sense in 1942.¹ This was that "a medical practitioner who knows that a death has occurred in circumstances which would put a coroner on inquiry under the Coroners (Amendment) Act, 1926, owes a common-law duty to report the death to the coroner, quite apart from his duty of certifying the death to the registrar under the Registration Acts."

In these esoteric matters, in the absence of a judicial decision, there must be room for more than one view.—I am, etc.,

C. F. J. BARON

Esher, Surrey

¹ *British Medical Journal Supplement*, 1942, 2, 25.

Escherichia coli O148 and Diarrhoea in Adults

SIR,—Your leading article "Dropouts' Diarrhoea" (10 August, p. 373) referred to the discovery of the O148 serogroup of *Escherichia coli* during an investigation of travellers' diarrhoea in Aden.¹ Subsequent work in the U.S.A. demonstrated its pathogenicity in laboratory systems as well as in human volunteers² and showed that this enteropathogenicity was due to an enterotoxin. The epidemiological observations have been confirmed by further field studies, though the results have not been published. Because of the withdrawal of British troops from Aden these confirmatory studies were carried out in 1968 at Sharjah, a base in the Arabian Gulf area. As in the Aden study, the work involved a newly arrived unit of about 620 men, and the bacteriological and epidemiological observations followed the scheme used in Aden.¹

The incidence of diarrhoea in the newly arrived troops was almost three times that seen in the seasoned garrison troops. In the newly arrived troops shigella infection was found in 18% of the cases of diarrhoea and *E. coli* O148 was isolated from 50 (25%) of those cases in which shigellae were not found. The cases with *E. coli* O148 showed a peak incidence in the first three weeks after arrival, whereas the shigella infections occurred in later weeks. In the seasoned troops shigella infection was found in 29% of cases whereas *E. coli* O148 occurred in only 4%. Thus the incidence of infection with *E. coli* O148 was much lower in seasoned troops, but seasoned and newly arrived troops were affected equally by the shigella infections. In both groups the peak incidence of the bacillary dysentery occurred over the same period and was mainly caused by two outbreaks due to *Shigella dysenteriae* 3 and *Sh. dysenteriae* 6, though there were some cases due to other shigella serotypes.

Samples of all meals served by the camp kitchen were examined bacteriologically and *E. coli* O148 was found in 12%. It was found in samples of all types of meal over the whole period of the study and therefore no single food could be exclusively incriminated as the source of infection. Faeces from 140 food handlers were examined and three were excreting *E. coli* O148, one being a local civilian and two British soldiers. Flies occurred in the kitchen area and 8% were infected with *E. coli* O148.

As in the Aden study, *E. coli* O148 was clearly related to the diarrhoea and 83% of all the isolates were from specimens taken during the acute phase of the disease. Serial

faecal specimens were taken from as many subjects as possible and these showed that *E. coli* O148 was acquired 3-7 days before the onset of diarrhoea, appeared in pure culture in the acute phase, and remained for a variable period in the convalescent stages. This is a similar pattern to that seen in infantile enteritis due to enteropathogenic *E. coli*.

E. coli O148 was the commonest single serogroup found in faecal specimens, accounting for 8.5% of all isolates; similarly in the meals it was the commonest serogroup, accounting for 23% of all *E. coli* isolates. During the 1968 study it was not possible to investigate in detail the origin of *E. coli* O148 in the meals, but in a later study it was shown that the food supplied to the kitchen was free from *E. coli* O148 but became infected during preparation and serving, either from infected food handlers or from flies.

