In 1969, during an outbreak of giardiasis in a children's psychiatric hospital, six children aged from 2 to 10 years suddenly developed bizarre behaviour after infestation. In each case after treatment with metronidazole and when the stools had become free from cysts the child's behaviour returned to its previous pattern. The E.E.G. in one mentally retarded patient aged 5 while infested with *G. lamblia* showed generalized, non-classical spike and wave complexes suggesting a cerebral lesion, probably at a subcortical level, or a metabolic disorder. At the same time he was withdrawn and irritable, with loose, offensive stools. After eradication of the infestation the E.E.G. became normal and the child became active and took an interest in his surroundings. The E.E.G. of the other five children showed minor abnormalities before infestation and it was not repeated.

Children returning from abroad are often referred for child guidance therapy for behaviour disorders. Giardiasis should be borne in mind in these cases. A stool examination might save months of psychological investigations. *Entamoeba histolytica* is known to cause meningoencephalitis.^{1,2} The infection may be acquired from swimming in fresh water in hot weather, and the infection of the olfactory lobes of the brain together with inflammation and ulceration of the nasal mucosa points to the cribriform plate as the most likely portal of entry.³ Probably a similar chain of events may occur in giardiasis.—I am, etc.,

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¹ Culbertson, C. G., *American Journal of Clinical Pathology*, 1961, 35, 1952.

² Symmers, W. St. C., *British Medical Journal*, 1969, 4, 449.

³ *British Medical Journal*, 1970, 1, 581.

Deaths during Dentistry

SIR,—After referring to four deaths that had occurred with operator anaesthetists Dr. P. J. Tomlin (2 November, p. 288) continues: "There may well have been a fifth case involving a 10-year-old boy in Lancashire who died after nitrous oxide, oxygen, and halothane anaesthesia." For the record, the anaesthetic in this case was in fact given by a consultant anaesthetist.

In Dr. Tomlin's final case, that of a 13-year-old boy in Croydon who died during recovery from a brief administration of nitrous oxide, oxygen, and halothane, the anaesthetic was given, as Dr. Tomlin correctly states, by a "separate anaesthetist." This was in fact a medical practitioner who since the war has practised dental anaesthesia to the exclusion of all other work and estimates his experience at about 175,000 administrations. Dr. Tomlin attributes this death to pulmonary oedema. I gave evidence at the inquest and Dr. Tomlin must surely have noted from the details the coroner sent him that the anaesthetist, the pathologist, and I were agreed that the death was almost certainly caused by fainting.—I am, etc.,

J. G. BOURNE

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Delirium after Surgery

SIR,—We wish to correct some important misconceptions arising from your leading article on this subject (21 September, p. 702).

Most of the data presented on cardiac

surgery were from a paper published by Tufo *et al.* in 1970.¹ The early operative mortality in this series was 15% and, more significantly, abnormal neurological signs were detected in no fewer than 44% of the 85 survivors; 15% of these still had neurological abnormalities at the time of discharge from hospital. No mention was made of Branthwaite's more recent study, which reported an incidence of neurological dysfunction of 19% in 417 patients surviving open heart surgery, of whom only 4% had residual neurological disability on discharge.²

We believe that in 1974 the incidence of postoperative neuropsychiatric complications in most cardiac surgical units has been still further reduced. This is due largely to improvement in perfusion techniques directed towards eliminating microembolism during cardiopulmonary bypass. Our own hospital mortality for 166 open heart operations during the year between 1 September 1973 and 31 August 1974 was 3.6%. Eight patients showed postoperative neurological or psychiatric abnormalities and none of these were permanent.—We are, etc.,

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¹ Tufo, H. M., Ostfeld, A. M., and Shekelle, R., *Journal of the American Medical Association*, 1970, 212, 1333.

² Branthwaite, M. A., *Thorax*, 1972, 27, 748.

