(1) The authors fail to mention the work of Schultze *et al.*,¹ who described six patients developing acute renal failure which was attributed to gentamicin therapy though all six were receiving cephalothin simultaneously.

(2) The choice of antibiotic therapy in the three cases they quote gives cause for alarm. Two of the patients seemed to be suffering from gastroenteritis and one wonders whether the use of any antibiotic, systemically or orally, let alone gentamicin and cephalothin, was indicated. Case 3, a patient with staphylococcal septicaemia, should presumably have received benzylpenicillin or cloxacillin (methicillin), depending on sensitivities, unless the organism was methicillin-resistant or the patient allergic to penicillins. If either of these possibilities obtained, why was a combination of gentamicin and cephalothin used? A methicillin-resistant *Staphylococcus aureus* would not respond to a cephalosporin in any case; and in the allergic patient either drug would be sufficient alone.

(3) The authors state that "a combination of these antibiotics [gentamicin and cephalothin] in the treatment of severe Gram-negative infections is fully justified." Why is this so? What does cephalosporin add to gentamicin in treating Gram-negative infections?

(4) In all three cases the patients received extremely prolonged courses of both drugs in high doses. Even if these patients had been suffering with severe Gram-negative sepsis, would such a prolonged course be necessary? In our combined experience of treating serious sepsis in hospital patients we find that gentamicin is usually sufficient when administered for 7-10 days, providing that any relevant underlying pathology is also dealt with.

(5) Another disturbing feature of this paper is the apparent total failure to monitor gentamicin therapy by assaying serum concentrations. A number of assay methods now exist, many of which are within the scope of routine medical microbiology laboratories. Surely a hospital which employs immunofluorescent staining techniques on renal biopsy specimens to detect antibodies to gentamicin and cephalothin should be able to assay those antibiotics in serum. In our own experience we find, in most adult patients, that a dose regimen of 5 mg/kg/day (in divided doses) is needed to achieve adequate serum concentrations (5-12 µg/ml). However, with continued therapy, even in those with normal renal function, the same dose may lead to gradually increasing serum concentrations, particularly after 7-10 days. Continued laboratory monitoring is essential for detecting this trend so that dosage may be modified. Thus laboratory assay forms an integral part of gentamicin therapy.

(6) No mention is made of ototoxicity in any of these patients, even though each had a prolonged course with a high dose. Even the absence of ototoxicity would be significant in these patients.

(7) A final point which should be clarified is whether the renal failure really was of sudden onset "out of the blue," or whether there were premonitory signs of proteinuria, urinary casts, rising blood urea, falling urine output, etc. If there were such warnings it would be valuable to look for them.

In conclusion we would like to note that

gentamicin is currently the drug of first choice for treating life-threatening Gram-negative sepsis because of its broad spectrum and rapid bactericidal activity. However, its use should be monitored by laboratory assay of serum concentrations (a) to achieve adequate dosage and (b) to avoid toxicity. It should not be used inappropriately or indiscriminately, while combinations of antibiotics should always be chosen for definite reasons.—We are, etc.,

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¹ Schultze, R. G., Winters, R. G., and Kauffman, H., *Journal of Infectious Diseases*, 1971, 124 (Suppl.) p. 145.

SIR,—I read with interest the report by Professor J. P. Fillastre and others (19 May, p. 396) describing three patients with acute renal failure associated with combined cephalothin and gentamicin therapy. Recently I managed a similar problem.

