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.,

MARY DOUGLAS
ALLAN O. LANGLANDS
J. A. ORR

Department of Radiotherapy,
Western General Hospital,
Edinburgh

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.,

R. B. WELBOURN
Chairman of Working Party

Department of Surgery,
Royal Postgraduate Medical School and
Hammersmith Hospital,
London W.12

ALAN G. COX
Co-ordinating Secretary

Clinical Research Centre and
Northwick Park Hospital,
Harrow, Middlesex

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.,

ROSS FORGAN-SMITH
J. H. DARRELL

Department of Bacteriology,
Royal Postgraduate Medical School,
London W.12

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.,

D. G. FLECK

Public Health Laboratory,
St. George's Hospital,
London S.W.17

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

	Control Group		Treated Group		P
	No.	Mean $\pm$ S.E.M.	No.	Mean $\pm$ S.E.M.	
Total anuric period (diuresis <100 ml/day) (days) ..	19	10.58 $\pm$ 1.14	21	8.43 $\pm$ 1.66	>0.2*
Total oliguric period (diuresis <500 ml/day) (days) ..	17	15.59 $\pm$ 1.77	17	11.94 $\pm$ 1.26	>0.05*
No. of dialyses	22	6.09 $\pm$ 1.15	20	5.50 $\pm$ 0.72	>0.5†
Time to reach spontaneous decrease of blood urea (days) ..	22	22.05 $\pm$ 2.41	19	19.53 $\pm$ 1.69	>0.2*

*Student's *t* test.

†Mann and Whitney test.

differences between the two protocols utilized. (1) They used higher doses of frusemide—2,000 mg in repeated daily doses until dialysis became unnecessary. (2) It is not stated in their series whether patients treated with frusemide were similar to the controls in all respects—for example, aetiology and severity; were the two patients with obstructive uropathy and acute glomerulonephritis in the treated or control group? (3) What was the mode of randomization? The very disparate numbers of patients treated with frusemide (39) and without (19) during the second period (1969-72) is disturbing, particularly if "treatment was allocated on an alternated patient basis." As suggested a few lines below this statement, the explanation for this difference is perhaps that some patients were excluded from the control group because they had received frusemide before referral to the hospital. If so, the two groups become dissimilar and cannot be submitted to further statistical evaluation.

Since the results of our strictly randomized study do not confirm a beneficial effect of frusemide in established acute renal failure, we do not agree with the conclusions reached by Dr. Cantarovich and his colleagues.—We are, etc.,

D. GANEVAL

D. KLEINKNECHT

L. A. GONZALES-DUQUE

Hôpital Necker,
Paris

Correction of Serum Calcium Measurements

SIR,—It will not be long before the clinicians at this hospital read the two articles on the above subject (15 December, p. 640 and p. 643) and ask when I intend to correct my serum calcium measurements for the patient's serum albumin level. This will put me in somewhat of a dilemma. For a measured serum calcium of 8.0 mg/100 ml and a serum albumin level of 3.8 g/100 ml corrected calcium level, according to Dr. E. M. Berry and his colleagues (p. 640), would be 8.7 mg/100 ml, yet according to Dr. R. B. Payne and his colleagues (p. 643) it would be 8.2 mg/100 ml. Should I therefore give them both corrections and let them exercise their clinical freedom in choosing which correction best suits the clinical situation?—I am, etc.,

C. SANDERSON

Biochemistry Department,
Airedale General Hospital,
Keighley, Yorks

Acute Pancreatitis and Diabetic Ketoacidosis in Hypothermia

SIR,—In their paper reporting the apparent association of acute pancreatitis and diabetic ketoacidosis with hypothermia Dr. D. Maclean and his colleagues (29 December, p. 757) fail to mention whether arterial or

venous samples were used for the measurement of serum amylase and blood glucose levels. Conclusions drawn from venous samples taken during hypothermia are notoriously unreliable because of stagnant blood flow in the cold.¹ The mean serum amylase value for the series $\pm$ 1 S.D.) was 386 $\pm$ 556 Somogyi units/100 ml and that of blood glucose 149 $\pm$ 158 mg/100 ml, indicating a huge scatter of values. Because of this scatter it is likely that these means would not be significantly different from means of values measured in a control group of subjects with normal body temperatures.

Even acid-base calculations made from arterial samples can be misleading unless corrected to what they would be at normal body temperatures.² It is generally accepted that acidosis is not usually severe during hypothermia but may be during rewarming.³ It is likely to be dangerous to the patient if measures are taken because of diagnoses made from biochemical estimations subject to error due to cold.—I am, etc.,

R. E. G. SLOAN

Cheltenham, Glos

- Cooper, R. E., in *Recent Advances in Medicine*, ed. D. N. Baron, N. D. Compston, and A. M. Dawson, 15th edn., p. 343. London, Churchill, 1968.
- Hockaday, T. D. R., and Fell, R. H., *British Journal of Hospital Medicine*, 1969, 2, 1083.
- Keatinge, W. R., *Survival in Cold Water*, p. 70. Oxford, Blackwell, 1969.

