

We were interested to read the comments made by Dr. D. J. S. Hunter (27 January, p. 229) and by Drs. D. J. S. Hunter and K. C. Vaughton (2 June, p. 552) concerning placental bed retraction, especially regarding the timing of the pH fall in the second stage. We accept that placental bed retraction may well be important in the development of fetal anoxia, but whatever the cause, the result is the same, so early detection must be the main objective.

Drs. P. Donnai and A. D. G. Nicholas (27 January, p. 229) are concerned that compression of the buttock and the associated venous stasis may contribute to a falling buttock pH and, therefore, not reliably reflect the fetal condition. In our experience there is a very good correlation between the buttock pH and the subsequent fetal condition, provided a free flow of blood is obtained. As we pointed out in our paper, oedema gives a falsely high reading.

We are aware of the work of Drs. T. Wheeler and K. R. Greene (30 March, p. 802) and we have already discussed with them the relative merits of fetal blood sampling as against continuous heart monitoring. With further experience we have no reason to change our opinion that fetal blood sampling gives an earlier warning of fetal anoxia. Later and gross changes are detected by the cardiocotograph recordings, but as our aim is to expedite delivery in those infants which are found to be anoxic early in the second stage, we feel that fetal blood sampling is of greater value.—We are, etc.,

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### Metabolic Effects of Oral Contraceptives

SIR,—The report by Drs. P. G. T. Bye and M. Elstein (19 May, p. 389) on the efficacy and side-effects of a combined-type oral contraceptive containing a daily dose of 0.03 mg ethinylestradiol appears to show no significant differences between this product and formulations containing the same amount of progesterone plus 0.05 mg ethinylestradiol. As they do not report on comparative metabolic effects, we feel our findings on the dose-related effects of oral contraceptive components on plasma proteins may be relevant.<sup>1,2</sup>

We have administered the two components (ethinylestradiol and norgestrel) separately and together at various doses and measured changes in the concentrations in the plasma of proteins known to be sensitive to exogenous oestrogen. A summary of our results is given in the table. Each woman received 21 consecutive oral doses of a particular steroid formulation. Blood was collected immediately before treatment and again 21 days later. Plasma proteins were

determined on each specimen. Methodological details are given elsewhere.<sup>3</sup>

It will be seen from the table that concentrations of each protein were not significantly different (as judged by Student's *t* test) at the 0.03 and 0.05-mg ethinylestradiol doses in the presence or absence of norgestrel. It should be noted, however, that the presence of norgestrel has a highly significant effect ( $P < 0.001$ ) in each case on the oestrogen-induced changes.<sup>2</sup>

As the clinical and biochemical effects of 0.03 mg ethinylestradiol daily in oral contraceptives appears to be no different from those of 0.05 mg daily, it will be interesting to see from epidemiological studies whether the use of low-oestrogen oral contraceptives has any effect on the incidence of thromboembolic disease.—We are, etc.,

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1 Briggs, M. H., and Briggs, M., *Contraception*, 1971, 3, 381.

2 Briggs, M. H., and Briggs, M., *Life Sciences*, 1972, 11, (1) 949.

3 Briggs, M. H., and Briggs, M., *Biochemistry Pharmacology*. In press.

### Copper Absorption from I.U.C.D.s

SIR,—While the use of an intrauterine contraceptive device in a nulligravida (Mr. D. G. Bluett, 9 June, p. 615) might be debated, we do not agree with the author's statement that "the degree of copper absorption is unknown" in women using the Gravigard copper 7 I.U.D.

Significant changes in serum levels of copper in women using copper I.U.D.s have not been detected; Hagenfeldt<sup>1</sup> has reported that the average loss of copper from the copper I.U.D. was 45 µg/day and that only the endometrial copper levels were elevated and these returned to normal within the first cycle following the removal of the copper I.U.D.