A 68-year-old man was admitted with hyperosmolar non-ketotic diabetic coma and a *Klebsiella* sp. septicaemia. On admission his blood urea was 123 mg/100 ml. He was started on intravenous cephalothin 130 mg/kg/day and intramuscular kanamycin 24 mg/kg/day. After four days probenecid was added in a dose of 0.5 g 12-hourly. The diabetic problem was easily managed and his renal functional impairment rapidly improved, with the blood urea falling within four days to 43 mg/100 ml and the serum creatinine to 0.9 mg/100 ml. However, after 10 days of this regimen his fever was not adequately controlled and the kanamycin was replaced by intramuscular gentamicin in a dose of 2 mg/kg/day. The cephalothin and probenecid were continued in the same dose. At this time the blood urea was 33 mg/100 ml and serum creatinine 1.1 mg/100 ml. After seven days of treatment with the combination of cephalothin, gentamicin, and probenecid the blood urea was 85 mg/100 ml and the serum creatinine 2.0 mg/100 ml. After 10 days the patient developed acute oliguric renal failure and was transferred to this unit. The patient had received no frusemide or other diuretic. The acute renal failure persisted for 24 days and required six peritoneal dialyses. His renal function thereafter improved but he had several other medical problems which resulted in death due to bronchopneumonia. At necropsy 39 days after the onset of the acute renal failure and 49 days after the commencement of the cephalothin and gentamicin the renal histology was consistent with a resolving acute tubular necrosis, particularly of the proximal tubules. Minor diabetic glomerular changes were also present.

The patient reported here compares very closely with those described by Professor Fillastre and also by Bobrow *et al.*¹ and Kleinknecht *et al.*² The gentamicin dosage in this case was lower than in the other reported cases, but the dose of cephalothin was comparable and the levels of the latter would have been increased by the administration of probenecid. It would seem most likely that the renal lesion in these patients is the result of potentiation of cephalothin nephrotoxicity by the addition of gentamicin. This antibiotic combination is popular in many units and it would appear important to prevent the serum level of cephalothin from becoming excessive. It is also important to be aware that cephalothin nephrotoxicity may

be considerably enhanced by the administration of frusemide.³—I am, etc.,

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¹ Bobrow, S. N., Jaffe, E., and Young, R. C., *Journal of the American Medical Association*, 1972, 222, 1546.

² Kleinknecht, D., Ganeval, D., and Droz, D., *Lancet*, 1973, 1, 1129.

³ Linton, A. L., Bailey, R. R., and Turnbull, D. I., *Canadian Medical Association Journal*, 1972, 107, 414.

Prevention of Pulmonary Embolism

SIR,—In your excellent leading article (7 April, p. 1) you state that the "hopeful but less critical" surgeon will use prophylactic methods provided that they are not associated with increased morbidity. My recent experience is that antithrombotic regimens may not only cause significant bleeding but also fail to prevent pulmonary embolism.

For four months of 1972 one litre of dextran 70 was administered intravenously over 12 hours after major gynaecological operations because this was reputed to be both safe and effective.¹ Some patients developed large abdominal haematoma which required drainage and blood transfusion or at least parenteral iron to correct anaemia, whereas others had infected pelvic haematoma which drained spontaneously per vaginam. Many had a prolonged hospital stay with increased morbidity. After an abdominal hysterectomy one patient had a large pelvic haematoma with ileus which persisted for 11 days, treated by gastrointestinal suction and parenteral fluids and requiring a blood transfusion to correct severe anaemia. Three days after discharge she was readmitted with pulmonary infarction which she fortunately survived, being finally sent home on the 36th postoperative day.

Since then no further prophylactic antithrombotic drugs have been used and the incidence of postoperative haematoma has been greatly diminished and the morbidity much reduced. No patient has had a pulmonary embolus. Although impressed with your correspondents' results²⁻⁴ and those recently reported from the Chelsea Hospital for Women,⁵ I still take no special precautions save that of giving my patients a litre of Hartman's solution routinely after major surgery as well as replacing blood lost and instructing that patients with pain in the calf or in the chest, however mild, are immediately considered for intravenous heparin therapy.—I am, etc.

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¹ Bonnar, J., and Walsh, J., *Lancet*, 1972, 1, 614.

² Wells, C., *British Medical Journal*, 1973, 2, 612.

³ Sharnoff, J. G., *British Medical Journal*, 1973, 2, 612.

