and fitness and the application of clinical knowledge to its assessment. Almost all medical men are called upon at one time or another to examine men for the Services, and the despairing efforts of the newly qualified medical officer when faced with a group of recruits whose fitness he is expected to assess is well known. The fault lies essentially with the teaching rather than with the new doctor.

One of the difficulties in using any system of medical classification is the wide divergence of opinion among medical men regarding assessment generally and more particularly the influence of various diseases and other morbid conditions on assessment. In the literature which has been produced by the Services on the Pulheems system an attempt has been made to issue some guidance in this matter. It is hoped that with increasing experience this aspect of the subject will be reviewed from time to time and greater precision will be achieved. It remains for civilian bodies to carry the project one stage further. If it is possible to achieve the necessary liaison between civil and military medical authorities there seems to be no reason why in the end all medical men should not be able to allot to each individual the same medical assessment, a development which would be more than welcome to the Services.

Conclusion

The Pulheems system of medical classification has been introduced in the Services to remedy the shortcomings of previous systems used and to facilitate the optimum employment of man-power. Our objectives briefly are: to set up a common system for use by all three Services; to provide a functional assessment of the individual's capacity for work; to assist in expressing the physical and mental attributes appropriate to individual trades and employments within each Service; to allocate men to the employment for which they are most suited in view of their physical, intellectual, and emotional make-up; and to provide a system which is administratively simple to apply in both peace and war.

I consider that the introduction of Pulheems by the fighting Services marks a great step forward in this field of activity. The conception of a uniform assessment of the functional abilities of the population as a whole, whether in terms of war requirements or of industrial potential, is striking enough to require no further elaboration.

ARMY PUBLICATIONS

Pulheems—System of Medical Classification for the Fighting Services, dated November, 1946.

The Application of the Pulheems System of Medical Classification to the Army (W.O. Code No. 1792—restricted).

These pamphlets are in the process of being rewritten, and it is hoped that the first, which deals with the medical aspect entirely, will be available for purchase at H.M. Stationery Office early this year.

I wish to express my thanks to the Director-General of the Army Medical Services, Lieutenant-General Neil Cantlie, C.B., M.C., F.R.C.S., K.H.P., for permission to publish this paper. My gratitude is also due to the Director of Hygiene, Brigadier A. E. Richmond, C.B.E., K.H.S., and my colleagues Lieutenant-Colonel A. N. B. Odert, O.B.E., R.A.M.C., and Major R. B. Stalbow, General List, for much valuable help and criticism in the presentation of this paper.

Offenders who are remanded on bail under provisions of Section 26 of the Criminal Justice Act, 1948, may now be sent to certified institutions or certified houses (among other places) for medical examination and report. The Mental Deficiency (Amendment) Regulations, 1948, which came into operation on Dec. 27, prevent such an offender being received in a certified institution or certified house which is already accommodating the full number of patients for which it has been certified as suitable unless the Minister consents to his reception.

"PALUDRINE" (PROGUANIL) IN PROPHYLAXIS AND TREATMENT OF MALARIAL INFECTIONS CAUSED BY A WEST AFRICAN STRAIN OF *P. FALCIPARUM*

BY

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"Paludrine" was first used for the treatment of human malaria at the Liverpool School of Tropical Medicine in 1945 by Maeagraith and his colleagues, who published records relating to 22 patients naturally infected with West African strains of *Plasmodium falciparum*, 16 of whom were considered to be suffering from primary attacks. The dosage of paludrine administered varied from 50 to 600 mg. twice daily for 14 days. The clinical response was satisfactory in all cases, and was as rapid in those receiving 50 mg. of the drug twice daily as in those who were given a dosage ten times as great. Owing to difficulties in follow-up it was not possible to determine the radical cure rate (Maeagraith *et al.*, 1945).

Subsequently an extensive series of prophylactic and therapeutic trials with paludrine on volunteers exposed to infection with New Guinea strains of *P. falciparum* and on troops suffering from malaria contracted in that area was undertaken by Fairley and his colleagues at the Land Headquarters Medical Research Unit, Cairns, Australia, on the same lines as those previously employed at this centre with mepacrine. Paludrine was found to act as a true causal prophylactic against infections due to New Guinea strains of *P. falciparum*. Radical cure was effected in 41 out of 41 natural and in 46 out of 47 experimentally induced sporozoite infections treated with a ten-days course of 100 mg. of the drug thrice daily. In most cases there was rapid clearance of asexual parasites from the peripheral blood, but, though the overt attack was readily controlled even by very low dosage, the clinical response was described as "not rapid." Gametocytes were not destroyed in the peripheral blood but were rendered non-infective to mosquitoes for a variable period, depending on the size of the dose administered (Fairley *et al.*, 1946).