We have made a comparison of serum levels of copper caeruloplasmin (the main copper-carrying protein) and caeruloplasmin oxidase activity in three groups of women in their active reproductive years. Two groups of women were using I.U.D.s—a copper-releasing I.U.D. (i.e., Gravigard copper 7) or a Dalkon Shield which contains copper within its matrix as a support for the plastic but which is not released to any extent. The third group of women were taking combined oral contraceptives, either 1.0 mg norethisterone + 50 µg ethinyl oestradiol or 0.5 mg norethisterone + 50 µg ethinyl oestradiol. There was no statistically significant difference in the serum levels of copper,

caeruloplasmin, and caeruloplasmin oxidase activity in those women who used the two different I.U.D.s. However, in the women taking the oral contraceptive preparations these parameters were markedly elevated, the biological significance of which remains to be elucidated.

Further studies of copper and copper-bearing proteins in the menstrual cycle and in different endocrine states and at intervals after the continued use of a copper-releasing I.U.D. are in progress.—We are, etc.,

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1 Daunter, B., and Elstein, M., *Journal of Obstetrics and Gynaecology of the British Commonwealth*. In press.

2 Hagenfeldt, K., *Contraception*, 1972, 6, 191.

### Contraceptives on the N.H.S.

SIR,—Perhaps some heat might be taken out of this debate if we distinguish between contraceptive equipment and contraceptive advice.

The unquestioning dishing out on demand of condoms, or pills for that matter, may or may not be an expedient social service. It is not conscientious clinical medicine. Doctors may properly resent being expected to do it, by either patient or state.

In contrast, skilful contraceptive advice-giving can be constructive whole-patient medicine indeed. It offers the opportunity to discuss the patient's attitude to sexuality and to personal relationships. It can be used to aid the stability of those relationships and thus of the family and of society. Unfortunately this is rarely part of the crowded medical school curriculum. Despite the availability of Family Planning Association post-graduate seminars, few doctors have the time, the training or even the taste for this minor specialty. The Act will soon be upon us and we must do what we can. But perhaps we should aim to work in future towards a situation where only doctors so trained should do this work, as with the obstetric list? Behind its trendy public facade, the F.P.A. has in its doctors and nurses a fund of conscientious professional expertise which would make training programmes perfectly feasible.—I am, etc.,

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SIR,—Surely the answer to the condom controversy is for G.P.s to prescribe condoms one at a time. In this way many patients will be discouraged from wasting their doctor's time, for 20p is a high price for one condom.—I am, etc.,

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### Renal Failure in Combined Gentamicin and Cephalothin Therapy

SIR,—We would like to make the following comments about the paper by Professor J. P. Fillastre and others (19 May, p. 396) describing acute renal failure during treatment with high doses of gentamicin and cephalothin.

Effect of Oral Contraceptive Steroids on Plasma Proteins

Steroid Administered	No. of Women	Dose of Ethinylestradiol (mg/day)	Change in Protein Concentration (% pre-treatment value after 21 oral doses)		
			A	B	C
Ethinylestradiol alone	11	0.05	195 ± 21	76 ± 24	70 ± 23
	9	0.03	185 ± 31	78 ± 17	71 ± 25
Ethinylestradiol + d (-)-norgestrel (0.25 mg/day)	15	0.05	138 ± 38	94 ± 10	81 ± 23
Ethinylestradiol + d (-)-norgestrel (0.25 mg/day)	10	0.03	130 ± 46	96 ± 13	84 ± 26

Protein A = caeruloplasmin, B = haptoglobin, C = orosomucoid.  
Values given are means ± 1 S.D. d (-)-Norgestrel has twice the progestogenic activity of dl-norgestrel.

(1) The authors fail to mention the work of Schultze *et al.*,<sup>1</sup> who described six patients developing acute renal failure which was attributed to gentamicin therapy though all six were receiving cephalothin simultaneously.

