vicaine are all of equal potency. Borica *et al.*[1] in a double-blind investigation involving 6,788 cases of mepivicaine administration found that in regard to penetrance, latency, and potency this drug was indistinguishable from lignocaine. Reporting over 1,000 cases given prilocaine, Crawford[2] states, "On the basis of this study, it would appear that prilocaine is equally potent with lignocaine and mepivicaine." Lund and Cwik[3] found that with epidural blocks 2% prilocaine gave the same degree of analgesia and motor blockade as 2% lignocaine.

That 2% solutions of these three agents occasionally produce inadequate anaesthesia when given epidurally in *conscious* patients is undeniable. Bonica *et al.* using mepivicaine found that only 86.6% of patients required no additional sedation, and that the 2% solution often failed to produce abdominal paralysis in epidural blocks. Crawford found that 2% prilocaine gave an incidence of successful epidural block of 92%, and this was increased to 98% when 3% solutions were employed. In a double-blind trial with a smaller number of cases Ekblom and Widman[4] compared epidural blocks with 0.5% L.A.C.-43 (a new local analgesic under trial), 2% mepivicaine, and 2% prilocaine (all with 1:200,000 adrenaline) and found that, while all agents gave perfect analgesia, only occasionally was complete muscular relaxation obtained.

In my own experience over the last two years 2% prilocaine has given consistently good results in epidural analgesia when concomitant general anaesthesia was used. In those cases where it is desirable for the patient to remain conscious throughout surgery I believe that the 3% solution should be employed. The great advantage of prilocaine is that this high concentration can be used with reasonable safety, as 3% prilocaine has a similar toxicity to 2% lignocaine.[5]

Dr. Mostert is quite right in pointing out that prilocaine induces methaemoglobinaemia. It must be remembered, however, that cyanosis due to this cause is not comparable with cyanosis due to hypoxia. While it requires 5 g. per 100 ml. of reduced haemoglobin to produce cyanosis, only 1.5 g. per 100 ml. of methaemoglobin is necessary for the same effect. This small reduction in the oxygen-carrying capacity is seldom of clinical importance, and patients at rest are completely symptom-free. Moreover, rapid reversal of methaemoglobinaemia can easily be achieved with intravenous methylene blue (1 mg./kg.), which itself is an extremely safe drug. Cyanosis has only occurred in my cases when 900 mg. of prilocaine has been given, though other authors have seen it after 600 mg. There are very few local analgesic procedures that require such high dosage. That cyanosis due to methaemoglobin can follow prilocaine should be borne in mind, as the clinical picture may be confused, but in itself it is not a serious drawback to the use of the drug.—I am, etc.,

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N.A.C. and Antibiotics in Cystic Fibrosis

SIR,—In the course of studies into the penetrability of respiratory tract mucus by antibiotics, both in the normal and in cystic fibrosis, we have noted the observations of Nakken *et al.*[1] and Reas[2] that penicillin is inactivated by cysteine and its esters. As N-acetylcysteine (N.A.C.) given by inhalation is coming into use as a mucolytic agent in cases of cystic fibrosis,[3] who are also likely to be on antibiotic treatment, we have investigated the effect of N.A.C. on a variety of antibiotics.

The effect was determined by titration in broth of various antibiotics against the *Oxford Staphylococcus* with and without the addition of N.A.C. at 5% (w/v). The test antibiotics were used at final concentrations of 0, 0.1, 0.5, 1.0, 2.0, 5.0, 7.0, and 10 μg./ml. in nutrient broth (2 ml. volumes). After addition to the broth and broth plus N.A.C. the mixtures were left at 37° C. for one hour before inoculation to allow inactivation to take place.

The inoculum used was 1 drop of a nutrient broth culture of *Oxford Staph.* 2×10^8 orgs./ml. per 2 ml. broths delivered from a Pasteur pipette. The tests were incubated for 18–24 hours at 37° C. and the minimal inhibitory concentrations read.

The Effect of N-acetyl Cysteine on Antibiotics

Test Antibiotic	Minimal Inhibitory Concentrations (μg./ml.)	
	Without N-acetyl Cysteine	With 5% N-acetyl Cysteine
Ampicillin	2·0	> 10·0
Benzyl penicillin	< 0·1	2·0
Cloxacillin	0·5	> 10·0
Methicillin	1·0	> 10·0
Oxacillin	< 0·1	> 10·0
Quinicillin	0·5	> 10·0
Ceporin	< 0·1	> 10·0
Erythromycin	1·0	1·0
Fucidin	2·0	2·0
Tetracycline	1·0	2·0

The results (see Table) show that there is inactivation of the penicillins tested, Ceporin (cephaloridine), and tetracycline, but that erythromycin and fucidin are unaffected.

These findings do not necessarily contraindicate the use of N.A.C. in conjunction with the susceptible antibiotics. Antibiotic therapy is not normally given solely by inhalation; and if adequate blood levels are maintained by other routes it may well not be important that their action at the surface of the respiratory tract is inhibited for the short periods for which N.A.C. inhalations are normally given. But our findings do suggest the inadvisability of relying on such antibiotics given solely by inhalation with, or immediately following, N.A.C.

