claim as regards *man*. The italics are mine.—I am, etc.,

SELWYN SELWYN-CLARKE

London N.W.6

¹ Royal College of Physicians of London, *Smoking and Health Now*, London, Pitman, 1971.

Toxic Effects of Intermittent Rifampicin

SIR,—We were pleased to read the informative letter from Drs. D. J. Girling and W. Fox (23 October, p. 231). Patients in Hong Kong receiving various doses of rifampicin intermittently appear to have suffered toxic effects similar to those we reported (7 August, p. 343), though generally milder. Furthermore, the original dose of rifampicin used once weekly in the M.R.C. trial described produced sufficiently adverse reactions to necessitate a reduction in dosage. This accords with our belief that the adverse reactions occurring during intermittent regimens are probably dose-dependent.

We, like Drs. Girling and Fox, also feel it would be a great pity if our report were to be interpreted as discouraging further investigations into intermittent rifampicin usage. Furthermore, we have not terminated our investigation of the intermittent use of the drug, as they have stated in the first paragraph of their letter.

It may be reassuring to Drs. Girling and Fox, and any other readers interested in the subject, to re-state the last paragraph of our paper. "It is to be hoped that further large-scale trials of rifampicin, particularly those under the auspices of the British Medical Research Council, will elucidate the problems posed by our findings and determine an effective safe dose to use in intermittent regimens. Meanwhile, we feel unable to continue to use rifampicin at a dose of 1,200 mg twice-weekly." (Our italics.)

Far from terminating our investigation, the rifampicin regimen has been amended. After the first three months of daily treatment, rifampicin 600 mg, isoniazid 900 mg, plus pyridoxin 10 mg, are given twice-weekly. We hope to report on this regimen in due course.—We are, etc.,

GRAHAM POOLE
PETER STRADLING
SHEILA M. WORLEDGE

Departments of Medicine and Haematology,
Royal Postgraduate Medical School,
London W.12

Streptokinase and Myocardial Infarction

SIR,—The study of the European Working Party (7 August, p. 325) on streptokinase in recent myocardial infarction calls for certain criticisms.

The heparin-treated group included more patients with recurrent infarction than did the group treated with streptokinase. The mortality among these was higher than in the rest of the series: eight in the streptokinase group and 20 in the heparin group ($P=0.066$). The remaining mortality in the first episodes of myocardial infarction was 61 in the streptokinase group and 74 in the heparin group. The difference in the mortality assumes a peculiar aspect when one reads that the most striking effect the streptokinase infusion had in diminishing the mortality occurred before infusion was started ($P=0.011-0.0036$, the top significance

in all the series). Afterwards its effect was less remarkable ($P=0.046$).

Only a minute difference was seen in the patients with a history of less than three hours: the mortality in the streptokinase group was 12 out of 108 (11.1%) and in the heparin group 10 out of 82 (12.2%). Also in all the patients with a history of less than 12 hours—the group also studied by Schmutzler—the difference is very slight: the mortality was 50 out of 292 (17.1%) in the streptokinase group and 52 out of 257 (20.2%) in the heparin group. To conclude, in the series no significant difference in mortality was seen in patients with a history of less than 12 hours.

In the older cases, however, the difference in the mortality between the groups is much more marked than this 50 versus 52. It is most remarkable in the group "unknown interval between onset of symptoms and infusion, including preinfusion deaths," in which the mortality in the streptokinase group was 1 out of 2 cases and 19 out of 21 cases in the heparin group.

Further, instead of studying the streptokinase series against a non-streptokinase series the authors have compared the streptokinase series with a series treated with

heparin. This means that even if a difference in the mortality was seen one could equally well conclude that heparin was superior to streptokinase in increasing the mortality as that streptokinase was superior to heparin in reducing it—the conclusion reached by the authors of the article.

Finally, though the work in question did not show any benefit from the streptokinase given, it did show that only by breaking the rules of common sense can one obtain figures indicating that streptokinase would be helpful in myocardial infarction. I cannot agree with the authors even when they say that further trials of streptokinase in myocardial infarction would be desirable. I think this problem has now been investigated fully enough and further studies would only be a waste of time and money.

