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.,

A. C. DANIEL

Retford, Notts

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.,

D. T. L. TURNER

Royal Portsmouth Hospital,
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.,

J. H. NEWMAN

General Hospital,
Nottingham

- 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

quantities by the Radiochemical Centre for use by investigators, who are continually evaluating its properties.¹ We have had the opportunity of testing this² and comparing it with the silicate and with yttrium-90 citrate from France. The silicate consistently gave good retention in the knee, equivalent to that previously found with the resin colloid, while the ferric hydroxide-based colloid and the citrate were less well retained in the knee. In addition the citrate was associated with early lymph node uptake of considerable amounts of radioisotope.

We have also analysed the chromosomal damage noted after treatment with these four radiocolloids and have found a low rate of chromosomal damage—equivalent to that after iodine-131 treatment for hyperthyroidism—with the ferric hydroxide and silicate forms of yttrium-90. With the citrate there was considerably more chromosomal damage, roughly equivalent to that found with gold-198.⁴

You mention that there is a reduction of lymph node uptake with hydrocortisone. This is noted only when using gold-198, with which there is a very considerable lymph node uptake of radioactivity. We have attempted the same work with yttrium-90 silicate, but because there is very little lymph node uptake with this latter preparation we have been unable to demonstrate material differences between hydrocortisone-treated patients and control patients in terms of lymph node uptake.—I am, etc.,

J. M. GUMPEL

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Harrow, Middlesex

¹ Peacegood, J. A., Radiochemical Centre, Amersham. Private communication.

² Beer, T. C., et al., *Annals of the Rheumatic Diseases*, 1973, 32, Supplement, p. 41.

³ Gumpel, J. M., et al., *British Journal of Radiology*. In press.

⁴ Gumpel, J. M., and Stevenson, A. C., *Rheumatology and Rehabilitation*. In press.

Acneiform Lesions in Combined Rifampicin Treatment in Africans

SIR,—In treating urinary tuberculosis with daily rifampicin in combination with isoniazid and thiacetazone troublesome acneiform lesions have been observed in a significant number of Zambian African patients. The lesion disappeared spontaneously within three weeks after withdrawal of rifampicin. I report here eight such cases among 24 male patients.

Thirty-four adult African patients (30 men and four women) have been treated in our urology clinic for urinary tuberculosis in the past 18 months. Of these 34, 24 (20 men and four women) were treated with oral rifampicin 10 mg/kg (but not exceeding 750 mg) daily for the first 12 to 18 weeks in combination with oral isoniazid 300 mg and thiacetazone 150 mg daily, which was continued after the withdrawal of rifampicin. All were treated as outpatients and were seen every three weeks at the beginning of treatment while on rifampicin. Eight of the 20 men (and none of the women) developed chronic papular acneiform lesions on the face, neck, and shoulders. The lesions were severe in four, moderately severe in three, and mild in one. They developed gradually from around the fifth week to become severe from about the eighth to the tenth weeks.

In all eight cases withdrawal of rifampicin at the twelfth to the eighteenth week led to the disappearance of the lesions within three weeks. Only in one case was it necessary to withdraw rifampicin promptly at 12 weeks because of severe lesions which had to be treated by a dermatologist. The results of liver function tests and a blood count in these eight patients before and during treatment showed no significant changes and were within normal limits. Cutaneous reactions to rifampicin have been reported before.—I am, etc.,

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Lusaka, Zambia

¹ Aquinas, M., et al., *British Medical Journal*, 1972, 1, 765.

Treatment of Genital Herpes

SIR,—I was most interested in the letter by Dr. S. M. Laird and Mr. R. B. Roy (27 July, p. 255) reporting their successful treatment of genital herpes simplex infections with co-trimoxazole. I have been using this compound for type 1 H.S.V. infections with considerable success since March 1972.

Studies carried out at the Northern Regional bacteriology laboratory under Dr. H. Williams showed that trimethoprim inhibits the replication of H.S.V. in vitro, but only in concentrations above the serum level achieved with the normal (and clinically effective) dosage. This was difficult to understand until we observed that patients who were already receiving penicillin or ampicillin when they developed their H.S.V. infections did not benefit from co-trimoxazole and then recalled that penicillin is added routinely to virus cultures to prevent overgrowth with bacteria, which suggests that, at least so far as H.S.V. is concerned, there may be some antagonism between trimethoprim and the penicillins.

More recently Dr. E. G. Buchanan and I have separately treated some patients suffering from herpes zoster with co-trimoxazole, with quite good results. So far early relief from pain and rapid resolution of the rash with minimal scarring have been the most obvious features. This treatment is so simple—and produces such grateful patients—that it would certainly seem to merit widespread trials.—I am, etc.,

PAULA H. GOSLING

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Alternative Health Service

SIR,—Perhaps one of the more remarkable features of the current row over the economic failure of the N.H.S., has been the failure of all the political parties to put forward a realistic alternative to the present system. The non-viability of a "free" health service became apparent soon after it was born but no government has yet had the courage to admit this or the vision to make radical changes. Injecting more money at this stage would merely stave off the collapse for a short time.

I therefore suggest that it is up to us to explore the alternatives, even to the extent of

restructuring the whole service if necessary, rather than wasting time in the "us and them" squabble. The columns of the *B.M.J.* could provide the neutral ground for a dispassionate appraisal of the health services of other countries less bankrupt than our own. Let us hear about Australia, New Zealand, Denmark, Czechoslovakia, and other countries whose graduates are in Britain at the present time. Let us tap the wisdom of non-government financial experts like the directors of B.U.P.A. and invite the comments of the chairman of a large insurance company on the subject of universal insurance against loss of earnings and doctors' fees, etc. (How much would it save the tax payer if the Prudential ran the Health Service?) Where are the psychologists who gauged public reaction to decimalization so well?

These are the people whose opinions could collectively throw a lot of light on our seemingly hopeless situation and whose ideas, together with our experience, could help whichever government prevails out of the impasse.—I am, etc.,

P. JOAN BISHOP

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N.H.S. Contraceptive Services

SIR,—I agree with Sir George Pickering and others (3 August, p. 340) that we ought to work the proposed free family planning scheme at once. It is necessary to our patients and the fee of £1.72, while it does not exactly make my mouth water, would be sheer extra buncie for the very large number of us who have never charged for contraceptive advice. The French Chamber of Deputies has recently voted that advising on contraception is "a medical transaction, like any other." There was one dissenter.

If the Secretary of State were to institute the scheme, allowing doctors to take part in it if they chose, I guess that half the G.P.s would be in it within a month and 90% within a year.—I am, etc.,

DAVID CARGILL

Maldon, Essex

Saudi Arabian Medical School

SIR,—I noticed that the 13 July issue of the *B.M.J.* (pp. xx-xxii) carried four large display advertisements for both preclinical and clinical teaching posts at the University of Riyadh Medical School, Saudi Arabia, and that all three specifically stated: "Applications are invited from male honours graduates." The advertisements also mentioned that the university had established a medical school in association with the University of London, which advises on "the appointment of academic staff." While I appreciate that as a result of cultural prejudices there may as yet be no female doctors in Saudi Arabia, I fail to see any objection to medical students being taught by women, and am amazed to find such sexist practices being openly supported by a British university.—I am, etc.,

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