If N.A.C. were absorbed into the blood-stream and effective blood levels were maintained, it might indeed interfere with the action of such antibiotics by whatever route they were given.

We have attempted, therefore, in a single case, to measure the effect of N.A.C. inhalation on penicillin blood levels as follows:

A child was given 250 mg. cloxacillin and 0.5 ml. blood samples were taken at 15, 30, 60, and 90 minutes, by finger-prick. The cloxacillin levels were estimated using the "fish-spine" bead method of Lightbown and Sulitzeanu,[4] standards being made up in the patient's serum taken before administration of the antibiotic. This was repeated after 24 hours on the same patient, 2 ml. of N.A.C. 20% w/v being given as an aerosol spray by compressed air at 30 minutes. No significant lowering in cloxacillin blood levels was noted.

We have also found that N.A.C. is rapidly inactivated by high oxygen concentrations.

Further studies are under way, but the following are our current conclusions:

(1) N.A.C. will destroy the effect of certain antibiotics at the surface of the respiratory epithelium during, and probably for a short time after, inhalation of this agent.

(2) It seems unlikely that it will have any appreciable effect on the blood levels of such antibiotics given by mouth or by injection.

(3) N.A.C., which is a reducing agent, is rapidly destroyed by high oxygen concentrations, and oxygen should therefore not be used as a vehicle for its administration through an inhaler.

This work was carried out under a research grant from the Cystic Fibrosis Research Foundation Trust, to whom acknowledgment is made.

—We are, etc.,

Queen Mary's Hospital for Children, Carshalton. DAVID LAWSON. B. A. SAGGERS.

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Obstruction of Gut by Colloid Laxatives

SIR,—I was interested to read Mr. W. A. Souter's article (16 January, p. 166), as I have recently seen several cases of retention of faeces with overflow in elderly patients on colloid-type laxatives (Normerol, I-so-gel). On rectal examination the gut was found to be enormously distended by a porridgy, semi-plastic mass of the laxative—obviously several days' accumulation. The obstruction was cleared and normal defaecation restored by a simple enema in each case. It would seem probable that partial dehydration in the colon produces a doughy plastic mass, which expands laterally under the forces of the peristaltic wave, tending thereby to obstruct the gut. I must say these experiences have rather damped my optimism in the use of "bulk" laxatives of this type in the senile gut.—I am, etc.,

Leeds 2. J. L. HORNER.

Cardiac Arrest after Triple-strength Plasma

SIR,—The case of cardiac arrest after rapid infusion of triple-strength plasma reported by Drs. J. S. M. Zorab, B. S. Gulsham, D. June Whitney, and B. D. Perrott (9 January, p. 105) reminds me of a very similar case which occurred in my practice two years ago. I report this briefly below to emphasize further the danger of rapid infusion of concentrated plasma, due I feel sure to its high potassium content.

The patient, a primigravida of 28, was brought into the Wrexham Obstetric Unit by the Flying Squad having had a moderately severe concealed accidental haemorrhage at home at 38 weeks pregnancy. By the time she reached hospital she had received one pint (570 ml.) of blood and one bottle of plasma (normal dilution), and her blood-pressure had risen from 90/70 to 120/80. As the foetal heart was still audible it was decided to deliver by caesarean forthwith. A Fi-test at this stage showed no evidence of fibrinogenopenia.

A living male baby weighing 6 lb. 13 oz. (3.1 kg.) was delivered through a lower-segment

incision, and a large clot was found behind the placenta. During the operation very free bleeding of non-clotting blood was occurring from the cut tissues. Suspecting fibrinogenopenia a bottle of triple-strength plasma was made up, and after the second bottle of blood was through this was infused under positive pressure, taking 10 minutes to do so. Shortly after this, cardiac arrest occurred as the abdomen was being closed. The chest was opened through the 5th left interspace, and internal cardiac massage was applied. The usual stimulants were given and after two to three minutes a spontaneous heart beat was restored. The chest was closed some 30 minutes later.

After a relatively uneventful puerperium she was discharged home with her baby 20 days after operation, with no ill effects.

Although we had no biochemical or electrocardiographic confirmation we thought the most likely cause for this near disaster was the high potassium content of the plasma infused.—I am, etc.,

D. B. WHITEHOUSE.

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Phenylbutazone and Leukaemia

SIR,—The possible association between phenylbutazone and leukaemia continues to evoke interest.[1–13] Innis,[6] in commenting on our paper,[3] believed that we were mistaken in saying that before accepting a relationship of cause and effect between the drug and the disease it would be necessary to show that leukaemia occurred in treated patients in a significantly greater proportion than in the general population. He believes that the controls should be patients with rheumatoid arthritis who have not been treated with phenylbutazone. However, of the five patients reported none was diagnosed as having rheumatoid arthritis. It is true that all had "arthritis," but re-examination of the case records shows that in no case was a definite diagnosis of rheumatoid arthritis made. Ideally the controls should be persons of the same age and sex with the same medical condition, but this is impracticable. The controls we in fact used were cases of chronic leukaemia, lymphoma, and allied disorders. Doll[7] suggested that patients with different forms of cancer might be suitable as controls, and this deserves further consideration. The matter would be best approached by doing a prospective study comparing phenylbutazone with another drug. This has been suggested to our rheumatology colleagues, but, at least in Australia, appears to be unworkable. It might, however, be practicable in other countries with large populations of rheumatic patients, and we would like to see such a trial started.

