haemoglobinuria had values of less than five days. The $t\frac{1}{2}$ in normal control subjects in this laboratory ranges from 24 to 33 days and that in G-6-PD-deficient subjects in the steady state 20 to 26 days (Chan *et al.*, 1971).

When ^{51}Cr-labelled compatible G-6-PD-deficient red cells were transfused into four G-6-PD-normal patients with viral hepatitis the $t\frac{1}{2}$ values were 17, 18, 20, and 22 days respectively. The values for G-6-PD-deficient cells in 18 compatible G-6-PD-normal subjects not suffering from viral hepatitis varied from 19 to 35 days (Chan and Todd, unpublished).

The haemoglobin pattern and haemoglobin F levels were normal and the Coombs antiglobulin test result was negative in all patients.

Discussion

This study confirms previous reports (Pitcher and Williams, 1963; Kattamis and Tjortjatou, 1970) that a mild to moderately severe haemolysis occurs in G-6-PD-normal subjects suffering from viral hepatitis. In the present series of patients the anaemia was not severe, the haemoglobin levels being over 9 g/dl and the $t\frac{1}{2}$ of ^{51}Cr-labelled red cells varied from 16 to 19 days (normal range 24 to 33 days). The increase in the absolute reticulocyte count was appropriate in the 20 patients studied, indicating adequate erythropoiesis in the bone marrow. The cause of the haemolysis, however, was not determined. Red cell GSH was normal in amount and stable and in no case was there a positive Coombs test result or evidence of coincidental thalassaemia.

Eight of the 18 G-6-PD-deficient patients had clinically more severe haemolysis than the G-6-PD-normal patients (table I) but in most recovery was uneventful. The higher bilirubin levels in the G-6-PD-deficient patients were at least partly due to a more-pronounced haemolysis as evidenced by a significant inverse relationship between the lowest haemoglobin levels and the serum bilirubin levels in this group (fig. 2). The higher serum transaminase levels could also have been caused by the more severe anaemia (Wilkinson, 1962). Studies of the survival of the G-6-PD-deficient red cells in patients with viral hepatitis, however, of which two were autologous and four entailed cross-transfusion into G-6-PD-normal recipients, showed that the ^{51}Cr $t\frac{1}{2}$ values were shortened but to an extent similar to that seen with G-6-PD-normal red cells (table II). The comparable results in the cross-transfusion group indicated that the relatively good red cell survival time in the two patients transfused with autologous cells was not due to younger and less vulnerable cells being used for study. The discrepancy between these results and the observation that haemolysis was more marked in the G-6-PD-deficient group may be attributed to the fact that the red cell survival studies were carried out one to two weeks after the onset of the clinical hepatitis, whereas in the G-6-PD-deficient patients the maximum fall in haemoglobin level and rise in reticulocyte count occurred in the first week or at the beginning of the second week of the illness.

In four of the G-6-PD-deficient patients acute massive intravascular haemolysis occurred. Unlike the rest of the group they had relatively low reticulocyte counts, indicating some degree of depressed bone marrow erythropoietic activity. In addition the red cell GSH levels were low. Though it has been reported that GSH levels are low in uraemia (Thiel *et al.*, 1961) we have been unable to confirm this. Out of 10 G-6-PD-normal patients with uraemia before dialysis four with acute renal failure had GSH levels between 1·9 and 2·8 mmol/l (57·2 and 87·2 mg/100 ml) and six with chronic renal failure had GSH levels between 1·6 and 2·6 mmol/l (49·3 and 81·0 mg/100 ml) (normal: 1·7-3·3 mmol/l; 53-100 mg/100 ml) (Chan and Todd, unpublished). In none did the GSH level decrease significantly after incubation with acetylphenylhydrazine for two hours. Therefore, it is unlikely that uraemia per se was the cause of the low GSH levels. On the other hand, all the four patients had taken a multiplicity of drugs which included paracetamol, amidopyrine, and others of undetermined nature during the preicteric stage of their illness, so that an additional oxidative stress may have been responsible for the low GSH levels and acute massive haemolysis. The necropsy results indicated that death in the three was not due to a more fulminating form of hepatitis. Therefore, while oxidant drugs should be avoided by all G-6-PD-deficient patients this is of particular importance in those with low enzyme levels who have or may have viral hepatitis.

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MEDICAL MEMORANDA

Frusemide-induced Pancreatitis

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Frusemide is a commonly used diuretic which inhibits sodium reabsorption in the ascending limb of the loop of Henle and probably in other segments of the tubule. We report here a case of acute pancreatitis in which frusemide was strongly implicated as the aetiological agent.

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Case Report

A 64-year-old housewife was admitted to hospital having sustained a myocardial infarction complicated by mild left ventricular failure. She had a history of anterior chest pain radiating to the left arm. On admission the patient's condition was good; her pulse was regular at 80 beat/min, and her blood pressure was 150/90 mm Hg. A fourth heart sound was audible at the apex and crepitations were heard at the lung bases. Her medical records showed that the patient had once developed a transitory drug rash after removal of uterine polyp, but no record of the offending drug had been made.

