to provide permanent protection for the population living in the area.—I am, etc.,

HUGH L. B. RUSSELL

University Department of Community Medicine,
Usher Institute,
Edinburgh

Alpha-fetoprotein and Rh Alloimmunization

SIR,—An increase in alpha-fetoprotein (AFP) has been reported in amniotic fluid from fetuses with fetal distress, including fetal distress of Rh alloimmune origin.^{1,2}

We have assayed by radioimmunoassay³ specimens of amniotic fluid from a number of Rh alloimmune pregnant women and report the results of the assay of: (1) 72 specimens from 46 women with 27-42-week-old normal or subnormal fetuses and (2) 27 specimens from 12 women with 27-38-week-old fetuses with severe haemolytic anaemia which, 3-14 days after amniocentesis, either died or required intrauterine blood transfusion or were born with levels of haemoglobin below 10 g/100 ml. Results of AFP determinations are shown in the figure.

Amniotic AFP determination at various gestational ages in cases of severe Rh alloimmunization (X) and normal controls and/or mild cases (●). Means represented by horizontal bars (—).

There was an overall tendency to higher levels in the groups of fetuses with severe alloimmune anaemia, at least until the 36th week of gestation before which most of our specimens were taken.

From a practical point of view, we think that because of wide individual variations and consequent overlapping with controls, AFP determinations on amniotic fluid from Rh alloimmune pregnant women provides less information than bilirubin determination.

We also think that recent observations by Whyley *et al.*⁴ of significant AFP increase in the amniotic fluid of pregnant women whose fetuses did not survive may be explained by the AFP rise which takes place shortly before fetal death.—We are, etc.,

A. JOUVENCEAUX

Blood Transfusion Centre,
Hôpital E. Herriot,

P. SIZARET

N. MARTEL

International Agency for Research on Cancer,
Lyons

- 1 Seppala, M., and Ruoslahti, E., *Obstetrics and Gynecology*, 1973, **42**, 701.
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Renal Amyloidosis in Chronic Granulomatous Disease

SIR,—The association of chronic granulomatous disease and amyloidosis has not been previously documented. We report the development of renal amyloidosis in a boy with long-standing chronic granulomatous disease.

The patient had had recurrent bacterial infections, particularly with *Staphylococcus aureus* and *Salmonella typhimurium*, from the age of 8 months. The diagnosis of chronic granulomatous disease, the subject of a previous report,¹ was made at the age of 10 years on the basis of a nitroblue-tetrazolium test and cutaneous granulomas.

He presented at the age of 16 years with a pure nephrotic syndrome (oedema, serum albumin 2 g/100 ml, serum cholesterol 260 mg/100 ml, proteinuria 2 g/24 hr) without microscopic haematuria or hypertension. In contrast to his previous hypergammaglobulinaemia, low levels of serum immunoglobulins (IgG 146 mg/100 ml) with elevated urinary levels (IgG 450 mg/l.) were observed. Long-standing *S. typhimurium* septicaemia responded to rifampicin. Oedema was controlled by diuretics and a low-sodium diet. Renal biopsy revealed renal amyloidosis, predominantly glomerular but also involving interstitial, peritubular, and vascular structures.

Recent studies indicate that amyloidosis is largely composed of fragments of kappa light chains.² In patients with chronic suppuration amyloidosis has been attributed to prolonged antigenic stimulation producing excessive immunoglobulin synthesis with deposition of immunoglobulin fragments as amyloid material.³

Continuing antigenic stimulation is the most likely mechanism of amyloid production in this patient. Immune function is normal in chronic granulomatous disease⁴ and Gram-negative endotoxin has been shown experimentally to stimulate amyloid formation.⁵ Alternatively, abnormal immunoglobulin catabolism may be involved, as in hypogammaglobulinaemia or agammaglobulinaemia,⁶ or dysfunction of the reticuloendothelial system.⁷

In vitro amyloid can be phagocytosed by leucocytes⁸ and the reticuloendothelial system⁹ and this is probably the mechanism of the regression of amyloid deposits reported in liver and kidney.¹⁰ Defective catabolism of immunoglobulins and amyloid substance might also occur in chronic granulomatous disease, in which phagocytic degradative activity is known to be defective, in both leucocytes¹¹ and the reticuloendothelial system,¹² particularly in respect of bacterial phagocytosis.—We are, etc.,

R. DE SEIGNEUX
A. KANFER
P. TERRIOUX
J. D. SRAER
J. A. WHITWORTH

Service de Nephrologie,
Hôpital Tenon,
Paris

- 1 Grunberg, J., *et al.*, *Annals de Pédiatrie*, 1970, **17**, 560.
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Haemodialysis and Forced Diuresis for Tricyclic Antidepressant Poisoning

SIR,—The encouraging experience of Drs. H. W. Asbach and H. W. Schüler (18 May, p. 386) in using haemodialysis for the treatment of two young children with severe imipramine poisoning has stimulated us to report a recent dramatic clinical success we have had in an adult who took a massive overdose of tricyclic antidepressants.

