hurts, whereas if the anterior (subscapularis) or posterior (infraspinatus) part of the cuff contains the lesion pain occurs on resisted medial or lateral rotation respectively. The importance of accurate anatomical location of the lesion is that it enables one to know in which tissue to seek a tender area before giving a steroid infiltration. Merely injecting "the tender spot" is haphazard, since it may be misleadingly placed.

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¹ Cyriax, J., *Textbook of Orthopaedic Medicine*, 6th edn, p 213. London, Baillière Tindall, 1975.

Prolonged malaria prophylaxis

SIR,—Your expert's answer (17 September, p 757) to a question concerning antimalarial drugs suitable for prolonged prophylaxis in airline pilots calls for dissenting comments on several points.

There is no evidence that chloroquine taken at the dose of 300 mg base once a week causes any visual impairment, let alone blindness. Neuroretinal changes have been observed in a small number of persons whose cumulative dosage of this drug over a period of years was of the order of 100 g. This would require in theory some eight years of continuous taking of 300 mg of chloroquine base once a week or four years of a regimen at double this dosage. It is inconceivable that the postulated "extra chloroquine" for occasional treatment of malaria could significantly increase the risk of visual impairment in persons on the usual chloroquine dosage. On the other hand, chloroquine is the most reliable antimalaria prophylactic, precisely in Africa where no resistance of plasmodia to this compound has been proved to exist. Both proguanil at 100-200 mg daily and pyrimethamine at 25 mg once a week produce fewer side effects than other drugs but are less certain to protect from malaria infection in Africa and elsewhere, as areas of plasmodial resistance to antifolate compounds are much wider and less well known.

Maloprim (pyrimethamine 12.5 mg with dapsone 100 mg) is a reasonably effective prophylactic but not "against malaria anywhere in the world," since areas of resistance to antifolates with sulphones have been reported, especially in south-east Asia. Unfortunately the dosage of two tablets a week quoted by your expert is excessive. Side effects of Maloprim at two tablets a week have been reported from some parts of the world. Haemolysis in certain subjects and agranulocytosis are particularly to be guarded against and the manufacturers of this otherwise valuable drug combination stress that the dosage of one tablet a week should not be exceeded.

Your expert's unqualified condemnation of alcohol, apparently "increasing the susceptibility to malaria and many other diseases," is overstated and not quite fair to the acceptable, moderate, social "sundowner" with minimal if any side effects.

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*Our expert replies: "(1) Professor Bruce-Chwatt states that neuroretinal changes have been observed in a few people who have taken a cumulative dosage of 100 g chloroquine,

equivalent to 300 mg weekly for eight years, which is not long, since an airline pilot might fly to malarious areas for about 30 years and take 300 mg chloroquine weekly on Professor Bruce-Chwatt's advice. This is equivalent to about 400 g of chloroquine—well over the dangerous amount. Many airline pilots are aged between 40 and 55, a time of life when increasing impairment of vision is common, and long-term consumption of chloroquine might have an additive effect. Further evidence of chloroquine retinopathy has been the recent study of five patients from West Africa with visual impairment and a history of chloroquine ingestion for several years.¹

"(2) Airline pilots have the duty to fly planes safely, and presumably this requires perfect physical health and above all perfect vision. Thus the preservation of vision and, arguably, the avoidance of chloroquine might take precedence over the relative risk of acquiring malaria, especially since there are other drugs available for prophylaxis. Proguanil 100-200 mg is a safer chemoprophylactic than chloroquine, and, although it may be less effective than chloroquine, breakthroughs of malaria do occur with any of the drugs used. Therefore ideally facilities to examine blood films for malaria should be available at all international airports that receive travellers from areas endemic for malaria. Examination of blood films for malaria should be made on all pilots who feel unwell and have been in an endemic area.

"(3) Maloprim has proved to be an effective chemoprophylactic against malaria in both chloroquine-resistant² and chloroquine-sensitive³⁻⁴ areas and is marketed in Britain and many other countries. The manufacturer's recommended dose in adults is, as Professor Bruce-Chwatt indicates, one tablet weekly. This may be the optimum dose for tropical people weighing 50 kg, but possibly not for airline pilots weighing on average 80 kg, in whom two tablets weekly might be a more appropriate dose. Also diformyl dapsone (a chemical congener of dapsone) 400 mg with pyrimethamine 25 mg weekly for six months has been given to villagers in Thailand without toxicity.⁵ Fansidar (pyrimethamine 25 mg with sulfadoxine 500 mg in each tablet) is the most effective chemoprophylactic against chloroquine-resistant falciparum malaria⁶⁻⁷ and is available in most endemic areas, although it is not marketed in Britain. The drug is effective given once a month (three tablets) or every two weeks (two tablets), but one tablet weekly is a convenient regimen.

