was osteosclerosis, affecting especially cortical bone and more marked in the three fingers most severely affected by soft-tissue atrophic changes. Osteosclerosis is an unusual but recognized change in ischaemic digits, and arteriograms would have been informative in our case, but were refused by the patient.

Localized scleroderma (morphea) may occasionally be associated with certain sclerotic bone disorders such as melorheostosis, the soft tissue change corresponding to the distribution of the bone abnormality (Dillehunt & Chuinard, 1936; Muller & Henderson, 1963), but scleroderma with bound-down skin was not present in our case and the bone changes were not those characteristic of melorheostosis, in which the disorder is usually confined to the bones of one limb and there may be severe bone pain. There was no evidence of certain systemic conditions associated with increased bone formation, such as generalized osteopetrosis (Albers-Schönberg disease), osteopoikilosis, polyostotic fibrous dysplasia, lead poisoning and fluorosis.

It is of some interest that the clinical appear-

ance of the left ulnar three fingers was suggestive of an ulnar nerve lesion, and that there was additionally reduction of sensory conduction velocity in the left ulnar nerve below the wrist, although in the presence of apparently frank muscle wasting other signs of neuropathy (reduced motor conduction velocity and electromyographic evidence of denervation of the muscles supplied) would have been expected. Assuming that an ulnar nerve lesion was present, it is possible to speculate that this occurred as a result of endarteritis of the vasa nervorum supplying the more distal fibres of the ulnar nerve, associated with the long-standing Raynaud's disease.

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Diabetes mellitus, Addison's disease and pernicious anaemia

R. C. TURNER
M.A., M.R.C.P.

ARNOLD BLOOM
M.D., F.R.C.P.

Whittington Hospital, London, N.19

THESE three diseases in a patient are an unusual combination. That Addison's disease and pernicious anaemia may be associated with a disorder of autoimmune mechanisms raises the possibility of a similar association for diabetes mellitus. The evidence for this suggestion is discussed.

Case history

Mrs D.G., born 1901, developed vitiligo when aged 28, her hair went grey aged 40. In 1956 she first presented complaining of nervousness and fainting. She was markedly pigmented but Addison's disease was thought unlikely in view

of obesity, raised blood pressure (160/100 mm Hg) and lack of buccal pigmentation. Since 1963 she had lost 3 stones in weight and later experienced increasing lightheadedness and fainting. In 1965 she was given a 2-month course of prednisone for lichen planus. She then developed thirst and polyuria and was found to have glycosuria. A 50 g glucose tolerance test whilst on 5 mg prednisone/day revealed diabetes (fasting blood sugar 238 mg/100 ml rising to a maximum of 270 mg, falling to 256 mg after 2 hr). This responded to chlorpropamide and later to dietary restriction alone. However, her pigmenta-

tion and weakness increased and she developed morning retching. She was admitted for investigation in 1966.

In the *family history* her mother and maternal grandmother were diabetic, and one sister had rheumatoid arthritis.

On *examination* there was marked pigmentation, maximal in skin creases, and vitiligo but no buccal pigmentation. Her blood pressure was 110/70 mmHg falling to 90/60 on standing.

Investigations: Haemoglobin 10 g/100 ml. Film: macrocytosis and anisocytosis MCV 106 μ^3 , WBC 5200/mm³ with 41% neutrophils with shift to right. Marrow: megaloblastic with giant metamyelocytes. Serum vitamin B₁₂ 30 pg/ml. Serum iron 110 μ g/100 ml. Kay's test: histamine fast achlorhydria. Blood urea 50 mg/100 ml, sodium 137 mEq/l; potassium, 4.4 mEq/l. 24-hr urine 17-hydroxycorticosteroids 7.7, 6.9 mg; after 3 days ACTH 100 units/day 8.2 mg/24 hr. Plasma 11-hydroxycorticosteroids 15.6 μ g/100 ml 30 min after 0.25 mg Synacthen i.m. 15.3 μ g. X-ray abdomen, no adrenal calcification. Mantoux negative. 50 g glucose tolerance test: fasting blood sugar 130 mg/100 ml rising to a maximum of 168 mg, falling to 164 mg after 2 hr. Intravenous glucose tolerance test 0.5 g/kg, K (total increment)=0.3. Serum antibodies to gastric parietal cells and adrenal cells demonstrated by immunofluorescent techniques. No antithyroid antibodies or anti-intrinsic factor antibodies.

