reduction in perfusion pressure and arterial blood flow and vena caval obstruction by a reduction in venous return and cardiac output.—I am, etc.,

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¹ Eckstein, K. L., and Marx, G. F., *Anesthesiology*, 1974, 40, 92.

SIR,—Strain-gauge plethysmography measures arterial inflow on the basis of the increase of limb circumference during venous occlusion. It is arguable whether a limb with previously distended veins due to uterine compression of the inferior vena cava is susceptible to arterial blood flow measurements by this technique, as is implied by Dr. G. B. Drummond and his colleagues in their paper (15 June, p. 587). Further venous distension after inflation of the cuff will be limited by the elasticity of the vein walls and by tissue pressure, which may well lead to a faulty low reading.

Reduced cardiac output leads to reflex vasoconstriction via the sympathetic nervous system and an increase in circulating catecholamines. The authors' failure to demonstrate reduced upper limb blood flow in the supine position suggests an unaltered cardiac output.

I suggest that the study reported confirms increased venous distension in the legs when a pregnant woman is supine but does not prove reduced arterial inflow into the legs or reduced cardiac output. The conclusions regarding a left lateral tilt for the patient during caesarean section appear logical and clear for two reasons—better uterine venous drainage to protect the baby and less venous stasis in the patient's legs to reduce the intraoperative onset of deep vein thrombosis.—I am, etc.,

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Medicine in Belgium

SIR,—I read with interest the article by Drs. P. A. Emerson and M. S. Lewis on clinical medicine and research in Belgium (1 June, p. 488). Nevertheless, I am sorry it omitted to mention the Wetenschappelijke Vereniging der Vlaamse Huisartsen (W.V.V.H.; Scientific Association of Flemish General Practitioners) among the Belgian medical organizations. This was founded in 1963 to promote, mainly by postgraduate education, scientific medical knowledge in general practice. An identical association though of later origin, the Société Scientifique de Médecine Générale (S.S.M.G.), exists in the Walloon part of Belgium. These scientific associations are separate from the Chambre Syndicale (which protects the material interests of doctors) and may be compared with the British Royal College of General Practitioners. We are now preparing the programmes for in-service training mentioned by Drs. Emerson and Lewis, and we are organizing an international congress for general practitioners in Antwerp in May 1975, in which we have asked the Royal College of General Practitioners to co-operate.—I am, etc.,

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Non-comatose "Diabetic Coma"

SIR,—Dr. M. McB. Page and his colleagues (29 June, p. 687) review the treatment of 38 patients with "diabetic coma," of whom 10 were fully conscious and 20 drowsy. The practice of describing conscious patients as having diabetic coma is common, though many authors refer to "coma" rather than coma to indicate that they do not mean what they say. This curious misuse of words has long mystified me, especially as there exists the widely accepted term "diabetic ketoacidosis." Admittedly there are a few patients gravely ill from diabetes who are not ketotic—those with the hyperosmolar state—so even "diabetic ketoacidosis" is strictly inaccurate if it refers to all patients needing urgent treatment for diabetes. Perhaps "grave metabolic disturbance from diabetes" would be a satisfactory blanket term. Anything would be better than describing fully conscious patients as comatose.

I do not take this view just for pedantic reasons. I suggest that the constant improper reference to diabetic coma leads to serious mistakes. It seems that many doctors have gained the impression that if a patient is not comatose the situation cannot be all that bad. Only recently a middle-aged woman was admitted to my hospital moribund with peripheral circulatory failure and a blood glucose level of 1,250 mg/100 ml; she died a few hours later. Her experienced and knowledgeable general practitioner had seen her the previous day, when she was breathing rapidly and had vomited but was fully conscious. And by far the commonest reason why a diabetic on insulin is *in fact* comatose is hypoglycaemia. If he is brought to hospital he may be sent to the ward with the label "diabetic in coma." The house physician may then receive an urgent summons to see the new case of "diabetic coma." He—raw and inexperienced but aware of having heard repeated references to "diabetic coma"—may ask himself the absurd question, "Is it a hyper or a hypo?" If he then catheterizes the patient and finds the urine loaded with sugar he may make the grotesque error of giving insulin. I have known this happen—with fatal results.—I am, etc.,

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Gut Motility Changes Causing Drug Malabsorption

SIR,—We were interested in the study of Dr. A. S. Evered and Jacqueline M. McMullen (29 June, p. 728) showing that both metoclopramide and phenobarbitone impair the transfer of xylose across everted sacs of rat small intestine. However, while in no way wishing to argue with their results, we feel that the importance of intestinal motility should not be underestimated.