It really is too bad that streptokinase, which is a very effective and important drug in so many thromboembolic disorders and really opens to us a new era in the fight against them, is also recommended for indications in which its use has no place.—I am, etc.,

RAUNO HEIKINHEIMO

Tampere City Hospital,
Tampere, Finland

Epilepsy and Folate Deficiency

SIR,—Following the finding of macrocytosis in mentally retarded patients with Down's syndrome and in mentally retarded epileptic patients on long-term anticonvulsant therapy in the absence of anaemia,¹ a direct relationship between the degree of macrocytosis and phenobarbitone dosage was demonstrated in the latter group of patients.² Following reports of folate deficiency in psychiatric patients^{3,4} it was decided to investigate red cell folate concentrations in epileptic patients treated with anticonvulsants. Because of reports of the presence or absence of toxicity when pure folic acid was given it was decided that natural yeast should be used, a substance containing many members of the vitamin B group, including folic acid and vitamin B₁₂.

Yeast tablets at the rate of three tablets per day were given to 27 male and 33 female non-anaemic epileptic mentally retarded patients, and to a similar group of non-epileptic mentally retarded patients, after routine blood samples had been collected from them, for a period of 18 weeks, in addition to any other treatment. This period of dosage was chosen since red cell folate deficiency has been produced in normal volunteers in this time.⁵ Conversely, folate is incorporated in the developing nucleated red cell, and is not released again in significant amounts until the senescent cell is broken down at about the end of its 120 days of life in the circulation.

Response of Non-anaemic Patients to Yeast Therapy, Initial Serum Folate being less than 6ng/ml and/or Red Cell Folate being less than 150 ng/ml. Showing Significant Increases in Serum and Red Cell Folate Concentrations in Epileptics ($P<0.001$) and Significant Increase in Red Cell Folate in Non-epileptics ($P<0.001$).

Epileptics		Before yeast	After yeast for 18 weeks
21 Female 20 Male 9 Female 13 Male	Serum folate	3.51 ± 1.02 ng/ml	7.72 ± 10.60 ng/ml $P<0.001$
	Red cell folate	101.67 ± 26.93 ng/ml	184.23 ± 78.06 ng/ml $P<0.001$
Non-epileptic 17 Female 14 Male	Serum folate	4.68 ± 1.34 ng/ml	5.95 ± 1.70 ng/ml $P>0.05$
	Red cell folate	117.17 ± 22.61 ng/ml	190.91 ± 21.00 ng/ml $P<0.001$

the risk of mutual interference between folic acid and anticonvulsants in the intestine.^{8,9}

If our interpretation of our findings is correct, then we have found a simple, harmless, and very cheap method for the treatment and prevention of folic acid deficiency in chronic epileptics, which would also remove the necessity for very large numbers of tedious time-consuming laboratory estimations of serum and red cell folate concentrations in such patients. This treatment might also have a place in the treatment of chronic psychiatric patients and geriatric patients admitted in a poor dietary state.—We are, etc.,

R. D. EASTHAM
J. JANCAR

Department of Pathology,
Fenchay Hospital,
Bristol

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Diagnosis of Cystic Fibrosis

SIR,—Your leading article (28 August, p. 489) regarding the diagnosis of cystic fibrosis mentions that a simple test of the albumin content of meconium may prove useful in screening for cystic fibrosis at birth.

If such a test is used it must be clearly understood that a proportion of patients with cystic fibrosis have no clinical evidence of malabsorption (approximately 10-15%) and that such cases may not show a positive meconium test.

We have recently seen one such false negative case. Meconium from the day old sister of a child with cystic fibrosis was tested according to the Green and Schwachman technique¹ and gave a normal result. Later sweat tests, however, showed elevated sodium and chloride and the infant was proved to have cystic fibrosis, but without significant malabsorption. She responded well to antibiotic and physiotherapy for any pulmonary problems but did not require pancreatic enzyme replacement.—We are, etc.,

A. G. F. DAVIDSON
CHARLOTTE M. ANDERSON

University of Birmingham,
Institute of Child Health,
Birmingham

- 1 Green, M. N., and Schwachman, H., *Pediatrics*, 1968, 41, 989.

Predicting Fetal Maturity

SIR,—Mr. T. Lind (9 October, p. 116) implies that obstetricians cannot work out the gestational age of a fetus from a predicted expected date of confinement (E.D.C.). This is obviously untrue. Indeed, it is a fallacy to believe that it is possible to predict an E.D.C. for a fetus without first assessing its gestational age. Our reason for projecting forward from a maturity estimation to an E.D.C. was in an attempt to assess objectively the value of the predictions by each

of the methods used. Mr. Lind is surely mistaken if he believes that the Nile blue sulphate test is generally regarded as a "historical landmark" and there are recent publications to suggest otherwise.¹⁻³