⁴ Doran, F. S. A., *British Medical Journal*, 1973, 2, 612.

⁵ Ballard, R. M., *et al.*, *Journal of Obstetrics and Gynaecology of the British Commonwealth* 1973, 80, 469.

Unsaturated Fatty Acids in Multiple Sclerosis

SIR,—In a double-blind study of linoleate supplementation of the diet in multiple sclerosis (M.S.), Dr. J. H. D. Millar and others (31 March, p. 765) reported a slight

TABLE I.—*Inhibition of the P.P.D.- and Thyroid-induced Lymphocyte Response by Fatty Acids in Normal Subjects and M.S. Patients, measured with the Macrophage Electrophoretic Mobility Test*

Subject No.	P.P.D.							Thyroid Antigen								
	No Fatty Acids	C 18 : 1			C 18 : 2		C 20 : 4		No Fatty Acids	C 18 : 1			C 18 : 2		C 20 : 4	
		% Slowing* (a)	% Slowing* (b)	% Inhibition†	% Slowing* (b)	% Inhibition†	% Slowing* (b)	% Inhibition†		% Slowing* (b)	% Inhibition†	% Slowing* (b)	% Inhibition†	% Slowing* (b)	% Inhibition†	
Normal Subjects																
1	18.3	17.8	2.7	7.1	61.2	—	—	—	—	—	—	—	—	—	—	
2	17.5	16.0	8.6	6.3	64.0	3.4	82.0	—	—	—	—	—	—	—	—	
3	17.6	16.6	5.7	6.6	62.5	3.8	78.4	—	—	—	—	—	—	—	—	
4	18.2	17.5	3.8	7.2	60.4	3.6	80.2	19.6	18.7	4.6	8.5	57.0	4.5	72.0	—	
5	17.4	17.2	1.2	6.6	62.1	3.7	78.8	—	—	—	—	—	—	—	—	
6	17.5	17.0	2.7	6.9	60.5	4.2	76.0	19.5	18.6	4.6	8.8	54.9	4.5	76.9	—	
7	18.1	17.8	1.7	7.2	61.2	3.6	80.1	19.8	19.6	1.0	9.7	50.0	6.6	67.0	—	
8	18.3	18.2	0.5	7.0	61.7	3.8	79.2	—	—	—	—	—	—	—	—	
M.S. Patients																
9	17.7	17.5	1.1	2.9	84.0	0.9	95.0	—	—	—	—	—	—	—	—	
10	14.1	13.8	2.1	1.8	87.2	0.8	94.3	—	—	—	—	—	—	—	—	
11	11.2	11.0	1.8	1.3	88.4	0.3	97.3	—	—	—	—	—	—	—	—	

*Reduction of macrophage mobility brought about by lymphocyte-antigen reaction.

†Percentage change in macrophage slowings calculated: $\frac{a-b}{a} \times 100$.TABLE II.—*Inhibition of the Encephalitogenic-Factor-induced Lymphocyte Response by Fatty Acids in M.S. Patients and Patients with Other Neurological Diseases Measured With the Macrophage Electrophoretic Mobility Test*

Case No.	No Fatty Acids % Slowing* (a)	C 18 : 1		C 18 : 2		C 20 : 4	
		% Slowing* (b)	% Inhibition†	% Slowing* (b)	% Inhibition†	% Slowing* (b)	% Inhibition†
Multiple Sclerosis							
9	18.4	17.9	2.7	1.9	87.7	1.2	93.5
10	14.7	14.4	2.0	1.8	87.7	0.6	96.0
11	14.8	14.3	3.4	1.8	87.8	0.8	94.6
Other Neurological Diseases							
12	17.2	16.6	3.5	9.4	45.4	5.4	68.6
13	14.7	14.5	1.4	7.7	47.6	4.5	69.4
14	18.3	17.9	2.2	9.8	46.4	5.6	69.4

*Reduction of macrophage mobility brought about by lymphocyte-antigen reaction.