Management of Lithium Treatment

SIR,—Dr. S. P. Tyrer and others (12 October, p. 108) miss two main points of our paper (14 September, p. 650). We reported that when a patient takes Priadel once a day the plasma lithium varies two- to four-fold in the course of 24 hours. We also showed that oral propantheline bromide, known to delay stomach emptying, lowers this plasma swing when taken with the Priadel. Therefore gastrointestinal function to some extent determines plasma lithium level. How tablets release lithium into solutions of different acidity in the laboratory is a secondary matter which may or may not be relevant to the clinical finding.

Our lithium tolerance test is no more than a name for the practice of measuring the plasma lithium at several times on the same day after a routine dose (instead of only once) to see how much diurnal swing in plasma lithium is taking place in the course of treatment. This is quite different from the renal lithium clearance test, mentioned by Dr. Tyrer and his colleagues, which is a set of measurements at the start of treatment so as to calculate the dose needed to establish in that patient any given basal plasma lithium level—on the assumption that renal and gastrointestinal functions remain constant. They also draw attention to their finding that subjects taking slow-release lithium tablets may have 4% or more of the lithium dose in their stools (up to 7 mEq/24 hours). We originally thought this might be so and set out to look for it in a number of patients without, however, finding it, as we noted. I hope they will publish their results in more detail, showing the psychiatric natures of the subjects, their previous medical histories, the periods

during the course of lithium treatment when these positive findings in the stools were obtained, and so on, so that we can judge whether lithium in the stools is a general or a particular phenomenon and why there is this discrepancy between our findings.

In this connexion I should mention that we have so far failed to confirm another finding from Dr. Hullin's laboratory—that patients taken off lithium after a long course of treatment continue to excrete small amounts of lithium in the urine intermittently for months thereafter. In our metabolic ward, long-established and run by two experienced sisters and two experienced night nurses, we thought at first we had confirmed the finding. All our seven patients have single rooms and either excrete in their rooms or in a toilet for which a nurse holds the key. In spite of these arrangements we eventually discovered a patient who was not only incapable or unwilling in keeping her faeces uncontaminated by her urine but who also managed to introduce her lithium-containing urine into the specimens produced by patients off lithium treatment and also into the urine from patients who had never had lithium. Since her exclusion from the ward we have had no further positive findings.

I think, therefore, when reporting lithium in stools or urine it is necessary also to report the metabolic ward conditions under which specimens were obtained. In the end these depend on co-operation from subjects, and some are by personality or illness incapable of co-operating consistently. They also depend on capable, experienced staff, but it is necessary to check that each nursing shift in fact had such a nurse on it. Everybody has days off, holidays, sickness, attendance at hospital meetings which may take them off the ward at crucial times.

Dr. E. H. Bennie (26 October, p. 232) raises the question of what constitutes a toxic plasma level of lithium but fails to consider either how such levels can be discovered or that the duration, and possibly the degree of intermittency, of a particular lithium level is important as well as its height. Most of the advice on toxic levels derives from seriously-ill or fatally toxic cases where it is not known for how many days or weeks beforehand the level has been over 2 mEq/l., and advice is given on the assumption that patients will be seen only infrequently. My experience is that short periods of high lithium levels are not injurious and are permissible when the patient is under very close supervision with laboratory support. However, as our paper tried to show, there is as yet no evidence that such high lithium levels have any therapeutic value.—I am, etc.,

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Uterine Contractions due to Heparin

SIR,—We would like to report an unusual side effect of intravenous heparin.

A 32-year-old multigravida in her thirty-second week of pregnancy was admitted to hospital suffering from pain in her right calf muscles of 24 hours duration. Examination revealed deep vein thrombosis of her right leg. She was started on 10,000 IU of heparin intravenously. Twenty minutes later she had severe abdominal pain

together with uterine contractions and signs of fetal irritability. Relief was achieved with a pethidine injection. The relationship of the heparin injection to the uterine contraction was noticed but we decided to continue the treatment. After the second dose of heparin six hours later the patient immediately had the same abdominal pain, which was again relieved by pethidine. At this point we became sure that the uterine contractions were due to the heparin injections. Heparin was stopped, no other anticoagulants were given, and the patient was treated conservatively.