INVESTIGATIONS AND TREATMENT

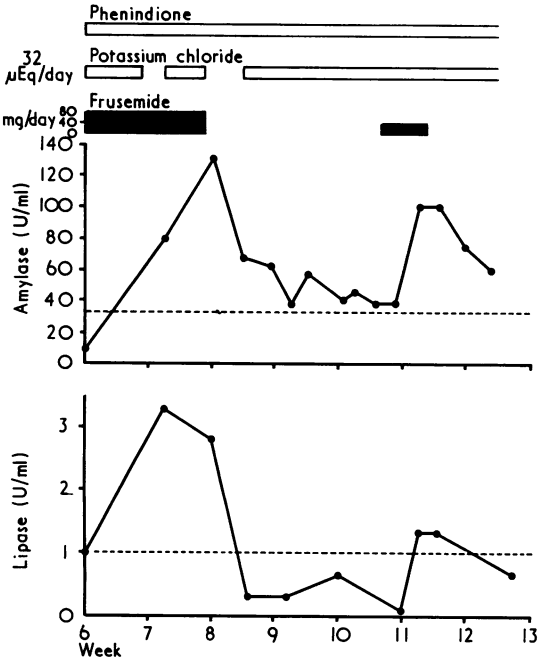
Serum aspartate aminotransferase was 50 U/ml (normal < 40 U/ml), and serum lactic dehydrogenase was 1200 U/ml (normal

< 500 U/ml). An electrocardiogram showed T-wave inversion in the inferolateral leads.

Dihydrocodeine 50 mg given intramuscularly resulted in vomiting and was given once only. The following drugs were then given by mouth: frusemide 40 mg daily, potassium chloride 16mEq daily, and phenindione. Four days after admission the patient developed further anterior chest pain, crepitations were heard over a more extensive area of the lung fields, and the electrocardiograms showed extension of the infarction. Diamorphine 10 mg and a combination of morphine 10 mg and cyclizine 50 mg (Cyclimorph) both induced vomiting and were each given once only. Frusemide was increased to 80 mg daily and potassium chloride to 32 mEq/day. The prothrombin ratio was maintained within the therapeutic range. Progress was satisfactory until the end of the fourth week, when the patient developed hiccuping, eructations, and upper abdominal discomfort. Ten days later vomiting began and there was tenderness and guarding in the right hypochondrium.

Investigations showed plasma bilirubin 1·7 mg/100 ml, serum amylase 80 U/100 ml (normal < 33 U/100 ml), and serum lipase 3·3 U/ml (normal < 1 U/ml). A diagnosis of acute pancreatitis was made.

Potassium chloride was stopped at the end of the patient's sixth week in hospital (see graph). Her condition remained unchanged, serum amylase continued to rise, and potassium chloride was restarted in the seventh week. At the end of the seventh week both frusemide and potassium chloride were stopped. Within 36 hours the abdominal pain had eased considerably and the eructation and vomiting had also diminished. Serum amylase and lipase, which had continued to rise up to this time, began to fall (see graph). Over the next two weeks the patient's condition continued to improve, and serum amylase and lipase returned to near normal levels. Potassium chloride was restarted during the eighth week without ill effect. A cholecystogram made at this time showed nothing abnormal.



Serum amylase and lipase determinations against time. Dotted line represents upper limit of normal.

Because of the probability of the patient needing diuretic therapy in the future we considered reintroducing frusemide under close supervision. The situation was explained to the patient and her family, and all agreed to this approach. Frusemide was restarted at the end of the 10th week in a dose of 40 mg daily when the patient had been symptom free for 10 days. The next day she complained of epigastric discomfort and the eructations returned. On the fifth day there was upper abdominal pain and tenderness and serum amylase rose from 40 U/ml to 100 U/ml and serum lipase from 0·3 U/ml to 1·3 U/ml. Frusemide was stopped on the fifth day and within 36 hours there was marked symptomatic improvement. In addition serum amylase and lipase began to fall towards normal levels (see graph).

Serum calcium remained within normal limits throughout the period in hospital and after discharge, and plasma urea rose to 50 mg/100 ml during the first attack of pancreatitis and to 85 mg/100 ml during the second attack. After recovery, plasma cholesterol was 365 mg/100 ml and lipoprotein electrophoresis showed a Frederikson type II A pattern.

Three months after discharge serum amylase and lipase were within normal limits and have remained so. The patient remained well though she still suffers occasional eructations.

Comment

In about 30% of cases of acute pancreatitis no causative factor is identified. Biliary tract disease and chronic alcoholism remain the commonest associated disorders (Trapnell, 1972) though some cases have been due to drugs (Kowlessar, 1971). This report is the first to present strong evidence implicating frusemide. In a previous case report of pancreatitis the role of frusemide was questioned (Wilson *et al.*, 1967), but the drug was later considered to be non-contributory (Davies, 1967).

In our case other causes of pancreatitis were unlikely. The patient did not take alcohol, the biliary tree was radiographically normal, and no opiates were given before the second episode of pancreatitis. Pancreatitis is associated with types I, III, and V hyperlipoproteinaemia, but the patient's lipid profile was type II A, and the triglycerides were normal. Potassium chloride was stopped without clinical or biochemical improvement, and during the initial recovery period it was restarted with no untoward effect. Anticoagulation with warfarin sodium has been reported as causing pancreatitis by Larsen *et al.* (1962), but both their patients were also receiving thiazide diuretics. Phenindione was continued throughout patient's stay in hospital. Finally, the response to stopping frusemide and the recurrence of pancreatitis when a second challenge was undertaken strongly suggest that this was the aetiological agent.

Acute haemorrhagic pancreatitis has been reported in a few patients treated with chlorothiazide and hydrochlorothiazide (Johnston and Cornish, 1959; Wenger and Gross, 1964). Pancreatitis has also been observed after chlorthalidone treatment (Jones and Caldwell, 1962). The mode of action on the pancreas is unknown, cellular derangement by hypokalaemia, impaired blood flow, inspissated secretions in the ducts, or allergic mechanisms are all possible. Nevertheless, that frusemide is capable of producing this potentially dangerous complication is of importance to all who use it.

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