to the drug. However, today I received in the post a new data sheet on cefamandole nafate (Kefadol)—the most recent addition to the ever-growing ranks of cephalosporins—and was disturbed to find that it contained a fundamentally important statement that is contradicted by reports available seven months ago. The antibiotic is described in the data sheet as being "resistant to degradation by penicillinases from *Staphylococcus aureus* and by β -lactamases from certain members of the enterobacteriaceae"; moreover, the promotional letter which accompanied the sheet states unequivocally that "cefamandole has greater resistance than earlier cephalosporins to β -lactamases."

In reality my colleagues and I have shown that cefamandole is highly susceptible to β -lactamases from both Gram-positive and Gram-negative bacteria with the exception of the relatively unimportant type Ia enzyme of *Enterobacter cloacae*, to which the antibiotic possesses a modest degree of resistance.¹ In contrast, greater stability to most enzymes is a feature of some of the well-established cephalosporins, notably cephadrine and to a lesser extent cephalexin. The findings in relation to the enzymes from Gram-negative bacteria have been corroborated by Vuye and Pijck,² who concluded that "cefamandole nafate displayed the highest vulnerability among the cephalosporins tested against the broad-spectrum enzyme" (IIIa or TEM-type). The ability to produce this clinically most important enzyme has evidently been transmitted by plasmids from *Escherichia coli* to the gonococcus and *Haemophilus influenzae* in recent years.³ This alarming trend is likely to negate the one undoubted advantage that cefamandole possesses over other cephalosporins—its enhanced activity against fully sensitive strains of *H. influenzae*.

Unfortunately the manufacturers of this antibiotic are not the only authoritative source of potentially misleading information; in a very recent general review on antibiotics we read that cefamandole is "extremely stable to β -lactamases, especially those produced by Gram-negative organisms."⁴ The general confusion surrounding the cephalosporins has been greatly heightened by the fact that the company in question now markets four of these antibiotics simultaneously in Britain and at least six throughout the world (and yet another new one, cefuroxime, was introduced by a different company last month). A rational choice in this group depends largely on antibiotic stability to β -lactamases.⁵ Cefamandole fails on this score, but several other essential considerations also apply.⁶ In particular, pharmacokinetic features are very important. However, again the picture presented by cefamandole is not very promising since it is relatively highly protein-bound and has a short half life in the body and a relatively low volume of distribution.⁷ This particular "second-generation" cephalosporin seems, alas, ill-qualified to replace the more sprightly of its older relatives.

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¹ Geddes, A, *Medicine* (3rd series), 1978, No 3, p 155.
² Williams, J D, *Journal of Antimicrobial Chemotherapy*, 1978, 4, 109.
³ Selwyn, S, *Lancet*, 1976, 2, 616.
⁴ Gower, P E, and Dash, C H, *European Journal of Clinical Pharmacology*, 1977, 12, 221.

* * * We sent a copy of this letter to the medical adviser to the manufacturers of cefamandole, whose reply is printed below.—Ed, *BMJ*.

SIR,—As Dr Selwyn himself points out, not everyone agrees with his assessment of the stability of cefamandole to β -lactamases,¹ but the more important question is the extent to which such properties are relevant outside the laboratory. For example, later in Vuye and Pijck's paper is the statement that "cefamandole was shown to be by far the most active compound, a property that may probably compensate for the vulnerability of this compound to other resistance mechanisms." Also, in the article by Professor J D Williams is an admission that, unlike penicillins, a clear association of β -lactamase with resistance to cephalosporins is often not obvious even in vitro and that correlations between in-vitro tests and in-vivo results have yet to be established. Specifically in relation to *Haemophilus influenzae* there is, fortunately, clear evidence that strains which produce TEM-type enzyme do not show any increased resistance to cefamandole,² which must cast doubts on the relevance of tests showing cefamandole to be inactivated by that enzyme.

A recent editorial in the *Lancet*³ explained that there are at least three factors to be considered: (1) stability to β -lactamase, (2) penetration through the cell wall and periplasmic space, and (3) inherent antibacterial activity. It is a combination of these factors, not any one of them alone, which determines the effectiveness of cephalosporins; and there is ample evidence, which we would be happy to supply on request, that cefamandole is very well qualified to be considered for use in patients with appropriate infections and as a possible replacement for earlier cephalosporins.

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¹ Farrar, W E, et al, *Journal of Infectious Diseases*, 1976, 133, 691.

² Kattan, S, et al, *Journal of Antimicrobial Chemotherapy*, 1975, 1, 79.
³ *Lancet*, 1978, 1, 863.

The MRCP (UK) examination in Commonwealth countries

SIR,—Since taking up the post of professor of medicine in this university four months ago I have become acutely aware of the problems faced by my junior medical staff when they decide to sit the MRCP (UK) examination. This diploma is highly regarded in Malaysia and Singapore and, now that the Australasian college has changed its regulations, is the only internationally recognised higher qualification in medicine available to postgraduates in South-east Asia.