A 50-year-old woman with a long history of depression ingested a large quantity (precise number of tablets not known) of imipramine and amitriptyline, possibly with a few tablets of opi-pramol, trifluoperazine, haloperidol and thiothixene. About six hours later she was admitted to hospital deeply comatose, areflexic, and hypothermic, with a sinus tachycardia and a systolic blood pressure of 80-90 mm Hg. An electrocardiograph showed an intraventricular conduction defect. The patient was intubated and given gastric lavage. She was treated with continuous gastric aspiration, body warming, intermittent positive pressure respiration, and a noradrenaline infusion. Forced diuresis was commenced through the central venous pressure line.

Nine hours after admission the patient had shown no signs of clinical improvement and it was decided to commence haemodialysis. An arterio-venous shunt was placed in her leg and dialysis started using two hollow fibre kidneys in parallel (dialysate flow rate 500 ml/min; arterial flow rate 150 ml/min) and a standard dialysate solution. Dialysis was continued for six hours. Within four hours of commencing dialysis the vital signs improved significantly and there was a definite improvement in the level of consciousness. This improvement was maintained over the next 48 hours and the patient made a full recovery.

Chemical analyses of the gastric lavage showed the presence of a large amount of imipramine and amitriptyline and a very small quantity of a phenothiazine. Plasma imipramine levels were determined by a modification of the method of Grove and Halliwell.¹ No attempt was made to distinguish between imipramine and its fluorescent metabolites and results are reported as imipramine. Samples were taken soon after admission and during the period of haemodialysis. The plasma imipramine level fell from 6.3 µmol/l. to 1.7 µmol/l. within 14 hours. These results are shown in the figure. According to Niyogi,² 1.7 µmol/l. is the upper limit of the therapeutic range for plasma imipramine.

During the period of forced diuresis the urine volume was 23,370 ml, and contained 151.5 µmol (43 mg) of imipramine. No imipramine was detected in the dialysate when it was analysed by the same method as used for plasma. A 20-fold

concentration of the dialysate still gave a negative result.

This woman clearly had a massive overdose of tricyclic antidepressants and it was considered that her chances of survival were extremely poor. It seemed to us that haemodialysis was responsible for a dramatic clinical improvement. This does not seem to be supported by the analyses for the drug we were able to make. In fact the decrease in plasma imipramine level did not approach the half-time of $3\frac{1}{2}$ hours reported by Ciba-Geigy (N.Z.) Ltd. (personal communication). From our results no increase in the rate of fall of plasma imipramine occurred during dialysis. Unfortunately the lack of samples prior to dialysis leaves some doubt on this point. Our inability to locate any imipramine in the dialysate may be explained by the interesting comments of Drs. Asbach and Schüller (24 August, p. 524) who claim that imipramine is taken up by the polyvinyl chloride of the extracorporeal blood-line system. Our limited experience, that of Harthorne *et al.*³ and the recent letters from Drs. Asbach and Schüller have encouraged us to give early consideration to this form of treatment in patients with severe poisoning. However, the recovery of significant amounts of drug by forced diuresis may yet indicate that this method is the most suitable way of eliminating absorbed imipramine and other tricyclic antidepressants.—We are, etc.,

ROSS R. BAILEY
JOHN R. SHARMAN
JENNIFER O'ROURKE
A. L. BUTTIMORE

Departments of Renal Medicine and
Clinical Biochemistry,
Christchurch Hospital,
Christchurch,
New Zealand

¹ Grove, J., and Halliwell, J. V., in *Manual of Analytical Toxicology*, ed. I. Sunshine, p. 189, Cleveland, Chemical Rubber Company Press, 1969.

² Niyogi, S. K., *Forensic Science*, 1973, 2, 67.

³ Harthorne, J. W., Marcus, A. M., and Kaye, M., *New England Journal of Medicine*, 1963, 268, 33.

Poisoned Children

SIR,—I was interested to read Mr. M. Calnan's letter (28 September, p. 802). I believe that the distinction he draws between true poisoning and poisoning scares is not clinically useful. In practice parents are rarely certain exactly how much of a poisonous substance their children have taken. Sending children home who have probably taken only a negligible amount of a poisonous substance would be bound to lead to the occasional disaster. Mr. Calnan, in defining "true poisoning," says that the presence of a symptom or sign is necessary. However, it is the aim of treatment by rapid stomach emptying to prevent symptoms or signs occurring. I am in the process of examining prospectively cases of child poisoning admitted to hospitals in Cardiff under the age of 5 years. Of 85 cases so far studied, in only seven was the substance ingested innocuous. Indeed, it seems from Mr. Calnan's own figures that if only 44% of his cases were admitted overnight, the majority of children taking innocuous substances would be sent home and not figure in the 16,500 children admitted nationally each year for accidental poisoning.

