chromatosis. The patient was treated initially with diet and chlorpropamide. In 1961 insulin was started, the dose gradually increasing to 130 U daily. In 1964 he complained of nausea, lethargy, and impotence. Examination showed generalised pigmentation, hepatomegaly, reduced body hair, atrophic testes, and definite lipodystrophy at injection sites. A diagnosis of haemochromatosis was confirmed by a serum iron concentration of 48 $\mu\text{mol/l}$ (268 $\mu\text{g}/100\text{ ml}$) (TIBC 53.2 $\mu\text{mol/l}$; 297 $\mu\text{g}/100\text{ ml}$) and a liver biopsy specimen which showed typical features of haemochromatosis. There was no history of blood transfusion or of excessive alcohol intake.

Background diabetic retinopathy was first noted in 1964. In 1967 peripheral new vessels were seen in the left fundus, but by 1970 these had not progressed. Three years later new vessels were growing from the left optic disc and there were peripheral new vessels in the right fundus. Despite repeated light coagulation he suffered from recurrent preretinal haemorrhages, though retaining useful vision. In 1976 he developed a neuropathic ulcer on the left foot which failed to heal and required a below-knee amputation.

Results of combined pituitary function test (luteinising hormone-releasing hormone 100 μg · thyrotrophin-releasing hormone 200 μg · Actrapid insulin 0.5 U/kg body weight intravenously)

	Minutes			
	0	30	60	120
LH (U/l)	1	1	2	
FSH (U/l)	1	1	1	
TSH (mU/l)	8	8	19	
Cortisol (nmol/l)	928	—	484	668
Growth hormone (mU/l)	6	3	4	2
Testosterone (nmol)	10.0			
SHBG (mol/l)	3.96 $\times 10^{-8}$			
Prolactin (mU/l)	260			
Blood sugar (mmol/l)	25.0	10.5	8.0	10.0

LH = Luteinising hormone. FSH = Follicle-stimulating hormone. TSH = Thyroid-stimulating hormone. SHBG = Sex hormone binding globulin.

Conversion: SI to traditional units—Cortisol: 1 nmol/l $\approx$ 0.04 $\mu\text{g}/100\text{ ml}$. Testosterone: 1 nmol/l $\approx$ 0.29 ng/ml. Glucose: 1 mmol/l $\approx$ 18 mg/100 ml.

In 1975 a combined pituitary function test showed impaired function (table). Hypoglycaemia did not occur during the test, but shortly after insulin administration the blood pressure fell precipitously and he collapsed. Further blood samples for growth hormone measurement were taken on two subsequent occasions roughly 15 minutes after the onset of hypoglycaemic symptoms, the concentrations being 6 mU/l and 7 mU/l. Blood sugar concentrations were 4.0 mmol/l and 2.8 mmol/l (72 and 50 mg/100 ml) respectively. Other investigations showed a normal skull x-ray film, normal blood urea concentration, and incomplete left bundle-branch block on electrocardiography. His HLA type is A1,3,B7.

Comment

This is the first report of proliferative retinopathy in a patient with idiopathic haemochromatosis and diabetes mellitus. It has recently been suggested that blunted growth hormone secretion may protect the retina in patients with haemochromatosis.⁵ Assessment of growth hormone secretion in our patient has been limited but the evidence suggests that secretion is impaired though not absent. In spite of this the retinopathy has progressed, as might be expected in severe diabetic angiopathy.

Since regular venesection has become an established treatment for haemochromatosis the survival of these patients has been greatly extended. Thus, from the belief that they are immune from retinopathy, we arrive at the point where long-term complications are seen to be no different from those which occur in "idiopathic" diabetes.

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High circulating concentrations of glucagon in non-anaemic uraemic patients

A refractory, normocytic, normochromic anaemia occurs almost without exception in end-stage renal disease (ESRD) and contributes greatly to the morbidity of this condition. A similar anaemia has been described in the rare glucagonoma syndrome.¹ High circulating concentrations of glucagon have been reported in ESRD,^{2,3} and glucagon may have a causative role in the pathogenesis of anaemia in uraemic patients.³ We recently investigated three patients who maintain normal or high packed cell volumes despite ESRD requiring regular dialysis treatment.

Patients, methods, and results

Case 1—A man developed chronic renal failure as a result of poststreptococcal glomerulonephritis and has been on dialysis for four years. Despite this he has a tendency towards polycythaemia, and haemoglobin and packed cell volume are maintained within normal limits only by regular monthly venesection of one unit of blood.