Many drugs are now known to cause malabsorption of xylose, glucose, fat, folic acid, and vitamin B₁₂,¹ but relatively little is known about the effects of one drug on the absorption of another. Reported interactions include the effects of propantheline and metoclopramide on the absorption of paracetamol² and digoxin³ and the delayed absorption of anticonvulsants, phenylbutazone, and griseofulvin caused by amphetamines,⁴ desipramine,⁵ and phenobarbitone¹ respectively. With the exception

of phenobarbitone, all these drugs act on the autonomic nervous system and could therefore affect absorption by altering gastrointestinal motility.

For many drugs the rate-limiting step in absorption is the dissolution of the tablet rather than the transfer of the drug across the small-bowel mucosa. Manninen *et al.*,³ for example, suggested that the changes in digoxin absorption produced by metoclopramide and propantheline could be due to an alteration in the time available for dissolution and showed that propantheline had no effect on the absorption of digoxin given in liquid form. Even when mucosal function is known to be impaired it may not be safe to assume that impaired drug absorption is due to this. Absorption of digoxin is impaired in patients with various malabsorption syndromes,^{7,8} but this effect is associated with decreased transit times and appears to be more marked when digoxin is given in tablet form than in solution.

We have recently shown¹ that in 15 subjects a short course of phenobarbitone significantly reduced xylose absorption, which could be explained by the mucosal effect reported by Dr. Evered and Miss McMullen, though Riegelman *et al.*⁶ have suggested that phenobarbitone may also affect gut motility.

Malabsorption of xylose may be due to impaired mucosal function, but care is obviously needed when using xylose absorption studies to explain changes produced by one drug on the absorption of another. Mucosal damage may impair drug absorption in some instances, but such evidence as there is suggests that, at least for drugs with a slow dissolution rate, gastrointestinal motility changes are more important.—We are, etc.,

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- Kendall, M. J., and Chan, K., *Xenobiotica*, 1973, 3, 727.
- Nimmo, J., *et al.*, *British Medical Journal*, 1973, 1, 587.
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- Frey, H. H., and Kampmann, E., *Acta Pharmacologica et Toxicologica*, 1966, 24, 310.
- Consolo, S., *et al.*, *European Journal of Pharmacology*, 1970, 10, 239.
- Riegelman, S., Rowland, M., and Epstein, W. L., *Journal of the American Medical Association*, 1970, 213, 426.
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- Heizer, W. D., Smith, T. W., and Goldfinger, S. E., *New England Journal of Medicine*, 1971, 285, 257.

Venoarterial Difference in α_1 -Antitrypsin Levels

SIR,—Like Dr. J. Lieberman (13 July, p. 93) we have attempted to confirm the finding of Woolcock *et al.* of a venoarterial difference for α_1 -antitrypsin in patients with chronic obstructive lung disease. We used both immunodiffusion and biochemical methods (trypsin inhibitory capacity). We were also unable to find significant differences between venous and arterial levels in 10 such patients.

Woolcock *et al.* postulated that their findings were possibly due to binding of α_1 -antitrypsin to a protease during passage of blood through the lungs, with alteration of the antigenic properties of α_1 -antitrypsin. We tested this latter suggestion by adding increasing amounts of trypsin to serum and then carrying out immunodiffusion assays on the serum samples. We found the apparent

concentration of α_1 -antitrypsin fell linearly with increasing amounts of trypsin until the trypsin inhibitory capacity was reached, when there was no further reduction in the apparent concentration. This final level (when all α_1 -antitrypsin was in the complexed form) was about 40% of the original level. Thus if the venoarterial observed difference is 10% it indicates that about 17% of α_1 -antitrypsin is in the complexed form.