Effect of Viruses on Lymphocyte Reactivity

SIR,—Studies of lymphocyte sensitization in health and disease continue to appear in large numbers. The important observations made by Miss Elizabeth Thompson and others (22 December, p. 709) are therefore most timely, since it is not widely appreciated how exposure of lymphocytes (both in humans and experimental animals) to certain common viruses may greatly influence their reactivity to antigens. The phenomenon first obtruded itself in the M.R.C. Demyelinating Diseases Unit in Newcastle in early 1972, when the occurrence of an influenza epidemic was accompanied by wildly random results in the macrophage electrophoretic mobility test.^{1,2} Between 25 January and 2 March all normal guinea-pigs within the colony used to prepare macrophages for the test were found to be sensitized to P.P.D. as well as to encephalitogenic factor (E.F.). A description of what occurred has been published,³ and the episode led to a systematic study of the manner in which guinea-pig lymphocytes reacted to the above antigens after injection with some common viral vaccines. It was found that cellular sensitization occurred not only to the specific inoculum but also to P.P.D. and to E.F., and indeed in lesser degree to other apparently unrelated antigenic stimulants.⁴

Not only do cells from subjects exposed to banal viral infections develop unusual reactivity, but they appear to be "on edge" in the sense that they undergo "spontaneous" transformation in vitro to a greater degree than normally. Such irritability of the cells may persist for some weeks and may indeed occur in the presence of an influenza epidemic even when the subject concerned has not suffered obvious clinical infection.⁵

From the experience gained in the winter of 1971-2 it was possible by introducing the most rigorous discipline in the animal house and laboratories (especially the wearing of masks and removal of workers with "colds") to prevent a recurrence of the troubles in the winter of 1972-3. Inadvertent guinea-pig exposure to infections may be monitored by measuring the response of peritoneal exudate cells to P.P.D. or E.F. in the manner described by Sundaram *et al.*⁶ and Diengdoh and Turk.⁷ A rise above 1.5% in macrophage slowing should be regarded as unacceptable. Recent studies of the sensitivity of lymphocyte-antigen interaction to the presence of linoleic acid⁸⁻¹⁰ will very probably also be highly susceptible to the same errors.

All who hope to achieve consistent and meaningful results while working with lymphocyte reactivity, especially during the winter months, must be prepared to exercise the greatest care in the supervision of animal stocks and should at least inquire about recent exposure of human subjects to influenzal infections.—I am, etc.,

E. J. FIELD

Institute of Pathology,
Newcastle General Hospital,
Newcastle upon Tyne

- Field, E. J., and Caspary, E. A., *Lancet*, 1970, 2, 1337.
- Caspary, E. A., and Field, E. J., *British Medical Journal*, 1971, 2, 613.
- Field, E. J., and Caspary, E. A., *Lancet*, 1972, 1, 963.
- Field, E. J., Caspary, E. A., Shenton, B. K., and Madgwick, H., *Journal of the Neurological Sciences*, 1973, 19, 179.
- Parker, J. W., and Lukes, R. J., in *Proceedings of the 4th Leucocyte Culture Conference*, ed. O. Ross McIntyre. New York, Appleton, 1971.
- Sundaram, K., Phondke, G. P., and Sunderesan, P., *Immunology*, 1967, 13, 433.
- Diengdoh, J. V., and Turk, J. L., *International Archives of Allergy*, 1968, 34, 297.
- Mertin, J., Shenton, B. K., and Field, E. J., *Journal of International Research Communications Systems (Medical Sciences)*, 1973, 1, No. 7, 18.
- Field, E. J., Shenton, B. K., Joyce, G., and Mertin, J., *Journal of International Research Communications Systems (Medical Sciences)*, 1973, 1, No. 7, 17.
- Field, E. J., *Lancet*, 1973, 2, 1080.

Incidence of Postpartum Deep Vein Thrombosis in the Tropics

SIR,—I refer to the articles by Mr. M. A. Hassan and others and by Mr. O. B. Williams and others on postoperative deep vein thrombosis (3 March 1973, pp. 515 and 517) and the letter from Mr. K. R. Orr (9 June, p. 615) which suggests a low incidence of this phenomenon in Vietnam. Since the incidence of postpartum thromboembolic complications in Thailand is also supposed to be rare, 41,056 clinical charts from the Chulalongkorn Hospital for the years 1970-71 were analysed retrospectively to determine the occurrence of postpartum thromboembolism (see table).

The prevalence of postpartum thromboembolic complication was 1.7 per 10,000 deliveries. The results of a similar study at