tion of emetine, especially in view of its known myocardial toxicity.

Having thus dismissed emetine as a potential treatment for bronchopulmonary aspergillosis, we would confirm the views expressed in your article that amphotericin B is currently the most effective treatment available. Similarly, 5-fluorocytosine is effective against sensitive yeasts (provided they remain so), but we would like to point out that while clotrimazole does cause gastrointestinal side effects, it has also been shown to have no detectable effect against bronchopulmonary aspergillosis using clinical and mycological criteria.²—We are, etc.,

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¹ Jesiotr, M., *Scandinavian Journal of Respiratory Diseases*, 1973, **54**, 326.

² Crompton, G. K., and Milne, L. J. R., *British Journal of Diseases of the Chest*, 1973, **67**, 301.

New Curriculum

SIR,—I was fascinated to read the letter from Dr. M. F. Green (31 August, p. 578) describing the new curriculum at the Royal Free Hospital. The preclinical course concerning "Man and his Environment" is of great interest. It is, however, surprising that he does not mention any contribution to this course from general practitioners—who are daily concerned with treating man in his environment. It is equally surprising that the teaching in sexual matters is to be covered by preclinical staff, obstetricians, and a specialist in community medicine, while the management of most of the sexual problems which present in the National Health Service is conducted by general practitioners.

It would seem that the Royal Free Hospital could only improve their course by obtaining assistance from those doing the bulk of the clinical work in these fields. Some of the London schools and all the medical schools in the provinces have found that using the resources provided by patients in general practice and their doctors for teaching about subjects rarely encountered in the teaching hospital is remarkably successful.—I am, etc.,

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Complications of Carbenoxolone Therapy

SIR,—The letter from Dr. A. N. Kingsnorth (31 August, p. 579) stimulated by the recent article by Dr. G. J. Davies and others (10 August, p. 400) tends to cloud the issue. The presentation of carbenoxolone side effects is not invariably congestive cardiac failure, and this is clearly demonstrated in the original paper. In the absence of ileus the oral administration of potassium supplements is equally effective as, and less hazardous than, their intravenous infusion: to overcome the cumulative deficit of hundreds of milliequivalents of potassium will in any case require days rather than hours. Most serious of all, there is no "good case" for the use of an "aldosterone-antagonist-like diuretic agent." Quite the reverse, since it

has been shown¹ and is accepted in undergraduate textbooks² that spironolactone will actually prevent the effect of carbenoxolone in healing gastric ulcers. Thiazide diuretics¹ will prevent the fluid retention without altering the healing, but will certainly further exacerbate potassium loss. The only way to combat this is to administer large quantities of potassium-containing drugs.³

The best current policy is to use carbenoxolone only in patients with normal serum potassium and blood urea and without signs or history of heart failure or hypertension. The course of treatment should be carefully monitored to ensure prompt detection of weight gain or hypokalaemia. If it is desired to reverse or prevent the fluid retention or potassium loss, then thiazides plus substantial amounts of potassium chloride are indicated on present information. The aldosterone antagonist spironolactone is definitely contraindicated.

In the situation where the patient is committed to three different drugs totalling maybe more than a dozen tablets daily a single potassium-retaining diuretic tablet might well be preferable. Criteria for the ideal diuretic are adequate prevention of sodium and water retention, prevention of potassium loss, and freedom from antagonism of the healing action of carbenoxolone. The possibly useful agents available are triamterene and amiloride, which have both been proposed.⁴ Our search of the literature has not found any work establishing the value of either of these agents with carbenoxolone therapy and we are at present engaged in a trial to evaluate amiloride.—We are, etc.,

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¹ Doll, R., Langman, M. J. S., and Shawdon, H. H., *Gut*, 1968, **9**, 42.

² Laurence, D. R., *Clinical Pharmacology*, 4th edn., p. 215. Edinburgh, Churchill-Livingstone, 1973.

³ Bateson, M. C., *American Heart Journal*, 1974, **88**, 124.

⁴ Cranston, W. I., in *Modern Diuretic Therapy*, ed. A. F. Lant and G. M. Wilson, p. 175. Amsterdam, Excerpta Medica, 1973.

SIR,—The article by Dr. G. J. Davies and others (10 August, p. 400) raises certain questions and requires clarification.