Discussion

The simultaneous presence of the two diseases Addison described and partly confused in 1849 and 1855 underlines the irony that they may prove to be aetiologically related. Addison's disease and diabetes mellitus, however, form an unexpected combination since destruction of the suprarenal glands usually leads to hypoglycaemia. Because of glucocorticoid deficiency, control of diabetes in these patients by insulin is often characterized by pronounced lability of blood glucose. Where possible control with sulphonylureas is less troublesome, and for this patient chlorpropamide is effective when she is taking 37.5 mg cortisone daily as replacement therapy. On this dose her postural hypotension has improved and her pigmentation decreased.

There are 129 cases of Addison's disease with diabetes mellitus in the literature (Bibergeil & Geisler, 1964; Burke & Emanuel, 1965; Monroe Bourne & Howard, 1963; Moorehead *et al.*, 1964; Mowbray, 1965; Phair, Bondy & Abelson, 1965; Plattner, 1965; Selby, 1962; Solomon *et al.*, 1965; Tzagourins & Hamwi, 1967; Wehrmacher, 1961);

the combination, though rare, may be more than a chance occurrence. Thus of the fifteen cases of Schmidt's syndrome (thyroid and adrenal insufficiency) reported by Carpenter *et al.* (1964) ten had diabetes. Tzagourins & Hamwi (1967) found 17% of forty-one patients with Addison's disease were diabetic. Of the 130 cases (including this patient) who had diabetes and Addison's disease eighty-five (65%) were due to adrenal atrophy and twenty (15%) due to tuberculosis with 20% unspecified. Thirty-one (24%) also had thyroid disease (myxoedema, thyrotoxicosis or Hashimoto's disease) and of these twenty-eight (81%) were due to adrenal atrophy and two (6%) to adrenal tuberculosis. During the same period the incidences of tuberculous and non-tuberculous Addison's disease were about equal (Dunlop, 1963; O'Donnell, 1950; Thorn *et al.*, 1949) so that it appears that diabetes was associated more frequently with adrenal atrophy than might be expected by chance. The high incidence of associated thyroid disease may be relevant.

For 50 years an association has been suggested between diabetes and pernicious anaemia. Comparative population studies have been invoked to show that the diseases occur more commonly together than one might expect by chance (Arapakis *et al.*, 1963) but if allowance is made for the higher incidence expected because of the older age group of each disease compared with the general population the relationship is less impressive. Fixa *et al.* (1964) found no increase in the incidence of chronic gastritis in diabetes compared with controls.

That diabetes mellitus may be associated with diseases in which autoimmunity occurs suggests that this may sometimes be important in this disease also: Mackay & Burnet (1963) enumerated markers, such as this association, which may indicate immune mechanisms. Other markers have also been demonstrated in diabetes. From the serological aspect Moore & Neilson (1963) found gastric and thyroid complement-fixing antibodies were statistically more common in eighty-three diabetics than in hospital in-patient controls matched for age and sex. Anti-thyroid antibodies were found in 17% of diabetics and 4% of controls, and antigastric antibodies in 22% of diabetics and 8% of controls. Landing *et al.* (1963) found anti-thyroid antibodies by immunofluorescent techniques in 18% of diabetics compared with 1-5% controls. Ungar *et al.* (1967) found antibody to intrinsic factor in the serum of seven of 150 diabetics compared with none in controls.

Antibodies to the pancreas and to insulin have

been shown in the sera of diabetics. Chetty & Watson (1965) confirmed the work of Pav and demonstrated antibody-like activity against insulin measured by complement consumption in the sera of 58% of diabetics not treated with insulin, and in 26% of controls. Antibodies can be shown easily in patients treated with insulin, but in untreated subjects the anti-insulin activity suggests a reaction with endogenous insulin, though it is not certain that this represents an auto-antibody. Mancini *et al.* (1965) using immunofluorescent techniques found antibodies to β islet cells which he believed to be anti-insulin antibodies. These occurred in fifteen out of twenty-four diabetics treated with insulin, and in two out of five untreated diabetics. However he reported only three controls and his work has yet to be confirmed. Herskovic *et al.* (1966) confirmed Murray & Thal's work and showed precipitates to pancreatic homogenates by double gel diffusion in 20% of thirty-five diabetics but in only one out of fifty-two controls.

