Lastly, we must point out that when hyperthermia is given together with cytotoxic drugs, as is current practice in Edinburgh, the combined treatment is associated with a definite mortality. It therefore appears to us that further controlled studies and considerably more data are required before hyperthermia can be accepted as having a significant role to play in cancer management.—We are, etc.,

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¹ Henderson, M. A., and Pettigrew, R. T. P.,
Lancet, 1971, 1, 1275.

Glucagon Therapy in Acute Pancreatitis

SIR,—Your leading article (1 December, p. 503) and the subsequent letter from Mr. C. W. Imrie and Professor L. H. Blumgart (5 January, p. 38) reflect a surge of interest in the treatment of acute pancreatitis. Though there are disagreements about many aspects of this condition, there is no dispute that its mortality rate is unacceptably high.

Unfortunately, very few trials of methods of treatment have been designed in ways which can lead to scientifically valid conclusions. As a consequence many misleading claims for different drugs have been made. It is for this reason that the Medical Research Council has set up a working party which is about to start a randomized, controlled clinical trial to compare glucagon, aprotinin (Trasylol), and a placebo in the treatment of acute pancreatitis.

One of the difficulties in assessing the treatment of acute pancreatitis in Britain is the fact that no single centre has the opportunity to treat sufficiently large numbers. Therefore our trial will be conducted on a multi-centre basis and many colleagues have already indicated their willingness to participate. We know that when our findings are reported they will be subjected to close scrutiny and that they may be criticized on the grounds of faulty dosage. We therefore wish to stipulate at this stage that the purpose of the trial is to test current claims for glucagon and aprotinin. If these prove to be wrong, it will be possible to test alternative dosages and alternative drugs.—We are, etc.,

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Amphotericin Pharmacophobia and Renal Toxicity

SIR,—Professor W. St. C. Symmers (24 November, p. 460) has emphasized the need to treat systemic fungal infection with amphotericin B. He also quotes evidence that the drug is nephrotoxic and that this fact has deterred physicians from prescribing it. Renal toxic manifestations of amphotericin B tend to return to normal on cessation of therapy, particularly if the total

dosage is less than 5 g.¹ Winn² has reported irreversible renal toxicity in patients who received total doses of 14 g, 167 g, and 21 g respectively of amphotericin. Reports of irreversible renal toxicity with total doses of less than 5 g are rare. There is evidence^{3,4} that a total dose of at least 2 g and preferably 3 g is necessary for cure of systemic fungal disease. Drutz *et al.*⁵ have criticized this recommendation and have successfully treated 13 patients with a variety of mycotic diseases using daily serum levels as a guide to therapy, adjusting dosage to achieve twice the minimum inhibitory concentration against the causative organism. Five of Drutz's 13 patients, however, in fact received a total dose of at least 2 g of the drug. The rapid infusion⁶ of moderate doses (never more than 45 mg daily) of amphotericin over a prolonged period, to achieve a total dose of 2.5-3 g, is probably the best way to use this drug. Renal toxicity should not give cause for anxiety until the blood urea reaches 100 mg/100 ml and should not lead to premature cessation of treatment before this.—We are, etc.,

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¹ Abernathy, R. S., *Medicine*, 1973, 52, 385.

² Winn, W. A., *Medical Clinics of North America*, 1962, 47, 1131.

³ Tolhurst, J. C., Buckle, G., and Williams, S. W., *Chemotherapy with Antibiotics and Allied Drugs*, p. 115. Canberra, Australian Government Publishing Service, 1972.

⁴ Edwards, V. E., Sutherland, J. M., and Tyrer, J. H., *Journal of Neurology, Neurosurgery, and Psychiatry*, 1970, 33, 415.

⁵ Drutz, D. J., Spickard, A., and Koenig, M. G., *Antimicrobial Agents and Chemotherapy*, 1966, 6, 202.

⁶ Fields, B. T., Bates, J. H., and Abernathy, R. S., *Applied Microbiology*, 1971, 22, 615.

