the first group the average dose was 88 mg. and in the second group it was 96 mg. Very few of my patients have had more than 50 mg.; most have had 30 to 40 mg. This may account for the higher incidence of muscle pains encountered by Dr. Churchill-Davidson.—I am, etc.,

Glasgow, S.2.

A. KILPATRICK.

Malaria Prophylaxis

SIR,—In "Any Questions" under the heading of "Malaria Prophylaxis" (*Journal*, January 9, p. 107) it is advised that daily proguanil ("paludrine") prophylaxis should begin a fortnight before entering a malarious area. Why a fortnight? There appears to be no pharmacological basis for this procedure, and one of the advantages of proguanil as a prophylactic drug is that a loading dose is unnecessary. Provided 100 mg. is being taken every day, I know of no advantage in administering it before the individual enters a malarial area, other than establishing the habit of the daily dose. The question is one of considerable practical importance. In air travel in malarious countries, for example, it is not feasible to give proguanil to travellers and air crews for a fortnight before each journey.

Evidence that proguanil prophylaxis need not be commenced before exposure to infective biting was first obtained by Fairley *et al.*¹ Seventeen out of 17 non-immune volunteers receiving one single dose of either 50 mg. or 100 mg. of proguanil between 39 and 120 hours after exposure to mosquitoes harbouring a New Guinea strain of *P. falciparum* failed to develop malaria, though the controls did. Nine out of 10 volunteers receiving a single dose of 25 mg. of proguanil between 48 and 131 hours after exposure were likewise protected, and 6 out of 8 volunteers receiving a single dose of only 10 mg. of proguanil between 48 and 120 hours after exposure to infective biting were completely protected. On the other hand, a single dose of 100 mg. of proguanil failed to protect 24 hours and 144 hours or later after exposure to infective biting. Two out of 3 volunteers receiving a single dose of 300 mg. of proguanil at 168 and 192 hours respectively after exposure to infective biting developed overt malaria; the third who received 0.3 g. at 144 hours was protected.

Subinoculation experiments² in non-immune volunteers experimentally infected with *P. falciparum* while taking a daily dose of an antimalarial drug for the prevention or suppression of malaria revealed that with quinine, mepacrine, and chloroquine asexual parasites appeared in the blood of the recipient in sub-microscopic density on the 7th day (>144 hours) just as they did in the controls, whereas with proguanil asexual intracorporeal parasites were never demonstrable in the recipients who invariably failed to develop malaria.

The Cairns experiments indicated that in *falciparum* malaria (New Guinea strain) (1) proguanil in one single dose of 50 to 100 mg. prevented malaria if given between the 39th and 131st hours following exposure to infective biting, (2) pre-erythrocytic parasites were much more susceptible to proguanil than were the corresponding asexual blood parasites, (3) when daily proguanil was being given to prevent malaria asexual trophozoites never reached the circulating blood.

As far as is known, these results hold for typical strains of *P. falciparum* everywhere. Even with the atypical West African strain studied by Covell *et al.*³ where proguanil failed to clear the blood of *falciparum* parasites during overt malaria, no difference was demonstrated in its action as a causal prophylactic. Thus 10 out of 10 individuals receiving proguanil in a dosage of 50 or 100 mg. daily were completely protected against multiple infective biting.

In vivax malaria evidence obtained by subinoculation experiments² showed that (1) vivax parasites appear in the blood on the 9th day (>192 hours) after infective biting in volunteers taking quinine, mepacrine, or chloroquine just as they do in controls taking no drug, but with proguanil

they never do so, and (2) proguanil inhibits schizogony of the pre-erythrocytic cycle, delays the appearance of asexual parasites in the blood, and prolongs indefinitely the incubation period while the drug is being taken. The fact that vivax relapses occur after proguanil administration is not due to failure of the drug to eradicate parasitaemia in typical strains of *P. vivax* but to the persistence of late exoerythrocytic parasites in the liver which from time to time erupt asexual trophozoites into the blood stream.

In the B.O.A.C. it has been the practice for the past 8 years to give 100 mg. of proguanil from the day of departure until the 10th day after leaving a malarious area. Sir Harold Whittingham, Director of Medical Services, B.O.A.C., informs me that during this period there have been only one or two malaria infections a year among a B.O.A.C. air crew strength of 1,360, about 1,000 of whom were constantly at risk. During this period the malaria rate has not exceeded 0.2% per annum, and careful inquiry has shown that every member of the air crew developing malaria had failed to take proguanil regularly.

No antimalarial drug has been studied more completely in man than proguanil. It would be unfortunate if a dosage regimen for malaria prevention and suppression so clearly indicated by extensive experimental studies under controlled conditions were not followed.—I am, etc.,

London, W.1.

N. HAMILTON FAIRLEY.

REFERENCES

- ¹ *Trans. roy. Soc. trop. Med. Hyg.*, 1946, 40, 133.
- ² Fairley, N. H., *et al.* (1946). *Ibid.*, 40, 670.
- ³ *Ibid.*, 1949, 42, 343.

SIR,—Dr. Mary G. Phillips's experience with the ineffectiveness of pyrimethamine ("daraprim") as a prophylactic against *P. falciparum* is interesting (*Journal*, January 16, p. 155).

There can by now be little doubt that proguanil ("paludrine") taken daily, and the dose never missed, is by far the most effective drug in the prophylaxis against malignant tertian malaria; proguanil is, of course, a true causal prophylactic against the *P. falciparum* parasite. One wonders whether the dose of pyrimethamine, or alternatively the frequency of its administration, might be increased before it is condemned as being useless as a prophylactic against malignant tertian malaria.—I am, etc.,

Isleworth, Middlesex.

JOHN C. L. ADAMS.

"Status Lymphaticus"

SIR,—Dr. H. B. Dodwell must be congratulated for tracing so satisfactorily to its ultimate source the "myth of status lymphaticus" (*Journal*, January 16, p. 149). The concept is fed to every student of medicine; it is mentioned in most textbooks of surgery and pathology, and most anaesthetic textbooks devote a section to the matter. It will be a difficult task to abolish the notion that status lymphaticus does exist, especially as it offers a plausible excuse for some "anaesthetic" deaths.

Some such deaths occurring in the first few minutes of anaesthesia could without doubt be traced to some lapse on the part of the anaesthetist, but may be ascribed to the "myth" on official records. This does not necessarily reflect upon the integrity of the anaesthetist, who may sincerely believe at the time that nothing untoward had occurred during the administration up to the moment of death; however, later investigation by an independent observer would, I am sure, bring to light little incidents which could in retrospect be interpreted as danger signals—the little cough, breathholding, tinge of cyanosis, pulse irregularities, etc.—and which could have been corrected by appropriate action in time to obviate the crisis.

Most cases of death allegedly due to status lymphaticus fall naturally into the age group 0-20 years, where the thymus is probably still in evidence and has not atrophied to the extent of making the diagnosis untenable or even ridiculous. The majority of cases of which I have heard occur in babies or young children undergoing a surgical operation of a comparatively trivial nature—for example, circumcision, herniotomy, excision of small skin tumours, tonsillectomy, incision of abscesses, etc.; occasionally