Immune mechanisms may be involved in diabetic complications. Berns *et al.* (1962) demonstrated that nodular diabetic glomerular lesions bind fluorescent conjugated insulin, anti-human-globulin and anti-insulin serum. This suggests that there is an insulin/anti-insulin complex on these lesions. Coleman *et al.* (1962) showed that retinal capillary aneurysms bind fluorescent insulin. Mohos, Hennigar & Fogelman (1963) produced renal lesions in rabbits very similar to those described by Kimmelstiel & Wilson. The rabbits were immunized with insulin in Freund's complete adjuvant followed by subcutaneous injections of insulin. The lesions appeared to be due to a delayed sensitivity phenomenon.

Pancreatic islet infiltration with lymphocytes has been described in children presenting and dying in diabetic coma (Le Compte, 1958). Similar changes have been produced by injection of homologous or heterologous insulin with adjuvant into cows (Le Compte *et al.*, 1966). Grodsky *et al.* (1966) immunized nine rabbits with bovine insulin with adjuvant producing islet lymphocytic infiltration in all cases, and diabetes in two of the rabbits.

Markers which have not been described include evidence of increased γ -globulins in diabetics, associated thymic abnormalities and improvement on steroids (except in patients with resistance to exogenous insulin).

Diabetes is a syndrome with many possible causes, and it may be that some cases are connected with abnormalities of immune mechanisms. There is suggestive evidence that this is so but further investigation is necessary.

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Lymphosarcoma during the course of myeloid leukaemia

J. J. TAYLOR

M.B., B.S., M.C.Path.

Consultant Haematologist,
United Birmingham Hospitals

D. W. EVANS

B.Sc., M.D., M.R.C.P., D.C.H.

Consultant Physician,
United Cambridge Hospitals

THE co-existence of malignant lymphoma and chronic myeloid leukaemia has rarely been recorded. Because of the theoretical implications of such an association, the occurrence of lymphosarcoma in a woman with busulphan-treated chronic myeloid leukaemia is here reported.

Case report

The patient, a 52-year-old housewife and shop assistant, presented in October 1964 with complaints of excessive tiredness recently, anorexia and weight loss. The latter may have occurred over a longer period of perhaps 9 months. The only abnormal clinical findings at that time were mild pyrexia (99°F), an appendicectomy scar and a palpable spleen tip, approximately 1 in. below the costal margin.

Investigations. Hb 12.9 g/100 ml, PCV 37%, WBC 49,400/mm³; 70% of the white cells were polymorphonuclear neutrophils, 10% metamyelocytes 6% myelocytes and 2% 'blast' cells. By the time she was admitted to hospital, 3 months later, the spleen was palpable 4 in. below the costal margin, Hb had fallen to 11.1 g/100 ml and total WBC had risen to 186,900/mm³ (69 neutrophils 11% metamyelocytes, 8% myelocytes and 3% promyelocytes). Platelet count was then 793,000/mm³. Radiography revealed no evidence of hilar lymphadenopathy.

Busulphan therapy was commenced in January 1965. The courses and doses of this drug, and periodic white cell and platelet counts are shown in Fig. 1. Hb levels remained about 10 g/100 ml

until the terminal phase of the illness in September 1966.

FIG. 1. Response of white cells and platelets to treatment over a 2-year period.

She began to feel well again March 1965 but was troubled by new symptoms of numbness and tingling in fingers and thumbs in July 1965. There was some blunting of pain sensation at the tips of these digits and sensory neuropathy was diagnosed. Serum B₁₂ was normal and there was no response to oral vitamin B₁. The paraesthesiae had disappeared by May 1966 and she remained well until June 1966 when she became aware of rapidly-enlarging tender lymph nodes on both sides of her neck. On examination there proved to be tender, mobile, rubbery nodes up