The suggestion of Woolcock *et al.* also implies that the proteases transported from the lungs are deposited in the tissues. What would be the load thus transported and deposited? Assuming the average result from their study—a 10% venoarterial difference, which represents 17% α_1 -antitrypsin complexed, a serum α_1 -antitrypsin of 400 mg per 100 ml, a 1:1 molar binding with protease of similar molecular weight to α_1 -antitrypsin, and a total plasma flow of 3 l./min—we get the astonishing figure of 2.9 kg of protease transported a day. Even if the molecular weight of the protease were assumed to be one-half or one-third that of α_1 -antitrypsin the amount of daily transport implied by any measurable venoarterial difference would seem impossibly large.—I am, etc.,

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¹ Woolcock, A. J., Green, W., and Crockett, A., *British Medical Journal*, 1972, 2, 134.

Perinatal Metabolism of Diazepam

SIR,—Dr. D. M. Hailey and others have not found oxazepam in the neonatal plasma when diazepam is given to the mother less than 15 hours before delivery (22 June, p. 670). Neither have we.¹ Instead we found oxazepam in neonatal plasma when 10–15 mg of diazepam was given to the mothers daily for 6–21 days before delivery, as we stated in our letter (30 March, p. 641).

The diazepam concentrations in tissues increase if diazepam is used continuously. We have found a relatively high accumulation of diazepam and its metabolite especially in the fetal liver.² The total amount of diazepam and its metabolites in the fetus or newborn may be remarkably high, though the concentration in the plasma is not higher than after 10 mg of diazepam as a single dose. This may explain the discrepancy between the results of Rosanelli³ and Adoni and others.⁴ However, in the cases of neonatal icterus even the slightest concentrations of the drugs, which are eliminated by glucuronidization, may have a slowing effect on the conjugation rate of bilirubin.

When using diazepam or any psychotropic drug during pregnancy the possible benefits must, of course, be compared with the possible adverse effects. Diazepam is not a teratological agent in therapeutic doses.⁵ For the management of pre-eclampsia we have diuretics and real antihypertensives. Psychic disorders may sometimes require the use of some psychotropic drug, but preferably only temporarily. During delivery we use diazepam for following reasons: (1) to remove maternal anxiety and nervousness; (2) to relax pelvic musculature; (3) to potentiate the influence of analgesics; (4) to control maternal hyperventilation; (5) to control eclamptic or other convulsions; and (6) to

try, when necessary, to effect a retrospective amnesia. We do not use a total dose of diazepam larger than 10–20 mg parenterally except in cases of convulsions, when we may use up to 100 mg.—We are, etc.,

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- ¹ Kanto, J., Erkkola, R., and Sellman, R., *Annals of Clinical Research*, 1973, 5, 375.
- ² Erkkola, R., Kanto, J., and Sellman, R., *Acta Obstetrica et Gynecologica Scandinavica*, 1974, 53, 135.
- ³ Rosanelli, K., *Geburtshilfe und Frauenheilkunde*, 1970, 30, 713.
- ⁴ Adoni, A., *et al.*, *American Journal of Obstetrics and Gynecology*, 1973, 115, 577.
- ⁵ Hüter, J., *Klinische Wochenschrift*, 1968, 46, 681.

Was it a Drug?—Forceval Protein

SIR,—I have been prescribing this product for a patient with “biochemically proven hypoproteinaemia” due to malabsorption caused by Crohn’s disease with a blind-loop syndrome following an ileo-transverse anastomosis. The hypoproteinaemia in this case does not appear to fit into either of the categories mentioned by Dr. A. A. Lewis (20 July, p. 173). It has at times been sufficient to cause marked oedema and because of the tendency to diarrhoea in this condition it is not easy to give a diet sufficiently rich in protein to counteract the deficiency. In these circumstances it seemed reasonable to me to suggest giving a protein supplement on prescription under the terms of the Clayton Committee and this met with the approval of the consultant gastroenterologist who has been treating her.

