

GENERALISED ALLERGIC REACTION WITH SYNTHETIC HUMAN INSULIN

SIR,—Dr Carveth-Johnson and colleagues (Dec. 4, p. 1287) report on a patient who had an urticarial reaction to highly purified beef or pork insulin and then to synthetic human insulin. They investigated this by patch testing: they should have done skin prick or intracutaneous tests. Patch testing is used to investigate contact sensitivity. We are not told the strengths of the insulins used or how long the patch tests were applied—or indeed how long it took a weal-and-flare of 5 mm to develop.

It seems strange that, when desensitisation was started, each dose of insulin was mixed with dexamethasone 0.05 mg: since dexamethasone is neither antihistaminic or anti-anaphylactic, it was wise to discontinue it.

Carveth-Johnson and colleagues conclude that their case-report indicates that a highly atopic individual may have a generalised allergic response to synthetic human insulin after previously being sensitised to beef insulin. This conclusion cannot be reached on the basis of one patient with a history of urticaria and penicillin allergy who was not atopic as usually defined. It is highly likely that, on the low dosage of insulin required, she is not allergic to her own endogenous insulin.

Department of Medicine,
Guy's Hospital Medical School,
London SE1 9RT

A. W. FRANKLAND

SIR,—Dr Carveth-Johnson and colleagues have described a generalised allergic response induced by synthetic human insulin in a highly atopic individual previously sensitised to beef insulin. We would like to draw attention to recent events in a previously reported patient with generalised allergy to both porcine and beef insulin.¹ In our patient we were able to demonstrate cross-reactivity of both porcine and beef insulin antibodies with human insulin. After insulin withdrawal IgE antibodies disappeared at 6 months and IgG antibodies at 18 months. At that time, human insulin was kindly provided by Novo and administered to the patient. No allergic response occurred and after 12 months' treatment no antibodies have been demonstrated. Our interpretation is that, in the presence of porcine or beef insulin antibodies, synthetic human insulin is "recognised" and reacts as a hapten though it is not immunogenic in its own right. Once these antibodies had naturally decayed human insulin failed to produce an allergic response. In immunological terminology the immunogenic porcine and beef insulins could be seen as having "hapten carrier" characteristics relative to the "haptenic" role of human insulin in the induction of immune responses.²

In view of the above findings we were not surprised that an allergic response to synthetic human insulin occurred in the patient reported by Carveth-Johnson et al. If insulin treatment is mandatory then desensitisation is best attempted, but if time allows for natural decay of insulin antibodies then human insulin may be successfully introduced at a later date.

Department of Medicine,
Leicester Royal Infirmary,
Leicester LE1 5WW

R. L. BLANDFORD
H. SEWELL
P. SHARP
J. R. HEARNshaw

SAFETY OF PLASMA EXCHANGE

SIR,—Plasma exchange is now used in the management of several disorders, and your Nov. 6 editorial on the potential hazards was timely. We have used plasma exchange extensively for the treatment of glomerulonephritis and other immunologically mediated diseases, and have recorded the infective complication in some detail.³ One of the striking findings of that study was the frequency

of septicæmic episodes in patients in whom vascular access had been achieved by arteriovenous shunt (13 episodes in 50 patients, 26%). As a result of that observation we changed to using direct venepuncture to obtain access to the circulation.

We have now examined the incidence of septicaemia in the 18 months following this change. 55 patients have undergone 758 exchanges; there are inadequate data on an additional 5 patients who had 23 exchanges. All the patients were receiving concurrent immunosuppression which included prednisolone, cyclophosphamide, or azathioprine; none were neutropenic. 4 septicaemic episodes occurred (7.8% of patients), none of which were fatal. The causative organism was *Pseudomonas aeruginosa* in 2 cases, a non-*aeruginosa* in the third, and *Serratia* in the fourth. We are studying this surprising finding further, and the details will be published in full elsewhere.

The successful reduction in the incidence of septicaemia emphasises the hazards of arteriovenous shunts in this population, but it is apparent that infection remains a problem in plasma exchange. As with the other problems you discussed, safe use of this technique depends on careful monitoring in units treating large numbers of patients.

Departments of Medicine and Bacteriology,
Royal Postgraduate Medical School,
London W12 0HS

D. SINGER
J. COHEN

FULMINANT DELETION OF MYOGLOBIN FROM MYOCARDIAL FIBRES IN STATE OF ACUTE CARDIAC FAILURE INDUCING SUDDEN CARDIAC ARREST

SIR,—One of the most difficult problems in forensic pathology is the diagnosis of so-called acute heart failure where there are no significant findings to explain the death. In Japan, and perhaps in Asia too, there is an unknown disease (*pok-kuri* disease), which attacks mainly young males (15–40 years old), especially in the middle of the night, and causes sudden death. Every year several hundred apparently healthy and well-developed males are found dead in bed in the Tokyo district alone. Sometimes loud moaning during sleep is reported, presumably at the time of sudden death. Although slight hypoplasia of the heart and aorta and poorly developed coronary arteries (but not coronary sclerosis) have been noted by several investigators, no pathological or histological explanation has been provided.

We have examined formalin-fixed and paraffin-embedded heart tissues of typical cases of acute cardiac failure by the immunoperoxidase technique and found fulminant loss of myoglobin in the myocardial fibres which could explain the functional coronary insufficiency and fatal cardiac arrest.

Heart muscle from various sites (left and right walls and septum) from five fatal cases of acute heart failure without any coronary disorder was supplied from the Tokyo Medical Examiner's Office. The necropsies had been done within about 20 h of the suspected time of death and the specimens had been preserved in formalin for between 3 months and 3 years. Paraffin sections were prepared and stained by the indirect immunoperoxidase method.¹ The primary antibody was commercial rabbit anti-human-myoglobin serum (Cappel Laboratories, Cochranville, Pennsylvania) and peroxidase-conjugated goat anti-rabbit-IgG was obtained from Dako Immunoglobulins A/S, Denmark.

In all cases there was deletion of myoglobin from the myocardial fibres in multiple disseminated foci together with a striking deposition of the released myoglobin in the interstitial spaces (fig. 1). This abnormality was found mainly in the intramural and epicardial regions of myocardium. In intact myocardial fibres of hearts from other cases of sudden death due, for example, to acute asphyxia, a neck wound, and severe coronary sclerosis, no changes were found (fig. 2). These experiments show that the myoglobin loss is not simply an artefact. The appearances on haematoxylin/eosin and haematoxylin/basic fuchsin/picric acid staining method² were

1. Nakane PK, Pierce GA. Enzyme-labelled antibodies for the light and electron microscopic localization of tissue antigens. *J Cell Biol* 1966; **33**: 307–18.
2. Delage C, Mullick FG, Irey NS. Myocardial lesions in anaphylaxis, a histochemical study. *Arch Pathol* 1973; **95**: 185–89.

1. Simmonds JR, Russell GI, Cowley AJ, Sewell HF, Hearnshaw JR. Generalised allergy to porcine and bovine monocomponent insulins. *Br Med J* 1980; **281**: 355.
2. Thompson RA. The practice of clinical immunology, 2nd ed. London: Edward Arnold, 1978: chap. 2.
3. Cohen J, Pinching AJ, Rees AJ, Peters DK. Infection and immunosuppression: a study of the infective complications of 75 patients with immunologically mediated diseases. *Quart J Med* 1982; **51**: 1–15.