"(4) Alcoholism (here defined as evidence of physical or mental disease caused by alcohol) is a common problem and its prevalence in doctors or airline pilots has not yet been determined. But three pilots, who had all regularly passed their official six-monthly physicals, showed biochemical and physical evidence of alcoholic hepatitis when seen by an independent examiner last year.⁸ Alcohol impairs driving ability and presumably flying ability as well. A liver function test, the determination of serum gamma-glutamyl transaminase (GGT) activity, gives raised values in two-thirds of alcoholics.⁹ The prevalence of alcoholism could be determined with a view to treatment if the GGT and blood alcohol levels were determined randomly at six-monthly intervals on all people with crucial jobs, such as doctors and airline pilots. It should be remembered that most airplane accidents are due to pilot error.¹⁰⁻¹²

"(5) It is therefore desirable that airline

pilots avoid alcohol, tobacco, and other toxic substances, and drugs. However, pilots flying to malarious areas in Africa should probably take an antimalarial drug regularly for prophylaxis. Proguanil 100-200 mg daily is the least toxic drug. Pilots who fly to malarious areas outside Africa are very unlikely to contract malaria, but one tablet of Fansidar weekly should be considered."¹³—ED, BMJ.

¹ Kelsey, J H. In preparation.

² Segal, H E, et al, *Journal of Tropical Medicine and Hygiene*, 1973, 76, 285.

³ Lucas, A O, et al, *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1966, 63, 216.

⁴ Weber, M C, et al, *Central African Journal of Medicine*, 1975, 21, 177.

⁵ Pearlman, E J, et al. In press.

⁶ Pearlman, E J, and Hall, A P, *Annals of Internal Medicine*, 1975, 82, 590.

⁷ *British Medical Journal*, 1976, 2, 1215.

⁸ Hall, A P. In preparation.

⁹ Spencer-Peet, J, Wood, D, and Glatt, M M, *Lancet*, 1972, 1, 1122.

¹⁰ Beatty, D, *The Human Factor in Aircraft Accidents*. New York, Tower Publications, 1969.

¹¹ Power-Waters, B, *Safety Last*. London, Dial Press, 1972.

¹² Godson, J, *Papa India: The Trident Tragedy*. Salisbury, Compton Press, 1974.

Megaloblastic anaemia associated with sulphasalazine treatment

SIR,—The report by Drs Robert E Schneider and Linda Beeley of megaloblastic anaemia associated with sulphasalazine therapy (25 June, p 1638) and the subsequent correspondence (16 July, p 190; 27 August, p 580) were most interesting and prompt this report of a similar case.

A woman, now 40 years old, presented in 1969 with bloody diarrhoea. Ulcerative proctitis was diagnosed on the basis of positive sigmoidoscopic findings and a normal barium enema. Repeated radiological examinations of both small and large intestines have since failed to show any abnormalities proximal to the rectum. In July 1976 routine haematological investigation revealed a haemoglobin concentration of 12.6 g/dl and a mean cell volume (MCV) of 108 fl (108 μm^3). On examination of the blood film occasional macrocytes and hypersegmented neutrophils were seen. At this time her therapy was codeine phosphate 30 mg twice daily, ferrous sulphate 200 mg thrice daily, diazepam 4 mg each night, acetarsol suppositories 250 mg each night, and sulphasalazine 2.5 g daily. She had been on varying doses of this last drug since 1969 and her serum total sulphapyridine levels were repeatedly in the therapeutic range of 20-50 mg/l. Her proctitis was in remission and she ate a normal diet. Further investigations were: serum vitamin B₁₂ 600 ng/l; serum folate 0.8 $\mu\text{g/l}$ and RBC folate 43 $\mu\text{g/l}$ (microbiological assay); and serum folate 0.8 μg and RBC folate 88 $\mu\text{g/l}$ (radioassay). Small-intestinal biopsy showed microscopically normal appearances. Her sulphasalazine therapy was continued, since on several past occasions her disease had relapsed on lowering the dosage of this drug, and she was started on oral folic acid 5 mg daily. After one month her haemoglobin level was 13.8 g/dl and her MCV 92 fl (92 μm^3). Serum and RBC folate levels by microbiological assay were high in the normal range (16.5 and >275 $\mu\text{g/l}$ respectively). On continuing this therapy she has remained well and haematologically normal.

In this case assays of serum and RBC folate concentrations by both microbiological and radioassay methods gave comparable results, making it most unlikely that the low levels were due to any in-vitro effect of the absorbed sulphapyridine or any other drug. None of her medications has reported associations with folate deficiency, her diet did not lack sources of folate, and there was no radiological or histological evidence of small-intestinal disease. As a trial of sulphasalazine withdrawal was