The possible relationship of the rheumatic disorders and leukaemia requires further study. Abbatt and Lea,[8] using Ministry of Pensions records, found a positive correlation between leukaemia and "rheumatic diseases." These rheumatic diseases included all forms except those of traumatic origin. Rheumatoid arthritis, ankylosing spondylitis, and osteoarthritis were included, but information is not available as to how many of each type there were.[9] Court-Brown and Doll[10] found that the incidence of leukaemia was higher in patients with ankylosing spondylitis who had been treated with radiotherapy when compared with controls. They considered a simple association between leukaemia and ankylosing spondylitis to be unlikely. In their study no great attention was paid to drug ingestion and it is possible that some of the leukaemic patients may in fact have received phenylbutazone as well as irradiation. Court-Brown and Doll[7] are studying a group of spondylitics who have not been irradiated to see if there is any excess of leukaemia among those treated with phenylbutazone.

Even if phenylbutazone is causally associated with leukaemia it must account for only a small proportion of cases, and the risks to an individual patient taking the drug are not high.[11] It has an important bearing, however, in considering the aetiology and pathogenesis of leukaemia. If the drug does cause leukaemia, however small the numbers, this must be considered in relation to the problem of leukaemia as a whole.—We are, etc.,

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"Unprepared" Pyelograms

SIR,—I have been impressed by the value of "unprepared" intravenous pyelograms in the management of renal colic, yet have been unable to find any reference to the subject in the literature, despite inquiry through appropriate urological authorities. By an "unprepared I.V.P." I mean simply films taken at 15 and 30 minutes only, rather than the usual series, plus, of course, a plain film if one has not been done on admission, or in the previous two or three days, the films being taken as soon as possible after admission, and without preparation of any sort. Such an I.V.P. will often show a non-functioning kidney, or a nephrogram only, giving clear evidence of an obstruction below, whereas if one waits for an appointment for an I.V.P.—usually some days or some weeks hence—the usual result is normal function of both kidneys.

I have been stimulated to write this letter by the fact that in recent weeks we have had a couple of patients from what might be described, in current usage, as from "fully developed" countries who had had several previous attacks of renal colic, but an I.V.P. on each occasion (done in the usual leisurely out-patient fashion) had shown perfectly normal function of both kidneys, and no cause for the colic could be established. These people had attacks of colic here, and an I.V.P. was done as soon as possible after admission (in practice, as soon as the *x*-ray department opened on the morning after admission—for both were admitted during the night). In both cases the I.V.P. showed a non-functioning kidney on one side. In one case the causal stone could be seen as an opacity in the line of the lower ureter. In the other case the cause of the colic could not be seen radiologically, but we could be certain there was a cause because of the changes shown in the pyelogram. The patient was repatriated to his own country before investigations could be completed here. It is immediately admitted that we did not pin-point the cause in this latter case, but it is worth notice that an I.V.P., done unprepared as soon as possible after admission, did show pathology, whereas previous I.V.P.s had been normal.—I am, etc.,

J. M. FOREMAN.

Lautoka Hospital, Fiji.

Mammography and Breast Cancer

SIR,—The figures given in your leading article (2 January, p. 5) suggests to me that the use of this method to screen the population may become at least as vital as is cytology in the detection of cervical carcinoma. Breast cancer is commoner than carcinoma of the cervix. It has been said that five per cent. of all women develop it.[1] Detection of the growth while it is localized is of the first importance in both situations.

The problems of cost and of training cytologists have now been faced by the profession and the Ministry of Health in so far as cervical smears are concerned, but only after years of procrastination. If the value of mammography is established perhaps we should try to give a lead on this occasion instead of lagging far behind other countries. The impetus should come from surgeons and radiologists and screening should not be delayed until the women themselves clamour for it. Cervical cytology was finally demanded by the National Federation of Women's Institutes.—I am, etc.,

J. M. GATE.

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Need for New Medical Schools

SIR,—Mr. T. Stuart-Black Kelly's letter (9 January, p. 124) is particularly timely, and emphasizes the extent of the impending crisis in medical education. In the West Country, where people in some regions have to wait lengthy periods for some forms of medical care, we are well aware of the need to train more doctors and to staff more hospitals.

Mr. Kelly rightly stresses the fact that a latent period of ten years before the new schools could produce results is excessively and unnecessarily long. The present writers have pointed out, in a letter recently printed in the *B.M.J.* (8 August, p. 383), that the new universities which have schools of pharmacy could readily undertake the instruction of students in the preclinical part of the medical course.

This institution is to become a university at Bath in the near future, and is staffed and equipped to teach physiology, biochemistry, and pharmacology to the required