In Aden the isolates of *E. coli* O148 were all flagellar type H28, whereas in Sharjah the epidemic strain was flagellar type H53 with a few isolates of flagellar type H30. In the studies of infantile enteropathogenic *E. coli* it has been observed that within an O group more than one H type may cause disease.³

It appears that *E. coli* O148 is prevalent in Arabia but uncommon in the British Isles; since 1968 we have identified approximately 20,000 strains of *E. coli* isolated in the British Isles, and of these strains only 20 were *E. coli* O148. In the present studies it seemed that persons newly arrived in Arabia became infected with this enteropathogenic serogroup and developed diarrhoea. It must be stressed that *E. coli* O148 is not the only cause of travellers' diarrhoea but seems responsible for a significant proportion in Arabia.—I am, etc.,

B. ROWE

Salmonella and Shigella Reference Laboratory,
Central Public Health Laboratory,
London N.W.9

- 1 Rowe, B., Taylor, J., and Bettelheim, K. A., *Lancet*, 1970, 1, 1.
- 2 Dupont, H. L., et al., *New England Journal of Medicine*, 1971, 285, 1.
- 3 Ewing, W. H., Davis, B. R., and Montague, T. S., *Studies on the Occurrence of Escherichia coli Serotypes associated with Diarrhoea Disease*. Communicable Disease Center, Atlanta, Georgia, 1963.

Tetracycline-resistant Group A Streptococci

SIR,—Dr. Emslie's interesting letter (17 August, p. 467) has stimulated me to see if similar variations in the prevalence of tetracycline-resistant streptococci were recorded from cultures received from north Glasgow. Overall the figure which I reported in late 1973¹ remained the same for the whole of the year at 34%. However, though the numbers were small, ranging between 20 and 34 per quarter, there were variations, the first two quarters of the year having about double the proportion of tetracycline-resistant streptococci compared with the second two quarters of the year. The first two quarters of 1974 have reverted to the pattern seen in the first two quarters of 1973, between 40 and 50% of cultures being tetracycline-resistant. The overall resistance in the first half-year of 1974 is approximately 47%. However, if the pattern seen in 1973 recurs, the overall percentage of tetracycline-

resistant strains will probably be less than the figure for the first half-year.

A comparison was made between the tetracycline-resistance of streptococci isolated from the respiratory tract and that of those coming from non-respiratory sources. Overall, in 1973 29% of strains from the respiratory tract were tetracycline-resistant compared with 41% of strains from non-respiratory sources. The same pattern has been seen in the first two quarters of 1974, 38% of respiratory strains being tetracycline-resistant compared with 56% of strains from non-respiratory sources.

It is difficult to know whether there is any significance in the findings of both Dr. Emslie and myself that rather more non-respiratory strains are tetracycline-resistant than respiratory strains. It would be interesting to have information from other laboratories. However, there is no doubt that tetracycline resistance in streptococci remains a problem in the west of Scotland, whether the organisms are isolated from patients in the country or the town.—I am, etc.,

R. J. FALLON

Department of Laboratory Medicine,
Ruchill Hospital Glasgow

¹ Fallon, R. J., *British Medical Journal*, 1973, 4, 300.

Trasylol for Pancreatitis

SIR,—I would not dispute the generally optimistic conclusions of your leading article on Trasylol (aprotinin) treatment for acute pancreatitis (20 July, p. 133), but the statements that it is a "harmless" remedy with an "absence of side effects" cause me some concern and prompt me to report two cases seen in this hospital.

Case 1, a 38-year-old woman, was admitted with a diagnosis of acute pancreatitis. Her serum amylase was 1,960 Somogyi units/100 ml (normal range > 200/100 ml) and her serum calcium 7.1 mg/100 ml (normal range 9.10-2/100 ml). Treatment with aprotinin was started with a dose of 200,000 units followed by 100,000 units six-hourly together with gastric suction and intravenous fluids. Within 48 hours she had markedly deteriorated and become confused and shocked. There was no overt bleeding but coagulation screening tests were abnormal (see table). Intravenous glucagon 1 mg four-hourly was added to the treatment together with lincomycin, ampicillin, and oral gentamicin. Two days later she suffered a respiratory arrest and required intermittent positive pressure ventilation. Microscopic examination of the tracheal aspirate showed fragments of lung tissue and indicated the development of a "shock lung syndrome." The aprotinin infusion was stopped. The patient's condition steadily improved. She was discharged fully recovered 27 days after admission.

