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.,

AVINASH MITHAL

Central Lincolnshire Chest Unit,
Lincoln

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.,

ROSEMARY S. SHANNON
ROBERT P. C. BARCLAY

Paediatric Unit,
Stobhill Hospital, Glasgow

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.,

M. H. BRIGGS

Biochemistry Department,
Alfred Hospital,
Melbourne, Australia

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.,

BRYAN WILLIAMS

Chichester

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.

Some intrauterine devices are easily seen on a plain x-ray. The Dalkon Shield, however, has a lower level of radio-opacity, and unless certain x-ray techniques are used the device may be difficult or impossible to see. The radio-opacity is achieved by the addition of barium sulphate, which has the undesirable effect of rendering the device more brittle. To enable the Dalkon Shield to be bent during insertion through the cervical canal it must be as thin and as pliable as possible, and the concentration of barium sulphate is therefore kept lower than in other devices.

Three techniques for the radiographic location of the Dalkon Shield are suggested for the average-sized patient: (1) "Regular" technique: machine setting 200 mA, 76 kV, 3/5 sec. (2) "Soft-tissue" technique A: machine setting 200 mA, 76 kV, 1/2 sec. (3) "Soft-tissue" technique B: machine setting 200 mA, 70 kV, 2/5-1/2 sec. We would recommend the use of one of the above radiological techniques should radiographic location of a Dalkon Shield be required.—We are, etc.,

URSULA E. MOUNTROSE
W. L. WHITEHOUSE

Academic Unit of Obstetrics,
Queen Mary's Hospital,
London S.W.15.

¹ Hall, R. E., *American Journal of Obstetrics and Gynecology*, 1967, **99**, 808.

Musical Bumps

SIR,—The patients Dr. P. Curtis describes (27 April, p. 226) with "guitar nipple" must surely have received faulty instruction in positioning the instrument. The classical guitar is played by a right-handed player with the instrument resting on the left knee and the base of the instrument cradled inside the right knee. The top edge of the soundbox should then overlie the region of the left nipple. Thus a right-sided player would be expected to develop left-sided mastitis. Perhaps the concept of "total patient care" should include pointing out the error of these players' ways.—I am, etc.,

JOHN MEYRICK THOMAS

St. Bartholomew's Hospital,
London E.C.1

SIR,—We wonder if Novalis was fully aware of the significance of his aphorism, "Every sickness is a musical problem." Cases of "guitar nipple" (27 April, p. 226) and "cello scrotum" (11 May, p. 335) have been reported. We should like to add a more serious condition, "guitarist's groin."

A classical guitarist aged 24 was admitted with a deep venous thrombosis of his left calf and thigh. Quite marked varicose veins in this leg were also noted. He was used to 4-6 hours of daily practice in the sitting position, with the left leg fully flexed and the guitar belly compressing the medial aspect of the thigh. Stasis in the long saphenous vein was inevitable and provided an aetiological clue.—We are, etc.,

ROBERT SEMPLE
JEREMY GILLINGHAM

Ninewells Hospital, Dundee

SIR,—Did Dr. J. M. Murphy's patient (11 May, p. 335) hold his cello in an un-

orthodox way? Personal observation suggests that the body of a cello is normally separated from the scrotum by several centimetres. Perhaps the patient supplemented his meagre musician's salary by sweeping chimneys.—I am, etc.,

PETER J. SCHEUER

Royal Free Hospital,
London W.C.1

Amitriptyline and Imipramine Poisoning in Children

SIR,—In reply to Dr. R. W. Newton (20 April, p. 176) we should explain more fully when and why we consider diphenylhydantoin (DPH) may be of use in treating tricyclic antidepressant poisoning.

We agree with Matthew¹ that muscular twitching and hyperexcitability may precede convulsions and should be treated. He suggests the use of phenobarbitone to prevent convulsions, but others have stressed the potential respiratory depression of barbiturates² and we feel that parenteral DPH is a good alternative. According to Matthew¹ sinus tachycardias need not be treated, but excessive ventricular extrasystoles and possibly sinus tachycardia precede more severe dysrhythmias. Obviously several drugs are available to prevent and treat these dysrhythmias³ and include intravenous practolol, DPH, and procainamide.