†Percentage change in macrophage slowings calculated: $\frac{a-b}{a} \times 100$.

improvement in clinical course in a group of patients treated over a two-year period. Several investigations have revealed significant alterations in the fatty acid composition of brain lipids^{1,2} and of the serum^{3,4} M.S., so that the effect of such a diet might be regarded as an attempt at substitution therapy. However, the results of Turnell *et al.*⁵ indicate that free fatty acids may play an important part in the immunosuppressive effect of corticosteroids, and so it seemed possible that the increase of the linoleate serum level might have an immunosuppressive effect in these patients.

To test this hypothesis we studied the effects of oleic acid (C 18:1), linoleic acid (C 18:2), and arachidonic acid (C 20:4) on the human lymphocyte response to three antigens—purified protein derivative of tuberculin (P.P.D.), encephalitogenic factor, and thyroid antigen (F₁ + F₂), using the macrophage electrophoretic mobility test.^{6,7} In this test the percentage slowing of normal guinea-pig macrophages in an electric field measures lymphocyte-antigen interaction. It is these percentages which are shown in tables I and II. Lymphocytes from normal subjects as well as from patients with M.S. and other neurological diseases were studied.

With a dosage of fatty acid of 0.08 mg/ml (corresponding to the normal serum level of unesterified oleic and twice the normal level of unesterified linoleic acid) we found a significant inhibition caused by both linoleic

and arachidonic acid, whereas oleic acid was virtually without effect. The inhibition occurred only when the fatty acids were added to the lymphocytes before the antigen. When antigen was allowed to interact with the lymphocytes for 1-5 min and linoleic acid was then added no inhibition was to be observed, suggesting that the acid may inhibit the recognition of antigen by the lymphocytes. The interference with lymphocyte-antigen interaction by linoleic and arachidonic acid occurred not only with P.P.D. and thyroid as antigens in normal subjects (table I) but equally with P.P.D. and encephalitogenic factor in M.S. patients and those with other neurological diseases (tables I and II). The percentage inhibition was higher in M.S. patients than in the control groups.

In the context of M.S. the present results may offer an explanation for the findings by Dr. Millar and his colleagues of the beneficial effect of linoleic acid treatment. Such treatment might be expected to reduce lymphocyte attack upon brain antigen in situ and (if such an autoaggressive process is indeed at the root of M.S. pathogenesis) so hold up the progress of the disease.

Further studies of the possible immunoregulatory effect of unsaturated fatty acids (dependent perhaps on chain length and degree of unsaturation) in normal subjects, in M.S., and in the wider field of clinical immunology are indicated.

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—We are, etc.,

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Newcastle upon Tyne1 Gerstl, B., Eng, L. F., Tavaststjerna, M. Smith, J. K., and Kruse, S. L., *Journal of Neurochemistry*, 1970, 17, 677.2 Jatzkewitz, H., and Mehl, E., *Hoppe-Seyler's Zeitschrift für Physiologische Chemie*, 1962, 329, 264.3 Thompson, R. H. S. *Proceedings of the Royal Society of Medicine*, 1966, 59, 269.4 Berlin, J., Pettet, N., Smith, A. D., Thompson, R. H. S., and Zilkha, K. J., *Journal of Neurosurgery and Psychiatry*, 1971, 34, 25.5 Turnell, R. W., Clarke, L. H., and Burton, A. F., *Cancer Research*, 1973, 33, 203.6 Field, E. J., and Caspary, E. A., *Lancet*, 1970, 2, 1337.7 Caspary, E. A., and Field, E. J., *British Medical Journal*, 1971, 2, 613.

Fibrinolysis in Cholestatic Jaundice

SIR,—The paper by Dr. A. Jedrychowski and his colleagues (17 March, p. 640) reporting decreased fibrinolytic activity in patients with cholestatic jaundice prompts us to report the preliminary results of a similar study.