Case 2, a 44-year-old man, was admitted with an acute onset of rigors and respiratory difficulty. Blood culture confirmed a Gram-negative septicæmia (*Klebsiella* spp.) and the serum amylase was only 240 Somogyi units/100 ml. He was treated with intravenous gentamicin, ampicillin, and hydrocortisone but rapidly developed evidence of a bleeding diathesis (see table). He became severely oliguric and peritoneal dialysis was begun. Signs of acute pancreatitis then appeared, with mild jaundice and a serum amylase of 4,000 Somogyi units/100 ml. He was given aprotinin 500,000 units immediately and 200,000 units four-hourly together with glucagon 1 mg six-hourly. Over the succeeding three days, despite continuing peritoneal dialysis and hydrocortisone, his lung function deteriorated and the aprotinin infusion was discontinued. Renal and pulmonary function slowly improved, but some neurological deficit persisted. He died of an unexpected cardiac arrest. Necropsy showed extensive necrosis of the pancreas and of the renal tubular epithelium. No definite vascular thromboses or fibrin deposits were seen in any of the organs examined.

Day after Admission	Aprotinin (Trasylol) Therapy	Investigation*							
		Prothrombin Time (12-15 sec)	Thrombin Time (12-15 sec)	Fibrinogen Titre (1/256-1/512)	Fibrin Degradation Products (<1/32)	Platelet Count (150-400 × 10 ⁹ /mm ³)	Euglobulin Lysis Time (2-7 hr)	Factor V (50-200 %)	Factor VIII (50-200 %)
Case 1									
2	+	29	29	1/256	—	110	—	—	—
3	+	20	18	—	—	66	—	—	—
4	+	19	20	1/256	1/64	79	26	60	750
5	—	16	22	1/512	1/128	28	{ > 5 } { < 18 }	100	270
6	—	—	—	—	1/256	53	—	—	—
12	—	16	14	1/256	1/16	Ample	{ > 5 } { < 21 }	—	—
Case 2									
0	—	48	27	1/128	—	43	—	6	40
3	+	20	24	—	—	31	—	—	—
5	+	18	—	—	—	84	—	—	—
6	—	17	16	1/512	1/32	132	{ > 5 } { < 18½ }	100	770
7	—	15	17	—	1/128	Ample	—	—	—
11	—	18	—	—	1/16	Ample	—	—	—

*Normal values for each test in parentheses.

Three cases of disseminated intravascular coagulation in patients with acute pancreatitis have been reported.¹ Two of the three patients died, and at necropsy renal cortical necrosis was found associated with multiple microthrombi in many organs. The patient who survived was treated with heparin. The same authors reported¹ that a trypsin infusion in dogs produced significant defibrination with numerous microthrombi deposited in the lungs and kidneys. Acute respiratory distress syndrome, ascribed to the effects of fluid overload² or an alveolar-capillary block,³ is a well-recognized complication of pancreatitis. Pulmonary fibrin deposition does not seem to have been considered as a possible cause of lung damage in pancreatitis, though it is common in disseminated intravascular coagulation⁴ and probably plays a significant role in the shock lung syndrome.⁵

Both our patients had good laboratory evidence of a consumptive coagulopathy associated with acute pancreatitis. Aprotinin is a very active fibrinolytic inhibitor and 100 times more potent than tranexamic acid in terms of molar concentration.⁶ If fibrin deposition has a significant role in the production of organ damage in pancreatitis any inhibition of fibrinolysis would obviously be harmful. Some reports have suggested that heparin or even streptokinase would be a more logical form of treatment.⁷ The deterioration in pulmonary function in our patients associated with aprotinin therapy and the recovery on stopping the infusion may have been fortuitous. Nevertheless, there was a definite reduction in plasma lytic activity in one patient during the infusion and a striking rise in fibrin breakdown products in each case after the treatment ceased. Far from being a harmless remedy, aprotinin may well be contraindicated in acute pancreatitis when there is evidence of disseminated intravascular coagulation.