The patient appears to have benefited and I do not feel in the least resentful at having to write “A.C.B.S.” on the prescription when vast quantities of preparations of much more questionable therapeutic value are being widely prescribed without any official interference by a “third party sitting behind a desk.” Perhaps the experts would care to comment.—I am, etc.,

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Antibiotics in *Bacteroides fragilis* Infections

SIR,—I read Dr. D. A. Leigh’s article on the importance of infections due to *Bacteroides fragilis* (27 July, p. 225) with interest. However, it is doubtful whether his results make a case for the use of clindamycin or lincomycin “in the primary treatment of all suspected abdominal infections”—particularly in view of recent reports of pseudomembranous colitis, including some fatalities in association with these antibiotics.^{1–3}

This view is supported by my personal experience. Within the last six months in the Portsmouth hospitals we have encountered four cases of colitis including two typical cases of the pseudomembranous type (proved histologically), both severe enough to be life-threatening. Ultimately all recovered. Dr. Leigh has demonstrated only marginal benefits from the use of clindamycin in wound infections, and it should be reserved for severe, proved bacteroides

infections where the benefits outweigh the possible side effects.—I am, etc.,

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Portsmouth

- ¹ Scott, A. J., Nicholson, G. I., and Kerr, A. R., *Lancet*, 1973, 2, 1232.
- ² Wise, R., Tudway, A. J. C., and Pelta, D. E., *Lancet*, 1974, 1, 878.
- ³ Steer, H. W., *Lancet*, 1974, 1, 1176.

Cloxacillin Levels in Synovial Fluid

SIR,—Septic arthritis still causes problems in management, and debate continues over the use of intra-articular antibiotics. It has been suggested that such use is unnecessary¹ and indeed there is some evidence that the very high concentration achieved in this way may cause a persistent synovitis.² *Staphylococcus aureus* still causes the majority of such infections in Britain and cloxacillin is often considered the antibiotic of choice. Bactericidal levels of cloxacillin have been demonstrated in non-infected synovial fluid after oral administration³ but few studies have shown the levels achieved in infected synovial fluid.⁴ It is unusual for opportunities to measure antibiotic levels in infected synovial fluid to arise, but I have recently had the chance to measure the level of cloxacillin achieved.

A 10-year-old girl with septic arthritis of her hip was treated with cloxacillin 500 mg six-hourly for two days before her infected hip was explored. Synovial fluid and serum were obtained at that time and the antibiotic levels were measured. The time between administration of the last antibiotic dose and obtaining the specimens was 2 hours 50 minutes. The cloxacillin level in the serum was 7.7 $\mu\text{g/ml}$ and in the synovial fluid 3.8 $\mu\text{g/ml}$.

The level of cloxacillin achieved in the infected synovial fluid in this case is well in excess of that normally required for bactericidal action. This, therefore, lends support to those who maintain that intra-articular administration of antibiotics is unnecessary and undesirable.—I am, etc.,

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- ¹ Nelson, J. D., *Pediatrics*, 1972, 50, 437.
- ² Argen, R. J., Wilson, C. H., and Wood, P., *Archives of Internal Medicine*, 1966, 117, 661.
- ³ Howell, A., Sutherland, R., and Rolinson, G. N., *Clinical Pharmacology and Therapeutics*, 1972, 13, 724.
- ⁴ Parker, R. H., and Schmid, F. R., *Arthritis and Rheumatism*, 1971, 14, 96.

Medical Synovectomy

SIR,—Your leading article on medical synovectomy (29 June, p. 682) is an excellent summary of the current feeling about the use of radioisotopes in the treatment of arthritis and outlines some of the hazards. However, yttrium-90 resin colloid, which you suggest as the radiocolloid of choice for use in the knee, has not been available for some time. It was withdrawn by the Radiochemical Centre, Amersham, because of difficulties in manufacture in 1972.

At present two radiocolloids are routinely available from the Radiochemical Centre for therapeutic applications. Yttrium-90 silicate and gold-198 colloid. A more recently developed material, yttrium-90 ferric hydroxide colloid, is currently being prepared in limited