diabetic tissue. The results are recalculated on a tissue protein basis in the Table and a difference in activity of phosphofructokinase was still noted.

DISCUSSION

Adipose tissue from the adult diabetics tested in this study shows a pronounced reduction in activity of phosphofructokinase. This appears even when the enzyme is maximally activated by sulphate ions and suggests that there is an absolute reduction in level of enzyme protein. Phosphofructokinase is an enzyme which is thought to exert control over glycolysis by activation/inhibition reactions which are mediated by a variety of small metabolites (adenosine triphosphate, adenosine diphosphate, adenosine monophosphate, phosphate, and citrate). Our data might indicate that over a long-term the level of the enzyme protein alters too. An unexpected observation was that in human diabetic tissue there was no associated depression in activity of hexokinase, despite the reports (Katzen, 1966; McLean *et al.*, 1967) that this enzyme is reduced in adipose tissue of rats made diabetic by streptozotocin or alloxan. Perhaps hexokinase disappears only in states of absolute insulin deficiency, and our diabetic group would not fall into this category since the majority required no insulin therapy.

As regards the functional significance of this alteration in enzyme activity, intact adipose tissue of adult diabetics metabolizes less glucose than tissue from non-diabetics (Field *et al.*, 1961; Kahlenberg and Kalant, 1964). This has been attributed to a defect in membrane transport of glucose into the diabetic cell (Kahlenberg and Kalant, 1964). Our data, how-

ever, raise the possibility that an intracellular deficiency of a key glycolytic enzyme, phosphofructokinase, might impair glucose utilization by the whole cell and perhaps contribute to the delayed clearance of blood glucose during a tolerance test.

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Medical Memoranda

Myasthenia Gravis, Haemolytic Anaemia, and Lymphoreticular Malignancy

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The relation of autoimmune disease to the development of lymphoreticular malignancy has been the subject of much conjecture, debate, and research. Myasthenia gravis may well be a part of the ever-growing spectrum of autoimmunity. Reported below is the case of a patient with myasthenia gravis and haemolytic anaemia of unknown origin who developed reticulum cell sarcoma.

CASE REPORT

A 53-year-old man was admitted to the New England Medical Center Hospitals on 27 October, 1967 complaining of fever and pain in his left leg. In 1945 splenomegaly was noted and as the result of a positive serological test for syphilis he was treated with penicillin. In 1951 myasthenia gravis developed. Because of the splenomegaly haematological examinations were carried out repeatedly from 1951 to 1967. All gave normal results, apart from an occasionally somewhat low haemoglobin level. Recurrent cholecystitis necessitated cholecystectomy in February 1961. At laparotomy the liver was normal. The spleen was twice the normal size and smooth. The haemoglobin was 11.8 g./100 ml.; haematocrit value 35%; and bilirubin 0.4 mg./100 ml. direct reading, 1.6 mg./100 ml. total.

In December 1961 increasing fatigability and jaundice were noted. The haemoglobin was 7.6 g./100 ml.; packed cell volume 25%; white blood cell count 3,840/cu. mm., normal differential; platelets 95,000/cu. mm.; reticulocyte count 1.2%; and direct reacting bilirubin 0.4 mg./100 ml., indirect 1.6 mg./100 ml. The

bone marrow showed normoblastic erythroid hyperplasia with greatly increased haemosiderin deposits. Chromium-51-labelled red cells showed "definite decreased survival." Four units of whole blood were transfused with little change in haemoglobin concentration or packed cell volume. For the next six years the haemoglobin concentration ranged between 9 and 11 g./100 ml. and further transfusions were not required.

In January 1967, after six asymptomatic years on anticholinesterase drugs, weakness and jaundice recurred. The haemoglobin concentration was 5.0 g./100 ml. and the ⁵¹Cr red cell half-life 15 days. Two units of whole blood were administered and he was transferred to this hospital. The sclerae were slightly icteric and both liver and spleen were enlarged. No ecchymoses or petechiae were visible. The haemoglobin was 4.2 g./100 ml.; packed cell volume 11.5%; platelets 137,000/cu. mm.; reticulocyte count 3.0%; and leucocyte count 3,200/cu. mm., with a differential showing a "left shift" of the granulocytic series. The direct reacting bilirubin was 1.4 mg./100 ml., indirect 5.3 mg./100 ml. Bone marrow biopsy showed erythroid hyperplasia with an increase in reticulum cells and lymphocytes.

At laparotomy the spleen (1,560 g.) was excised. The liver and retroperitoneal structures were macroscopically normal. On histological examination the spleen showed congestion of the red pulp, moderate extramedullary haemopoiesis, and islands of reticulum cells. Postoperatively after transfusion the haemoglobin level stabilized at 8.5 g./100 ml.; the packed cell volume was 28%; reticulocyte count 11.9%; and ⁵¹Cr red cell half-life 13 days, donor cells being used. Within four months the haemoglobin had risen to 15.6 g./100 ml.; the packed cell volume was 48%; reticulocyte count 0.4%; and leucocyte count 11,800, normal differential.