So far as we know no such reaction to heparin has been reported before. We thought of a small retroplacental haemorrhage due to heparin as a possible cause of pain, but the speed of the reaction and the relatively small dose of heparin and absence of complications afterwards made this unlikely.—We are, etc.,

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Treatment of Aspergillosis

SIR,—We were interested in the studies of Drs. L. J. R. Milne and G. K. Crompton (28 September, p. 803) on the in-vitro action of emetine on strains of aspergilli, as we have also studied the effect of emetine on fungi.

Abd-Rabbo¹ reported the anti-fungal effect of dehydroemetine in two cases of tinea favosa, and Abd-Rabbo and Yusef² reported in-vitro action against *Microsporum gypseum* and *Thielavia sepedonium*. Jesiotr³ reported the inhibitory action of emetine against a single strain of *Nocardia asteroides* and one of *Cryptococcus neoformans*. Because of these reports we have studied one strain of *N. asteroides* and eight strains of *Candida albicans* in addition to two strains of *Aspergillus fumigatus*.

The minimum inhibitory concentration of each strain was determined by an agar-dilution method or tube dilution. The studies of Child *et al.*⁴ showed that emetine accumulates in rat lung and that levels up to 17.7 µg/g wet tissue were obtained. In view of these findings we have tested our strains of *Candida* at levels up to only 32 µg/ml and the other organisms at levels up to 200 µg/ml. None of the organisms showed inhibition of growth at these concentrations.

We support the views expressed by Drs. Milne and Crompton and wish to add that emetine would appear to be of no value in the treatment of infections with the other organisms we have studied.—We are, etc.,

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- 1 Abd-Rabbo, H., *Lancet*, 1964, 2, 1013.
- 2 Abd-Rabbo, H., and Yusef, H. M., *Journal of Tropical Medicine and Hygiene*, 1966, 69, 51.
- 3 Jesiotr, M., *Scandinavian Journal of Respiratory Disease*, 1973, 54, 326.
- 4 Child, K. J., *et al.*, *Journal of Pharmacy and Pharmacology*, 1964, 16, 65.

Use of Intravenous Urography

SIR,—I believe that the conclusions drawn by Dr. R. Kreel and his colleagues (5 October, p. 31) on the use of intravenous

urography (I.V.U.) in the investigation of haematuria are ill-founded and potentially dangerous. It is proposed that "a considerable saving in radiological resources might be made by ensuring that in cases of this sort a midstream specimen of urine is examined followed by cystoscopy." Presumably it is suggested that if these two investigations are normal the I.V.U. can be omitted.

Surely one of the features of urological malignancies is that they bleed one day and not the next? Certainly the absence of microscopic haematuria does not exclude neoplasm. If we are to change our practice and do cystoscopy before I.V.U. where does this leave us? If the bladder is normal we need an I.V.U. to exclude upper tract neoplasia, and if cystoscopy shows a bladder tumour we need to know if there is upper tract dilatation or co-existing urothelial malignancy in the renal pelvis or ureter. Worse still, if the subsequent I.V.U. shows no contrast medium excretion on one side the cystoscopy must be repeated to perform retrograde pyelography or ascending ureterography.