Toxoplasmosis and Embryopathy

SIR,—The letter from Drs. Jean M. Scott and M. Layinka Swinburne (17 November, p. 422) and the resolution of the 13th Congress of Medical Women's International Association on Toxoplasmosis have oversimplified the problem as it is known in the U.K. Ruoss and Bourne¹ followed up 3,700 pregnant women throughout their pregnancies. Seven women converted from serologically negative to positive with the dye test; all seven produced normal uninfected babies. The Public Health Laboratory Service performs almost all the tests for toxoplasma antibody in England and Wales and finds about 50 congenital toxoplasmosis cases per year, which is equivalent to 1 in 14,000 pregnancies. Ross *et al.*² estimate an incidence of 1:30,000. It is reasonable to suppose, however, that cases may be misdiagnosed and that the incidence is higher. There is good evidence that the incidence in the U.K. is between 1 in 4,000¹ and 1 in 14,000. This is lower than in France and Germany and probably lower than the incidence of rubella and even cytomegalovirus disease. Clearly more work needs to be done to find the incidence more accurately.

If it is decided that this incidence is too high, what can be done about it? The therapy of toxoplasma infection during pregnancy is not as effective as that against syphilis so that the testing of sera during pregnancy, which would be expensive, would be unlikely to be very beneficial in prevent-

ing cases. It is also doubtful whether treating congenitally infected newborn babies is very rewarding. Might it not be more useful to protect women of childbearing age by instructions in avoiding the eating of raw meat and contact with the oocysts from infected cat faeces? More information is needed about the route of the oocyst; does it travel from soil, uncooked food, or flies to man?

In the long run protection by infection before pregnancy may be best. Is this to be achieved by vaccines? Such vaccines as have been tried in animals are of very limited value. Rubella is controlled by the use of an effective vaccine, but the immunity mechanism is probably different from that in toxoplasmosis. Perhaps we should persuade the veterinarians to make a vaccine for cats, or simply encourage contact between cats and young girls so that the childbearing population is protected before pregnancy.

I apologize for raising so many unanswered questions and speculations, but I hope this letter illustrates that the time is not yet ripe for a publicity campaign to the public when the medical profession has not yet enough knowledge to give sensible advice.—I am, etc.,

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¹ Ruoss, C. F., and Bourne, G. L., *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 1972, 79, 1115.

² Ross, C. A. C., Bell, E. J., Kerr, M. M., and Williams, K. A. B., *Scottish Medical Journal*, 1972, 17, 252.

High-dose Frusemide in Renal Failure

SIR,—We wish to make some comments about the paper of Dr. F. Cantarovich and his colleagues (24 November, p. 449) concerning the beneficial use of high-dose frusemide in established acute renal failure, since our own results appear different from those reported.

We conducted a single-blind randomized study on 66 patients with acute oliguric renal failure between 1971 and 1973. Criteria for retaining the patients in the study were as follows. (1) Presence of established acute renal failure with initial urine output less than 500 ml/day and remaining less than 20 ml/hr after correction of shock and/or hypovolaemia when present; low urinary urea concentration; normal or high sodium concentration and/or urine:plasma osmolality ratio less than 1.1. (2) Absence of obstructive uropathy; absence of glomerulonephritis or systemic disease involving the kidney.

Plasma urea levels were maintained below 200 mg/100 ml, using haemodialysis when necessary. To 33 of the patients a first dose of frusemide (3 mg/kg) was given intravenously and followed every four hours by doses ranging from 1.5 to 6.0 mg/kg, according to the diuretic response. The maximum daily dose was 1,200 mg. If no diuretic response was observed after three injections (diuresis <20 ml/hr) frusemide was temporarily discontinued, but further treatment with the same protocol was attempted every five days until diuresis occurred. The remaining 33 patients did not receive frusemide and served as controls; this group did not differ significantly in respect of aetiology of acute renal failure, sex ratio, initial urine output, or mortality from the treated group. No significant differences in the results of treatment were seen between the two groups (see table).

The differences between the results obtained by Dr. Cantarovich and his colleagues and our own lead us to point out the salient