I thank Mr. L. T. Cotton and Dr. R. W. Williams for permission to report the cases of patients under their care.

—I am, etc.,

M. L. LEWIS

Department of Haematology,
King's College Hospital Medical School,
London S.E.5

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2 Spierer, R., *Annals of Internal Medicine*, 1973, **78**, 788.

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Alpha-fetoprotein in Amniotic Fluid in Early Normal Pregnancy and Intrauterine Fetal Death

SIR,—A number of investigators have recently stressed the importance of the assay of alpha-fetoprotein (A.F.P.) for the prenatal diagnosis of congenital malformations. The radioimmunoassay method, which is used most often, is rather complex and unsuitable for small laboratories with restricted equipment.

The simple and rapid immunodiffusion method of Mancini as modified by Fahey and McKelvy¹ has been applied by us for evaluation of the A.F.P. levels in amniotic fluid which has been previously concentrated in 50% gum arabic.

The levels of A.F.P. in amniocentesis samples taken from 37 normal pregnant women at the 10th-12th week of pregnancy and from six patients in whom intrauterine fetal death had been diagnosed are shown in the table. The average A.F.P. value (29 µg/ml) in the amniotic fluid from normal pregnancies was in agreement with those reported by Brock and Sutcliffe² and by Nevin *et al.*³ In the samples of the fluid from the cases of intrauterine fetal death, however, the mean value (55.4 µg/ml) was significantly higher.

Group	No. of Cases Studied	Alpha-fetoprotein Concentration in Amniotic Fluid (µg/ml)	
		Mean ± S.D.	Range
Normal pregnancy	37	29.0 ± 7.5	17.5-41.5
Intrauterine fetal death	6	55.4 ± 32.0	24.6-100.0

The results obtained indicate that the method applied by us can be useful for routine assays of A.F.P. in material derived from both normal and abnormal pregnancies. Thus it could be of great importance in the antenatal diagnosis of congenital defects. The concentration of the amniotic fluid makes estimations possible even in cases in

which the levels of A.F.P. are low.—We are, etc.,

L. WIŚNIEWSKI

Z. SKRZYDLEWSKI

J. ORCIUCH

Department of Clinical Genetics,
Institute of Obstetrics and Gynaecology,
Medical School,
Białystok,
Poland

1 Fahey, J. L., and McKelvy, E. M., *Journal of Immunology*, 1965, **94**, 84.

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Prazosin in Patients with Chronic Renal Failure

SIR,—I was interested to see the letter from Drs. Priscilla S. Kincaid-Smith and A. S. P. Hua (24 August, p. 520) on beta-adrenergic blocking agents in renal failure and would like to add a few comments with particular reference to the use of prazosin in patients with chronic renal failure.

Prazosin, a relatively new vasodilator drug, is a valuable addition to the range of drugs now available for the treatment of hypertension. I have found it valuable when used in combination with other drugs including propranolol, methyldopa, clonidine, frusemide, and chlorothiazide in the treatment of severe hypertension in patients with chronic renal failure. In the patients studied the initial ⁵¹Cr-EDTA clearances varied from 28 to 47 ml/minute. The addition of prazosin to the antihypertensive regimen produced a significant fall in the blood pressure which was associated with an average fall in the ⁵¹Cr-EDTA clearance of 8 ml/min (4-13 ml/min). Thereafter the ⁵¹Cr-EDTA clearance stabilized. I would, however, like to add a note of caution when prazosin is employed in patients with chronic renal failure. I have found that such patients may be very "sensitive" to the drug, and small doses such as 1 mg twice daily should be used initially. In the patients I have studied the maximum daily dose has not exceeded 6 mg.

It is claimed that prazosin does not produce any significant postural effects. I have found, however, that the addition of prazosin to the antihypertensive regimen produces significant postural falls in both systolic and diastolic blood pressure. It was not possible to determine in my study whether the observed postural falls in blood pressure were due to the direct effect of prazosin or perhaps