Since the publication of the Liverpool and Cairns trials a number of prophylactic and therapeutic trials with paludrine have been carried out in India and in Malaya, with generally favourable results. The drug has proved exceedingly useful in both these countries, particularly among labour forces and village populations, where a single-dose treatment of 300 mg. has been generally adopted. It should be noted, however, that the great majority of the subjects treated have been semi-immunes, and there is little evidence regarding the radical cure rate. Chaudhuri (1948) drew attention to the existence in India of strains of *P. falciparum* infections from which are not radically cured by a dosage of 300 mg. of paludrine daily for ten days, and cited the case of a patient who experienced a second overt attack nine days after the completion of treatment and a third attack 11 days later. Other reports from clinicians practising in India and in Malaya indicate that for the treatment of *P. falciparum* infections in non-immune persons paludrine is not entirely adequate in the dosage originally recommended.

In Sardinia, Bettini (1948) treated 94 cases of *falciparum* malaria with 100 mg. of paludrine thrice daily for 10 days

followed by a weekly dose of 100 mg. for three months. The clinical response and clearance of parasites from the peripheral blood were satisfactory, but in 17 of the cases relapses* occurred within this period.

Widely divergent accounts regarding the efficacy of paludrine in the treatment and prophylaxis of malaria have emanated from different parts of Africa, including Kenya, Tanganyika, Rhodesia, Uganda, the Gold Coast, and Nigeria. Some of these have been favourable, whilst in others it has been alleged that the drug has proved unsatisfactory in the treatment of *P. falciparum* infections, in respect of both clinical response and radical cure, as well as for prophylaxis. The most frequent criticism has been that, owing to its slowness of action, serious symptoms have persisted in many cases for three or four days, sometimes longer, necessitating reinforcement of the treatment with mepacrine or quinine.

As the result of trials in the Belgian Congo, van Riel (1948) reported that in a dosage of 100 mg. thrice weekly paludrine failed to act as a causal prophylactic against *P. falciparum* in non-immune subjects constantly exposed to infection. This statement was based on the grounds that one out of 11 persons so treated developed an overt malarial attack on the last day of drug administration and four others did so shortly after this had been discontinued, under conditions precluding the possibility of reinfection. It should be noted, however, that administration of the drug was discontinued approximately 40 hours after the last possible exposure to infection, a period which on Fairley's findings leaves little if any margin of safety and which can scarcely be regarded as sufficient to ensure adequate protection. The clinical response in 156 cases of *P. falciparum* malaria in African labourers treated with 100 mg. of paludrine thrice daily was reported by van Riel to be as satisfactory as that achieved by mepacrine or quinine, but the radical cure rate was not stated.

The investigations recorded below were undertaken in an endeavour to clear up some of the points at issue regarding the use of paludrine for the prophylaxis and treatment of infections with African strains of *P. falciparum*. The strain of parasite used was obtained from a native child resident in Lagos, Nigeria, in November, 1947, and has been maintained at Horton since that date by successive blood and mosquito inoculation. None of the subjects through whom the strain has been passed received paludrine, except the second in the series, who was given 300 mg. of the drug in a single dose on two successive days. The mosquitoes used for transmission were *Anopheles stephensi* (Type), a colony of which was established at Horton during the winter of 1947-8 from specimens imported by air from India. The subjects of the trials were patients in Horton Hospital, all of whom had undergone malaria therapy for neurosyphilis with the Madagascar strain of *P. vivax* or with European strains of *P. falciparum* nine or more years previously but had not been exposed to malarial infection of any kind in the intervening period.

Prophylactic Trials

Twenty-seven patients were arranged in groups as shown in Table I. The patients were infected once weekly over a period of six weeks,† alternate subjects under prophylaxis either being bitten by five to ten heavily infected mosquitoes or receiving by intravenous injection a suspension of the salivary glands of one heavily infected mosquito by the technique described by Shute (1937). Infections were

*Throughout this paper the term "relapse" has been applied to any recrudescence of fever with demonstrable parasitaemia subsequent to the primary attack.

†Except the two individuals under quinine prophylaxis (Group V), who were infected three times only, over a period of three weeks.