When I came to Kuala Lumpur I was under the impression that there was no barrier to trainee specialists sitting the part I examination locally, thus sparing them the enormous expense of a journey to the United Kingdom, which could then be deferred until they were ready to sit the part II examination and would allow them to undertake a period of

postgraduate training at the same time. I have since discovered, however, that the part I examination is held only once a year in Kuala Lumpur (Singapore candidates have also to come here for the examination). Thus in the event of failure (and this fate can befall even a very well-prepared candidate) he or she cannot sit the examination again locally for a period of 12 months. This, as can be imagined, places an immense strain on candidates and interferes seriously with their hospital training programme. All that is bad enough, but it has now come to my notice that the number of candidates admitted to the part I MRCP (UK) examination in Kuala Lumpur is restricted to 150 and that because of the demand for places the list is closed almost as soon as it is opened. Consequently many excellent candidates (and the standard of medicine in Malaysia and Singapore is not far behind that of the United Kingdom) are, through no fault of their own, being denied the opportunity of even sitting the part I examination.

I took up this matter with the president of the Royal College of Physicians of Edinburgh, who made the rather lame comment that because of administrative difficulties the number being allowed to sit the part I examination overseas is severely restricted. While I can appreciate that it might be difficult (although not impossible) to increase the number of part I examinations per year in countries like Malaysia, it would surely not be beyond the capability of the royal colleges to relax the restrictions imposed on the number of candidates. It cannot be much more difficult to collect and correct (by computer) 200 instead of 150 multiple-choice question papers.

In these days of declining British commercial influence it is very encouraging that British medicine and British medical qualifications should enjoy such a high reputation in this part of the world, and I feel sad that the royal colleges are apparently not prepared to make a positive effort to help young Commonwealth medical graduates and the medical schools which are training them by easing the present restrictions on the part I MRCP (UK) examination. This would, I suspect, be of much more practical value than "goodwill" visits by presidents to countries where these restrictions exist.

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The Rothschild principle

SIR,—In reviewing the results of applying the Rothschild recommendations to medical research (6 May, p 1167), you not only ignore what was just and sensible in Rothschild's criticism of the previous system but fail to make any constructive suggestions about how they might be met.

We are particularly concerned by at least one aspect of the manner in which the Medical Research Council categorises and organises its coverage of medical research and, as representatives of the British Paediatric Association, have expressed this long ago to the council. Although such important clinical areas as obstetrics and embryological and fetal growth are concealed by the incomprehensible title of the responsible "cell biology and disorders" board, these subjects do appear to be

¹ Imambaccus, Y, et al, in *Current Chemotherapy*, ed W Siegenthaler and R Lüthy, vol 1, p 495. Washington, D C, American Society for Microbiology, 1978.

² Vuye, A, and Pijck, in *Current Chemotherapy*, ed W Siegenthaler and R Lüthy, vol 1, p 492. Washington, DC, American Society for Microbiology, 1978.

³ *British Medical Journal*, 1977, 1, 1618.

specifically represented at Park Crescent. Paediatrics (or, better, child health) is not.

When it comes to health the child is father of the man; and research into the nature and origins of neonatal and childhood conditions is more likely to improve the health of our nation than further exploration of what to do when it is already too late to mend. For too long medicine, surgery, and obstetrics, with the emphasis on the adult and his or her problems, have been allowed to dominate the university schools and the interests of grant-giving bodies; yet when these subjects were named by the GMC more than 100 years ago as the fundamental elements of medical practice they included paediatrics, which is now no longer the case. Paediatrics may once have been the study of diseases peculiar to children and therefore on a par with other minor specialties; but it is now the general medicine and surgery of childhood. Its basic science is growth and development. Just as general and special pathology embraces all the clinical disciplines, so does paediatrics.

We ourselves heartily approve of the customer-contractor principle for a substantial proportion of nationally sponsored medical research. We do not identify the difficulties as you do. For us they derive from the frequent incapacity of the practising clinician to formulate projects from the problems he understands well enough; and the equally frequent incapacity of the basic researcher to comprehend the questions which only he has the skills to answer. Each is too often tragically and sometimes hilariously lost in the other's territory, and this is where the customer-contractor idea goes aground. The old, often-rehearsed wrangle about pure and applied science is comparatively irrelevant.

It is surely not too banal to beg for a constructive approach to these fundamental matters. A few clinical fellowships to enable the clinician to try his hand are quite inadequate. Nothing short of a quite massive change of attitude towards the training of some young clinicians so that they can be good customers from a position of some experience as contractors can create this vital relationship. Let us all be far more active in promoting this new climate even in the face of accumulating clinical apathy. Let us also formally recognise child health as a primary area of contractual demand. And may you, sir, come to understand that the inadequacies of the customer-contractor principle lie not in the principle but in deficiencies in both customer and contractor which are accessible to improvement if we all make the effort.

JOHN DAVIS
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What kind of cot death?

SIR,—We would like to reassure Dr A S Cunningham (6 May, p 1216) that the DHSS multicentre study of postneonatal mortality is very much aware of the need to investigate the relationship between sudden infant death syndrome (SIDS) and breast-feeding. A detailed interview is carried out with the parents of the infants who died and of living control infants. A great deal of the information collected at the interview relates to infant feeding practices.