Thus if there are signs of impending dysrhythmias, either cardiac or of the central nervous system, parenteral DPH may be a useful prophylactic agent. The more direct approach of opposing the anticholinergic effects of tricyclic antidepressants with an acetylcholinesterase inhibitor which can cross the blood-brain barrier—namely, physostigmine salicylate^{4,5}—is obviously indicated in severely ill patients. But this is not without its dangers, and many side effects have been observed, including oversalivation, vomiting, convulsions, and bradycardia. Perhaps physostigmine salicylate should be reserved for toxic effects refractory to other forms of treatment.

In the wider context of paediatric care we support the view of Drs. K. M. Goel and R. A. Shanks (23 March, p. 575) that there should be a more critical approach to the use of tricyclic antidepressants in the treatment of enuresis and that careful warning should accompany their prescription.—We are, etc.,

R. J. POSTLETHWAITE
D. A. PRICE

Booth Hall Children's Hospital,
Manchester

¹ Matthew, H., *Prescribers' Journal*, 1971, **11**, 120.

² Rasmussen, J., *Lancet*, 1965, **2**, 850.

³ Matthew, H., *Medicine*, 1972, **51**, 273.

⁴ Rumack, B. H., *Pediatrics*, 1973, **52**, 449.

⁵ Newton, R., *British Medical Journal*, 1974, **2**, 176.

Was it a Drug? (Optimax)

SIR,—Under the heading "Was it a Drug?" (*Supplement*, 13 April, p. 16) there appeared a report of a decision by referees that in several cases general practitioners had been surcharged under regulation 16 of the N.H.S. (Service Committees and Tribunal) Regulations 1956 in respect of part of the constituents making up Optimax Powder. I think your readers should be aware that in the three cases where the

practitioners were represented by the Medical Defence Union applications have been made to the High Court for a writ of certiorari on the basis that the referees exceeded their jurisdiction and that their finding is erroneous in law. These cases are therefore sub judice and, pending the hearing of the application, the Department of Health has, I understand, deferred all action about numerous other similar cases.—I am, etc.,

J. W. BROOKE BARNETT
Secretary,
Medical Defence Union

London W.1

Adjustment of Plasma Calcium Measurements

SIR,—Dr. A. M. Parfitt (16 March, p. 520) suggested that the formulae relating total calcium to albumin concentration in plasma or serum proposed by Dr. E. M. Berry and others (15 December, p. 640) and by ourselves (p. 643) might introduce significant errors if applied when ionized calcium values were high or low. He is right. The slope of the regression of total calcium on albumin is steeper than normal when albumin is varied in the presence of a high ionized calcium and shallower than normal when ionized calcium is low. However, adjusted values are higher than they should be when the ionized calcium is high and lower than they should be when it is low, so, if anything, the clinical usefulness of the adjustment is enhanced.

We agree with Dr. Berry and the U.C.H. group (6 April, p. 53) that the selection of an albumin level as a point of reference for the adjustment of total calcium is arbitrary. We had considered avoiding the problem by suggesting that the adjustment should be to zero albumin concentration (total calcium minus the product of the slope of the regression and the albumin concentration). This would have given "unbound calcium" and would bring the Leeds and the U.C.H. adjustments closer together. However, such values would be unfamiliar to clinicians.

Dr. H. M. Hodgkinson (27 April, p. 223) asks whether we can discount the possibility that our estimate of the regression of calcium on albumin is biased because hypoalbuminaemia is often associated with hyperglobulinaemia, and globulins may contribute to the protein-binding of calcium. The association in our data between albumin and total globulins is a relatively weak one ($r=0.299$ for 200 pairs). Pedersen¹ calculated that less than 4% of normal total plasma calcium is bound to globulins, while he found negligible binding to the gamma-globulins in hypergammaglobulinaemia—by far the commonest globulin abnormality in our patients. Furthermore, the intercept of our regression line at zero albumin concentration, 5.7 mg/100 ml, is close to reported values for normal plasma ultrafiltrable calcium,^{2,4} indicating that our regression coefficient is not in serious error.

However, we should like to emphasize that we excluded patients with the nephrotic syndrome from our investigation and stated that our adjustment cannot be applied to them. Nephrotics have higher calcium levels than patients with the same degree of hypoalbuminaemia from other causes,^{5,6} possibly owing to an increased plasma concentration