TABLE I

Group	No. in Each Group	Drug Administered	Dosage
I	5	Paludrine	100 mg. daily
II	5	"	50 mg. daily
III	5	"	100 mg. twice weekly at 3 to 4 days' interval
IV	5	"	300 mg. once weekly
V	{ 1	Quinine hydrochloride	{ 5 gr. (320 mg.) daily
VI (controls)	{ 1	No drug	{ 10 gr. (650 mg.) daily

given on a different day each week, so as to simulate as closely as possible conditions which might arise in nature. Drug administration was started three days before the first infection in each group, and was continued until six days after the last infection. One or more controls were infected from each batch of mosquitoes used during the course of the experiment. Blood examinations (thick smears) were made twice weekly as a routine, and daily in the case of any rise of temperature above the normal level.

Results

No member of any of the paludrine groups (I to IV) showed parasites in the peripheral blood either during the period of drug administration or subsequently. One member of Group II (50 mg. of paludrine daily) had intermittent pyrexia for four days, starting a fortnight after his first infection. Sub-inoculation of his blood into a non-immune subject proved negative. The donor was found to have only a trace of paludrine in his blood at this time, whereas a few days later the concentration of the drug was of the same order as that of the other four members of the group, the inference being that by some means he had avoided taking the drug regularly as prescribed. Despite the negative results of sub-inoculation and blood examination it is possible that the pyrexia was the result of a partially suppressed malarial infection, but in the circumstances stated this case cannot be regarded as a genuine breakthrough.

Neither of the two individuals under quinine prophylaxis (Group V) showed pyrexia or parasites in the peripheral blood while taking the drug. Both developed overt attacks of malaria after the drug had been discontinued, the first after the lapse of seven days and the second five days later. This is in accordance with the well-established fact that quinine is not a causal prophylactic of malarial infections, its action being suppressive only. All the five control cases developed overt malarial attacks within the normal incubation period, thus demonstrating that each batch of mosquitoes used was infective.

Ten weeks after the cessation of drug administration 18 of the 20 individuals who had been on paludrine prophylaxis were inoculated intravenously with sporozoites of the same strain of *P. falciparum*. All without exception developed overt attacks of malaria within a period of seven to ten days, thus proving their susceptibility to infection with the Lagos strain.

Three members of the laboratory staff were bitten repeatedly while handling heavily infected batches of mosquitoes throughout the period of the investigation, taking no precautions to avoid infection. Each took 200 mg. of paludrine in a single dose twice weekly at three to four days' interval. None of them developed malarial attacks. It is of interest also that two members of the staff who visited Nigeria in November, 1947, were inoculated intravenously in Lagos with a suspension of the salivary glands of a heavily infected specimen of *Anopheles gambiae* caught in a native hut. The species of parasite cannot be stated with certainty, but since the great majority of positive

blood smears examined at this time contained parasites of *P. falciparum* it is more than likely that they were infected with sporozoites of this species. They had each taken 100 mg. of paludrine daily until and including the day before infection, after which the drug was discontinued. Neither developed signs or symptoms of malaria.

From the evidence presented above paludrine has been shown to act as a true causal prophylactic against the Lagos strain of *P. falciparum* in each of the regimes under trial. It is considered, however, that non-immune persons residing in or visiting West Africa should be advised to take not less than 100 mg. of the drug daily for the prophylaxis of malaria. For semi-immune subjects, such as native labour forces and locally recruited Government employees, a weekly dose of 300 mg. is recommended. We do not regard the other two systems tested as offering a sufficient margin of safety.

Therapeutic Trials

Twenty-five patients were arranged in groups as shown in Table II. Each patient was infected by intravenous

TABLE II

Group	No. in Each Group	System of Treatment
I	5	Paludrine 300 mg. once daily for 14 days
II	5	Paludrine 300 mg. twice daily for 7 days
III	5	Paludrine 300 mg. twice daily for 10 days, plus quinine hydrochloride 10 gr. thrice daily on the first day of treatment only
IV	5	Paludrine 300 mg. twice daily for 10 days, plus mepacrine 300 mg. thrice daily on the first day only
V	5	Quinine hydrochloride 10 gr. twice daily for 10 days

inoculation of a suspension of the salivary glands of two specimens from the same heavily infected batch of mosquitoes. Treatment was started in all cases as soon as the temperature reached 100° F. (37.8° C.), provided that parasites had also been seen in the peripheral blood (thick smear).