Carbenoxolone has been in clinical use for over a decade and over 400 papers relating to it have now been published. Thus the incidence and nature of any side effects have been carefully and widely documented in the world literature, as have all those cited by the authors. That some of these complications can be quite severe has long been recognized and this information widely disseminated to the medical profession by the pharmaceutical firm marketing it. The data sheets on Biogastrone¹ (used in the treatment of gastric ulcer) and Duogastrone² (duodenal ulcer), which have been sent to every practising doctor in the United Kingdom, carry very clear warnings regarding their use, including any contraindications, and the message is quite clear. Carbenoxolone sodium treatment has to be regularly and medically supervised. However, this in no way compromises either the efficacy of or the indications for such treatment, as has also been borne out by a recent critical review of carbenoxolone in the treatment of peptic ulcer.³

An analysis of the case histories cited by Dr. Davies and his colleagues would indicate that the severity of the complications was avoidable in cases 1, 3, 4, 6, and 8; case 2 was treated with the inappropriate preparation of carbenoxolone in too large a dose and for too long, while the remaining two patients should not have been treated with it at all. As Dr. Davies and his colleagues themselves admit, a proper awareness of the usage of carbenoxolone would have avoided most of the complications which they describe.

It would also be of great interest to know over what period of time these cases were assembled and the actual incidence of complications they represent. Finally, until further properly controlled clinical trials have clearly disproved the value of carbenoxolone in other gastrointestinal conditions then it is misleading to conclude that the only indication for its use is in proven benign gastric ulcer.—I am, etc.,

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¹ A.B.P.I. Data Sheet Compendium 1974, p. 88. London, A.B.P.I., 1974.

² A.B.P.I. Data Sheet Compendium 1974, p. 91. London, A.B.P.I., 1974.

³ Lewis, J. R., *Journal of the American Medical Association*, 1974, **229**, 460.

Channel Tunnel

SIR,—Dr. J. B. Kelynack (7 September, p. 631) makes a good point about noise and the channel tunnel rail link, but might I draw attention to another and potentially far more serious hazard associated with the tunnel itself?

The tunnel will be the first land link between Britain and the Continent and we will thus lose our physical isolation. Wild animals must inevitably get through to make a mockery of our quarantine regulations. With rabies spreading steadily westwards across Europe and with the fox an increasingly important carrier, I trust someone can give us reliable assurance of our continued protection from this disease.—I am, etc.,

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Prazosin and Hydralazine in the Treatment of Hypertension

SIR,—We noted with interest the preliminary report by Drs. G. S. Stokes and M. A. Weber (11 May, p. 298) on the anti-hypertensive effects of prazosin. We have conducted a double-blind crossover trial comparing the antihypertensive effects of prazosin and hydralazine in combination with a beta-blocking agent and a thiazide diuretic, the results of which will shortly be published.

The double-blind addition of capsules containing either 1 mg of prazosin or 25 mg of hydralazine produced a significant fall in the blood pressure in this study. We had assumed from open studies that 25 mg of hydralazine was equivalent to approximately 1 mg of prazosin, but the results of the controlled trial suggest that the hypotensive effects of 25 mg of hydralazine may be rather greater than those of 1 mg of prazosin.

In this crossover study it was possible to achieve very satisfactory control of the blood pressure with few side effects during each treatment period in which a vasodilator (either prazosin or hydralazine) was combined with a beta-adrenergic blocking agent and a thiazide. Blood pressure control had not been satisfactory before addition of the vasodilator capsules. All blood pressures were estimated with the London School of Hygiene and Tropical Medicine sphygmomanometer.—We are, etc.,

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Transfusion Policy

SIR,—I am prompted to write in support of your leading article entitled "Component Transfusion Therapy" (31 August, p. 544) and of the letter from Dr. J. Darnborough and others (p. 573).

Your leading article states that "if clinicians in hospitals would accept a greater part of the blood used as partially packed red cells, then the supply of AHG concentrate could be greatly increased to augment and gradually replace the supply of cryoprecipitate preparations for haemophilia, for the latter preparations vary widely in their AHG content." To the best of my knowledge and belief this policy has been carried out at the Royal Infirmary, Sheffield, for some years with no detriment to non-haemophilic patients.

Personal experience in the Leeds and Sheffield Regional Transfusion Centres impels me to support the views of Dr. Darnborough and his colleagues in Cambridge, Edgware, and Manchester respectively.—I am, etc.,

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Wartime Penicillin

SIR,—While supporting Sir Ian Fraser's contention (14 September, p. 685) that the use of penicillin by the army for treating gonorrhoea was restricted during the period of very short supply, I feel bound to place on record one qualification to this. I was a member of a committee of the three services and the Medical Research Council which debated this problem, exactly when I am not sure, but perhaps rather after the time of which he writes, and there were strong representations that an exception should be made for the sake of the morale as well as fitness for duty of certain key Service personnel. The committee therefore recommended that treatment of gonorrhoea with penicillin should be permitted only in fighter pilots, tank crews, and commandos. Whether this rather lame compromise was then translated into an official order I never heard.