Case 2—A man has polycystic disease and has been treated with dialysis for four years. Haemoglobin concentration and packed cell volume were normal until a few months ago, when iron deficiency anaemia developed which responded promptly to oral iron.

Case 3—A woman has ESRD of unknown cause and has been on dialysis for 2½ years. She too has always had normal blood counts.

Fasting blood samples were obtained from these three patients, from three other ESRD patients with anaemia, and from three normal subjects. The samples were immediately put into chilled glass test tubes containing EDTA and 500 U aprotinin (Trasylol) per ml of blood collected. The tubes were kept on ice until centrifugation at 4°C as soon as possible after collection. The plasma was stored at -20°C. The samples were thawed at room temperature, mixed by inversion, and centrifuged at 4°C for 15 minutes at 2000 rpm just before assay. Plasma glucagon was measured in duplicate in two dilutions using a modification of the radioimmunoassay described by Unger *et al*.⁴ Unger's 30K antiserum, specific for pancreatic glucagon, was used. The sensitivity of the assay is 10 pg/ml.

Both groups of ESRD patients had grossly raised plasma glucagon concentrations (table) compared with the normal subjects ($P < 0.0125$), but there is no obvious difference between the two groups with ESRD ($P > 0.05$).

Plasma glucagon and haemoglobin concentrations

	Case No	Glucagon (pg/ml)	Haemoglobin (g/dl)
<i>Group I</i>			
ESRD	1	610	14.4
Normal Hb	2	800	14.5
	3	510	14.2
<i>Group II</i>			
ESRD	4	620	7.3
Anaemia	5	720	6.8
	6	575	7.4
<i>Group III</i>			
Normal subjects	7	170	13.8
	8	150	14.2
	9	250	14.0

Comment

The exact cause of the anaemia of renal failure is unknown. Current opinion favours a combination of erythropoietin deficiency plus the effect of unidentified uraemic toxin(s) on the bone marrow. Most nephrologists nevertheless see patients occasionally who inexplicably maintain normal haemoglobin concentrations and packed cell volumes despite renal disease of comparable severity with those who do not. Many of these patients have polycystic disease, and we suggest that sufficient islands of normal renal tissue remain scattered between the cysts to maintain adequate production of erythropoietin, as perhaps has occurred in case 2.

The similarity of anaemia of renal failure to the anaemia found in the much rarer glucagonoma syndrome and the carbohydrate intolerance common to both indicate that glucagon could be incriminated in the pathogenesis of the anaemia of uraemia.³ Furthermore, cobaltous chloride has been claimed to be effective in the treatment of anaemia in renal failure, and this substance interferes with glucagon secretion and activity in the rat.⁵ Nevertheless, the findings of equally high concentrations of circulating glucagon in our three patients with

normal haemoglobin and in the anaemic patients reported here and elsewhere³ argues against a causative role for glucagon in the anaemia of end-stage renal disease.

We are grateful to Dr Nina C Mendoza for allowing us to study patients under her care.

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Shwachman's syndrome and acute lymphoblastic leukaemia

The association of hypoplasia of the exocrine pancreas and bone marrow dysfunction has been recognised since 1964.¹ A wide range of haematological disorders has been described, but we report a new association—acute lymphoblastic leukaemia.

Case report

A 14-year-old boy presented with a two-month history of recurrent chest infections. Despite antibiotic treatment he had deteriorated with increasing weight loss, pallor, and breathlessness. His medical history was unremarkable with no symptoms suggestive of a bowel disorder, although his sister had died aged 9 years of suspected coeliac disease. On admission he was pale and small for his age; his abdomen was protuberant with ascites; and his ankles swollen. He had generalised lymphadenopathy and gross hepatosplenomegaly. The results of initial investigations showed haemoglobin 5.2 g/dl, total white cell count $525 \times 10^9/l$ with neutrophils 2% and blast cells 98%. Plasma concentration of sodium was 134 mmol/l (134 mEq/l), potassium 3.4 mmol/l (3.4 mEq/l), urea 43 mmol/l (257 mg/100 ml), uric acid 0.3 mmol/l (5.0 mg/100 ml), bilirubin 11 μ mol/l (0.6 mg/100 ml). Serum albumin was 38 g/l and globulins 27 g/l; immunoglobulin concentrations were normal. Chest x-ray films showed chronic infective changes but no mediastinal widening. Bone marrow aspirate was hypercellular because of a dense infiltrate of blast cells which showed "block" periodic acid Schiff positivity but no myeloperoxidase activity. The abnormal cells also reacted with an antibody raised against leukaemic lymphoblasts.