The results are summarized in Table III. The most striking features brought out by these results are: (1) the

TABLE III

Group	Average Duration of Fever*	Average Duration of Parasitaemia* (Asexual)	Subsequent History
I (P. only)	76 hours	3.2 days	All 5 cases relapsed within 3 weeks and were treated with 300 mg. paludrine twice daily for 10 days. A second relapse occurred in one case
II (P. only)	68 "	3.0 "	Four out of 5 cases relapsed within 3 weeks and were treated with 300 mg. paludrine twice daily for 10 days. A second relapse occurred in 2 cases
III (P. plus Q.)	78 "	2.0 "	No relapse (observed 3 months)
IV (P. plus M.)	50 "	2.5 "	" " "
V (Q. only)	55 "	2.5 "	" " "

* After beginning of treatment.

P. = Paludrine, Q. = Quinine, M. = Mepacrine.

conspicuous failure of paludrine unaided to effect radical cure; (2) the absence of relapse following courses of paludrine reinforced with quinine or mepacrine on the first day of treatment, and of quinine alone; and (3) the rapid termination of the clinical attack effected by reinforcement of a paludrine course with mepacrine on the first day of treatment.

Effect of Paludrine on Gametocytes.—Gametocytes were observed, often in very large numbers, in the peripheral blood of eight of the nine patients who experienced relapses, for which they were treated with 300 mg. of

paludrine twice daily for ten days. Mosquitoes were allowed to feed repeatedly on the two patients who showed the greatest density of gametocytes over a period of 24 days, but none became infected. By this time the gametocytes had become too scanty for infection to occur even had no drug been given.

Discussion

The chief objectives in the treatment of *P. falciparum* infections are: (1) Termination of the clinical attack with the least possible delay. In countries where malignant tertian infections are prevalent this is an essential requirement, particularly when, as often happens, the patient has been ill for some days before the beginning of specific treatment. (2) Prevention of relapses, which may be little less dangerous to life than the primary attack. (3) Sterilization of gametocytes for as long a period as possible. (4) Low toxicity on the part of the drugs used for treatment and for prophylaxis.

The investigations here recorded have confirmed the findings of others working in different countries that the action of paludrine on the clinical attack in malarial infections is generally less rapid than that of mepacrine or quinine, and have shown that, though it acts as a true causal prophylactic of the Lagos strain of *P. falciparum*, it cannot be relied upon, unaided, to effect radical cure of infections with that strain. When administered in sufficient dosage, however, it effectively sterilizes gametocytes for as long as these are present in the peripheral blood in numbers sufficient to infect mosquitoes, while its toxicity is of a lower grade than that of any other known antimalarial drug.

Mepacrine, when administered in the dosage now usually prescribed—i.e., starting with a "loading dose" of 600 to 900 mg. on the first day or first two days of treatment and continuing at 300 mg. daily for five to seven days—will effect a rapid termination of the clinical attack and a high rate of radical cure of *P. falciparum* infections. It does not, however, sterilize gametocytes, and its toxic effects, though of rare occurrence, are by no means negligible. This applies particularly to the so-called mepacrine psychosis, which may evoke symptoms of mental aberration or even of maniacal excitement. The yellow coloration of the skin which sometimes follows a course of mepacrine is an additional disadvantage.

Quinine, when administered in a daily dose of 20 to 30 gr. (1.3 to 2 g.) over a period of seven to ten days, will, like mepacrine, ensure in most cases a rapid termination of the clinical attack and a high radical cure rate. It has no effect on the infectivity of gametocytes. A greater disadvantage, however, is its long-recognized association with the precipitation of blackwater fever. Findlay and Stevenson (1944) have recorded a marked reduction in the incidence of this disease following the substitution of mepacrine for quinine in the treatment of *P. falciparum* infections among British troops stationed in West Africa.

We have shown that reinforcement of a course of paludrine 300 mg. twice daily with mepacrine 900 mg. given in three doses on the first day of treatment brings about rapid termination of the clinical attack and also results in a high rate of radical cure.* It does not seem likely that a single day's reinforcement with mepacrine will cause mental disturbances, which occur almost exclusively towards the end of a full mepacrine course or during the first week after this has been completed. Since paludrine in doses of 300 mg. twice daily for ten days

*It is possible that reinforcement with 600 mg. of mepacrine would prove sufficient for this purpose.

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)

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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.