concentration of $\alpha_1$-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 $\alpha_1$-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 $\alpha_1$-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% $\alpha_1$-antitrypsin complexed, a serum $\alpha_1$-antitrypsin of 400 mg per 100 ml, a 1:1 molar binding with protease of similar molecular weight to $\alpha_1$-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 $\alpha_1$-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 Rosanelli[3] 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 tocological 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 Obstetricia 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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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 unnecessary[1] 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 administration[3] 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 $\mu$g/ml and in the synovial fluid 3·8 $\mu$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