(2) The choice of antibiotic therapy in the three cases they quote gives cause for alarm. Two of the patients seemed to be suffering from gastroenteritis and one wonders whether the use of any antibiotic, systemically or orally, let alone gentamicin and cephalothin, was indicated. Case 3, a patient with staphylococcal septicaemia, should presumably have received benzylpenicillin or cloxacillin (methicillin), depending on sensitivities, unless the organism was methicillin-resistant or the patient allergic to penicillins. If either of these possibilities obtained, why was a combination of gentamicin and cephalothin used? A methicillin-resistant *Staphylococcus aureus* would not respond to a cephalosporin in any case; and in the allergic patient either drug would be sufficient alone.

(3) The authors state that "a combination of these antibiotics [gentamicin and cephalothin] in the treatment of severe Gram-negative infections is fully justified." Why is this so? What does cephalosporin add to gentamicin in treating Gram-negative infections?

(4) In all three cases the patients received extremely prolonged courses of both drugs in high doses. Even if these patients had been suffering with severe Gram-negative sepsis, would such a prolonged course be necessary? In our combined experience of treating serious sepsis in hospital patients we find that gentamicin is usually sufficient when administered for 7-10 days, providing that any relevant underlying pathology is also dealt with.

(5) Another disturbing feature of this paper is the apparent total failure to monitor gentamicin therapy by assaying serum concentrations. A number of assay methods now exist, many of which are within the scope of routine medical microbiology laboratories. Surely a hospital which employs immunofluorescent staining techniques on renal biopsy specimens to detect antibodies to gentamicin and cephalothin should be able to assay those antibiotics in serum. In our own experience we find, in most adult patients, that a dose regimen of 5 mg/kg/day (in divided doses) is needed to achieve adequate serum concentrations (5-12 µg/ml). However, with continued therapy, even in those with normal renal function, the same dose may lead to gradually increasing serum concentrations, particularly after 7-10 days. Continued laboratory monitoring is essential for detecting this trend so that dosage may be modified. Thus laboratory assay forms an integral part of gentamicin therapy.

(6) No mention is made of ototoxicity in any of these patients, even though each had a prolonged course with a high dose. Even the absence of ototoxicity would be significant in these patients.

(7) A final point which should be clarified is whether the renal failure really was of sudden onset "out of the blue," or whether there were premonitory signs of proteinuria, urinary casts, rising blood urea, falling urine output, etc. If there were such warnings it would be valuable to look for them.

In conclusion we would like to note that

gentamicin is currently the drug of first choice for treating life-threatening Gram-negative sepsis because of its broad spectrum and rapid bactericidal activity. However, its use should be monitored by laboratory assay of serum concentrations (a) to achieve adequate dosage and (b) to avoid toxicity. It should not be used inappropriately or indiscriminately, while combinations of antibiotics should always be chosen for definite reasons.—We are, etc.,

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<sup>1</sup> Schultze, R. G., Winters, R. G., and Kauffman, H., *Journal of Infectious Diseases*, 1971, 124 (Suppl.) p. 145.

SIR,—I read with interest the report by Professor J. P. Fillastre and others (19 May, p. 396) describing three patients with acute renal failure associated with combined cephalothin and gentamicin therapy. Recently I managed a similar problem.

A 68-year-old man was admitted with hyperosmolar non-ketotic diabetic coma and a *Klebsiella* sp. septicaemia. On admission his blood urea was 123 mg/100 ml. He was started on intravenous cephalothin 130 mg/kg/day and intramuscular kanamycin 24 mg/kg/day. After four days probenecid was added in a dose of 0.5 g 12-hourly. The diabetic problem was easily managed and his renal functional impairment rapidly improved, with the blood urea falling within four days to 43 mg/100 ml and the serum creatinine to 0.9 mg/100 ml. However, after 10 days of this regimen his fever was not adequately controlled and the kanamycin was replaced by intramuscular gentamicin in a dose of 2 mg/kg/day. The cephalothin and probenecid were continued in the same dose. At this time the blood urea was 33 mg/100 ml and serum creatinine 1.1 mg/100 ml. After seven days of treatment with the combination of cephalothin, gentamicin, and probenecid the blood urea was 85 mg/100 ml and the serum creatinine 2.0 mg/100 ml. After 10 days the patient developed acute oliguric renal failure and was transferred to this unit. The patient had received no frusemide or other diuretic. The acute renal failure persisted for 24 days and required six peritoneal dialyses. His renal function thereafter improved but he had several other medical problems which resulted in death due to bronchopneumonia. At necropsy 39 days after the onset of the acute renal failure and 49 days after the commencement of the cephalothin and gentamicin the renal histology was consistent with a resolving acute tubular necrosis, particularly of the proximal tubules. Minor diabetic glomerular changes were also present.

