Dr. Godfrey described the increased inhibition of bronchoconstriction after 60 mg indomethacin, compared with 50 mg taken by the same patient on a different occasion as a “quite extraordinary dose-related phenomenon.” Admittedly the dose-response curve in this one patient appears to be steep, newsmore so than in the controls, but it is not clear what one would expect of a drug with antagonist activity. Many more experiments with patients receiving several doses of indomethacin seem necessary to determine that this dose relationship is unusual. Professor Bianco and his colleagues claimed that indomethacin prevented specific airway conductance falling below the pretreatment control level in all cases. This is inconsistent, however, with the results published for cases 2, 3, 9, and 10 in their table III. Fortunately, these inconsistencies do not detract from the authors’ overall conclusions. From our analysis of their work we would conclude that under the limitations imposed by their methodology the evidence is consistent with indomethacin preventing exercise-induced bronchoconstriction in five patients, decreasing it in five, and not inducing improvement in one. It would be of interest to learn from the investigators how the patients’ symptomaticity was affected by alpha-blockade. For it could be argued that indomethacin abolished the asthmatic symptoms it prevented exercise-induced “asthma” while only partially antagonizing exercise-induced “bronchoconstriction.”—We are, etc.,

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Drugs for Rheumatoid Arthritis

Sir,—We are interested in the recent article by Professor H. L. F. Currey and others (28 September, p. 763) reporting a comparison of gold, cyclophosphamide, and azathioprine in the treatment of rheumatoid arthritis. Such studies are essential if the management of these dangerous and difficult remedies is to be rationalized. However, the conclusions that are reached suggesting advantages in the case of azathioprine and cyclophosphamide are dependent on the statistical interpretation of the data and it is clear that there is more than one possible interpretation. We would suggest that interpretation could differ in the following ways.

Table II shows good evidence that the randomization has not been controlled properly for “number of joints involved.” The use of percentage reduction is dangerous when applied, as here, and not leading to any difference in their initial scores, particularly when some of these are near zero.

In Table III the use of the $x^2$ test is valid here, but Yates’s correction for continuity should not have been applied, as here, since this is consistent with the chi-squared statistics: azathioprine v. gold, $x^2=3.72$ (not significant); cyclophosphamide v. gold, $x^2=4.66$ (significant at 5% level). Nevertheless, the appearance of six patients on gold with marked deterioration is noteworthy. The explanation may be that the patients on gold were in a more advanced stage of the disease on average.

In Table IV the doses of steroid at entry differ considerably so that to compare mean reduction of dose is scarcely valid. An interesting comparison would be between the actual levels of prednisolone being taken at 72 weeks and hence the basic data would be very helpful here.

These points all underline the desirability of “blocking” in clinical trials—thus it is to be hoped that the patients should be divided up into groups which are more or less homogeneous with respect to severity of disease and prognosis before randomization. Separate randomization for each group is then called for.

It is felt that, while not diminishing the value of the study, these points would afford some modifications to the conclusions, in particular the conclusion that these anti proliferative agents offer an advantage in the management of the early stages of rheumatoid arthritis.—We are, etc.,

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Dr. W. Southgate writes:

Sir,—My thanks for your kind offer. It is a fine prospect and I am delighted you are to be the Chairman of the Local Rheumatism Committee.

Professor A. A. Ingelfinger reports in the New England Journal of Medicine (29 August) that the clinical characteristics of polyarteritis nodosa and microscopic polyangiitis are similar, and that the number of patients with microscopic polyangiitis has been underestimated. The discovery is timely and important. I hope that you may like to keep the matter in mind as you plan the work of the Committee.

Yours faithfully,

G. T. DIXON

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BENIGN INTRACRANIAL HYPERTENSION ASSOCIATED WITH NITROFURANTOIN THERAPY

Sir,—Benign intracranial hypertension following nitrofurantoin (Furadantin) therapy does not seem to have been reported previously. We have recently produced the case of a 10-month-old infant who was admitted to the paediatric services of this hospital with bulging of the anterior fontanelle which had first been noticed by the parents two days earlier. The infant had been treated for a urinary tract infection with nitrofurantoin 25 mg thrice daily for seven days before admission. There was no history of head injury or ear discharge or of the administration of drugs other than nitrofurantoin. The patient's weight was 20 lb (9 kg), length 78 cm, and head circumference 46 cm. He was conscious but responded to stimulation poorly. He was in no apparent distress and accepted feeds well. The anterior fontanelle measured 3.0 x 2.5 cm and was bulging and tense. There was no suboccipital nuchal stiffness and Kernig's sign was negative.

Except for the dull sensorium there was no other neurological deficit. E.N.T. examination was normal. Investigations: haemoglobin 10.0 g/100 ml; total leucocytes 9,600/mm$^3$; polymorphs 40%, lymphocytes 58%, monocytes 2%; cerebrospinal fluid pressure 40 cm H$_2$O; cells absent, protein 25 mg/100 ml, sugar 50 mg/100 ml.

Nitrofurantoin was discontinued and the baby was started on acetazolamide 1 tablet (62.5 mg) twice daily. General activity improved over the next 72 hours. The anterior fontanelle, however, lasted until normal only after the age of 14 months the infant was developing normally and his head circumference was 48.5 cm.

Benign intracranial hypertension was the most likely diagnosis in this infant. In view of no other known predisposing factor it seems possible that this was a complication of nitrofurantoin therapy. —We are, etc.,

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Distribution and Supervision of Oral Contraceptives

Sir,—The letter you published (19 October, p. 161), subscribed by 17 esteemed gynaecologists, was considered by the Surrey Local Medical Committee at its meeting on 22 November. They passed a resolution (which has been forwarded to the General Medical Services Committee for information) stating their firm opinion that the prescribing of oral contraceptives should remain the responsibility of qualified medical practitioners.

My committee feels that the importance of this opinion outweighs all arguments in favour of widening prescribing responsibility and that it is unable to support the recommendations proposed in the letter.—I am, etc.,

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