We are impressed, however, with the numbers of SIDS victims who have received

neither cow's milk supplements nor cereals at any time during their life. This has resulted in much bewilderment being shown by bereaved parents who had been taught that breast-feeding would "protect" their baby. Similarly, much guilt is being felt by mothers who for one reason or another cannot breast-feed when they are told that their baby is at increased risk of SIDS because he is bottle-fed.

There can be little doubt that incorrect bottle-feeding contributes to infant deaths from hypernatraemic dehydration in conjunction with gastroenteritis and respiratory tract infections, but the relationship between bottle-feeding and SIDS is less clear. Of course "breast is best" as a general rule, but it may be that *correct* bottle feeding with "humanised" formulae is a very close second. Much harm can be caused by pressurising unwilling mothers into attempting to breast-feed, just as harm can be caused by neglecting to support mothers who *do* wish to breast-feed.

We intend to use multicentre data to examine the relationship between present-day infant feeding practices and SIDS and to present this in an early report.

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Prediction of gangrenous and perforating appendicitis in children

SIR,—For many years clinicians have been attempting to predict the severity of disease by means of clinical criteria. Most methods have been devised by clinicians who have quantified the differences between patients who have mild and severe forms of the same disease. Given that the populations at risk are identical, a predictive test should discriminate with similar accuracy wherever it is used. While it is gratifying to see that Mr D P Drake and Mr J G Knott (22 April, p 1052) have evaluated our clinical scoring index in children with appendicitis (26 November, p 1375), in effect they are comparing symptoms and signs from patients in a highly specialised regional paediatric centre with those from a district general hospital. The fact that Bangour General Hospital does not admit children under the age of 7 years and also that, of the 200 patients studied, children aged 7 to 16 years made up only 8% of the total may account for their criticisms of the method of prediction.

Since perforated and gangrenous appendices account for approximately 24% of all patients undergoing appendectomy, your correspondents would have correctly identified six of their 26 patients by applying probability theory alone. In fact the clinical scoring index correctly predicted 11 of their patients with macroscopic and microscopic perforation (groups I+II) and a further four patients were correctly predicted who had acute inflammation only. This results in an overall accuracy of 57%. It would therefore appear that although the two series of patients were not strictly comparable, the clinical scoring index was of more value than they imagine.

I would, however, agree that in children the three predictive factors listed may be poor discriminants. Increasing severity of pain may be described by an adult, but children are frequently unable to give an accurate description of the severity of their pain. The pulse rate in a child may be elevated by fear

and pain and similarly the total leucocyte count in normal children is frequently higher than in the adult.¹ We have now found our computer program for the differentiation of acute from gangrenous and perforated appendicitis to be sufficiently accurate to dispense with the routine estimation of the white cell count, although in adults when clinical features are used alone it is a reliable prognostic factor.

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¹ Doraiswamy, N V, *British Journal of Surgery*, 1977, **64**, 342.

Deep-vein thrombosis after hip replacement

SIR,—The recent article by Mr J D Stamatakis and others (22 April, p 1031) highlights the problem of the unpredictable results of prophylaxis against deep-vein thrombosis (DVT) in patients undergoing hip replacement. Papers have been published in favour of and against the use of low-dose heparin, warfarin, dextran-70, plaquenil, and now aspirin. It is of interest to consider why resistance to the effectiveness of prophylactic agents should be offered by this group of patients in particular when the results in the general surgical population are consistently favourable.

The answer is obviously multifactorial, but may lie partly with the severity of the operation of hip replacement. In support of this Nicolaides and Irvine¹ list the severity of the operation as a risk factor which predisposes to DVT. It is also known² that the rate of clinically detected thromboembolism rises with revisional hip surgery, where the operation time and blood loss are increased. At Gartnavel General Hospital patients undergoing hip replacement are monitored for the development of DVT using the fibrinogen uptake test and venography. We have observed that 50% of thrombi have begun forming on the first postoperative day (the day limb counting begins) and 80% in the first three days. We agree with others on this point. Although indirect, this evidence suggests that the operation itself is an important stimulus to thrombogenesis.

We began a prospective study in 1975 into the use of dextran-70. At this time all hip replacement patients underwent normotensive general anaesthesia and alternate patients were given 500 ml of dextran-70 in theatre. An early assessment revealed that, used in this way, dextran-70 had no effect on the overall incidence of DVT. What did influence the development of DVT, however, was the operative blood loss (measured gravimetrically), which was found to be significantly higher (mean 958±69 ml) in the 36 patients who subsequently developed DVT than in the 28 who did not (741±55 ml; $P<0.02$). The age, operative time, and risk factors were comparable in the two groups.

It may be, therefore, that operative blood loss is linked with the severity of the operation. This has significance in that anaesthetic techniques exist which are associated with reduced operative blood loss—for example, spinal or epidural (local), or hypotensive (general) anaesthesia. Use of such a technique for hip replacement procedures is therefore theoretically advantageous in this respect