Adverse Reactions to Beta-adrenergic Blockade

SIR,—Your leading article (6 April, p. 3) prompts me to report the clinical details of a patient referred to me this year.

The patient, a 61-year-old man, had noticed progressive shortness of breath on exertion for 18 months. At about the same time he had been put on oxprenolol 40 mg three times a day for angina pectoris. He had no further chest pain but had begun to get breathless. He had had a productive cough for many years but this had improved when he stopped smoking three years ago. A chest x-ray suggested emphysema only. Ventilatory tests when the patient was seen on 14 February were FEV₁ 1.2 l. and FVC 2.4 l. These were unchanged after isoprenaline, aerosol. Oxprenolol was stopped on 19 February. On 8 April the FEV₁ was 1.2 l. and the FVC 2.5 l. After isoprenaline aerosol they were 1.6 l. and 3.1 l. respectively.

Initial assessment suggested fixed (irreversible) airways obstruction. There was no left ventricular failure. On stopping oxprenolol the patient felt much better. The reversibility of airways obstruction was unexpected. It may be that beta-adrenergic blockage aggravates asymptomatic airways obstruction in patients other than those with bronchial asthma—a recognized contraindication, as mentioned in your article.—I am, etc.,

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Sodium Citrate and Hypernatraemia in Infancy

SIR,—Prescribing sodium citrate tablets for vomiting and other feeding problems in infancy is still fairly common practice.

We found that the addition of one 125-mg sodium citrate tablet (B.P.) to a 6-oz (170-ml) and to a 4-oz (114-ml) full-cream milk feed raised the sodium concentration from 22 mmol/l. to 28 mmol/l. and 32 mmol/l. respectively. The feeds had been freshly made up according to the manufacturers' instructions. Recent reports have drawn attention to the frequency with which mothers make up feeds using excessive amounts of milk powder. Sodium concentrations of over 30 mmol/l. were found in milk feeds sampled by Taitz and Byers.¹ The addition of sodium citrate to an incorrectly made up feed must raise the sodium concentration to a dangerous level.

We feel that the indiscriminate use of sodium citrate tablets may contribute to the risk of hypernatraemia in infancy and should be discouraged.—We are, etc.,

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¹ Taitz, L. S., and Byers, H. D., *Archives of Disease in Childhood*, 1972, 47, 257.

Thromboembolism and Oral Contraceptives

SIR,—Your leading article (9 February, p. 213) and the recent letter from Professor M. P. Vessey and Sir Richard Doll (26 January, p. 158) cite the major references

on this controversial theme. May I also draw attention to a recent book¹ in which the two sides of the case are presented by Dr. V. A. Drill and Sir Austin Bradford-Hill and discussed by a number of leading international authorities? The balance of opinion appears to be that the link between thromboembolic disease and oral contraceptives is real and is proportional to the daily oestrogen dose. Women of blood group A are much more at risk than those of group O.

The question that cannot yet be answered is whether the two oestrogens used in oral contraceptives (ethynylestradiol and mestranol) are associated with different risks at any particular dose. A further problem is whether the risk associated with either oestrogen is modified by the particular progestogen with which it is combined. There are about half a dozen chemically different progestogens used in oral contraceptives, while some are used at two or three different dose levels. Examination of the data published by Inman *et al.*² suggests that progestogens do indeed modify the oestrogen effect.

The biochemical basis for an increased thromboembolic risk with oral contraceptives is still uncertain, but marked changes in blood coagulation and fibrinolytic factors occur in women during treatment.³ Recent studies^{4,5} of oestrogen-sensitive proteins in plasma from women receiving various contraceptive steroids indicated that mestranol had less effect than the same dose of ethynylestradiol, while the addition of norgestrel actually reversed some of the changes induced by oestrogen alone. Other progestogens did not share this property.

The accompanying figure illustrates the effect on blood coagulation factor VII of changing from an oral contraceptive containing 1 mg norethisterone acetate (Minovlar) to another containing 0.25 mg D(−)-norgestrel (Nordiol) or vice versa. Both contain 0.05 mg ethynylestradiol. The subjects were healthy young women who had been taking oral contraceptives for at least three months. Factor VII was assayed on specimens collected during the last

cycle on the original product and again after at least one cycle on the new product. Results are expressed as percentages of the value for pooled plasma from untreated women. While numbers are small, all who changed to the norgestrel-product showed a decrease in factor VII, while those who changed from this product showed an increase.

These findings suggest that norgestrel-containing oral contraceptives have less effect on components of the blood coagulation mechanism than products with other progestogens. It is possible that norgestrel will therefore reduce the risk of thromboembolism associated with oral contraceptives. There has been insufficient time from the introduction of norgestrel-based products in most countries for any effect on the incidence of thromboembolisms to be determined.—I am, etc.,

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¹ Briggs, M. H., and Diczfalusy, E. (eds.) *Pharmacological Models in Contraceptive Development*. Stockholm, Karolinska Institutet, 1974.

² Inman, W. H. W., *et al.*, *British Medical Journal*, 1970, 2, 203.

³ Bingel, A. S., and Benoit, P. S., *Journal of Pharmaceutical Science*, 1973, 62, 179.

⁴ Briggs, M. H., and Briggs, M., *Life Sciences*, pt. I, 1972, 11, 949.

⁵ Briggs, M. H., and Briggs, M., *Biochemical Pharmacology*, 1973, 22, 2277.

Evolution of an Examination

SIR,—“I learn all my surgery from those chaps sitting the Fellowship,” a distinguished chief of mine used to say, and examinations should play an important part in the continued education of examiners themselves.

With multiple choice questions, in addition to the intensive mathematical and computer study being devoted to them, it is surely essential for there to be opportunity of checking and discussing what the examiners think may be the correct answers, and this can be done only if the questions actually set are regularly published. We are told (13 April, p. 104) that out of 3,000 M.R.C.P. (U.K.) questions kept in a bank under lock and key, only 200 have been published.

The enormous number of possible questions and the rapid changes in medicine make it improbable that any candidate could learn by heart a battery of answers to likely questions, as used to happen with some law exams. Also the chances of there being any black market in old questions would be eliminated.—I am, etc.,

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Radiographic Location of the Dalkon Shield

SIR,—Uterine perforation is a potentially dangerous complication of the intrauterine contraceptive device. The exact incidence of perforation is not known. Hall¹ reported an incidence of 0.5% perforations in 3,988 insertions. Suspicion of perforation is aroused when the threads cannot be seen at the cervix or have shortened appreciably, and location of the device is then essential. If this is not achieved by pelvic examination or by probing the uterus, radiography is employed to exclude unnoticed expulsion.