Mr. Lind's point scoring system of estimating fetal maturity by cytological and biochemical means appeared in print after we had completed our study. If his initial results are confirmed by other workers then it will be a significant contribution towards solving this difficult obstetric problem. However, we are concerned that some of his maturity groupings are so large. For example, the fetal mortality from prematurity at 31 weeks is many times greater than at 34 weeks, but no distinction is made between these gestational ages by his scoring system. As shown by our paper, maturity estimations by ultrasonic cephalometry have an almost identical predictive accuracy to those made from optimal dates. Most obstetricians would settle for that at the present time.—We are, etc.,

ROSEMARY A. UNDERHILL
J. M. BEAZLEY
S. CAMPBELL

Institute of Obstetrics and Gynaecology,
University of London,
Queen Charlotte's Hospital,
London W.6

- 1 Gordon, H. J., and Brosens, I., *Obstetrics and Gynecology*, 1967, 30, 652.
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Solar Flares and the Concorde

SIR,—Your leading article on "Solar Flares and the Concorde" (16 October, p. 127) is rather inaccurate and misleading. I am rather surprised by some of the inaccuracies since the parameters of Concorde are by now well publicized.

May I begin by saying that the Americans (we have not got a manned space programme in this country) require, I believe, an altitude attainment of 200,000 ft (60,960 m) as part of the requirement to qualify as an astronaut. There is enormous difficulty for a supersonic passenger to get near this figure.

Primarily, I would remind you that Concorde will cruise at about 58,000 ft (17,678 m: atmospheric pressure, 80 g/cm²) not as stated in your leader, and considerable attention has been given to the question of solar flares as outlined in previous communications of mine.^{1,2} Recently the subject has been reviewed by the International Congress on Protection against Accelerator and Space Radiation, CERN, in April 1971, and Fuller and Day³ gave an authoritative review. Solar flares are now well recognized. Their forecasting, though improved, is still considered unreliable; their energy spectrum and quality are unpredictable. Your leader is wrong in saying we are at the end of a safe period; solar maximum was in 1969, a minimum will occur in about 1975. Let me add, however, that we have had a remarkably quiet solar maximum. Concorde's initial flights have been statistically in the worst period.

I presume your leader implies the general population when quoting 0.5 rem as an I.C.R.P.⁴ maximum permissible radiation dose. A classified worker can, of course, be exposed to 5 rem per year, but I hasten to

add that no one expects crew or passengers to approach anything like these doses. Representative forecasts⁹ are that Concorde crew on maximum flying hours will get a dose of 0.65 rem/year at high and 0.3 rem/year at low latitudes and that a well-travelled passenger (50,000 miles) will collect 0.041 and 0.018 rem/year. The occurrence of solar flares will be detected by an airborne radiation warning meter (A.W.R.M.), and with appropriate action on the part of the crew¹ a very tiny amount of extra radiation dose will be incurred. Later the leader acknowledges solar flares as rare events, and actual measurements are confirming our predictions. Concorde 002 is currently collecting less than 1 milli-rem/hr at high altitude, and this is almost identical to I.C.R.P.⁸ postulations.

Astronaut dose rates are very different in magnitude, and the problems have been surveyed by Janni and Holly,⁵ Pickering,⁶ and Berry.⁷ However, it would appear that even a very severe flare would not jeopardize safe return of the capsule from the moon surface, nor possibly in fact total mission attainment.

Finally, may I say that the leading article's 30° nose dive is frighteningly ludicrous. I have already indicated^{1,2} that should Concorde meet one of these rare solar events (pessimistically 1-2/year) then, following warning from the A.R.W.M., descent can occur from 56,000-58,000 ft (17,068-17,678 m) to 45,000 ft (13,716 m) in about 5 min, including crew appreciation time. One of the most violent solar flares recorded was in 1956, and this produced a calculated dose rate of 2 rad/hour at 60,000 ft (18,288 m), so that even if the build-up were instantaneous, then crew and passengers at this height would have only incurred a few millirems extra dose before being down to a shielded height.

For this rapid descent may I assure your readers that at no time will the cabin of Concorde change in elevation to below the horizon; deceleration will be about 0.2 g horizontal, with unnoticeable changes in cabin conditions. In fact, Concorde for this manoeuvre shows less cabin tip-down than, for instance, a DC8 (2°) or VC10 (4°). I do not think that we would ever contemplate marketing an aeroplane that needed to deposit its passengers' gin-and-tonics on the cabin roof as an operating procedure. Regrettably for your leader, Concorde is as sedate as present subsonic jets, and I hope you will agree that radiation hazards, though possibly present on rare occasions, are well catered for (A.R.W.M.) and readily and comfortably avoided.—I am, etc.,

F. J. ENSELL

Senior Medical Officer

British Aircraft Corporation Ltd.,
Bristol

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