The patient reported here compares very closely with those described by Professor Fillastre and also by Bobrow *et al.*<sup>1</sup> and Kleinknecht *et al.*<sup>2</sup> The gentamicin dosage in this case was lower than in the other reported cases, but the dose of cephalothin was comparable and the levels of the latter would have been increased by the administration of probenecid. It would seem most likely that the renal lesion in these patients is the result of potentiation of cephalothin nephrotoxicity by the addition of gentamicin. This antibiotic combination is popular in many units and it would appear important to prevent the serum level of cephalothin from becoming excessive. It is also important to be aware that cephalothin nephrotoxicity may

be considerably enhanced by the administration of frusemide.<sup>3</sup>—I am, etc.,

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<sup>1</sup> Bobrow, S. N., Jaffe, E., and Young, R. C., *Journal of the American Medical Association*, 1972, 222, 1546.

<sup>2</sup> Kleinknecht, D., Ganeval, D., and Droz, D., *Lancet*, 1973, 1, 1129.

<sup>3</sup> Linton, A. L., Bailey, R. R., and Turnbull, D. I., *Canadian Medical Association Journal*, 1972, 107, 414.

### Prevention of Pulmonary Embolism

SIR,—In your excellent leading article (7 April, p. 1) you state that the "hopeful but less critical" surgeon will use prophylactic methods provided that they are not associated with increased morbidity. My recent experience is that antithrombotic regimens may not only cause significant bleeding but also fail to prevent pulmonary embolism.

For four months of 1972 one litre of dextran 70 was administered intravenously over 12 hours after major gynaecological operations because this was reputed to be both safe and effective.<sup>1</sup> Some patients developed large abdominal haematoma which required drainage and blood transfusion or at least parenteral iron to correct anaemia, whereas others had infected pelvic haematoma which drained spontaneously per vaginam. Many had a prolonged hospital stay with increased morbidity. After an abdominal hysterectomy one patient had a large pelvic haematoma with ileus which persisted for 11 days, treated by gastrointestinal suction and parenteral fluids and requiring a blood transfusion to correct severe anaemia. Three days after discharge she was readmitted with pulmonary infarction which she fortunately survived, being finally sent home on the 36th postoperative day.

Since then no further prophylactic antithrombotic drugs have been used and the incidence of postoperative haematoma has been greatly diminished and the morbidity much reduced. No patient has had a pulmonary embolus. Although impressed with your correspondents' results<sup>2-4</sup> and those recently reported from the Chelsea Hospital for Women,<sup>5</sup> I still take no special precautions save that of giving my patients a litre of Hartman's solution routinely after major surgery as well as replacing blood lost and instructing that patients with pain in the calf or in the chest, however mild, are immediately considered for intravenous heparin therapy.—I am, etc.

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<sup>1</sup> Bonnar, J., and Walsh, J., *Lancet*, 1972, 1, 614.

<sup>2</sup> Wells, C., *British Medical Journal*, 1973, 2, 612.

<sup>3</sup> Sharnoff, J. G., *British Medical Journal*, 1973, 2, 612.

<sup>4</sup> Doran, F. S. A., *British Medical Journal*, 1973, 2, 612.

<sup>5</sup> Ballard, R. M., *et al.*, *Journal of Obstetrics and Gynaecology of the British Commonwealth* 1973, 80, 469.

### Unsaturated Fatty Acids in Multiple Sclerosis

SIR,—In a double-blind study of linoleate supplementation of the diet in multiple sclerosis (M.S.), Dr. J. H. D. Millar and others (31 March, p. 765) reported a slight