3,486 in 1946. Wastage during training averaged 10.4% of the registrations. It is interesting that for the first time since 1902 there was no longer any midwife practising out of the 12,500 untrained women who were admitted to the Roll by virtue of having been in *bona fide* practice as midwives for a year or more before the passing of the Midwives Act, 1902.