The writer whom Sir Ian Fraser criticizes chose an unconvincing example; most pneumonia was still responding well to sulphonamides. The agonizing choice was whether to afford enough penicillin to treat a case of staphylococcal septicaemia or of

subacute bacterial endocarditis when the amount necessary would cure scores of people suffering from less lethal infections whose rapid restoration to health may have been important to the war effort. A frequently quoted example was sepsis following industrial accidents, which if untreated could cause prolonged disablement. Mercifully the period during which these desperate decisions had to be made soon came to an end as penicillin production gained momentum.—I am, etc.,

Wokingham, Berks

LAWRENCE P. GARROD

SIR,—In reply to Sir Ian Fraser's letter (14 September, p. 685) I confirm from personal experience that penicillin was used to treat gonorrhoea in Germany in 1946-8 while German children died with pneumonia, meningitis, etc. The special centre in which I worked frequently had to turn away distraught parents begging for this drug, often bringing their dying child as proof of their desperate need. Their only hope of obtaining this drug was via the Swedish and Danish Red Cross and the delay invariably meant death to the child.

Sex in this context did have priority over the sick child, but of course the child was unfortunately on the wrong side of the war. Perhaps this point was not made clear in the original quotation.—I am, etc.,

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The Disc Sensitivity Test

SIR,—Your leading article on this subject (13 July, p. 74) reviewed the current situation in regard to testing of bacterial sensitivity to antibiotics, in particular the regional and international attempts that have been made to standardize test techniques. As one of the editors of the report from the International Collaborative Study (I.C.S.) on antibiotic sensitivity testing,¹ I wish to point out some misunderstandings expressed in your article concerning the I.C.S. recommendations.

The I.C.S. report studiously avoided recommendation of *standard* methods for universal use. *Reference* methods were proposed against which locally accepted techniques could be evaluated. Methods closely resembling one of those described in the I.C.S. report—a quantitative variant of the paper disc diffusion test—have, however, been widely and successfully used in Scandinavia for more than 20 years.

According to your article essential features of both the I.C.S. method and the method evolved by Kirby *et al.*² and recommended by the U.S. Food and Drug Administration are "the use of large plates . . . and the translation of inhibition-zone diameters directly into categories of sensitivity by reference to tables." The I.C.S. report¹ recommended that plates be "poured to a depth of approximately 4 mm. This corresponds to 60 ml for plates of 14 cm internal diameter . . . and 25 ml for plates of 9 cm internal diameter" (p. 69). No preference was stated for plates of either size. In my laboratory we use 14-cm plates, but many other Swedish laboratories which strictly

observe the I.C.S. recommendations use 9-cm plates. The I.C.S. method does *not* directly translate inhibition-zone diameters into categories of sensitivity. Zone diameter is first translated into the minimum inhibitory concentration (M.I.C.) of antibiotic, using regression lines. These lines are evolved by the Swedish maker of test discs in collaboration with research laboratories. The categorization of microbial sensitivity is thereafter based on the relationship of the M.I.C. to antibiotic levels in blood and other tissue fluids and on clinical experience (p. 76).

Your article further states that "the main objection to the F.D.A. or I.C.S. method is . . . simply that it is uncontrolled." The I.C.S. report,¹ however, included detailed comparisons of regression-line studies in different countries. Statistical analyses of these comparisons were published in the report (p. 50). Moreover, checks against agreed bacterial strains now form part of the daily routine work with the I.C.S. method in Scandinavia. Whenever systematic deviations from expected results appear the laboratory is urged to search for the responsible factors.

The I.C.S. may, admittedly, have given inadequate consideration to variations in commercially available media, since one single batch was used and not all potential variables were investigated for influence on test results. The effect of gentamicin on magnesium was not known at the time of the I.C.S. and indeed this antibiotic was not studied. Now, however, an improved medium is available. The microbiological performance of each batch is checked in relation to regression lines and is guaranteed when the medium is marketed.

Standardization of techniques and materials for the disc sensitivity test has been achieved in Scandinavia by informal collaboration between colleagues and without the intervention of public bodies. Our policy in regard to single-disc testing is undogmatic. At the time when the F.D.A. approved use of separate discs for each proprietary brand of antibiotic Swedish bacteriologists maintained that only one disc was required to test sensitivity to a whole group of microbiologically and chemically closely related substances. But the need for special discs in certain circumstances has always been recognized and catered for, as has the need for discs of different potencies in tests against antibiotics with a wide dosage range, such as benzylpenicillin.

In conclusion, I should like to comment upon the Stokes method that appears to be popular in Britain. This method does not eliminate one of the most important sources of error—variations in inoculum of standard and test strains. Moreover, the importance of the concentration of antibiotic in the urine, which is recognized also in your article, necessitates the use of different standard strains in different clinical situations. For example, urine may be sent to the laboratory at a time when the clinical picture indicates simple cystitis, but when the result of the sensitivity test is delivered the infection may have progressed to deep-seated pyelonephritis. The clinician may then be misled in his assessment of the antibiotic dosage required to meet the clinical situation.

None of the I.C.S. members, and certainly not the two editors of the report, believed