If urological malignancy is to be detected at an early and curable stage I believe that every case of haematuria must be carefully and methodically investigated. I.V.U. provides the basic fundamental information on the urinary tract on which supplementary special investigations may be selected if necessary. Attempts to short-circuit this well-established diagnostic routine in an attempt to save "radiological resources" are likely to be made at the expense of considerable clinical confusion, which in time is likely to lead to the loss of a patient's life owing to delay in the diagnosis of curable cancer.—I am, etc.,

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Alpha-adrenoceptor-blocking Drugs in Asthma

SIR,—We were interested to read the report by Professor S. Bianco and others of the prevention of exercise-induced asthma by an alpha-adrenoceptor-blocking drug, indoramin (5 October, p. 18). Following our demonstration of a significant reduction in histamine-induced asthma by an alpha-receptor-blocking drug, thymoxamine,¹ which has little antihistaminic activity,² we have been interested in the possible role of alpha-receptors in the bronchial muscle in the pathogenesis of bronchoconstriction in asthma.

Some years ago Szentivanyi³ postulated that bronchial asthma might result when there is an imbalance between bronchial beta - receptors (bronchodilator) and bronchial alpha - receptors (bronchoconstrictor). If this were so enhanced bronchodilatation might occur when a beta-stimulant drug is given concurrently with an alpha-blocking drug. We have recently completed experiments where this hypothesis has been tested using aerosol salbutamol with intravenous indoramin or thymoxamine. We found that when salbutamol was given with either alpha-receptor-blocking drug a statistically significantly greater increase in the forced expiratory volume in one second (FEV₁) was obtained than with salbutamol alone, whereas the alpha-blocking drugs

alone had no greater intrinsic bronchodilator activity than placebo.

These results will be published in detail later but meantime we feel that these observations have possible therapeutic implications. It has been shown in vitro that patients with severe asthma have high leucocytic adenylate cyclase activity. This activity was not further increased by isoprenaline alone or by an alpha-blocking drug alone (thymoxamine) but was increased when isoprenaline and thymoxamine were given together.⁴ Patients with severe asthma—or status asthmaticus—are characteristically unresponsive to beta-adrenoceptor-stimulant drugs and may remain so for a period even when large doses of corticosteroids are given parenterally. Is this possibly because the alpha-adrenoceptors are more active than normally? There is evidence that this is the case in human bronchial muscle exposed to bacterial endotoxins in vitro.⁵ Since bacterial infection is often a precipitating cause of severe asthma it would seem reasonable to give such patients an alpha-receptor-blocking drug, such as thymoxamine or indoramin, intravenously in an attempt to restore rapidly sensitivity of the beta-receptors to beta-adrenoceptor-stimulant drugs. We have done this in a small number of cases and have seen this beneficial effect in some but not all patients.—We are, etc.,

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¹ Gaddie, J., *et al.*, *British Journal of Diseases of the Chest*, 1972, 66, 141.

² Gaddie, J., Skinner, C., and Palmer, K. N. V., *Lancet*, 1972, 2, 657.

³ Szentivanyi, A., *Journal of Allergy*, 1968, 42, 203.

⁴ Alston, W. C., Patel, K. R., and Kerr, J. W., *British Medical Journal*, 1974, 1, 90.

⁵ Svedmyr, N., *Postgraduate Medical Journal*, 1971, suppl. vol. 47, p. 120.

Chemoprophylaxis against Tuberculosis

SIR,—Permit me to add a footnote as a complementary paragraph to your leading article (12 October, p. 63) as this is a subject which interests many of your readers both at home and abroad.

Babies born of mothers with open tuberculosis incur the obvious risk of infection if breast-fed, or alternatively an equally severe and often fatal gastroenteritis (in developing countries) if not so breast-fed and looked after by the mother. In such cases it is possible to: (1) allow the mother to breast-feed her baby; (2) give the baby isoniazid chemoprophylaxis; and (3) immunize the baby with isoniazid-resistant B.C.G. vaccine.¹—I am, etc.,

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¹ Hendrickse, R. G., in *Management and Treatment of Tropical Diseases*, ed. B. G. Maegraith and H. M. Gilles, p. 200. Oxford, Blackwell, 1971.

Variability in Response to Drugs

SIR,—Professor Michael D. Rawlins in his admirable article (12 October, p. 91) surveys some of the factors which determine the response to drugs. He refers in particular