Mr. Calnan mentions unnecessary procedures performed on children which may in fact do harm; by that I suspect he means gastric lavage. However, now the majority of paediatric departments are using ipecacuanha emesis, a procedure that is as effective as gastric lavage with minimal risk.¹ I cannot believe that the current debate on childhood poisoning is alarmist if 22 children died in 1972 from this cause.² Many more would certainly have died without therapy.

I am sure that Mr. Calnan is right that the health education campaign may not be as beneficial as it has been hoped. This is not only because of his evidence that 79% of medicines were in use within 24 hours of the accident. We have found that so far in our study in Cardiff serious stress is commonly found in the families of accidentally poisoned children, and at such times the parents are unlikely to remember health education propaganda.—I am, etc.,

J. R. SIBERT

Department of Child Health,
Cardiff Royal Infirmary,
Cardiff

¹ Reid, D. H. S., *Archives of Disease in Childhood*, 1970, 45, 428.

² Registrar General's Statistical Review of England and Wales for 1972, Part 1, Tables, Medical, p. 176. London, H.M.S.O., 1974.

Liver Hamartomas in Patients on Oral Contraceptives

SIR,—The report by Dr. G. Vosnides and others (31 August, p. 580) of a case of liver hamartomas and its possible association with oral contraceptives merits comment in order to place this implied risk of adverse effects of oestrogen-progestogen preparations on the liver in perspective. Reports such as these might cause undue concern in women on the Pill.

The patient in question was receiving large doses of "oral contraceptives" and, in particular, was receiving doses of mestranol between 50 and 150 µg per day, well in excess of that recommended by the Committee on Safety of Medicines resulting from the findings of Inman *et al.*¹ We have shown² that in women taking this preparation there can be a high output of endogenous oestrogen at times. The significance of this remains to be clarified, but it does suggest that excessive ovarian activity can occur on occasion in women taking these preparations. In such a patient who is maintained on haemodialysis there is thus a possibility that large amounts of oestrogen, both exogenous and endogenous, might accumulate.

It would be preferable to use, and the menorrhagia is more likely to be kept in check by, an oestrogen-progestogen preparation which had a bias towards a major anti-oestrogenic effect on the genital tract such as the preparations containing larger amounts of norethisterone or its acetate with the oestrogen within the recommended dose rather than a low-dose combined preparation. If this proved to be inadequate to control the heavy bleeding the antioestrogenic effect could be augmented by adding extra norethisterone or its acetate as the case might be. This would obviate increasing the dose of both the oestrogen and progestogen as was done in the case reported. This would be particularly relevant

in the circumstances described and would minimize the risk of an accumulation of oestrogens within the body.—I am, etc.,

MAX ELSTEIN

Faculty of Medicine,
University of Southampton,
Southampton

¹ Elstein, M., *et al.*, *British Medical Journal*, 1974, 1, 11.

² Inman, W. H. W., *et al.*, *British Medical Journal*, 1970, 2, 203.

Cardiovascular Disease and Peptic Ulcer

SIR,—In your leading article (28 September, p. 760) you describe the problems in determining whether the association between cardiovascular disease and peptic ulcer is real. In two recent articles my colleagues and I discussed aspects of this association. In the first article¹ we reported 51 patients who underwent surgery for their abdominal aortic aneurysms. Twelve of these 51 patients were found to have an associated peptic ulcer at operation. Seven of these 12 patients developed complications following the resection of their abdominal aneurysm which were due to the associated peptic ulcer—namely, to haemorrhage or to perforation of the ulcer. On the basis of these findings we felt that this association was not only real but should influence the management of patients with abdominal aortic aneurysms.

In our second article² we analysed the amputation rates in 300 patients who underwent arterial reconstructive surgery for severe ischaemia of the leg. Seventy-one of these 300 patients also had an associated ulcer. In those with an ulcer the chances of losing a leg were from two to three times as high as in those without, and the chances of losing both legs were four times as high. In every other respect—sex, age, pattern of disease, and type of surgical treatment—the two groups (those with and those without an associated ulcer) were comparable.—I am, etc.,

A. P. BARABAS

West Suffolk Hospital,
Bury St. Edmunds

¹ Bouhoutsos, J., Barabas, A., and Martin, P., *British Journal of Surgery*, 1973, 60, 302.

² Bouhoutsos, J., Barabas, A., and Martin, P., *Postgraduate Medical Journal*, 1972, 48, 671.

Understanding Blindness

SIR,—Dr. J. A. Shaw in his Personal View (21 September, p. 738) does a great service not only in publicizing the difficulties of his unseeing fellows, but also in helping those of us who work with the visually handicapped by improving our insight into a situation which a sighted person can never fully appreciate.

I have always found personal accounts of illness written by medical men particularly helpful in my attempts to understand a patient's point of view. I believe we could learn a great deal if more doctors with impaired vision would put their thoughts on paper. I do not believe that doctors' awkwardness with the blind is simply a result of their frustration at not being able to cure blindness. Indeed, I think Dr. Shaw's suspicion that doctors' attitudes are no different from those of laymen is correct. Blindness is, after all, a state entirely beyond