Acute lymphoblastic leukaemia was diagnosed and he was entered into the appropriate MRC trial. Initial treatment was with intravenous vincristine 1.5 mg weekly and oral prednisolone 40 mg daily. The primitive cells disappeared from the peripheral blood within six days. During the ensuing pancytopenia he developed epistaxis and gastrointestinal bleeding necessitating frequent transfusions of red cells and platelets. He also developed a severe klebsiella pneumonia, which persisted despite appropriate antibiotic treatment. Diuretics caused a rapid disappearance of the peripheral oedema but the ascites increased. In the later stages of his illness he also developed persistent offensive diarrhoea. He died six weeks after treatment was started, still in a stage of profound pancytopenia. Bone marrow examination five days before death showed severe hypoplasia of the normal marrow tissue but no evidence of active leukaemia.

Postmortem examination showed consolidation of both lungs and evidence of massive gastrointestinal haemorrhage. The liver and spleen were enlarged, the liver histologically showing increased fibrosis. There was no sign of residual leukaemia in the liver or any other organ examined. The most striking histological abnormality was the total absence of exocrine pancreatic tissue, the islet cells being surrounded by fatty tissue with a few dilated ducts.

Comment

Though rare, hypoplasia of the exocrine pancreas is said to be the most common pancreatic disorder of childhood once cystic fibrosis has been excluded.² Haematological abnormalities described in association with this condition include anaemia, neutropenia, and

thrombocytopenia, and bone marrow examinations have shown hypoplasia or a maturation arrest in one or more cell lines.¹⁻³ Only two cases have been described in association with leukaemia: one monocytic³ and the other myeloblastic.⁴ The association with lymphoblastic leukaemia is more difficult to explain. Lymphoreticular malignancy in patients with immunoglobulin deficiency is well recognised and some cases of Shwachman's syndrome have recently been described with low immunoglobulin concentrations.⁵ In our case, however, the immunoglobulin concentrations were normal.

Shwachman's syndrome is often familial^{1,2} and interestingly our patient's sister had died with a malabsorption syndrome. There was no evidence from the biopsy specimen of coeliac disease and she failed to respond to a gluten-free diet, so probably she also had pancreatic hypoplasia.

Requests for reprints should be addressed to Dr J S Lilleyman.

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Deaths in cold water

Most efforts to reduce the heavy loss of life in water accidents are directed to improving the ability to swim, but a recent Home Office report of the Working Party on Water Safety gives further emphasis to the fact that many of the people who die can swim. Of those whose swimming ability was known, most of those in the 15- to 35-year-old age group who died could swim, while most of those who died in the sea at any age were either good or very good swimmers. It is still not always realised that even summer waters around Britain are cold enough to kill during prolonged immersion, and that in winter and spring the high viscosity and other effects of water near 0°C can cause excellent swimmers to drown in as little as 90 seconds.¹ Advice about simple precautions to be taken in cold water, which can prevent or greatly reduce these hazards, was widely distributed by water sport clubs and schools after a conference organised by the Central Council for Physical Recreation in 1971. We have now analysed the Registrar General's Statistical Reviews to see whether this action was followed by any major changes in the accident rates.

Statistical analysis

The table shows the deaths in different age groups during the four years up to and the four years after 1971. The deaths are those registered as definitely accidental and due to sinking of boats, falling from boats, and other drownings and submersions (categories E830, E832, and E910) for England and Wales only. They show that the number of deaths fell significantly ($P < 0.001$ by the χ^2 test), in the 5- to 14-year-old age group only. The total deaths in the group were 549 in 1968-71 (18.3/million) and 438 in 1972-5 (13.9/million). This represents a reduction of 111 deaths or a little more if the

Accidental deaths in water

Age	1968-71		1972-5	
	Total deaths	Deaths/million	Total deaths	Deaths/million
0-4	400	24.7	337	23.1
5-14	549*	18.3	438*	13.9
15-44	879	11.5	864	11.3
45-64	346	7.3	345	7.4
65+	233	9.3	268	9.9

*Figures for 1968-71 differ from those for 1972-5 $P < 0.001$.