- (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 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? 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 μ g/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 Gramnegative 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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Schultze, R. G., Winters, R. G., and Kauffman, H., Fournal 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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 Kleinknecht, D., Ganeval, D., and Droz, D., Lancet, 1973, 1, 1129.
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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 haematomata which required drainage and blood transfusion or at least parenteral iron to correct anaemia, whereas others had infected pelvic haematomata 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 haematomata has been greatly diminished and the morbidity much reduced. No patient has had a pulmonary embolus. Although impressed with your correspondents' results24 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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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