In July 1967 he complained of abrupt onset of pain in the left thigh and buttock, worse when sitting upright, and faecal and urinary incontinence. Anaesthesia of sacral dermatomes 3 and 4 was found, and a myelogram showed a cauda equina tumour with a block of the spinal canal at the first sacral segment. An epidural

tumour was resected which proved to be a reticulum cell sarcoma. The pain persisted despite local radiation therapy followed by prednisone and vinblastine. Two weeks before readmission he felt a left cervical lymph node. He had lost 15 lb. (6.8 kg.) in weight over the three months before admission, but he denied other symptoms.

On admission in October he complained of severe back pain. The blood pressure was 124/76 mm. Hg, the rectal temperature was 102.2°F. (39°C.), he had a sinus tachycardia, and rales were heard over the right lower lung field. Examination showed mild ptosis of the left eye lid and absent anal sphincter tone. There was generalized lymphadenopathy and the liver was enlarged to 6 cm. below the right costal margin. Minimal flexion or extension of the lumbosacral joint produced extreme pain. There was hypoaesthesia over the saddle area, with sacral radiation dermatitis, but leg weakness was symmetrical and mild. The ankle jerks were absent.

The haemoglobin was 9.2 g./100 ml.; packed cell volume 28.5%; and leucocyte count 18,000/cu. mm., with a left shift. The platelet count was 540,000/cu. mm. Reticulocytes were absent. Bone marrow showed orderly reactive hyperplasia of erythroid, myeloid, and megakaryocytic elements, with a definite increase in reticulum cells and iron stores. The bilirubin was 0.5 mg./100 ml. direct, 0.9 mg./100 ml. indirect; total protein 6.0 g./100 ml., with raised α_1 and α_2 and greatly depressed gammaglobulin levels. Stool guaiac was negative. Immunoelectrophoresis showed IgG slightly depressed at 4.8 mg./ml., but normal IgA and IgM levels. The bromsulphophthalein retention was 12.5% at 45 minutes; alkaline phosphatase 8.2 Bodansky units; prothrombin activity 55%; and serum alanine aminotransferase 60 units. Serum iron was 169 μ g./100 ml., with a total iron-binding capacity of 226 μ g./100 ml. Chromium-51 red cell survival (half-life) was less than one day. Chest x-ray picture showed right lower lobe pneumonia, though sputum pathogens were not cultured. Urine culture grew many klebsiella sensitive to cephalothin. Immunological testing showed a positive latex fixation titre and antithyroglobulin antibody present in 1:5 titre, but negative results for the serological test for syphilis, anti-muscle antibody, and antinuclear antibody. Dinitrochlorobenzene did not cause skin sensitization.

Intravenous cephalothin, nitrogen mustard, and methylprednisone were infused. The patient's transfusion requirements increased, but serial reticulocyte counts never rose above 0.1%. He became afebrile within two days and lymphadenopathy decreased, but the liver was noted to be nodular. Because the chest infiltrate was clearing, cephalothin was discontinued after six days. On 8 November the rectal temperature rose to 106°F. (41.1°C.) and an unspun urine sediment showed many Gram-negative bacilli. Chloramphenicol and kanamycin were administered, but hypotension, bronchospasm, and irreversible cardio-respiratory arrest ensued within a few hours. Aerobacter grew from blood and urine cultures. Permission for necropsy was not granted.

COMMENT

A relation between autoimmune disease and lymphoreticular malignancy has been suggested for many years. This is believed to be the first report of the association between myasthenia gravis and a lymphoreticular malignancy, though Simpson (1966) alluded to a myasthenic patient who developed reticulum cell sarcoma eight years after thymectomy and stated that he knew of two similar unreported cases. Myasthenia followed by chronic lymphocytic leukaemia and autoimmune haemolytic anaemia has also been described (Cohen and Waxman, 1967).

The obvious variation in whether the autoimmune or the lymphoproliferative disease appears first suggests that the two may actually appear independently of one another, each as a result of some underlying defect in the host. This hypothetical defect would be the inability of the host to destroy mutant cells which might have the potential to produce autoimmune or lymphoproliferative disease (Dameshek and Schwartz, 1959).

In the present case the reticulum cells found in spleen and marrow tissue four months before the appearance of the cauda equina tumour were, in retrospect, the first evidence of a developing reticulum cell sarcoma. Undoubtedly it also involved the liver, which became progressively nodular in the terminal stages of the disease, as well as the cervical and axillary lymph nodes, which were all definitely enlarged. The thymus could not be examined post mortem, but this organ has been found to be completely atrophied (Cohen and Waxman, 1967) or hyperplastic (Castleman and Norris, 1949) when autoimmune and lymphoproliferative disorders are associated. The aetiology of the haemolytic anaemia could not be defined despite the diagnostic studies performed. Erythrophagocytosis was not striking in the lymphoreticular tissue examined.

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